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Congenital Anomalies

From the Embryo to the Neonate

Edited by Stefania Tudorache

CONGENITAL ANOMALIES - FROM THE EMBRYO TO THE NEONATE

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Contributors

Shigehito Yamada, Haruyuki Makishima, Vesna Milojković Marinović, Blagoje Grujić, Aleksandra Stojanović, Dalibor Sabbagh, Petar Rašić, Artúr Beke, Fanni Rebeka Erős, Diana Ramašauskaitė, Tanya Kitova, Borislav Kitov, Aida Masmoudi, Denis Milkov, Liana Ples, Gorduza Eusebiu Vlad, Demetra Socolov, Socolov Razvan, Gorazd Rudolf, Luca Lovrecic, Ales Maver, Borut Peterlin, Marija Volk, Dragusin Roxana, Pătru Ciprian, Șorop-Florea Maria, Lucian George Zorila, Cristian Marinaș, Bogdan Virgiliu Sorop, Nicolae Cernea, Cristian Neamțu, Dominic Iliescu, Umar Boston, Ken-Michael Bayle, Christopher Knott-Craig, Tk Susheel Kumar, Vrabie Sidonia, Liliana Novac, Dijmarescu Lorena Anda, Manolea Maria Magdalena, Siminel Mirela, Marius Novac, Amal Zubani, Amjad Al-Kouatli, Irfan Asra, Sidonia Maria Sandulescu, Andreea Veliscu Carp, Ramona Mircea Vicol, Adela Serban, Cristian Vaduva, Alexandru Comanescu, Florentina Tanase, Maria Cristina Comanescu, Razvan Cosmin Pana, Madalina Barbu, Adrian Claudiu Ratiu, Mihaela Amelia Dobrescu, Florin Burada, Mihai Gabriel Cucu, Gratiela Chelu, Mihai Ioana, Alina Cimpoeru, Anca Lelia Riza, Razvan Mihail Plesea, Simona Vladareanu, Mihaela Bot, Costin Berceanu, Claudia Mehedintu, Simona Popescu, Iuliana Ceausu, Cringu Antoniu Ionescu, Claudiu Marginean, Mona Zvanca, Alina Veduta, Dragos Nemescu, Capitanescu Razvan, Andreea Elena Ceausescu, Andreea Docea, Marina Dinu, Stefan Degeratu, Monica Cara

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Meet the editor

Stefania Tudorache, PhD, MD, MPH, is a university associate professor at the Department of Mother and Child, University of Medicine and Pharmacy of Craiova, Romania. She received a degree from the University of Medicine and Pharmacy in Craiova, Romania, in 1994. In 2002, she was a research fellow at the university and obtained the position of lecturer and associate professor afterward. Currently, she is the head of the Prenatal Diagnostic Unit. She has been trained mainly in the fields of maternal-fetal medicine, invasive maneuvers, and the prenatal diagnosis. She holds her master's degree in Healthcare Management. She is the director of postgraduate courses and an invited speaker in many international conferences and congresses. She has authored and coauthored articles on ultrasound, including original investigations published in peer-reviewed journals, books, and book chapters.

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Preface

Nowadays, nobody can imagine practicing obstetrics without using obstetrical ultrasound.

Working in the prenatal diagnosis field requires dedication, patience, skills, experience, caution, and empathy.

The concept of this book was guided by the desire to provide some help to the ultrasound operators. On a daily basis, they are confronted with the challenging task of ruling out or suspecting/confirming the diagnosis of fetal anomalies, either structural or chromosomal.

We have witnessed the paramount effort to commute, adjoining to the screening for chromosomal abnormalities—all major structural defects diagnosed earlier from the second-trimester scan to the late first-trimester scan. Sometimes, minute structural defects can betray major functional damage or may trigger a comprehensive genetic workup. Such achievements were unthinkable until recently. The most important aim of prenatal ultrasonography remained to reassure the parents as early as possible that fetal development is within the normal ranges. At times, if a malformation is detected, it is necessary to counsel the patient about the nature and the natural history of the respective condition. Most anomalies develop early, and we now have the tools to detect these as early as 10–16 weeks.

Still, all operators must acknowledge the dynamics of the prenatal life and maintain the alertness in scanning all the three trimesters, regardless of the normalcy of the previous data, in each case.

This book is structured in three sections.

The **first** section, the largest one, is dedicated to fetal structural anomalies.

The first chapter is a run-through of the most significant anomalies that can be detected in the antenatal life, which is divided into fetal systems. The second chapter, committed to sonoembryology, contains images from one of the largest collections of human embryos. It covers the embryonic normal development and growth and includes the embryos with congenital anomalies.

Subsequently, the fetal systems are addressed in a natural consecution: the central nervous system, the fetal face, the fetal heart, the thorax, the abdomen, the kidneys, the genitalia, and the extremities.

Finally, this book section ends with two chapters describing the fetal adnexal (placenta and umbilical cord) anomalies.

All authors proved an outstanding effort to cover extensive researched fields, in a detailed and accurate manner, for each condition addressed. The reader will find a large number of

appropriate, informative, and high-quality ultrasound images and adequately referenced chapters.

The **second** section of the book highlights the unbreakable bond between obstetrics and medical genetics. Whereas the first chapter is a review in regard to biochemical and ultrasound markers of chromosomal anomalies, the second one is dedicated to the genomic testing. A separate chapter is addressed to the genetic aspects of congenital heart diseases, and the last one is a comprehensive approach in counseling the couples whose fetuses have chromosomal abnormalities.

The **third** and last section of the book contains two important chapters, in regard to the management of pregnancy and delivery in these cases and the approach to be taken toward a dysmorphic neonate.

To conclude, the chapters of this book contain objective and exhaustive updated reviews of the existing pertinent literature, so that the reader would have a wide reference basis on each subject. Yet, many authors scan the fetus themselves or are directly involved with managing pregnancies with structural malformations or chromosomal anomalies.

From the bottom of my heart, I would like to thank all the distinguished colleagues who invested their valuable time in writing the chapters of this book.

I sincerely believe that this book is beneficial for many professionals working in the prenatal diagnosis.

Stefania Tudorache, MD, PhD, MPH
Associate Professor
Prenatal Diagnosis Unit
University of Medicine and Pharmacy of Craiova
Romania

Fetal Structural Anomalies

Chapter 1

Congenital Fetal Anomalies and the Role of Prenatal Ultrasound

Fanni Rebeka Erős and Artúr Beke

Additional information is available at the end of the chapter

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Abstract

The ultrasound is the most widely used diagnostic tool in obstetrics nowadays, in particular in the detection of developmental disorders. However, it is important to know which are those disorders that can be detected prenatally with great certainty, and which ones can be detected only partially or not at all prior to giving birth. Pregnant women have high expectations, that any abnormalities should be fully recognizable and detected early during pregnancy, and this often leads to damages lawsuits. Thus, the right information is essential, so the doctors providing information also must have up to date knowledge about the effectiveness of ultrasound diagnostics. Prenatal diagnostics also entails enormous medical professional responsibility, since the consequences of an accidental inaccurate diagnosis can have significant consequences for both the fetus and the family. Thus, it is important to determine that how early and in what proportion the ultrasound protocol of the current Hungarian pregnancy care system is able to detect the individual disorder groups.

Keywords: congenital malformations, prenatal ultrasound, ultrasound detection

1. Introduction

Nowadays, 2D ultrasound is the most important diagnostic technique in obstetrics, especially in the diagnosis of congenital malformations.

The first diagnostic ultrasound screening usually takes place at around 11–13 weeks of pregnancy, when the thickness of the nuchal translucency is measured and the presence of the nasal bone is confirmed. Nuchal translucency (NT) is an excess fluid under the nuchal skin of the fetus in the first trimester. In 1866, Langdon Down described this phenomenon as trisomy 21 patients' having "too large skin" [1]. In the 1990s it was recognized that the excessive fluid

is responsible for this thickening and that it was possible to measure the thickness of this fluid at the back of the neck around the third month of pregnancy [2, 3]. A thicker nuchal translucency might suggest chromosomal abnormality, but it can be present in cardiovascular malformations and genetic syndromes as well.

NT is usually measured around 11–13 weeks of gestation. The thickness of the nuchal oedema is proportional to the crown-rump length (CRL) of the fetus so it is measured when the CRL is 45–84 mm. The higher the NT is at a specific CRL, the higher the risk for chromosomal abnormalities is [2]. For example, in Turner-syndrome, the NT value is around 8 mm higher than the median [2].

In Down-syndrome, nasal bone is absent in 60–70% of the affected fetuses. Langdon Down observed that those with 21-trisomy had small noses, caused by the hypoplasia of the nasal bone. The hypoplasia of the nasal bone can also be detected during pregnancy. According to a meta-analysis, the nasal bone was absent in 1.4% of healthy fetuses, while in 69% of fetuses with trisomy 21. Furthermore, the maxilla was shorter in 25% of the affected fetuses, and ductus venosus flow was abnormal in 80% [1, 2].

In Edwards-syndrome (trisomy 18), early growth retardation and bradycardia can be detected at 11–13 weeks. Also, the nasal bone is absent in 55% of the cases and 75% has a singular artery in the umbilical cord.

In Patau syndrome (trisomy 13), 70% of the fetuses have tachycardia. Early growth retardation, megacystis and holoprosencephaly are also frequently present [2].

The second ultrasound screening is usually done around 18–20 weeks of gestation. The goal of this screening is to diagnose congenital malformations and to detect other signs of chromosome anomalies and other syndromes. Therefore, this ultrasound examination is called "genetic screening."

Structures to be examined:

- cranium (BPD, occipito-frontal diameter-OFD, head circumference-HC)
- face
- spine (spina bifida)
- heart
- diaphragm
- stomach (filling of the stomach)
- abdominal wall (anteroposterior and transversal diameter-AD, abdominal circumference-AC)
- kidneys, bladder
- extremities (femur length-FL, humerus length-HL)
- placenta, umbilical cord
- amniotic fluid
- uterine artery Doppler

Malformations are usually easier to diagnose later in pregnancy as the organ develops and grows (i.e., heart malformations). Also, it is easier to detect anomalies when the defect grows with the gestational age (i.e., pyelectasis).

2. Central nervous system

Brain anomalies are one of the most common group of congenital malformations. To be examined: the cerebellum, choroid plexuses, cisterna magna, lateral ventricles, cavum septi pellucidi. There are three major scan planes for the fetal brain:

1. thalamic view: BPD, HC measurement, thalamus, cavum septi pellucidi
2. ventricular view: lateral ventricles, choroid plexuses, arteria
3. cerebellar view: cerebellum, cisterna magna (Between the 15–22 weeks of gestation, the diameter of the cerebellum in mms is usually equal to the gestational weeks of the pregnancy.) [3, 4]

Any abnormality in these views may suggest a brain malformation, such as: neural tube defects, ventriculomegaly, holoprosencephaly, hydranencephaly, Dandy-Walker malformation, agenesis of the corpus callosum, porencephaly, intracranial tumor. The sensitivity of the ultrasound is high in the diagnosis of these malformations [5, 6].

Neural tube defects (NTDs) are the second most common types of malformations. The incidence of NTDs is around 1:1000 in the USA and 8:1000 in the UK. Anencephaly, encephalocele/meningocele and spina bifida are the most common NTDs [7–9].

Anencephaly is the absence of a major portion of the skull and the brain hemispheres caused by an abnormal closure in the cranial part of the brain. Exencephaly is an early stage of anencephaly, when the brain is still present but is located outside the skull. Anencephaly develops as the neural tissue degenerates. Exencephaly can be detected by first trimester ultrasound as floating brain tissue outside of the skull. CRL is usually lower than normal. In the second and third trimester, polyhydramnios is usually also present. Anencephaly is a fatal condition and most affected pregnancies are terminated after the diagnosis [7, 8].

Encephalocele and meningocele are defects of the skull. In the former, brain tissue and meninges protrude through the defect of the skull, while in the latter only the meninges are affected. The defect of the skull can be detected with ultrasound. In 75% of the cases the defect is occipital.

Spina bifida is present when the spine does not close properly. There are three types based on what structures are affected:

1. occulta: no protrusion, covered with skin
2. cystica: protrusion, covered or not covered (**Figure 1**)
   - **a.** meningocele: contains meninges and cerebrospinal fluid
   - **b.** myelomeningocele: contains meninges, cerebrospinal fluid and neural structures
3. rachischisis/myeloschisis: the neural tube is completely open, no meninges or skin

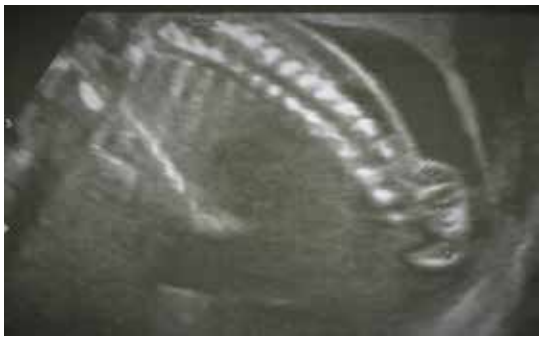

Figure 1. Spina bifida cystic. The spine does not close properly. The cystic protrusion contains meninges and cerebrospinal fluid.

The ultrasound detection rate of spina bifida is almost 100% thanks to the specific markers: banana and lemon signs (**Figure 2**), small posterior fossa, small cerebellum, and ventriculomegaly. Also, there is a V-shaped appearance to the posterior elements of the spine [10, 11].

Around 88% of all NTDs can be detected with prenatal ultrasound (25–94%) [12]. More than 90% of anencephaly and encephalocele cases are detected, while only 44% of fetuses with spina bifida are diagnosed in the first trimester [13–15]. However, the efficacy of ultrasound in the detection of spina bifida is 92–95% in the second trimester [12, 16–18].

In ventriculomegaly, the ventricles are dilated by the cerebrospinal fluid. Fluid accumulation in the ventricles is caused by excessive production, abnormal absorption or impaired circulation. The pressure increases in the ventricles and compresses and ultimately damages the brain tissue (internal hydrocephaly). When the amount of cerebrospinal fluid increases in the subarachnoid space, we talk about external hydrocephaly. Macrocephaly is when the skull is dilated too. The first sign on the ultrasound is usually the dilation of the occipital horn of the lateral ventricles. We talk about ventriculomegaly, when the dilation is larger than 8 mm at 18 weeks of gestation. Later in pregnancy, ventriculomegaly is present when the lateral ventricle/hemisphere ratio is higher than 0.5 (**Figure 3**) [4, 5]. When measured in the atrium (the connecting point of the occipital and temporal horns), a 10–15 mm dilation is mild, while

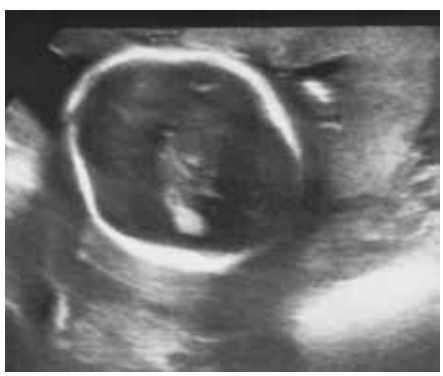

Figure 2. Lemon sign. In cases of spina bifida, special signs like lemon sign are visible in some cases.

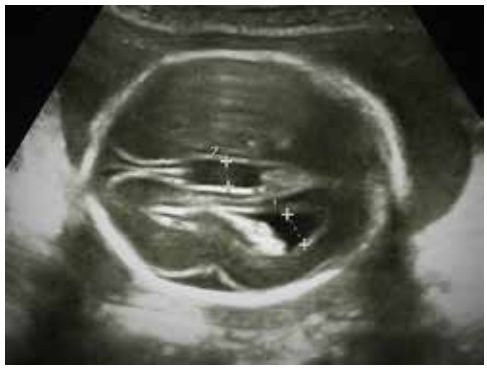

Figure 3. Agenesis/dysgenesis of corpus callosum. The teardrop shaped lateral ventricles, in some cases absence of a normal cavum septi pellucidi, dilatation of the third ventricle may suggest this malformation.

a >15 mm dilation is severe. Furthermore, BPD is increased in most cases. After the detection of ventriculomegaly, toxoplasma and virus serology should be considered. When present with other anomalies, chromosomal examination is also due. The postnatal management is shunt implantation in most cases [4, 5, 11].

Holoprosencephaly is present when the prosencephalon (forebrain) of the embryo fails to divide into two hemispheres. This causes a sequence of malformations: cyclopia, cyclotia, ethmocephalia, proboscis, cebocephalia, premaxillary agenesis, cheilognathopalatoschisis.

Types of holoprosencephaly:

1. alobar: the longitudinal fissure, the falx cerebri, the septum pellucidum and the corpus callosum are absent
2. semilobar: the frontoparietal part of the brain is undivided
3. lobar: hemispheres are separated, absence of the septum pellucidum, fusion of the lateral ventricles
4. arhinencephaly: absence or hypoplasia of the olfactory tract and bulb

Birth prevalence is around 1:10,000–1:15,000, but the prevalence is much higher in miscarriages. Chromosome abnormality is associated in half of the cases, most frequently 13-trisomy. The alobar type is fatal, while patients with lobar or semilobar holoprosencephaly suffer from severe physical and mental disabilities [4, 5, 18].

Agenesis of the corpus callosum (ACC) (**Figure 3**) is among the most frequent malformations of the developing brain with an incidence of around 5:1000 [8, 11]. Corpus callosum can be visualized at the end of the first trimester using the Doppler flow technic [2]. The absence of a normal cavum septi pellucidi, teardrop shaped lateral ventricles, colpocephaly and dilatation of the third ventricle may suggest ACC [4, 11].

Dandy-Walker malformation consists of hydrocephaly, hypoplasia/agenesis of the cerebellar vermis and dilatation of the fourth ventricle (cyst of the posterior fossa). The birth prevalence is 1:12,000. Dilation of the cisterna magna and the forth ventricle can be seen on the ultrasound [5, 8].

Based on our findings, 255 out of 351 congenital craniospinal malformations were diagnosed prenatally (72.65%).

We found that the sensitivity of ultrasound was high in case of the anencephaly/exencephaly (95%), spina bifida (88.89%), hydanencephaly (87.5%) and ventriculomegaly (80%) groups. However, the sensitivity of ultrasound was lower in the corpus callosum agenesis (50%), microcephaly (25%) and Arnold-Chiari malformation groups.

3. Face

Malformations of the facial structures are often minor anomalies, therefore, they do not cause any functional impairment. However, they can suggest chromosomal abnormalities or other, more severe congenital anomalies (malformations of the heart or brain) so diagnosing these minor anomalies is important.

Facial structures to be examined are the nose, lips, ears and chin. The efficacy of prenatal ultrasound is low in case of these malformations and they are often left undiagnosed. As ultrasound techniques develop, the detection of anomalies such as cleft lip and palate (**Figure 4**) before birth is getting more accurate, reaching a sensitivity of 14–25% [19, 20]. 3D technique proved to be more effective in assessing the facial structures of the fetus [21].

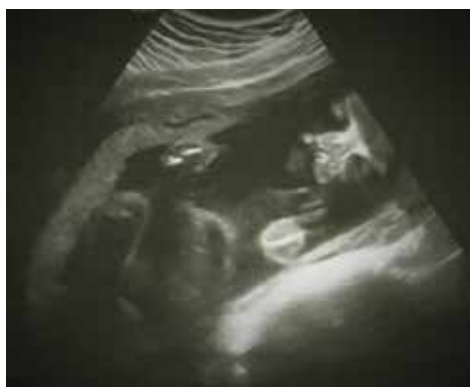

Figure 4. Cleft lip. The detection of anomalies such as cleft lip and palate before birth is getting more accurate.

In our study, only 43 out of 135 face malformations were diagnosed prenatally (31.85%). We found that cleft lip and palate was detected with the highest sensitivity (53.33%), while no choanal atresia cases and only 9.09% of micrognathia cases were found.

4. Cardiovascular system

Congenital malformations of the cardiovascular system are the most common malformations with a birth prevalence of 8:1000. Half of these malformations are severe and life-threatening

[18, 22, 23]. 30–40% of these anomalies occur in association with other malformations or chromosomal abnormalities [24, 25].

Risk factors are abnormal NT, heart malformation in the mother's history (mother, family, previous pregnancies), diabetes of the mother, heart rate anomalies in early pregnancy, teratogenic explosion in early pregnancy. The presence of even one of these factors means that the pregnancy is high risk for congenital heart malformations [5, 23, 26].

Low-risk pregnant women go through a routine screening ultrasound at 18–22 weeks. During routine screening both the four-chamber and the two outflow tract views are to be examined. The four-chamber view can be visualized in a transversal plane above the diaphragm. The size of the fetal heart, its location, rhythm, the cardiac axis, the two atriums, the two ventricles, the ventricular septum, the atrial septum primum and the atrioventricular valves can be examined in this view [27]. Around 60% of major cardiovascular malformations can be detected in the four-chamber plane. The outflow tract views (left and right) give information about the anatomy of the aorta, pulmonary artery, aortic and pulmonary valves and the origin of the aorta and pulmonary arteries. They can be visualized by sliding the transducer toward the fetal head from a four-chamber view [27]. The detection rate of cardiovascular anomalies was higher when the four-chamber and outflow tract views were all examined [5, 26, 27].

In the high-risk group, an early fetal echocardiography is performed. Fetal echocardiography can be done from 11 weeks of gestation, and almost all of the malformations can be detected by 14 weeks (84–95%) [28, 29]. The examination can be repeated around 20 weeks. Cardiomyopathies, valvular stenosis, and tumors can only be detected later in pregnancy [5, 30].

In our study, 67.7% of all cardiovascular malformations were diagnosed with ultrasound. We found high ultrasound sensitivity in the univentricular heart (96.43%), pericardial effusion (90.91%) and hypoplastic left heart syndrome (90%) groups. Though, atrial septum defect and pulmonary artery malposition cases were detected with the lowest sensitivity (31.71% and 33.33%).

5. Lungs, diaphragm

Malformations of the lung are rare anomalies, but diagnosing them prenatally is still important, especially to determine appropriate postnatal management. At 18 weeks of pregnancy, the lungs can be visualized around the heart, filling two-third of the thorax. The quantity of the amniotic fluid has an important role in the development of the lungs. Therefore, in severe oligohydramnios the lungs become hypoplastic (Potter-sequence).

Cystic malformations of the lungs can be separated into three groups: solitary and multiplex cystic anomalies and congenital cystic adenomatoid malformation (CCAM). The latter is a multicystic hamartoma that is usually confined to only one lobe. 47–80% of all lung malformations are CCAMs with a prevalence of 0.3–0.9/10,000 [31–33]. Ultrasound detection depends on the size of the cyst: Type I: 10–20 mm, Type II: 5–10 mm, Type III: small, not detectable.

If the anomaly is large it may dislocate the mediastinal structures, causing polyhydramnios through the compression of the esophagus. It is often associated with other malformations such as cardiovascular, urogenital, and skeletal anomalies or hydrocephalus.

In pulmonary sequestration, the hamartoma usually gets its blood flow from the systemic circulation, either from the abdominal or the thoracic aorta. Most often small cysts (Type III) can be seen on the ultrasound, but it is important to prove the hamartomas connection to the systemic circulation. The intralobular form is more prevalent, but is less likely to get diagnosed. 90% of the extralobular cases are located in the left lower lobe and it is easier to detect [33, 34].

In diaphragmatic hernia, abdominal organs get through a defect of the diaphragm to the thorax. The incidence of this malformation is around 1:3700. 90% of the hernias are present on the left side. The defect itself, abdominal organs in the thorax and mediastinal shift can be detected with ultrasound. Pulmonary hypoplasia can also develop in severe cases due to the volume expansion in the thorax [5, 35].

Malformations of the lungs were detected with a 52.94% sensitivity in our study, while diaphragmatic hernia cases were diagnosed with ultrasound in 86.79% of the cases.

6. Abdominal wall

Abdominal wall malformations (omphalocele, gastroschisis) are fairly prevalent malformations. Maternal serum alpha-fetoprotein level is often elevated in these malformations and intrauterine growth restriction (IUGR) is frequently present. IUGR and the involvement of the liver are important predictive factors for the outcome of these pregnancies [36, 37].

In gastroschisis, there is a defect on the abdominal wall that affects all the abdominal layers, including the amnioperitoneal membrane. It usually appears on the right side of the umbilical cord, but does not involve the cord itself. Gastroschisis has an incidence of 1:2000–1:5000 and is more prevalent in the fetuses of younger mothers. Gastroschisis is always associated with polyhydramnios. The efficacy of ultrasound in this anomaly is around 80% at 18–20 weeks [38, 39]. In early diagnosis, termination of pregnancy is an option and when diagnosed later, it is important to follow-up on the condition of the intestines and deliver the baby if signs of necrosis appear. Cesarean section is suggested in all cases, because vaginal delivery pose a higher risk of infection of the abdominal organs. The fetus is delivered before 35 weeks of pregnancy, because the chance of a successful reposition of the organs is lower afterwards [5, 36, 40].

In omphalocele, abdominal organs herniate into the amniotic fluid through the umbilicus. The defect is always associated with polyhydramnios, it is medially positioned and the organs are covered by the amnioperitoneal membrane. Omphalocele has an incidence of 1:6000 live birth. Herniation of the abdominal organs to the umbilical cord is normal before 11 weeks, but the defect usually closes by then. Therefore, omphalocele can be only detected with second trimester ultrasound at 18–20 weeks. The sensitivity of prenatal ultrasound in the diagnosis of this anomaly is around 75–90% [6, 7, 38, 39]. Performing echocardiography or cytogenetic

examination is justified in these fetuses as omphalocele is associated with other malformations and chromosomal abnormalities in more than half of the cases. The smaller the defect is, the higher the risk of aneuploidy is. When there is no associated malformation, the pregnancy can be carried to term [40].

Abdominal wall malformations were diagnosed with a high sensitivity in our study. All gastroschisis (12/12) and most of omphalocele (25/33, 75.76%) cases were diagnosed antenatally.

7. Gastrointestinal system

The fetal stomach can be visualized with ultrasound after 14 weeks. During the second and third trimester, the liver, gall bladder, spleen and intestines can all be examined with ultrasound in most cases. When the stomach cannot be seen it may suggest malformations such as esophageal atresia, diaphragmatic hernia, abdominal wall anomalies or neurological problems. When the filling of the stomach is not visualized during the examination, the ultrasound has to be repeated [5, 36].

Esophageal atresia is the absence of a part of the esophagus. The atresia is positioned higher than the trachea bifurcation in 85%, and a tracheoesophageal fistula is present in 90% of the cases. The birth prevalence of this malformation is around 1:3000. Signs on the ultrasound are polyhydramnios and the absence of the filling of the stomach. However, when a fistula is present, the stomach is filling, hence the low prenatal detection rate (10–40%) and late, third trimester diagnosis [14, 16, 34]. Later on, at around 24 weeks of pregnancy, the dilatation of the proximal end may be seen. About half of the cases are associated with other malformations, aneuploidy in 20%, growth retardation in 40% and most often with cardiovascular anomalies. Therefore, performing echocardiography and cytogenetic examination is important [5, 36, 41, 42].

The appearance of the intestines changes with the development of the fetus. Increased echogenicity of the fetal intestines can be a normal variant, but can also appear after the ingestion of blood. An increased echogenicity (as high as the bones) may appear in gastrointestinal malformations, Down-syndrome, cystic fibrosis or congenital infections (such as cytomegalovirus) [5, 36, 43].

Duodenal atresia may occur due to a real atresia, membranous closure or compression (annular pancreas) of the duodenum. The incidence of this condition is around 1:6000–1:10,000 birth. One-third of the cases are associated with Trisomy 21 and 50% develop as part of multiplex malformations. The specific ultrasound finding for duodenal atresia is the "double-bubble" sign. The two bubbles are the distended stomach and proximal duodenum. Usually polyhydramnios also appears. Echocardiography and cytogenetic examination is needed to detect the associated anomalies [5, 36].

Intestinal atresia only affects the small intestines in 95% of the cases with an incidence of 1:10,000 live birth.

Morphological types:

- Type 1: The intestines are intact after the atresia
- Type 2: There is a narrowing after the atresia and the intestines are often shortened
- Type 3: multiplex anomalies of the intestines
- Type 4: The dorsal mesentery is absent and the intestines are shortened

Intestinal atresia mostly occurs due to teratogenic effects. Polyhydramnios and dilated intestinal loops are usually seen on ultrasound. Atresia of the large intestines and of the anus is harder to detect due to the lack of polyhydramnios and less distended intestines. The dilated rectum that is filled with water may be visualized between the sacrum and the bladder [5, 36, 43].

Hirschsprung's disease is a congenital aganglionosis of the intestines that causes the distal large intestines to dilate. It occurs in 1:5000 live birth, mostly in boys. Dilated intestines and polyhydramnios are the most important signs on ultrasound after the second trimester. However, it is hard to differentiate between Hirschsprung's, cystic fibrosis and the atresia of the large intestines based on the ultrasound findings [5].

In our study, duodenum atresia was diagnosed with a high sensitivity of 94.74%, while atresia of the esophagus was diagnosed in only one-fifth of the cases.

8. Urogenital tract

Urogenital malformations are the most often diagnosed anomalies with a birth prevalence of 0.5%. Fetal kidneys can be first visualized with ultrasound at 14 weeks of pregnancy beside the spine and by 18 weeks, their structure can be analyzed too [44].

In the first 18 weeks of development, the amniotic fluid is derived from the placenta and membranes, but after 16 weeks, fetal kidneys gradually take over the production. Therefore, anomalies of the fetal urinary tract may result in impaired production of the amniotic fluid and eventually oligohydramnios. However, when one kidney is functional, the quantity of the amniotic fluid can be normal as well [44].

Renal agenesis is the absence of one or both kidneys. The birth prevalence of this abnormality is 1:4000. The fetal kidney or kidneys cannot be visualized with ultrasound, only the enlarged adrenal glands (lying down adrenal sign). When both kidneys are absent, the filling of the bladder is missing and oligohydramnios is severe. The severe oligohydramnios may cause Potter-syndrome: flattened nose and ears, peculiar look, hip dysplasia, club-foot, hypomelia, sirenomelia, arthrogryposis, fetal growth retardation and pulmonary hypoplasia (due to the impaired secretion and resorption of the amniotic fluid and compression) [5, 44–46].

Potter type I polycystic kidney is usually bilateral and shows an autosomal recessive inheritance pattern. It occurs in 1:10,000–1:40,000 birth. The cysts are small, 1–2 mm, originated from the collecting ducts. Cysts can also appear in the liver and renal and hepatic fibrosis may also

occur. The cysts are too small to be detected with ultrasound, but the enlargement and hyperechogenicity of the kidneys are seen. Furthermore, oligohydramnios and the absence of the filling of the bladder are also usually present. Potter-sequence may also appear due to the severe oligohydramnios [5, 44, 46].

In multicystic renal dysplasia, there is no normal parenchyma, but 10–20 mm cysts and connective tissue fill the kidneys. The anomaly is unilateral in two-third of the cases. The quantity of the amniotic fluid is usually normal, but oligohydramnios can appear in bilateral and sometimes polyhydramnios in unilateral cases. The incidence of this malformation is around 1:10,000 birth and it is more prevalent in boys. Most cases are diagnosed with ultrasound at 18 weeks as the cysts can be visualized and they are not connected to the renal pelvis. Also, the kidneys usually have an abnormal shape. Bilateral dysplasia is often fatal [44–46].

Obstructions of the urinary tract usually results in the dilatation proximally. Obstruction of the ureteropelvic junction is the main cause of hydronephrosis in the neonate. Pyelectasis is the dilatation of only the renal pelvis and the calyces, while when the parenchyma is also affected by the compression, we talk about hydronephrosis. The dilatation of the pyelon and calyces can be seen in pyelectasis, while hydronephrosis appears as a solid cyst or sac. Pyelectasis is defined as a pyelon larger than 4 mm before 20 weeks or larger than 7 mm after 34 weeks of gestation. The anomaly is often diagnosed (2–5.5% of all fetuses), but spontaneous regression is common [6, 7, 45, 47].

In the obstruction of the ureterovesical junction, the ureter distends as well, creating a megaloureter. This anomaly is 4 times more prevalent in boys. In the presence of a posterior urethral valve, the bladder, ureter and renal pelvises dilate too and the distention damages the kidneys as well. It may cause severe oligohydramnios and Potter-sequence. Also, the dilated organs may stretch the abdominal wall, causing rectus diastasis (prune belly syndrome) [5, 44, 45].

Ovarian cyst is the most common abdominal mass in female fetuses with a birth prevalence of 1:2600. The malformation is more and more often diagnosed prenatally. The etiology of the anomaly is unknown and the cyst is usually benign. Ovarian cysts are more prevalent in fetuses of mothers with diabetes, eclampsia or Rh isoimmunisation. Complications are rare: compression of other organs, rupture, bleeding. The most common complication is the torsion of the cyst may cause the ischemia and eventually necrosis of the ovary [47, 48].

Malformations of the female organs are mostly caused by the impaired development of the Müllerian duct. When the two ducts do not fuse properly it causes the female organs to be septate or doubled. MRKH (Mayer-Rokitansky-Küstner-Hauser) syndrome is a malformation of the Müllerian duct when the upper two-third of the vagina and the uterus are missing [49].

Malformations of the urogenital tract were diagnosed with ultrasound in 54.55% of the cases. The sensitivity of the ultrasound was high in polycystic kidney (100%), obstructions of the urinary tract (88.89%), multicystic renal dysplasia (80.57%), and pyelectasis (67.21%). However, genital malformations were harder to diagnose and a correct diagnosis was made in only 19.7% of the cases.

9. Extremities

Congenital malformations of the extremities may appear as solitaire anomalies or as multiplex abnormalities associated with syndromes. Most of these malformations are hard to diagnose prenatally, the sensitivity of ultrasound is around 25% [50, 51]. Measurements of the length of the femur and the humerus are part of the fetal biometry [52, 53].

Club-foot (**Figure 5**) is the most prevalent congenital malformation of the extremities with a birth prevalence of 1:1000. However, according to some studies, the malformation occurs in 1:250 in utero [54]. The affected foot is rotated internally. In half of the cases, both feet are affected and club-foot is associated with other abnormalities (such as Trisomy 18). Also, it may occur as part of the Potter-sequence, or in neuromuscular anomalies, neural tube defects or amniotic band constriction [54].

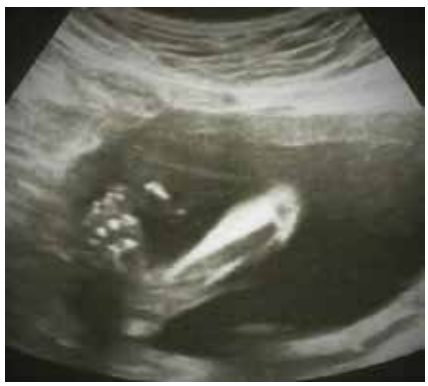

Figure 5. Club-foot. On the picture the affected foot is rotated internally.

In our study, malformations of the skeleton were diagnosed with a higher sensitivity than anomalies of the extremities (82.93% vs. 37.5%). We found higher ultrasound sensitivity in osteogenesis imperfecta (80%), reduction deformities (64.71%), and club foot (51.43%). Ultrasound was less effective in diagnosing hip dysplasia and malformations of the fingers.

10. Placenta, umbilical cord

The placenta is the organ that connects the mother to the fetus and ensures the normal development and growth of the fetus. It is important to examine the location (especially the relative position to the cervix) and morphology of the placenta [55].

Placenta praevia is an anomaly when the placenta is inserted either partially or totally in the lower, passive segment of the uterus. It can only be diagnosed after the second trimester because the site of insertion usually shifts upwards with the growth of the uterus. Placenta praevia has a birth prevalence of 2.8:1000 and it is more common in twin pregnancies and after a previous cesarean section [56, 57].

When the placenta is abnormally attached, it may reach the myometrium (placenta accreta), the serosa (placenta increta) or other organs (placenta percreta). The detection of placenta accreta is hard, but increta and percreta are easier to visualize. The birth prevalence of placenta accreta is 1:2500, while in placenta praevia cases, the prevalence is 1:10 [56, 57].

The maturity of the placenta was classified by Grannum in 1988 based on the ultrasound image:

- Grade 0: First two trimesters, the chorionic plate is smooth, uniform echogenicity
- Grade I: 18–29 weeks, indentations of the chorionic plate, occasional echodensities
- Grade II: 30–36 weeks, deeper indentations, echodensities
- Grade III: after 36 weeks, complete indentations, large echodense areas, calcification

When the maturity of the placenta and the fetal biometry are discordant, it suggests intrauterine growth retardation [55, 57, 58].

Examination of the insertion site of the umbilical cord is also important as it provides the nutrient supply going to the fetus. Marginal insertion is often associated with intrauterine growth retardation. In case of velamentous cord insertion, the umbilical vessels are only covered by the amniotic membrane, therefore they are less protected. Also, this anomaly is often associated with the presence of a single umbilical artery [57]. Single umbilical artery is present in 0.2–1% of the pregnancies. It is a minor anomaly that is often associated with cardiovascular, brain and urogenital malformations and Trisomy 13 or 18 [57, 58].

Normally, the umbilical cord is 50 cm long at terminus. When it is shorter than 30 cm, it is classified as short, while a long umbilical cord is over 80 cm. The length of the cord affects the mobility of the fetus, therefore it is important to examine this feature. Furthermore, the degree of coiling of the umbilical cord should be determined (CI: coiling index) as the absence of coiling may suggest chromosomal abnormality, fetal distress or retardation [57, 58].

11. Amniotic fluid

The amniotic fluid is made by the placenta and the membranes before 16–18 weeks, while after 16 weeks, fetal kidneys gradually takes over the production up until birth. Kidneys excrete around 5 ml/h of urine after 20 weeks, which increases to 50 ml/h by the end of pregnancy. Abnormal quantity of the amniotic fluid may indicate a congenital malformation or chromosomal abnormality. Amniotic fluid index (AFI) is an objective method for determining the amount of the amniotic fluid. In the "four quadrant technique," the vertical length of each pocket of fluid is measured in each of the four quadrants and then the measurements are summarized. A normal AFI is 8–24 cm after 16 weeks of gestation. The other technique is the "single deepest pocket" technique measures the vertical length of the deepest pocket with a normal value of 2–8 cm. The latter is mostly used in twin pregnancies [57, 58].

Oligohydramnios is the condition when there is less amniotic fluid than the normal (less than 500 ml in the third trimester).

Types based on pathophysiology:

- Amniotic: premature rupture of the membranes
- Maternal: smoking, fasting, low fluid intake
- Fetal: urogenital malformations
- Fetomaternal/placental

The fundus height is lower than normal and the fetal movements are dim, often painful. The AFI is less than 7 cm with the "four quadrant technique" and less than 2 cm measured in the deepest quadrant. Anhydramnios is the condition when the amniotic fluid is missing. Severe oligohydramnios may result in Potter sequence in the fetus. When oligohydramnios is caused by bilateral renal agenesis, the condition is called Potter-syndrome. In the third trimester, uterine contractions may result in the compression of the placenta and umbilical cord, endangering the fetus. Prenatal mortality in oligohydramnios is around 10% [58].

Polyhydramnios is an excess of amniotic fluid around the fetus, more than 2000 ml in the third trimester. It occurs in 1–2% of pregnancies.

Types based on pathophysiology:

- Amniotic: infection, chorioamnionitis
- Maternal: diabetes mellitus, preeclampsia, pyelonephritis, syphilis
- Fetal: twin pregnancy, congenital anomalies affecting the swallowing or resorption of the amniotic fluid
- Unknown

The fundus height is usually bigger than normal, the abdomen is large and tense. Mothers usually have dyspnea and the fetal heart sounds are faint. On ultrasound, a large echoless space can be seen between the fetus and the uterine wall with the umbilical cord freely floating. The polyhydramnios is mild when the vertical measurement of the deepest pocket is 8–11 cm, and severe when it is over 16 cm. AFI is usually more than 24 cm in the four quadrants. Cytogenetic examination is needed when polyhydramnios is associated with growth retardation as it may suggest chromosomal abnormality [57, 58].

Author details

Fanni Rebeka Erős and Artúr Beke*

*Address all correspondence to: beke.artur@noi1.sote.hu

Department of Obstetrics and Gynecology, Semmelweis University, Hungary

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Chapter 2

Congenital Anomalies in Human Embryos

Shiori Nakano, Haruyuki Makishima and
Shigehito Yamada

Additional information is available at the end of the chapter

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Abstract

Morphogenesis mainly occurs during embryonic stage, and congenital anomalies also occur at that time. The Kyoto Collection, one of the largest collections of human embryos, including a lot of those with congenital anomalies, is significantly helpful for analyzing embryonic growth. From the collection, normal and abnormal embryos have been selectively presented in this chapter. Recently developed imaging technology enabled three-dimensional (3D) imaging of embryos and fetuses in high resolution. The devices available for embryonic and fetal imaging and the results obtained therefrom are introduced in this chapter. In addition, new strategies for diagnosing congenital anomalies, such as autopsy imaging and genetic analyses, are discussed.

Keywords: human embryo, congenital anomalies, three-dimensional (3D) imaging, genetic analyses, autopsy imaging

1. Introduction

Congenital anomalies occur during the embryonic period, in which morphogenesis happens. The Kyoto Collection, one of the largest collections of human embryos, consists of over 40,000 human embryos and fetuses, including a large number of embryos with anomalies. Here we introduce embryonic cases with congenital anomalies, supplemented with valuable pictures, and discuss about the diagnoses of these anomalies at an early embryonic age using new 3D imaging modalities.

2. Normal development of human embryos

2.1. Staging of human embryonic development

Carnegie stage 13: Four limb buds and optic vesicle appear

32 days after fertilization

CRL (crown-rump length): 5 mm

At this stage, two upper and two lower limb buds become visible. The optic vesicle can be easily recognized and the lens placode begins to differentiate. Although more than 30 pairs of somites have formed by this time, the number of somites becomes increasingly difficult to determine and therefore will no longer be used for staging henceforth.

Carnegie stage 14: Lens pit and optic cup appear

34 days after fertilization

CRL: 6 mm

The lens pit begins to invaginate into the optic cup, although its closure remains incomplete at this stage. On the other hand, the optic vesicle emerges from the endolymphatic appendage and becomes easy to define. The upper limb buds elongate and taper, while the cephalic and cervical flexures become prominent in terms of the internal features; the future cerebral hemispheres and cerebellar plates differentiate at this point. The dorsal and ventral pancreatic buds have become noticeable, along with the development of the ureteric bud, which acquires a metanephrogenic blastema.

Carnegie stage 15: Lens vesicles are covered by surface ectoderm, nasal pit and hand plates form

34 days after fertilization

CRL: 8 mm

Lens vesicles have closed and are covered by the surface ectoderm at this time, while the nasal plate invaginates forming a nasal pit. At this stage, auricular hillocks arise, and hand plates begin to form. In the meantime, the foramen secundum develops in the heart while the lung buds begin to branch into lobar buds. The primary urogenital sinus completes its formation by the end of this stage.

Carnegie stage 16: Nasal pit faces ventrally, retinal pigment becomes visible, foot plates emerge

38 days after fertilization

CRL: 10 mm

Nasal pits deepen and start to face ventrally, while the retinal pigment becomes externally visible. In the meantime, hand plates become distinct and foot plates start to emerge. Furthermore, the nasolacrimal groove forms between the frontal and maxillary processes.

Carnegie stage 17: Nasofrontal groove become distinct, and finger rays exhibited

40 days after fertilization

CRL: 11 mm

In comparison with the previous stage, the auricular hillocks and nasofrontal (nasolacrimal) grooves have become more distinct, and the trunk has straightened. The hand plates have come to exhibit conspicuous digital rays, and the foot has acquired a rounded digital plate by this stage.

Carnegie stage 18: Elbows become discernible, toe rays appear, and eyelid folds appear

42 days after fertilization

CRL: 13 mm

The body shape has become more cuboidal by this time. Both cervical and lumbar flexures are denoted, the elbows are discernible and interdigital notches begin to appear in the hand plates. Toe rays are observed in the foot plate. As for the facial features, eyelid folds start appearing, and the auricular hillocks transform into specific parts of the external ear. Furthermore, ossification may begin in some skeletal structures.

Carnegie stage 19: Trunk elongation and straightening

44 days after fertilization

CRL: 16 mm

The trunk begins its elongation and straightening. Simultaneously, the eyes and external ears become distinct. As a result of the growing size of the brain, the eyes get positioned in the front part of the face. The upper and lower limbs are approximately parallel, with preaxial borders being cranial, and postaxial borders caudal. Moreover, intestines have developed and parts of them can be observed in normal umbilical cord (physiological umbilical hernia).

Carnegie stage 20: Longer upper limb bends at elbow

46 days after fertilization

CRL: 19 mm

The angle of the cervical flexure becomes smaller, and the head is directed upwards. Vascular plexus starts to appear in the superficial tissues of the head. Meanwhile, the coiled intestine finishes its development. Spontaneous movements are recognized at this stage. The upper limbs have increased in length at this time, and it is flexed at the elbows and hand joints. Fingers can be observed over the chest, in a slight curve.

Carnegie stage 21: Fingers grow longer, hands approach each other

48 days after fertilization

CRL: 21 mm

The head becomes round and the superficial vascular plexus spreads to surround the head. Meanwhile, the tail becomes rudimentary. At this time, the hands are slightly flexed at the wrists and are placed closely over the cardiac prominence.

Carnegie stage 22: Eyelids and external ears develop

50 days after fertilization

CRL: 23 mm

The vascular plexus of the head becomes more distinct at this stage. The eyelids start to thicken and encroach into the eyes. In the meantime, the tragus and antitragus of the external ear assume a more definite form, as the external ear repositions higher on the head. The tail is about to disappear.

Carnegie stage 23: The end of embryonic period

52 days after fertilization

CRL: 30 mm

At this stage, the head would be observed with a more rounded appearance and the trunk with a more mature shape. The eyelids and ear auricles have become conspicuous, the limbs have increased in length, and the forearms have ascended toward the level or higher than that of the shoulders. Meanwhile, the vascular plexus approaches the vertex of the head. Although external sex differences are not yet apparent, the external genitalia have developed relatively well by this time. The tail is no longer observed at this stage.

2.2. Facial development

At Carnegie stage 12, three pharyngeal arches appear. The first pharyngeal arch emerges from the maxillary and mandibular prominences (stage 13, **Figure 1**), which will later constitute the lateral and caudal boundaries of the stomodeum (i.e., primitive oral cavity), respectively.

The sides and front of the neck arise from the second pharyngeal arch, also known as the hyoid arch. Meanwhile, the frontonasal prominence (FNP) grows and covers the ventral part of the forebrain (stage 13), which will eventually form the forehead (frontal part of the FNP) and the primordial mouth and nose (nasal part of the FNP).

By the end of the fourth developmental week, nasal placodes (thickening of surface ectoderm that later becomes peripheral neural tissue) develop on the frontolateral aspects of the FNP (stage 13). The mesenchyme swells around the nasal placodes, which leads to the formation of medial and lateral nasal prominences (stage 16). The maxillary prominence merges with the medial nasal prominence, leading to its fusion. The fused medial nasal prominence will not only form the primary palate (stage 16–18), but also the midline of the nose and that of the upper lip.

The nasolacrimal groove divides the lateral nasal prominence from the maxillary prominence (observed in stages 16, 17).

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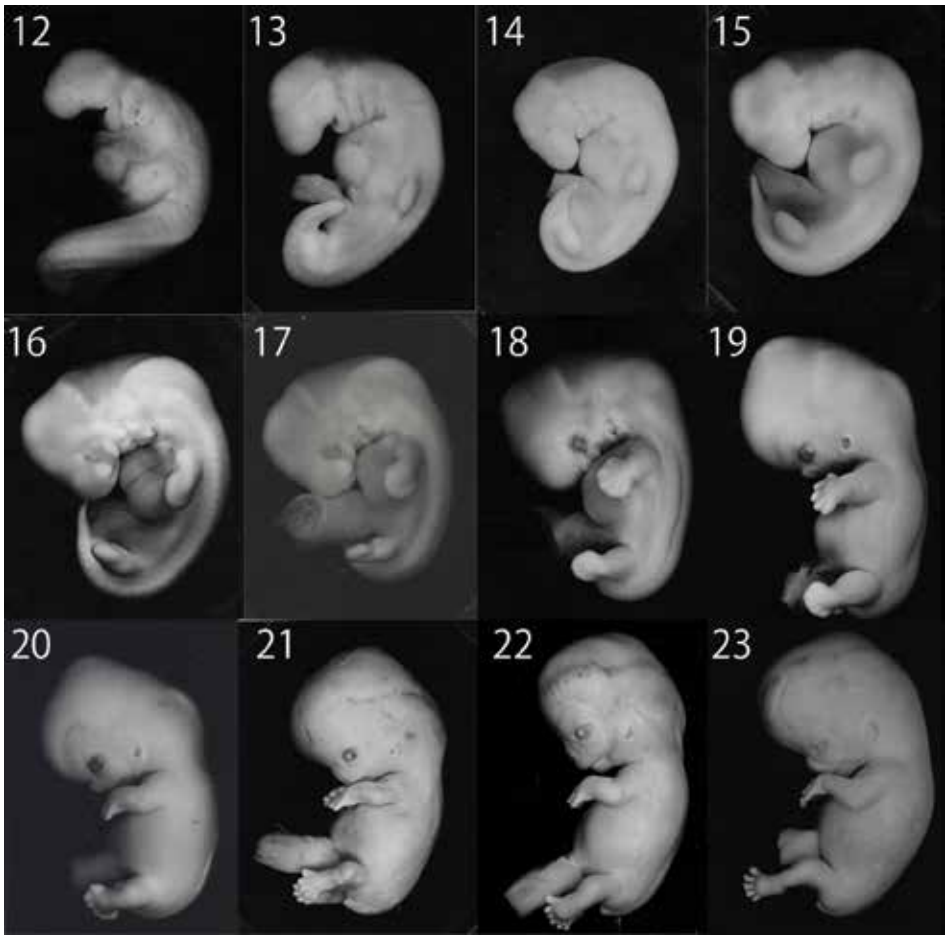

Figure 1. Development of human embryo, Carnegie stages 12–23.

During the fifth developmental week, primordial ear auricles form around the first pharyngeal groove, at the interface between the mandibular prominences and the hyoid arches (stage 16). While the auricle emerges from the auricular hillocks, the external acoustic meatus arises from the first pharyngeal groove. At an early stage of ear development, the external ears are located in the neck region, which then start to ascend toward the level of the eyes on either side of the head, simultaneously with the development of the mandible.

The maxillary and lateral nasal prominences fuse with the nasolacrimal groove during the sixth developmental week, which enables the nose and cheek to be continuous (stage 18).

The seventh developmental week is marked by the fusion of the medial nasal prominence and the maxillary and lateral nasal prominences (stage 19~). Merging of the maxillary and medial nasal prominences creates continuity between the upper jaw and lip, leading to the segregation of the nasal cavity and oral cavity.

2.3. Development of upper and lower extremities

The embryonic development of the limbs [1] is illustrated here using computer graphics [2].

- Carnegie stage 12: The upper limb buds begin to develop.
- Carnegie stage 13: The upper limb buds gain more definite shape, while the lower limb buds start to develop.
- Carnegie stage 14: The upper limb buds grow and taper toward the tip, which forms the hand plate later on. In the upper limbs, innervation and blood supply begin at this stage. The development of the lower limb buds is delayed with respect to the upper limb buds.
- Carnegie stage 15: The hand plates in the upper limb buds have become distinct. In the lower limbs, the rostral half is rounded, whereas the caudal half is tapered. At this stage, innervation begins in the lower limb buds as well.
- Carnegie stage 16: The hand plates form a central part, a carpal part, and a digital flange, whereas the lower limb buds form a femoral part, a crural part, and a foot plate.
- Carnegie stage 17: Finger rays can be recognized in the hand plate while the rim of the hand plate becomes crenated due to the appearance of individual fingers in some advanced specimens. The lower limb buds have increased in size and a rounded digital plate is set off from the crurotarsal region.
- Carnegie stage 18: The upper limbs have lengthened and are slightly bent at the elbow. Finger rays are distinct. As for the lower limb bud, toe rays begin to appear, although the notch on the rim of the foot plate is still incomplete.
- Carnegie stage 19: The upper limbs rotate medially, as if to hold the chest. Apoptoses occur in the mesenchymal tissues of interdigital areas to create deeper interdigital notches in the foot plate. Toe rays become prominent, and knees and ankles become noticeable.
- Carnegie stage 20: The upper limbs are bent at the elbow and hand joints, resulting in a pronated position. Meanwhile, the lower limbs are also bent at the knee joints, and notches are present between the toe rays in the foot plate.
- Carnegie stage 21: Elbows and knees become distinct in the upper and lower limbs, respectively. Hands are crossed over the chest. Meanwhile, fingers grow longer and distal phalangeal portions become slightly swollen, indicating the beginning of palmar pads. The feet are approaching each other at this stage.
- Carnegie stage 22: Hands get larger in front of the body and fingers elongate, which may clasp over with those of the other hand. Although toe digits are still webbed, feet approach closer.
- Carnegie stage 23: The upper and lower limbs have lengthened, well formed, and bent at joints. Fingers grow longer and toes cease to be webbed; all the digits are separate and distinct.

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3. Representative external anomalies of human embryos

3.1. CNS anomalies

3.1.1. Holoprosencephaly (HPE)

Holoprosencephaly (HPE) refers to an anomaly in which the differentiation of the prosencephalon from the neural tube is defective, thus leading to malformations of the forebrain, midface, and occasionally limbs. It can be recognized as early as CS12 or 13.

HPE can be classified into three categories, depending on the degree of defect in the development of prosencephalon: alobar holoprosencephaly, semi lobar holoprosencephaly, and lobar prosencephaly.

Alobar holoprosencephaly is the most severe, which usually associates with cyclopia, ethmocephaly, and cebocephaly. Cyclopia (**Figure 2A**) is characterized by a single eye centered in the middle of the face, caused by the fusion of the optic vesicles due to the lack of midline tissue. The name of this malformation is derived from the cyclops (or cyclopes) in Greek mythology, first mentioned in Homer's epic poem, "Odyssey" in the seventh century B.C. There are cases of cyclopia with incomplete fusion of optic vesicles, but either with the nose absent or complicated further with proboscis located above the orbit [3]. The cyclopic embryo presented in **Figure 1** shows single eye in the center of the face, without any nose.

Ethmocephaly is morphologically similar to cyclopia, except that both eyes exist with distinct orbits, although marked by hypotelorism, with proboscis located between the eyes (**Figure 2B**) [4]. Cebocephaly is also an anomaly that exhibits hypotelorism in the two distinct orbits, characterized by a single nostril, occasionally complicated by cleft lip and/or palate [5].

HPE is one of the most common lethal congenital anomalies that occur at embryonic stages, and the prevalence rate is approximately 1/250. However, most of them cannot survive to develop into a fetus, which makes it a rare anomaly in newborns (1/10,000–20,000) [6].

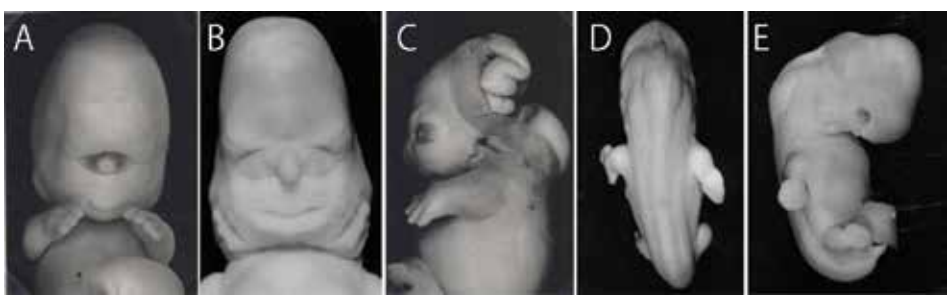

Figure 2. Congenital anomalies in the CNS. (A) Embryo presenting cyclopia, (B) embryo presenting ethmocephaly, with proboscis located between the eyes, (C) exencephaly presenting the opening in the neural tube, (D) spina bifida occulta observed dorsally, and (E) spina bifida occulta observed laterally.

Although it is yet to be proved, four main genes: *SHH*, *ZIC2*, *SIX3*, and *TGIF* are suggested to be associated with the onset of HPE, along with the aneuploidies in chromosomes 13 and 18. The existence of environmental factors is suggested, and a strong positive correlation of the occurrence with maternal age is noted [7, 8].

3.1.2. Exencephaly

The morphological characteristics of exencephaly are exposed brain and absence of the skull and scalp. This condition arises due to the failure to close the cephalic part of the neural tube, occasionally due to the overgrowth of neural tissue [9] (**Figure 2C**). Exencephaly can be recognized at CS 12 at the earliest, much ahead of the stage at which the development of the neural tube completes.

Neural tube defects such as exencephaly, anencephaly, and spina bifida are extremely common lethal congenital anomalies, and the prevalence rate is approximately 1/1000 [10]; most of these survive for only few hours, and all cases lead to death within a few days. Although the understanding remains unclear, folic acid deficiency is a suggested factor for anencephaly, along with the *MTHFD 1* gene, which is significant in folate metabolism [11].

3.1.3. Spina bifida

Spina bifida is the most common congenital anomaly of the CNS, resulting from the incomplete fusion of the vertebrae and hence exposure of the spinal cord. It can be classified into spina bifida occulta (**Figure 2D** and **E**), and spina bifida cystica (or aperta), which can be further classified into meningocele, meningomyelocele, and myelocele [12]. Spina bifida occulta is the mildest form, caused by the malformation of the bony arch that extends caudally, failing to fuse dorsal midline to the spinal cord. The spinal cord itself, however, is unaffected, extended caudally, or duplicated at the end, with no neurological damage. The bone defect is covered by skin, although sometimes patches of hair or pigment may be observed in the area covering the defect. **Figures 4** and **5** exhibit an embryo with spina bifida occulta, presenting a malformation of the bony arch, with neither neurological defect nor swelling.

On the other hand, spina bifida cystica refers to the malformation of the bony arch as well as the neural tube that has failed to close. Meningocele has a fluid-containing cystic swelling, emerging from a defect in the vertebral arch; the spinal cord is completely confined to the spinal canal, but may exhibit myelodysplasia.

Meningomyelocele and myelocele also refer to cystic swellings emerging dorsally through a vertebral arch, although the spinal cord (located inside the sac) bears its fundus. Myelocele is different from meningomyelocele in the following aspects: spinal cord is exposed to the external surface, often in the lumbosacral area; neutral folds stay flat, and will not elevate; not only the spinal cord, the brain is also often malformed, which may result in hydrocephalus, Chiari 2 malformation, and other defects [13].

Although spina bifida can be recognized as early as CS 12, it becomes observable earliest by CS 13, when the closure of the neural tube is supposed to be completed.

A significant amount of folic acid is known to prevent spina bifida; early postnatal treatments, including the closure of the spinal lesion within 48 h after birth, and medical management are essential for life henceforth [14].

3.2. Facial anomalies

3.2.1. Cleft lip

Cleft lip, often accompanied by cleft palate, is the most common congenital facial anomaly that causes dental defects, yielding defective speech and feeding disorders, and sometimes ear infections. The prevalence among the Asian and American Indian populations is as high as 1 in 500 births, which is relatively higher than that in European-derived or African-derived population, where prevalence rates are at approximately 1/1000 and 1/2500, respectively [15].

The morphological characteristic of cleft lip is the opening in the upper lip to the roof of the mouth, either located in the center (median cleft lip) (**Figure 3A**) or left and/or right side (bilateral/ unilateral cleft lip, **Figure 3B** and **C**), as a result of failed fusion of various processes. Median cleft lip is the rarest, and is commonly associated with mental retardation, attributed to the loss of midline structures.

As for lateral cleft lips, 80% of them are unilateral, out of which 70% are left-sided. Cleft lip can be recognized as early as CS 18, and is considered a multifactorial defect, involving genetic factors, environmental factors, teratogens, and maternal conditions. There are over 50 recognized syndromes that include this malformation, often caused by mutant genes [16].

The occurrence of isolated cleft lip is higher in male, whereas the occurrence of isolated cleft palate is higher in females [15].

3.2.2. Micrognathia

Micrognathia is a facial malformation characterized by an underdeveloped and receded mandible, thus presenting a bird-like face, as shown in **Figure 3D**. It was first mentioned in the clay tablets of ancient Babylonia, back in 1700 BC [17].

Micrognathia is often a part of chromosomal disorder; it is commonly seen in patients of Pierre Robin syndrome, and is associated with trisomy 13, trisomy18, Treacher-Collins syndrome,

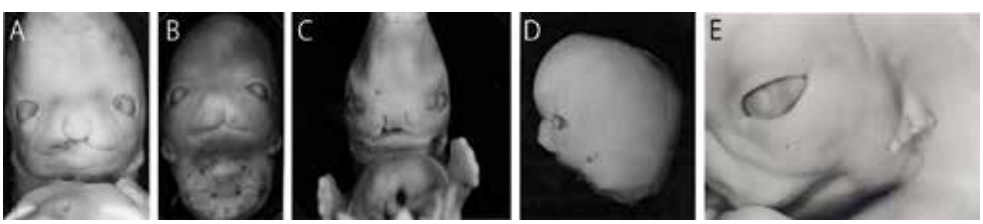

Figure 3. Congenital anomalies of face. (A) Median cleft lip, (B) left-sided unilateral cleft lip, (C) right-sided unilateral cleft lip, (D) micrognathia from lateral view, and (E) malformed pinna.

and Nager syndrome [18, 19]. The frequency of Pierre Robin syndrome is approximately 1 in 8500–14,000 births [20], and signs of micrognathia can be observed as early as CS 18. It is also often observed in association with cleft palate [21].

Because of the undersized jaw, most have feeding problems after birth and some may have major respiratory obstruction; however, there is usually no need for surgical treatment, since it can be naturally corrected through growth. However, micrognathia leads to dental anomalies, breathing problems, and tongue growth defect, which need close observation.

3.2.3. Low-set ears

Low-set ears refer to malpositioned auricles, located anteriorly to the horizontal line drawn at the level of the inner canthus (**Figure 3E**).The size of a low-set ear is usually smaller compared to that in a normally developed embryo, with the angle posteriorly rotated [22]. Low-set ears accompany a variety of congenital chromosomal defects, including Turner's syndrome, Patau syndrome, Treacher-Collins syndrome, trisomy 18, trisomy 13, Cri du chat syndrome, and Down syndrome. It is often observed along with micrognathia.

Malformations of the ear can be recognized earliest at CS 18, although it can be estimated earlier by observing the auricle hill. Besides being low-set, the auricles may also be malformed as shown in **Figure 3E**.

3.3. Anomalies of extremities

3.3.1. Polydactyly

Polydactyly is a limb malformation, characterized by additional digit(s) in the limbs (**Figure 4A** and **B**) [23]. There can be preaxial, postaxial, or median polydactyly, corresponding to extra digits on the radial or tibial sides, ulnar or fibular sides, or in between medial fingers, respectively [24].This malformation is more likely to occur in the hands than in the feet, and can be estimated at CS 16 [25]. The prevalence varies across races, and occurs more frequently in the right hand than the left, among the Japanese. Its frequency on each finger may also vary; the highest to lowest being in the order: thumb, little finger, middle finger, ring finger, and index finger in the Japanese population. Polydactyly is one of the most common hereditary malformations of the extremities, with *GLI3* and *SHH* genes being responsible [23]. The extra digit in preaxial polydactyly may be surgically treated after 8–12 months of birth, whereas that of postaxial polydactyly is dissected shortly after birth.

3.3.2. Cleft hand/foot

Cleft hand/foot, also known as split-hand/split-foot malformation (SHFM), is a limb malformation that imparts an appearance resembling a lobster claw, due to the absence of the middle finger and hence an abnormal gap between the second and fourth metacarpal bones and soft tissues (**Figure 4C**). The two fingers on either side of the cleft in a cleft hand may be fused, which would make it appear as if there are only two digits on one hand [26].

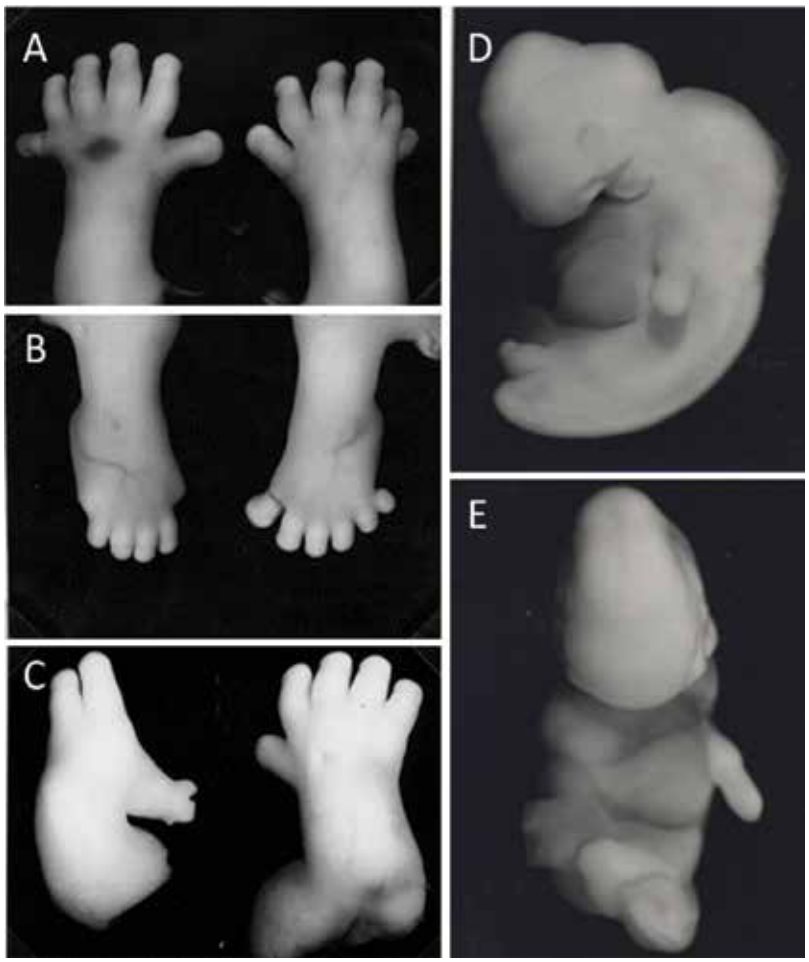

Figure 4. Congenital anomalies of extremities. (A) Polydactyly in hand; (B) polydactyly in foot; (C) cleft hand, (D) sirenomelia, lateral view, and (E) sirenomelia, anterior view.

Ectrodactyly, or oligodactyly refers to malformations of the limb such that there are digits less than 5, arising from either ulnar deficiency, radial deficiency, or median deficiency (cleft hand/foot) [26]. **Figure 4C** shows a cleft hand with four distinct digits, with a large gap in between the second and third digits, presenting a lobster claw-like feature.

The inheritance of cleft hand is autosomal dominant, caused by deletions or mutations in autosomes such as chromosomes 2, 3, 7, and 10. For example, the deletion in chromosome 2 results not only in ectrodactyly, but also in microcephaly, micrognathia, low-set ears, and mental retardation. Although ectrodactyly is often associated with other malformations, a single family has been reported for the inheritance of isolated ectrodactyly resulting from X-linked recessive inheritance [26]. Another well-known syndrome that is associated with this malformation is EEC (ectrodactyly-ectodermal dysplasia-cleft lip/palate) syndrome, which

comprises of ectodermal dysplasia and cleft lip, occasionally accompanied by cleft palate, due to an autosomal dominant inheritance [27]. The prevalence is approximately 1 in 18,000 births [28], and can be observed as early as CS 18, at the stage when the finger rays develop. There is no difference between females and males in terms of occurrence, and surgical treatment is scheduled when the child is 1 or 2 years old.

3.3.3. Sirenomelia (meromelia)

Sirenomelia, named after the Sirens (half-bird women in Greek mythology, often confused with mermaids), is an extremely rare form of malformation of the extremities, characterized by fused lower limbs hence resembling "merpeople" (**Figure 4D** and **E**) [29]. With only a single umbilical artery and vein, it is difficult for both limbs to develop, resulting in the formation of fused lower limbs [30]. It can be divided into categories, based on the degree of development of the lower limb: sympus apus, sympus monopus, and sympus dipus, referring to absence of feet, short feet, and a pair of feet, respectively. Anomalies of the kidneys, large intestine, and external genitalia are commonly observed as accompanying complications.

This lethal congenital anomaly begins to show up at CS 13, with an occurrence rate of approximately 1.5–4.2 in 100,000 births, with more than half of them born dead. All such cases lead to death within 5 h after birth [29]. Although chromosomal aneuploidy is not associated, maternal diabetes mellitus and monozygotic twins are considered important factors for increasing the risk of sirenomelia [31].

4. Diagnostic strategies for human embryos

4.1. Imaging modalities

4.1.1. Ultrasound

Fetal ultrasound was developed as A-mode in the late 1950s, then modified to B-mode in the 1970s, followed by real-time imaging in the 1980s, and 3D imaging [32, 33] in the 1990s. Currently, ultrasonography is applied throughout pregnancy. Transvaginal ultrasonography is useful for examining the gestational sac at approximately 5 weeks, the yolk sac at 5.5 weeks, flickering cardiac motion at 6 weeks, etc. Embryos and early fetuses within 12 weeks of gestation are usually examined by transvaginal ultrasonography, whereas those beyond 12 weeks of gestation are examined by transabdominal ultrasonography. Ultrasonography is used for examining embryos and fetuses for several reasons, one of them is to determine the gestational age and estimate the fetal weight. A formula for estimating the latter was first suggested in the late 1970s [34]. Since then, a number of formulae have been proposed and accepted [35–39], while new formulae for the estimation have also been frequently promoted [40, 41]. Another purpose of ultrasonography is to detect (and occasionally, to assess) congenital fetal anomalies. Ultrasonography was first applied to evaluate anencephaly [42], but now it is able to detect a wide range of anomalies. The definition of optimal fetal anatomy survey has been published as guidelines by the International Society of Ultrasound in Obstetrics

and Gynecology (ISUOG) [43] for performing effective screening of morphological anomalies. Meanwhile, studies conducted during the 1980s–1990s made it clear that soft markers in ultrasonography indicate an elevated risk of chromosomal abnormalities [44–46], even though they may not be directly harmful by themselves. Soft markers combined with maternal serum is capable of detecting aneuploidy with high precision [47].

4.1.2. Magnetic resonance imaging

Magnetic resonance (MR) microscopy refers to MR imaging for screening small samples. It is significantly useful for the 3D measurement of chemically fixed human embryos, due to the large amount of mobile or NMR responsive protons existing in the preservation fluid (formalin) [48]. Being a non-invasive and non-destructive imaging process, it has been applied to a number of animal models for understanding developmental embryology [49–52]. MR imaging provides highly beneficial features [50, 53, 54], reaching a resolution of 40 μm/pixel or higher when scanning a sample for an extended amount of time. Superconducting magnets with field strength of 1.0–9.4 T [52, 54, 55] have been used for describing human embryo using MR imaging. **Figure 5C–D** and **E–F** is obtained with MR microscopes equipped with 7.0 and 2.34 T magnets, respectively.

4.1.3. Phase-contrast X-ray computed tomography

X-rays are electromagnetic waves with characteristic amplitude and phase. When X-rays penetrate a sample, its amplitude decreases and the phase gets shifted. Conventional X-ray imaging (radiography) is based on absorption contrast (i.e. amplitude imaging) and represented by the internal mass density distribution within the sample (**Figure 6A** and **B**). Unfortunately, only sensitivity to X-ray distribution is not enough for a detailed analysis of the samples containing biological soft tissues such as embryos, unless it is either combined with contrast agents or performed at higher X-ray doses. Another way of solving this issue is by exploiting the phase information of X-rays. Since lighter elements, such as hydrogen, carbon, nitrogen, and oxygen are 1000 times more sensitive to phase-shift compared to the actual absorption [56], they can be used to detect the phase-shift. To that end, it is essential to convert the phase shift into a change in X-ray intensity, which can be measured easily by current-detecting devices. Conversion methods, such as interferometry and diffractometry, are applied for the

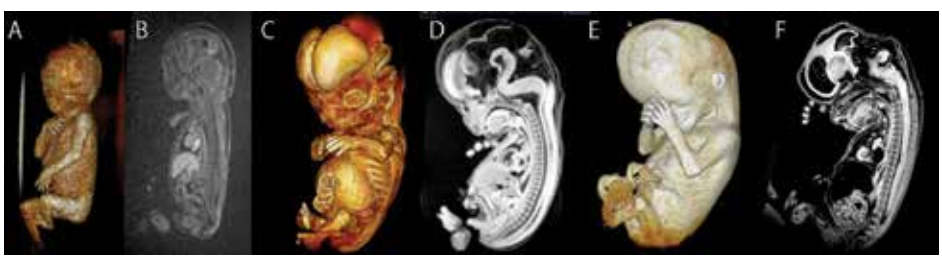

Figure 5. The results of MRI from several imaging devices. A, B: 2.34 T super parallel MRM (MR microscope), developed by Prof. Kose et al. in the University of Tsukuba. C, D: Pre-clinical MRI (Bruker BioSpin, 7 T) in the Human Health Sciences, Kyoto University Graduate School of Medicine, Japan. E, F: Clinical MRI (Siemens Magnetom, 3 T) in the Kyoto University Hospital, Japan.

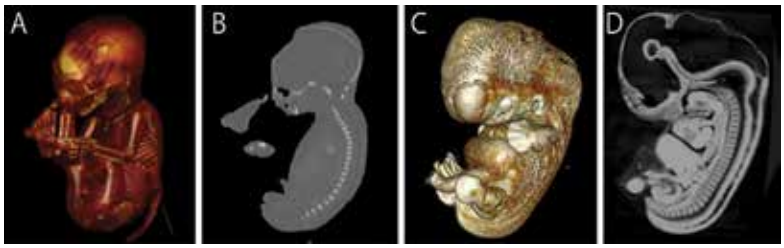

Figure 6. The results of X-ray CT. A, B: Clinical CT (Toshiba Alexion) in the Laboratory of Physical Anthropology, Graduate School of Science, Kyoto University, Japan. C, D: Phase contrast CT, Photon Factory of the KEK (High Energy Accelerator Research Organization) in Tsukuba, Japan. A, C: Surface reconstruction and B, D: midsagittal section.

generation of 2D and 3D images using synchrotron radiations from appropriate devices [57, 58]. An image of a human embryo at CS 17, obtained by applying a two-crystal X-ray interferometer [59], is displayed in **Figure 6C** and **D**.

4.2. New strategies for diagnosis of congenital anomalies

4.2.1. Autopsy imaging of human embryos and fetuses

Additional imaging modalities can be applied for dead embryos and fetuses. Classically, solid reconstruction and fine drawing were primarily the approaches used; the first 3D morphological imaging technique was the wax plate technique, using serial histological sections of human embryos, which was developed by Born [60]. Recently, the 3D reconstruction of serial sections has been carried out by using computer graphic methods, which has made the 3D reconstruction much easier and quicker than before. The 2D image stacks generated from serial sections have a high resolution, although the issues of section registration and distortion remain unsolved. A solution to this problem is a novel imaging modality for the generation of high-resolution 3D reconstructed images [61], which uses episcopic fluorescence image capture (EFIC). In EFIC imaging, tissue autofluorescence is used to image the block face prior to cutting any section. Although the samples are sliced and some lost during the procedure, the optical resolution of EFIC is reported to reach approximately 5–6 μm [62].

MRI is a useful imaging modality, not only for living prenatal embryos and fetuses, but also for dead embryos and fetuses in autopsy imaging. Despite the longer time taken to capture images, the higher resolution is definitely an advantage; the time required for a high-resolution imaging ranges from several hours to days. MR devices should be selected depending on the sample size; specially, MR microscopy, clinical MRI, and experimental MRI are suitable for small-sized embryos, larger fetuses, and embryos/fetuses with an intermediate size, respectively [39] (**Figure 5**) [2, 63, 64].

X-ray imaging is also used for dead embryos and fetuses. Since there is no need to consider the impact of radiation exposure on the tissue, longer time may be devoted to capture high resolution images. Conventional (absorption-contrast) X-ray CT (cCT) is used for fetal skeletal imaging (**Figure 6A** and **B**). Phase-contrast X-ray CT (pCT) is another method of X-ray imaging [40]. Since X-rays are electromagnetic waves, phase-contrast X-ray imaging is capable of recording the phase-shift of X-rays while passing through the samples and reconstructing

2D/3D images of the samples in combination with CT. An embryo or an early fetus, mostly composed of soft tissue, is suitable for pCT imaging (**Figure 6C** and **D**).

Ultrasonography of living embryos and fetuses is very commonly performed nowadays, and many malformations can be diagnosed during the early prenatal period. In the cases of pregnancy termination, not all the aborted fetuses are dissected and pathologically diagnosed, due to technical difficulties associated with the dissection of small fetuses. However, the imaging modalities presented here can be used for autopsy imaging of embryos and fetuses, regardless of their size. If any clue to the fetal anomaly (that might have led to the abortion) could be identified by using these imaging modalities, supplemented by appropriate genetic tests, then a final accurate diagnosis can be obtained. Based on the final diagnosis, parents would be provided with sufficient detailing of their lost pregnancy, which would enable them to receive a genetic counseling prior to the next pregnancy.

The imaging modalities described in this section are summarized in **Figures 5** and **6**. The appropriate modalities for imaging dead embryos or fetuses should be used depending on the stage of pregnancy.

4.2.2. Genetic analysis of the human embryo and fetus

Amniotic fluid, chorionic villi, and umbilical cord blood are used for genetic analyses of human embryos and fetuses. Recently, a new approach for prenatal testing was proposed in the name of noninvasive prenatal testing (NIPT) that uses DNA fragments derived from maternal villus cells to determine the genetic information of the fetus. In comparison to maternal serum analysis, NIPT has considerably higher sensitivity and specificity for aneuploidy [65]. However, due to the infrequent derivation of cell-free DNA (cfDNA) from multiple sources such as in placental mosaicism, maternal conditions including cancer, or fetal and/or maternal copy number variation (CNV) [66], NIPT has a risk of predicting false-positive and false-negative results.

The cell samples obtained from amniotic fluid and chorionic villi may be used for both screening and diagnostic tests. Traditional karyotype analysis is the most commonly used method to examine cells, obtained from chorionic villus sampling (CVS) and amniocentesis (AC), for the diagnosis of aneuploidies and large rearrangements. The diagnostic accuracy of traditional karyotype analysis is higher than 99% for aneuploidy and for chromosomal abnormalities larger than 5–10 Mb [67]. On the other hand, fluorescence in-situ hybridization (FISH) analysis can detect specific chromosomes or chromosomal regions by using fluorescently labeled probes. The turnaround for FISH results (usually within 2 days) is faster than that of conventional karyotyping results (7–14 days, including the cell culture period). Due to the existence of false-positive and false-negative reports, FISH [68–70] is considered as a mere screening test, although still commonly used to screen chromosomes 13, 18, 21, X, and Y. Therefore, clinical diagnosis using FISH results should be supplemented by other clinical and laboratory analyses such as abnormal ultrasonography, positive screening test using maternal serum and/or soft markers, confirmatory traditional metaphase chromosome analysis, or chromosomal microarray analysis (CMA).

CMA is capable of detecting small chromosomal aneuploidies that cannot otherwise be identified by conventional karyotyping [71]. Since CMA can be performed without cell or tissue culture, the results can be obtained within 3–7 days. Since CMA can also be carried out with

nonviable cells, which are not suitable for conventional karyotyping analysis, this technique [71] is applicable to the cases of fetal death or stillbirth. CMA can identify almost all the abnormalities, except for balanced translocations and triploidy. While the results of conventional karyotyping in the detection of structural abnormalities, seen in prenatal ultrasonography, did not show anything notable, approximately 6% of the fetuses were identified for chromosomal defects by CMA [72, 73]; CMA qualifies as the primary test, in case a structural abnormality is detected by fetal ultrasonography, as also recommended by the American Congress of Obstetricians and Gynecologists (ACOG) [71].

In the late 1980s, single gene disorders were diagnosed from fetal samples. Although only prenatal diagnosis of β-thalassemia was done using amplified fetal DNA [74] initially, the number of diagnosable diseases or genes has increased thereafter. Thus, the whole-genome sequencing, using DNA samples from amniotic fluid, was developed in the next-generation sequencing (NGS) era [75]. In fact, whole-exome sequencing (WES) is more appropriate for fetal genetic analysis, because the coding exons in WES contain 85% of disease-coding mutations, even though it accounts for only 2% of the entire genome. Prenatal WES, using fetal blood samples, has been performed since 2013 [76]. Meanwhile, massive parallel sequencing (MPS) using NGS opened the way to NIPT [77] in the late 2000s. Now, NIPT is widely used for aneuploidy, throughout the world [78], and even some of the fetal single-gene diseases can be detected using cell-free fetal DNA (cffDNA) obtained from maternal blood [79, 80]. Although the number of diseases detectable using cffDNA is gradually increasing, cffDNA analyses are merely screening tests and would not replace the diagnostic testing, as mentioned in the guidelines of professional societies [81–86].

Author details

Shiori Nakano, Haruyuki Makishima and Shigehito Yamada*

*Address all correspondence to: shyamada@cac.med.kyoto-u.ac.jp

Congenital Anomaly Research Center, Kyoto University Graduate School of Medicine, Japan

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Chapter 3

Fetal Central Nervous System Abnormalities

Andreea Ceausescu, Andreea Docea, Marina Dinu,
Stefan Degeratu, Dominic Iliescu and Monica Cara

Additional information is available at the end of the chapter

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Abstract

Central nervous system (CNS) is one of the most frequent sites for prenatal diagnosed congenital abnormalities (10 per 1000 live births, much higher than the heart—eight per 1000, kidneys—four per 1000, and other fetal systems). Due to the evolving pattern, ultrasound screening for fetal brain malformations is usually performed at 19–22 weeks' gestation, but severe congenital anomalies can be diagnosed much earlier. This chapter is a short review, structured in eight subchapters: the first one is dedicated to the normal ultrasound aspect of different CNS segments, and the following ones are to detect pathology in prenatal life. We used many ultrasound images and tried to correlate the prenatal findings with the ones obtained postpartum/postabortum for each case, by means of pathology/imaging techniques.

Keywords: cortex, spine, cerebellum, brain stem, malformations, development

1. Introduction

It has been said that the central nervous system (CNS) is the most complex among the fetal and adult systems. This is one of the most common sites of congenital malformation, both in fetuses with and without chromosomal abnormality. It is extremely difficult to diagnose structural abnormalities or mild ultrasound (US) abnormalities that have been linked to major functional problems. Just the opposite, major anatomic defects may not lead to significant malfunctioning of the system. It is extremely important to study the structure, in an attempt to understand the function of the normal and abnormal fetal central nervous system [1, 2]. The detection of CNS anomalies in fetal life is feasible using modern ultrasound equipment. Many

anomalies of the central nervous system develop early, and nowadays, we have the tools to detect some conditions at 11–13 weeks [3–8] or even earlier. The first-trimester detection of CNS anomalies is probably the most important advance in modern sonoembriology. Later in pregnancy, neurosonography is a powerful tool in diagnosing CNS pathology.

The following chapter is structured as follows:

1. Normal findings
2. Ventricular system (ventriculomegaly, aqueduct stenosis)
3. Neural tube defects (NTDs) (anencephaly, encephalocele, myelomeningocele)
4. Cortical formation abnormalities (schizencephaly, lissencephaly, heterotopia, microcephaly)
5. Midline abnormalities (holoprosencephaly, complete/partial agenesis of corpus callosum or abnormal corpus callosum, absent cavum septum)
6. Posterior fossa abnormalities (mega cisterna magna, Blake's pouch cyst, Dandy-Walker or variant cerebellar, vermian hypoplasia)
7. Vascular abnormalities (hemorrhage, hematoma, dural fistula, aneurysms)
8. Destructive lesions (hydranencephaly, tumors/mass lesions, cysts, periventricular leukomalacia, infections, dysplasias, other lesions).

2. Normal findings

Some intracranial segments of CNS are seen on ultrasound *extremely early* in development, especially when using high-resolution probes and modern electronic tools. Although many features are indeed recognizable, the clinical utility of such studies is yet to be proven (**Figures 1**–**3**).

In the *late first trimester*, current guidelines recommend checking for present cranial bones, for normal midline falx, and for the presence of choroid plexus and filled ventricles [9]. The most recommended planes for assessing the head anatomy are the axial ones. In terms of spine assessment, the guidelines state that "longitudinal and axial views should be obtained to show normal vertebral alignment and integrity, and an attempt should be made to show intact overlying skin" [9] (**Figure 4**).

From the early *second trimester* onwards, the commendation is to obtain in standard assessment three standard axial planes (transventricular, transthalamic, and transcerebellar), and, if technically feasible, the fetal profile [10] (**Figures 5** and **6**).

The measurements for fetal head *biometry* (the biparietal diameter—BPD and the head circumference—HC) are possible when using the transventricular (biventricular) and the transthalamic plane. In the most commonly used technique, the calipers are placed from the outer edge to the

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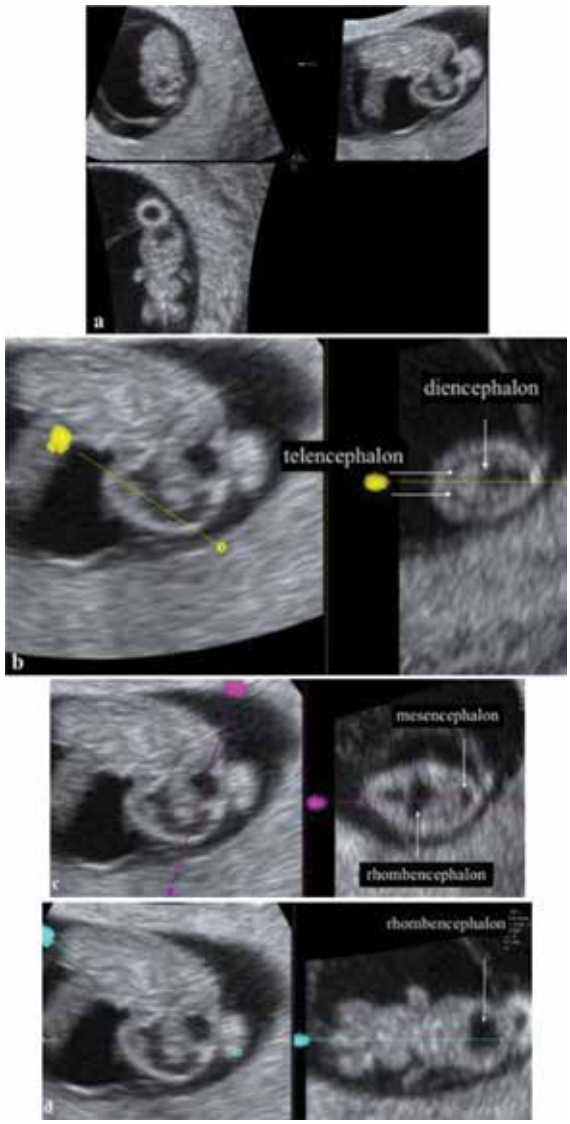

Figure 1. Dating ultrasound scan at 8 weeks of amenorrhea (WA) and 3 days (d). Volumetric ultrasound: sectional planes in the multiplanar mode (a). Subsequently, OmniView facility was used, the line mode (b, c, and d). The embryonic central nervous primitive vesicles can be observed.

inner edge (the "leading edge" technique), at the widest part of the skull, using a perpendicular angle to the midline falx. The HC is measured on the external contour. The cranial bones describe on axial planes a regular *ovoid* shape. The *midline* must be continuous, having no deviations, and the intracranial structures must be symmetrical, mirroring each other's half. Usually, the proximal hemisphere to the probe has a lower visibility, and only the distal one is described by the operator. On the *transthalamic plane*, the anatomic landmarks are (from anterior to posterior) the frontal horns of the lateral ventricles (LVs), the cavum septi pellucidi (CSP), located between

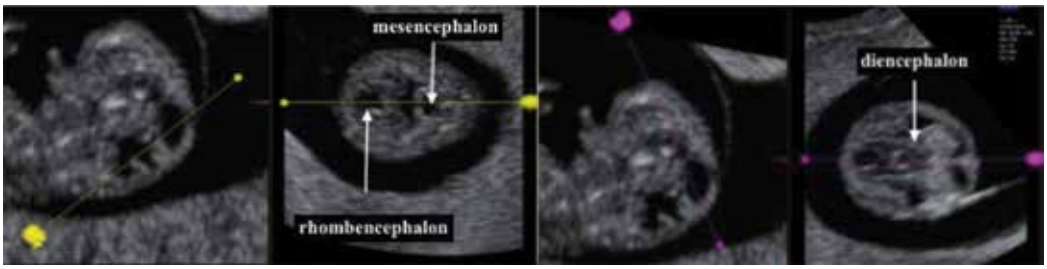

Figure 2. The same case, at 10 WA 1d. The same technique was used, after acquiring a static 3D volume.

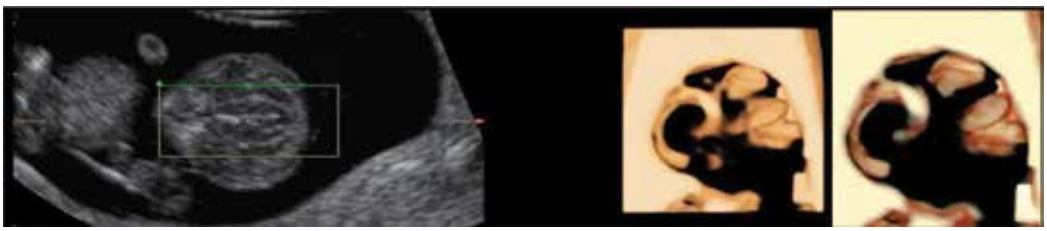

Figure 3. The same case, at 10 WA 1d. The region of interest is placed inside the head, and HD (high-definition) inversion mode surface rendering is applied. This imaging technique acts like a matrix, or a "mold," bringing forth fluid-filled cavities: the early ventricular system.

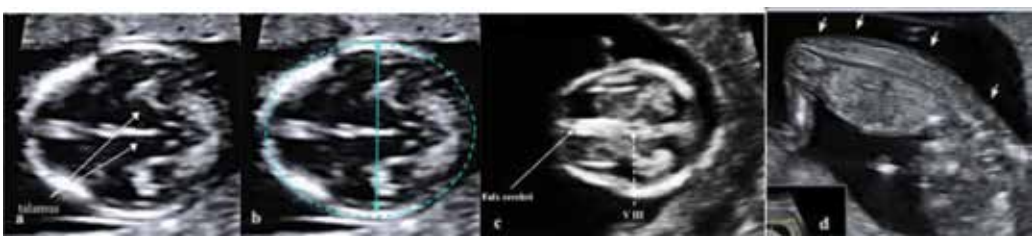

Figure 4. The thalamic plane (a and b), the third ventricle plane (c), and the longitudinal image of the spine, in a prone position (d). In b, the head biometry is represented (measurement of BPD and HC).

them as a fluid-filled structure, the two thalami (resembling together a "heart image"), the third ventricle between them, and the hippocampal gyrus. The *biventricular plane* is found just above the previous one and allows the visualization of the lateral ventricles, with the choroid plexus inside them. The width of the posterior horn of the lateral ventricle must be measured using the exact mark of the parieto-occipital sulcus, inside the echoes generated by the ventricular walls, by a direction aligned perpendicularly to the long axis of the ventricle. Before 25 WA, the measurement must be smaller than 8 mm. The *transcerebellar plane* is obtained just below the transthalamic one, in an oblique fashion. The slight posterior tilting allows the visualization of the frontal horns of the lateral ventricles, CSP, thalami, cerebellum, and cisterna magna [1, 10]. The transversal diameter of the cerebellum (in mm) equals roughly the gestational age (in weeks). In

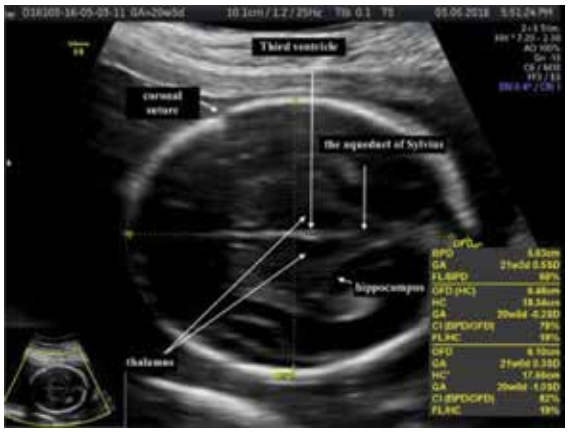

Figure 5. The thalamic plane.

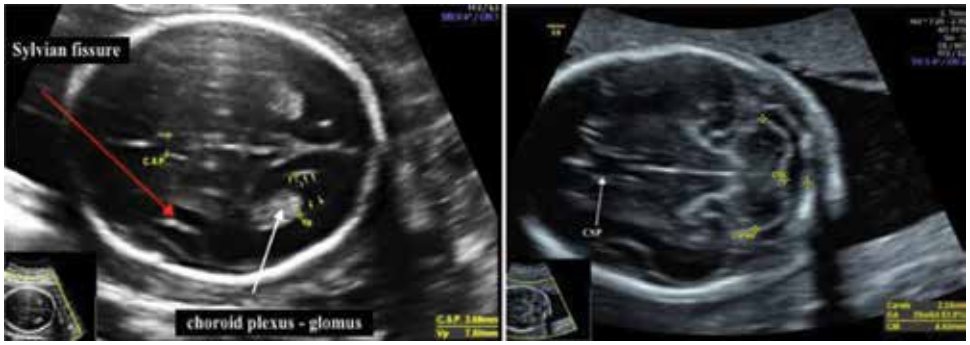

Figure 6. The biventricular (transventricular) and the transcerebellar plane.

the second half of gestation, the depth of the cisterna magna (measured between the cerebellar vermis and the intern margin of the occipital bone) is stable and should not exceed 10 mm.

The *neurosonogram* implies obtaining four more coronal planes and three sagittal/parasagittal planes and assessing the evolving cerebral fissures, gyrations, and circumvolutions [1]. The coronal planes are displayed in **Figure 7**.

The *transfrontal* plane is obtained through the anterior fontanelle. The interhemispheric fissure (IEF) in the median plane and the anterior horns of the lateral ventricles on both sides can be seen. This plane passes anterior to the genu of the corpus callosum (CC), and this is why the IEF appears uninterrupted. The *transcaudate* plane passes at the level of caudate nuclei and the genu of the CC. It interrupts the continuity of the IEF. CSP appears as an anechogenic triangular structure under the CC. Lateral ventricles are seen, surrounded by the cortex. Also, the Sylvian fissures may be identified, laterally. In the *transthalamic* plane, the thalami are seen adjoining. In some cases, the third ventricle is seen in the median plane. In this plane, at the base of the skull, the vessels of the circle of Willis and the optic chiasma

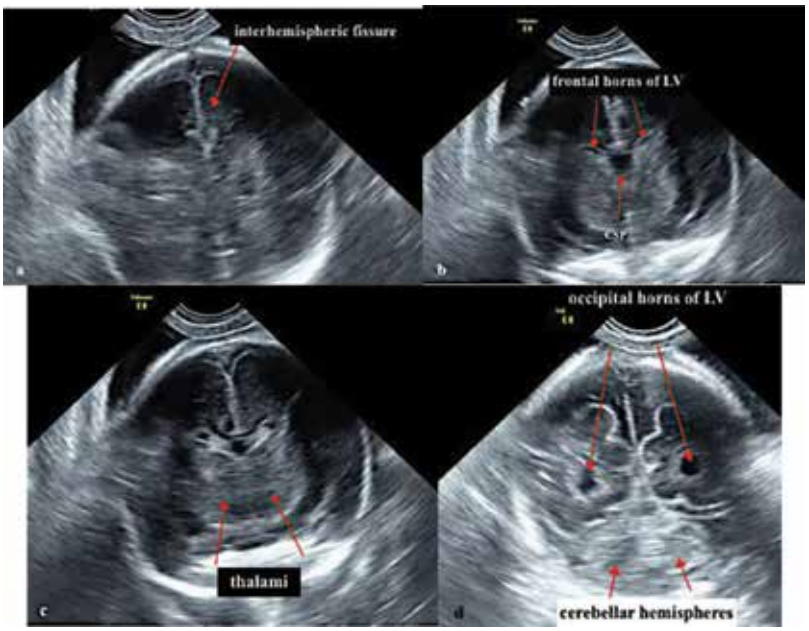

Figure 7. The transfrontal plane (the frontal-2), the transcaudate plane (mid-coronal-1), the transthalamic plane (mid-coronal-2), and the transcerebellar plane (occipital-1 and 2).

may be recognized. The *transcerebellar* plane is obtained through the posterior fontanelle. The occipital horns of the LV and IEF are seen, also the cerebellar hemispheres and the vermis.

The antero-posterior planes are displayed in **Figures 8** and **9**.

In the *midsagittal* (median) plane, all components of the CC (rostrum, genu, body, splenium) may be seen. Also, the CSP, the brain stem, pons, vermis, and posterior fossa. The parasagittal planes (right and left) depict the entire LV, the choroid plexus, the periventricular tissue, and the cortex.

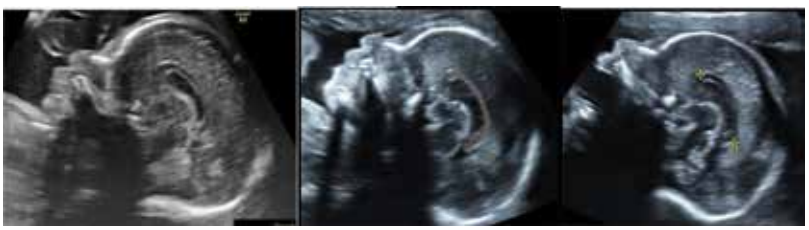

Figure 8. The sagittal plane. The corpus callosum is highlighted in the middle image.

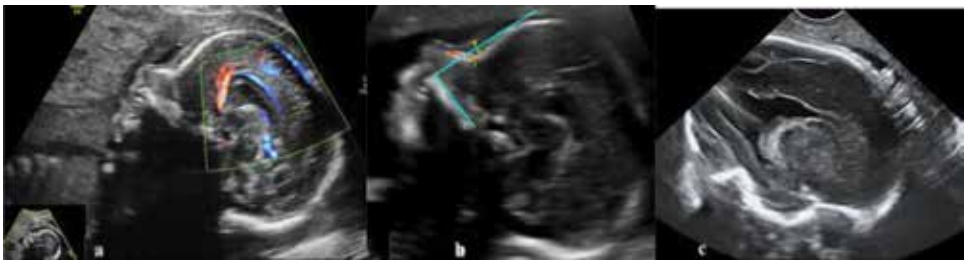

Figure 9. The sagittal plane with HD flow applied, displaying the pericallosal artery (a), the measurement of the nasal bone and the fronto-maxillary facial angle, and the parasagittal or oblique plane-1 (c).

2.1. The spine

In the sagittal and parasagittal planes, the ossification centers of the vertebral body and posterior arches form two parallel lines that converge in the sacrum, in the prone position of the fetus. Efforts must be made to demonstrate the integrity of the overlying skin.

In the second and third trimesters, these planes allow imaging of the spinal canal and of the spinal cord within it. The conus medullaris is usually found at the level of L2–L3 vertebrae (**Figure 10**).

In transverse planes or axial planes, the vertebrae have different shapes at different levels [1]. Fetal thoracic and lumbar vertebrae have a triangular shape, the first cervical vertebrae are quadrangular in shape, and sacral vertebrae are flat.

The normalcy of the vertebrae and ribs' arches may be very easily demonstrated in the coronal plane, using the 3D technique, skeletal mode. Both can be readily numbered (**Figure 11**).

In the prenatal scanning, many normal and abnormal structures may vary and evolve intensively. Thus, using descriptive terms is advisable. The observer may use a thorough detailed depiction of the visualized structures and features, may note the absent normal structure/structures, and may signalize an abnormal structure. This approach is preferred to issuing a specific diagnosis.

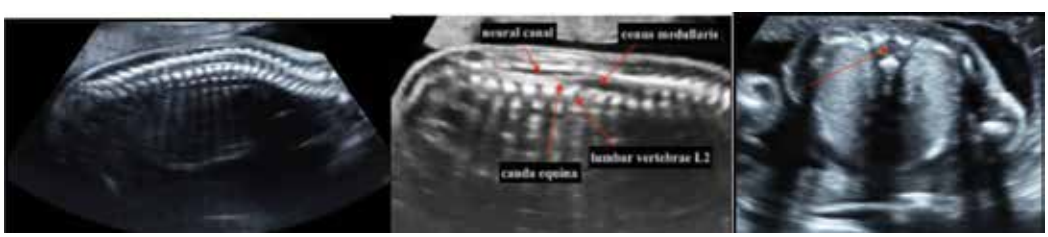

Figure 10. The imaging of the spine and the distal region of the spinal canal. Axial thoracic vertebrae.

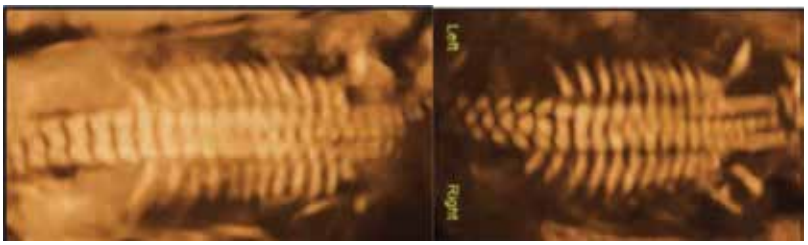

Figure 11. Imaging the spine in the coronal plane. In left image, a supernumerary lumbar rib case is shown.

3. Abnormalities of the ventricular system

Ventriculomegaly is the most frequent abnormal CNS finding diagnosed in utero and is the most common indication for second-level neurosonography and fetal magnetic resonance imaging (MRI) [11].

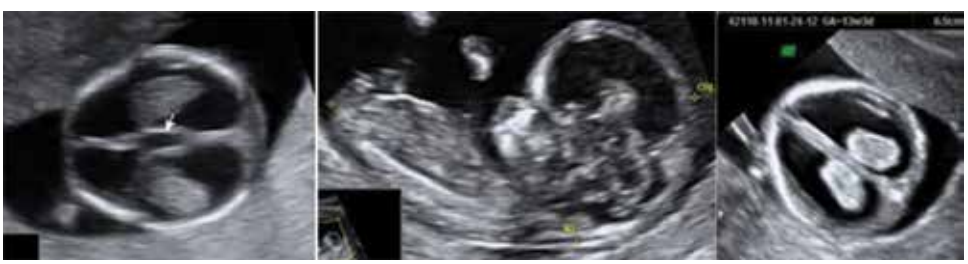

Figure 12. Early ventriculomegaly cases.

Figure 13. Severe obstructive ventriculomegaly, with unknown origin. Pathologic differentiation of diencephalon and mesencephalon. Conventional necropsy confirms the enlarged ventricles. Microscopy: marked astrocyte cell line proliferation, neuronal migration defects, and cortical fibrosis (stained with hematoxylin and eosin, ob. 40×).

Establishing its class of severity is based on the width of the atrium of the lateral ventricle measurement: ventriculomegaly is considered to be mild when the atrial width is 10–12 mm, moderate between12 and 15 mm, and severe if larger than 15 mm.

In rare cases, ventriculomegaly is accessible in early pregnancy (**Figure 12**).

Yet, this is usually a second- and third-trimester diagnosis. The prevalence of mild ventriculomegaly, based on current criteria, is estimated to be around 0.7% [12]. The finding of ventriculomegaly should trigger a thorough analysis of the fetal brain to investigate all associations (malformative, clastic, tumoral, and syndromic). If no underlying pathophysiology and etiology are found, ventriculomegaly is referred to as "isolated." Melchiorre et al. [13] demonstrated the particularly difficult counseling in such cases. Aqueductal stenosis is the most common cause of ventriculomegaly and its extreme form—fetal hydrocephalus. Published studies of neonates with aqueductal stenosis have noted variable outcomes, with normal development seen in 24–86% of cases [14] (**Figures 13–15**).

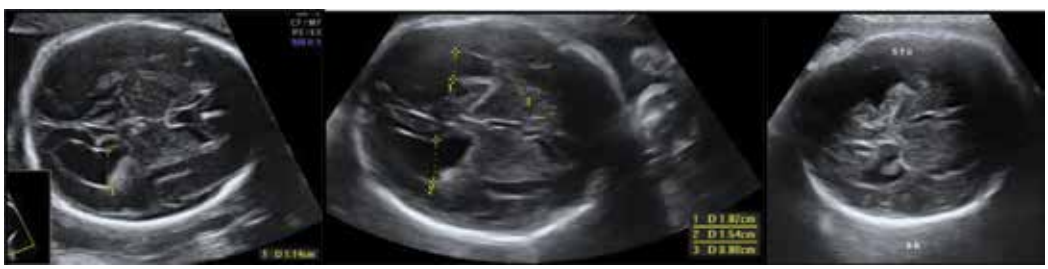

Figure 14. Different cases of unilateral borderline isolate ventriculomegaly, symmetric, and asymmetric.

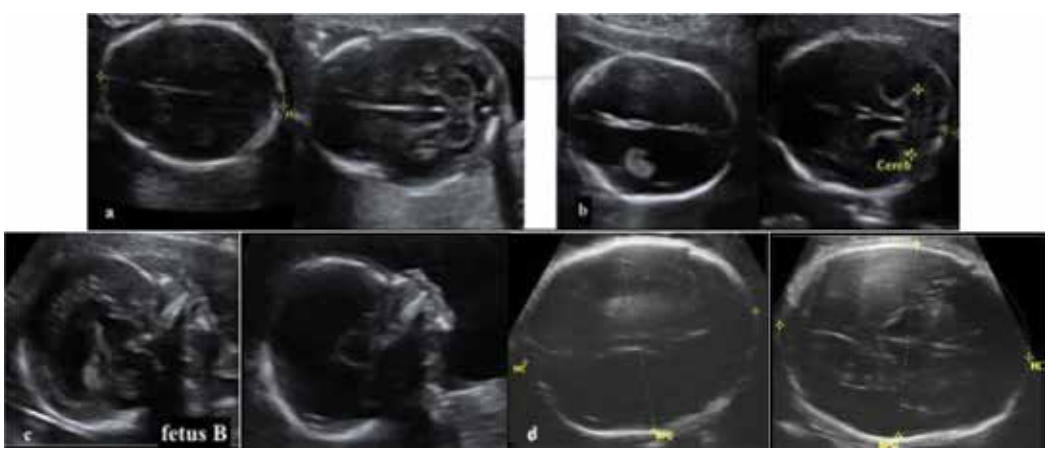

Figure 15. Twin monochorionic diamniotic pregnancy, with discordant major SNC anomaly: severe ventriculomegaly due to aqueductal stenosis. The images display comparatively the same planes: the transthalamic (a) and transcerebellar plane (b), the fetal profile (c) at 17 WA. The transthalamic plane at 25 WA (d). The long-term evolution of fetus B was favorable (after ventriculo-peritoneal shunt).

4. Neural tube defects

Neural tube defects (NTDs) are a frequent group of severe anomalies of the central nervous system. The most frequent conditions are anencephaly, spina bifida, and cephalocele [15]. The open NTDs occur as a result of a primary failure of the neural tube closure between the 17th and 30th postfertilization days. They have a rather stable prevalence. This highlights the importance of primary prevention by folic acid supplementation and the paramount meaning of accurate prenatal diagnosis. In rare cases, some forms of NTDs may be recognized very early in pregnancy (**Figure 16**).

Yet, the vast majority of cases are approached in the late first trimester (11–13 WA), due to the fact that the role of this scan has evolved [5, 7, 8, 16–18]. The technique has grown, no longer being a screening for aneuploidy tool [19–22]—but a method to almost assess the complete fetal anatomy. This became the first anomaly scan in many units [4, 5, 18, 23–25].

In terms of central nervous system, the newest area of debate is the significance of posterior fossa ultrasound semiology. At 11–14 weeks of gestation, it is possible to visualize and measure many spaces in the posterior brain: the brainstem (BS), the fourth ventricle or intracranial translucency (IT), and the cisterna magna (CM). In some settings, such anatomical spaces are assessed routinely by ultrasound in parasagittal or oblique views of the fetal face, as part of the nuchal translucency (NT) scan [26, 27]. Abnormalities of the posterior brain spaces or deviations of their measurements have been proposed as markers of congenital malformations of the posterior fossa [26–29]. Subsequently, the correlation between the decreased amount of intracranial fluid and open spina bifida (OSB) has been established [16, 30]. More recently, it has been suggested that increased fluid may indicate the presence of cystic posterior fossa anomalies such as Dandy-Walker malformation (DWM) and Blake's pouch cyst (BPC) [31–35].

Also, the axial planes offer many indirect signs of OSB and have competed with the sagittal planes in the efficacy of first-trimester screening for OSB [36–38]. It seems that in experienced hands, OSB may reach 100% early detection rates, being reliably diagnosed at 11–14 weeks of screening [39].

In our view, both sagittal and axial planes of the fetal head may be used in OSB screening, depending on the operator's skills and the equipment used. Also, the small BPD may be useful [40, 41].

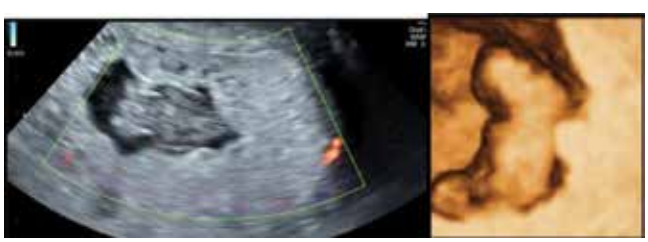

Figure 16. Early embryonic demise, in a case of suspected exencephaly.

2D planes and markers for fetal central nervous system (CNS) morphologic assessment at the first-trimester ultrasound scan are shown in **Figure 17**: left column, a normal fetus; right column, isolated OSB fetus.

In the thalamic plane, the regularity of the skull and the bone ossification should be assessed. Also, measurements may be performed: the biparietal diameter (BPD), the head circumference (HC), and optional—the occipito-frontal diameter (OFD). Thalamus, the third ventricle (red arrow), and symmetry of the intracranial structures may be subjectively assessed. In this plane, the "crash sign" may be subjectively evaluated (the aqueduct of Sylvius position) or the distance between this feature and the occipital bone may be measured (the aqueduct—indicated by the blue quadrant, and mesencephalon—normal by the yellow contour and pathologic by the red contour).

In the lateral third-ventricle plane, aside from the regularity of the skull and the bone ossification assessment, the following structures should be visualized: the midline falx echo, the choroid plexuses, the interhemispheric fissure, the posterior horns of the lateral ventricles (LVs), the lateral walls of the anterior horns of the LV, and the thin brain mantle. In this plane, the "dry brain phenomenon" is usually present in OSB cases: the subjective large choroid plexus for the skull (**Figure 18**).

In the sagittal plane (often called the *mid-sagittal* plane), many CNS structures may be identified and measured: the thalamus (T), the brain stem (BS), the medulla oblongata (MO), the midbrain (M), and the future cisterna magna (CM). In OSB cases, some mild signs may be found: the alteration of the BS (brainstem diameter)/BSOS (brainstem to occipital bone diameter) ratio and the decreased frontomaxillary facial (FMF) angle. The most valuable in screening seems to be the alteration of the cisterna magna (**Figure 19**).

Along with the mild early signs of spinal neural tube defects, other major malformations reach 100% detection rates in many reports. **Figures 20–22** show several such cases, showing correlations between the ultrasound data and the specimen aspects.

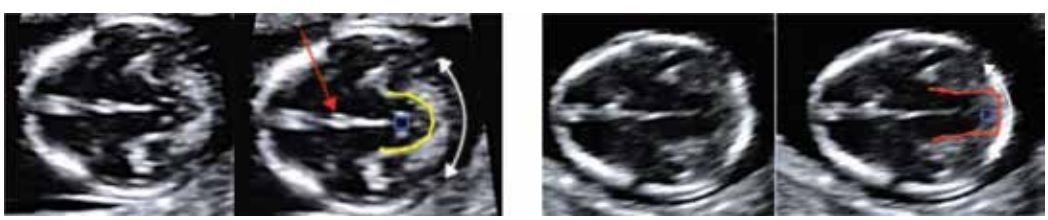

Figure 17. The transthalamic view of cranium in a normal (left) and an OSB case (right).

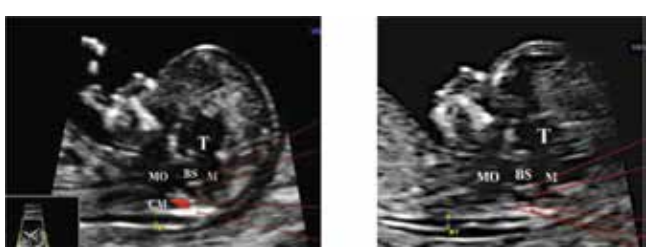

Figure 18. The sagittal plane of cranium in a normal (left) and an OSB case (right).

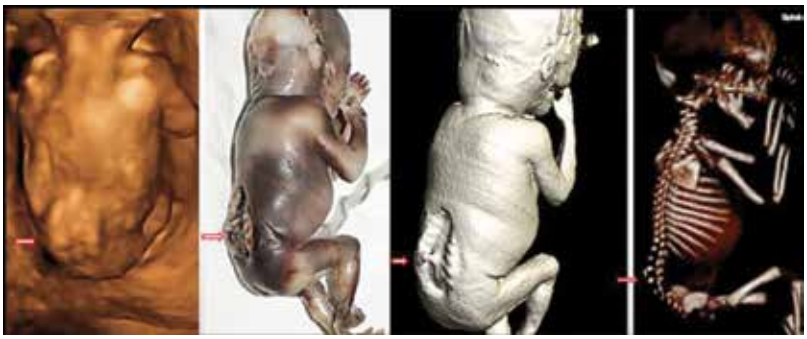

Figure 19. Rachischisis. Medical termination of pregnancy at 16 WA. 3D ultrasound in a surface-rendering mode (a), pathologic specimen (schisis of the lumbar skin, with exposing the meninges and the spinal canal structures) and MRI details of specimen, confirming the hemivertebra suspected on US.

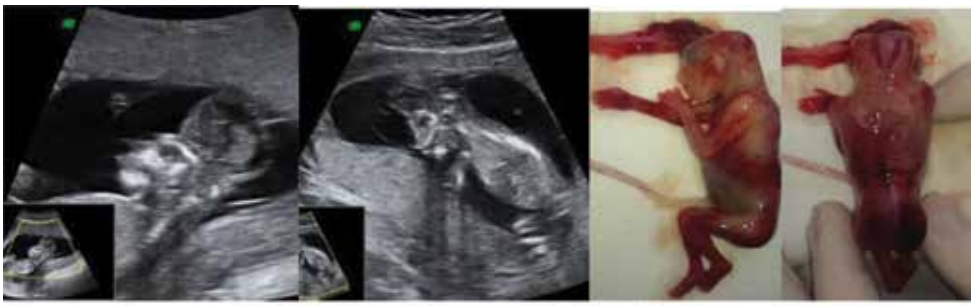

Figure 20. Exencephaly. Ultrasound images and the pathologic specimen at 12 WA.

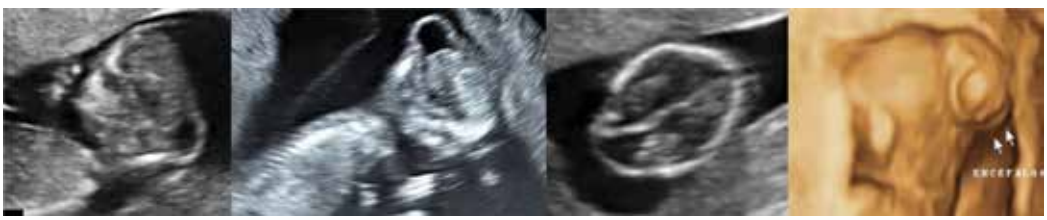

Figure 21. Encephalocele at 12 W. Conventional 2D ultrasound and 3D surface rendering.

Figure 22. Complex lethal facial and cerebral anomaly. The red arrow indicates the single orbit. The pathologic specimen confirms ciclopy, proboscis, exencephaly (a). Second-trimester case of anencephaly: 2D conventional and 3D ultrasound (b).

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5. Cortical formation abnormalities

The cerebral *cortex development* implies evolvement through three steps: neuronal precursor proliferation and differentiation; migration of immature neurons; and cortical maturation (the laminar organization and occurrence of synapsis). Neurons migrate from the ventricular zone (called the germinal matrix) toward the pial surface, along radially oriented glial scaffolds [42–44]. Gyration and sulcation occur afterword, beyond 32 WA. Disruption of any of these steps in cerebral development, due to inherited or acquired causes, can result in a wide spectrum of abnormalities.

Schizencephaly is a congenital cerebral defect in clefting, where clefts extend through the hemispheres from the ventricles to the pial surface [45]. Having two clinical types (open and closed), it seems to be caused by a primary failure of development of the cerebral mantle in early pregnancy. The condition is different from *porencephaly*, being characterized by the presence of heterotopic gray matter lining the cleft. Although primary, it has also been reported as a destructive process mediated by vascular injury also.

Lissencephaly means literally "smooth brain." This is a rare brain malformation, gene-linked, characterized by the absence of normal convolutions in the cerebral cortex, leading to *microcephaly*. In most cases, neonates have usually a normal sized head at birth. The "cobblestone lissencephaly" is characterized by the irregular surface of the brain on the pathological specimen. This is due to aberrant neuroglial overmigration into the subarachnoid space. The formation of an extracortical agyric neuroglial layer occurs. It seems that the primary cause is the deficit of glycosylation of dystroglycans, resulting in neuroglial overmigration [44–50].

The presence of neurons in any position other than the cortex is called *neuronal heterotopia*. This is caused by an abnormal phenomenon of migration during fetal development. The most frequent type is *periventricular* heterotopia, given by an abnormal development of the neuroependyma [44, 50]. It consists of groups of disorganized neurons and glial cells that are located along the walls of the lateral ventricles. They may be isolated (X-linked and non-X-linked forms) or associated with other CNS malformations. The prevalence in the general population is unknown, but it has been related with epilepsy, seizures, and/or developmental delay, with different grades of severity. The prenatal diagnosis has been reported, but the condition is underdiagnosed in the vast majority of screening settings. The true *microcephaly* is considered part of a complex disorder [48–51], occurring in syndromes (with or without chromosomal anomalies). It may be associated exclusively with cerebral anomalies (due to either primary cerebral maldevelopment or clastic events like the ischemohemorrhagic ones) or infectious diseases; the latter has gained a particular interest lately, in light of the recent emergence of microcephaly related to Zika virus infection [48–51]. *Macrocephaly* may result from macrocrania, hydrocephalus, or a major subarachnoid space abnormality. If not associated with other conditions, macrocephaly is synonymous with megalencephaly, meaning an increase in the weight and size of the brain [52] (**Figure 23**).

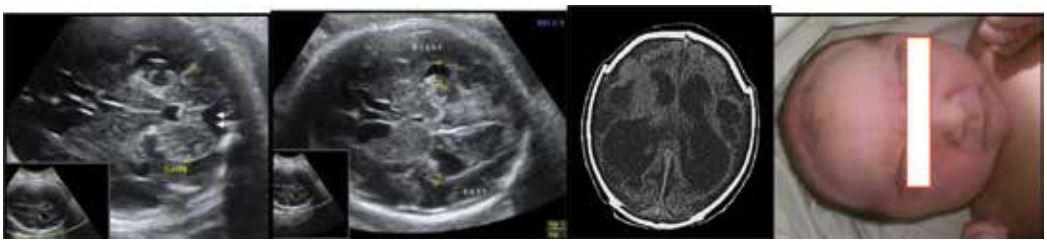

Figure 23. Complex cortical anomaly. Nodular periventricular heterotopia seen. Cortical hypoplasia. Microcephaly. Periventricular leukomalacia. The postpartum image highlights the abnormal excessive ossification of the coronal suture and the dysmorphic facial features of the neonate.

6. Midline abnormalities

Holoprosencephaly is a congenital induction disorder, occurring extremely early in pregnancy (3–6 WA), with failing the segmentation of the neural tube [53–57]. This leads to incomplete separation of the prosencephalon. It has been classified into four subtypes: alobar, semilobar, lobar, and a middle interhemispheric fusion variant (syntelencephaly).

The alobar holoprosencephaly is the most severe type, having a complete lack of separation of the cerebral hemispheres; this lead to a single ventricle, absence of the CC and IEF, and fused thalami. In the semilobar type, the cerebral hemispheres are fused anteriorly. In lobar holoprosencephaly, the fusion of the cerebral hemispheres is present at the frontal lobes. The middle interhemispheric fusion variant results from nonseparation of posterior frontal and parietal lobes.

The *corpus callosum* is the largest commissure of the brain, and its development is accelerated between 8 and 20 WA. Any disturbance of this process may lead to CC agenesis or partial agenesis (hypogenesis or dysgenesis). Many CC abnormalities (in terms of dimensions and shape) are frequently diagnosed during pregnancy although their significance is still debated [58–67]. Abnormal CC has been described among patients assessed for mental retardation.

In a similar way, the absence of fluid in the CSP (with or without intact *septum pellucidum* and corpus callosum) may indicate subtle or severe midline brain abnormalities. All these conditions may have significant implications for postnatal neurological development [58, 61, 63–68] (**Figures 24** and **25**).

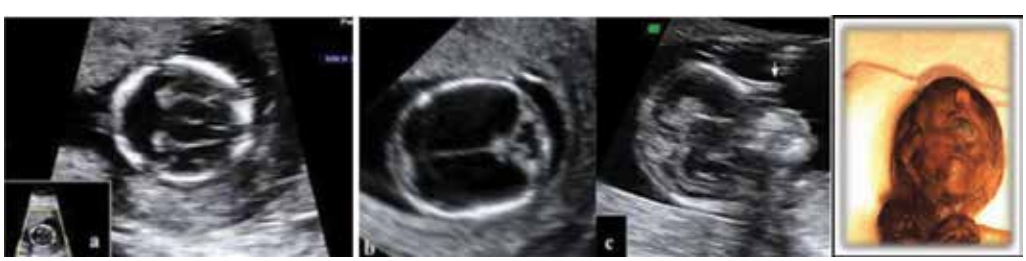

Figure 24. Different cases of holoprosencephaly in the first trimester (a,b). c. a case which associates proboscis.

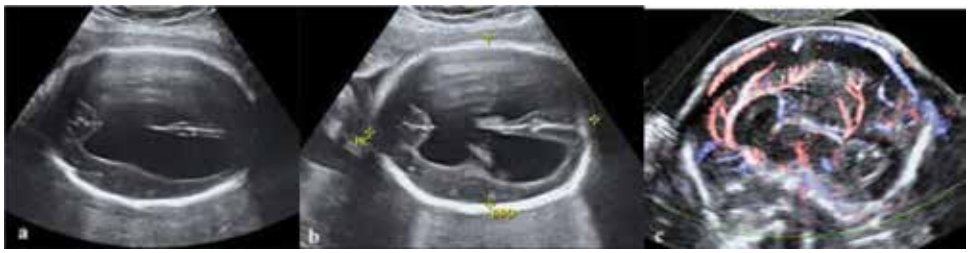

Figure 25. Second-trimester alobar holoprosencephaly (a and b). Short and thick corpus callosum (c).

7. Posterior fossa abnormalities

Posterior fossa abnormalities include the Dandy-Walker malformation (complete or partial agenesis of the cerebellar vermis, cystic dilatation of the fourth ventricle, and enlarged posterior fossa, with upward displacement of the tentorium, torcula, and transverse sinuses); the mega cisterna magna (a CM measuring more than 10 mm and a normal vermis); the Blake's pouch cyst (the presence of an upwardly displaced normal cerebellar vermis, normal appearance of the fastigium, tentorium, and size of the cisterna magna); and isolated vermian hypoplasia (a normally formed vermis but of smaller size, with an otherwise normal size and anatomy of the posterior fossa) [69, 70]. It seems that the Dandy-Walker malformation, even if apparently isolated on ultrasound imaging, carries a high risk for chromosomal and associated structural anomalies. Isolated mega CM and Blake's pouch cyst have a low risk for aneuploidy and associated structural anomalies. The isolated vermian hypoplasia is extremely rare; thus, the literature does not offer definite conclusions about its significance. This needs to be further assessed (**Figure 26**).

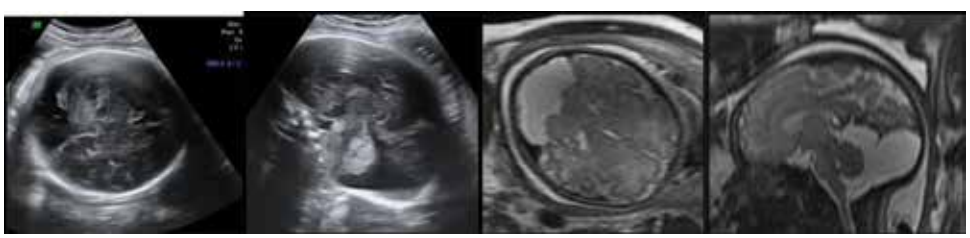

Figure 26. Isolated mega cisterna magna. US and MRI images of the same third-trimester case.

8. Vascular abnormalities

Possible causes of hemorrhage include arteriovenous malformation, benign or malignant, intracranial tumors, fetal infection, drug toxicity, and clotting disorders, such as isoimmune or alloimmune thrombocytopenia [71–79].

Fetal *hemorrhagic* and *hypoxic-ischemic* insults can lead to antenatal brain damage and fetal stroke. These are associated with fetal death, postnatal seizures, mental retardation, psychomotor delays, and cerebral palsy [72]. Fetal intracranial hemorrhages and strokes can be

prenatally diagnosed by ultrasound and MRI. The classification of intracranial hemorrhages includes five major types: intraventricular hemorrhage, cerebellar, subdural, primary subarachnoid hemorrhages, and other intraparenchymal hemorrhages. Intraventricular hemorrhage is the most common variety of neonatal intracranial hemorrhages and is characteristic of the immature brain. Intraventricular hemorrhages are subdivided according to their severity into four grades: the first three grades are limited to the ventricles, while the fourth grade includes parenchymal involvement.

The outcome of bleeding into the ventricles ranges from hemorrhage absorption and resolution without residual deficit, to brain damage, with neurological and mental deficits, epilepsy and in extreme cases to fetal or neonatal death. Different scoring systems have been developed to predict the prognostic significance of fetal intraventricular hemorrhage. They depend upon ventricular enlargement and the presence or absence of brain parenchymal damage [72–79].

Spontaneous antenatal subdural hemorrhage is rare [71].

Vein of Galen aneurysmal malformation is a rare congenital malformation (1% of all abnormalities of the fetal cerebral arteriovenous system [80]. It occurs in isolation, although there have been reported cases related to cardiac abnormalities or cystic hygroma. The current hypothesis is the early occurrence (between the 6 and 11 WA), as a result of the persistence of an abnormal connection between the primitive choroidal vessels and the proximal region of the prosencephalic median vein. The persistence of the connection leads to the appearance of some abnormal arteriovenous shunts and the formation of the vein of Galen (**Figures 27** and **28**).

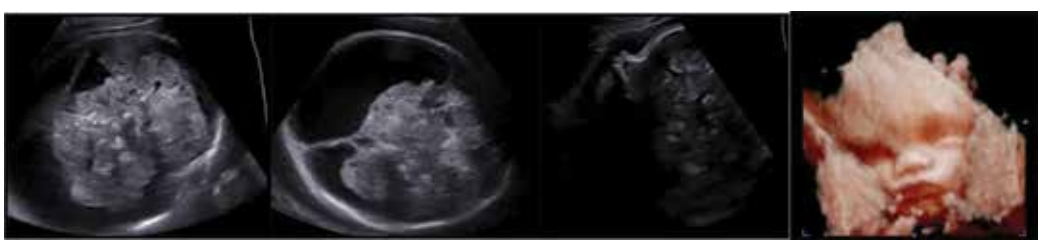

Figure 27. Massive intraparenchymatous hemorrhage in a case of fetal/neonatal alloimmune thrombocytopenia.

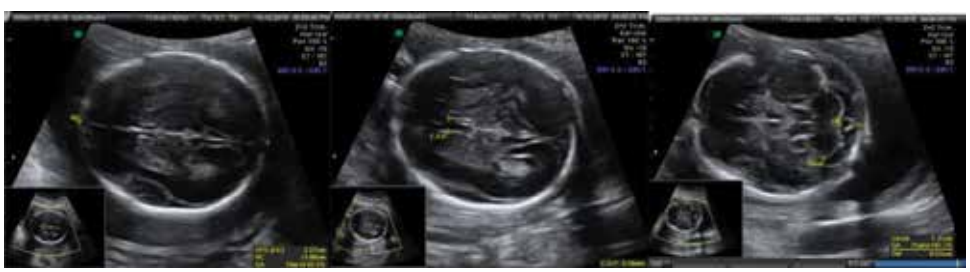

Figure 28. The same case. The fetus has had a complete normal neurosonogram in mid-trimester.

http://dx.doi.org/10.5772/intechopen.76208

9. Destructive cerebral lesions

The destructive lesions may include an extremely wide range of conditions: hydranencephaly, tumors/mass lesions, cysts, periventricular leukomalacia, infections, dysplasias, intracranial hemorrhage, and other lesions. Identification of these abnormalities can be extremely helpful in providing the patients with management options. Moreover, it has the potential to modulate the neonatal therapy [81–85].

Hydranencephaly is a severe congenital condition: most of the cerebral hemispheres are replaced by a membranous sac. The pathogenic mechanism and the prognosis remain controversial. Still, fetal and postnatal neuroimaging data and histopathologic findings suggest an early bilateral internal carotid artery occlusion occurring at 8–12 WA [81].

Fetal brain *tumors* are rare and have a different histologic pattern [84]. The definitive diagnosis relies on histopathology. The distinction between potentially curable tumors and tumors rapidly fatal after birth is extremely difficult. Moreover, some intracranial masses are not real tumors. Among the histological structure, we mention teratoma, glioblastoma, fetus-in-fetu, craniopharyngioma, and hemangioma.

The acronym TORCH is used to refer to congenital *infections*: toxoplasmosis, other infections (syphilis, varicella zoster, and parvovirus B19), cytomegalovirus, and herpes simplex virus. Zika virus has emerged as an important worldwide congenital infection. Many maternal and fetal symptoms are common. All mentioned infections may cause neurologic damage (ventriculomegaly, intraventricular adhesions, subependymal cysts, intracerebral calcifications, and microcephaly). The Zika virus leads to a more severe spectrum of CNS abnormalities and affects mildly other organ systems [85]. All congenital infections have rather nonspecific ultrasound findings. For the imagist professional, the awareness of imaging features of common congenital infections may facilitate early diagnosis and may, at times, lead to prompt initiation of therapy.

Periventricular leukomalacia has been reported in preterm and growth-restricted fetuses and neonates, and in monochorionic complicated pregnancies. It manifests as punctate white matter lesions or focal white matter necrosis. In clinical settings, cranial US has a limited sensitivity in detecting them. MRI is a more useful tool [78, 86].

Unfortunately, *cortical dysplasias*, involved as an epileptogenic substrate, are the most subtle lesions to identify, diagnose, and characterize [87, 88]. Improved MRI techniques with a multimodality approach (magnetoencephalography, positron emission tomography) will probably increase sensitivity and specificity for identifying them.

The most used classification [88] tried to unify the terminology of cortical dysplasias, which are seen as a subset of all malformations of cortical development. This proposal is based on histopathologic data, clinical and imaging findings, being currently under review [87] (**Figures 29–31**).

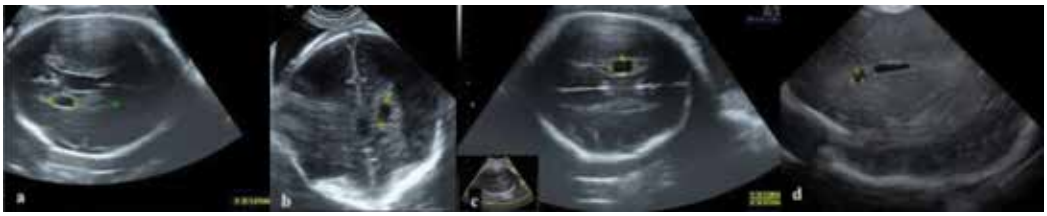

Figure 29. Benign, small dimensions, non-evolving intracerebral cyst: 28 WA (a and b), 30 WA (c), and postpartum, by means of transfontanellar ultrasound assessment (d).

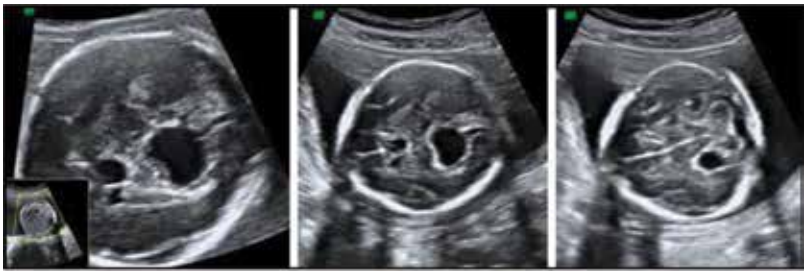

Figure 30. Porencephaly.

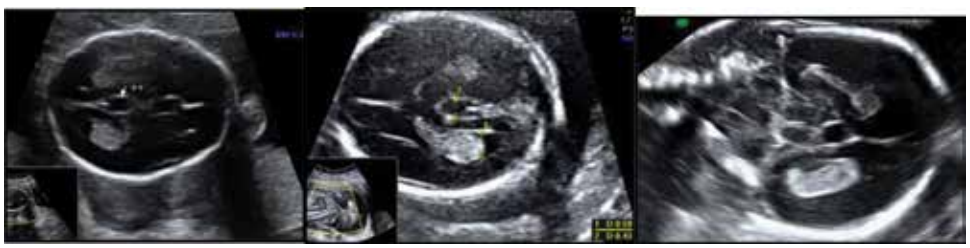

Figure 31. Arachnoid cyst.

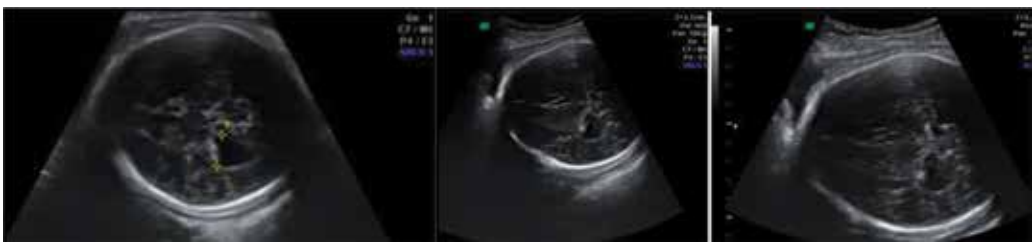

Figure 32. Midline abnormality and unilateral asymmetric borderline ventriculomegaly.

The above division of CNS congenital anomalies is an arbitrary one. In the most severe cases, several types of cortical malformation may be found simultaneously. Moreover, many types succed one another, or overlap in time.

Figures 32–34 show several examples of such associated abnormalities.

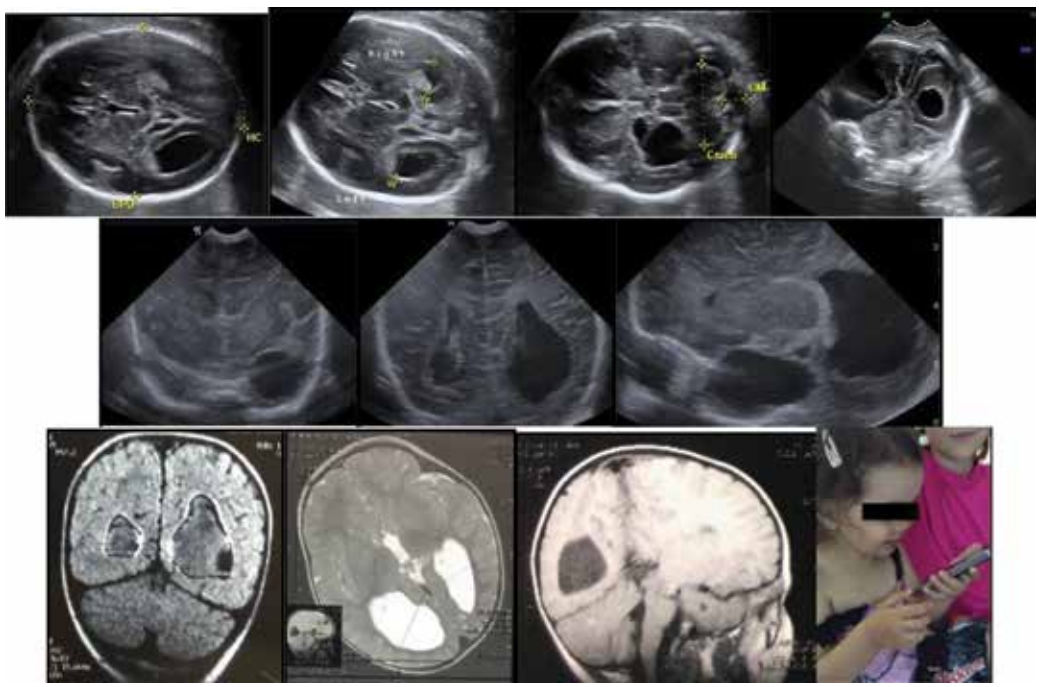

Figure 33. Complete agenesis of the corpus callosum. Unilateral voluminous intracerebral cyst. Severe unilateral asymmetric ventriculomegaly. Subsequently, the short-term and long-term evolution was completely normal.

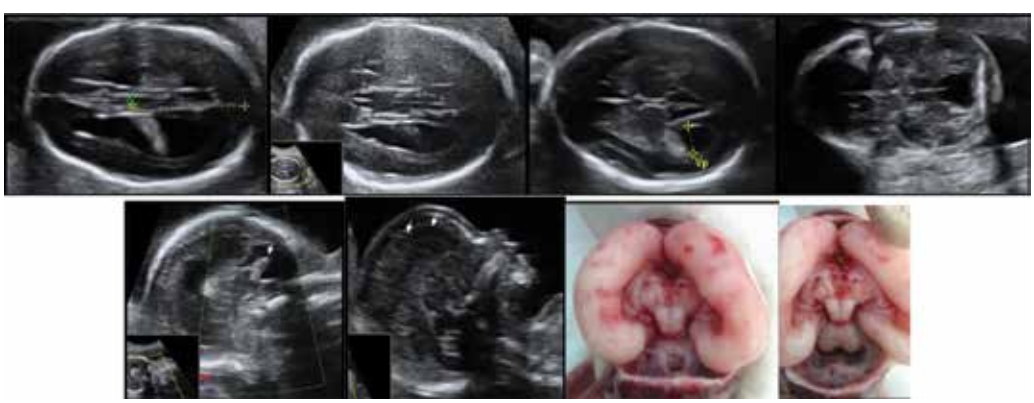

Figure 34. Complete agenesis of the corpus callosum. Cystic dilatation of the fourth ventricle and enlarged posterior fossa, with upward displacement of the tentorium, torcula, and transverse sinuses. Confirmation of the absence of CC by means of conventional autopsy.

Author details

Andreea Ceausescu[1]*, Andreea Docea[1], Marina Dinu[1], Stefan Degeratu[2], Dominic Iliescu[3] and Monica Cara[4]

*Address all correspondence to: and_deea2006@yahoo.com

1 Department of Obstetrics and Gynecology, Emergency University Hospital, Craiova, Romania

2 Department of Obstetrics and Gynecology, University Hospital, Craiova, Romania

3 Prenatal Diagnostic Unit, University of Medicine and Pharmacy of Craiova, Craiova, Romania

4 Department of Public Health, University of Medicine and Pharmacy, Craiova, Romania

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Chapter 4

Correlations between Ultrasound and Pathology in Fetal Ventricular System Anomalies

Tanya Kitova, Borislav Kitov, Denis Milkov and Aida Masmoudi

Additional information is available at the end of the chapter

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Abstract

A total of 113 cases of fetal hydrocephalus with a lethal outcome (FHLO) from the Embryo-Fetopathologic Clinic at the Center for Maternity and Neonatology, Tunis, Tunisia and Obstetrics and Gynecology Clinic at St. George EAD University Hospital, Plovdiv, Bulgaria were studied, 86 of which had syndrome malformations: neural tube defects (NTDs)—29.2%, chromosomal abnormalities—23.9%, skeletal dysplasias—9.8%, VACTERL association—5.3%, Dandy-Walker malformation—3.4%, Other—14.2%. Risk factors for FHLO are miscarriages (odds ratio (OR): 19.500; confidence interval (CI): 4.020-94.594), stillbirths (OR: 10.897; CI: 1.169-10.564) and previous birth of a malformative child (OR = 5.385; CI: 1.385–18.896). FHLO is significantly associated with a maternal age over 40 years and third degree consanguinity of the fetus (OR = 18.500; CI: 1.146–298.547). The trisomies in our study were 27 (23.9%) and are significantly associated with an age above 38 years and FHLO (OR = 13.689; CI: 3.952–52.122). In medical abortion, stillbirth, or neonatal death, a fetopathological study enriches our knowledge of malformations, complements and completes the ultrasound examination, modifies genetic counseling, and determines the medical behavior in subsequent pregnancies. Also, associated risk factors and fetopathological changes in FHLO must be studied to increase the ultrasound prenatal diagnosis success.

Keywords: congenital hydrocephalus, ultrasound, MRI, cerebral anomalies, risk factors

1. Introduction

Congenital hydrocephalus (CH) is a severe malformation which is often associated with other abnormalities. The prenatally diagnosed serious birth defects, especially those associated

with a high risk of premature death, stillbirth, or neonatal death, are often referred to as "lethal," as it is assumed that their potential treatment will be unsuccessful, which is the basis for the decision for the interruption of pregnancy due to medical reasons [1, 2]. Depending on the clinical criteria used in the definition of the disease, its incidence varies from 1 to 32 per 10,000 live births [3]. An increase in the prenatal diagnosis of CH has been observed, whereas the incidence of stillbirths remains stable. The interruption of pregnancy due to medical reasons reduces by almost a half the rate of hydrocephalus in live births. Currently, prenatal ultrasound is able to visualize ventriculomegaly, which can be caused by a number of reasons. Knowledge of the risk factors associated with CH may increase the chances of an early prenatal ultrasound diagnosis. Animal experiments have found that a wide range of environmental factors can cause hydrocephalus. They include alcohol consumption, X-rays, infections, eating disorders, and exposure to chemicals during pregnancy [4]. It has been established that one gene (L1 of Xq28 encoded for L1CAM) is connected with CH in humans. Although X-linked CH has a frequency of about 2–7% of all cases, L1CAM is found in about 15% of sporadic cases [5]. L1CAM mutations are closely related to stenosis of the cerebral aqueduct, the major pathology causing hydrocephalus in these cases. Sipek et al., in their study of CH for the period 1961–2000 in the Czech Republic, found that a mother's age of over 37 years was statistically significantly related to CH, unlike the study by Van Landingham et al. [4, 6].

2. Aim of the study

To study the prenatally ultrasound diagnosed ventriculomegaly by fetopathological autopsy in fetuses, which ended in interruption of pregnancy due to medical reasons, stillbirth, or neonatal death, by searching associated with the congenital hydrocephalus isolated or syndromic malformations as well as the eventual risk factors for their occurrence.

3. Materials and methods

A total of 113 fetuses with CH were studied whose outcome was lethal. One hundred and three of them were received over a period of 3 years (2006–2009) and autopsied at the Embryo-Fetopathologic Clinic at the Center for Maternity and Neonatology, Tunis, Tunisia, out of a total of 21,316 births. Ten of the cases were from the Obstetrics and Gynecology Clinic at St. George EAD University Hospital, Plovdiv, Bulgaria, during the year 2016 out of a total of 2104 deliveries. The incidence of fetal hydrocephalus with a lethal outcome (FHLO) in both centers is almost identical—4.8 and 4.9 per 1000 births.

The fetuses are the result of interruption of pregnancy due to medical reasons, spontaneous abortions, and stillbirths. The maternal and fetal data were collected from the obstetric history, and a classical autopsy was performed immediately following the expulsion of

the fetus, after authorization for macroscopic and microscopic examination. The autopsy includes observation, biometry of the fetus, and in situ examination of the body cavities. The examination of the brain was performed 6 months later, after conservation with 10% formalin. It began with biometrics, measurement of the biparietal and frontal-occipital diameters, and study of the relationship between ocular distance and eyelid length. After opening the cranial cavity, the meninx, brainstem, cerebellum, cerebral hemispheres, gyrification, and morphology were observed. The biometry of the brain—weight and bitemporal and fronto-occipital diameters of the encephalon, and weight and transverse diameter of the cerebellum—was also studied. The ventricular system was examined by horizontal or vertical hemispheric slices until the central part of the lateral ventricle was opened. The presence, shape, and thickness of corpus callosum were examined. With a linear meter, the ventricular width in the central part was measured. At a width of more than 10 mm, ventricular dilatation was diagnosed as hydrocephalus and at a diameter of over 15 mm—major hydrocephalus. In each study, material was taken for histological examination of the cerebral cortex, cerebellum, brainstem, choroid plexus, and cerebral meninx. SPSS version 19 was used for the interpretation of the data. A descriptive analysis and χ^2-analysis were used.

4. Results

- **Age structure of the mothers:** The age range of mothers carrying fetuses with FHLO was 21–43 years. Under 26 years of age were 24 mothers (22%), 27–35 were 64 (58%) and 36–50 years of age were 21 mothers (19.3%). The average age of the mothers was 29.5 ± 0.72.
- **Number of previous pregnancies of the mothers:** Most of the mothers carrying FHLO had one previous pregnancy (38.1%), followed by mothers with two previous pregnancies (19.5%). The average number of previous pregnancies is 2.50 ± 1.808, with a range of 1 to 5 pregnancies. There were no data for previous pregnancies for only 2.7% of the mothers.
- **Number of previous births of the mothers:** In the studied group, most of the mothers had one previous birth (36.6%), followed by mothers without previous births (31.3%). The average number of births is 1.24 ± 1.23, with a range of 0–5.
- **Blood group of the mothers:** Data were collected for the mothers' blood groups, but unfortunately there is no information for about 21% of the mothers carrying a fetus with FHLO of the studied group. It is noteworthy that most of the mothers were of blood group O(+) – 36 (32.0%), followed by A(+) – 23 (over 20.0%).
- **Consanguinity:** In our study, 27.4% of the marriages were consanguineous, with those of first degree being 15.4%, those of second degree 8.3%, and of third 3.7%.

5. Risk factors

In the present study, 80 of the pregnancies (70.7%) were without risk factors, and only 33 (29.3%) were under the influence of such. The risk factors were grouped into three categories: obstetric risk factors from past events, risk factors due to diseases of the mother, and exogenous risk factors.

1. **Obstetric risk factors.** This group includes spontaneous abortions—13 (11.5%), voluntary abortions—1 (0.9%), birth of a child with malformations—11 (9.8%), stillbirths—2 (1.8%), multifetal pregnancy—2 (1.8%), and multi-year sterility—4 (3.5%).
2. **Endogenous risk factors.** The risk factors from the mother include maternal age, hypertension—1 (0.9%), diabetes mellitus—2 (1.8%), bronchial asthma—2 (1.8%), thalassemia—2 (1.8%), and epilepsy—3 (2.7%).
3. **Exogenous risk factors.** Exogenous risk factors for the pregnancy include pregnancies carried in geographical areas near mines and underground mineral water deposits and consanguineous marriages. In our study, the pregnancies from geographic regions with mining and underwater mineral water deposits were 5 (4.4%). Supplementation with folic acid is mandatory in Tunisia and Bulgaria. There were no women without folic acid supplementation.

The term of pregnancy termination is presented in **Figure 1**. Most interrupted pregnancies are between the 20th and 24th gestational weeks. Six pregnancies were carried to birth.

Motives for pregnancy termination. Interruption of pregnancy due to medical reasons was performed in 87 cases (77%); spontaneous abortions were 13 (11.5%), and there was 1 voluntary abortion (0.9%). There were 2 live births (1.8%) and 2 stillbirths (1.8%). In eight of the cases (7%), there is no information on the motive for pregnancy interruption (**Figure 2**).

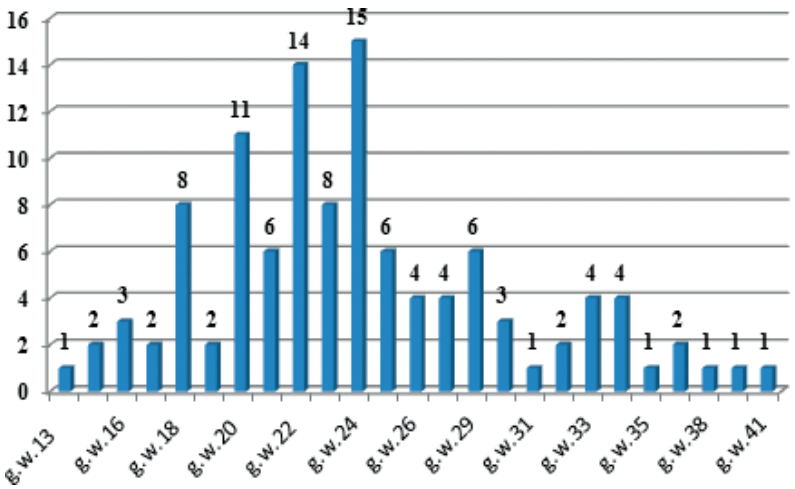

Figure 1. Term of pregnancy termination.

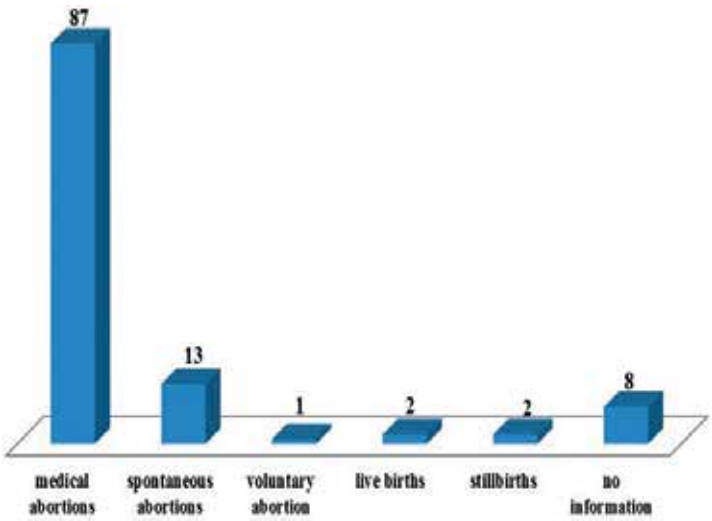

Figure 2. Motives for pregnancy termination.

6. Anthropometric characteristics of the fetuses

Distribution of lethal hydrocephalus by gender (sex ratio). The genders were equally affected, but the mean weight of male fetuses (842.17 ± 115.2) was less than that of female fetuses (892.06 ± 101.1), without the difference being statistically significant ($u = 0.51$, $p > 0.05$).

Age of the fetus. The average pregnancy term in the entire study is 24 ± 0.45 gestational weeks. The fetal expulsion in two-thirds of the cases occurred before the 24th gestational week, with the smallest fetus being 13 gestational weeks (**Figure 1**).

Fetus weight. The average weight of the fetuses is 865.99 ± 809.8 g with a range of 23–3800 g. It is worth noting that 50 fetuses (44.2%) weigh less than the corresponding gestational age.

7. System anomalies of the fetus

The head, extremities, and respiratory system anomalies associated with FHLO are presented in **Table 1**.

The cardiovascular system abnormalities are a total of 32 and are from all groups. The digestive system abnormalities are 56 and are broken down into groups: mesenteric (affecting the small intestine and colon), parenchymal (affecting the liver and spleen), anal imperforation (affecting the terminal part of the intestines), gall bladder agenesis, and situs inversus. The parenchymal and mesenteric abnormalities are evenly distributed. The gender abnormalities are present in both male and female fetuses with a ratio of female to male of 8:7. Hermaphroditism was established in four (3.5%) fetuses. The fatal hydrocephalus-associated anomalies of the cardiovascular, digestive, excretory, and genital systems are presented in **Table 2**.

Association of hydrocephalus with other brain abnormalities. In 85 fetuses (76%), hydrocephalus was associated with other brain abnormalities: polygyria—12 (10.7%); lissencephaly—2 (1.8%); agenesis of corpus callosum—18 (16%); agenesis of the cerebellar vermis—19 (16.9%); diastamatomyelia—1 (0.9%); stenosis of the Sylvian aqueduct—5 (4.4%); holoprosencephaly—1 (0.9%) and cyst of the choroid plexus—2 (1.8%) (**Table 3**, **Figure 4**). The relations between the prenatal and postnatal diagnosis of hydrocephalus-associated brain abnormalities are shown in **Figure 3**.

The hydrocephalus-associated syndromes and malformations are presented in **Table 4**.

Systems	Types of anomalies	Anomalies	*N*/%
Lips, soft and hard palate	Clefts	Cleft lip	6/5.3
		Cleft palate	3/2.7
		Labia palate cleft	4/3.5
		Uvula cleft palate	1/0.9
	Configurations	High palate	25/22.1
	Total		39/34.5
Anomalies of the nose	Configurations	Snub nose	4/3.5
	Agenesia	Arrhinia	1/0.9
	Atresia	Choanal atresia	1/0.9
	Total		6/5.3
Head and limb abnormalities	Head	Macrocrania	70/61.9
	Limb	Curved foot	23/20.4
	Agenesia	Short limbs	13/11.5
	Clinodactyly	Agenesia of finger	6/5.3
	Polydactyly	Finger clinodactyly	28/24.7
	Syndactyly		6/5.3
	Total		9/7.9
			182/161
Anomalies of the respiratory system	Hypoplasia		21/18.6
	Incorrect lobulation		16/14.2
	Hypoplasia and		6/5.3
	Incorrect lobulation		
	Situs inversus		2/1.8
	Liver agenesis		1/0.9
	Total		46/40.7

Table 1. Hydrocephalus-related abnormalities of the head, extremities, and respiratory system.

Most are neural tube defects followed by trisomies and skeletal dysplasias. The VACTERL association has been established in six fetuses (5.3%), four of which were male and two female, and the Dandy-Walker malformation in four fetuses (3.5%) (**Figure 4**).

The Meckel-Gruber syndrome, which is a ciliopathy, was established six times (5.4%). A karyotype study was performed on 23 fetuses (20.5%)—one by fluorescent in situ hybridization (FISH) and the rest by chromosome study. A magnetic resonance tomography (MRI) was performed in three cases.

Systems	Types of anomalies	Anomalies	N/%
Anomalies of the cardiovascular system	Position	Dextroradia	1/0.9
	Organomegaly	Cardiomegaly	2/1.8
	Defects	Atrial septal defect (ASD)	3/2.7
		Ventricular septal defect (VSD)	11/9.7
		Both together	2/1.8
		Tetralogy of Fallot	2/1.8
		Minor form of AV channel of the heart	2/18
		AV channel of the heart	2/1.8
	Stenoses	Aortic valve stenosis	1/0.9
		Pulmonary valve stenosis	1/0.9
	Transposition	Transposition of the great vessels (TGV)	1/0.9
	Isomerism	Isomerism of incoming vessels of the heart	3/2.7
	Hypoplasia	Hypoplastic right heart syndrome (HRHS)	1/0.9
	Total		32/28.3
Digestive system abnormalities	Mesenterial	Common mesentery	1/0.9
		Hemi-mesenter	22/19.5
	Parenchymal	Hepatomegaly	8/7.1
		Splenomegaly	3/2.7
		Hepato-splenomegaly	5/4.4
		Polysplenia	6/5.3
		Accessory spleen	1/0.9
	Imperforations	Imperforate anus	8/7.1
	Agenesis	Gallbladder Agenesis	1/0.9
	Situs inversus		1/0.9
	Total		56/49.5

Systems	Types of anomalies	Anomalies	*N*/%
Anomalies of kidney and urinary tract	Kidneys	Ptosis of the kidney	10/8.8
		Horseshoe kidney	4/3.4
		Agenesis (uni- and bilateral)	8/7.1
		Hydrophoresis	5/4.4
		Tubular necrosis	1/0.9
		Dysplasia	2/1.9
		Cystic dysplasia	6/5.3
	Urinary tract	Pelvicalyceal dilatation	4/3.4
		Megaureter	2/1.8
		Mega-bladder	2/1.8
		Hypoplasia of bladder	3/2.7
		Colovesical fistula	1/0.9
		Agenesis of ureter	5/4.4
	Total		53/46.9
Anomalies of the genitals	Female	Bicornuate uterus	5/4.4
		Ovarian hypoplasia Vaginal Atresia	1/0.9
		Hydrocolpos	1/0.9
			2/1.8
	Male	Hypospadias	4/3.4
		Posterior urethral valve	1/0.9
		Cryptorchism	2/1.8
	Hermaphroditism		4/3.4
	Total		19/16.8

Table 2. Hydrocephalus-related abnormalities of cardiovascular, digestive, excretory, and genital systems.

The degree of hydrocephalus according to the fetopathological study is major hydrocephalus (hydrancephaly; >15 mm)—15 cases (13.3%) and ventriculomegaly (>10 mm)—77 cases (69%). Obstructive hydrocephalus as a result of intraventricular hemorrhage was found in 20 fetuses (17.7%) (**Table 5**, **Figure 4**).

The assessment of the significance of spontaneous abortions, abortions due to medical reasons, stillbirth, and a previous child with malformations as risk factors for the occurrence of hydrocephalus was accomplished by means of a χ^2-analysis (**Table 6**).

The proportion of spontaneous abortion is almost four times higher, and the abortion due to medical reasons is more than four times higher, when compared to other risk factors for FHLO. Hydrocephalus is almost three times more likely to develop in cases of previous stillbirths in the obstetric history and more than two times more likely to occur in the presence

Brain associations	Number of cases	%
Polygyria	12	10.6
Lissencephaly	2	1.8
Agenesis of corpus callosum	18	15.9
Agenesis of cerebellar vermis	19	16.8
Cerebellar hypoplasia	25	22.1
Diastematomyelia	1	0.9
Aqueductal stenosis (stenosis of the aqueduct of Sylvius)	5	4.4
Holoprosencephaly	1	0.9
Choroid plexus cysts	2	1.8
Total	85	75.2

Table 3. Distribution of associated brain abnormalities with lethal hydrocephalus.

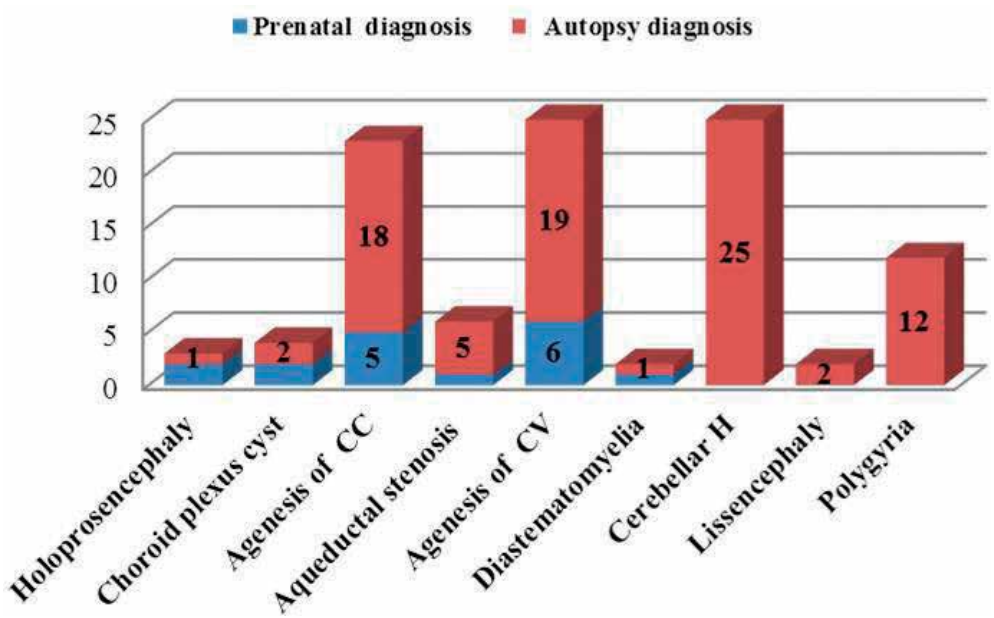

Figure 3. Relations between the prenatal and postnatal diagnosis of hydrocephalus-associated brain abnormalities. Abbreviations: CC, corpus callosum; CV, cerebeller vermis; H, hypoplasia.

of a pre-term birth of a child with a malformation, compared to the studied risk factors. The assessment of the significance of the different degrees of consanguinity in the presence of a child with malformations, epileptic mother, as well as the mother's age is shown in **Table 7**.

The incidence of FHLO is nearly six times higher when it is the result of a consanguineous marriage with a history of a previous pregnancy with a malformation, relative to the presence of hydrocephalus of a non-consanguineous marriage with no such a history. Almost 13 times higher is the incidence of FHLO in cases of maternal epilepsy with a consanguineous marriage of first degree (first cousins), when compared to the proportion of FHLO in a fetus

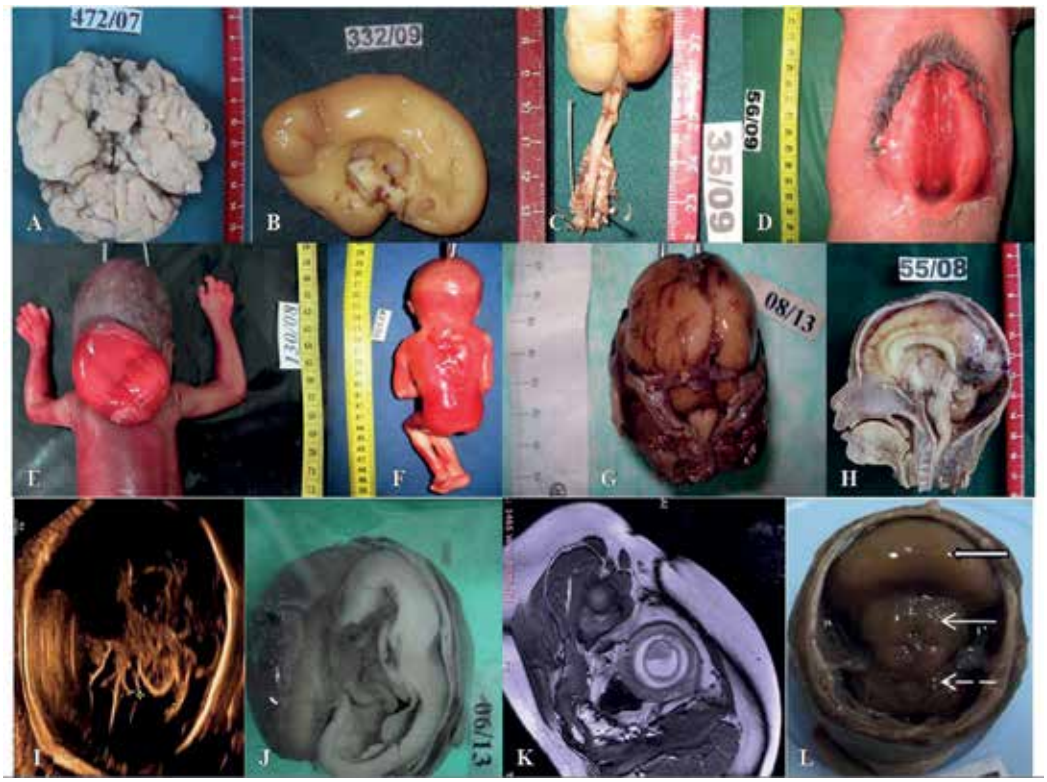

Figure 4. (A) Polygria (inferior view of the brain); (B) Agenesis of corpus callosum (medical view of hemisphere); (C) Extracted brain and spinal cord from the skull and vertebral canal. Split of the cord. Diastematomyelia; (D) Thoraclumbar spina bifidia; (E) Occipital meningo-encephalocele; (F) Rachischisis; (G) Wedging of the cerebellar tonsils through the foramen magnum. Arnold-Chiari malformation; (H) Cystic dilatation of IVth ventricle, elevating of the tentorium, cerebellar hypoplasia. Dandy-Walker malformation; (I) Ventriculomegaly-ultrasound examination; (J) Ventriculomegaly (horizontal section of the right hemisphere); (K) Holoprosencephaly. Fetal MRI; (L) Holoprosencephaly. Fetal autopsy (White-black arrow—hemisphere, white arrow—brain stem, dotted arrow—cerebellum).

carried by an epileptic mother but not from such a marriage. Over four times higher is the proportion of FHLO in cases of consanguinity of second degree, when compared to hydrocephalus influenced by the other studied maternal risk factors. Almost four times higher is the proportion of FHLO with a maternal age between 27 and 35 years compared to other ages, with maternal risk factors present. The rate of hydrocephalus when the maternal age is over 40 years and with consanguinity of third degree is 13 times greater than women over 40 years of age without the risk factor consanguinity. The assessment of the degree of risk of consanguinity, the presence of spontaneous abortion, and the mother's blood group is presented in **Table 8**.

When the mother is from the A(+) blood group and has a consanguineous marriage (giving second-degree consanguinity in the fetus), FHLO has a two times higher incidence than in cases without consanguinity. Around two times higher is the incidence of FHLO, carried by mothers with O(+) blood group and a history of a previous spontaneous abortion,

Types of anomalies	Anomalies	*N*/%
Neural tube defects	Spina bifida	10/8.8
	Myelomeningocele	6/5.3
	Encephalocele	6/5.3
	Meningocele	6/5.3
	Rachischisis	5/4.4
	Total	33/29.2
Chromosomal abnormalities	Trisomy 21	4/3.4
	Trisomy 18	18/15.9
	Trisomy 13	2/1.8
	Trisomy 15	1/0.9
	Trisomy 7 + 2	1/0.9
	Triplodia	1/0.9
	Total	27/23.9
Skeletal dysplasias	Ellis-van Creveld syndrome	1/0.9
	Thanatophoric dysplasia	3/2.7
	Osteochondrodysplasia	1/0.9
	Osteogenesis imperfecta	2/1.8
	Arthrogryposis	3/2.7
	Total	10/9.8
VACTERL association		6/5.3
Dandy-Walker malformation		4/3.4
Other syndromes and malformation	DiGeorge syndrome	1/0.9
	Isomerism	3/2.7
	Meckel-Gruber syndrome	6/5.3
	Fraser syndrome	1/0.9
	Fryns syndrome	1/0.9
	Arnold-Chiari malformation	4/3.4
	Total	16/14.2

Table 4. Distribution of syndromes and malformations associated with lethal hydrocephalus.

compared to the occurrence when there is no such history. The degree of significance of the mother's age for the incidence of polygyria and abortions, obstetric and other risk factors, as well as the blood group for the occurrence of agenesis of the cerebellar vermis are shown in **Table 9**.

According to the degree of hydrocephalus	Number of cases	%
Major hydrocephalus (hydranencephaly)	15	13.3%
Ventriculomegaly	78	69.0%
Hydrocephaly due to intraventricular hemorrhage	20	17.7%
Total	113	100.0%

Table 5. Distribution of data on the extent and origin of hydrocephalus.

Indicators	Groups	Without risk factors		Risk factors		Total		χ^2	Fisher	OR
		N	%	*N*	%	*N*	%		*P*	(CI)
Miscarriage	No	78	78	22	22	100	100.0	21.816	0.000	19.500
	There are	2	15.4	11	84.6	13	100.0			(4.020–94.594)
	Total	80	70.8	33	29.2	11	100.0			
Abortion	No	78	81.3	18	18.8	96	100.0	33.727	0.000	32.500
	There are	2	11.8	15	88.2	17	100.0			(6.817–154.954)
	Total	80	70.8	33	29.2	113	100.0			
Stillbirth	No	79	73.1	29	29.6	108	100.0	6.529	0.011	10.897
	There are	1	20	4	80	5	100.0			(1.169–10.564)
	total	80	70.8	33	29.2	113	100.0			
Baby with malformation	No	76	75.4	26	25.5	102	100.0	6.988	0.008	5.385
	There are	4	36.4	7	63.6	11	100.0			(1.385–18.896)
	Total	80	70.8	33	29.2	113	100.0			

Abbreviations: No, number; CI, confidence intervals; OR, odds ratio; χ^2, chi-square; *P*, sig.

Table 6. Risk factors and lethal hydrocephalus.

The association of FHLO and polygyria is more than three times higher in cases where the mother is over 35 years of age, when compared to cases with a mother's age less than 35 years. More than 2.5 times higher is the incidence of FHLO associated with agenesis of the cerebellar vermis in cases of a mother with a previous abortion, when compared to cases without a previous abortion. In the present study, the incidence of the association FHLO and agenesis of the cerebellar vermis is more than two times higher when exposed to the obstetric risk factors. Almost three times higher is the incidence of the association of FHLO and agenesis of the cerebellum in cases in which the mother's blood group is A(+), when compared to other maternal blood groups. The assessment of the importance of the

Indicators	Groups	No malformation		Baby with malformation		Total		χ^2	Fisher P	OR (CI)
		N	%	N	%	N	%			
Consanguinity	No	74	96.1	3	3.9	77	100.0	9.768	0.002	7.309
	There are	27	77.1	8	22.9	35	100.0			(1.806–29.584)
	Total	101	90.2	11	9.8	112	100.0			
Indicators	**Groups**	**Without epilepsy**		**Epilepsy**		**Total**		χ^2	**P**	**OR**
		N	**%**	**N**	**%**	**N**	**%**			**(CI)**
Consanguinity first degree	No	77	96.1	3	3.9	77	100.0	25.742	0.000	24.667
	There are	7	50.0	7	50.0	14	100.0			(5.189–117.247)
	Total	84	89.0	10	11.0	94	100.0			
Indicators	**Groups**	**Without risk factors**		**Risk factors**		**Total**		χ^2	**P**	**OR (CI)**
		N	**%**	**N**	**%**	**N**	**%**			
Consanguinity second degree	No	71	93.4	5	6.6	76	100.0	4.014	0.045	75.680 (0.872–36.997)
	There are	5	71.4	2	28.6	7	100.0			
	Total	76	91.6	7	8.4	83	100.0			
Maternal age	Others	81	95.3	4	4.7	85	100.0	4.247	0.039	4.203 (0.977–18.601)
	27–35 years	19	82.6	4	17.4	23	100.0			
	Total	100	92.6	8	7.4	108	100.0			
Indicators	**Groups**	**Under 40 years of age**		**Over 40 years**		**Total**		χ^2	**P**	**OR (CI)**
		N	**%**	**N**	**%**	**N**	**%**			
Consanguinity third degree	No	74	97.4	2	2.6	76	100.0	7.447	0.006	18.500
	There are	2	66.7	1	33.3	3	100.0			(1.146–298.547)
	Total	76	96.2	3	3.8	79	100.0			

Abbreviations: No, number; CI, confidence intervals; OR, odds ratio; χ^2, chi-square; *P*, sig.

Table 7. Consanguinity, risk factors, and lethal hydrocephalus.

maternal age for the association of hydrocephalus with trisomies, as well as the mother's blood group for the association of hydrocephalus and agenesis of corpus callosum is presented in **Table 10**.

The rate of FTLO associated with trisomy is more than six times higher when the mother's age is over 38 years of age, than in younger than 38-year-old mothers. Almost three times higher is the share of the association of FHLO with agenesis of corpus callosum in the fetus in cases of O(+) maternal blood group.

Indicators.	Groups	Another group		A+		Total		χ^2	P	OR
		N	%	N	%	N	%			(CI)
Consanguinity first degree	No	63	81.8	14	18.2	77	100.0	4.206	0.04	3.375
	First	8	57.1	6	42.9	14	100.0			(1.010–11.279)
	Total	71	78.0	20	22.0	91	100.0			
Indicators	**Groups**	**Another group**		**O+**		**Total**		χ^2	P	OR
		N	%	N	%	N	%			(CI)
Miscarriage	No	74	74.0	26	26.0	100		4.315	0.038	3.321
	There are	6	46.2	7	53.8	13				(1.022–10.789)
	Total	80	70.8	33	29.2	113				

Abbreviations: No, number; CI, confidence intervals; OR, odds ratio; χ^2, chi-square; *P*, sig.

Table 8. Blood groups, risk factors, and lethal hydrocephalus.

Indicators	Groups	Without polygyria		Polygyria		Total		χ^2	P	OR
		N	%	N	%	N	%			(CI)
Maternal age	≤35	82	92.1	7	7.9	89	100.0	4.894	0.027	4.894 (1.094–13.94)
	≥35	15	75.0	5	25.0	20	100.0			
	Total	97	89.1	12	11.0	109	100.0			
Indicators	**Groups**	**Without agenesis of cerebellar vermis**		**Agenesis of cerebellar vermis**		**Total**		χ^2	P	OR
		N	%	N	%	N	%			(CI)
Abortion	No	83	86.5	13	13.5	96	100.0	4.886	0.027	3.483
	There are	11	64.7	6	35.3	17	100.0			(1.099–1.040)
	Total	94	83.2	19	16.8	113	100.0			
Obstetric risk factors	No	71	87.7	10	12.3	81	100.0	4.432	0.035	2.905
	There are	22	71.0	9	29.0	31	100.0			(1.048–8.052)
	Total	93	83.0	19	17.0	112	100.0			
Risk factors	No	47	90.4	5	9.6	52	100.0	3.898	0.046	3.463
	There are	19	73.1	7	26.9	26	100.0			(0.977–12.274)
	total	66	84.6	12	15.4	78	100.0			
A+ blood group	No	78	86.7	12	13.3	90	100.0	3.830	0.050	2.844
	There are	16	69.6	7	30.4	23	100.0			(0.969–8.342)
	Total	94	83.2	19	16.8	113	100.0			

Abbreviations: No, number; CI, confidence intervals; OR, odds ratio; χ^2, chi-square; *P*, sig.

Table 9. Brain abnormalities, risk factors, and lethal hydrocephalus.

Indicators	Groups	Without trisomy		Trisomy		Total		χ^2	*P*	OR
		N	%	*N*	%	*N*	%			(CI)
Maternal age	≤38	88	90.7	9	9.3	97	100.0	20.518	0.000	13.689
	≥38	5	41.7	7	58.3	12	100.0			(3.952–52.122)
	total	93	85.3	16	14.7	109	100.0			
Indicators	**Groups**	**Without agenesis of corpus callosum**		**Agenesis of corpus callosum**		**Total**		χ^2	*P*	**OR (CI)**
		N	%	*N*	%	*N*	%			
O+ blood group	No	53	86.9	8	13.1	61	100.0	4.441	0.035	3.614
	There are	11	64.7	6	35.3	17	100.0			(1.044–12.510)
	Total	64	82.1	14	17.9	78	100.0			

Abbreviations: No, number; CI, confidence intervals; OR, odds ratio; χ^2, chi-square; *P*, sig.

Table 10. Risk factors, trisomy, agenesis of corpus callosum, and lethal hydrocephalus.

8. Discussion

Currently, prenatal ultrasound is able to visualize ventriculomegaly. Knowledge of the risk factors associated with CH may increase the success of the prenatal ultrasound study. It has been established that a wide range of factors can cause hydrocephalus in animal experiments including alcohol consumption [7], X-ray [8], infections, food disorders, exposure to chemicals [9] and medications taken during pregnancy [10].

Our study is similar to those of Fernell et al., Stoll et al., and Porto et al. which showed that CH was significantly associated with previous abortions, stillbirth, and birth of a child with a malformation [11–13]. Our findings show that the risk of FHLO is increased in cases of previous spontaneous abortions (odds ratio (OR) = 19.500, confidence interval (CI): 4.020–94.594), stillbirth (OR = 10.897; CI: 1.169–10.564), and births of a child with a malformation (OR = 5.385; CI: 1.385–18.896). Pregnancy complications, such as an increase in the amniotic fluid over 1500 ml (polyhydramnios) or a reduction below 500 ml (oligohydramnios), are also considered as potential risk factors for CH [12, 13].

The role of consanguinity is also known for the occurrence of congenital malformations such as hydrocephalus, postaxial polydactyly of the hands, and defects of the lips and palate [13, 14]. In our study, FHLO is significantly associated with a maternal age over 40 years and third-degree consanguinity of the fetus (OR = 18.500; CI: 1.146–298.547). FHLO, previous pregnancies with malformations, and consanguinity are also significantly associated (OR = 7.309; CI: 1.806–29.584). FHLO with agenesis of the cerebellar vermis is significantly associated with the effect of obstetric risk factors (OR = 2.905; CI: 1.048–8.052).

Almost all studies have documented a slightly higher percentage of male fetuses in cases of CH in live births and stillbirths as well as in fetopathologic autopsies [15–18]. Van Landingham et al. did not find a difference in the genders of the children with hydrocephalus compared to the general population [4].

According to the study of Van Landingham et al. in 2009, the mother's age is not associated with CH, unlike the study by Sipek et al. for the period 1961–2000 in the Czech Republic which found that a mother's age over 37 years was significantly associated with CH [4, 6]. Hydrocephalus is significantly associated with a mother's age above 40 years and third-degree consanguinity, and it is 18 times higher compared to women above 40 years of age without consanguinity (OR = 18.500; CI: 1.146–298.547).

In regard to maternal disease, it is known that mothers suffering from diabetes mellitus have a significantly higher risk for giving birth to a child with congenital malformations, especially cardiovascular and neural tube defects [4, 19, 20].

Hydrocephalus is often divided by genetic specialists into a syndromic and non-syndromic form, depending on the presence of associated malformations [21, 22]. Some authors prefer to differentiate hydrocephalus in which the phenotype is characterized mainly with brain malformations and hydrocephalus which is associated with significant physical anomalies and clinical symptoms [23]. In cases with a specific clinical syndrome or genetic changes, hydrocephalus is best to be defined as hydrocephalus associated with the corresponding syndrome.

Some enzyme mutations result in defective neuron connections with the extracellular matrix, abnormal formation of the limiting glial membrane, and disturbances in the neuronal migration [24, 25]. As a result, characteristic brain malformation develops—loss of cerebral gyrification, abnormal white matter of the hemispheres as well as brainstem anomalies (flat pons, enlarged tectum, and curved medulla oblongata), often associated with an aqueductal stenosis and cerebellar cysts. These findings often cannot be found by the prenatal examination, especially in cases of significant ventriculomegaly, making the MRI study essential [26]. In our study, the risk increases almost five times for the association of FHLO and polygyria when the mother's age is above 35 years (OR = 4.894; CI: 1.094–13.94). The association of FHLO and agenesis of the cerebellar vermis is significantly associated with previous abortions (OR = 3.483; CI: 1.099–1.040) and the effect of risk factors (OR = 3.463; CI: 0.977–12.274). Ventriculomegaly is significantly associated with agenesis of corpus callosum, as well as O(+) blood group of the mother, when compared to other blood groups (OR = 3.614; CI: 1.044–12.510). Hydrocephalus may be associated with other brain malformations such as holoprosencephaly, rhombencephalosynapsis, Aicardi syndrome, agenesis of corpus callosum, and periventricular heterotopia [27–31].

Some cytogenetic malformations are associated with hydrocephalus, including trisomy 13, 18, 21, and triploidy [32]. The trisomies in our study were 27 (24.1%) and their occurrence is significantly associated with a mother's age above 38 years (OR = 13.689; CI: 3.952–52.122).

NTD-associated hydrocephalus has a multifactor genesis. Experiments with animals have found that the intrauterine leak age of cerebrospinal fluid causes the Arnold-Chiari type II malformation, which causes an obstruction of the cerebrospinal fluid flow [33, 34]. Genetic mutations responsible for planar cell polarity such as Fuzzy (FUZ), VANGL1, and CELSR1 add to the development of NTDs [35–37]. Other mutations of genes with a relation to planar cell polarity (CELSR2 and MPDZ) may cause hydrocephalus regardless of the presence of NTDs [38, 39]. The specific pathogenetic mechanism is not completely clear, but it is accepted that a disjunction of the ependymal cilia is present [40]. The neural tube defects in our study were 33 (29.4%), with the most common being spina bifida, followed by myelomeningocele, encephalocele, and meningocele.

9. Conclusion

Congenital hydrocephalus with a lethal outcome is the result of a significant number of risk factors and is often associated with other malformations. Therefore, it is important to perform a prenatal ultrasound study in pregnancies with risk factors to diagnose possible CH or other malformations. Currently, the prenatal ultrasound is able to visualize ventriculomegaly and should be directed toward the search of other associated malformations, and when they are suspected, an MRI study and genetic testing must follow. In cases of medical abortion, stillbirth, or neonatal death, a fetopathological study must be carried out which enriches our knowledge of malformations, complements and completes the ultrasound examination, modifies genetic counseling, and determines the behavior to be followed when taking responsibility for a subsequent pregnancy. It is also important to further study the associated risk factors and the fetopathological changes in CH in order to increase the success of the ultrasound prenatal diagnosis.

Author details

Tanya Kitova[1]*, Borislav Kitov[2], Denis Milkov[4] and Aida Masmoudi[3]

*Address all correspondence to: tanyakitova@yahoo.com

1 Department of Anatomy, Histology and Embryology, Medical University of Plovdiv, Plovdiv, Bulgaria

2 Department of Neurosurgery, Medical University of Plovdiv, Plovdiv, Bulgaria

3 University of Tunis—El Manar, Faculty of Medicine of Tunis, Center of Maternity and Neonatology of Tunis, Tunis, Tunisia

4 Medical Faculty, Medical University of Plovdiv, Plovdiv, Bulgaria

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Chapter 5

Congenital Abnormalities of the Fetal Face

Maria Șorop-Florea, Roxana-Cristina Dragușin,
Ciprian Laurențiu Pătru, Lucian George Zorilă,
Cristian Marinaș, Virgiliu-Bogdan Șorop,
Cristian Neamțu, Alina Veduța,
Dominic Gabriel Iliescu and Nicolae Cernea

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Abstract

Even at the early stages of gestation, the fetal face can be examined. There have been observations of the normal anatomy, such as orbits and the forehead, starting with the 12th week of gestation. However, nowadays, ultrasound equipment still cannot distinguish the soft tissues of the face, which are too thin. Yet, after the age of 14 weeks, we can easily examine the forehead, orbits, nose, lips, and ears. Recently, three-dimensional ultrasound (3D) images of the fetus can also be obtained. However, two-dimensional (2D) ultrasonographic (US) images are more easily, rapidly, efficiently, and accurately obtained. At the first stage of embryogenesis, the main part in the development of the fetal face is taken by the genetic factors. Later, the influence of the environment becomes more important. It is known that the outcome of chromosomal aberrations and of teratogenic factors is the facial malformation. Therefore, examining the facial dimorphism may get us useful hints in revealing chromosomal or genetic abnormalities. This chapter focuses on the fetal face anomalies more frequently found while performing the prenatal diagnosis. It is divided into anomalies of the orbits, nose, lip, palate, and mandible.

Keywords: fetal face, facial malformation, ultrasound, prenatal diagnosis, congenital abnormalities

1. Introduction

The study of the fetal face may be performed during the early stages of gestation. Depending on the gestational age, we can identify various elements of anatomy, such as the orbits or the

forehead, from the 12th week. Yet, after that time, we can easily identify and study the forehead, the nose, the lips, the ears, and the orbits of the fetus [1]. Prenatal recognition of facial abnormalities during pregnancy has many benefits. It can lead to the diagnosis of multiple genotypic syndromes and chromosomal anomalies. Also, it allows more adequate counseling and preparation of the parents. Considering that the sonographic assessment of the fetal face is a major part of the anatomic survey of the fetus, sagittal, axial, and coronal planes are used when examining the fetus.

The facial anomalies are divided into nose, orbit, lip, mandible, and palate anomalies. The US method may reveal also benign and less frequent anomalies, for example, lacrimal duct cysts, hemangiomas, and so on.

1.1. Sagittal planes

In order to assess the normality of the fetus profile, sagittal planes of the face are used (**Figure 1**).

One of the US parameters used to obtain an exact measurement of the position of the anterior end of the maxilla to the forehead is the angle between the surface of the palate and the frontal bone examined in a mid-sagittal view of the fetal face, called the frontomaxillary facial angle [2]. This angle is increased in fetuses with trisomy 21, and it is believed that the reason for this is the hypoplasia or posterior displacement of the palate [2, 3].

Ears are well visualized in parasagittal scans tangential to the calvarium. In late gestation, significant details of the anatomy of the external ear can be seen.

1.2. Axial planes

Orbits may be visualized simultaneously, by means of an axial plane, slightly caudal to the one used to measure the biparietal diameter (**Figures 2–4**) [4].

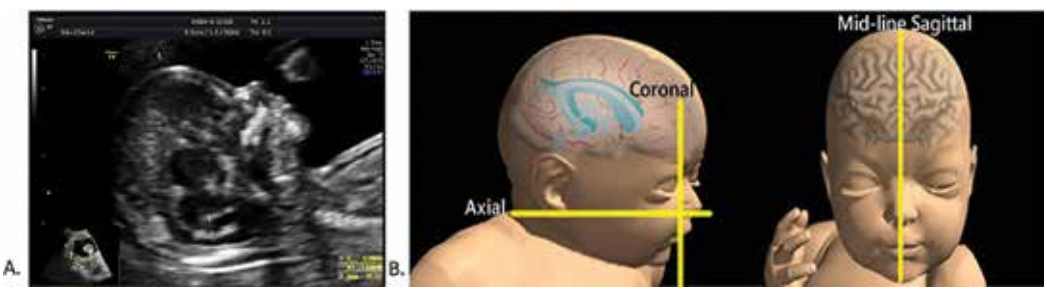

Figure 1. (A). Normal fetal profile at 12–13 weeks. (B). Schematic representation of the scanning planes to be used for obtaining axial and coronal views of the fetal face.

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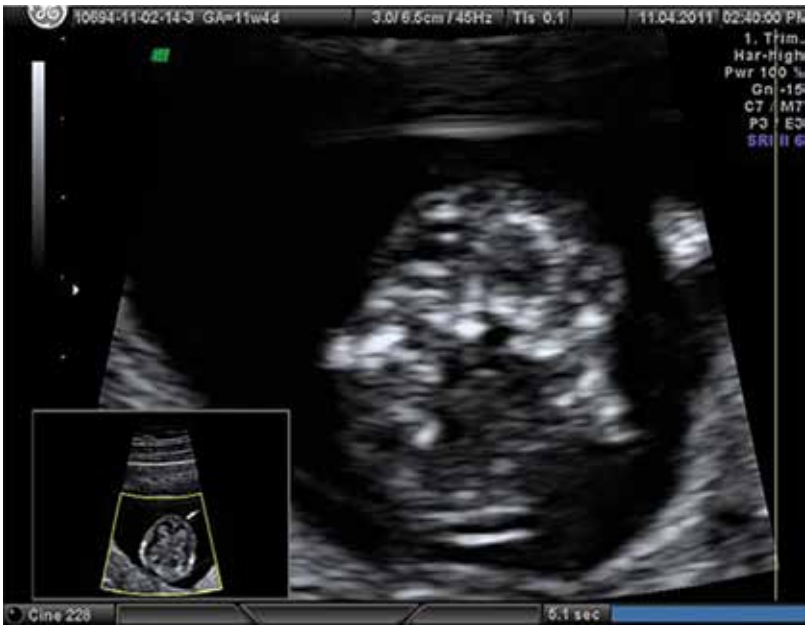

Figure 2. Axial scan passing through the orbits of a normal second trimester fetus.

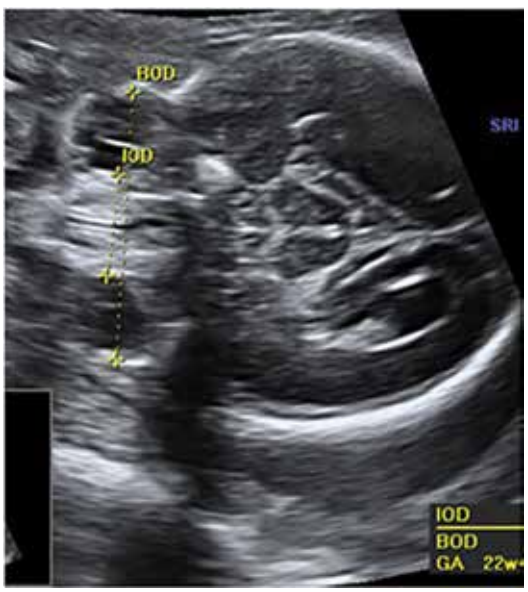

Figure 3. The interocular distance (IOD) and binocular distance (BOD) are demonstrated in this scan. The lens is visible inside the orbit.

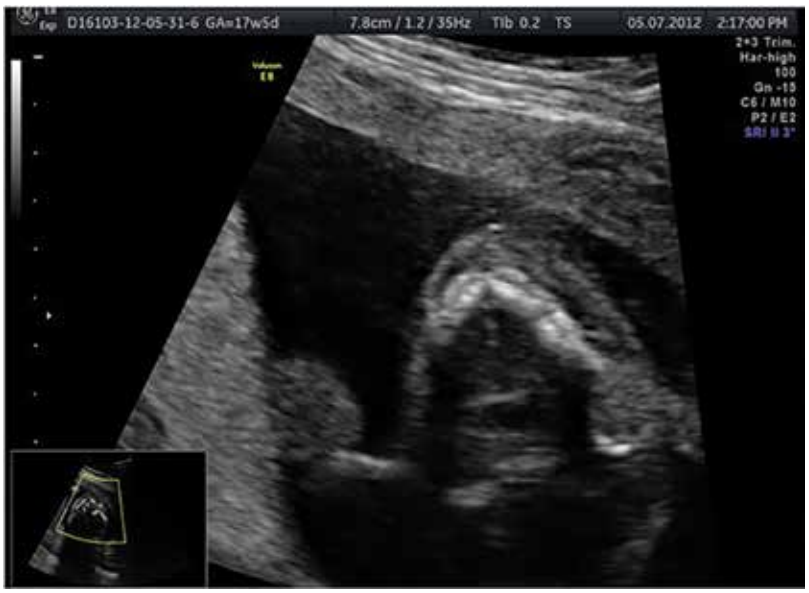

Figure 4. Axial scan of the lower fetal face demonstrating the upper lip and the anterior palate.

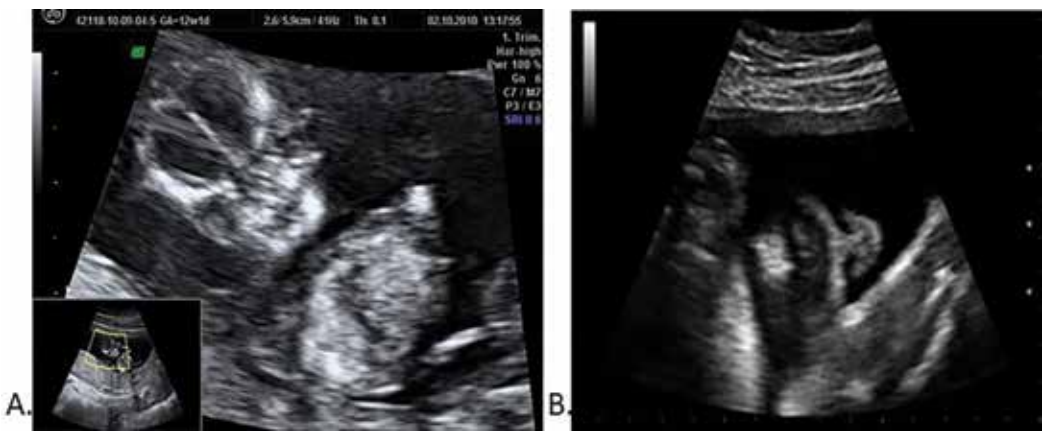

Figure 5. A. Coronal anterior plane in a late first trimester (FT) fetus: The lens inside the corpus vitreum B. The tip of the nose, the alae nasi, and the columna are seen above the upper lip. The nostril typically appears as two little anechoic areas.

1.3. Coronal planes

Evaluation of the integrity of the facial anatomy is assessed by visualizing the eyelids, orbits, lips, forehead, and nose, whose nostrils usually appear as two little anechoic areas. For these features, coronal planes are more important than the previous one (**Figure 5**).

1.4. Fetal face profile

One of the most common "soft sonographic sings" providing essential clues of congenital syndromes [1] is the deviations from the proportions normally found during a sagittal fetal

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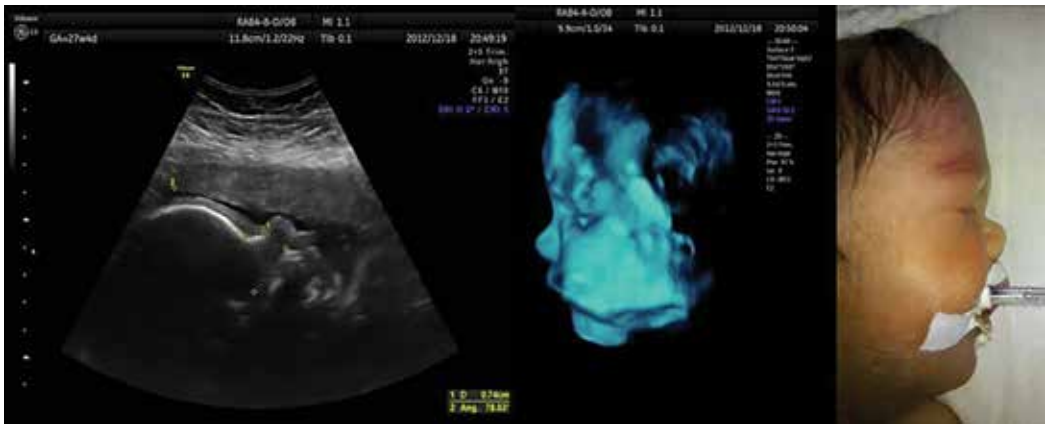

Figure 6. Sonographic pictures of fetal bossing forehead at 24 weeks of gestation. The postnatal aspect of the neonates with bossing forehead.

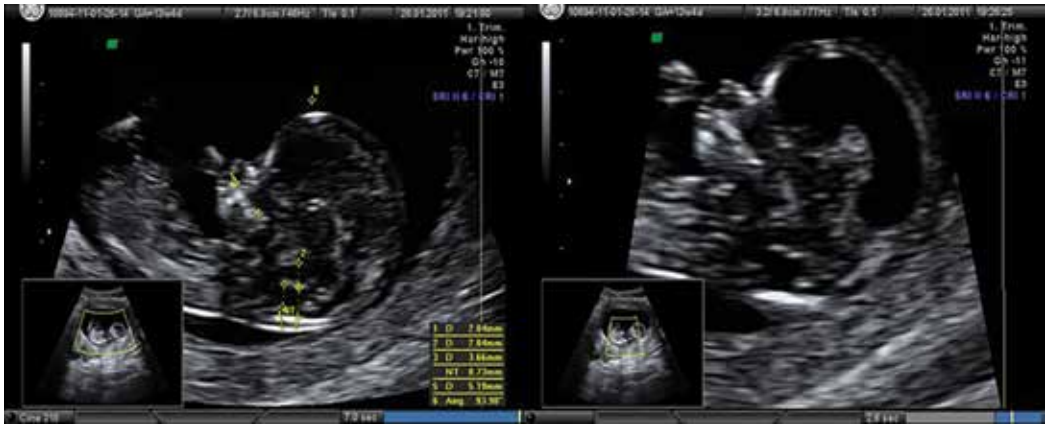

Figure 7. Sagittal scan of a fetus at 13–14 weeks of gestation shows FT bossing forehead.

face examination (**Figures 6**, **7**). Apert or Carpenter syndromes are ruled out by examining the bridge of the nose. [5] The cleft lip is excluded when the normal prominent lips are visible. [1]. As for micrognathia or prognathia, these can be noticed in the subjective abnormal appearance of the jaw [6].

2. The fetal eyes

From the late FT or in the early second trimester onward, we should consider the visualization of the fetal orbit and lens. The orbits will appear as echolucent circles on the upper fetal face, whereas the lens will be visualized inside these structures, as circular hyperechogenic rings. These images can be obtained during almost all scans, beginning with the late first trimester. Any deviation from the relative size might suggest congenital malformations of the orbits and lens. To assess them, coronal and especially axial planes of the fetal head are the best approach.

2.1. Anomalies of the orbits

2.1.1. Hypertelorism

Definition: Hypertelorism is an increased interocular distance.

Embryology and pathogenesis: At the first stage of the development of the human embryo, the eyes are to be found laterally, like in animals with panoramic vision. As the pregnancy evolves, the fetal eyes migrate toward the midline, thus generating the conditions for the stereoscopic vision to develop (**Figure 8**).

There are at least two theories as to why hypertelorism may appear. The first theory states that there are several mechanisms causing it: the forward migration of the first half of the eyes, a midline tumor, meningoencephalocele for instance, causing the second half, or skull bones with abnormal growth vectors. The second theory links a splanchnocranium, which presents an abnormal growth, to the undeveloped bones which derive from the first branchial arches [8].

Pathology: Three parameters are used to measure the fetuses' ocular spacing: interpupillary distance, canthal distance, and interorbital distance. Hypertelorism is bilateral most of the times, with little incidents of unilateral cases associated with plagiocephaly and proboscis lateralis. Also, this condition is either isolated or accompanied by other malformations or clinical syndromes such as the median cleft syndrome and craniosynostoses. In craniosynostoses, hypertelorism syndromes such as Apert, Crouzon, and Carpenter are usually present [9].

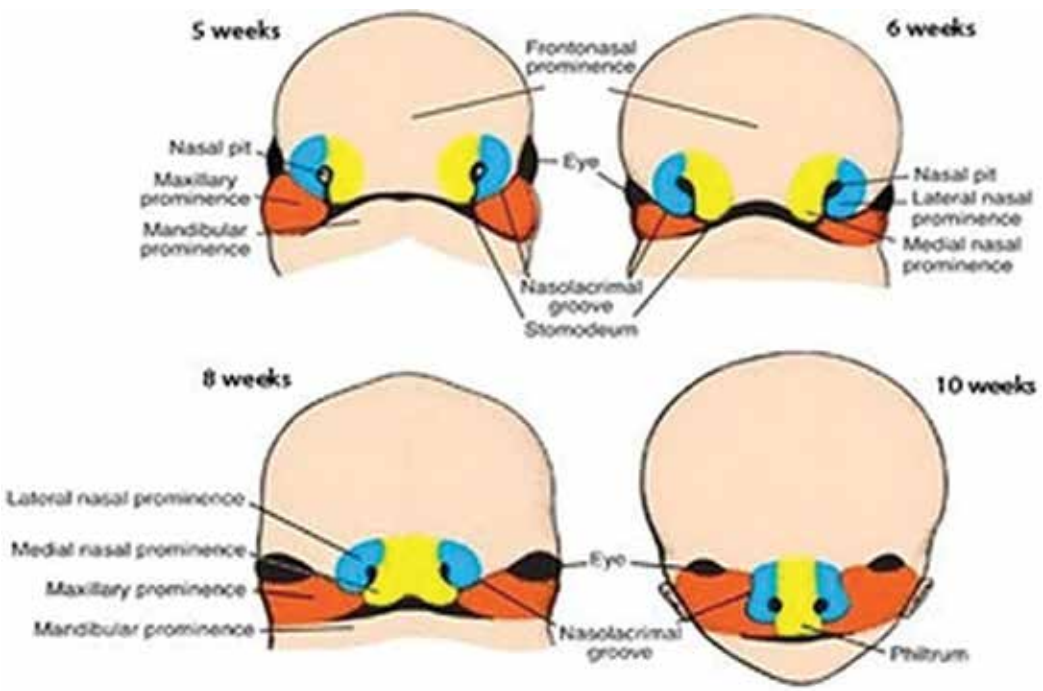

Figure 8. The facial structures development, represented schematically between the 5th and the 10th week of gestation. During the early stages, we can notice the primitive eyes on both sides of the cephalic pole. However, they move toward the median line as gestation goes on [7].

Ultrasound diagnosis: Interorbital diameter is larger than 95th. The accuracy of ultrasound exam in the hypertelorism diagnosis has not been established.

Investigations: Detailed ultrasound examination for associated defects. Invasive testing for karyotyping and array.

Follow up: Standard follow-up in isolated cases. Any underlying syndrome antenatal care should be adjusted, considering the additional risk of the condition.

Delivery: Standard obstetric care and delivery.

Isolated: It is good, even if there might be esthetic implications in severe cases as well as impaired stereoscopic binocular vision. For these cases, there are several operative procedures such as canthoplasty, orbitoplasty, surgical positioning of the eyebrows, and rhinoplasty.

Syndromic: The prognosis of hypertelorism is usually poor, and it does have a risk of mental retardation. However, normal life span and normal intellect are to be expected in the case of medial facial cleft syndrome [8]. The esthetic aspect should not be underestimated.

Recurrence: Isolated: no increased risk of recurrence.

2.1.2. Hypotelorism

Definition: Hypotelorism is a decreased interorbital distance.

Prevalence: 1 in 20,000 births.

Etiology: Hypertelorism is almost always associated with other severe abnormalities, especially with the sequence of holoprosencephalic abnormality.

Embryology and Pathogenesis: Out of the mesenchymal mass there comes the craniofacial skeleton. This mass has two points of origin: the mesoderm and the neutral crest, the latter migrating to the region. The development of the median facial structures (forehead, nose, interorbital structures and upper lip) is closely linked to the forebrain differentiating process. It is possible that these two development steps are induced by the tissue, which lies between the prosencephalon and the stomodeum (the root of the primitive mouth), namely the prechordal mesenchyma. Thus, defects of the facial midline, for example, hypotelorism, are often linked to cerebral abnormalities, most often with holoprosencephaly. Hypotelorism can be found in association with trigonocephaly, microcephaly, Meckel syndrome and chromosome aberrations [10, 11].

Ultrasound diagnosis: It is based on the documentation of a reduced interocular distance. The interorbital diameter is lower than <5th and, together with the almost always present holoprosencephaly (**Figure 9**), is to be found among the midline migration defects; in this case, the hypotelorism can be extreme, as in cyclopia [10].

Associated abnormalities: In half of the cases, we encounter chromosomal defects, especially trisomy 13, as well as genetic syndromes [9].

Investigations: A thorough ultrasound examination should be conducted, including neurosonography, in order to find associated defects as well as invasive testing for karyotyping and array.

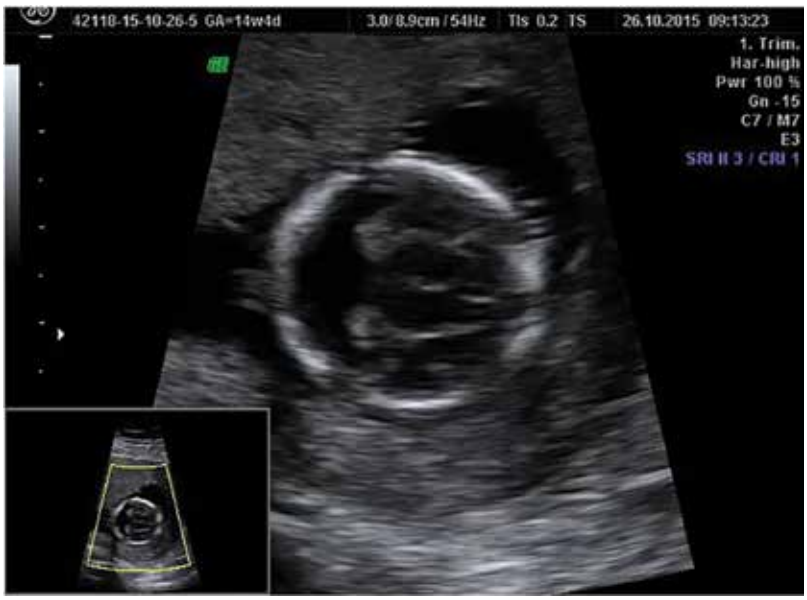

Figure 9. Axial scan a fetus at 14–15 weeks with alobar holoprosencephaly.

Prognosis: The prognosis and the management are decided on the accompanying malformations. Usually, the prognosis is poor, with high levels of mortality. In cases with normal karyotype, there is a high risk of mental retardation, depending on the degree of holoprosencephaly.

Recurrence: Isolated: no increased risk. One percentage risk of trisomy and 13.25% risk of being part of an autosomal recessive condition [11].

2.1.3. Microphthalmia/Anophthalmia

Definition: Microphthalmia refers to the decreased size of the eyeball, whereas anophthalmia refers to absence of the eye. However, the pathologist should demonstrate not only the absence of the eye but also of the optic nerves, chiasma, and tracts.

Prevalence: While it is difficult to define, it accounts for 1 in 20,000 births, and for 4% of the cases of congenital inheritable blindness.

Etiology/Pathology: Microphthalmia is usually associated with other anomalies. Microphthalmia is either as a sporadic disorder or as a condition inherited with an autosomal dominant, recessive, or X-linked pattern. We use the term "cryptophthalmia" to define fused eyelids, a condition often associated [9, 10].

Ultrasound diagnosis: Microphthalmia and anophthalmia can be unilateral or bilateral. Diagnosis can be suspected by demonstrating an orbital diameter below the fifth percentile for gestational age (**Figure 10**). If the diagnosis is suspected, a thorough search for associated anomalies (microtia, micrognathia, syndactyly, camptodactyly, median cleft, feet abnormalities, such as rocker bottom and talipes, hemivertebrae, and congenital heart defects) should be performed.

Figure 10. This picture shows a case of anophthalmia, prenatal and postnatal aspects.

Associated abnormalities: Chromosomal defects, especially trisomy 13, are found in more than 50% of the cases. The most common include: Goldenhar syndrome (1:3000 births), Fraser syndrome, Fryns syndrome and Meckel-Gruber [9].

Investigations: Besides detailed ultrasound, karyotyping and array should be offered. Also, a fetal brain MRI may be useful to diagnose abnormalities (e.g., the absence of the optic nerve).

Prognosis and obstetrical management: Isolated: good, with an altered life quality because of the esthetic aspect of the lesion: plastic surgery might be considered. Syndromic: prognosis is very poor. Management depends on the specific syndrome [11].

Recurrence: Isolated: no increased risk. Part of an autosomal recessive condition: 25%.

2.1.4. Dacryocystocele

Definition: Dacryocystocele is a congenital obstruction of the nasolacrimal duct, resulting in cystic dilatation of the proximal part of the duct. (**Figure 11**).

Prevalence: 1 in 4000.

Ultrasound diagnosis: Cyst (75% unilateral and 25% bilateral) between the lower part of the orbit and the nose. About 90% of the cases are due to delayed canalization of the lacrimal duct beyond 32 weeks gestation.

The differential diagnosis: includes an anterior cephalocele, hemangiomas, and dermoid cyst. Usually, hemangiomas have a solid appearance or multiple septae, and they are shown as exophytic lesions with an echogenicity, similar to the placenta. Among the complications of hemangiomas, we should include ulceration, bleeding, infection, and scar formation. The dermoid cysts have often a superolateral location. It is difficult to differentiate anterior cephaloceles from these lesions. If hydrocephaly is present, we should suspect a cephalocele [12, 13].

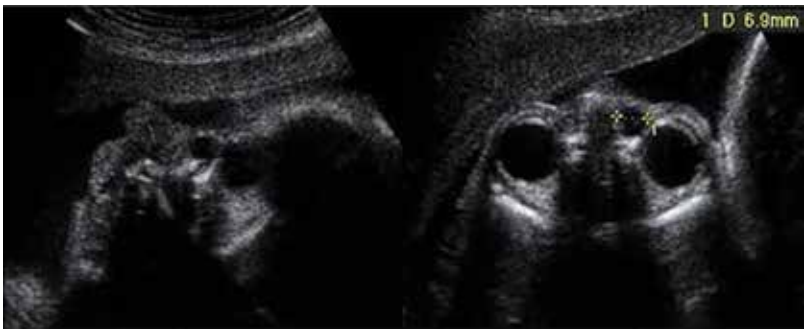

Figure 11. Ultrasonographic aspect of the congenital dacryocystocele.

Associated abnormalities: Not associated with chromosomal or other abnormalities.

They resolve spontaneously in 78% of the cases by 3 months, 91% by 6 months, or during the third semester.

2.1.5. Cyclopia

Definition: Cyclopia is another type of anomaly, in which the fetus has only one single orbital fossa, with bulbs, eyelids and lacrimal apparatus fused to a variable degree. In many cases, there is one single eye or one partially divided eye, in a single orbit and arhinia with proboscis (**Figure 12**), [14, 15].

Incidence: Cyclopia results from the incomplete cleavage of the prosencephalon into right and left hemispheres, a process which should be occurring between the 18th and the 28th day of pregnancy, and it is a lethal human malformation, relatively complex, but also quite rare. Moreover, holoprosencephaly occurs in 1/16,000 live births [16].

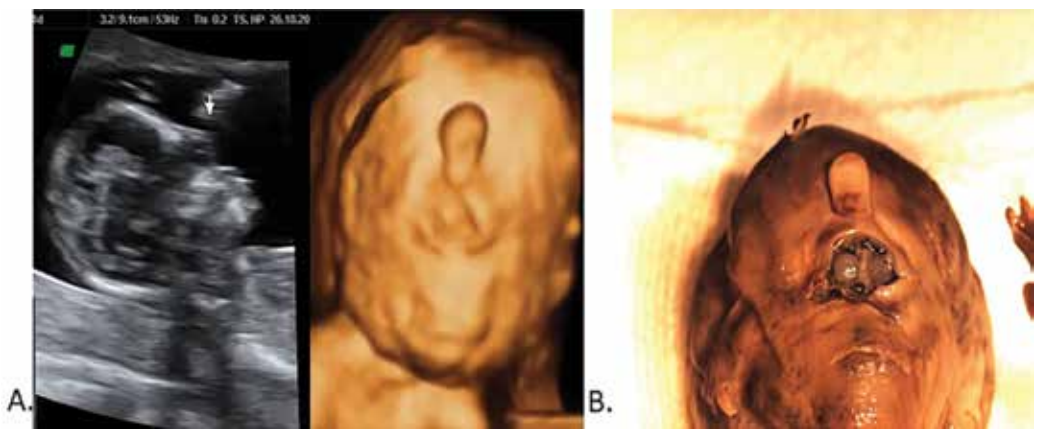

Figure 12. A. Axial and sagittal scans of a fetus at 15 weeks of gestation show cyclopia and proboscis. B. Ethmocephaly—Postmortem demonstrating hypotelorism and proboscis.

The etiology of this rare syndrome incompatible with life is still not known in detail, because most cases are sporadic, even if the implication of heterogeneous risk factors has been proven. Among risk factors, we include maternal diabetes (the only formally recognized environmental factor, with a 1% risk and a 200-fold increase in fetal holoprosencephaly), infections during pregnancy (TORCHs), active drugs during pregnancy physical agents (ultraviolet light), and chromosomal (mostly trisomy 13) and genetic causes (familial occurrences in twins and in consanguineous marriages [17].

In order to get **the differential diagnosis** of these cases, we must distinguish between ethmocephaly and cebocephaly. In other words, we must be able to trace extreme hypotelorism, arhinia and blinded proboscis located between the eyes as opposed to hypotelorism and a single nostril nose without midline cleft. In case the image shows united palatine and lacrimal bones, as well as no sign of nasal bones, maxilla and nasal septum, then the diagnosis is ethmocephaly [15].

2.1.6. Cataracts

Definition: any opacity of the eye lens.

The incidence of cataract is as follows: 1–6 newborn infants every 10,000 births [18] for congenital cataracts in newborn babies, whereas 8.3–25% is considered to be inherited.

Etiology: There are several ways in which a fetus might inherit congenital cataracts: autosomal dominant, autosomal recessive, or X-linked fashion. However, the most frequent and the strongest penetration is the autosomal dominant. A series of other complications are associated with cataracts: genetic syndromes, congenital infections, metabolic disorders, and chromosomal abnormalities. The genetic cause is present in 30% of the unilateral cataracts and in 50% of the bilateral ones [19].

During the examination of the fetal cataracts solid, either some echogenic discs or echogenicity areas within an echolucent orbit will be noticed (**Figure 13**), having either unilateral or bilateral

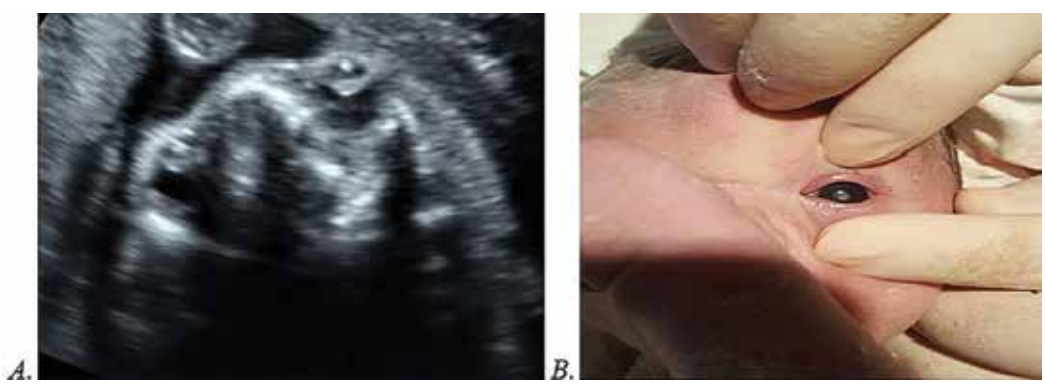

Figure 13. A. Sonographic pictures of fetal cataracts at 24 weeks of gestation. Coronal views of echogenic lens. B. The postnatal aspect of the lens.

opacity of the lens. Usually, the bilateral lesions are generally syndromic, with a poor prognosis; as for unilateral lesions, they are generally linked to a fetal infection. The genetic aspect of cataracts can be linked to microphthalmia.

Associated abnormalities: there is not any high risk of chromosomal abnormalities. It is in only 10% of the cases that genetic syndromes are found, and these include the chromosomal defects. In about 10% of the cases, genetic syndromes are found, and the most common include: Walker-Warburg syndrome and chondrodysplasia punctata. Only a fifth of the congenital cataracts cases are linked to infections such as rubella, toxoplasmosis, or CMV [20].

Investigations: ultrasound, karyotyping, array and TORCH.

Prognosis: Usually good for isolated cases. Postpartum ophthalmologic surgeries have good results, which do not affect the quality of life. Prognosis is quite poor for syndromic cataract, though.

3. The ear

The most frequent clinical characteristic in diagnosing the Down syndrome has been the short ear length. Sonographic studies implied that measurements of the short ear length could be a useful predictor of fetal anomalies. In late gestation, important details of the anatomy of the external ear became accessible. In good conditions for scanning, and using high-resolution systems, the helix, scaphoid fossa, triangular fossa, concha, antihelix, tragus, antitragus, intertragic incisure, and lobule are sometimes visualized [21].

4. The nasal bone and nostrils

A small nose is very commonly seen during postnatal examination of fetuses or neonates who also present trisomy 21 as well as for more than 40 other genetic problems. The nasal bone can be measured using a mid-sagittal profile for normal singleton fetuses between the 14th and 34th week of gestation. Thus, the length of the nasal bones increase from 4 mm at 14 weeks to 12 mm at 35 weeks gestation. A possible improvement in screening for trisomy 21 by examining the fetal nasal bone with ultrasound at 11–14 weeks of gestation has been considered [22].

4.1. Anomalies of the nose

4.1.1. Arhinia

Definition: Absence of the nose.

Etiology: Unknown. It can either be an isolated malformation or be part of a malformation complex, such as holoprosencephaly or mandibulofacial dysostosis (Treacher Collins syndrome) [23].

Embryology: Around the 6th week of gestation, the primitive nasal and oral cavities communicate freely using an opening, which will close progressively when the palate starts developing.

When the lateral palatine processes fuse with the nasal septum in the middle, the oral and the two nasal cavities are formed and separated; this takes place around the 12th week of gestation. The external nose starts at the lower portion of the frontonasal prominence, merging on both sides with the maxillary processes (**Figure 9**). If the frontonasal prominence does not fully develop, the result is partial or complete nasal aplasia. This anomaly is part of a more complex spectrum of midfacial defects, which, in the holoprosencephalic sequence, are considered to appear from a primitive defect of the prechordal mesenchyma, the tissue responsible for the induction of both facial and cerebral structures [24, 25].

Prognosis depends on the associated anomalies; however, isolated arhinia is not life incompatible.

4.1.2. Proboscis

Definition: A proboscis is a trunk-like appendage, with one or two internal openings, and it is usually associated with the absence of the nose.

Incidence: Cyclopia and cebocephaly, two of the main conditions for a proboscis to be present, occur in 1:40,000 and 1:16,000 births, respectively [26].

Embryology: The presence of a proboscis is frequently associated with holoprosencephaly. Apparently, a primary disorder in the prechordal mesenchyma develops into an abnormal induction of the midfacial structures. If the nasal prominences develop abnormally, this may lead to a fusion of the olfactory placodes and to the formation of a proboscis [27].

Pathology and associated anomalies: Usually there is a single central opening in the proboscis, and it does not have any connection to the choanae. The ethmoid, the nasal conchae, and the nasal and lacrimal bones are absent. Usually, in cyclopia, ethmocephaly, and cebocephaly, the cleft of the lip and the palate are absent. The presence of a proboscis is seldom found in the absence of holoprosencephaly. In rare cases, a bilateral proboscis can be noticed [28].

Diagnosis: The diagnosis relies on the demonstration of a trunk-like structure, usually with a single central opening either occupying the normal position of the nose or hanging above the orbits [29] (**Figure 8**).

5. The tongue

Fetal macroglossia and microglossia are associated with several chromosomal defects.

5.1. Macroglossia

Prevalence: Depends on the underlying disorder (present in 97.5% of Beckwith-Wiedemann syndrome cases: incidence 0.73:10,000 live births, congenital hypothyroidism: incidence 2.5:10,000 live births) [30].

Etiology: If it is isolated, it is usually sporadic and it relates to the underlying disorder; there have been only two families with autosomal dominant transmission.

Pathogenesis: In cases of Beckwith-Wiedemann syndrome, it is part of the generalized visceromegaly probably secondary to fetal hyperinsulinism. The most common cause of Beckwith-Wiedemann syndrome is the uniparental paternal disomy, a result which was found using 11p15.5 markers. It is the same region in which the code for insulin-like hormones is found [30].

Diagnosis: Considering the imaginary line between the mandible and the maxilla on the sagittal scanning plane, the diagnosis is confirmed by the protruding tip of the tongue past that line; if we consider the axial scan, the diagnosis is confirmed by the protruding tip of the tongue past the lower lip.

Associated anomalies: It is diagnosed by prenatal ultrasound in cases of Beckwith-Wiedemann syndrome, in association with hydramnios (due to impaired fetal swallowing and possibly to increased urine production), omphalocele, nephromegaly, gigantism (sometimes hemihypertrophy), hepatomegaly, genital anomalies, cystic adrenal glands, and heart defects. In the absence of an omphalocele, a careful search for markers of trisomy 21 is indicated [31].

6. Anomalies of the lip and palate

Facial cleft

Synonyms: The Cleft lip and the cleft palate.

Definition: This term refers to a wide spectrum of lateral clefting defects, usually involving the upper lip (**Figure 14**), the palate (**Figure 15**) or both.

Incidence: Facial clefting is the second most common congenital malformation, around 13% of all anomalies. It is usually encountered in 1 in 1000 live births; however, it can be higher for fetuses, many of them having other malformations as well. The occurrence of the cleft palate is 1 of 2500 white births, cleft lip being more common to boys, and cleft palate being more

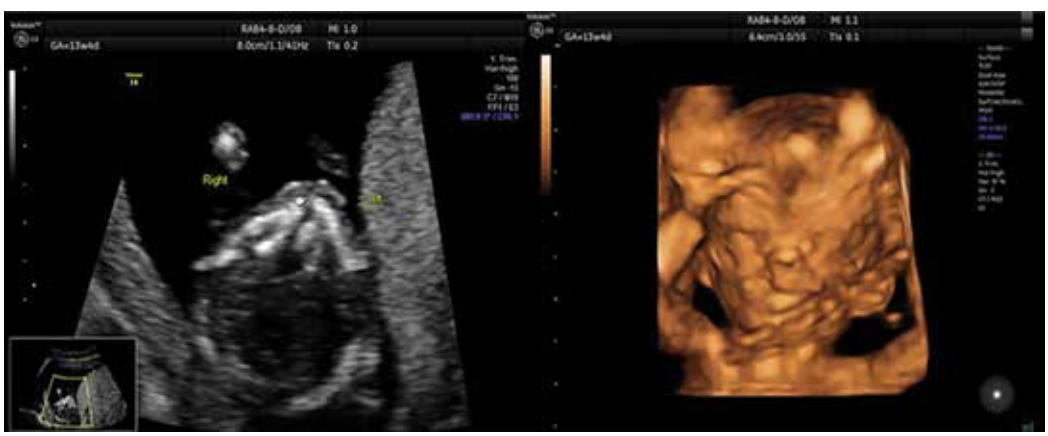

Figure 14. 2D and 3D ultrasonographic pictures of cleft lip.

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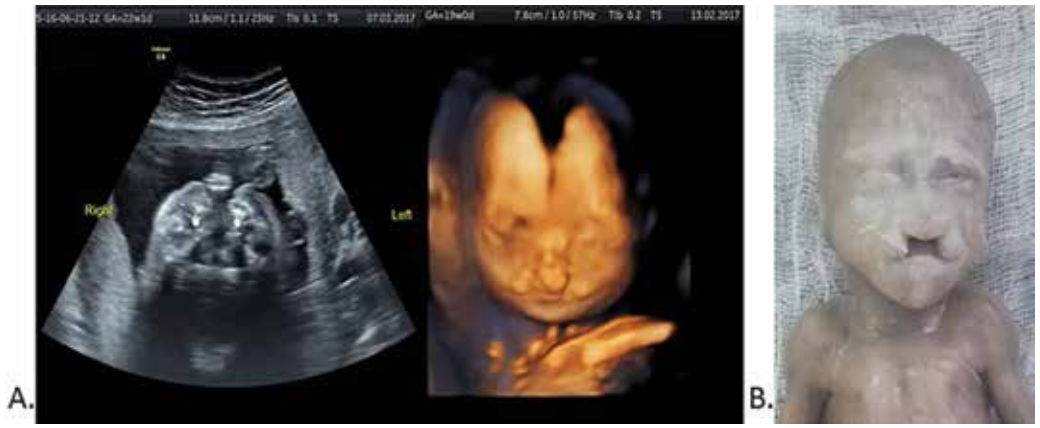

Figure 15. A. Sonographic pictures of the bilateral cleft palate (22 weeks of gestation). B. The postnatal aspect of the cleft palate.

common to girls. In 50% of cases, both the lip and palate are affected, in 25% only the lip and in 25% only the palate. The condition is unilateral in 75% of cases (more common on the left side) and bilateral in 25% [1, 32].

Etiology: The cleft lip is one or more splits (clefts) in the upper lip, ranging from a small indentation in the lip to a split in the lip, which may extend up into one or both nostrils. In the clear majority of patients, the cleft lip (CL) and the cleft palate (CP) have a multifactorial etiology, including genetic and environmental factors. CL (with or without CP) and isolated CP are two different anomalies. CL-CP and isolated CP can be noticed as a component of a well-defined syndrome in 3% of the cases (syndromic) and in 97% of cases (nonsyndromic). CL-CP can develop either as a result of a multifactorial defect or the combination of an autosomal dominant with incomplete expressivity and penetrance (25%) or a sporadic disorder (75%). If the affected parent is the mother, the recurrence risk is decreased, and if it is the father, the recurrence risk is increased. The opposite is true for CL-CP. Chromosomal abnormalities are present in less than 1% of clefting abnormalities [33].

Embryology: The cleft lip results from the persistence of the grooves between the frontonasal, maxillary, and mandibular prominences and develops in about the 6th to 8th week of gestation, when the structures of the upper jaw do not fuse properly and the upper lip does not completely merge. The formation of the cleft is due to the collapse of the mesenchymal tissue under the groove [12]. At times, usually between the 7th and the 12th week of gestation, the cleft palate bones and tissues do not join totally during fetal growth. This leads to the nasal cavity, palate and upper teeth to be affected by the roof of the mouth that remains opened. The cleft palate varies in severity and type according to the place on the palate where the cleft occurs and whether the layers of the palate are affected completely. Sometimes, if some tissues cover the cleft, a milder form of cleft palate will not be visible. A more severe form of the cleft palate, the complete one, involves tissues from all layers of the soft palate, encompasses the hard palate as well, and it might continue to the lip and nose. From time to time, the cleft palate problems also include deformities of the nasal cavities [33].

Pathology: Facial clefts encompass a large spectrum of severity, from minimal defects, such as a bifid uvula, linear indentation of the lip, or submucous cleft of the soft palate, to large, deep, defects of the facial bones and soft tissues (**Figure 16**).

Diagnosis: To set a diagnosis, both transverse and coronal planes can be used. The accuracy of ultrasound in detecting small lesions has not been established; however, color Doppler might be useful to demonstrate the flow across the palate in the case of the cleft palate. Diagnosis of isolated cleft palate is difficult. Diagnosis of the cleft lip and palate at 11–13 weeks gestation can be obtained using axial planes at the level of the bony palate. In rare cases, the retronasal triangle in a coronal view and the maxillary gap in the standard mid-sagittal view of the face may be helpful [35].

Associated anomalies: There have been found associated anomalies in 50% of the patients with isolated CP and 13% of those with CL-CP In cases of isolated CL or CP, the most frequent anomaly is clubfoot, whereas in cases of CL-CP, it is polydactyly. It is particularly important to notice the association with congenital heart disease [36].

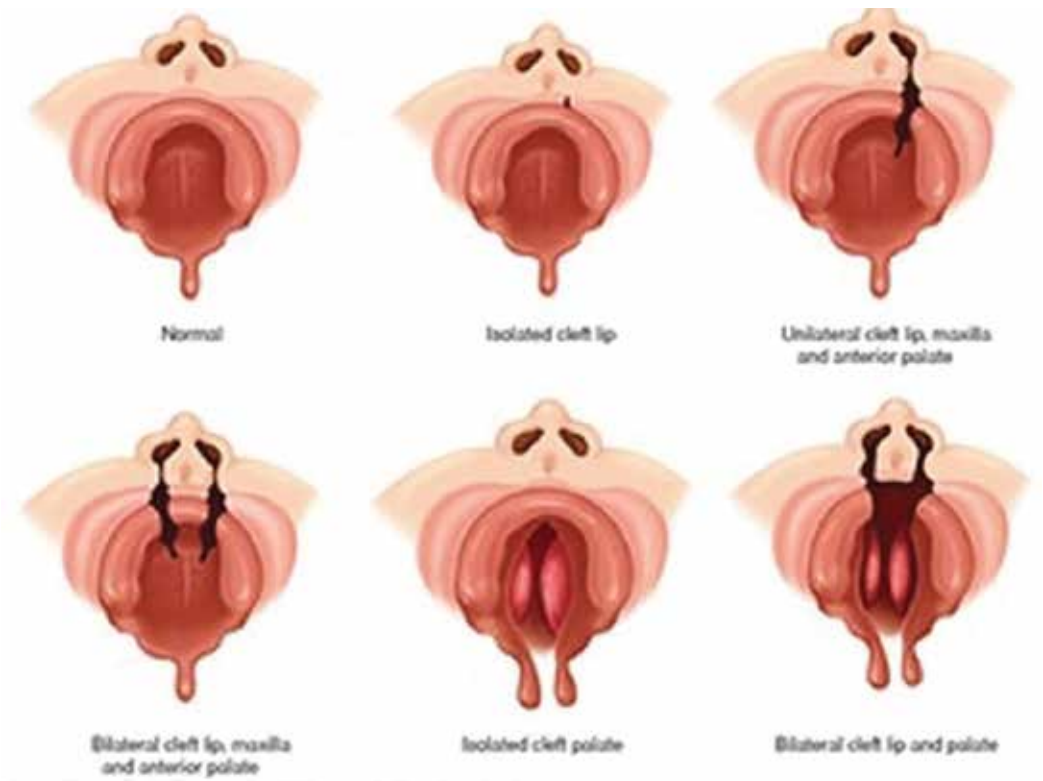

Figure 16. Schematic representation of various types of the cleft lip and the cleft palate. (A) Normal, (B) Isolated cleft lip, (C) Unilateral cleft lip, maxilla and anterior palate, (D) Bilateral cleft lip, maxilla and anterior palate, (E) Isolated cleft palate, and (F) Bilateral cleft lip and palate [34].

Prognosis: If the defects are minimal, as is the case with the lineal indentations of the lips or submucosal cleft of the soft palate, surgical correction may not be required. If the defects are larger and cause esthetic, swallowing, and respiratory problems, then surgical correction is a must, and recent advances in surgical techniques have had good results. Anyhow, the prognosis depends primarily on the presence and type of associated anomalies [37].

The advisability of karyotype is controversial due to the low incidence of chromosomal anomalies in clefting defect. Fetuses should be delivered in a tertiary center because of the possibility of respiratory and feeding problems.

6.1. Median cleft lip

Synonyms: Complete median cleft lip, pseudomedian cleft lip, and premaxillary agenesis.

Definition: A quadrangular or triangular median defect of the upper lip, which could extend to the posterior of the nose (**Figure 17**) [38].

Incidence: Median cleft lip (MCL) is noticed in 0.2–0.7% of all cases of the cleft lip [39].

Embryology: The maxillary prominences are joined by the frontonasal prominence, from where the maxilla and the median region of the upper lip start (**Figure 9**). It is the exact area which is left underdeveloped or absent in the median cleft lip cases. There is a strong link between the development of the midline facial structures and the process by which the forebrain is differentiated. The prechordal mesenchyma, the tissue interposed between the prosencephalon, and the roof of the primitiva mouth (stomodeum) are likely to induce both events [40]. Cerebral anomalies, such as holoprosencephaly, are often linked with the midline abnormalities of the face.

Etiology and pathology: MCL is described only as part of two distinct syndromes: MCL with orbital hypotelorism, in itself a synonym for holoprosencephaly, and MCL with orbital hypertelorism. In the former case, the premaxillary bone, nasal septum, nasal bones, and crista galli

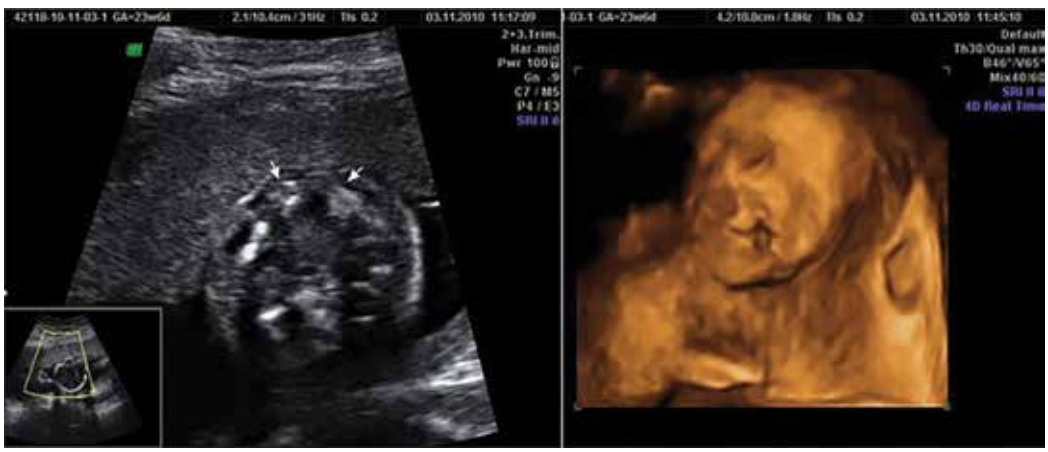

Figure 17. Axial scan of the median cleft lip.

are absent. The ethmoid bone (that set the interorbital distance) is hypoplastic. The secondary palate may or may not be involved. MCL with hypertelorism (also known as "median cleft face syndrome" or "frontonasal dysplasia") is characterized by the presence of a bifid nose and cranium bifidum occultum, as well as of the premaxilla, while the brain is normal in most cases.

Diagnosis: The defect, involving both the upper lip and the palate, is better seen in axial scans of the palate (**Figure 17**). A useful hint in this process is the visualization of the tongue in a position within the oral cavity, which is higher than normal. The sonographer should be alerted to a possible pitfall in the diagnosis of MCL because sometimes the defect may be masked by the tongue, giving a false impression of an intact palate [41].

Prognosis and obstetrical management: Prognosis depends entirely on the association with other anomalies. MCL syndrome is associated in 80% of cases with normal intelligence. Radical cosmetic surgery is required. If alobar holoprosencephaly present, it is uniformly lethal [42].

6.2. Epignathus

Definition: A teratoma that arises from the oral cavity or pharynx.

Incidence: 2% of all pediatric teratomas occur in the nasopharyngeal area (including oral, tonsillar, and basicranial areas). The majority of cases occur in newborn [43, 44].

Pathology: Tumors arise mainly from the sphenoid bone; they rarely arise from other areas (the hard and soft palate, the pharynx, the tongue, and jaw). These tumors grow into the oral or nasal cavity or intracranially. Obstruction of the mouth is responsible for polyhydramnios. Most tumors are benign, consisting histologically of tissues derived from any of the three germinal layers. They can fill the mouth and airways and lead to acute asphyxia immediately after birth [44].

Ultrasound diagnosis: Solid tumor arising from the sphenoid bone, hard and soft palate, the pharynx, the tongue, and the jaw. The tumor may grow into the oral or nasal cavity or intracranially. Calcifications and cystic components may also be noticed. The differential diagnosis will include neck teratomas, encephaloceles, conjoined twins, and other tumors of the facial structures. Polyhydramnios (due to pharyngeal compression) is usually present.

Associated abnormalities: This is a sporadic condition, with no increased incidence of chromosomal defects or genetic syndromes; only 6% of these tumors have associated anomalies, and the facial ones being attributed to the mechanical effects of the tumor on developing structures [45].

Investigations: Scans every 4 weeks to monitor the growth of the tumor and assess the amniotic fluid. If polyhydramnios develops, amniodrainage may be balanced. Fetal MRI is recommended at 32 weeks to assess the spatial relation of the tumor to adjacent structures.

Prognosis: It depends on the size of the lesion and the involvement of vital structures. The lesions are usually very large, and the polyhydramnios associates a poor prognosis. The major cause of neonatal death is asphyxia due to airway obstruction. Surgical resection is possible at times. There are no reported cases of malignancies [46–49].

Fetuses with large tumors are best delivered by cesarean section, and an expert pediatric team must be available to intubate of the infant.

7. Abnormalities of the mandible

7.1. Robin anomalad

Synonyms: Cleft palate, micrognathia and glossoptosis, and Pierre Robin syndrome.

Definition: This anomaly is associated with micrognathia and glossoptosis, with a posterior cleft palate or a high arched palate.

Incidence: The frequency is 1:30,000 [50].

Etiology: In 40% of the cases, the anomaly is isolated and mostly sporadic, although sometimes familiar cases suggest both autosomal recessives and autosomal dominant patterns of transmission. It is most frequently seen in association with other anomalies or with recognized genetic and nongenetic syndromes [51].

Embryology: The mandible starts at the point in which the two mandibular prominences join to delimit the inferior part of the stomodeum. The fusion of the three palatine processes forms the palate. Finally, the frontonasal prominence creates the median, and the maxillary processes create the two lateral ones. It is apparent that the three components of this defect are related to one another. Possibly, an early hypoplasia of the mandible creates this defect, as it leads to the tongue being displaced toward the posterior region, which prevents the posterior palatine processes to close as they should in a normal situation [52].

Associated anomalies: The Robin anomaly is found as an isolated lesion in 39% of all patients. In 36%, one or more associated anomalies are present. In 25% of patients, a known syndrome is found.

Robin anomaly is to be suspected when polyhydramnios is associated with micrognathia (**Figure 18**). Congenital heart disease occurs in 10% of affected neonates, so fetal echocardiography is recommended [53].

Prognosis: The Robin anomaly is a neonatal emergency in many cases. Glossoptosis may lead to the obstruction of the airways and suffocation.

It is mandatory that a pediatrician be present in the delivery room and be prepared to intubate the infant. Karyotype should be considered [54].

7.2. Otocephaly

Definition: Otocephaly is a grotesque anomaly, characterized by the absence or hypoplasia of the mandible, proximity of the temporal bones, and abnormal horizontal position of the ears. This malformation is considered to be the result of an improper development of the mandible, probably caused by a defect in the migration of the neural crest cells. The ears position

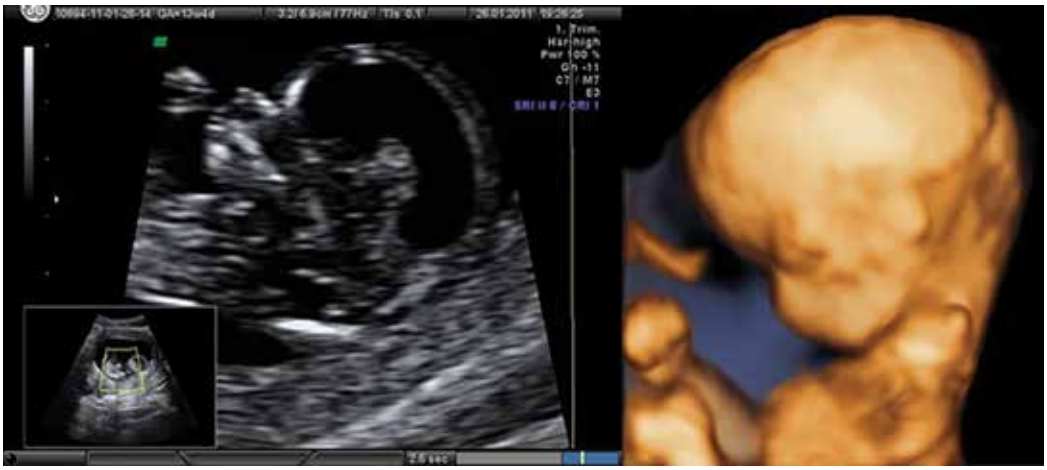

Figure 18. Sagittal scan a fetus at 13 weeks of gestation shows prominent forehead and retrognathia (polyploidy).

themselves horizontally, with the lobules closer to the midline, most certainly because of either absence or extreme hypoplasia of the mandible (**Figure 8**).

The anatomic lesions range from ears closely opposed to the midline (synotia), agnathia, absence of the mouth to varying degrees of micrognathia and low set ears (melotia).

Otocephaly may be part of very severe malformation complexes, such as conjoined twins and holoprosencephaly [55].

Associated anomalies: Holoprosencephaly, neural tube defects, cephaloceles, midline proboscis, hypoplastic tongue, tracheoesophageal fistula, cardiac anomalies, and adrenal hypoplasia [56].

Diagnosis: This anomaly is to be suspected when the jaw cannot be visualized and the ears are noticed in a very low position. Fetuses with extremely severe anomalies, such as anencephaly, holoprosencephaly, and cephaloceles, also present this defect. In cases of milder anomalies, it is difficult to distinguish the otocephaly from other conditions characterized by very low set ears, for instance Treacher Collins syndrome, during a prenatal ultrasound examination [57, 58].

Prognosis and obstetrical management: This condition is incompatible with life. Pregnancy termination could be offered any time in a pregnancy when a confident diagnosis is made [57].

8. The chin: Micrognathia-retrognathia or prognathia

Abnormal size of the chin, micrognathia and macrognathia, and abnormal length of the philtrum (short or long) are morphological features in numerous syndromes.

8.1. Micrognathia-retrognathia

Prevalence: 1: 1500 births.

Ultrasound diagnosis: Subjective finding of prominent upper lip and receding chin in the mid-sagittal view of the face (**Figure 18**). These findings might be due to micrognathia (short mandible) or retrognathia (backward displacement of the mandible). Severe micrognathia is associated with polyhydramnios (>25 weeks gestation), due to glossoptosis (normal tongue obstructing small oral cavity).

Associated abnormalities: Chromosomal abnormalities, mainly trisomy 18 and triploidy, are found in about 30% of cases. Any one of >50 genetic syndromes are found in most fetuses. Micrognathia is usually associated with >50 genetic syndromes, including Pierre-Robin anomaly, Treacher Collins syndrome, otocephaly [59].

Investigations: ultrasound including echocardiography, karyotyping and array.

Follow up: Ultrasound scans every 4 weeks to monitor growth and amniotic fluid.

Delivery: In hospital with facilities for neonatal intensive care, while a pediatrician is present in the delivery room and be prepared to intubate the neonate.

Prognosis: Neonatal mortality >80% due to associated abnormalities. In Pierre–Robin anomaly, the survival rate is good.

Recurrence: Genetic syndromes: 25–50%. Trisomies: 1%. Isolated: no increased risk of recurrence.

Author details

Maria Șorop-Florea[1], Roxana-Cristina Dragușin[1], Ciprian Laurențiu Pătru[1], Lucian George Zorilă[1], Cristian Marinaș[2], Virgiliu-Bogdan Șorop[3], Cristian Neamțu[4], Alina Veduța[5], Dominic Gabriel Iliescu[1]* and Nicolae Cernea[1]

*Address all correspondence to: dominic.iliescu@yahoo.com

1 Department of Obstetrics and Gynecology, Prenatal Diagnostic Unit, University Emergency County Hospital, University of Medicine and Pharmacy Craiova, Romania

2 Department of Anatomy, University of Medicine and Pharmacy Craiova, Romania

3 Department of Obstetrics and Gynecology, University of Medicine and Pharmacy "Victor Babeș" Timișoara, Romania

4 Department of Pathophysiology, University of Medicine and Pharmacy Craiova, Romania

5 Department of Obstetrics and Gynecology, University of Medicine and Pharmacy "Carol Davila" Bucharest, Romania

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Chapter 6

Congenital Abnormalities of the Fetal Heart

Dominic Gabriel Iliescu, Ștefania Tudorache,
Dragos Nemescu, Monica Mihaela Cirstoiu,
Simona Vlădăreanu, Claudiu Marginean,
Iuliana Ceausu, Daniel Muresan,
Marius Calomfirescu Vicea, Mona Elena Zvanca,
Cezara Muresan, Laura Monica Cara,
Ciprian Laurentiu Patru,
Roxana Cristina Drăgușin and Maria Sorop-Florea

Additional information is available at the end of the chapter

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Abstract

Congenital heart defects (CHDs) are the most frequent congenital malformations, the costliest hospital admissions for structural defects and the leading cause of infant general and malformations related mortality. Fetal echocardiography represents a skilled ultrasound examination, because of the complexity, physiological and structural particularities of the fetal heart. The efficiency of the cardiac scan is reported with great variation, depending on the scanning protocol, examiner experience and equipment quality but CHDs remains among the most frequently missed congenital abnormalities.

Keywords: heart defects, congenital, ultrasonography, echocardiography

1. Epidemiology. Incidence and risk factors for cardiac abnormalities

Congenital heart defects (CHD) are the most frequent congenital malformations (5–12 per 1000 live births), the costliest hospital admissions for structural defects and represent the leading cause of infant general and malformations related mortality (42%) [1, 2]. Prenatal CHD detection allows proper counseling, provides the options of pregnancy termination [3], in utero treatments (antiarrhythmics, valvuloplasties, etc.) [4–7] and allows for delivery planning in a referral center [8–11].

CHD etiology includes many genetic, environmental and teratogenic factors [12–16], but 90% of heart malformations have no identified cause. Conversely, the risk may be reduced with periconceptionally folic acid intake [17].

2. Indications and settings for fetal echocardiography (FECG)

A detailed sonographic examination, used to characterize fetal cardiac anatomy has traditionally been reserved for high-risk populations [18–22]: advanced maternal age, more than 35 years old, family history of CHD or disorders that involves potential CHD, infectious, autoimmune or metabolic diseases, exposure to drugs and teratogens. FECG was also proposed in certain pregnancy findings: structural defects, non-immune hydrops, arrhythmia, suspected chromosomal abnormalities, enlarged nuchal translucency, monochorionic multiple gestation. Nowadays, professional guidelines recommend a screening heart evaluation to all pregnancies, as most of the CHD cases are not associated with known risk factors [38–45].

Guidelines and training requirements have been developed [18, 19]. An accurate visualization of heat features is commonly achieved at 18–22 gestational weeks. FECG is a relatively brief but skilled ultrasound examination, because of the complexity and prenatal physiological and structural particularities of the fetal heart. Consequently, FECG has not been widely implemented, and the prenatal diagnosis of even severe CHD varies considerably, with less than half prenatally detected.

3. Fetal heart evaluation. The cardiac sweep and longitudinal views

Optimal views of the fetal heart are obtained when the cardiac apex is orientated toward the anterior maternal wall. Heart anatomy is evaluated using a sequential segmental analysis, starting from the venous plane (atria with veins connections), following the blood flow to ventricles and great arteries [23]. The information regarding fetal heart anatomy is achieved by examining five axial and three longitudinal scanning planes [18, 19, 24], described below, with examples of cardiac abnormalities. In general practice, only the axial sectional planes are evaluated during the cardiac sweep [25] (**Figure 1**).

1. **Upper abdominal view** facilitates the evaluation of normal abdominal situs by identifying the stomach, descending aorta and inferior vena cava position (**Figure 1(1)**).
2. **Four-chamber view (4CV)** is visualized in the lower half of the fetal chest, where the heart, with crux cordis occupying its central portion and a complete rib are present (**Figure 1(2)**). The evaluation parameters include:
    - *Situs*—the heart is normally left-sided, namely levocardia, or situs solitus. Rarely, a complete situs inversus is present. In the presence of an abnormal heart situs CHD but also congenital diaphragmatic hernia should be considered (**Figure 2**), as the presence of significant ectopic abdominal content in the chest displaces the heart.

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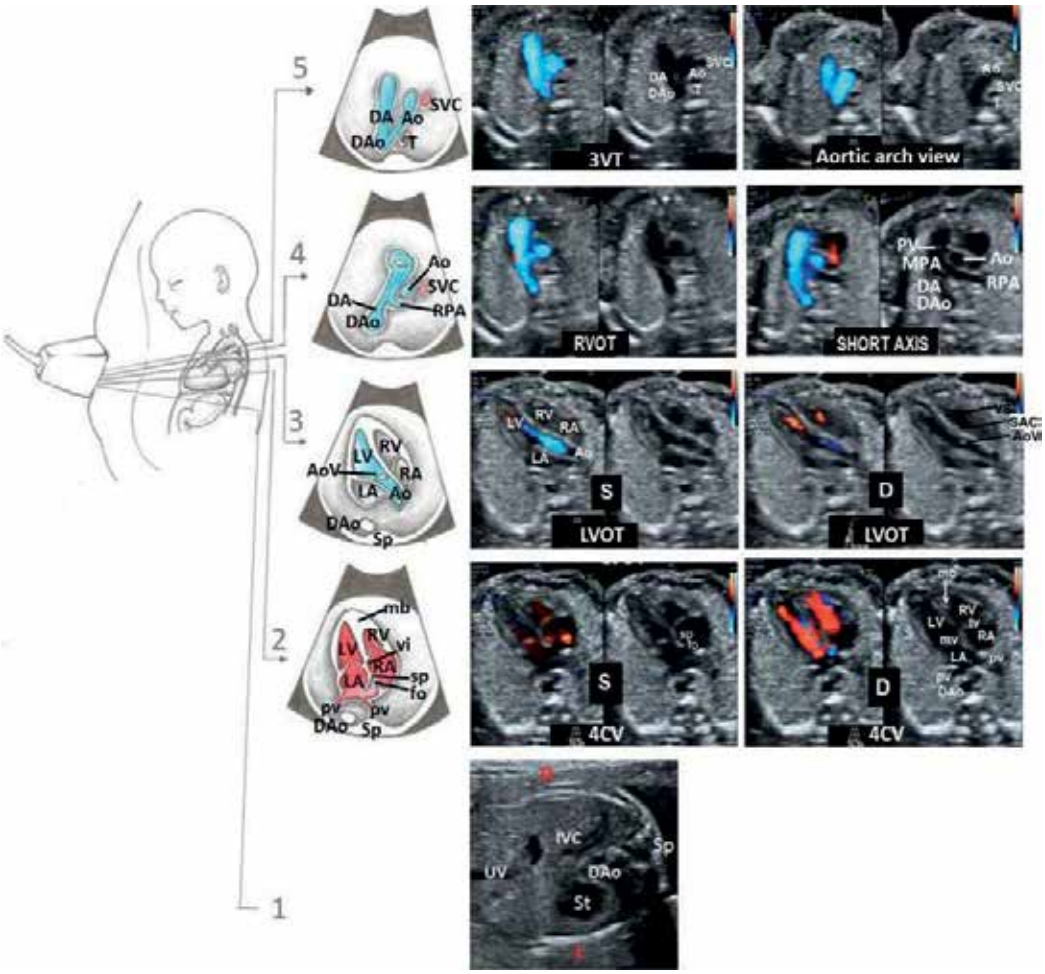

Figure 1. Normal heart visualized during fetal cardiac sweep. Visualization of the cardiac transverse planes, by sweeping the transducer from the four-chamber plane toward the fetal neck as shown in the left of the image. Schematic presentation of the cardiac planes in duplex mode (gray-scale and color Doppler) that become apparent: (1) upper abdominal view, and abdominal situs; (2) four-chamber view (4CV). The atrioventricular Doppler flow is red because of the direction toward the direction during diastole. When the atrioventricular are closed, during systole, the atrioventricular flow is absent; (3) left ventricular outflow tract (LVOT). Note the continuity of the ventricular septum (VS) with the aortic wall. When the aortic valve (AoV) is closed, during diastole, the aortic flow is absent; (4) right ventricular outflow tract (RVOT) and (5) three-vessel and trachea (3VTV) and aortic arch views. L, left; R, right; St, stomach; D, diastole; and S, systole; UV, umbilical vein; DAo, descending aorta; IVC, inferior vena cava; SVC, superior vena cava; LV, left ventricle; RV, right ventricle; LA, left atrium; RA, right atrium; mb, moderator band; mv, mitral valve; tv, tricuspid valve; vi, valve insertion; pv, pulmonary veins; sp., septum primum; fo, foramen ovale, DAo, descendent aorta; MPA, main pulmonary artery; DA, ductus arteriosus; RPA, right pulmonary artery; PV, pulmonary valve Sp, spine; T, trachea. Modified with permission [26].

- *Heart axis*—normally, the apex points toward the left side at 45 ± 15–20° (**Figure 1(2)**). Some studies on CHDs suggested that an abnormal cardiac axis is present in more than two-thirds of the cases [27] (**Figure 15C**).
- *Area of the heart,* is abnormally increased if higher than 1/3 of the thorax area, or cardio-thoracic circumference ratio is above two standard deviations [28] (**Figure 3**). It can arise

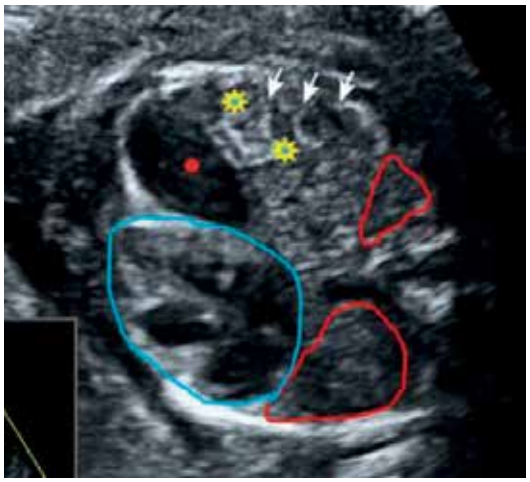

Figure 2. Two-dimensional US images in the cross-sectional plane of the thorax at the level of the four-chamber view of the heart. Stomach (red star) and small bowel loops (yellow stars) are identified intrathoracic and displaces fetal heart (figured by the blue tracing line) to the right; the lungs areas are highlighted by red tracing lines. With permission, Tudorache et al. [34].

from a number of situations which include CHD, particularly tricuspid atresia or dysplasia, including Ebstein's anomaly, twin to twin transfusion syndrome, fetal dilated cardiomyopathies, hydrops fetalis, or may be due to abnormal shunting from arteriovenous malformations, as the vein of Galen malformation or placental chorioangioma (**Figure 3**).

- *The atria* present similar size. The pulmonary veins enter the posterior left atrium and both vena cava enter the anterior right atrium (**Figure 1(2)**). Various condition may alter this spatial relation, as fetal isomerism and the normal atrial dimensions, where Ebstein's anomaly is the most representative condition (**Figure 4**).

- *The ventricles* should be visualized with similar width and contractility. The right ventricle is anterior, with more coarse lining and trabeculation. Abnormal shape of the ventricular wall lining may be an indicator for cardiac tumors, as tuberous sclerosis (**Figure 5**) or rhabdomyoma (**Figure 6**). Normally, the left ventricle forms the apex of the heart, the right ventricular apex contains the moderator band and septal insertion of the tricuspid valve is more apical than the mitral valve (**Figure 1(2)**). In later gestation, the right ventricle becomes slightly larger, but 2D or M-mode nomograms correlated with the gestational age or fetal biometry and Z-scores for fetal heart area and axis and cardiothoracic ratio, atrioventricular valve annuli, ventricular lengths and walls thickness, but also for emerging vessels, are available [29, 30].

  A diminutive ventricle may be associated with significant CHD, as the hypoplastic left/right heart syndrome (**Figure 7**). Also, an abnormally small left ventricle may be an indirect sign of aortic coarctation (**Figure 19A**). However, less significant cardiac abnormalities may associate a larger right heart, as the persistence of left superior vena cava (**Figure 8**).

- *Ventricular septum integrity* is better evaluated from a lateral incidence, with the ultrasound beam perpendicular to the septum. A dropout of echoes or an opening of the

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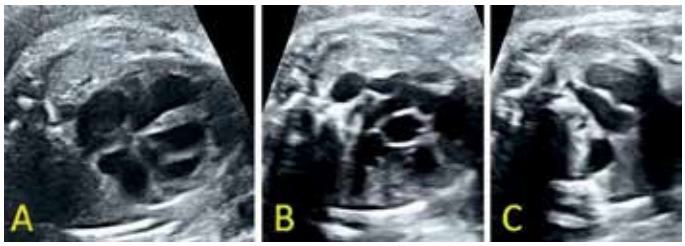

Figure 3. Cardiomegaly. (A) Increased area of the heart, occupying half of the thorax area. (B and C):Outflow tract appears dilated in relation to the fetal thorax.

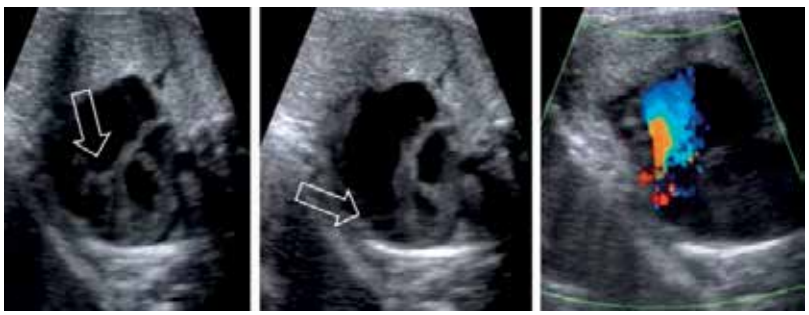

Figure 4. Ebstein's anomaly. The arrow indicates the dysplastic tricuspid valve with septal and posterior leaflets of the tricuspid valve displaced toward the apex of the right ventricle. Color Doppler investigation shows significant valvular regurgitation.

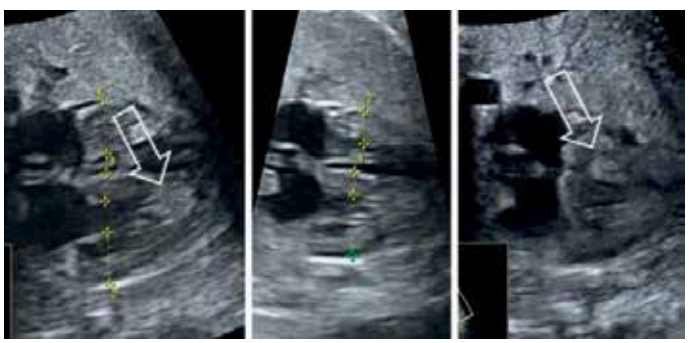

Figure 5. Tuberous sclerosis. Increased thickness of ventricular walls and presence of solid tumors in ventricular cavities, highlighted with open arrows.

ventricular septum, causing communication between the two ventricles suggests the diagnosis. The entire septum must be swept (**Figure 9**) for a more confident diagnosis, and Doppler investigation enhances the diagnosis, especially for small defects (**Figure 10**). Ventricular septal defects are the most common cardiac abnormality and accounts for almost one third of all cardiac defects.

- *Atrial septum primum* presence, at the crux of the heart, along the *atrioventricular valves* insertion which is more apical for tricuspid valve. Atrioventricular septal defects, known

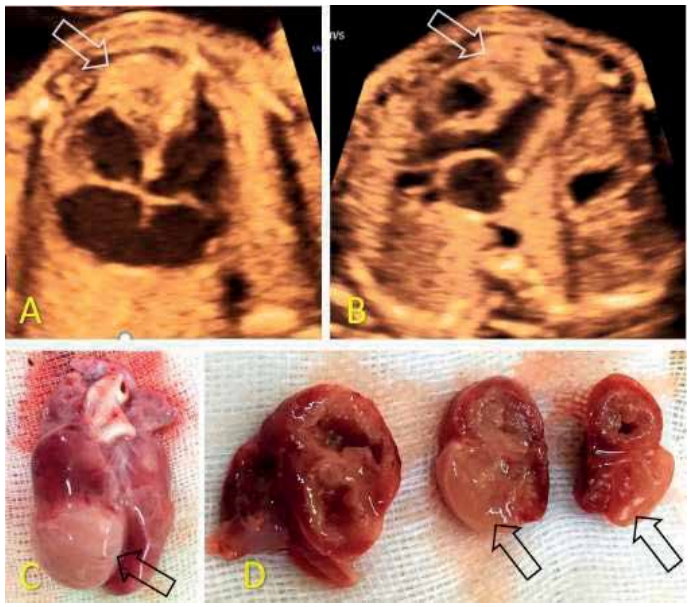

Figure 6. Rhabdomyoma of the right ventricle, visible in 4CV (A) and left ventricle outflow tract view (B), and confirmed postabortum (C and D), penetrating the ventricular wall (C).

as endocardial cushion defects are situated in the central core of the heart. It involves the association of septum primum and ventricular septal defect and a variable degree of abnormal atrioventricular valves (**Figure 11**).

- *Foramen ovale* represents about one third of the atrial septum and the flap bulges in the left atrium. A restrictive foramen ovale, because of a narrow foramen ovale orifice, or premature adhesion of the foramen ovale valve to the atrial septum, has repeatedly been discussed as a cause of fetal hemodynamic compromise [31]. Foramen ovale aneurysm is defined as dilatation of the atrial septum with bulging of the septum at least half the distance to the left atrial wall (**Figure 12**), is primarily a defect of septum primum which results in: septum primum bulging, loss of the normal biphasic motion of foramen ovale and arrhythmia. Associated abnormalities include: atrial septal defect, tricuspid atresia, hypoplastic right heart, aortic stenosis, transposition of the great vessels, Ebstein anomaly, atrioventricular valve and pulmonary venous obstruction.

- *Pericardial effusion* should be absent, or less than 2–4 mm. Greater effusions usually occur as a component of hydrops, as one of the earliest findings, and are also associated with cardiac structural abnormality, arrhythmia and an increased incidence of chromosomal anomalies (**Figure 12**) [32, 33].

- *Heart rate and the regularity* of the rhythm is assessed based on the cardiac cycle length measured using M-mode or pulsed Doppler interrogation. Most common arrhythmias are transient and without clinical relevance, as brief episodes, less than 1–2 minutes of a bradycardic, tachycardic or irregular heart rhythm.

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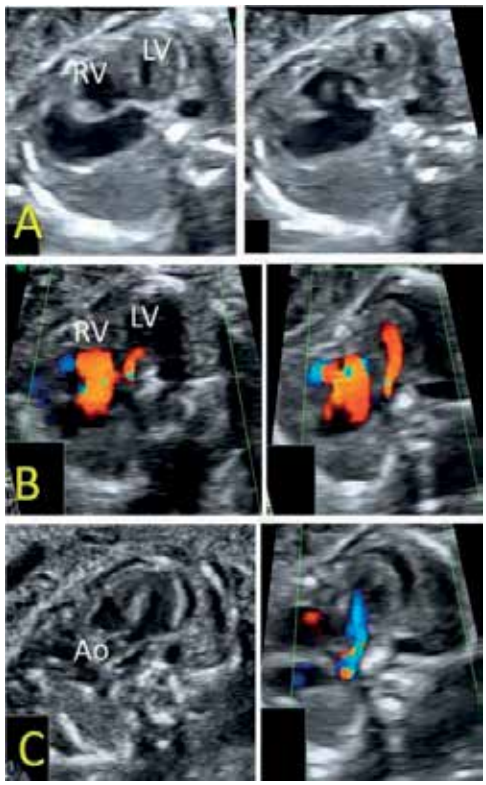

Figure 7. Hypoplastic left heart syndrome (HLHS), with discordance of the heart chambers, ventricular cardiomyopathy and hypertrophic left ventricle (A), markedly reduced filling at Doppler evaluation (B), fibroelastosis, and reduced aortic caliber and flow (C).

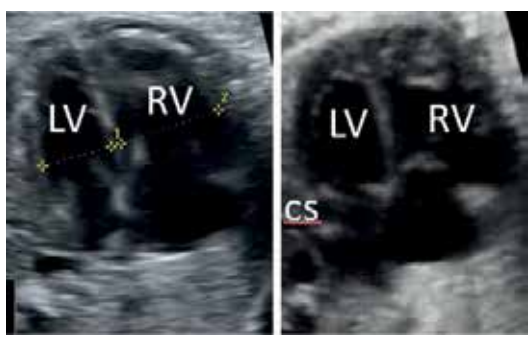

Figure 8. Discordance of the cardiac ventricles, with enlarged right ventricle and dilated coronary sinus (CS), in the presence of persistent left superior vena cava.

Irregular cardiac rhythm represents the most common rhythm anomaly and is almost always associated with isolated premature atrial contractions (PACs). Frequently blocked PACs will result in bradyarrhythmia that can mimic bradycardia (**Figure 13**). In rare cases, irregular rhythm may progress to supraventricular tachycardia.

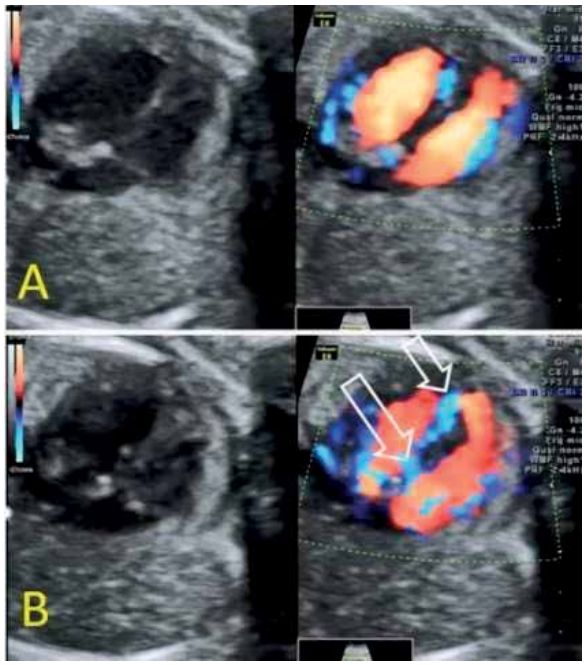

Figure 9. Multiple VSDs, apical and membranous, unapparent in certain 4CV incidence at gray-scale and color Doppler evaluation (A), but present in nearby planes, as the cardiac sweep is conducted (B). The entire interventricular septum must be carefully swept.

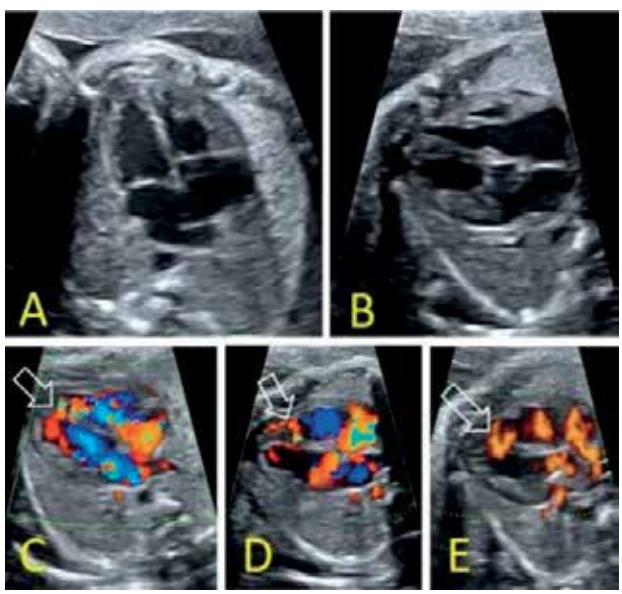

Figure 10. Multiple VSDs, apical and muscular, inapparent in gray-scale evaluation. (A): Apparently normal ventricular septum in apical and (B): lateral four-chamber view. (C–E): Muscular VSDs diagnosed using color Doppler in lateral four-chamber view—open arrows.

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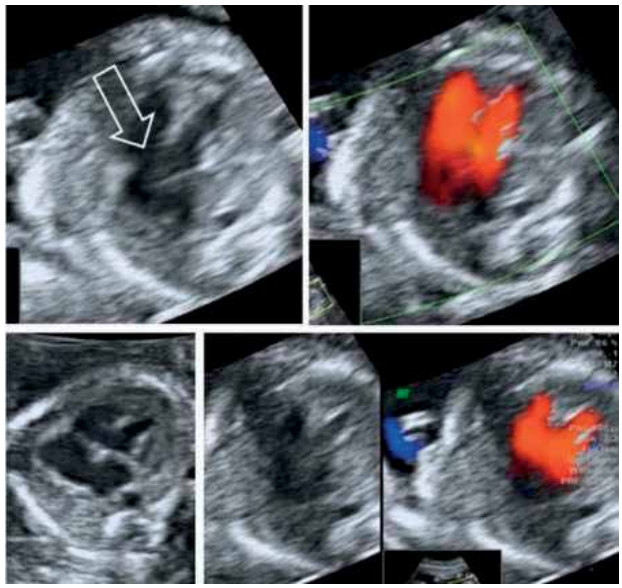

Figure 11. Atrioventricular septal defect. A large defect (open arrow) is present in the area where normally crux cordis is identified.

Fetal bradycardia represents a persistently slower heart rate, of less than 100–120 beats/min. More concerning is the observation of sustained bradycardia induced by sinus bradycardia, atrial bigeminy and complete heart block. Heart block is frequently associated with maternal anti-Ro autoantibodies and CHD and the most common condition is an unbalanced atrioventricular septal defect associated with left isomerism.

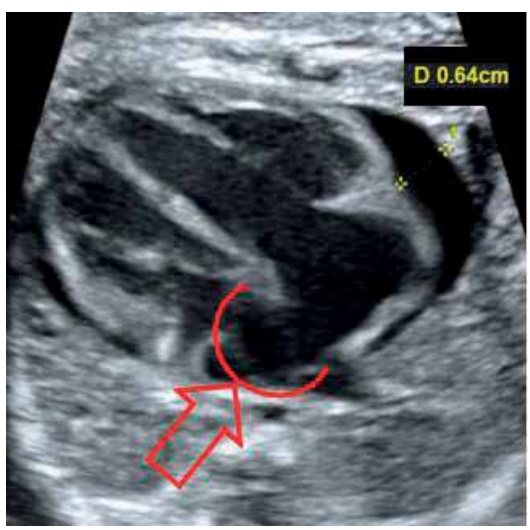

Figure 12. Foramen ovale aneurysm (red arrow) in a case where pericarditis is associated.

Fetal tachycardia implies atrial and ventricular rates above 180 bpm. Fetal anemia, hypoxia, infections, and maternal thyrotoxicosis may induce this condition. The main causes of fetal tachycardia are supraventricular tachycardia (**Figure 14**), the most common cause, with atrioventricular re-entry due to a fast conducting accessory pathway), sinus tachycardia, and atrial flutter (with atrial rate 300–500 bpm and only every second or third atrial beat conducted across the atrioventricular node, resulting in ventricular rates of 150–250 bpm). The use of echocardiography is important to differentiate these conditions and their hemodynamic impact, because the severe conditions may lead to low cardiac output, hydrops and fetal demise.

- *Coronary sinus*, may be demonstrated by fine sweeping caudally from the 4CV (**Figure 8**).

Given all these information, the 4CV is much more than a simple count of cardiac chambers, but certain abnormalities, especially involving great vessels, cannot be detected at the 4CV level alone [35]. Recent revised and updated guidelines and recommendations from several professional bodies [18, 36, 37] plead for the routinely screening evaluation of the outflow tract views along the 4CV, based on strong medical evidence regarding the prenatal detection of CHD [38–40].

3. **Left ventricular outflow tract (LVOT)** is visualized cranially from the 4CV plane and directed toward the fetal right shoulder. In this five-chamber view, the ascending aorta appears arising from the left ventricle (**Figure 1(3)**), with no proximal *transversal branching*, allowing for its differentiation from the main pulmonary artery.

   - *Septoaortic continuity*, should be visualized as a continuous line between ventricular septum and aortic wall. The discontinuity of this structure is seen in the presence of a

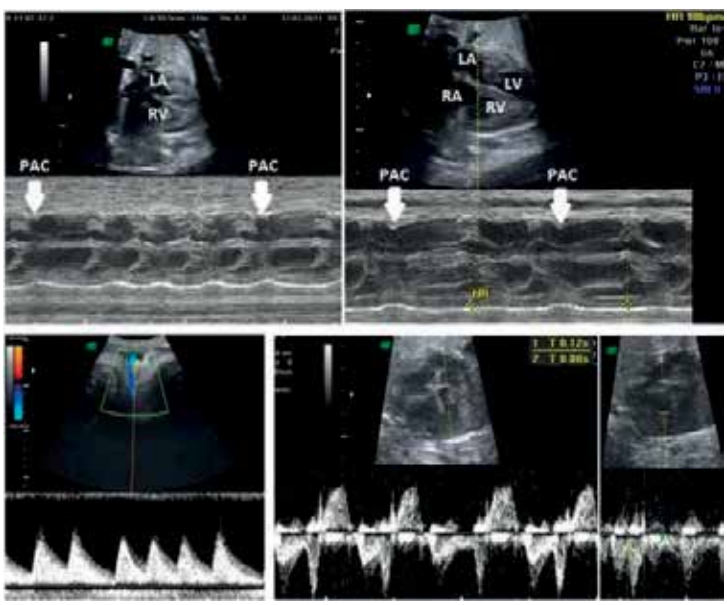

Figure 13. Fetal bradyarrhythmia, M-mode and pulsed Doppler evaluation. Premature atrial contractions (PACs, highlighted with arrows) are blocked, resulting in bradycardic irregular cardiac rhythm. Normal values for the mechanical PR interval by pulsed Doppler interrogation at the mitral-aortic region in prediction of heart block risk.

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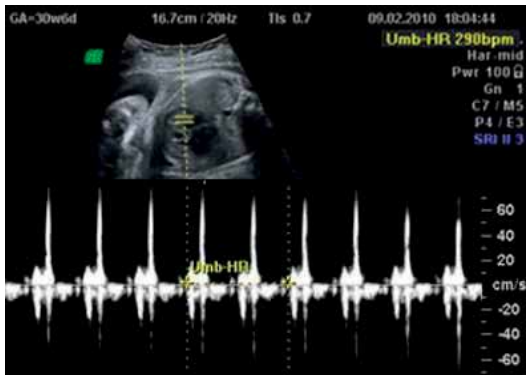

Figure 14. Tachyarrhythmia and measurement of cardiac rhythm using pulsed Doppler.

sub-aortic septal defect that is frequently associated with overriding. A good example of this condition is present in tetralogy of Fallot cases (**Figure 15**).

- The *aortic valve* cusps should open freely, disappearing in systole and not thickened. Aortic dysplastic and stenotic valves do not fully open this will decrease the blood flow into the aorta. Aortic stenosis impairs the left ventricular development, leading to hypoplastic left heart syndrome (**Figure 16**).

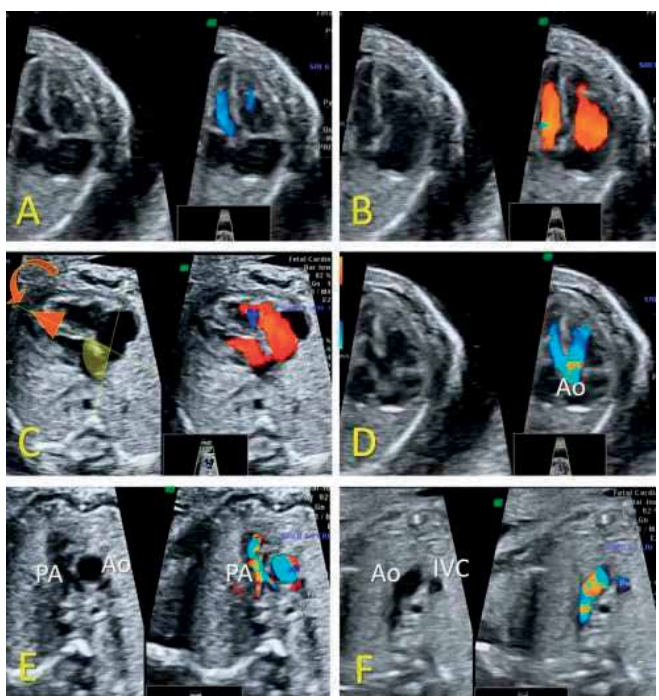

Figure 15. Tetralogy of Fallot. Inapparent four-chamber view (A and B) with increased cardiac axis (C). Septal defect with septoaortic discontinuity and aortic root overriding at the level of mixing flows form ventricles (D). Diminutive stenotic pulmonary artery is identified in right outflow tract view (E) and three-vessel and trachea view (F).

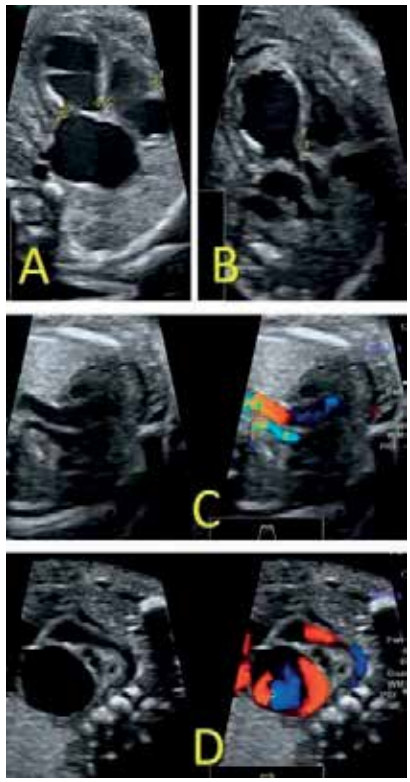

Figure 16. Aortic stenosis. Abnormal left ventricle with atretic inlet and fibroelastosis (A), stenotic aortic root (B) and aortic arch in axial (C) and longitudinal (D) views.

- *The width* of the aorta should be approximately equal with the pulmonary artery. Unbalanced blood flows through the outflow tracts as in Fallot Tetralogy, determine a larger aorta, because the aortic root receives blood from both ventricles due to overriding (**Figure 15D** and **E**). Valvular dysplasia and aortic arch stenosis/coarctation (**Figure 16**) determine a smaller aortic caliber.

4. **Right ventricular outflow tract (RVOT)** and short axis view are visualized cranially from the LVOT plane (**Figure 1(4)**), where the main pulmonary artery root arises from the anterior right ventricle with a short and straight course and soon *branching* into a large vessel, the ductus arteriosus directed straight posteriorly toward the descending aorta as an extension of the main artery, and the smaller pulmonary arteries directed laterally.

   - The pulmonary *valve cusps* should have a similar aspect as described for the aortic valves. The dysplastic stenotic valves may appear thickened and with incomplete opening during systole (doming) (**Figure 17A**) and determine pulmonary stenosis.

   - The approximately equal *width* of the two outflow tracts should be noted. Pulmonary stenosis may be associated with valvular stenosis, total anomalous pulmonary venous drainage, septal defects, supravalvular aortic stenosis, Noonan syndrome and tetralogy of Fallot. On color and pulsed Doppler investigation, pulmonary stenosis cases display turbulent or retrograde flow in and increased velocities distal to the valve (**Figure 17B**

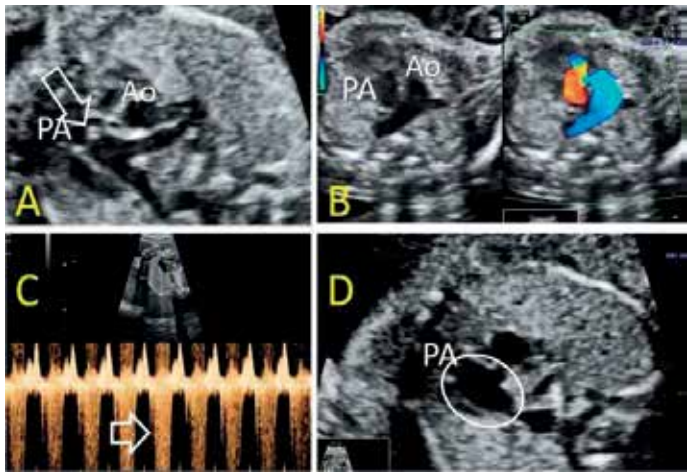

Figure 17. Pulmonary stenosis. (A): Dysplastic pulmonary valves, with incomplete opening and doming; (B): reversed and turbulent flow in the RVOT; (C): post-stenotic increased velocities in pulmonary artery course; (D): post-stenotic dilatation.

and **C**), with PSV higher than the aortic flow. A post-stenotic dilatation of the proximal pulmonary artery may be seen (**Figure 17D**). A variable degree of hypoplastic right ventricle with hypertrophic wall, dilatation of the right atrium, and tricuspid insufficiency may be present, while congestive heart failure and hydrops may occur in severe stenosis.

- *Spatial relationship* evaluation should note crossing of aorta at a right angle and characteristic early transversal branching of the pulmonary artery (**Figure 1(4)**). In the absence of these ultrasound features, transposition of the great arteries should be suspected (**Figure 18**).

5. **Three-vessel and trachea view (3VTV)** is obtained sliding cranially in the upper thorax during cardiac sweep (**Figure 1(5)**). Superior vena cava (SVC) on the right side, the aortic arch and ductal arch, anterior and to the left of the aorta, are visualized. The approximately equal arterial arches form a *"V"-shaped confluence* toward the descending aorta, in the left of the spine. This plane is also used for thymus evaluation [41].

   This view may be altered with regard to several features. Their width may be discrepant, as due to aortic coarctation, where the aortic isthmus is significantly smaller than the arterial duct (**Figure 19**). However, this diagnosis is challenging and affected by high rates of false-positive diagnoses. Thus, to improve detection, a multiple-criteria prediction model is adopted, as a combination of isthmic/duct and ventricular diameters ratios and Z-scores, visualization of CoA shelf and isthmic flow disturbance [42, 43].

   Another abnormality of 3VTV plane is represented by the impossibility to identify all the three vessels. One of the arterial arches may not be seen, as in the presence of an interrupted aortic arch (**Figure 20**), or more than three vessels may be present, as in persistent left superior vena cava (**Figure 21**).

   The superior vena cava may be identified contralateral, on the left side, as in the persistent of left superior vena cava (**Figure 8**).

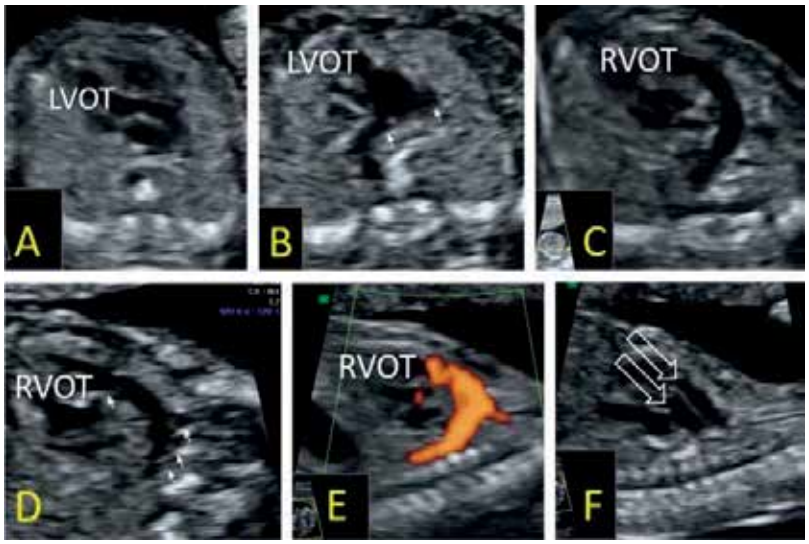

Figure 18. Transposition of the great arteries. (A): Emergence of the vessel arising from the left ventricle, showing early branching (B) that suggest pulmonary outflow tract. (C): Emergence of the vessel arising from the right ventricle with no evident branching in the transversal plane. (D): Sagittal view of the thorax showing branching characteristic to aortic arch of the vessel arising from the anterior ventricle in gray scale and after power Doppler is applied (E). (F): Parallel course of the great vessels.

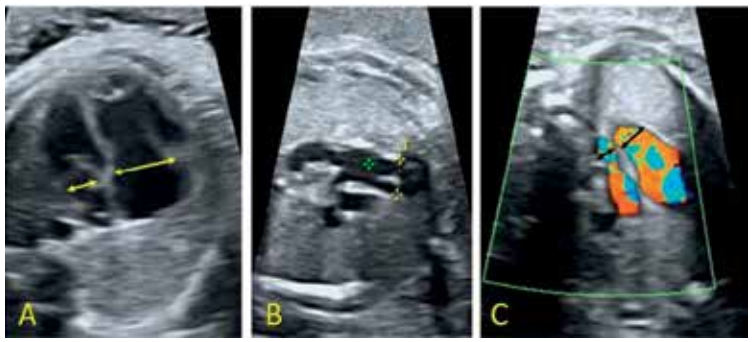

Figure 19. Discrepancy between the large right ventricle, pulmonary root and arterial duct and the diminutive left ventricle, aortic arch and isthmus in aortic coarctation. Calculations for mitral and tricuspid valves (A), arterial arches (B), isthmus and ductus (C).

Absence of a normal "V"-sign confluence of the arterial arches can be used to detect aortic arch abnormalities: right aortic arch, double aortic arch (**Figure 22**) and interrupted aortic arch (**Figure 20**).

6. Aortic and ductal arches views

- *The aortic* and *ductal arches* are visualized in longitudinal planes aligned with the respective ventricular outflow tracts. Aorta origins from the middle of the heart, with a typical "hook" shape, with the neck vessels arising longitudinally (**Figure 23A**).

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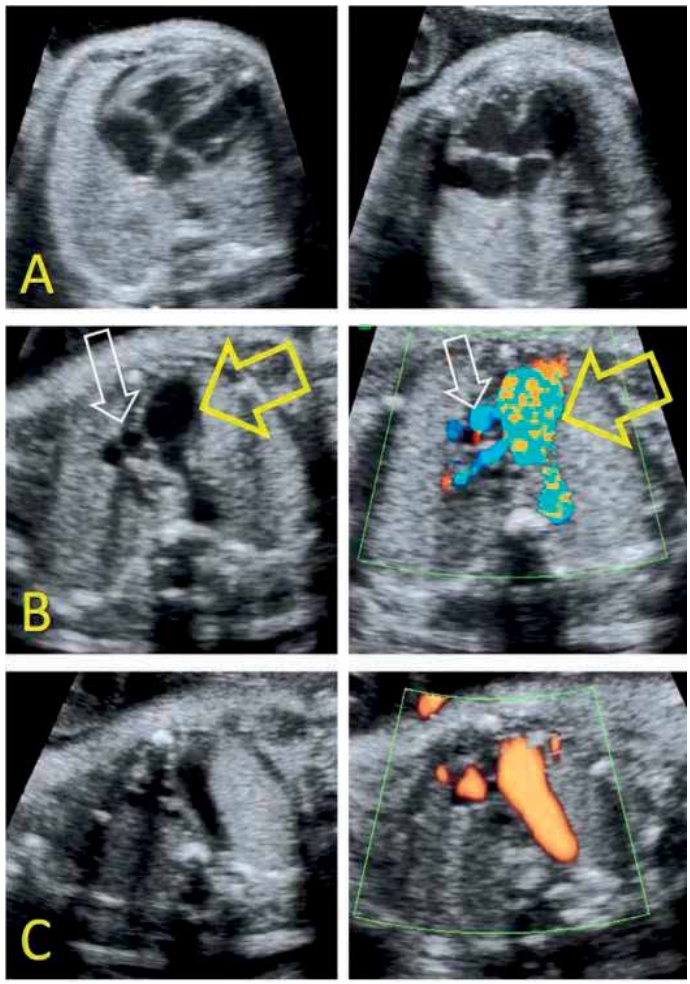

Figure 20. Interrupted aortic arch. (A): The ventricular discordance is not present, because of the septal defect, not evident in four-chamber views, but sub-aortic, when the entire septum is swept. (B): Enlarged pulmonary trunk (yellow arrow), and thin aorta (white arrow) in 3VT view. (C): Discontinuity of aortic arch in upper mediastinum axial planes.

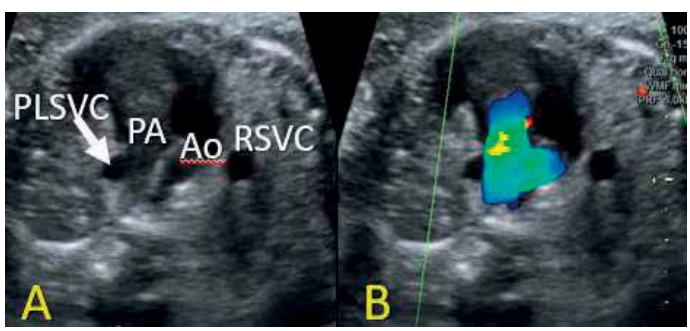

Figure 21. Persistent left superior vena cava (PLSCV), indicated with arrow in duplex gray-scale (A) and color Doppler (B) evaluation.

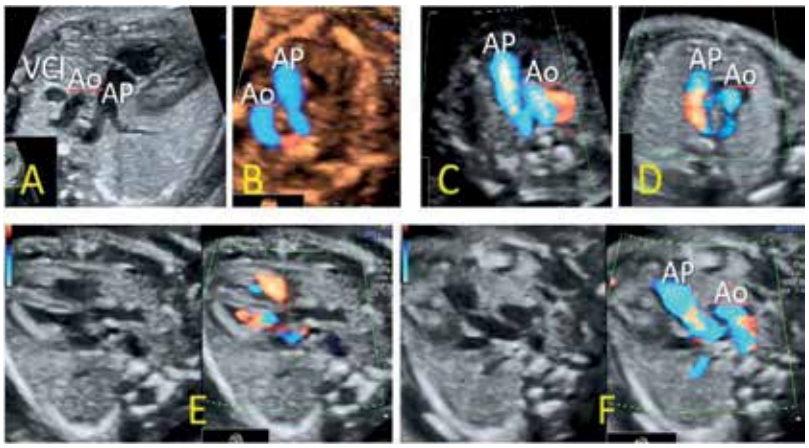

Figure 22. Right aortic arch (RAA) types. RAA and left ductus, forming a "U" shape of the arterial arches confluence as an almost complete vascular ring (A and B). Note the aorta coursing to the right of the spine, on the same side with superior vena cava (A), and a visible vascular incomplete ring behind the trachea. Double aortic arch, color Doppler evaluation (C and D) with complete vascular ring between the aortic branches. RAA with right ductus (E and F), described before with normal heart [44], duplex mode evaluation. Both arterial arches are directed to the right of the spine, resulting a "V"-shaped confluence on the right of the spine.

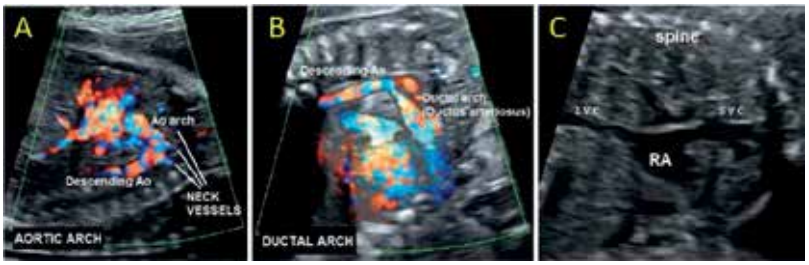

Figure 23. Aortic (A) and ductal (B) arches in longitudinal view. Note the differences mentioned in the text, regarding the origin, curvature and branching. (C): Bicaval view. IVC, inferior vena cava; SVC, superior vena cava; RA, right atrium.

A diminutive caliber accompanied by an altered shape may be present in aortic arch coarctation (**Figure 24A**) or stenosis (**Figure 16D**). Also, the course of the arch may be misshaped and interrupted, with lack of communication with the descending aorta, as in interrupted aortic arch (**Figure 24C**).

The vessel may appear irregular and thin, as in pulmonary stenosis (**Figure 24B**), or heavily dilated, as in aortic arch stenosis or interruption (**Figure 24D**). The ductus may be absent, as is usually in the most frequent variant of absent pulmonary valve syndrome-associated with tetralogy of Fallot. Another type of the syndrome—accompanied by tricuspid atresia, is characterized by a normal or narrowed ductus arteriosus, along the dysplastic right ventricle. Contrarily, the isolated type of absent pulmonary valve syndrome, with intact ventricular septum, associates a severe right ventricular hypertrophy with pulmonary artery and ductus arteriosus dilatation.

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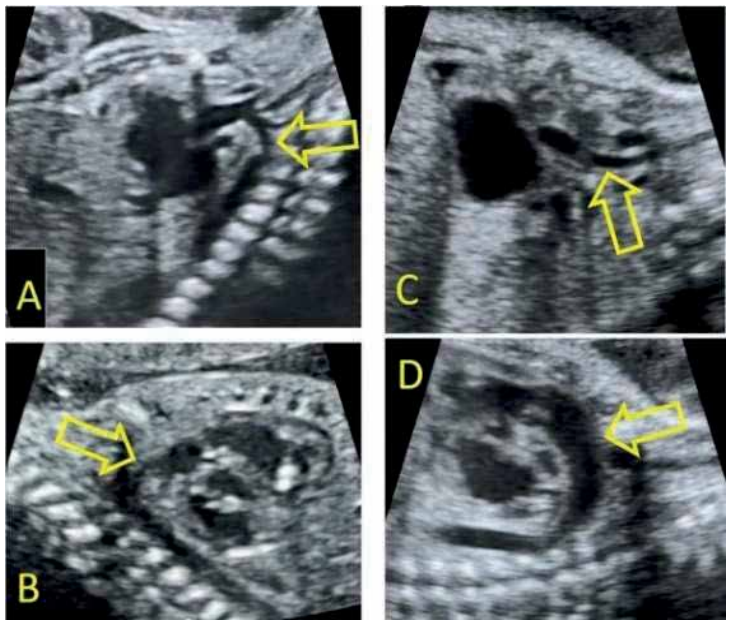

Figure 24. Pathologic aortic and ductal arches in longitudinal view. (A): Aortic coarctation with stenotic isthmus (arrow); (B): pulmonary valvular stenosis, with irregular course and stenotic ductal areas; (C and D): interrupted aortic arch, with ascending aorta that fails to curve, but courses straight cranially (C), and heavily enlarged ductal arch (D).

- *Superior and inferior vena cava views*/caval long-axis view/bicaval view is found longitudinally on the right of the spine, in line with the superior and inferior vena cava confluence with the right atrium (**Figure 23C**). The normal aspect is altered in fetal isomerism, interrupted inferior vena cava or persistent left superior vena cava.

4. Doppler imaging

Color Doppler and *high definition directional power flow* sonography allows for a better understanding of the cardio-vascular anatomy and function [18, 45, 46], particularly in detecting regurgitation, small septal defects and first trimester anatomic and physiological features of heart, as presented below. The ductus venosus appearance, flow and connections depend on the Doppler identification and interrogation of this small vascular structure. Agenesis of ductus venosus was associated with a high incidence of cardio-vascular and genetic abnormalities (**Figures 25** and **26**).

Pulsed Doppler sonography is an adjunct to evaluate the cardiac rhythm, but also the blood flows at the level of various arteria or venous vascular sites and valves.

B-flow and classic power Doppler display in some cases greater sensitivity in imaging cardio-vascular blood flow, but they are not routinely used.

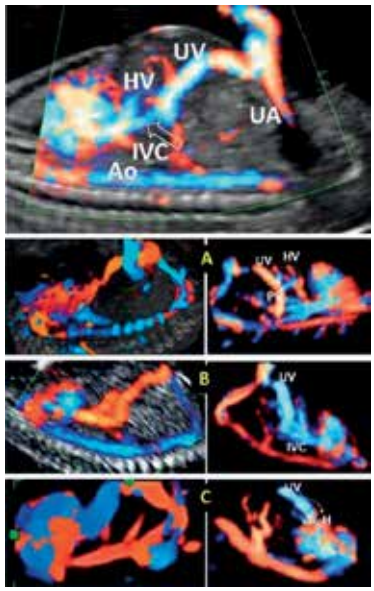

Figure 25. The upper image presents the normal appearance of ductus venosus in 2D color Doppler imaging. (A–C): Agenesis of ductus venosus: with hepatic (A), caval (B) and cardiac (C) drainage. UV, umbilical vein; IVC, inferior vena cava; H, heart; HV, hepatic veins; UA, umbilical artery; PV, portal vein; Ao, aorta.

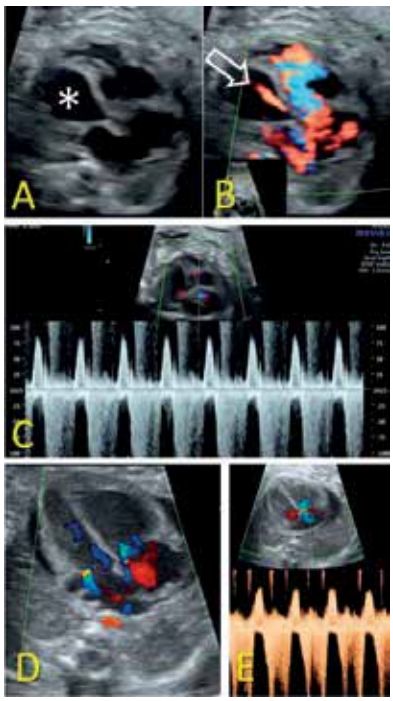

Figure 26. Applications of color and spectral Doppler. (A): Critical aortic stenosis with dysplastic left ventricle (*), atretic valve and aortic regurgitation (arrow, (B)). (C): Same case, tricuspid regurgitation, pulsed Doppler evaluation. (D): Atrioventricular valves regurgitation associated with cardiomegaly. (E): Same case, spectral Doppler evaluation of atrioventricular flow.

5. 4D spatiotemporal image correlation (STIC)

Volume datasets obtained with 4D STIC ultrasonography allow the evaluation of virtual planes not available for direct visualization with 2D technique, and facilitates the reconstruction of the spatial relationships between the cardio-vascular structures (**Figure 27**). This technology has the potential to increase the CHD detection rate by decreasing the dependency on sonographer skills and experience. However, due to the expensive costs and lack of specialists for training and interpretations, the technique is not routinely used.

In selected cases, it may offer important information as the comprehensive assessment of complex CHD cases [47–50] and the evaluation of cardiac function and quantification of fetal hemodynamic parameters, such as cardiac output [51].

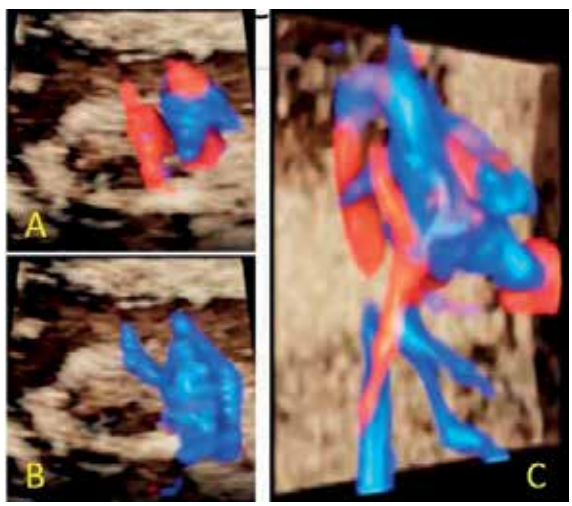

Figure 27. Double outlet right ventricle in 4D STIC. Axial planes show the origin of the great vessels (A) and the communication of the pulmonary artery with the left ventricle, due to a septal defect (B). Oblique longitudinal plane with the anterior origin of the two outflow tracts (C).

6. Cardiac function

It should be considered for suspected structural or functional cardiac anomalies [18, 19]. Some *qualitative* markers are identified during standard scanning: cardiomegaly, atrioventricular valve regurgitation, and hydrops. The *quantitative* assessment of heart function includes the study of myocardial movement such as tissue Doppler, myocardial/ventricular strain, strain rate imaging, fractional shortening and the myocardial performance index [52–54].

7. Efficiency of the fetal cardiac scan

Although the most frequent congenital malformations, CHDs are among the most frequently missed [18, 55]. The efficiency of the cardiac scan is reported with great variation, depending

on the scanning protocol, examiner experience, equipment quality and scanning conditions [18, 56–58]. It appears that the use of 4CV alone detects up to 77% of CHD, while adding OTV increases prenatal detection to 83–92% of major abnormalities.

8. Early evaluation of the fetal heart, at the first trimester (FT) morphogenetic scan

Congenital heart defects appear during the first 8 weeks of the fetus development, thus cardiac sonography at the genetic scan, during 11–13 gestational weeks (GW) is feasible (**Figure 28**) and identifies numerous abnormalities (**Figures 29–35**) [59–61]. The rate of complete cardiac evaluation increases with gestational age, from 20% at 11GW, to more than 92% at 13–15 GW, especially when transvaginal route was used [62, 63].

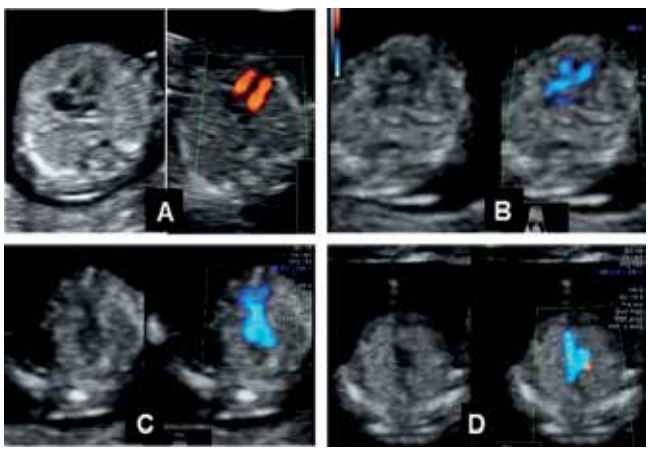

Figure 28. FT cardiac sweep of a normal heart, duplex mode. (A): 4CV plane: gray-scale imaging shows, crux cordis and pulmonary veins entering left atrium; color Doppler imaging shows equal atrioventricular flow and no flow between ventricles. (B): LVOT plane with the aortic emergence, septoaortic continuity and aortic flow. (C): Crossing of the great vessels. (D): 3VT plane – the confluence of arterial arches on left of spine with normal direction and equal flow.

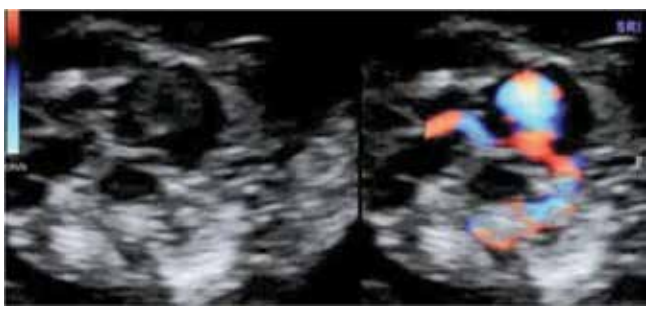

Figure 29. Monoventricular heart.

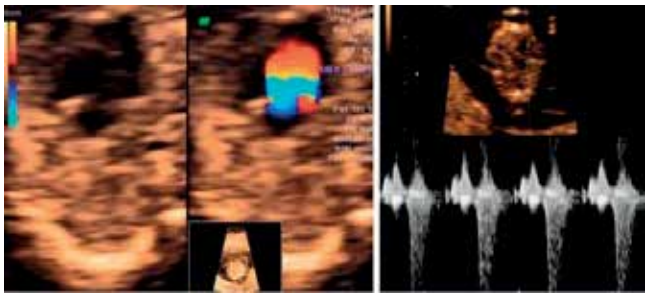

Figure 30. Atrioventricular septal defect. Thickened common valve, large communication between the cardiac chambers, absence of crux cordis and regurgitation.

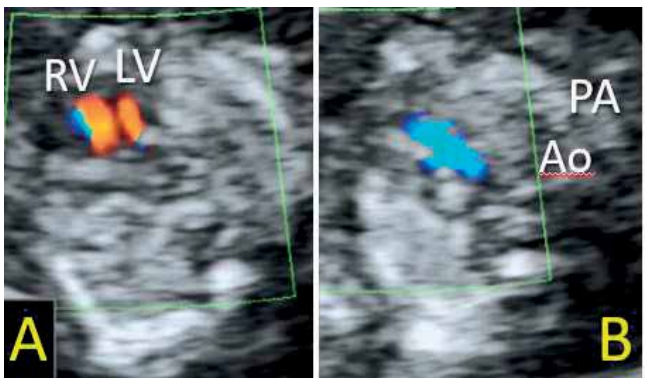

Figure 31. Hypoplastic left heart. A diminutive left ventricle (A) and aorta (B) are identified with the aid of color Doppler. RV, left ventricle; LV, left ventricle; PA, pulmonary artery; Ao, aorta.

Regarding the *imaging technique*, gray scale is the basis of a reliable fetal cardiac scan in the ST, but much less informative in the FT [64].

For safety reasons, routine use of pulsed color Doppler is advised against in the FT [65], although tricuspid and ductus venosus flows are commonly used [66–72] and color Doppler improves early visualization of cardio-vascular features, due to the low discrimination of the heart structures in gray-scale mode [73–75], while respecting the ALARA principle (As Low As Reasonably Achievable) [76].

At a lesser extent, the FT *examination protocol* is similar to the second trimester cardiac scan [77, 78], as presented in **Figure 28**. 4D-STIC is feasible in the FT and likely to improve CHD detection in expert hands.

The *efficiency* of FT cardiac scan varies widely (detection rate 5.6–90%), depending on the protocol used, population risk and scanning route (TV, TA or both). High detection rates for major CHD were reported even in unselected or low risk population 80–90%, when using an extended standardized protocol [74, 75]. A systematic review of the literature [79] reported a pooled sensitivity and specificity of 85% (95% CI, 78–90%) and 99% (95% CI, 98–100%),

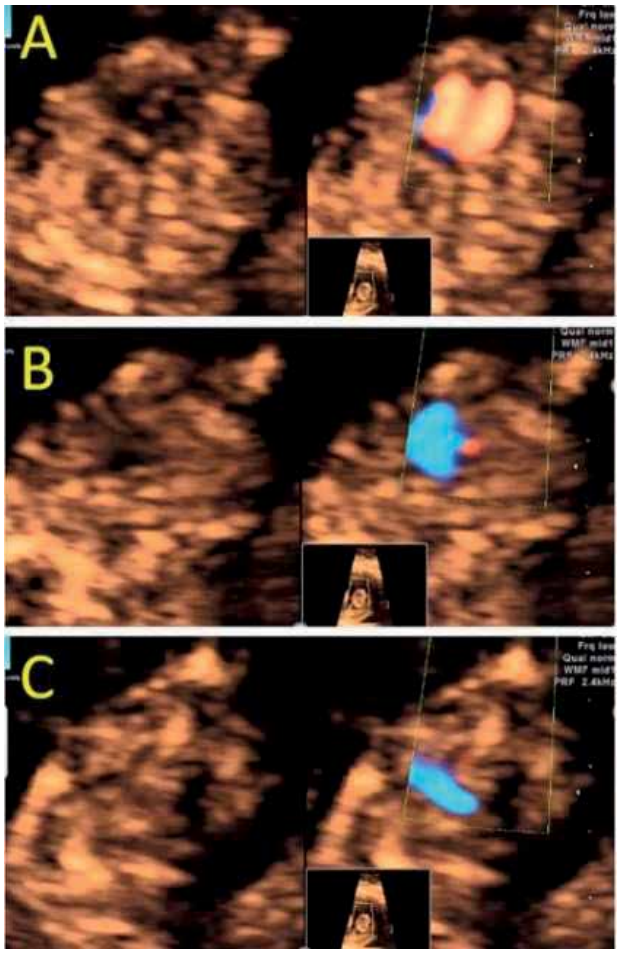

Figure 32. Transposition of great arteries. Inapparent four-chamber view (A), with parallel course of the arterial arches (B) and the impression of only one arterial arch at the level of 3VT view (C).

respectively. Thus, FT cardiac scan has a high accuracy in major CHD detection and a reasonable accuracy to diagnose normal heart. We should underline during parents counseling that normal fetal cardiac features examinations at any time of pregnancy do not exclude CHD, as some diseases evolve in utero and become apparent later during pregnancy: coarctation of aorta, pulmonary stenosis, tetralogy of Fallot, hypoplastic left heart syndrome, cardiomyopathy or cardiac tumors [80–83]. Ventricular septal defects are the earliest missed lesions because of the small size of the lesion and low flow velocities in the FT. A normal cardiac scan in the FT should not be considered a replacement for the second trimester echocardiography.

Markers for cardiac abnormalities (**Figure 36**) may also be useful in early pregnancy, as increased nuchal translucency (NT) and abnormal ductus venosus and tricuspid flows. Increased *NT* was associated with cardiac dysfunction and abnormalities, even in chromosomally normal fetuses, but not obviously related to any particular type of cardiac anomaly [84–86]. The prevalence of CHD when NT is the 95th percentile is up to 20% [87] and about six times higher

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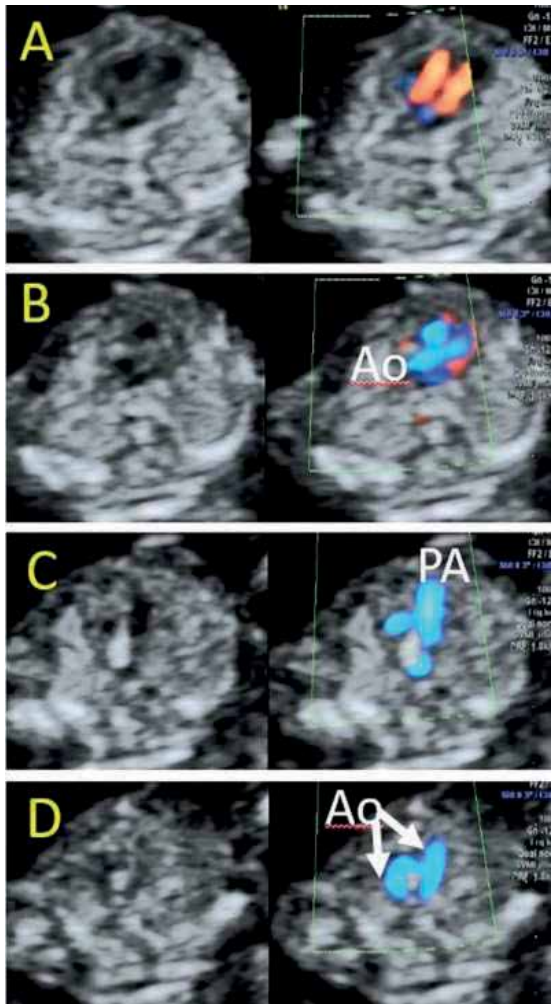

Figure 33. Double aortic arch. Four-chamber view with normal appearance (A), normal emergence of the aorta (B) and pulmonary artery (C), with the aorta coursing to the right of the spine and dividing in two branches that form a vascular ring around the trachea (D).

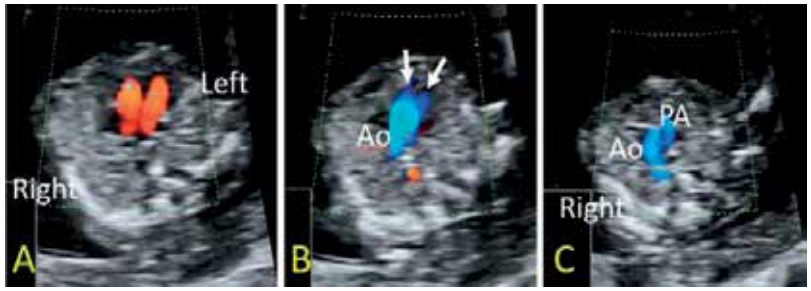

Figure 34. Tetralogy of Fallot with right aortic arch. (A): Normal appearance of atrioventricular flows; (B): overriding aorta; (C): aorta coursing to the right of the spine along the diminutive pulmonary artery.

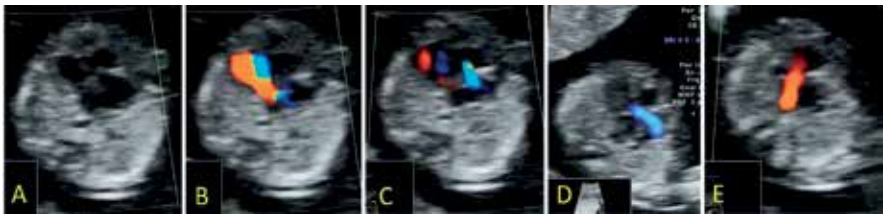

Figure 35. Hypoplastic right heart syndrome. Tricuspid atresia with intact septum. (A): Dysplastic thickened tricuspid valve in 4CV assessment, with lack of antegrade blood flow (B) and regurgitation (C). Normal aortic flow is visualized (D), and reversed ductal flow (E), by using color Doppler.

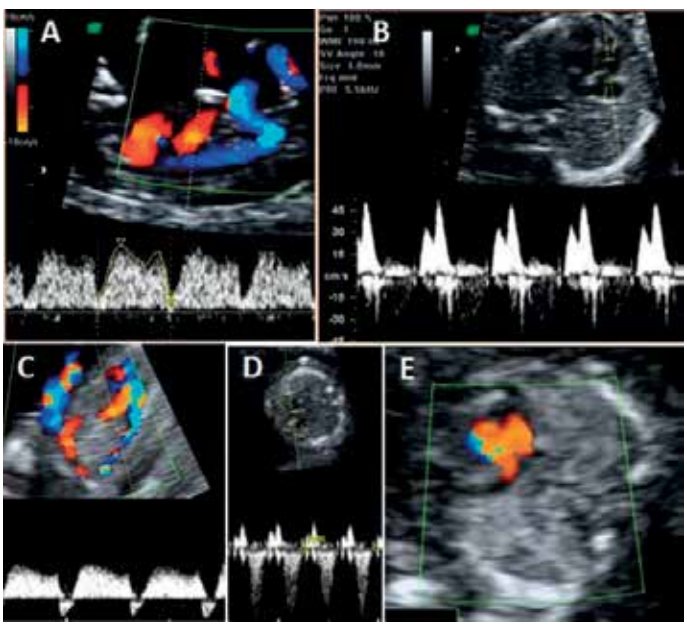

Figure 36. Normal flows at the pulsed Doppler interrogation of ductus venosus (A) and tricuspid valve (B). Ductus venosus with reversed a-wave (C) and tricuspid regurgitation (D) in fetus with atrioventricular septal defect (E).

than unselected population for NT ≥99th percentile [88]. Still, NT measurement is not a reliable screening test for CHD during FT, because of the overall low detection rates for CHD (around 15%) in unselected or low-risk populations [89, 90].

The performance of early screening for CHD achieved by measurement of fetal NT is improved by the assessment of ductus venosus and tricuspid valve flow pattern. In fetuses with enlarged NT (above 95 centile) and *absent or reversed a-wave in DV flow* the risk for major CHD is tripled [91]. The finding of reversed a-wave in chromosomally normal fetuses increases by almost 10 times the risk of CHD, with a predominance of right-heart anomalies regardless of the measurement of NT [86]. Also, chromosomally normal fetuses with *tricuspid valve regurgitation* have an 8-fold increased risk for CHD [92, 93].

Author details

Dominic Gabriel Iliescu[1], Ștefania Tudorache[1], Dragos Nemescu[2*], Monica Mihaela Cirstoiu[3], Simona Vlădăreanu[4], Claudiu Marginean[5], Iuliana Ceausu[3], Daniel Muresan[6], Marius Calomfirescu Vicea[7], Mona Elena Zvanca[3], Cezara Muresan[8], Laura Monica Cara[9], Ciprian Laurentiu Patru[1], Roxana Cristina Drăgușin[1] and Maria Sorop-Florea[1]

*Address all correspondence to: dnemescu@yahoo.com

1 Department of Obstetrics and Gynaecology, University of Medicine and Pharmacy, Craiova, Romania

2 Department of Obstetrics and Gynaecology, University of Medicine and Pharmacy, "Gr.T.Popa", Iasi, Romania

3 Department of Obstetrics-Gynecology, University of Medicine and Pharmacy, Bucharest, Romania

4 Department of Neonatology, University of Medicine and Pharmacy, "Carol Davila", Bucharest, Romania

5 Department of Obstetrics and Gynaecology, University of Medicine and Pharmacy, Targu-Mures, Romania

6 Department of Obstetrics and Gynaecology, University of Medicine and Pharmacy, "Iuliu Hatieganu", Cluj-Napoca, Romania

7 Secretary, Romanian Society of Ultrasound in Obstetrics and Gynecology, Bucharest, Romania

8 Department of Obstetrics and Gynaecology, University of Medicine and Pharmacy, "Victor Babes", Timisoara, Romania

9 Department of Public Health, University of Medicine and Pharmacy, Craiova, Romania

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Chapter 7

Neonatal Ebstein's Anomaly

Umar Boston, Ken-Michael Bayle,
TK Susheel Kumar and Christopher Knott-Craig

Additional information is available at the end of the chapter

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Abstract

Ebstein's anomaly is a congenital heart disease that results from failure of delamination of the tricuspid valve with resulting apical displacement of the septal and posterior leaflets of the tricuspid valve. Age at presentation can vary greatly but neonatal presentation is associated with extraordinary high mortality rates. Comprehensive multispecialty care is required starting at the time of fetal diagnosis. Fetal echocardiography is vital in monitoring progression of the disease in utero. Fetal echocardiogram can evaluate for complications such as arrhythmias, pericardial effusion, or fetal hydrops. Post-natal evaluation should include evaluation of functional pulmonary atresia or circular shunt. Despite advances in surgical technique for Ebstein's anomaly, mortality for it remains high with early surgical intervention. Aggressive medical management should be used to support patients with Ebstein's anomaly during the neonatal period. Surgical procedures for neonatal Ebstein's vary widely from systemic to pulmonary shunts with or without tricuspid valve closure to tricuspid valve repair.

Keywords: neonatal Ebstein's anomaly, Ebstein's anomaly, tricuspid valve dysplasia, Fetal Ebstein

1. Introduction

Ebstein's anomaly (EA) was first described by Wilhelm Ebstein in 1866 noting the septal and inferior leaflets of the tricuspid valve arose from the right ventricular myocardium [1]. EA is a rare congenital heart disease with a prevalence of 2.4 per 10,000 live births [2]. Embryologically, EA is a result of varying degrees of failure of leaflets to delaminate from the underlying endocardium that results in a number of characteristic features. There are varying degrees of apical displacement of the tricuspid leaflets with the septal leaflet most severely affected followed by the posterior leaflet. Furthermore, the right ventricle (RV) is myopathic and is separated into

two zones, with an "atrialized" poorly functional portion between the true annulus and the hinge point of the apically displaced septal leaflet, while the "functional" RV is the portion below the leaflet hinge point. Depending on the degree of leaflet displacement this functional RV volume can be quite diminutive.

The clinical manifestations of EA vary widely from mild forms presenting in adulthood, to severe forms with high mortality in the neonatal period. In utero, EA can result in hydrops and arrhythmia. Furthermore, an in utero diagnosis of EA has an incidence of 48% fetal demise [3]. Mortality rates are highest in the neonatal period ranging from 17 to 56% [4] and poses significant medical and surgical challenges.

2. Associated anomalies and arrhythmias

Ebstein anomaly is known to have several additional cardiac manifestations. A patent foramen ovale or atrial septal defect is normally present. The right to left shunting across the defect accounts for the relative hypoxia exhibited in certain patients. RV outflow tract obstruction in the form of anatomical pulmonary atresia occurs in about half of the symptomatic neonates requiring surgical intervention [5]. In the setting of pulmonary atresia, a patent ductus arteriosus is required as the source of pulmonary blood flow [6–8]. Left ventricular non-compaction cardiomyopathy has been noted to be associated with EA. A retrospective study demonstrated that 10 of 61 patients (16%) with EA also had left ventricular non-compaction [7]. This was associated with a higher mortality risk of 30% in those with LVNC compared to 13% with EA alone. Wolff-Parkinson-White (WPW) is present in about 10–30% of cases. In about 20% of cases with WPW, there may be more than two accessory pathways present. The accessory pathways are usually present on the tricuspid valve annulus [9, 10]. Due to large right atrium, EA patients are at risk for atrial tachycardia, atrial flutter, intra-atrial reentrant tachycardia, atrial fibrillation, AV node reentrant tachycardia, and ventricular arrhythmias.

3. Pathologic anatomy

Carpentier et al. described the characteristic features of this disorder that are relevant to surgical management [11].

1. Failure of delamination of the TV leaflets is the hallmark of EA whereby the leaflets are tethered to the endocardium by fibromuscular attachments or abnormal foreshortened chordae. Each leaflet exhibits varying degrees of apical displacement and tethering with the septal leaflet most severely affected followed by posterior then anterior leaflets. This results in anterior and apical displacement of the functional annulus.
2. The anterior leaflet is attached to the true anatomical annulus but is large or sail like.

3. The portion of the RV above the functional annulus ('atrialized right ventricle') is dilated and thin. The true tricuspid annulus is almost always enlarged. In a neonate this measures approximately 21 mm.
4. The cavity of the effective RV is reduced ('functional right ventricle').
5. The infundibulum of the RV can be obstructed by the redundant tissue of the anterior leaflet and its chordal attachments to the infundibulum.

In addition to the leaflet abnormalities there is a variable degree of ventricular myocardial dysfunction. Morphometric histopathologic studies have demonstrated that there is an absolute decrease in the number of myocardial fibers in addition to thinning of the wall of the dilated RV in EA [12].

Carpentier et al. also described four grades of Ebstein's anomaly [11].

Type A: The anterior leaflet has normal morphology and the RV is adequate.

Type B: The anterior leaflet has abnormal chordae but normal mobility. The RV is reduced in volume but adequate.

Type C: The anterior leaflet is restricted in movement. The RV is small with a large atrialized component.

Type D: Also called 'tricuspide sac' as the leaflets form a complete sac of fibrous tissue adherent to the RV. The only functional part of the RV is the infundibulum.

3.1. Perinatal period

The long term prognosis of a fetus diagnosed with EA is poor and remains one of the highest mortalities amongst congenital heart disease patients. One multicenter study showed that a fetal diagnosis of EA resulted in a 17% fetal demise. Furthermore, there was an additional 32% in-hospital attrition of live-born babies with EA with an overall 45% perinatal mortality [4]. Risk factors for perinatal mortality include lack of antegrade flow across the pulmonary valve, large cardiothoracic ratio, earlier in utero diagnosis, large tricuspid valve annulus, pericardial effusion, and right ventricular dysfunction [13–16]. Pulmonary valve regurgitation may be the most ominous risk factor representing the end result of severe tricuspid regurgitation with resultant volume load on a myopathic right ventricle that has to pump against retrograde flow from the PDA. This triad of diminished preload, increased afterload and a dysfunctional right ventricle leads to inadequate preload to the left ventricle and subsequent heart failure, cardiogenic shock and perinatal demise. These factors in-utero lead to hydrops and arrhythmias and ultimately fetal demise.

4. Pathophysiology of the newborn

Neonates are symptomatic as a result of ineffective RV cardiac output and severe TV regurgitation. There is usually some degree of cardiomegaly which can be quite severe compressing

the lungs. Furthermore, cyanosis results from systemic venous return being shunted across the ASD to the left side of the heart. Neonatal pulmonary vascular resistance (PVR) is elevated and this is a major impediment to effective antegrade flow from the diminutive and myopathic RV. In the first week of life when pulmonary vascular resistance is high pulmonary blood flow is dependent upon the PDA. This results in a physiological state referred to as "functional" pulmonary atresia. When the PVR decreases over the first week of life, the RV may then be able to overcome the afterload to establish antegrade flow. True anatomical pulmonary atresia where there is luminal discontinuity between RV and pulmonary artery is also often seen in these symptomatic neonates. These patients will have ductal dependent pulmonary circulation until a surgical procedure is performed to establish pulmonary blood flow. Left ventricular dysfunction can also play a critical role in the development of decompensated heart failure. This is related to left ventricular displacement of the interventricular septum as a result the severely dilated dysfunctional RV. This "pancaking" of the LV cavity impedes filling and diminishes systemic cardiac output. In less severe forms of EA the RV can generate effective antegrade flow especially when the PVR decreases. Antegrade flow across the RV outflow tract is accompanied by clinical improvement in symptoms. Neonates with severe TR or gross cardiomegaly who are otherwise asymptomatic have an associated mortality of 45% within the first year of life without intervention [17, 18]. The natural history of being diagnosed with EA during infancy is sobering [19]. However those who survive early childhood can expect reasonable longevity. When the disease is mild symptoms are not noticed until later in adult life. Symptoms are often related to exercise intolerance or cyanosis from progressive tricuspid regurgitation.

5. Diagnostic evaluation

5.1. Chest X-ray

Depending on the severity of disease, the chest roentgenograms usually demonstrates massive cardiomegaly with decreased pulmonary vascular markings (**Image 1**).

5.2. Electrocardiography

The electrocardiograms for patients with EA are usually abnormal. The most common finding on ECG are tall P waves and right bundle branch block. The tall P waves are indicative of a large right atrium. The right bundle branch block occurs because abnormal development of the right bundle branch which appears to be associated with septal leaflet and medial papillary muscle development on necropsy studies [5]. Some patients may have a prolonged PR interval from long intra-atrial conduction times from a large right atrium. Wolff-Parkinson-White syndrome is associated with EA, thus ventricular pre-excitation may be seen on ECG.

5.3. Echocardiography

Echocardiography is the gold standard for obtaining the diagnosis for EA. Two dimensional (2-D) echocardiography can evaluate the tricuspid valve leaflets and their excursion. The apical four

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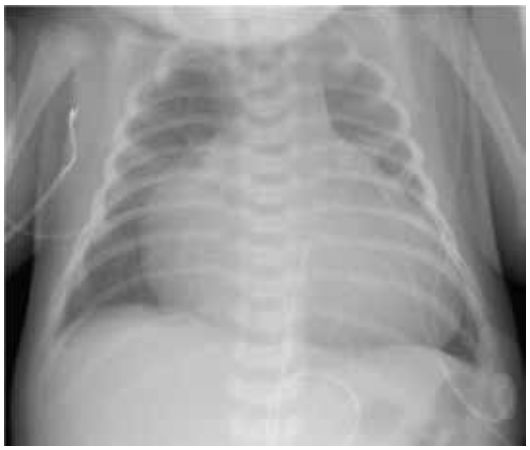

Image 1. Chest x-ray of an infant with EA. there is marked cardiomegaly with a significant cardiothoracic ratio. With marked cardiomegaly lung development can be impaired.

chamber views allow calculation of the displacement index, which measures the distance from the true septal annulus to the level of the apically displaced septal leaflet hinge point (**Image 2**). Distance is indexed to body surface area and values >8 mm/m^2 are consistent with EA [20]. Color Doppler echocardiography can demonstrate the presence and location of tricuspid valve regurgitation (**Image 3**) [21]. However, severity can be difficult to quantitate due to apical displacement. RV dysfunction and functional or anatomic pulmonary atresia can be evaluated by 2-D and color echocardiography [21] **Image 4**. The Great Ormond Street Echocardiogram (G.O.S.E.) score is a mortality risk stratification score for neonates with EA. It is calculated from the apical four chamber view by adding the right atrium and atrialized right ventricular volume and dividing by the sum of the functional right ventricular volume, left atrial and ventricular volumes. (18) A G.O.S.E score of 3 (ratio of 1.1–1.4) with cyanosis or 4 (ratio > 1.5) has a mortality of nearly 100% [18] **Image 5**.

Echocardiography can define other associated abnormalities with EA such as the presence of a patent ductus arteriosus, size and direction of shunting through the atrial septal defect/patent foramen ovale, presence of a ventricular septal defect, and hypertrabeculated left ventricle suggesting left ventricular non-compaction cardiomyopathy.

Fetal echocardiography is a useful diagnostic tool for prenatal diagnosis and monitoring progression of disease in utero. The 4-chamber view of the fetal heart will demonstrate apical displacement of the tricuspid valve annulus, enlarged right ventricular and atrial size, and large tricuspid valve annulus (**Image 6**). Color flow imaging can be used to evaluate the degree of tricuspid valve regurgitation. The pulmonary valve can be evaluated by 2-D and color flow imaging to assess for pulmonary atresia. M-mode assessment can determine any rhythm abnormalities such as supraventricular tachycardia [22]. In addition, signs of hydrops such as pericardial effusions can be visualized (**Image 7**).

Fetal echocardiogram is important for monitoring clinical status of the fetus during pregnancy. A large multicenter study performed by Freud et al. evaluated over 400 fetal echocardiograms of patients with EA. They demonstrated that larger cardiothoracic ratio, more than moderate

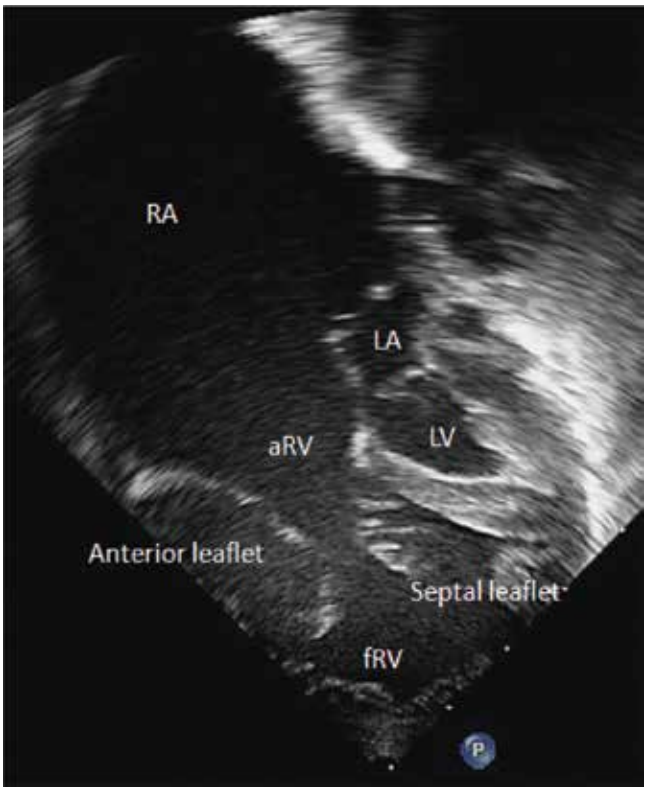

Image 2. Apical 4 chamber view of Ebstein's anomaly with severe enlargement of the right atrium and atrialized portion of the right ventricle. There is apical displacement of the tricuspid valve with tethering of the septal leaflet leading to poor coaptation and tricuspid valve regurgitation. RA: Right atrium. LA: Left atrium. aRV: Atrialized right ventricle. LV: Left ventricle. fRV: Function right ventricle.

tricuspid regurgitation, larger tricuspid annulus diameter z-score, larger diameter vena contracta for tricuspid regurgitation, lack of antegrade pulmonary blood flow, pulmonary regurgitation, and pericardial effusion were associated with increased perinatal mortality [4]. Furthermore, Tierney et al. demonstrated that only 31% of fetuses had no predictive risk factors for poor hemodynamic status at time of diagnosis, and of those, 61% went on to develop one or more signs later in gestation. As such, frequent fetal echocardiograms are necessary to monitor the clinical status of fetuses with EA [23].

5.4. Computed tomography/magnetic resonance imaging

There is limited utility for the use of CT, MRI, or cardiac catheterization in neonatal EA.

5.5. Treatment

5.5.1. Medical

In a study of 415 neonates presenting with symptomatic EA the overall hospital mortality was 24% [19]. Furthermore, surgical intervention in the neonatal period across US hospitals is

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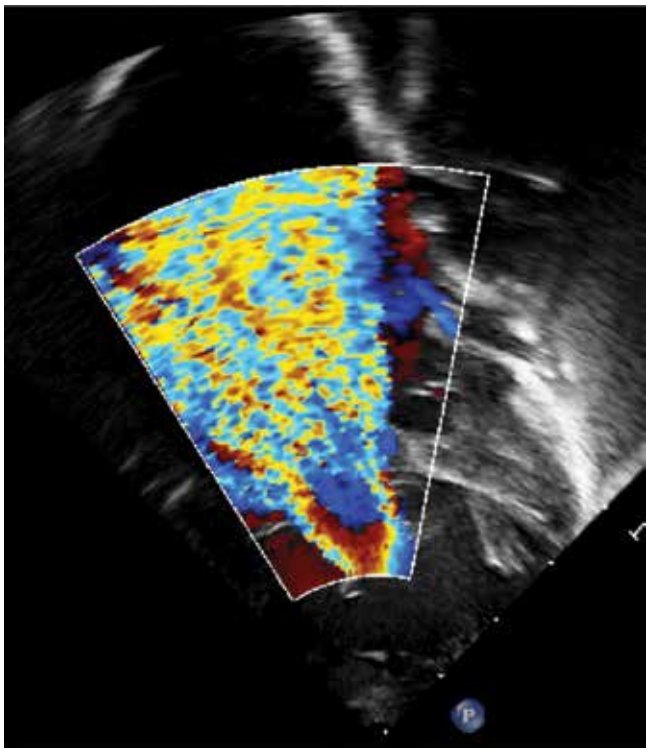

Image 3. Apical 4 chamber with color flow imaging of the tricuspid valve. There is severe tricuspid valve regurgitation due to poor coaptation of the tricuspid valve leaflets.

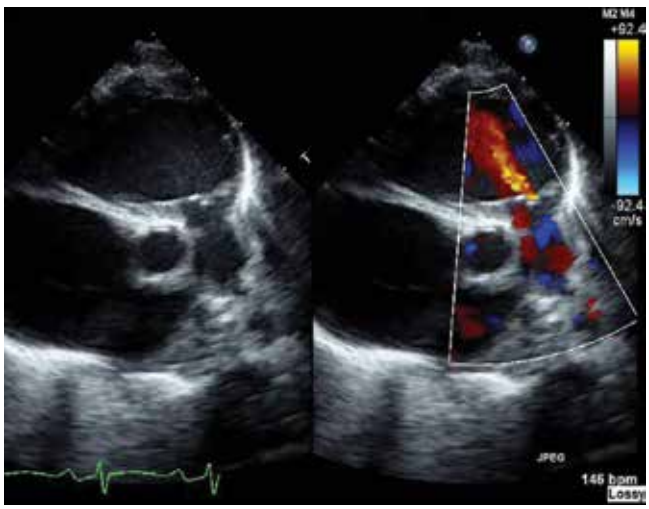

Image 4. Color compare parasternal short axis view demonstrates the small functional right ventricle and pulmonary atresia. The tricuspid valve is rotated in a fashion that the effective orifice opens to the right ventricular outflow tract. Color Doppler demonstrates swirling of blood in the functional right ventricle, tricuspid regurgitation, and no antegrade pulmonary blood flow. aRV: Atrialized right ventricle.

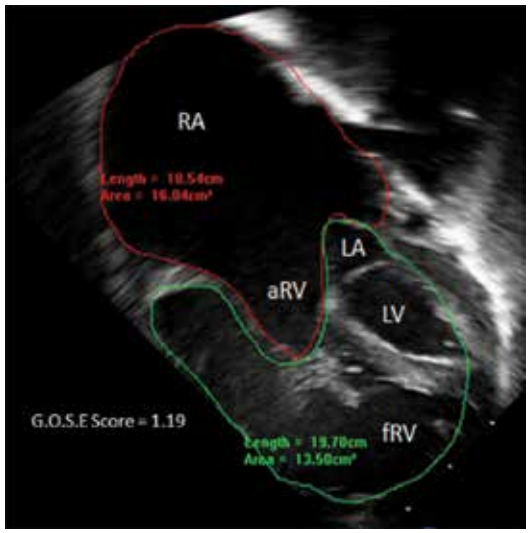

Image 5. Apical four chamber view demonstrating the right atrium, atrialized portion of the right ventricle, functional right ventricle, left atrium and left ventricle. There is a grade 3 GOSE score which correlates with 100% mortality in presence of cyanosis. RA = right atrium. aRV = atrialized right ventricle. fRV = functional right ventricle. LA = left atrium. LV = left ventricle.

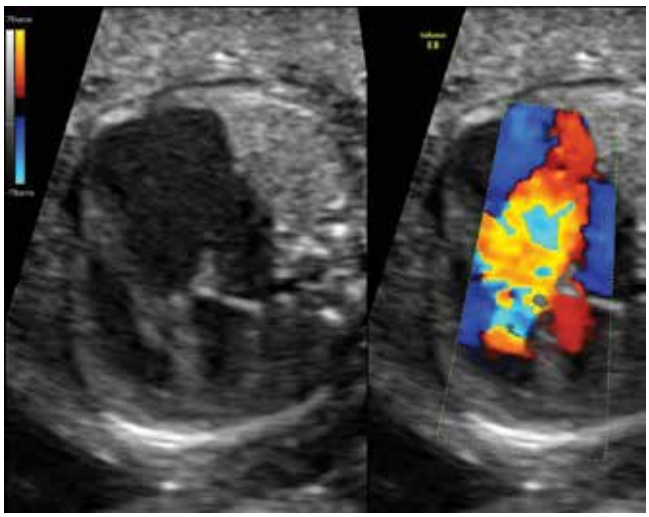

Image 6. Fetal echocardiogram performed at 22 weeks and 3 days gestation. There is severe enlargement of the right atrium with severe tricuspid valve regurgitation demonstrated on color Doppler evaluation. The tricuspid valve annulus dimension is markedly enlarged.

associated with a mortality of 27–36% depending on the procedure performed [19]. There is significant improvement in surgical outcome if the patient can be medically managed out of the neonatal period [24]. As such the best survival rates for EA occurs outside of the neonatal period, thus medical management with supportive care is crucial for improving outcomes.

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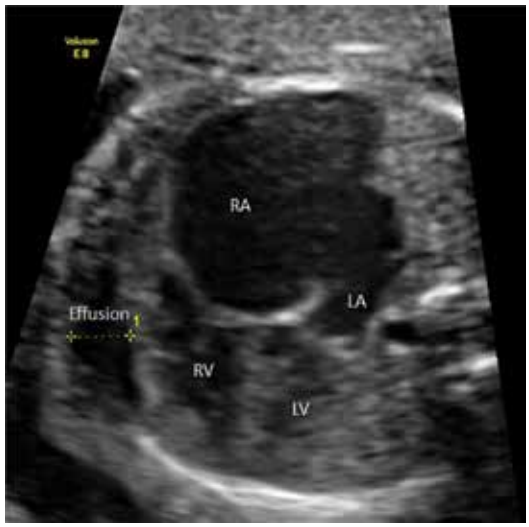

Image 7. Fetal echocardiogram at 22 weeks and 3 days gestation with a four chamber view of the heart. The heart mass takes up the entire thoracic cavity. There is severe enlargement of the right atrium with evidence of a pericardial effusion. RA: Right atrium. RV: Right ventricle. LA: Left atrium. LV: Left ventricle.

Relatively stable but symptomatic patients can be treated with prostaglandin infusion to maintain ductal patency if functional or anatomical pulmonary atresia is evident. Supplemental oxygen should not be greater than 21% fractional inspired oxygen to avoid pulmonary overcirculation and volume loading of the heart. During this phase oxygen saturation should be maintained between 75 and 85%. As the pulmonary vascular resistance decreases, prostaglandin therapy can be discontinued. This will also allow for proper evaluation of antegrade pulmonary blood flow as the ductus closes. If saturations decrease under 80% then agents to lower pulmonary vascular resistance can be administered to promote antegrade flow, these include supplemental oxygen and nitric oxide.

Use of prostaglandins in the presence of pulmonary valve regurgitation may exacerbate heart failure symptoms due to the development of a circular shunt. In this physiology blood flows from left ventricle to aorta, then it is shunted away from the systemic circulation via the large ductus to the pulmonary artery then retrograde via the pulmonary valve into the right ventricle to right atrium via the incompetent tricuspid valve then back to the left side of the heart via the ASD. This creates high output heart failure. Prostaglandins should be stopped if this physiology exists.

Further hemodynamic instability leads to cardiogenic shock. In these situations intubation and mechanical ventilation with large tidal volumes are key to promoting adequate ventilation in patients with massive cardiomegaly. Furthermore, sedation and possible paralysis to limit oxygen requirements may be required. Inotropic support in the form of milrinone complemented with low dose of dopamine or epinephrine may be necessary to assist with cardiac output. Tachyarrhythmias are common in this group of patients so utilization of catecholamine inotropes should be used sparingly.

Milrinone is a very effective drug since it has lusitropic and inotropic effects on the right ventricle. Furthermore, it decreases the pulmonary vascular resistance which promotes antegrade pulmonary blood flow. Frequent echocardiograms during the first week are useful to assess antegrade flow across the RV outflow tract and degree of TV regurgitation. This assessment will help guide weaning prostaglandins, and initiation of nitric oxide and inotropes.

In summary, medical management when pulmonary ductal dependency exists is analogous to single ventricle physiology whereby a balance between systemic and pulmonary circulation needs to be established. This is best done with maintenance of prostaglandins and low oxygen supplementation. Once the pulmonary vascular resistance drops and there is antegrade flow across the pulmonary valve then this management is more analogous to two ventricle physiology with a poor right ventricular pump. As such this is best managed by stopping prostaglandins and allowing for ductal closure. Concomitantly administration of nitric oxide, milrinone and higher oxygen supplementation will augment antegrade flow.

The goal of medical therapy is to avoid an operation particularly during the neonatal period when mortality is highest for any surgical procedure performed.

5.6. Surgical indications

Surgical indications for EA include failure to wean from mechanical ventilator support, failure to wean off prostaglandin with systemic oxygen saturation below 75%, functional or anatomic pulmonary atresia, Great Ormond Street Echocardiography (G.O.S.E.) score of 3 or 4, and patients with right heart failure.

5.7. Surgical procedures

To date there has been many procedures described for the surgical treatment for neonatal EA [11, 25–28, 31–35].

Danielson at the Mayo Clinic first described some of the essential principles for EA repair in any age group [25]. This includes plication of the atrialized RV, posterior tricuspid annuloplasty, closure of ASD and right reduction atrioplasty.

The cone reconstruction first described by da Silva and colleagues has now evolved into the technique of choice when repairing the tricuspid valve for EA [27]. In this procedure, the anterior and posterior leaflets of the tricuspid valve are mobilized from their attachments to the RV endocardium maintaining free edge attachments. The mobilized leaflets are rotated clockwise and then reattached to the true annulus [36]. To date there has been a growing number of reports of utilization of the Cone procedure for neonatal EA [27].

Starnes et al. reported a single ventricle palliation strategy for neonates with good outcome [29]. In the Starnes procedure the RV is excluded by performing a fenestrated patch closure of the tricuspid valve. An atrial septectomy allows for excellent mixing. Finally, a modified Blalock-Taussig-Thomas shunt is performed to establish a regulated source of pulmonary blood flow. Most neonates undergoing a Starnes RV exclusion procedure are then channeled down a single ventricle pathway with a bidirectional Glenn and Fontan procedures.

The two competing strategies for surgical treatment for neonatal EA are whether to perform a biventricular repair or a single ventricle palliative procedure (Starnes Procedure).

The decision for which type of repair is best for neonatal EA is controversial. Mizuno et al. described their center experience with neonatal EA repair. Their results demonstrated greater survival for the biventricular repair group compared to single ventricle palliation, 60 vs. 25% respectively [30]. A recent follow up study by Kumar et al. evaluated the median 7 year follow up for the Starnes procedure in 27 neonatal repairs [29]. Their overall survival for 5 year follow up was 81%. Boston et al. described their outcomes for neonatal biventricular repair for EA. Early survival was 78.1% in their series, while 15 year survival for EA with and without anatomical pulmonary atresia was 40 and 79% respectively. As such caution should be advised for biventricular repairs in EA neonates with anatomical pulmonary atresia [25, 36].

In summary, neonatal EA continues to carry a high perinatal mortality upon fetal diagnosis. A multidisciplinary approach is required for improved outcomes. Fetal echocardiography predicts outcome and is necessary for monitoring progression of EA complications. Comprehensive care with a multi-disciplinary team including high risk obstetrician, pediatric cardiologist, pediatric cardiothoracic surgeon, neonatal intensivist should occur at a tertiary care center. Surgical management during the neonatal period remains high. If possible medical management through the neonatal period improves mortality.

Author details

Umar Boston*, Ken-Michael Bayle, TK Susheel Kumar and Christopher Knott-Craig

*Address all correspondence to: uboston@uthsc.edu

Heart Institute at Le Bonheur Children's Hospital, University of Tennessee Health Science Center, Memphis, United States

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Chapter 8

Thoracic Anomalies

Cringu Ionescu

Additional information is available at the end of the chapter

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Abstract

The antenatal and postnatal prognosis for fetuses with chest noncardiac anomalies varies widely, depending of the type of lesion present. An important issue is to establish an accurate prenatal diagnosis, which allows an appropriate counseling of the couple, fetal karyotyping and eventually in utero fetal therapy, if possible. Also, another important feature is preparation for delivery in a tertiary center or an appropriate perinatal institution, able to provide care to the immediate neonatal consequences in such cases. The ultrasound exam is not only crucial in the diagnosis of such lesions, but also important in the serial antenatal follow up, some of them being progressive, and having the potential to lead to compromise of cardiac function and eventually to fetal death. Thus, the sonographer has an important role in the management of such difficult cases. Currently, perinatal centers provide multidisciplinary teams, with maternal fetal specialists, neonatologists, pediatric surgeons, all involved in counseling parents about the outcome and the management options for a fetus with a diagnosis of thoracic anomalies. Although the precise prenatal diagnosis is often possible, this does not necessarily ensure improvement of the postnatal outcome, due to associated pulmonary hypoplasia.

Keywords: thoracic anomalies, congenital cystic adenomatoid malformation (CCAM), bronchopulmonary sequestration (BPS), CCAM-BPS hybrid form, congenital diaphragmatic hernia (CDH), bronchogenic cyst, congenital high airway obstruction syndrome (CHAOS)

1. Introduction

The thoracic anomalies represent a group of abnormalities that can be found either in the lung parenchyma or mediastinum. The thoracic cavity has a conical shape and is delimited at the posterior level by the sternum, at the superior level by the clavicle, at the lower level by the diaphragm, and at the lateral level by the ribs. In the thorax, the organs that are examined by the

ultrasound are: the lungs, the heart and the mediastinum. The thoracic anomalies chapter refers to pulmonary and mediastinal fetal abnormalities, the cardiac abnormalities being a separate chapter. Congenital bronchopulmonary malformation comprises a group of abnormalities that are represented by the following entities: congenital cystic adenomatoid malformation (CCAM), bronchopulmonary sequestration (BPS), CCAM-BPS hybrid form, congenital diaphragmatic hernia (CDH), bronchogenic cyst, congenital high airway obstruction syndrome (CHAOS) and pulmonary hypoplasia/agenesis. Currently, it is recommended for the term bronchopulmonary anomalies to be used instead of congenital cystic adenomatoid malformation (CCAM) or bronchopulmonary sequestration (BPS), because it includes better the diagnosis given by the ultrasound, the prognosis and the therapeutic attitude. However, for teaching purposes, we will continue to keep the separate terms for each entity in part. The thoracic-pulmonary anomalies incidence is the following: CCAM—BPS around 40%, CDH around 40% and hydrothorax and other anomalies around 10% [1, 2].

The ultrasound investigation of the thorax is based on emphasizing of the following parameters:

- The size and shape of the rib cage,
- The aspect of the ribs, the pulmonary echogenicity,
- The mediastinal shift absence/presence,
- The diaphragm curvature.

The standard echographic image for assessing the fetal thoracic anatomy is represented by the four-chamber view image of the fetal heart. If a thoracic lesion is evident in this section, then it is necessary to subsequently use the midsagittal, parasagittal and coronal sections. In the midsagittal and parasagittal view, the presence of the diaphragm and the net delimitation between the thorax and the abdomen can be identified. The objectives, in case a congenital bronchopulmonary malformation is detected, are as follows:

- The description of the pulmonary anomaly
- The exclusion of other associated anomalies
- Establishing the prognosis
- Determining the effectiveness of the fetal therapy

According to the European Respiratory Society, we need to keep in mind the following aspects [1]:

- The bilaterality/unilaterality of the lesion,
- The localization (lateral or central),
- The cystic or hyperechoic characteristic,
- Cysts (number size, content), the presence or absence of a nutritive vessel,

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- Presence of hydrothorax,
- Mediastinal shift.

Thus, taking all these elements into account, we can classify the various thoracic anomalies as following:

- Unilateral hyperechoic lesions: CDH right sided, CCAM type III, BPS
- Unilateral anechoic lesions: CDH left sided, CCAM type I, unilateral fetal hydrothorax, bronchogenic cyst.
- Bilateral hyperechoic lesions: laryngeal atresia-CHAOS (congenital airway obstruction syndrome)
- Bilateral anechoic lesions: bilateral fetal hydrothorax
- Median hyperechoic lesions: mediastinal teratoma or hemangioma
- Median anechoic lesion: CDH

Depending on the location of the chest masses, we should consider the following possibilities:

- Left hemithorax: CCAM, CDH, BPS
- Right hemithorax: CDH, CCAM, BPS bronchogenic cyst, teratoma, hamartoma
- Anterior mediastinum: teratoma, thymoma
- Posterior mediastinum: teratoma, neuroblastoma, esophageal duplication
- Diaphragm: CDH

With the advantage of three-dimensional ultrasound (3D-US), we often can clarify the diagnosis of lung abnormalities. We can use 3D rendering, or reconstruction of the coronal plane, or minimal rendering mode, 3D with TUI (tomographic ultrasound image). With these ultrasound applications, it is possible to establish: liver position, liver outline, diaphragm outline, relationship between liver, pulmonary tissue and heart, presence of thoracic hypoplasia.

2. Congenital cystic adenomatoid malformation of the lung (CCAM)

2.1. Definition and incidence

Congenital cystic adenomatoid malformation of the lung (CCAM) is a lesion that is characterized by the presence of a mass of multicystic pulmonary tissue and is accompanied by bronchial proliferation. Its occurrence can be explained by:

- The lack of maturation of the bronchial tissue during the pseudoglandular stage of pulmonary development, which is between the 5th and 6th week of gestation [2]
- Focal pulmonary dysplasia with hamartomatous development at the terminal bronchioles [2]
- Secondary to the airway obstruction [3]

The estimated incidence is of 1 in 25,000 births, up to 1 in 30,000 births [4]. Most ultrasound detected CCAM lesions are unilateral and only 2–3% of them are bilateral and they are more frequently encountered in male fetuses [5]. In the case of unilateral lesions, a single lobe is usually involved and in rare situation it is the whole lung. Vascularization of the multicystic mass comes from a branch of the pulmonary artery. Recently, Stocker has classified CCAM in 5 types, depending on the group of airways involved: Type 0, the lesion is bronchial. Type 1, the lesion is bronchial/bronchiolar. Type 2, the lesion is bronchiolar. Type 3, the lesion is bronchiolar/alveolar. Type 4, the lesion is peripheral [6, 7]. A more practical classification is that which considers the ultrasound antenatal aspect, proposed by Adzick [8] and which describes the lesions as macrocystic or microcystic. Thus, CCAM has the following classification: Macrocystic type I with single or multiple cysts larger than 2 cm in diameter, CCAM type 2 with multiple cysts smaller than 2 cm and larger than 0.5 cm in diameter and type 3 with multiple cysts, less than 5 mm in size and with a hyperechogenic aspect. By advancing Adzick's classification, a simpler ultrasound classification was established by Wilson [9]. Thus, the ultrasound appearance is a cystic variant and a solid (or microcystic) variant. The cystic variant is multilocular lesions with cysts of various sizes from a few millimeters to 10 cm. The solid microcystic variant comprises a hyperechogenic mass.

2.2. Ultrasound diagnosis

CCAM ultrasound diagnosis is used for pointing out a cystic or solid lung tumor growth with the absence of systemic Doppler vasculature (**Figure 1**).

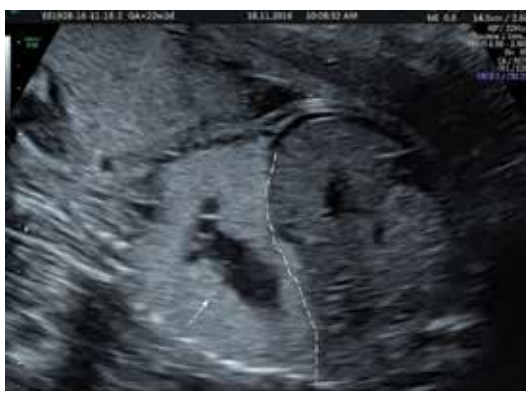

Figure 1. CCAM microcystic, parasagittal view: arrow—lung mass, line—diaphragm.

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It is possible to highlight the vascular flow of the lesion that comes from a branch of the pulmonary artery. The use of color Doppler is mandatory to highlight the absence of systemic vasculature and the presence of pulmonary vasculature for CCAM. From the ultrasound point of view, CCAM will be classified in macrocystic and microcystic (**Figures 2–4**).

Both the macrocystic form and the microcystic form can cause fetal hydrops and mediastinal shift (**Figure 5**).

The macrocystic types are rarely accompanied by fetal hydrops. The size of the lesion determines whether a fetus will develop hydrops or not [9]. Large scale macrocystic lesions cause mediastinal shift and cardiac decompensation, accompanied by increased venous central pressure, followed by the appearance of the fetal hydrops (**Figure 6**).

What is important to emphasize, is that the degree of the mediastinal shift has no predictive value for the appearance of the hydrops.

It should be underlined that there are CCAM hybrid lesions which refer to the presence of both pulmonary and systemic circulation that originates directly from the descending aorta [10].

The ultrasound differential diagnosis will consider the following: congenital diaphragmatic hernia (CDH), bronchopulmonary sequestration (BS), pericardial teratoma, enteric or bronchogenic cysts, bronchial atresia, esophageal duplication, neuroblastoma, brain heterotopia.

The differential diagnosis from CDH is not easy. The macrocystic form of CCAM can be confused with CDH left-sided; the intrathoracic stomach may resemble the macrocystic form. Highlighting intestinal peristalsis or emptying the herniated stomach can yield the diagnosis in favor of CDH. In addition, the size of the abdomen is normal, and the abdominal organs are in the normal position in case of CCAM (**Figures 7** and **8**).

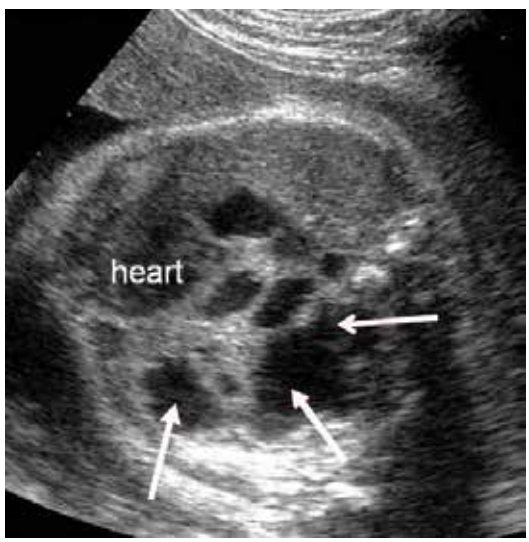

Figure 2. CCAM macrocystic: white arrow—lung cyst.

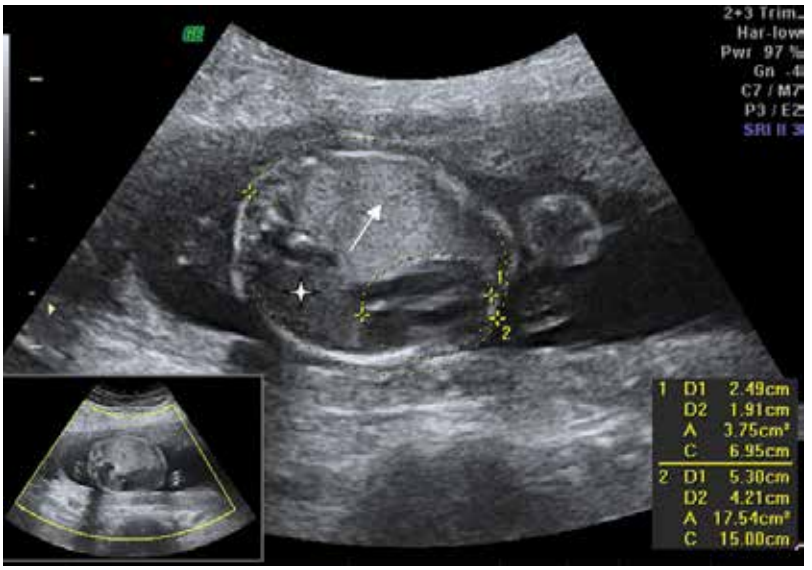

Figure 3. CCAM microcystic: arrow—lung mass, star—normal lung.

Bronchogenic cysts are uniloculated, rarely multicystic, located adjacent to the bronchus, but difficult to distinguish from the macrocystic form of CCAM. Pericardial teratoma may contain large cysts but they are usually associated with the pericardial fluid. The main differential diagnosis of microcystic form of CCAM is with BPS and CDH right

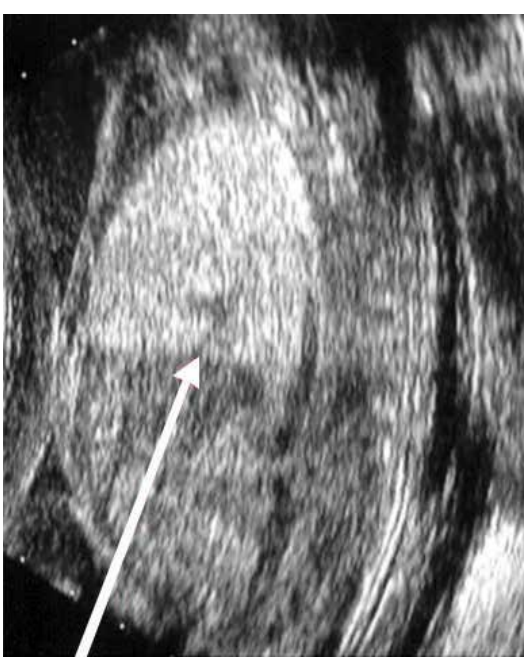

Figure 4. CCAM microcystic: white line—enhancement of diaphragm.

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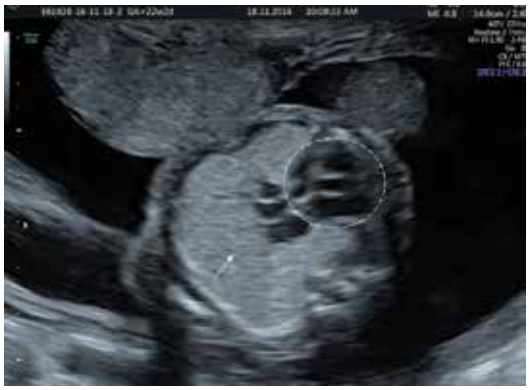

Figure 5. CCAM microcystic: arrow—lung mass, circle—cardiac shift.

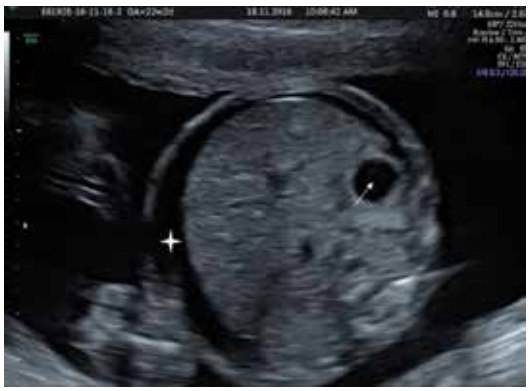

Figure 6. Fetal hydrops: arrow—stomach and star—ascites.

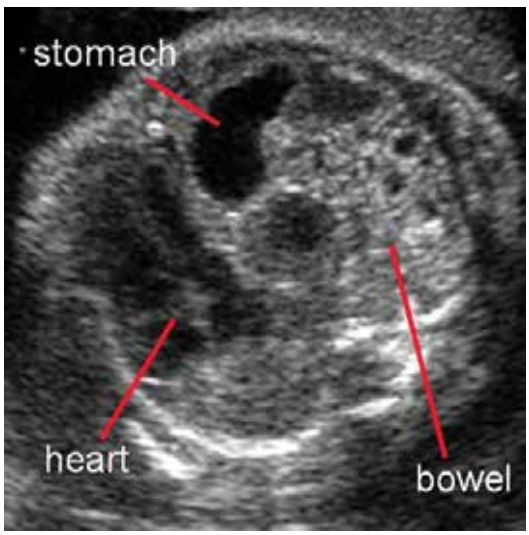

Figure 7. Differential diagnosis CCAM versus CDH left.

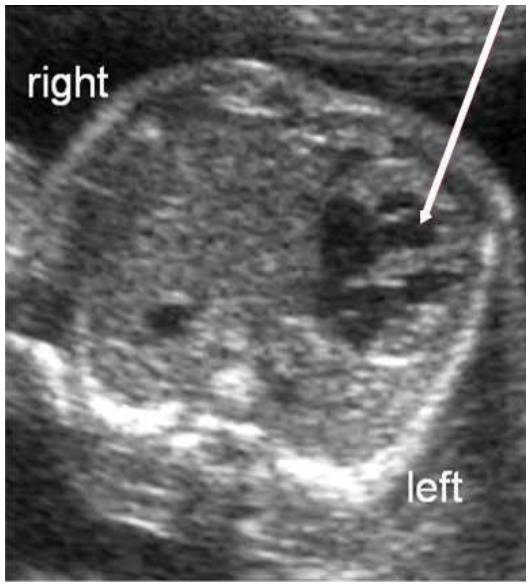

Figure 8. Differential diagnosis CCAM versus CDH right: white line—heart shift.

associated with liver herniation. Basically, the main distinguishing ultrasound element is that in BPS, vascularization originates from the systemic circulation, primarily the direct branch from the descending aorta, which can be easily demonstrated with Doppler color or HD-flow Color Doppler [9, 10]. The differentiation criteria between CCAM and BPS are shown in **Table 1**.

Therefore, the identification of the systemic circulation for a lung tumor mass is pathognomonic for BPS. Recently, Cass described 6 cases of CCAM that also had systemic vasculature and specific histological elements for BPS and CCAM, so these lesions were called hybrid lesions [10]. CDH right with hernia of the liver determines a significant mediastinal shift and secondary pulmonary compression. The highly hyperechogenic aspect of the CCAM microcystic form requires the differentiation from neuroblastoma as well. The association of CCAM with extrapulmonary abnormalities ranges from 0 to 26%, renal agenesis or dysgenesia being the most common associations [11, 12].

	CCAM	**BPS**
Location	Any lobes	Inferior left
Vascularization	Pulmonary	Systemic
Airway communication	Yes	No
Cysts	Yes	No

Table 1. Differential diagnosis CCAM versus BPS.

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2.3. Prognostic

CCAM is not associated with syndromes, the risk of chromosomal anomalies being extremely low. In the absence of hydrops, the long-term outcome of the fetuses with CCAM is good. The incidence of hydrops is 10% in cases of a large cystic mass [12]. Termination of pregnancy before 24-week gestation remains an option for the couple. In cases of prenatal diagnosis of CCAM, the parents should be counseled about the good prognosis even though the CCAM could need a surgical postnatal resection.

The most important factor for prognosis is the presence of hydrops, which is the most important predictor of poor prognosis. If hydrops is present, the chances of survival are very low, perinatal demise being the most frequent outcome, around 100%.

Another prognostic factor has been established with the use of 3D ultrasound, in determining the CAM volume ratio, (CVR) [13]. This parameter is calculated by dividing the volume of CCAM by the HC (head circumference). That is diameter (L × AP × T) × 0.52 divided by the HC. If CVR is more than 1.6 the incidence of hydrops is 75%.

2.4. Prenatal management

It is important to emphasize that the mass has an important potential growth between 20 and 26-week gestation, then there is a plateau, and afterwards the mass tends to regress. Thus, since the volume of a mass is not expected to increase after 26 weeks, and if there is no hydrops, then it is unlikely for the hydrops to appear after 26-week gestation. In cases of large masses, it is recommended to plan delivery in a tertiary center because of the risk of lung hypoplasia, cardiovascular decompensation and high mortality. The postnatal risk is high for large masses and low for small-medium masses (**Figure 9**).

Prenatal fetal therapy is indicated in cases that develop hydrops or cardiac failure.

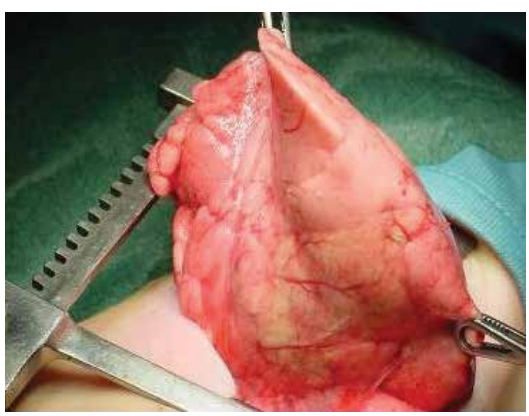

Figure 9. CCAM microcystic intraoperator view.

Karyotyping is not an indication if other anomalies are not present. However, amniocentesis for karyotyping is appropriate if fetal treatment is balanced or when the parents request it [14]. The attitude in CCAM associated with hydrops depends on the CVR value. Thus, if the CVR is less than 1.6 and we do not have a dominant cyst, then weekly fetal monitoring is indicated to identify early signs of hydrops. If we are dealing with a dominant cyst, even if CVR is less than 1.6, the fetus has a major risk of developing hydrops and a thoracoamniotic shunt should be considered at first signs of hydrops appearance. If CVR is above 1.6, the likelihood of developing hydrops is very high and monitoring is required 2 times a week.

The fetal therapy available nowadays is as follows: corticotherapy, in utero fine needle aspiration of macrocysts or thoracoamniotic shunt, laser vascular ablation and, finally, sclerotherapy [15]. A fetus with hydrops below 32-week gestation with a macrocystic lesion of CCAM will benefit from thoracoamniotic shunt. Also, the surgical resection is an option.

Corticosteroid treatment can be followed by the regression of the mass and it is especially indicated in cases of microcystic lesions. If CVR is equal to 1.6, corticosteroid therapy is indicated. Either fine needle aspiration or thoracoamniotic shunt improve the outcome of fetuses with macrocystic CCAM complicated with hydrops/hydrothorax. Microcystic lesions resulting in fetal hydrops of CCAM may need laser ablation of the feeding vessel, to improve survival and with regression of the lesion. The sclerotherapy is also indicated in microcystic cases and it is used Ethanolamine. But it must be emphasized that in most cases fetal CCAM needs only serial fetal surveillance, every 2 or 3 weeks, to confirm regression in size or the remaining at the same size.

3. Bronchopulmonary sequestration

3.1. Definition and incidence

Bronchopulmonary sequestration (BPS) represents a cystic mass of nonfunctioning pulmonary tissue with the blood supply from the systemic vessels and not from the pulmonary arteries.

The incidence reported is 0.5–6.0% of all prenatally diagnosed pulmonary lesions [16].

Pulmonary sequestration can be: intrapulmonary and extrapulmonary. Intrapulmonary sequestration (IPS) represents almost 75% of the cases, but this form is rarely diagnosed in utero. The abnormal lung tissue lies within the normal lung tissue. This variety is produced by the bronchial obstruction.

Extrapulmonary sequestration (EPS) is the most commonly form diagnosed in the prenatal life. The abnormal lung tissue has its own pleural covering, so the abnormal pulmonary tissue is separated from the normal pulmonary tissue and the pathologic tissue drains in the systemic circulation. The extrapulmonary sequestration is considered to be an abnormal pulmonary tissue that has no connection with the bronchial tree. The vascularization is provided by arteries emerging from the aorta.

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3.2. Ultrasound diagnosis

The prenatal ultrasound diagnosis of bronchopulmonary sequestration is based on the following elements:

- hyperechoic mass
- a mass with triangular shape, with a paraspinal localization, usually in the base of the left fetal chest.
- small or moderate size
- the large size can cause fetal hydrops
- color Doppler confirm the origin of the tumoral vessels as belonging to systemic vessels

Typically, BPS vascularization, and more specifically EPS, is supplied by a single artery, originating from the aorta (**Figure 10**).

The veins of the BPS drain in the azygos system and hemiazygos. At the opposite end, the venous drainage of the IPS is achieved through the pulmonary veins [17]. The hydrothorax can be associated with BPS, usually ipsilateral, and if it is important, it can cause a mediastinal shift.

Differential diagnosis includes the following: CCAM, bronchial atresia, lobar emphysema, CDH-particularly when the liver or spleen is the only component of herniation, mediastinal teratoma, neuroblastoma, mesoblastic nephroma, segmental thoracic obstruction, and thoracic kidney.

The differential diagnosis between CCAM and BPS, when no systemic feeding vessel is evident, is based on the echogenicity of the mass: the presence of cyst suggests CCAM, while the presence of a hyperechogenic triangular mass suggests BPS (**Figure 11**).

For extrapulmonary BPS, the differential diagnosis includes: mesoblastic nephroma, and neuroblastoma.

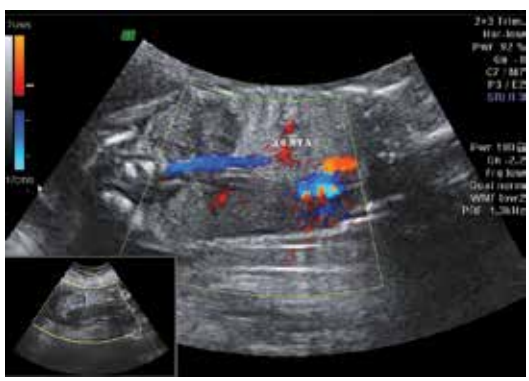

Figure 10. Bronchopulmonary sequestration: systemic vascularization.

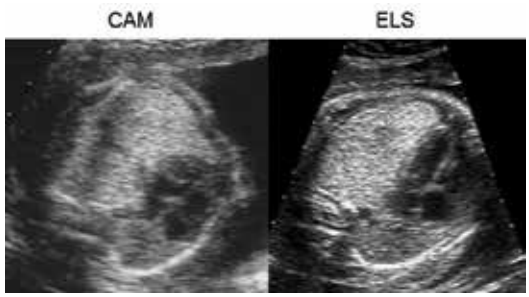

Figure 11. Differential diagnosis CCAM versus BPS.

3.3. Prognosis

The prognosis of BPS is favorable in the absence of other associated abnormalities. In many case series it was found that, similar to CCAM evolution and in BPS cases, there is often present a regression of the lesion [18, 19]. However, in fetuses with BPS associated with fetal hydrops, the prognosis is poor (**Figure 12**).

Fetal hydrops occurs only if a tension hydrothorax develops. The cause of unilateral hydrothorax associated with BPS is not well-defined. The torsion of a vascular pedicle or abnormal pressure gradient between the systemic artery and the pulmonary vein may be the cause [19]. Regardless the etiology, the persistence of the hydrothorax causes pulmonary compression with pulmonary hypoplasia and the impairment of the caval venous drainage due to mediastinal shift.

3.4. Prenatal management

In isolated BPS karyotyping is not mandatory, but it is recommended if any other abnormality is associated. Fetal MRI may be useful for differential diagnosis. The family may choose to terminate the pregnancy if the diagnosis is established before 24 weeks and it is associated with other abnormalities such as: esophageal atresia, neurenteric cyst, CDH, pulmonary hypoplasia, cardiac

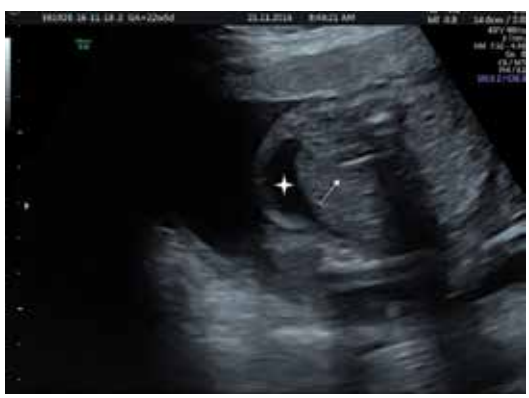

Figure 12. Fetal hydrops and BPS: arrow—BPS mass, star—hydrothorax.

anomalies and bronchogenic cyst. Fetal monitoring is required in the prenatal period, to identify the appearance of the hydrothorax. A fetus with isolated BPS has good chances of survival in the absence of hydrops, polyhydramnios or pleural effusion, because it can regress in 80% of cases. Fetuses over 30-week gestation should be considered for preterm delivery and ex-utero surgical resection. In the presence of hydrops before 30 weeks, placing a thoracoamniotic shunt may be offered. In hydrothorax, installing the thoraco-amniotic shunt may prevent the development of fetal hydrops. The postnatal therapy consists of the endoscopic removal of the pulmonary mass and alternatively the selective embolization of the artery that feeds the tumor [20–22].

In brief, for the two main anomalies CCAM and BPS, we can apply the following therapeutic scheme:

- CCAM/BPS stable as dimensions and stationary as evolution: near-term birth and ex-utero resection
- Regressive CCAM/BPS: term delivery and evaluation
- Progressive CCAM/BPS towards hydrops and mediastinal shift: it depends on the gestational age of the fetus. Thus, if it is less than 32 weeks, then a thoraco-amniotic shunt or resection in utero and cesarean delivery is recommended near term. After 32 weeks' gestational age, the iatrogenic preterm birth and resection ex utero are recommended.

4. Pulmonary hypoplasia and pulmonary agenesis

4.1. Definition and incidence

Congenital pulmonary hypoplasia consists of the lowering of the lung volume in comparison to the lung volume corresponding to the gestational age. The causes of pulmonary hypoplasia are represented by: congenital diaphragmatic hernia (CDH), oligohydramnios, skeletal dysplasia, chest tumors, neuromuscular disorders that obstruct fetal respiratory movements. A rare cause is represented by the obstructive cardiac abnormalities of the right-sided heart, which may be accompanied either by the absence of the development of a single lung or the absence of the development of both lungs. Regardless the mechanism, pulmonary hypoplasia is responsible for the neonatal mortality, of 10–15% [23]. Pulmonary agenesis can be classified into three groups [23, 24]: in group 1, there are bronchial and lung agenesis, in group 2 there is a rudimentary bronchus without bronchial tissue and in group 3 it is a bronchial hypoplasia and a hypoplasia of lung tissue. Pulmonary agenesis is usually unilateral, and occurs at 4 weeks of gestation. The etiology of this anomaly is unknown. The incidence of pulmonary agenesis, either unilateral or bilateral, is very low, 0.0097% or 1 at 10,000 pregnancy [22]. More than half of the fetuses with pulmonary agenesis have other associated abnormalities: gastrointestinal, cardiovascular and genitourinary. Unilateral pulmonary agenesis may be associated with numerous other abnormalities: patent ductus arteriosus (PDA), atrial and ventricular septal defects, anomalous pulmonary venous drainage, tracheoesophageal fistula and duodenal atresia, hemivertebrae with scoliosis, facial abnormalities and limb abnormalities.

4.2. Ultrasound diagnosis

The ultrasound diagnosis is established on the axial section of 4 chambers of the heart. Unilateral pulmonary hypoplasia determines the mediastinal shift to the hemithorax where the lung is absent and the existing lung is highly hyperechogenic. Usually, unilateral pulmonary hypoplasia (especially the right one) is part of the scimitar syndrome, which is an abnormal venous return in the inferior vena cava (both pulmonary veins are absent and replaced with a collecting vein that drains into the inferior vena cava and which at 3D ultrasound resembles a scimitar). In the case of unilateral pulmonary agenesis, the ultrasound aspect is somewhat similar to the one made in case of CDH, by the mediastinal shift, but there is no abdominal viscera noticed inside the rib cage. The color Doppler can be used to highlight the absence of the pulmonary vascular system. Pay attention to differential diagnosis of CDH with pulmonary compression and CCAM, for unilateral lung agenesis advocates the mediastinal shift to the agenesis side and the enlarged hyperechogenic lung herniated in the contralateral chest through the mediastinum.

Bilateral pulmonary hypoplasia is caused by a skeletal dysplasia that is associated with a significant reduction in thoracic volume. Quite rarely, bilateral pulmonary hypoplasia is primary, and it is more commonly secondary to a prolonged oligohydramnios after a long lasting very premature rupture of membrane. The ultrasound diagnosis is also done on the axial section of four chambers view of the heart. The aspect is that the heart fills all the thorax, there is no lung tissue and the rib cage is extremely small. There are nomograms in the literature for thoracic circumference versus gestational age or cardiothoracic ratio.

There is an association of unilateral/bilateral pulmonary agenesis with facial, radial anomalies, genitourinary anomalies, polyhydramnios or oligohydramnios.

The differential diagnosis of unilateral agenesis is done with CDH, CCAM and BPS.

4.3. Prognosis

Bilateral pulmonary hypoplasia is fatal. The risk of chromosomal anomalies is rare, but the risk of association with non-chromosomal syndromes is high. A study comparing eight echographic parameters for the prediction of lethal pulmonary hypoplasia showed that the use of the pulmonary area/abdominal circumference and thoracic circumference/abdominal circumference ratio are the most clinically useful in the prediction of bilateral pulmonary hypoplasia [23]. In the case of unilateral pulmonary agenesis, the duration of neonatal survival is higher for the left one in comparison to right one, probably due to the cardiac and mediastinal shift which is with less distortion of the blood vessels and bronchi. The fetuses with unilateral agenesis have a neonatal risk for repeated bronchopulmonary infections and respiratory distress syndrome. The cause of high neonatal mortality is the pulmonary infection and the association with cardiac abnormalities.

4.4. Prenatal management

In the case of unilateral hypoplasia, no karyotyping is required, but the birth is recommended to occur in a tertiary center because of the risk of orotracheal intubation immediately after the

delivery. Bilateral lung agenesis is incompatible with life. In the case of the primary bilateral pulmonary hypoplasia or associated with skeletal dysplasia, the importance of a correct diagnosis is not only for the current pregnancy that will evolve to the exitus of the fetus but also for a future pregnancy because skeletal dysplasia may not occur sporadically but exhibit recessive inheritance. In unilateral pulmonary hypoplasia associated with the scimitar syndrome, neonatal ventilation may be required. Fetal MRI may be useful in distinguishing between the pulmonary agenesis and CCAM [23, 24]. At the same time, the exclusion of associated fetal abnormalities can be done by MRI, in particular: ipsilateral upper extremities, mandible, face, or kidneys. There is no fetal intervention available in pulmonary agenesis.

5. Bronchogenic cysts

5.1. Definition and incidence

It comes from the primitive foregut early in the embryogenesis. It contains the columnar ciliary epithelium and the cartridges. They are usually located intrapulmonary but may also be mediastinal [25], or intrapericardial. They may also be located cervical or infradiaphragmatic. They can basically be located anywhere on the tracheoesophageal tract. It is extremely rare.

5.2. Ultrasound diagnosis

The diagnosis of bronchogenic cysts can be established on the axial section of the four chambers of the heart. It appears as a unilateral, circumscribed, thin wall lesion (**Figure 13**).

They may rarely be multilocular. The bronchogenic mediastinal cyst can compress the trachea or bronchi so that the distal lung becomes dense and expansive, in this way lending the specific echographic aspect for the cystic adenomatoid malformation [26]. The differential diagnosis includes: CCAM, esophageal duplication cyst, pericardial cyst, duplication cyst and lymphangioma. In CCAM, the tissue surrounding the cyst is hyperechogenic.

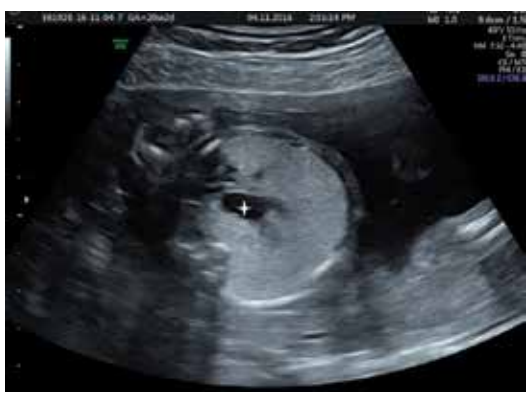

Figure 13. Bronchogenic cyst: star—lung mass.

5.3. Prognosis

One of the few negative prognostic factors is the size of the mass.

5.4. Prenatal management

The presence of bronchogenic cysts does not cause the death of the fetus in utero [25, 26]. It is not recommended to perform karyotyping because the risk of associated chromosomal abnormalities is extremely low. There is, however, the risk of an emergency intubation at birth, so birth is recommended to take place in a tertiary center.

6. Congenital high airway obstruction syndrome (CHAOS—laryngeal atresia)

6.1. Definition and incidence

Congenital high airway obstruction syndrome (CHAOS) occurs due to laryngeal atresia, tracheal atresia, or laryngeal cyst [27]. There are three types of laryngeal atresia: type I-agenesis of glottis, Type II agenesis of larynx, type III-agenesis of both [28]. The laryngeal atresia is difficult to differentiate using ultrasound from tracheal atresia and both are diagnosed based on intrathoracic signs. The exact incidence of this syndrome is unknown, but it is an extremely rare abnormality. The cause of tracheal/laryngeal atresia is not clear, but it appears to be a vascularization deficit during the embryogenic period [29, 30].

6.2. Ultrasound diagnosis

The ultrasound diagnosis is done on the four-chamber axial section. It is noted that both lungs are hyperechogenic, large in size, flattening the diaphragm due to the large volume of the lungs, the heart appears smaller due to the compression exerted by the lungs, the axis of the heart is zero, the dilatation of the tracheobronchial tree can be seen by the accumulation of liquid at its level (**Figure 14**).

On the coronal section, the dilated trachea and bifurcation of this, as well as the diaphragmatic flattening, can be better emphasized. The differential diagnosis of CHAOS does not have what entity to do, because it is a unique anomaly. At most, bilateral CCAM can be considered in the differential diagnosis, but bilateral CCAM is very rare and it does not present a severely increased volume of both lungs.

6.3. Prognosis

This anomaly is fatal. It may be part of the Fraser syndrome [29, 30], which includes: laryngeal atresia, renal agenesis, oligoamnios, microphthalmia, syndactyly, polydactyly. The prognosis is even more severe because the recessive autosomal is transmitted. The risk of chromosomal anomalies is low.

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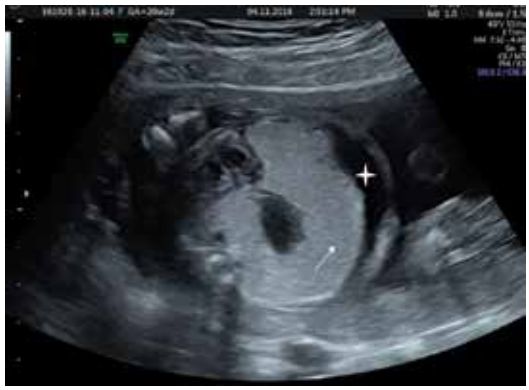

Figure 14. CHAOS: dilatation of tracheobronchial tree.

6.4. Prenatal management

Karyotyping is not indicated because the risk of chromosomal abnormalities is low. The ultrasound should also focus on the exclusion of structural heart or kidney abnormalities. Delivery should take place in a tertiary center. The only option that exists to save a fetus with CHAOS is the EXIT procedure (ex utero intrapartum treatment). So far, only 9 cases have survived through this procedure [29].

7. Fetal hydrothorax

7.1. Definition and incidence

Fetal hydrothorax (FHT) represents the accumulation of fluid in the pleural cavity, between the parietal and the visceral pleura. It can be unilateral or bilateral. It can be isolated or in the context of a generalized hydrops, or associated with other fetal abnormalities.

The incidence is not specified given the variability of the causes, but in the antenatal period, the secondary causes of hydrothorax are more common [31]. The causes that can lead to the occurrence of fetal hydrothorax are multiple: congenital infection (parvovirus, TORCH), isoimmunization, congestive heart failure, Down syndrome, Turner syndrome. Primary FHT is called chylothorax. Secondary FHT usually appears secondary to chromosomal, cardiac, gastrointestinal and infectious abnormalities. FHT generally precedes the installation of fetal hydrops. The appearance of primary FHT is due to a structural defect in the lymphatic system: the obstruction of bronchomediastinal trunks to the venous system, congenital absence of the thoracic duct, congenital hypoplasia of the pulmonary lymphatic vessel [31, 32]. It is a diagnostic of exclusion. In general, primary FHT occurs as a result of the obstruction of secondary lymphatic drainage to a heterogeneous group of developmental defects of the lymphatic system. Unilateral FHT may happen due to a unilateral pathological process such as: congenital diaphragmatic hernia, cystic adenomatoid malformation, pulmonary hypoplasia.

7.2. Ultrasound diagnosis

The diagnosis of fetal hydrothorax is established on the axial image of the four chambers of the heart, as an anechoic area around the pulmonary tissue which limits the mediastinum. Effusions can be unilateral or bilateral (**Figure 15**).

The hydrothorax aspect is that of a peripheral anechoic space in the thorax, compressing the lung tissue. In the case of large bilateral effusions, the aspect is that of the lungs balloting in the rib cage. At the same time, mediastinal shift and the eversion of the diaphragm occur with the displacement of the heart to the contralateral side and they can cause the disruption of the hemodynamic function and the installation of nonimmune hydrops. If the pleural effusion is part of the nonimmune hydrops, then it is also possible to see the edema of the thoracic subcutaneous tissue. It is important to note that FHT associates with the polyhidramnios in over 50% of cases, either due to a mediastinal shift that causes the compression of the esophagus or because of an alteration in the production of amniotic fluid by the compressed lungs.

The differential diagnosis is important because it should be determined whether FHT is primary or secondary. Primary hydrothorax is usually a chylothorax and it is unilateral and is a diagnostic of exclusion. However, the fetus with trisomy 21, Noonan syndrome, and Turner syndrome, may present either unilaterally or bilaterally hydrothorax [31]. For secondary hydrothorax, evidence of specific echographic elements for CDH, CCAM, BPS determines the diagnosis. In the case of the fetuses with hydrops, the presence of fetal anemia should be excluded.

7.3. Prognosis

The most important element of prognosis is whether fetal hydrothorax is associated with non-immune fetal hydrops, because in this situation the fetal mortality is increased. Other negative prognostic factors are FHT associated with cardiac abnormalities or with central nervous system anomalies. The only positive prognostic factor is the presence of FHT without another associated anomaly or other fluid effusion with another location. Isolated small FHT at the fetus without any other abnormalities, without hydrops or abnormal karyotype, has a favorable prognosis, because the fetus usually tolerates well small effusions [31, 32]. What is important to remember is that 10–25% of the cases of chylothorax can regress spontaneously

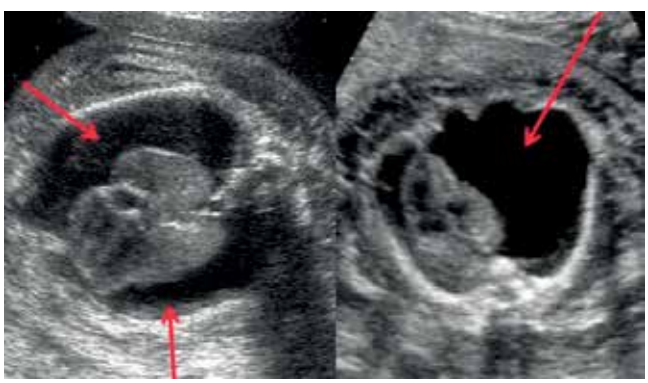

Figure 15. Bilateral hydrothorax: arrow—hydrothorax.

or after only a single drainage [32]. Delivery by vaginal route is an option although there is an increase incidence of the rate of cesarean section [33].

7.4. Prenatal management

It is mandatory to determine the karyotype in FHT due to the increased risk of association with chromosomal anomalies. Even if the fetus tolerates small isolated effusions, a serial echographic surveillance is required because small hydrothorax can progress rapidly to large effusions that may have negative hemodynamic consequences. Therefore, ultrasound monitoring is recommended every 1 or 2 weeks, due to the risk of polyhidramnios and preterm delivery. Birth in a tertiary center is recommended.

If FHT was diagnosed before 24 weeks, the therapeutic interruption of the pregnancy is an option. If the fetus with FHT has more than 32 weeks, then the serial ultrasound at one or 2 weeks distance is recommended, but we can also consider thoraco-amniotic shunt. If the fetus has less than 32 weeks we have three options: thoracocentesis, thoracoamniotic shunt, thoracomaternal cutaneous drainage. The initial step is the thoracocentesis and diagnosis for cell count, culture, or the viral culture. In general, thoracocentesis other than for diagnosis is ineffective because after it is done a re-accumulation of the pleural fluid occurs. The rapidity with which the effusion accumulates after the initial puncture is an indicator of the pleural effusion severity. For this reason, pleural cavity decompression is done through thoracoamniotic shunt. Large FHT is drained through thoracoamniotic shunt especially if hydrops is present. Shunting is especially effective if the fetus has less than 32 weeks of gestation [34]. The failure rate for thoracoamniotic shunt is of 26% [34, 35]. Shunt complications are: blockage, migration, fetal death. If a thoracoamniotic shunt is mounted the incidence of survival increases from 10 to 60%.

8. Fetal mediastinal cysts

8.1. Definition and incidence

Fetal mediastinal cysts are represented by: pericardial cyst, thymic cyst, esophageal duplication cyst, neurenteric cyst. The incidence of these masses is not known because they are rare pathological entities and only case reports are reported. The pericardial cyst is located at the costophrenic right angle level. The pericardial cyst is covered by mesothelium and has fluid content, and is usually asymptomatic. If the size of the cyst is important, then it can be associated with fetal hydrops, or with the change in heart function at birth [17]. If the pericardial cyst size is reduced in size, it can also regress.

The thymic cyst is very rare, representing 4% of postnatal mediastinal cystic masses [17, 35]. Thymic cysts are asymptomatic, but the prenatal diagnosis is possible.

The esophageal duplication cyst exhibits ectopic gastric mucosa, communicating with the gastrointestinal lumen. Sometimes they may not communicate with the gastrointestinal lumen [17, 36]. The communication with the gastrointestinal lumen is located either above the diaphragm or below the diaphragm.

The neurenteric cyst has a connection with the meninges and the spinal cord and it is usually associated with congenital scoliosis or spina bifida.

8.2. Ultrasound diagnosis

The prenatal diagnosis of esophageal duplication cysts is based on the spherical aspect of the cyst, rarely on the tubular aspect, but with a thick, hyperechogenic wall determined by the presence of the gastric mucosa. Usually, the cyst is connected to the esophagus. If the dimensions of the esophageal duplication cyst are large due to the compression effect on the esophagus, the appearance of polyhidramnios may occur [37, 38]. The thymic cyst is formed from remnants of the thymopharangeal duct; they are usually very small and localized to the anterior mediastinum [38]. The ultrasound aspect is of a transonic mass surrounded by the thymic tissue and located in the previous mediastinum.

Pericardial cyst, originating from the pericardium, appears at ultrasound examination as a thin walled, unilocular, fluid-filled transonic mass in the left or the right of the cardiophrenic angle. The cyst wall may communicate with the pericardial space.

Neurenteric cysts are very rare; only eight cases have been diagnosed in the prenatal stage by the ultrasound [37–39]. If the size of the cyst is large, it can exert cardiac compression with the subsequent appearance of the hydrops. It can also exert compressive phenomena on the bronchi, which causes neonatal respiratory distress. Association with anomalies of the membrane can be encountered [40].

The differential diagnosis among the described mediastinal masses is sometimes difficult. Several elements should be considered: pericardial cyst is located in the cardiophrenic angle of the right hemothorax, thymic cysts are located in the anterior mediastinum and are surrounded by thymic tissue, and the enteric duplication cyst is in close contact with the esophagus [41, 42]. For differential diagnosis, we can also use fetal MRI. The origin of the mass can be established sometimes only after perinatal autopsy [43].

8.3. Prognosis

The prognostic thymic cyst is favorable without affecting the condition of the fetus. The pericardial cyst can determine hydrops due to the compression on the heart. However, sometimes even in the case of reduced size, the pericardial cyst can be resorbed. The neurenteric cyst can cause cardiac compression and the appearance of hydrops as secondary effect. The esophageal duplication cyst determines polyhidramnios due to compression on the esophagus. The risk of chromosomal anomalies is absent, so karyotyping is not recommended.

8.4. Prenatal management

The indication of in utero treatment is represented by the presence of hydrops and the presence of compression of the tracheobronchial tree [44]. Puncture with cyst aspiration or the EXIT techniques are the treatment options in such cases.

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Author details

Cringu Ionescu

Address all correspondence to: antoniuginec@yahoo.com

Department of Obstetrics and Gynecology, Clinical Emergency Hospital St Pantelimon, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

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Chapter 9

Congenital Diaphragmatic Hernia

Adrian Claudiu Ratiu

Additional information is available at the end of the chapter

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Abstract

Over the past 20 years, prenatal detection of congenital diaphragmatic hernia (CDH) has improved worldwide, reaching up to 60% in Europe. Pulmonary hypoplasia and persistent pulmonary hypertension are the two main determinants of neonatal mortality and morbidity, so new tools have been focused on their evaluation. Fetal surgery for severe cases requires proper evaluation of the prognosis of fetuses with CDH. It is very important to identify reliable prenatal prognostic factors that can be used worldwide for several reasons: patient counseling is more accurate; the results of pre- and postnatal treatments will be comparable across different institutions; fetuses eligible for fetal surgery will be selected correctly; and a woman expecting a child with a very poor prognosis can prepare herself for the postnatal demise of her baby or, in some countries, opt for termination of pregnancy.

Keywords: congenital diaphragmatic hernia, thoracic anomalies, diaphragm anomalies

1. Introduction

Congenital diaphragmatic hernia (CDH) consists of a defect in variable size in the fetal diaphragm. It occurs more often on the left side and abdominal organs herniate into the thoracic cavity. Most if the time the diagnosis is made during the second trimester fetal morfology ultrasound examination. Diagnosis is based mainly on finding abdominal organs such as stomach, bowel, and liver in the chest cavity or in the presence of a chest mass which pushes the heart toward the lateral thoracic wall.

Although the surgical repair offers excellent results from the technical point of view, the problem with these patients are related to the impaired development of the lungs and their vasculature, therefore, the mortality and morbidity of these babies remain high even after surgery.

2. Spectrum of disease

2.1. Definition

Congenital diaphragmatic hernia (CDH) is defined by the presence of an orifice in the diaphragm that permits the herniation of abdominal contents into the thorax.

2.2. Epidemiology

CDH is a rare condition that occurs in <1–5:10,000 births [1]. The most common anatomic type encountered is the left-sided posterolateral hernia (Bochdalek hernia), including the vast majority of cases 85–90%, while the anterior hernia of Morgagni is rare. A bilateral defect accounts for 15–20% of cases; tissue defect involving most of the hemidiaphragm is called agenesis [2].

2.3. Causes

2.3.1. Environmental causes

No cases of CDH in humans have been unequivocally attributed to teratogenic or environmental exposures. Recently, a potential association with the immunosuppressive drug mycophenylate mofetil has been made, but the mechanism by which this drug could cause diaphragmatic defect is unknown [3].

2.3.2. Heritable causes

About 10% of all individuals with CDH have a chromosome abnormality. The most common abnormalities are trisomy 18 and isochromosome 12p (Pallister-Killian syndrome or PKS), although many additional abnormalities have been reported (**Table 1**). Some of the more common monogenic syndromes in which CDH occurs are listed in (**Tables 2** and **3**) [4].

2.4. Classification

There are six types of CHD (**Figure 1**):

1. Posterolateral defect (Bochdalek hernia) occurs most often on the left side and contains stomach, bowel, and spleen, and if right-sided, contains liver.
2. Parasternal defect (Morgagni hernia), located on anterior retrosternal or parasternal portion of the diaphragm, is rare and more often right-sided or bilateral and usually contains liver or bowel.
3. Other anterior hernias associated with Pentalogy of Cantrell are rare findings but are usually severe, probably derived from septum transversum. These cases are usually associated with Pentalogy of Cantrell (including defects in the midline abdominal wall supraumbilical, lower sternum, diaphragmatic pericardium, and heart).

Chromosome abnormality/locus	Frequency of congenital diaphragmatic hernia	
	Found in this disorder	**Attributed to this disorder**
Pallister-Killian syndrome/ (isochromosome or tetrasomy 12p)	~30%	? < 5%
Trisomy 13	Rare	Very rare
Trisomy 18	?1–2%	Rare among all CDH; most common chromosome abnormality in prenatally diagnosed CDH
Trisomy 21	Rare (Morgagni hernias > Bochdalek hernias)	Very rare
Del(4)(p16) (Wolf-Hirschhorn syndrome)	Rare	Very rare
+der (22) t(11;22)(q23;q11)	5–10%	Very rare
Del(15)(q26.2)	Unknown (?but possibly majority)	Unknown
Del(1)(q41-q42)	Unknown	Unknown
Del(8)(p23.1)	?30%	Unknown

Table 1. Common chromosome anomalies associated with CDH.

4. Central hernia is rare; the diaphragm defect involves the central tendinous (amuscular) part of the diaphragm. In these cases, the entire rim of diaphragmatic musculature is found to be present.
5. Hiatal hernia, extremely rare, occurs through a congenitally large esophageal orifice.
6. Diaphragmatic eventration is defined as an elevation or abnormal upward displacement of a part or entire normal diaphragm into the chest cavity. This rare type of CDH is caused by the existence of a thinner part of diaphragm which allows the upward displacement of abdominal organs.

For practical reasons regarding the imaging approach and counseling, it was proposed to classify CDH as intrapleural and mediastinal.

Intrapleural hernias occur through defects in the muscular diaphragm, which may result from deficient fusion of the pleuroperitoneal membranes and abdominal wall musculature or absence of the pleuroperitoneal membranes. Intrapleural hernia contents cause compressions on intrathoracic visceras, causing pulmonary hypoplasia and contralateral mediastinal shift. This category includes the traditionally classified Bochdalek hernias.

Mediastinal hernias can be classified into two types: retrosternal and central. Retrosternal hernias are categorized as Morgagni hernias, although a true Morgagni hernia is only a small anatomic located in the space between the sternal and costal heads of the diaphragm. True Morgagni hernia is considered to be a subtype of retrosternal mediastinal hernias, with larger

Syndrome	Frequency of CDH in this disorder	Mode of inheritance	Gene
Cornelia de Lange syndrome	?up to 5%	AD	*NIPBL*
			SMC3
	Unknown	XL	*SMC1A*
Craniofrontonasal syndrome	Rare	XL (but males less severely affected than females)	*EFNB1*
Denys-Drash syndrome	Rare	AD	*WT1*
Donnai-Barrow syndrome	~70%	AR	*LRP2*
Fryns syndrome	>80% (but ascertainment may be biased)	AR	Unknown (possible etiologic heterogeneity)
Matthew-Wood syndrome	~50%	AR	*STRA6*
Spondylocostal dysostosis (SCDO)	Rare	AR	*DLL3*
	Rare		*MESP2*
	Rare		*LFNG*
	Rare		*HES7*
Simpson-Golabi-Behmel syndrome	Rare	XL	*GPC3*

Table 2. Selected syndromes in which CDH is a feature.

ventral hernias which are defects in the central tendon stemming from septum transversum impaired development. Hiatal hernias, as their name shows, develop more through the esophageal hiatus and do not involve the central tendon. Differentiating ventral mediastinal hernias from intrapleural hernias is important because the intrapleural hernias, usually, do not lead to pulmonary hypoplasia, which is the major complication of CHD [5] (**Table 4**).

2.5. Embriology

The diaphragm starts to develop at approximately 4 weeks of gestation. It develops from several structures. The anterior central tendon develops from an infolding of the ventral body wall: the septum transversum. Another infolding on the posterolateral sides establishes the pleuroperitoneal membranes. Closure of the pleuroperitoneal canals occurs when the septum transversum fuses to the structures surrounding the esophagus, the esophageal mesentery, and connects to the pleuroperitoneal membranes. Closure of the pleuroperitoneal canals normally occurs around the eighth week of gestation in humans. The right side of the diaphragm closes before the left side [6].

The central portion and possibly anterior regions are thought to develop from the septum transversum, which is initially fused to the liver during development and becomes the unmuscularized central tendon of the diaphragm [7].

The posterolateral section, the place where Bochdalek hernia occurs, develops from the pleuroperitoneal folds (PPFs), which are triangular structures derived from mesoderm that form in

Syndrome	Gene (locus)
Apert syndrome	*FGFR2*
Beckwith-Wiedemann syndrome	Dysregulation of imprinted genes on 11p15.5
CHARGE syndrome	*CHD7*
C (trigonocephaly) syndrome	*CD96*
Coffin-Siris syndrome	Unknown
Czeizel-Losonci syndrome	Unknown
Gershoni-Baruch syndrome	Unknown
Goltz syndrome (focal dermal hypoplasia)	*PORCN*
Kabuki syndrome	Unknown
Marfan syndrome	*FBN1*
Mathieu syndrome	Unknown
Meacham syndrome	*WT1*
Microphthalmia with linear skin lesions syndrome	*HCCS*
PAGOD syndrome	Unknown
Pentalogy of Cantrell	Unknown
Poland anomaly	Unknown
Swyer syndrome	Unknown
Thoraco-abdominal schisis	Unknown

Table 3. Syndromes in which CDH is less frequently a feature.

the thorax in the early development of the diaphragm. These PPFs are part of the diaphragmatic connective tissue. The membranous diaphragm is later muscularized by migrating muscle precursor cells to the PPF from the cervical somites. This phenomenon happens before these cells proliferate, differentiate, and migrate onto the membranous diaphragm [8, 9]. The hypothesis is that a Bochdalek hernia occurs if the PPFs do not fuse with the septum transversum and the dorsal mesentery of the esophagus by the 10th week of gestation [4].

The lung originates as an outpouch of the ventral wall of the posterior end of the laryngotracheal tube and divides into two bronchial buds at 3–4 weeks of gestation [10]. As the two buds elongate, the primitive tubular foregut tube begins to pinch into two tubes, namely, the dorsal esophagus and the ventral trachea [11]. Further outgrowth of the lung-buds produces the secondary bronchi. In humans, the right lung has three lobes, whereas, the left lung is composed of two lobes. The branching of the primary bronchial buds are monopodial. Every secondary bronchus then undergoes progressive dichotomous branching as each branch bifurcates repeatedly. Reproducible branching in humans is completed at 16 generations in 16 weeks of gestation [12]. The last seven generations of airway are completed during the last part of gestation. Alveolization starts after 28–30 weeks in humans and is completed in postnatal period [13]. Reid [14] presented this process in her laws of development of the human lung:

1. The bronchial tree is completed by the 16th gestational weeks.
2. Alveoli, developed after birth, increase in number until 8 years of age and in size until the chest wall finishes growing.
3. Blood vessels are remodeled and increase, as new alveoli form, probably until the chest growth is complete.

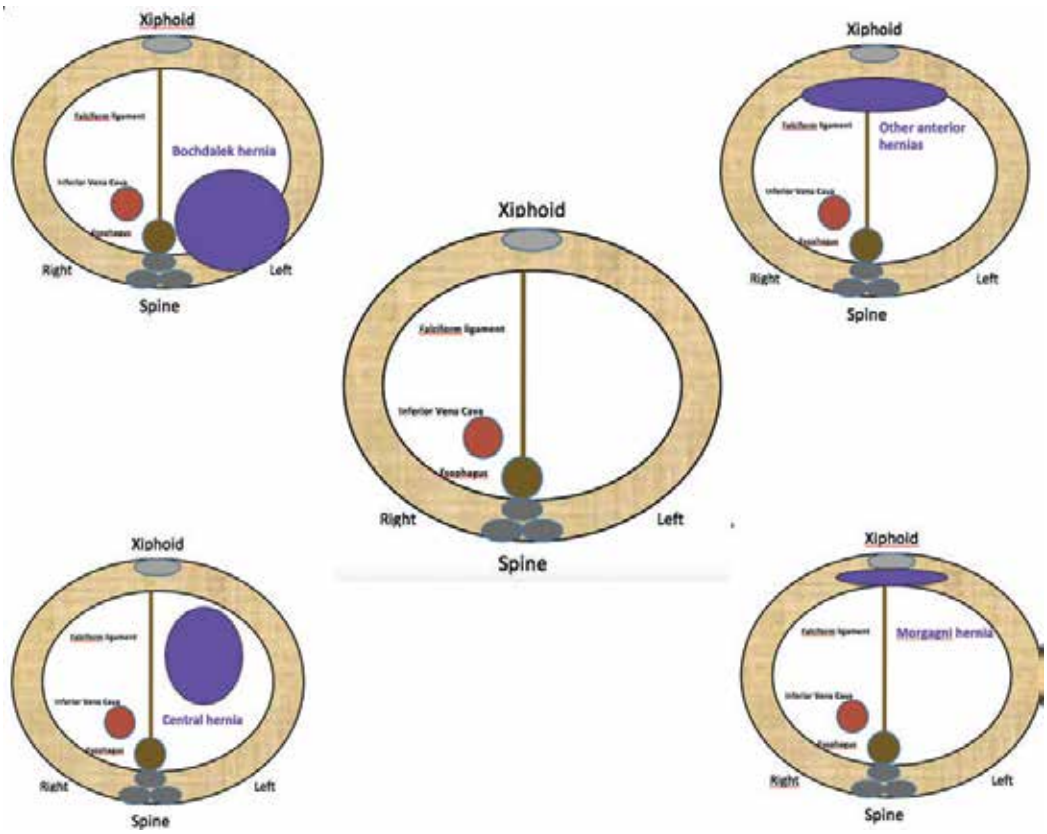

Figure 1. Types of congenital diaphragmatic hernia.

Hernia type	Location	Contents	Associated findings
Intrapleural	Lateral, usually left-sided	Stomach, bowel, spleen, variable-sized portions of the liver	Pulmonary hypoplasia
Mediastinal			
Ventral	Anterior and central	Liver, bowel	Pericardial effusion, pentalogy of Cantrell
Morgagni	Anteromedial, small, typically isolated	Liver, bowel	No pericardial communication
Hiatal	Posterior and central	Stomach, sometimes other organs	Congenital short esophagus

Table 4. Texas Children's Fetal Center classification of CDH.

2.6. Pathogenesis

The pathogenesis of CDH is poorly understood. The diaphragmatic defect is caused by delayed or impaired separation of the two compartments: thoracic and abdominal. This is due to closure of embryonic pleuroperitoneal canals influenced by the growth of the post-hepatic mesenchymal plate and of the pleuroperitoneal folds [15, 16]. In CDH, respiratory failure at birth is the result of pulmonary hypoplasia (PH), reduced airway branching, and surfactant deficiency. Extensive muscularization of the pulmonary vessels may result in persistent pulmonary hypertension (PPH) of the newborn. Historically, PH was believed to be the result of compression of the lungs by the herniating intrathoracic abdominal organs. However, our understanding of abnormal pulmonary development in relation to CDH has significantly improved and we know that pulmonary development is already affected prior to development of the diaphragmatic hernia, implicating that the lungs are primarily disturbed in their development before mechanical compression can happen [17, 18].

2.7. Associated anomalies

The most common associated anomalies are cardiovascular in 40–60% of live-born infants and in 95% of fetal demise; therefore, a detailed ultrasound examination must be performed in every case diagnosed with CDH [19] (**Table 5**).

2.8. Ultrasound diagnosis

Ultrasound evaluation of the thorax can be carried out easily until 25–26 weeks of gestation; after this period, the increased mineralization of the ribs limits the display of intrathoracic organs, especially for coronal or sagittal views. A number of thoracic anomalies evolve; they can appear only in the third trimester or they can regress before birth. Therefore, if an initial assessment of the thorax can be performed as early as at the 12th week of gestation, in order to follow up abnormal cases, late third-trimester scans may be needed.

Scanning planes: the most important view for the assessment of intrathoracic anatomy is the classic *four chamber view* of the fetal heart. In this plane, most thoracic viscera can be visualized, including the ribs, the sternum, and the cutaneous outline. The *midsagittal* and *parasagittal views* allow display of the diaphragm as a hypoechoic line below the lungs and the heart and above the liver and the stomach. The diaphragm shows a curved outline, convex toward the thorax.

Cardiovascular	VSD, ASD, tetralogy of fallot, hypoplastic left heart syndrome
Gastrointestinal abnormalities	Meckel diverticulum, anal atresia
Central nervous system	Neural tube defects, hydrocephalus, agenesis of corpus callosum
Limb abnormalities	Absence defects, polydactyly, syndactyly
Genitourinary abnormalities	Cryptorhydia, absent testes, ectopic kidney, horseshoe kidney
Eye abnormalities	Microphtalmia and anophtalmia

Table 5. Asociated anomalies.

Axial four-chamber view: the following structures should be checked: the two lungs appear as solid, homogeneous; weakly hyperechogenic that almost completely surrounds the heart, right larger than left lung; thoracic aorta behind the left atrium; the heart oriented toward the left; the ribs and overlaying cutaneous tissue; and posterior, the spine (**Figure 2**).

Three-vessel view: allows visualization of the thymus and its relationship with the great vessels and appears as a well-defined roundish solid structure interposed between the great vessels and the sternum. It is weakly hypoechogenic in comparison with the surrounding lungs. In front of the spine and behind the three vessels, the trachea, and, with some difficulty, the esophagus can be seen (**Figure 3**).

Midsagittal view: does not give significant information regarding the lungs because it is occupied mainly by the heart.

Right parasagittal view: the diaphragmatic hypoechogenic layer can be seen below the right lung.

Left parasagittal view: the diaphragmatic hypoechogenic layer can be seen below the left lung and the heart and allows to demonstrate that the stomach is located below the diaphragm.

The ultrasound diagnosis of CDH is, in general, indirect: the abnormal intrathoracic position of the stomach and/or the other migrated viscera and the displacement of the heart and the mediastinum is detected (**Figure 4**).

Left posterolateral CDH: in the *four-chamber view*, the stomach is in the left hemithorax or in the mediastinum (**Figure 5**).

Frequently, a few small bowel loops can be visualized near the stomach, while the heart and the mediastinum are pushed contralaterally. Much more rarely, the spleen and/or the left liver lobe may migrate as well. In few cases, only some ileal loops and/or the left hepatic

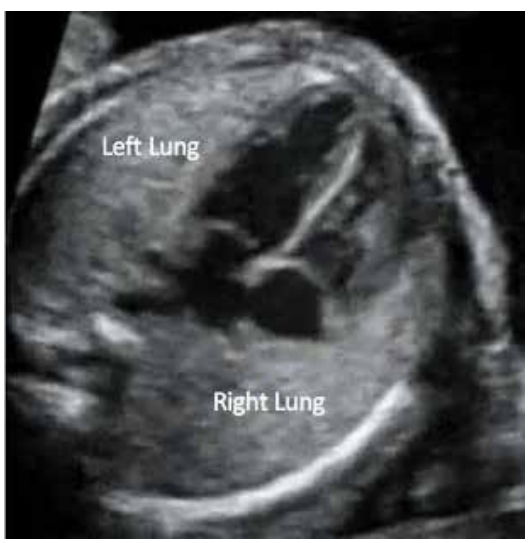

Figure 2. Four chamber view.

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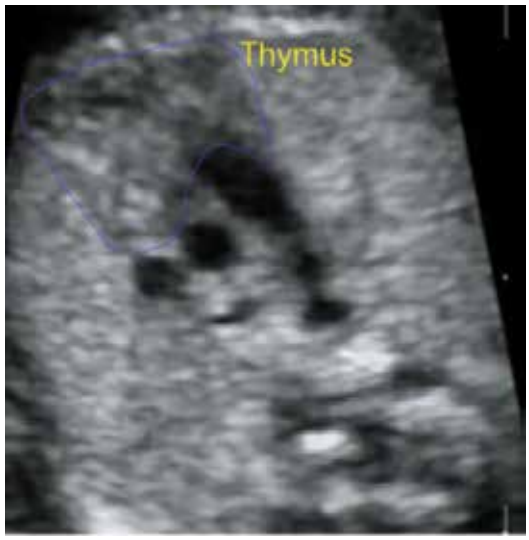

Figure 3. Three-vessel view. Note the thymus slightly hypoechogenic than lungs.

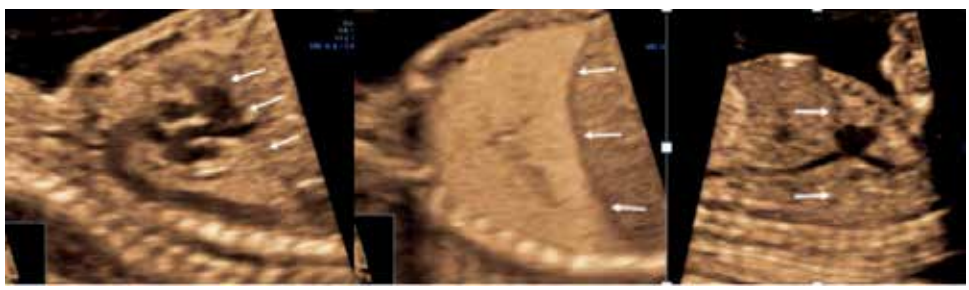

Figure 4. Sagittal view. Note the different echogenicity between lungs and abdominal viscera. Diaphragm appears as a hypoechogenic thin line.

lobe migrate into the thorax; therefore, the diagnosis is based only on dextrocardia and the unusual inhomogeneous appearance of the left hemithorax (**Figure 6**).

Kinking of the sinus venosus is a reliable sign in case of herniated left liver lobe; the bowing of the umbilical segment of the portal vein (portal sinuses) to the left of the midline and coursing of portal vessels to the lateral segment of the left hepatic lobe toward or above the diaphragm is considered the best predictor for liver herniation [20] (**Figure 7**).

It must be kept in mind that even though the diaphragmatic defect occurs in the first trimester, the visceral herniation is variable in time, from early second trimester to the first hour of life.

The sagittal views allow to detect some additional features that help confirm the diagnosis; the evidence of intrathoracic viscera on the four-chamber view is the basic requirement for a correct diagnosis of CDH.

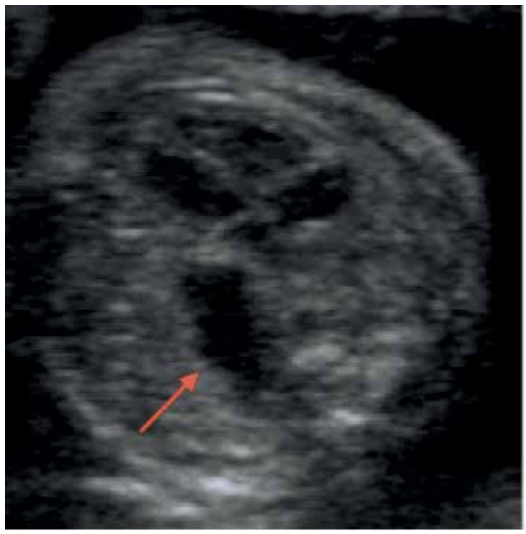

Figure 5. Left congenital diaphragmatic hernia. The stomach is in the left hemithorax and the heart is displaced to the right.

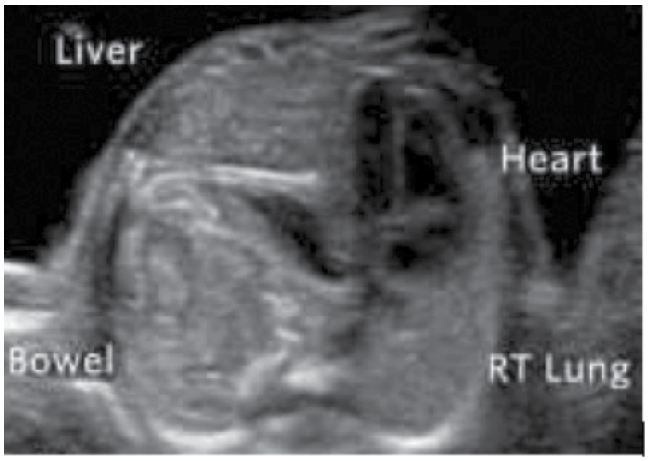

Figure 6. Left CDH. Herniation of left liver lobe and bowel loops. The heart is displaced to the right hemithorax.

Right-sided CDH: the diagnosis is difficult because the main feature, the intrathoracic displacement of the stomach, is absent because the defect is on the other side of the diaphragm. There are several indirect signs that lead to diagnosis. One is the leftward rotation of the heart with increase of the cardiac axis (**Figure 8**) and the upward displacement of the right hepatic lobe into the right hemithorax. This sign is best observed using color Doppler to identify the suprahepatic veins in the thorax because of the similar echogenicity of the lung and liver. Right-sided intrapleural hernias are less common, always contain liver, and may contain variable amounts of bowel and stomach. Rarely, intrapleural hernias may be bilateral; these tend to be associated with severe pulmonary hypoplasia. The midline position of the heart, the lack of

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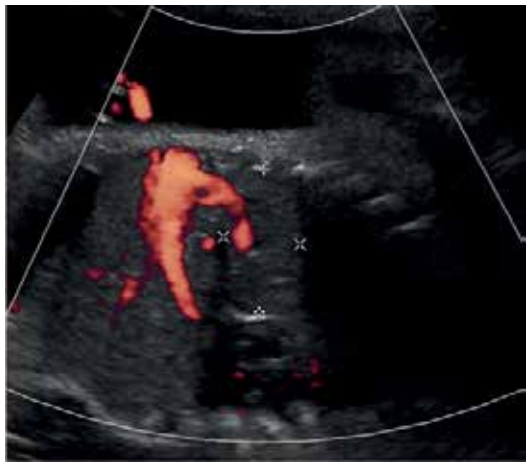

Figure 7. Portal vessels extending into the thorax. Left liver lobe (markers).

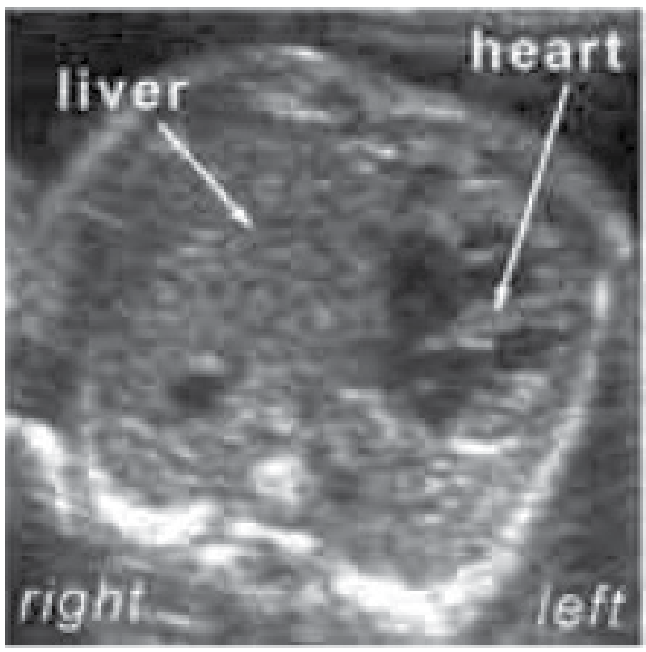

Figure 8. Leftward rotation of the heart with increase of the cardiac axis and upward displacement of the right hepatic lobe into the right hemithorax.

cardiomediastinal shift in cases of suspected intrapleural hernia should raise suspicion for the presence of bilateral intrapleural hernias.

Anterior and central CDH: the ventral type appears anteriorly because of the central tendons' defect. The central tendon of the diaphragm on his upper surface and the pericardium are

communicating, if there is a defect at this site a pericardial effusion may develop. Ventral hernias may push the heart posteriorly but do not tend to cause pulmonary hypoplasia (**Figure 9**).

The smaller Morgagni hernia, usually is an isolated anterior defect and given its small size and location does not cause compression of thoracic organs. Morgagni hernias do not communicate with the pericardial space; therefore, this feature is a key element in differentiation from mediastinal hernias (**Table 6**).

Hiatal CDH: on ultrasound examination, it may appear as a hypoechogenic image behind the fetal heart in the posterior mediastinum, anterior to the vertebral body in continuity with a small fetal stomach located in the abdominal cavity just below the diaphragm in a median position. Parasagittal sonographic sections of the fetal thorax show an intact diaphragm on both sides. During the examination, stomach peristalsis may be visualized or the up and down movements of the stomach into the fetal thorax [21, 22]. The absence of liver in a hiatal hernia should help distinguish it from a right-sided intrapleural hernia.

The diagnosis of diaphragmatic hernia is rare during the first trimester. Early diagnosis has been associated with poor prognosis and the presence of additional defects [23, 24]. A diagnosis of CDH is suggestive if a displacement of the fetal heart in association with an intrathoracic mass having the appearance of the liver or stomach is detected.

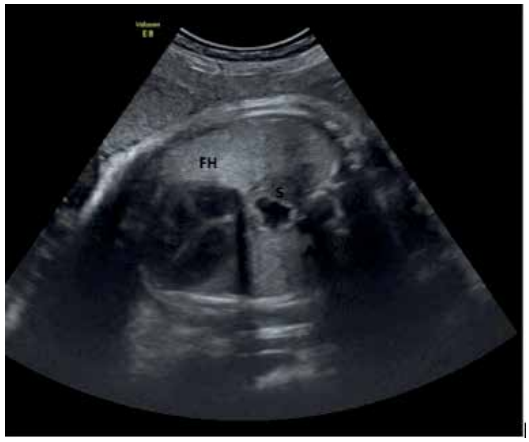

Figure 9. Transverse view of the fetal thorax with an anechogenic mass behind the heart; FH—fetal heart; Ao—aorta; S—stomach.

- Thoracic mass with mediastinal shift.
- Left-sided CHD: stomach is in thorax seen in *four-chamber view*, almost half of the cases have liver herniation.
- Right-sided CHD: almost always have liver herniation which is difficult to see; diagnosis is suspected in case of left mediastinal shift and Doppler reveals abnormal course of hepatic vessels.
- Polyhydramnios secondary to esophageal compression.

Table 6. Key sonographic features.

It was reported in a prospective study on 78,000 pregnancies at first trimester screening for chromosomal abnormalities by nuchal translucency thickness, 19 chromosomally normal fetuses with diagnosis of congenital diaphragmatic hernia. Only one of them was diagnosed in the first trimester; diagnosis was based on the visualization of the stomach in the thorax. In about one-third of the cases of diaphragmatic hernia, they found increased nuchal translucency. In the majority of the infants (83%) who died in the neonatal period due to pulmonary hypoplasia, nuchal translucency was increased, while the respective percentage for the survivors was 22%. The authors hypothesized that the accumulated nuchal fluid may be caused by venous congestion determined by intrathoracic compression due to early herniation of the abdominal organs [25].

The compression of herniated organs on esophagus or gastic outlet obstruction causes polyhydramnios which may became visible later in pregnancy. Another cause of polyhydramnios in cases with CDH is esophageal atresia with tracheoesophageal fistula, which may be very difficult to diagnose because the visualization of the proximal esophageal pouch is dependent on its being distended by swallowed amniotic fluid.

2.9. Differential diagnosis

Bronchogenic cysts (*foregut duplication*) contain several components of the bronchi, including respiratory epithelia, mucous glands, and cartilage and may occur anywhere along the length of the trachea or esophagus [26]. Most are diagnosed incidentally or if large enough, can compress the esophagus and/or trachea.

Congenital cystic adenomatoid malformation (CCAM): a developmental abnormality of the lung resulting from abnormal cell proliferation and decreased programmed cell death of lung tissue. Type I CCAM is most common and is distinguished by relatively large cysts and mucin production.

Cystic teratomas are benign tumors most often found in the anterior mediastinum. They consist of several differentiated cell types derived from endoderm, ectoderm, and/or mesoderm [27, 28].

Neurogenic tumors are the most common lesion found in the posterior mediastinum. They are likely to be of neural crest origin; the majority is benign: neurilemoma, neurofibroma, ganglioneuroma, pheochromocytoma, and neuroblastoma.

Pulmonary agenesis refers to partial or complete absence of lung tissue that is caused by failure of lung bud development.

Pulmonary sequestration results from primitive lung tissue that is not connected to the tracheobronchial tree. Sequestration may be intrapulmonary, occurring within the pleura of the normal lung or extrapulmonary, occurring outside the normal lung within its own pleural sac.

2.10. Prognostic indicators

The best validated measurement is contralateral lung area assessed by 2D ultrasound through the so-called lung area/head circumference ratio (LHR) [29]. Different methods for measuring were described but the most reproducible and accurate method involves tracing the lung contours.

Normal lung area develops four times more than the head circumference between week 12 and 32; therefore, the LHR needs to be adjusted according to gestational age. The effect of gestational age on LHR can be minimized by expressing the observed LHR as a ratio to the expected mean LHR for that gestational age.

2.10.1. The lung area to head circumference ratio

The lung-to-head circumference ratio (LHR) is a sonographic measure proposed to identify fetuses with congenital diaphragmatic hernia (CDH) that have a poor prognosis. The lung area contralateral to the CDH is measured at the level of *four-chamber view* by manual tracing of the lung which appears to be the most reproducible way of measuring the lung area [30]. The product is divided by the head circumference (HC) to obtain the LHR.

The lung area to head circumference ratio (LHR) = lung area/head circumference.

2.10.2. Observed/expected lung-to-head ratio

The observed LHR may be expressed as a percentage of the expected mean for gestational age as the observed/expected lung-to-head ratio O/E LHR [31, 32].

O/E LHR = (observed LHR/expected LHR) × 100

There has been proposed a four-step stratification of fetuses based on their observed/expected (O/E) LHR wherein it was also taken into account their liver position.

- Fetuses with an O/E LHR <15% have extreme pulmonary hypoplasia and there are no survivors reported.
- Fetuses with an O/E LHR between 15 and 25% have severe pulmonary hypoplasia and survival prediction is about 20%, those with the liver down having better prognosis than those with liver up in the thorax.
- Fetuses with an O/E LHR between 26 and 35% and those with an O/E LHR between 36 and 45% but with the liver up have moderate hypoplasia. They have an expected survival rate between 30 and 60%, which depends on the lung size.
- Fetuses with an O/E LHR between 36 and 45% with the liver down and those with an O/E LHR > 45% have mild hypoplasia and have better prognosis, >75% survival rate [33, 34] (**Table 7**).

• Prenatal prediction of postnatal outcome in CDH patients is based on ultrasound measurement of contralateral lung size and magnetic resonance total lung volumetry.
• The ratio of observed to predicted lung/head ratio is the most validated predictor for postnatal outcome; the liver position is also predictive.
• Fetal tracheal occlusion has been shown safe and feasible by minimally invasive means.

Table 7. Key points.

2.10.3. Fetal lung volumes

On fetal MR imaging there are several methods described for estimation of fetal pulmonary hypoplasia. All of these methods include the measuring of total fetal lung volume (TFLV). MR volumetry is considered the most accurate method for measuring ipsilateral lung and, therefore, for best estimation of fetal lung volumes, compared to three-dimensional ultrasound [35].

2.10.4. Fetal intervention

Because CDH is an anomaly with poor prognosis that can be identified in the prenatal period, it is justified to perform an intervention which improves lung function. Di Fiore and Wilson studied the concept of triggering lung growth by tracheal occlusion [36]. This was observed in an experiment of nature occurring in fetuses with congenital high airway obstruction syndrome (CHAOS), who display impressive lung growth. Through pregnancy, fetal lungs secrete fluid during their development, which creates a positive pressure under the glottis. Fluid secretion of the lung and a cyclical pressure change are essential for development and growth of the lung [37]. Fluid secretion increases the pressure in airways but during fetal breathing movements, the pressure gradient is normalized as glottis opens. This phenomenon creates cyclical periods of tissue stretch, which are important for an optimal balance between growth and differentiation [38]. Intrauterine tracheal occlusion acts like a closed glottis trapping the fluid causing subsequently increased tissue stretch, which triggers lung growth. The tracheal occlusion decreases the number of type II alveolocytes and lowers surfactant expression in occluded lungs [39–42]. This unwanted effect may be improved by either removing the tracheal occlusion before birth and/or by antenatal steroid administration [43, 44]. Experimentally, in-utero reversal of occlusion (clinically translated as a plug-unplug sequence) achieved morphologically better lung maturation [45].

3. Conclusions

As prenatal detection of fetal CDH improved in recent years, it is important to use standardized prognosis markers around the world. Currently, available markers are not 100% accurately predictive of outcome and their use is much less accurate in the presence of chromosomal anomalies or other malformations. This shows the fact that all fetuses diagnosed with CDH should undergo an ultrasound examination by a well-trained sonographer, as well as fetal echocardiography.

Conflict of interest

No conflict of interest to declare.

Author details

Adrian Claudiu Ratiu

Address all correspondence to: ratiu.adrian@umft.ro

University of Medicine and Pharmacy "Victor Babes", Timisoara, Romania

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Chapter 10

Fetal Abdominal Wall Defects

Roxana Cristina Drăgușin, Maria Șorop-Florea,
Ciprian Laurențiu Pătru, Lucian Zorilă,
Cristian Marinaș, Nicolae Cernea,
Cristian Neamțu and Dominic Gabriel Iliescu

Additional information is available at the end of the chapter

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Abstract

Abdominal wall defects (AWDs) represent a group of congenital anomalies that can be diagnosed early during pregnancy even at the time of the first trimester assessment, with direct impact on pre- and postnatal fetal prognosis and management decisions. The most frequent anomalies in this group are gastroschisis and omphalocele. The key method available, that allows the detection of any deviation from the physiologic midgut herniation, is the ultrasound (US) assessment. A precise algorithmic scan approach is imposed not only for an accurate detection of any abdominal wall defect, but also for a proper location of the defect and of the spatial relation to the umbilical cord insertion, fundamentally important in differentiating among various malformations. Other structural or chromosomal anomalies should be excluded. Suitable multidisciplinary counseling should be considered. Unfortunately, in utero surgery, in these cases, has not been yet successful. Postnatal early interventions are usually required in specialized pediatric centers.

Keywords: congenital anomalies, abdominal wall defect, gastroschisis, omphalocele, ultrasound

1. Introduction

Abdominal wall defects (AWDs) define a type of congenital anomalies characterized by the herniation of abdominal organs through an unusual opening surrounding the umbilical cord. The most common two types include omphalocele and gastroschisis. The omphalocele or exomphalos (in Greek, omphalos = umbilicus, kele = hernia, tumors) was firstly described in 1634 by Ambroise Pare, while gastroschisis (in Greek gastro = stomach—the term generally

used for abdomen; schisis = fissure, tear or gape) was first described by James Calder, a decade later. Other uncommon AWDS are ectopia cordis (EC), limb–body wall complex, cloacal and bladder exstrophy, urachal cyst, Prune belly syndrome and Cantrell pentalogy [1]. The correct prenatal detection and classification of these fetal malformations are extremely important for subsequent opportunities in parental counseling and pregnancy management. Nowadays, the intensive use of US assessment has allowed an increase in detection rates of AWDs, even from the first trimester nuchal translucency scan.

2. Embryology/pathophysiology and demographics

The embryologic developmental of the ventral body wall is reflected in its malformations. There are two types of defects, respectively, defects in the primaxial component and defects in the abaxial component. The first type of defects is often linked to neural tube-closure defects, whereas the second one manifest as limb–body wall or ventral body wall defects [2, 3]. Several hypotheses with respect to AWDS known as ventral body wall defects have been issued [4]. The embryologic origin of ectopia cordis, gastroschisis and bladder exstrophy is not yet known, but is thought to be more closely linked than that for omphalocele [5, 6]. It is considered that an abnormal closure of the ventral body wall folds during the 4th week of development is the main cause for these entities. In cases of gastroschisis, exposure to a teratogenic factor was suggested to be influential [7]. Some studies suggest that poor socio-economic status and prenatal care, as well as teratogens (e.g. recreational drugs, salicylates, paracetamol and pseudoephedrine) may be important contributors to the development of gastroschisis [8, 9]. A combination of genetic and environmental factors was also thought to be involved in the origin of gastroschisis, and also ectopia cordis and bladder exstrophy [10–12]. Chromosomal abnormalities are diagnosed in 1.2% of infants with gastroschisis [13], whereas approximately half infants (54–57%) with omphalocele present with aneuploidies or gene disorders [14]. However, one risk factor associated with gastroschisis was identified in young maternal age, mothers under 20 years old having the highest risk [10]. The oldest embryologic hypothesis date from 1963, and state the potential teratogenic effect on the folds, which result in gastroschisis [15]. Another theory pleads for the rupture of the amniotic membrane at the base of the umbilical cord [16] or for the disruption of the omphalomesenteric (yolk-sac and vitelline) artery, resulting in infarction and necrosis at the base of the umbilicus [17]. As there is no evidence that for the amniotic rupture almost exclusively on the right side and that the omphalomesenteric artery offers blood supply to the paraumbilical region of the abdominal wall [18], the first and oldest theory may be overlooked [5]. On the other hand, omphalocele is a different entity, with a known etiology, thought to be the failure to return of the loops of bowel after the physiological herniation from the 6th to 10th week post-fertilization, when the fetal midgut extends into the extraembryonic celom, occupying the proximal segment of the umbilical cord [19]. A physiological hernia seldom exceeds 7 mm in diameter or rarely persists after 12 weeks of gestation, when the midgut returns to the abdominal cavity [20]. Other pathogenic theories include failure of complete lateral-body migration and closure of the body wall [15]. Omphalocele is more prevalent in older mothers.

The prevalence of the two most frequent entities of AWDs is reported to be for gastroschisis 3.09 per 10,000 births, with a live birth prevalence of 2.63 per 10,000 and for omphalocele 3.29 and 1.13 per 10,000, respectively [21]. The prevalence of gastroschisis has increased in the last years, whereas that of omphalocele has remained stable [22]. Regarding the prenatal diagnosis of AWDs, both omphalocele and gastroschisis are easily diagnosed at the 11–14 weeks nuchal scan. So, large studies report sensitivity for both congenital anomalies from 90 to 100% [23, 24]. In fact, reports show that 22 and 35% of the chromosomally normal cases of gastroschisis and omphalocele, respectively, were diagnosed before 14 weeks, and 50 and 30% between 14 and 23 weeks. The overall prenatal detection rate was 91.6% for gastroschisis and 83.3% for omphalocele [21].

3. Prenatal diagnosis and classification of fetal abdominal wall defects

3.1. Gastroschisis

Gastroschisis is an AWD characterized by the herniation of the abdominal viscera represented by bowel loops and occasionally parts of other abdominal organs outside the abdominal wall with no covering membrane or sac, to the right of the insertion of the umbilical cord, and rarely to the left side [25, 26]. Even if the condition is not generally associated with other major congenital or chromosomal anomalies, an accurate fetal anatomy assessment is required. The reported rate of the proportion of gastroschisis associated with major defects is about 10% [27], arthrogryposis being present in a minority of these fetuses [28], with a reported mortality rate of 5–10% in all cases of gastroschisis [29]. Others report a higher rate (14%) of additional associated anomalies, the central nervous system and cardiac malformations being the most common anomalies [30]. Gastroschisis is often classified into simple (as an isolated defect) and complex (as associated with bowel-related complications: intestinal atresia, perforation, stenosis or volvulus) [31]. In cases with intestinal complications, there is a relevant risk of increased morbidity, higher rates of complications, as respiratory distress or sepsis and of course an increased length of hospital stays [32]. The key to an accurate diagnosis is fetal US in routine antenatal care, which affects patient management and prognosis. In the past, the detection was higher in the second trimester, between 16 and 22 weeks of gestation, in approximately 60% of cases, with a false positive rate of 5.3% [33]. Misdiagnosis of gastroschisis as omphalocele has serious implications, as gastroschisis is rarely associated with chromosomal anomalies and unnecessary amniocentesis may be needed with additional risks to the procedure [34]. Nowadays, the diagnosis of gastroschisis can be facilitated ultrasonographically as early as the late first trimester, 12–13 weeks of gestation [35]. After correctly identifying a normal umbilical cord insertion using color Doppler, gastroschisis is detected as herniation of the bowel loops with no covering membrane (e.g. **Figure 1a**). In most cases, the defect is on the right side of the umbilical cord with a normal umbilical cord insertion. Beside the location of the defect, it is important to establish the size and content of the defect and if present, the associated anomalies.

Figure 1. a. Ultrasound image of gastroschisis diagnosed in the second trimester (bowel loops floating in the amniotic fluid with no sac); b. Ultrasound image of gastroschisis diagnosed in the third trimester (thickened, echogenic bowel wall floating in reduced amniotic fluid).

Other ultrasound features may include an abnormal position of the stomach, dilatation of the bowel loops with a thickened and echogenic bowel wall (e.g. **Figure 1b**). Regarding the amniotic fluid, a decreased amount is often reported, rather than an increased amount. Subsequent bowel atresia is a frequent complication in fetuses with gastroschisis, due to inflammation and direct trauma of the amniotic fluid, on the herniated bowel [36]. The significance of certain associated ultrasound features in determining fetal outcome is debated, as prenatal predictors of gastroschisis complications. There is an associated risk of intrauterine death in 5% of cases of gastroschisis [37], as well as an increased incidence of fetal growth restriction or small for gestational age weight fetuses [38]. Antenatal US features of gastroschisis, such as extra- and intra-abdominal bowel dilatation, stomach herniation, stomach dilatation, bowel matting, growth restriction, abnormal umbilical artery (UA) Doppler ultrasounds and abnormal amniotic fluid volume were studied as prognostic factors. However, only extra-abdominal bowel dilatation proved to be a statistically significant marker of complex gastroschisis and associated morbidity [39].The incidence of complex gastroschisis is reported to be 10% [40], with increased risk for complications such as perivisceritis [41], as the amniotic fluid is extremely toxic to the exposed bowel and ischemic injury, because of constriction at the level of the abdominal defect [42]. Regarding the risk of intrauterine demise (IUD), an intense surveillance protocol was proposed and demonstrated to reduce the rate of IUD by 2.2% [43]. The proposed modalities of monitoring included cardiotocography, even daily in the third trimester, and umbilical and middle cerebral artery Doppler [37]. On the other hand, the diagnosis of fetal growth restriction can be difficult, as abdominal circumference measurements are affected by the herniated bowel. Formulas that do not include abdominal circumference can be helpful in fetal weight estimation, but there are still on debate for the moment [44].

3.2. Omphalocele

Omphalocele is another AWDs represented by a midline defect that leads to a herniation into the amniotic cavity through the base of the umbilical cord. The herniated abdominal content is covered by a membrane presented by the peritoneum on the inner side, amnion

on the outer side and Wharton's jelly in between [26]. Omphalocele must be differentiated by the physiological midgut herniation that usually disappears before 11–12 weeks of gestation [45]. Omphalocele may be classified in terms of shape, as "conical", that includes hernia of the umbilical cord or "globular", with a large sac having a small diameter base. The size of the defect can be small, up to 5 cm, also called "minor" or more than 5 cm, called "major". The sac may contain bowel loops, small or large intestine, stomach, bladder or ovary or bowel loops and liver [6]. The covering membrane of the omphalocele can be intact, or it can rupture, and the bowel loops can float freely in the amniotic fluid and resemble gastroschisis. The differential diagnosis can include also cord hernia that has a normal insertion into the umbilical ring with intact skin, while in omphalocele the large defect has no muscles or skin. In term of associated anomalies, omphalocele can be syndromic or non-syndromic. About 75% of cases have associated chromosomal and non-chromosomal anomalies [46]. Some authors report a risk for chromosomal abnormalities of 30–40% [34], while other found a lower rate, of only 25% [30]. The most frequent chromosomal abnormalities associated with omphalocele include trisomy 18 (80%), trisomy 13, triploidy and trisomy 21. Other genetic findings described are 45,X, 47,XXY and 47,XXX, partial aneuploidy such as dup (3q), dup (11p), inv. (11), dup (1q), del (1q), dup (4q), dup (5p), dup (6q), del (9p), dup (15q), dup(17q), Pallister-Killian syndrome with mosaic tetrasomy 12p and Miller-Dieker lissencephaly syndrome with deletion of 17p13.3 and uniparental disomy (UPD) such as UPD 11 and UPD 14 [47]. The risk of aneuploidy does not change if the omphalocele contains only bowel or also the liver, but instead correlates with nuchal translucency thickness [14]. Non-chromosomal abnormalities include cardiac defects (50%) (atrial and ventricular septal defects (VSDs) and tetralogy of Fallot (TOF)) and gastrointestinal defects that are present in 40%. Omphalocele is a disorder that characterizes Beckwith-Wiedemann syndrome, together with macroglossia, macrosomia, hypoglycemia, visceromegaly and embryonic tumors [48]. The diagnosis is possible even from the first trimester, after 12 weeks of gestation, during the US genetic assessment (e.g. **Figure 2a** and **b**). Still, no aggressive management should be taken until the second trimester, as in some cases the omphalocele slowly disappears, although no spontaneous resolution have been reported in cases with herniated liver [14, 49]. Omphalocele looks like a smooth central mass, protruding from the anterior abdominal wall covered by membranes (e.g. **Figure 2a** and **b**.). It usually contains small intestine and liver, or other organs such as large intestine, bladder, stomach and spleen. The useful tool to demonstrate umbilical cord is a color Doppler. Polyhydramnios is a specific feature of omphalocele. Ascites can be present as well. Once the diagnosis is established, search for other associated anomalies should be considered. Invasive testing offer is mandatory. Studies have shown that 26–39% of cases are misdiagnosed as isolated omphalocele and actually, associated anomalies are demonstrated postnatally [50, 51]. Regarding the prognosis, it is driven by the presence and nature of the associated anomalies. Also, there is a higher risk for postnatal complications, such as pulmonary hypoplasia with consequently respiratory insufficiency. An omphalocele is considered giant if the defect contains more than 75% of the liver [52]. In cases of a small omphalocele and no associated anomalies, there is a very good prognosis, with a survival around 80–90%. In chromosomal and structural abnormalities associated cases, the mortality rate is around 80–100% [53]. An increased prevalence of deficits in

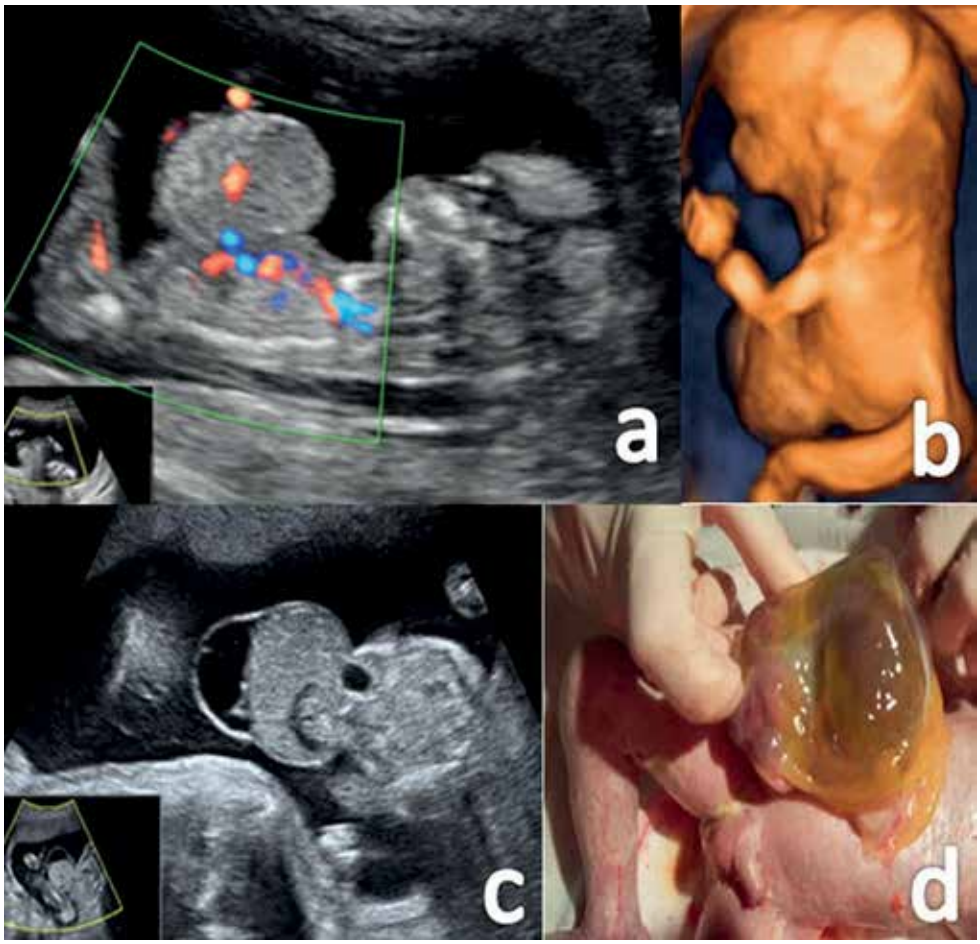

Figure 2. a. Ultrasound image of omphalocele diagnosed in the first trimester (a. Color Doppler image, b. 3D image); c. US image of omphalocele diagnosed in the second trimester; d. Postnatally image of omphalocele.

developmental achievements has been demonstrated in neonates with omphalocele [53]. An accurate prenatal diagnosis includes combining US evaluation with invasive testing. Even if high suspicion of omphalocele in the first trimester, the definitive diagnosis should be established after reevaluating the fetus in the second trimester. Besides karyotyping, also cytogenetic investigations should be offered. Termination of pregnancy is recommended after proper counseling, especially in cases of a large defect and severe associated anomalies.

3.3. Ectopia cordis

Ectopia cordis (EC) is a rare congenital AWD with poor prognosis. The defect is located in the anterior chest wall and abdominal wall, with abnormal placement of the fetal heart outside the thoracic cavity, with associated defect in the parietal pericardium diaphragm,

sternum and in most cases cardiac malformation [54] (e.g. **Figure 3a**). The most frequent intracardiac defects include ventricular septal defect (VSD, 100%), atrial septal defect (ASD, 53%), tetralogy of Fallot (TOF, 20%), left ventricular diverticulum (LVD, 20%) and pulmonary hypoplasia [55, 56]. The term of ectopia cordis was described for the first time in 1706, as a generally sporadic malformation [57]. Rarely, it is reported an association with chromosomal abnormalities like trisomy 18, Turner syndrome, 46,XX and 17q+ [58]. The condition affects 5–8/1 million live [59]. EC is classified into different types such as cervical (5%), cervicothoracic and thoracic (65%), thoracoabdominal (20%) and abdominal (10%) [57, 60]. Also, EC can be "partial", if the heart can be visualized pulsating through skin and "complete" when the heart is outside, naked, without the pericardial membrane [55]. The thoracoabdominal EC is one of the five features of pentalogy of Cantrell. The diagnosis of EC is possible using ultrasound assessment as early as the first trimester, even before 11 weeks of gestation [61, 62]. Still the associated abnormalities can be better evaluated in the early second trimester in nearly 90% [63]. Three-dimensional (3D) scan can improve the accuracy in detection of EC in rare cases of minor forms of ectopia cordis [64]. Invasive diagnosis of associated aneuploidy is mandatory in each case of EC [65]. This rare malformation has a poor prognosis, needing intensive care right from delivery, which includes resuscitation and coverage of the exposed heart with saline-soaked gauze pads wrappings, followed by aggressive surgical correction [66]. In most infants, this anomaly is fatal in the first hours or days after birth due to infection, cardiac failure or hypoxemia [67]. Early precise diagnosis of EC is necessary and essential, for a multidisciplinary team to provide optimal parental counseling. The couple must decide whether they opt for termination of pregnancy or for continuing it, despite the poor prognosis. There is no consensus regarding the mode of delivery, and parents should also decide autonomously if they prefer vaginal birth acknowledging the risk for fetal demise during labor. However, the alternative of performing a cesarean section does not change the outcome [63]. Prenatal care and accurate early ultrasound diagnosis is required especially in developing countries, in which the health care system is lacking currently important physical and material resources.

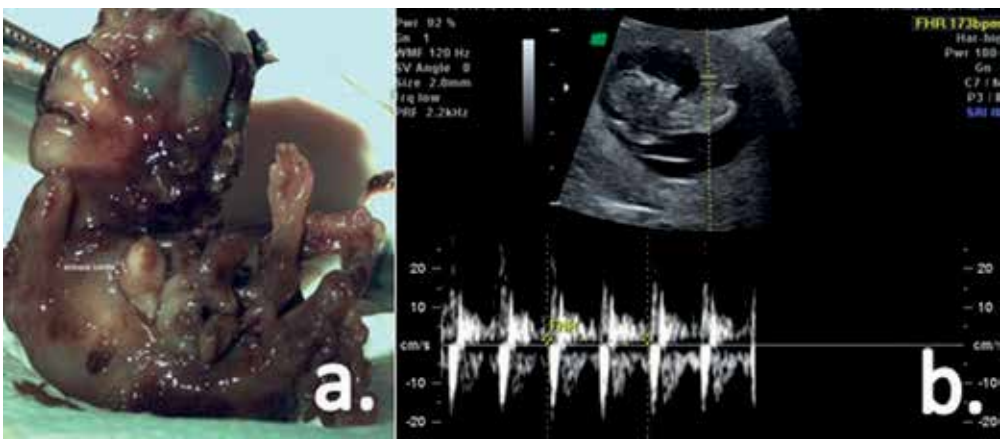

Figure 3. a. Ectopia cordis in a post-abortum fetus; b. Body stalk syndrome (ectopia cordis, fetus attached to the placenta).

3.4. Body stalk syndrome or limb: Body wall complex

Body stalk syndrome (BSS) represents the rarest and most severe AWD. This syndrome was described for the first time in 1987, as an association of three main features: exencephaly, facial clefts or encephalocele, thoraco or abdominoschisis and limb defects [68]. The anomaly is lethal, as there is a herniation of the peritoneal cavity in the extraembryonic coelomic cavity, with the fetus attached to the placenta [69] (e.g. **Figure 3b**). This is due to a large wall defect and due to a short or absent umbilical cord [26]. BSS is also known as the amniotic band syndrome, short umbilical cord syndrome or limb–body wall complex syndrome [70]. Usually, there is no association with chromosomal anomalies; still placental trisomy 16 or maternal uniparental disomy 16 have been reported [71]. The recurrence rate has been demonstrated to be low, and there is no correlation with parental age or fetal gender [68, 72]. The reported prevalence is 0.12 cases per 10,000 births (alive and still births) [73] or even higher 1 in 7500 pregnancies [74]. Two phenotypes have been described, respectively, as placento-cranial and placento-abdominal [75]. The diagnosis of BSS can be established by the end of the first trimester US scan [76] or at 11 weeks' gestation [77]. The US features of BSS show: the fetus is located (in its entirety or partially) outside the amniotic cavity, with an abnormal fetus, that cannot be separated from the placenta, and has lost his anatomic landmarks (**Figure 4a**, **b**). There can be also thoracoabdominal defects, spinal cord abnormalities, positional limb deformities and abnormalities of umbilical cord and membranes. As the US appearance can be confusing, the examination of the amniotic continuity, content of both the amniotic sac and coelomic cavity and a short umbilical cord helps in differentiating this condition from other AWD [77]. The differential diagnosis includes other polymalformative conditions, such as pentalogy of Cantrell, omphalocele-exostrophy-imperforate anus-spinal defects and isolated gastroschisis [78]. Also, kyphoscoliosis is often seen [74] and oligohydramnios can be present in the second and third trimester, situation in which only MRI can elucidate the anatomic structures [79]. Another finding is the presence of constriction rings, which can entangle the fetus [80]. Also, the fetuses with BSS present an increased nuchal thickness, a short umbilical cord and internal organ malformation, like abnormal mesodermal development [80]. So, the early diagnosis (at 11–13 weeks' gestation) is possible and necessary, as the anomaly is lethal and termination of pregnancy is offered. There is also a risk of spontaneously abortion reported, but in such cases an accurate diagnosis is often impossible. In the special situation represented by a twin pregnancy with a fetus with BSS and another unaffected fetus, the prenatal care should focus only on the healthy twin [80].

3.5. Cloacal and bladder exstrophy

Cloacal exstrophy (CE), even if rare, is a complex anomaly of the urogenital tract and intestinal tract that involves a low AWD with the exstrophy of all the structures that form the cloaca (rectum, bladder and lower genitourinary tract). The main embryologic event that is attributed to CE is represented by the premature rupture of the cloacal membrane before fusion with the urorectal septum. Still, many theories regarding the pathogenesis have been issued such as abnormal overdevelopment of the lower cloaca that prevents mesenchymal tissue migration [81, 82], abnormal fusion of the genital tubercle below the cloacal membrane or

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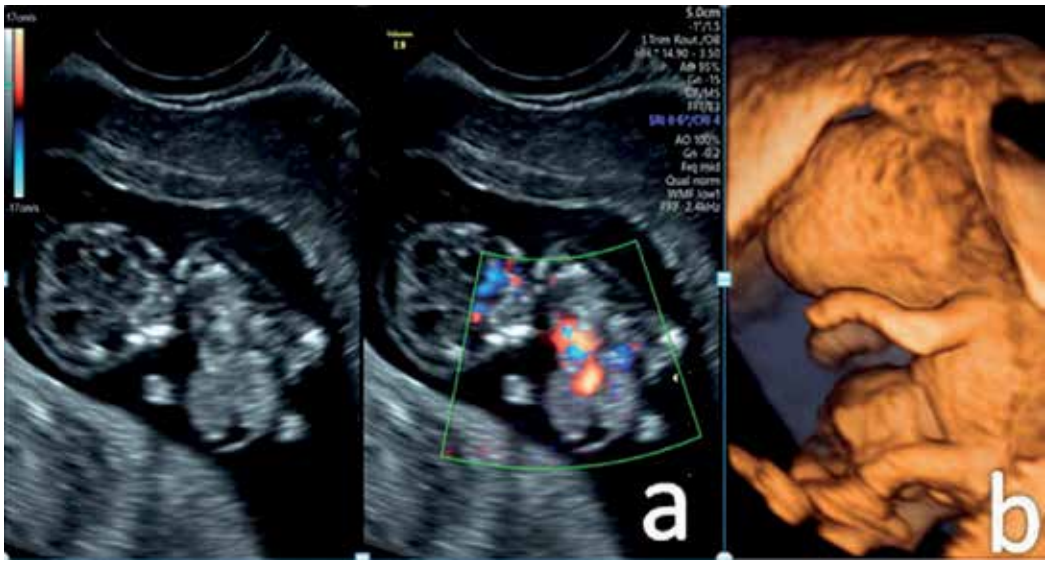

Figure 4. Ultrasound image of a BSS diagnosed in the first trimester: a. Gray scale and color image of the fetus with BSS; b. 3D image of the fetus with BSS.

abnormally caudal position of the body stalk and failure of mesenchymal ingrowth [83]. In the past, the estimated prevalence was reported higher as 1 case in 20,000 births [84], while more current studies describe a rate of 1 case per 200,000–400,000 live births [85]. Female fetuses are more likely to be affected by the anomaly. Prenatal US findings of CE include an absent normal bladder, with a lower abdominal wall defect, with herniated segments of the intestinal tract and a cystic pelvic mass in case of intact cloacal membrane. In fact, the first initial feature is often the omphalocele (in 70–90% of cases), but in a cranial part. Generally, the amniotic fluid index is normal, as the upper urinary tract has no obstruction to flow. Color Doppler examination of both umbilical arteries can help in accurate localization of the bladder [86]. Other associated anomalies may include spinal defects such as sacralization of L5, congenital scoliosis, sacral agenesis [87] and interpedicular widening, or cardiovascular and central nervous system anomalies or single umbilical artery. Also, is reported the association with gastrointestinal malformations such as malrotation (30%), double appendix (30%), absent appendix (21%), short small bowel (19%), small bowel atresia (5%) or abdominal musculature deficiency (1%) [88]. Also, upper urinary tract anomalies can be seen in 60% of cases as pelvic kidney, horseshoe kidney, hypoplastic kidney and solitary kidney, with subsequent hydronephrosis and oligohydramnios [89]. The US diagnosis can also describe "the elephant trunk sign", which is the protrusion of the ileum in the amniotic fluid, resembling the trunk of an elephant [90]. Typically, CE does not associate aneuploidies, but invasive diagnosis can be offered. The survival rates of this type of AWD are approaching 100% these days, because of important operative techniques and perioperative management progress [91]. Still, the reconstructive staged surgical management of patients with CE remains the most challenging for pediatric surgeons and urologists [92]. Early US detection is important, as termination of pregnancy can be offered to the couple before viability, after intense multidisciplinary counseling,

especially in cases where a wide range of disorders is associated with CE. If the couple decides to continue with the pregnancy, US assessment can help in correct planning of surgical intervention with minimal damage to the exposed organs.

Bladder exstrophy represents an AWD with a failure of the anterior bladder wall to close normally, due to the lack of muscular or connective tissue [93]. The reported incidence is 0.25–0.5 in 10,000 births, more common in males in the ratio of 2:1 [94]. The main US finding described for prenatal diagnosis is the absence or non-visualization of the bladder, as the bladder is open to the abdominal wall, and urine is released directly into the amniotic fluid. According to the American Institute of Ultrasound in Medicine guidelines, a normal bladder must be demonstrated from the first trimester as a midline fluid-filled structure flanked by the umbilical arteries in color Doppler examination [95]. Other US findings include: lower abdominal protruding mass, formed by the exstrophied bladder, lower umbilical insertion and an umbilical cord cyst and external genitalia malformation, represented by a small penis with anteriorly displaced scrotum. Also, in females, a bifid clitoris and uterine and vaginal anomalies can be identified [93], besides a widening of the iliac crests [96]. The accuracy and sensitivity of the US can be relatively low, as not all signs are always present, and an urachal cyst may mimic the presence of the bladder [97]. Bladder exstrophy should be considered if no urinary bladder is visualized, and there is no oligohydramnios associated or other renal abnormalities. Still, for the differential diagnosis with an empty bladder, the scan of the lower abdomen should be repeated in 15 minutes interval. Also, the exclusion of CE should be made, as the management is more complicated and the prognosis poorer. Prenatal US correct detection of the anomaly helps in parental counseling and recommendation for delivery in the tertiary center, as the prognosis is quite favorable. The postnatal management includes early surgical procedure to close the anterior wall defect within the first 3 days after birth. If the surgical repair is performed later, there is a higher risk of urinary incontinence or uterine prolapsed, infertility and increased risk of bladder adenocarcinoma [86]. Besides the bladder closure, pediatric surgeons must repair also the epispadias simultaneously, or in staged intervention, to offer an acceptable appearance and function of the external genitalia [98].

3.6. Urachal cyst

The urachus is a primitive structure between the umbilical cord and the bladder, in developing fetus. It disappears normally prior to delivery, but in rare cases, parts can persist. The urachal cyst is a sinus considered a congenital urachal remnant abnormalities [99]. It is diagnosed in children, by means of ultrasound and MRI. It usually suspected if there is bleeding in the cyst or infection. The infected urachal cyst can rupture into the peritoneal cavity, leading to peritonitis. The first line treatment is the surgical procedure of complete primary excision with excellent prognosis.

3.7. Omphalocele-exstrophy of bladder-imperforate anus-spinal deformities complex (OIES complex)

OIES complex represents the most severe expression of the abnormal development of the cloaca with the arrest of the urorectal septum in the 7th–8th week of gestation. The reported

incidence is rare, of only 0.025–0.04 in 10,000 live births [100, 101]. The diagnosis is accessible early in pregnancy, at the end of the first trimester. The imagistic findings include the presence of omphalocele and bladder exstrophy, associated with anomalies of the spine. The imperforated anus is often found postnatally, even if it can be detected antenatally, but with high suspicion by specialized observer. Other anomalies evaluated with OIES complex are spina bifida, genital anomalies, fistulas, renal anomalies, limb hypoplasia, craniofacial anomalies and single umbilical artery [86]. As the prognosis is poor when multiple structural defects are associated, termination of pregnancy is offered as an option to the couple, after multidisciplinary prenatal counseling. If desire to continue the pregnancy, there is a high risk of preterm delivery, low birth weight or intrauterine death. The proper treatment of OIES complex includes a series of surgeries depending on the severity of the condition [100, 101].

3.8. Prune belly syndrome

The prune belly syndrome is another rare congenital syndrome, characterized by deficient abdominal muscles, urinary tract abnormalities and cryptorchidism in male fetuses. The pathophysiology has not been completely elucidated, as some consider the syndrome as a consequence of severe bladder outlet obstruction and others consider an abdominal muscle deficiency, secondary to a migration defect of the lateral mesoblast between weeks 6 and 7 of pregnancy [102]. The incidence is estimated to be 1 in 35,000 to 1 in 50,000 live births. The antenatal diagnosis is obtained during the second trimester scan, when megacystis is noticed, and an abnormally distended abdomen, in the absence of keyhole sign. However, there are reports in regards to the early US diagnosis [103, 104]. In the most severe form of Prune belly syndrome, a high incidence of oligohydramnios, pulmonary hypoplasia and ultimately stillbirth is reported [105]. Often, termination of pregnancy is the couple's option in early pregnancy. The postnatal management may include a single comprehensive surgical approach or a multiple step one, with good long-term results, but with a considerable incidence of iterative surgery and progression of the disease [106].

3.9. Cantrell pentalogy

With an incidence of 5.5 cases per 1 million live births and a male predominance [107], pentalogy of Cantrell is characterized by a midline, supraumbilical AWD, with a defect of the lower sternum, deficiency of the anterior diaphragm, defect in the diaphragmatic pericardium and cardiac anomalies such as septal defects and tetralogy of Fallot [108]. The main event during embryogenesis, thought to be the cause of this rare anomaly, is an abnormal differentiation of the intraembryonic mesoderm, at approximately 14–18 days after conception [108]. Chromosomal anomalies, such as trisomy 13, 18 and Turner syndrome, are often associated, so the invasive diagnosis is mandatory. Other anomalies observed with pentalogy of Cantrell include craniofacial and vertebral anomalies. US diagnosis of Cantrell's pentalogy is possible early, at 10 weeks' gestation, using 2D and 3D scans [109]. The combination of omphalocele and ectopia cords highly indicates a case of pentalogy of Cantrell [110]. The pentalogy is "complete" if four or all five defects are present, and is "incomplete" when various combination of defects are observed, if a sternal abnormality is present [86]. The AWD may contain stomach, liver,

Abnormality	Covering membrane	Site of defect	Umbilical cord insertion	Additional findings
Omphalocele	Yes	Umbilical insertion	Omphalocele membrane	
Gastroschisis	No	Right of umbilical insertion	Normal insertion	
Umbilical hernia	Yes	No umbilical ring defect	Normal insertion	
Pentalogy of Cantrell	Yes	Above umbilical insertion	Omphalocele membrane	Anterior diaphragmatic hernia, sternal clefting, ectopia cordis, and intracardiac defect.
OEIS complex	Yes	Umbilical insertion	Omphalocele membrane	Bladder exstrophy, imperforate anus, and spina bifida.
Body-stalk anomaly	Herniated organs in extraembryonic coelom	Whole anterior abdominal wall	Cord absent or shortened	Kyphoscoliosis, cranial defects, and limb defects.
Bladder exstrophy	Not applicable	Below umbilical insertion	Low insertion	Non-visualisation of bladder, lower abdominal bulge (exstrophied bladder), small penis with anteriorly displaced scrotum (if male), and widening of the iliac crests.
Cloacal exstrophy	Not applicable	Below umbilical insertion	Low insertion	Renal anomalies, neural tube defect, omphalocele, vertebral anomalies, non-visualisation of the bladder, distended bladder, hydrocolpos, dilated or echogenic bowel, umbilical cord cyst, separated pubic bones, and 'elephant trunk' sign.

OEIS, omphalocele, bladder exstrophy, imperforate anus, spina bifida complex.

Figure 5. Ultrasound findings in fetal abdominal wall defects [26].

bowel or total abdominal contents, evisceration. There is a pleural and pericardial effusion and the fetal heart is completely external or just partially. The prognosis is fatal and the survival is uncommon. Prenatal diagnosis is important as termination of pregnancy is the only option for the couple.

The ultrasound features that best characterize fetal AWDs are presented in **Figure 5** [26].

4. Pregnancy surveillance

In cases with abdominal wall defects, fetal distress was reported in 43% of cases, with an abnormal neurological outcome in 16% of them [111]. There is also the risk of still birth, reported to be 11% in cases of gastroschisis and 20% in cases of omphalocele [112]. Fetuses with gastroschisis often tend to be small for gestational age and to develop oligohydramnios [113, 114]. In such cases, the assessment of fetal weight can be difficult, as measurements of the fetal abdomen are not valid [115]. Placental insufficiency can be indirectly estimated by umbilical artery Doppler velocimetry, cardiotocography and biophysical profile. Still,

intrauterine growth restriction and oligohydramnios seem not to worsen the prognosis of fetuses with gastroschisis [116]. Fetal bowel features can be also evaluated, to estimate postnatal bowel complications. A cut-off of 1 cm for bowel diameter was considered a far-seeing marker for bowel damage [117, 118]. Overall, there is not yet a consensus regarding how and when fetal monitoring during pregnancy. Because of the associated risk, recommended attitude is a careful monitoring and a monthly interval control scheme, somewhat arbitrarily chosen. In the third trimester, repeated fetal monitoring is indicated [111]. Hospital admittance was proposed at 35 weeks of gestation, as many patients with fetal AWDs deliver prematurely [112, 115].

5. Mode and time of delivery

Even with recent progress in major medical and surgical specialties, the mode and time of delivery of fetuses with antenatal diagnosed abdominal wall defects remains a controversy. Fetal delivery by elective cesarean section is advocated by some centers [119–125], while others consider a vaginal delivery more suitable in cases with diagnosed fetal abdominal wall defect [126–130]. More so, there is no difference in fetal outcome regarding the mode of delivery [131–135]. In cases of omphalocele, delivery by cesarean section is recommended in cases with a large defect, to prevent the sac rupture and the liver damage during labor [136]. However, some researchers found that features such as the size or liver herniation have no importance in establishing the outcome of vaginal delivery [137]. The gestational age for induced delivery or elective cesarean section is another controversy (preterm versus term delivery). Some authors reported more complications and longer hospitalization in preterm deliveries [138, 139]. Others recommend a preterm delivery to optimize the toxic damage of the amniotic fluid to the herniated bowel in gastroschisis [120, 124, 129, 140]. The most recent study presented good results using a protocol for a preterm elective delivery, between 35 and 36 + 6 gestational age for fetuses with gastroschisis. Preterm delivery is not indicated in cases of omphalocele [26]. Still, most studies agree that in utero transport to a specialized pediatric center, where the defect can be corrected, offers an optimal fetal outcome [126, 141].

6. Postnatal prognosis and management

6.1. Gastroschisis

Postpartum, fetuses with gastroschisis must benefit from intravenous fluid resuscitation and wrapped herniated loops in warm saline as there is an increased risk for water and heat losses by evaporation. Specialized management of gastroschisis includes repositioning of the herniated bowel into the abdominal cavity, with closure of the abdominal wall (primary reduction and repair). In such cases, there is a high risk of respiratory complication. The surgical procedure can be also postponed if the patient is unstable [18], but with subsequent longer time

to reach full enteral feeds. In cases of complex gastroschisis, the repair is usually delayed, as anastomosis is impossible immediately after delivery, having an inherent risk of infectious and cholestasis complications [18, 24].

6.2. Omphalocele

In contrast to gastroschisis, there is a low risk of fluid and health losses in neonates with omphalocele, but still a coverage with saline-soaked gauze is required. Postnatal outcome and surgical management depends on the associated anomalies, such as congenital heart disease and pulmonary hypoplasia. Also, fetal gestational age and the size of the defect are relevant [18]. In cases of a small AWD, primary closure is the preferred therapeutic procedure, while in cases of a larger defect, multiple surgeries may be required to repair the considerable defect. Various agents such as povidone-iodine, sulfadiazine, neomycin, silver-impregnated dressings, neomycin, polymyxin and bacitracin ointments have been reported to help with the formation of an eschar of the amnion sac. There are different surgical techniques for the cure of omphalocele that include serial reductions or closing the defect gradually after replacing the sac with a mesh [24].

7. Conclusion

Prenatal ultrasound offers a high accuracy in the diagnosis of fetal abdominal wall defects beginning with the first trimester nuchal scan. Most fetal abdominal wall defects have poor prognosis and termination of pregnancy if often offered at the time of the detection after multidisciplinary counseling. Management of gastroschisis can be challenging, and also is the surgical treatment of complex forms. On the other hand, omphalocele, relatively easy to diagnose and treat, is frequently associated with chromosomal and structural anomalies that worsen the prognosis and the final outcome. The importance of ultrasound diagnosis in early pregnancy must be highlighted. This should be available even in under-developed health systems.

Author details

Roxana Cristina Drăgușin[1]*, Maria Șorop-Florea[1], Ciprian Laurențiu Pătru[1], Lucian Zorilă[1], Cristian Marinaș[2], Nicolae Cernea[1], Cristian Neamțu[3] and Dominic Gabriel Iliescu[1]

*Address all correspondence to: roxy_dimieru@yahoo.com

1 Department of Obstetrics and Gynaecology, University of Medicine and Pharmacy, Craiova, Romania

2 Department of Anatomy, University of Medicine and Pharmacy, Craiova, Romania

3 Department of Physiopathology, University of Medicine and Pharmacy, Craiova, Romania

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Chapter 11

Gastroschisis: Prenatal Diagnosis and Outcome

Vesna Milojković Marinović, Blagoje Grujić, Aleksandra Stojanović, Dalibor Sabbagh and Petar Rašić

Additional information is available at the end of the chapter

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Abstract

The purpose of this retrospective cohort study was to investigate and identify prenatal predictors of perinatal outcomes of gastroschisis. Antenatal data included extra-abdominal bowel dilatation (EABD) and intra-abdominal bowel dilatation (IABD). Perinatal data included gestational age, sex, and birth weight. Surgical data included presence of intestinal atresia, necrosis, perforation, strictures, and method of closure. Outcome data included duration of mechanical ventilation and total parenteral nutrition, pseudoobstruction, sepsis, reoperations, length of hospital stay, and mortality rates. Results were analyzed in 65 patients. EABD was documented in 55 patients with no significant difference between simple and complex gastroschisis group. In 27 patients (in 32% of simple and 73% of complex cases), IABD persisted until the last ultrasound scan. Simple gastroschisis group had a shorter hospital stay, shorter ventilation support duration, less bowel pseudoobstruction, less need for reoperation, and received less parenteral nutrition. The most frequent extraintestinal complication was sepsis. The only factor that has been shown to predict poorer outcomes of gastroschisis is the presence of complex gastroschisis. Current available evidence suggests that antenatal bowel dilatation is not associated with increased risk of adverse perinatal outcome in infants with gastroschisis. Also, the absence of bowel dilatation cannot fully exclude complex patients.

Keywords: gastroschisis, primary fascial repair versus staged closure, management, outcomes complex versus simple, vanishing, prenatal diagnosis, intra-abdominal bowel dilatation, extra-abdominal bowel dilatation

1. Introduction

Gastroschisis is a birth defect of the abdominal wall, in most cases located to the right of the umbilicus and typically smaller than 2 cm, with the herniation of abdominal organs into the amniotic cavity [1, 2].

This anomaly occurs in approximately 0.01–0.06% of births and it could be detected prenatally in up to 95% of cases using the obstetric sonography. Identifying the gastroschisis by fetal echosonography is possible as early as in 12 weeks of gestation by observing the ventral wall defect with loops of bowel protruding outside the abdomen, floating freely in the amniotic fluid [3, 4].

Researchers still have not discovered the precise cause of gastroschisis [5]. Some of them claim that it is probably the results of mesenchymal damage and failure of the epidermis to differentiate at the site of the defect, which is caused by premature atrophy or abnormal persistence of the right umbilical vein [6]. Others have proposed that the condition may be caused by ischemia of the base of the cord due to intrauterine disruption of the right omphalomesenteric artery, which than lead to herniation of the gut through this infarcted area [7].

Furthermore, it is very important to make the distinction between various ventral wall defects, especially between gastroschisis and omphalocele [8]. Omphalocele is characterized by a midline defect of abdominal muscles, fascia, and skin at the umbilicus, resulting in herniation of intra-abdominal structures into the base of the umbilical cord. The herniated organs in omphalocele are always covered by an amniotic membrane, unlike to gastroschisis where the abdominal organs float freely in amniotic cavity, exposed to potentially negative influence of amniotic fluid [1]. However, it is proved that gastroschisis has got much better prognosis, because it is, on contrary to omphalocele, not associated with chromosomal abnormalities and usually not associated with other structural anomalies. Survival rates of gastroschisis are more than 90% [9, 10].

On the other hand, infants with gastroschisis are at high risk of postnatal complications, especially gastrointestinal ones. The most common gastroschisis-associated gastrointestinal anomaly is intestinal atresia [3]. Besides, we can identify intestinal stenosis, as one of the most common bowel complication, probably caused by lack of the blood flow as a result of compression of eviscerated bowel at the site of the abdominal wall defect. Intestinal atresia as well as other intestinal anomalies could lead to bowel dysmotility, peritonitis, small-bowel pseudo obstruction, perforation, necrotizing enterocolitis, cholestatic jaundice, short-bowel syndrome, vomiting, and fistulas. In fact, the most significant factor determining the prognosis is the condition of the bowel at birth. The more the bowel is damaged, the worse the long-term outcome is. If the bowel distension, atresia, or necrosis is identified, primary repair with the resection of necrotic segment could be usually done; however, staged repair is sometimes required. These infants often have long-term morbidity caused by severe intestinal hypoperistalsis and poor absorptive capacity, requiring prolonged or permanent parenteral nutrition with its associated risks of infection, growth restriction, metabolic disturbances, and liver disease.

Regarding to all above-mentioned parameters, researchers Molik et al. [11] proposed classification of gastroschisis into simple (**Figure 1**) and complex (**Figure 2**) cases. Complex gastroschisis was defined as gastroschisis associated with at least one of the following intestinal pathologies:

intestinal atresia, perforation, necrotic segments or volvulus. Simple gastroschisis was defined as gastroschisis in absence of any of these conditions causing additional bowel damage.

In addition, having good, early prenatal diagnosis of gastroschisis gives the possibility of following of the intrauterine development of fetus, identifying possible growth restriction or gastrointestinal obstruction. This could be helpful in making the strategy for perinatal treatment in a tertiary referral hospital. Having in mind that the prognosis of the infant born with gastroschisis depends primarily on the condition of the bowel at birth, researchers have tried to find sonographic predictors of bowel damage [4] which can be used to make decisions about the timing of delivery [12]. Recent researches show different results: some of them have shown connection between the dilatation of the herniated bowel and thickening of the bowel wall with postnatal gastrointestinal complications and poor outcomes [13]. Other studies, on the other hand, show that the dilatation of herniated bowel is not the predictor of poor outcome [14]. The results of our study did not show that there was a statistically significant difference in outcome between patients without prenatally detected bowel dilatation and those one who had dilated bowel prenatally identified. Future researches should be focused on discovering some other prenatal sonographic parameters in patients with gastroschisis which could be useful for poor outcome prediction.

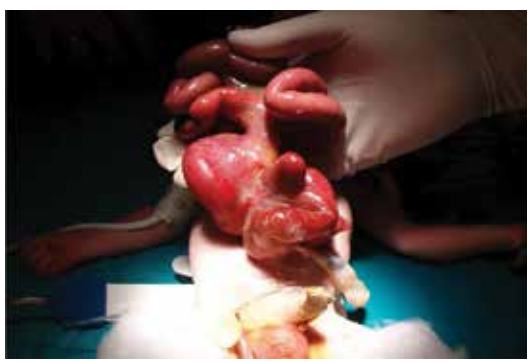

Figure 1. Simple gastroschisis.

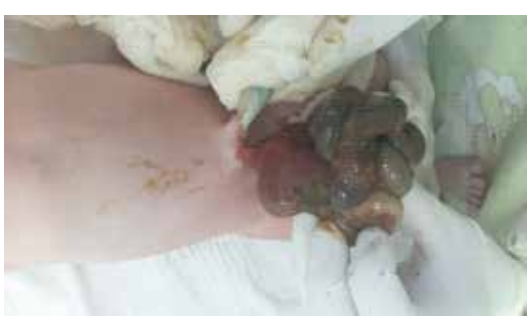

Figure 2. Complex gastroschisis—gastroschisis associated with intrauterine necrosis and perforation of the bowel.

Although numerous articles considering the optional management of gastroschisis are available in the professional literature, it still remains controversial. There are two preferable methods in operative approaches: primary closure and staged closure using customized silo [15]. Primary surgical repair is the method of choice of gastroschisis treatment at our Institution, whenever it is feasible. During the last decade, we have moved toward staged reduction of the herniated intestines (without intestinal anomalies) into the abdominal cavity using a silo (**Figure 3**), which is then followed by elective abdominal wall closure (**Figure 4**). We also reviewed differences of the outcome of newborn with simple and complex gastroschisis treated at our Institution over the past 15 years and tried to identify factors associated with mortality [9]. In majority of published studies reported mortality of gastroschisis is less than 10%, which is mostly the result of development of the modern neonatal intensive care, advanced pediatric surgery, and new prenatal diagnostic procedures [4, 16]. All this provides better results in overcoming the gastroschisis-associated complications such as extensive intestinal loss, short bowel syndrome, prolonged total parenteral nutrition, liver failure, sepsis, and early baby death.

Several studies have examined the different outcomes in fetuses with gastroschisis [14], but most of them have included all abdominal wall defects, not just gastroschisis [17, 18]. In future, more researches should be focused on discovering the factors which could indicate the presence of complex gastroschisis. Besides, new studies should provide improvement of prenatal diagnosis and postnatal management.

Figure 3. Eviscerated organs placed into silastic bag.

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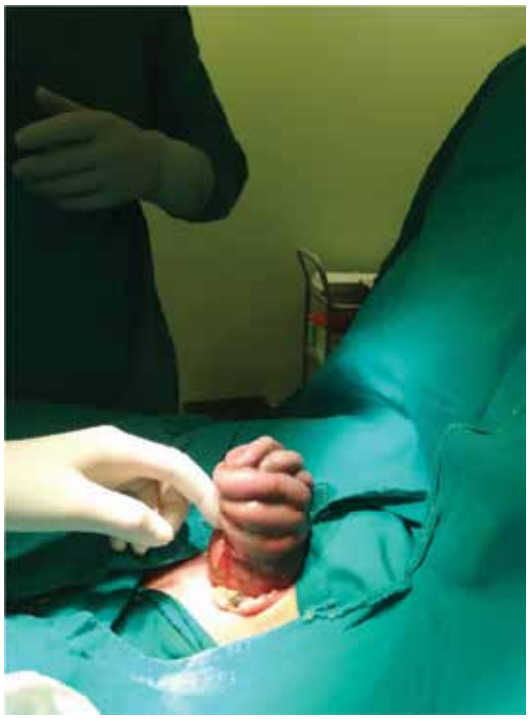

Figure 4. Eviscerated organs removed form a silastic bag, preparing for reducing into abdominal cavity and abdominal wall defect closure.

The aim of this study was to investigate and identify prenatal predictors of perinatal outcomes of gastroschisis. Also, we tried to compare the outcomes in infants with simple and complex gastroschisis.

2. Material and methods

We performed a retrospective cohort study where we included all the patients treated at the Institute for Mother and Child Health Care of Serbia "Dr. Vukan Čupić" in period 2001–2017 with the diagnosis of gastroschisis (n = 70). The exclusion parameters were prematurity (<34 weeks of gestation) and birth weight less than 1500 g, so the five patients were excluded (n = 5). We used patient records and neonatal intensive care unit database to obtain infant birth history, demographic and clinical parameters that were necessary for this research.

Antenatal data included extra-abdominal bowel dilatation (EABD) (bowel diameter ≥ 18 mm) and in particular intra-abdominal bowel dilatation (IABD). Perinatal data included birth age, gestational age, sex, and birth weight. Surgical records included presence of intestinal atresia, necrosis, perforation, strictures, and method of closure. Outcome data included duration of mechanical ventilation, duration of total parenteral nutrition, pseudoobstruction, sepsis (central line infection), reoperations, length of hospital stay, and mortality rates.

We defined patients with complex gastroschisis as cases with gastroschisis and one or more of the following anomalies: intestinal perforation, intestinal atresia, strictures, and ischemic bowel. Total length of hospital stay was defined as the number of days from first admission to first discharge or transfer to another hospital.

2.1. Data analyses

We compared the incidence of simple gastroschisis (defined as gastroschisis with intact bowel that is not compromised) and complex gastroschisis (defined as gastroschisis with presence of one or more of the following criteria: intestinal atresia, perforation or intestinal necrosis or strictures), in fetuses with gastroschisis with and without evidence of bowel dilatation.

Also, we compared outcomes in infants with simple gastroschisis and those with complex gastroschisis using nonparametric methods. An outcome analysis was performed regarding antenatal bowel dilatation (bowel diameter ≥ 18 mm) and in particular intra-abdominal bowel dilatation (IABD), birth weight, gestational age, sex, mode of the closure of the defect, presence of intestinal necrosis or perforation, pseudoobstruction, reoperation, duration of mechanical ventilation, and total parenteral nutrition. Outcome data included presence of sepsis, total length of hospital stay, and mortality rates. We used χ^2 test and Mann-Whitney U test for data analysis; p values <0.05 were considered significant. SPSS version 12 was used for carrying out all analyses.

3. Results

We identified 70 patients with gastroschisis between 2001 and 2017. Five patients were excluded from study (babies with birth weight less of 1500 g and premature infants (<34 weeks of gestation)), so that 65 patients were analyzed. The characteristics of all analyzed patients are presented in **Table 1**. There were 15 patients (23.07%) with complex gastroschisis. Statistically significant difference was not identified between the simple and the complex gastroschisis groups in gestational age (36.1 ± 1.4 versus 36.16 ± 1.6; p = 0.173) and birth weight (2248.4 ± 507.6 versus 2351.33 ± 633.8; p = 0.319). There were 39 males and 26 female patients (65 in total). In both groups, majority of patients were males: 54% and 80% in simple and complex gastroschisis group, respectively.

Forty-four patients (67.69%) received primary fascial repair (primary closure). Twenty-one patients (32.30%) received delayed fascial closure using silastic bag. All the patients with complex gastroschisis (n = 15) were treated with primary fascial repair.

The overall incidence of intestinal atresia was 7.69% (n = 5) in our patient population. Ischemic complications such as stenosis, strictures, necrosis, and perforation were the main complication in nine cases (60%) of the complex gastroschisis group. Closing gastroschisis was presented in one case (6.66%) with circumferential closure of the ring around the protruding bowel associated with midgut necrosis.

N Gender	Simple; n (%)	Complex; n (%)	p
	Mean ± SD (n = 50)	Mean ± SD (n = 15)	
Male	27 (54%)	12 (80%)	p = 0.071
Female	23 (46%)	3 (20%)	
Gestational age (wk)	36.1 ± 1.4	36.16 ± 1.6	p = 0.173
Birth weight (g)	2248.4 ± 507.6	2351.33 ± 633.8	p = 0.319
Primary closure	29 (58%)	15 (100%)	p = 0.0032
Performed spring-loaded silo	21 (42%)	0	
TPN duration (d)	13.64 ± 10.8	53.1 ± 42.6	p = 0.000019; p < 0.001
Ventilation support duration (d)	7 ± 6.54	24 ± 14.2	p = 0.000003; p < 0.001
Hospital stay (d)	32 ± 15	91 ± 64	p = 0.000198; p < 0.001
Sepsis (n)	19 (38%)	12 (80%)	p = 0.0043
Reoperation (n)	10 (20%)	10 (66.7%)	p = 0.00122
Pseudoobstruction (n)	9 (18%)	12 (80%)	p = 0.00067; p < 0.001
Neonatal death (n)	4 (8%)	3 (20%)	p = 0.338

Table 1. Patient characteristics of simple and complex gastroschisis groups.

Antenatal IABD (including stomach dilatation) was detected at any time during pregnancy in 55 patients, resolving in 4 after 1 ultrasound scan. In 27 patients IABD persisted until the last ultrasound scan in 32% of simple and 73% of complex cases. In these 27 patients, there were cases in both groups (simple and complex) where IABD was present earlier than 30 gestational weeks. All intra-abdominal bowel dilatation (IABD) are summarized in **Tables 2** and **3**. IABD was never present in seven simple cases and in three complex cases (2 atresia and 1 perforation).

All extra-abdominal bowel dilatation (EABD) are summarized in **Table 4**. There were 55 patients with extra-abdominal bowel dilatation (with precise EABD diameter). We have not identified statistically significant difference in EABD between the group of patients with complex gastroschisis [15 (15–31) mm] and the group of patients with simple gastroschisis [40 (13–50) mm], p = 0.91. EABD with the diameter ≥ 18 mm was documented in 72% of patients with simple gastroschisis as well as in 82% of patients with complex gastroschisis.

Patients with simple gastroschisis were put on enteral feeding earlier than patients with complex gastroschisis and received less parenteral nutrition: [(13.64 ± 10) vs. (53.1 ± 42.6) days; p = 0.000019 (p < 0.001)]. Also, they had shorter duration of ventilation support: [(7 ± 6.54) vs. (24 ± 14.2) days; p = 0.000003 (p < 0.001)]. Patients with simple gastroschisis had a shorter hospital stay: [(32 ± 15) vs. (91 ± 64) days; p = 0.000198 (p < 0.001)].

In complex gastroschisis group, the finding always dictated the method of closure, and all of these patients (n = 15) were closed primarily. In the simple gastroschisis group primary fascial closure was performed in 29 patients (58%). Our data show that the way of treatment of these

Complexity group (n = total in group)	Simple (n = 50)	Complex (n = 15)
IABD at last scan		
Number (% of complexity group)	16 (32%)	11 (73%)
IABD at ≥30 weeks to ≤34 GA		
Number (% of complexity group)	7 (14%)	10 (66%)
IABD at <30 weeks GA		
Number (% of complexity group)	4 (8%)	6 (40%)
Resolved IABD		
Number (% of complexity group)	3 (6%)	1 (7%)
Never had IABD		
Number (% of complexity group)	7 (14%)	3 (20%)

Table 2. All intra-abdominal bowel dilatation (IABD).

IABD diameter (mm)	Complex gastroschisis, n = 15	Simple gastroschisis, n = 50
	Number (% in group)	Number (% in group)
<10	0	4 (5%)
10 to <18	7 (47%)	10 (20%)
≥18	11 (73%)	16 (32%)

Table 3. Degree of intra-abdominal bowel dilatation (IABD).

EABD diameter (mm)	Complex gastroschisis n = 15	Simple gastroschisis n = 50
	Number (% in group)	Number (% in group)
<10	0	0
10 to <18	3 (20%)	11 (27.5%)
≥18	12 (82%)	29 (72%)

Table 4. Degree of extra-abdominal bowel dilatation (EABD).

patients depended primarily on characteristics of each case, which were quite heterogeneous. Routine silastic bag closure was performed in 21 patients (42%) with simple gastroschisis, and 19 patients (90.47%) of them had no complications.

Four patients with simple gastroschisis (8%) did not survive to be discharged. We identified gangrene of the bowels which were placed into silastic bag in two patients. Abdominal compartment syndrome was documented in two patients who were treated with primary closure. The need for repeated laparotomies was a result of various complications: sepsis, persistent metabolic acidosis, respiratory compromise, low urine output, and poor perfusion.

Three patients with complex gastroschisis (20%) did not survive to be discharged. We identified one patient (6.66% of complex gastroschisis and 1.53% of all gastroschisis) with closing gastroschisis—a boy born in 34th gestational week with birth weight of 1900 g. The abdominal wall defect was located to the left side of the umbilicus. This patient had jejunal atresia 20 cm distal to the ligament of Treitz. We identified midgut volvulus progressing to complete midgut necrosis of entire extra-abdominal bowel mass in the first day of life. We performed a midgut resection, jejunocolic anastomosis, and abdominal fascial closure. The procedure was successful. However, the baby died due to multiple organ dysfunction caused by sepsis in the 20th day of life.

Additional complications were identified in 21 (32.3%) of the 65 patients. A bowel pseudoobstruction and feeding problems were most frequent gastrointestinal complications: 9 (18%) of the patients with simple gastroschisis vs. 12 (80%) patients with complex gastroschisis ($p = 0.00067$). In 10 (20%) patients with simple gastroschisis and in 10 (66.7%) patients with complex gastroschisis ($p = 0.00122$) reoperation was necessary. Sepsis was the most common extraintestinal complication: in 19 (38%) and 12 (80%) patients with the simple and complex gastroschisis, respectively ($p = 0.0043$).

Forty-six (92%) patients with simple gastroschisis survived to be discharged and four (8%) patients died in the hospital. Twelve (80%) patients with complex gastroschisis survived to be discharged and three (20%) patients died in the hospital ($p = 0.338$).

4. Discussion

Recent studies have shown significant increase in the incidence of gastroschisis during the past 20 years [19]. The incidence of gastroschisis is as high as 4.4 per 10,000 live births, and it is proved that it depends on the mother's age [1, 20]. In fact, the incidence is several times higher in women younger than 20 years than in women 25–29 years old [1].

In our study, we classified gastroschisis cases into simple and complex, according to the presence of associated bowel damage such as atresia, perforation, and necrosis, as these factors may have influence on the way of treatment and outcomes. Reviews in large national databases in Great Britain and the United States have shown that complex gastroschisis represents 11.5% and 10.9% of all cases, respectively [21]. The prevalence of complex gastroschisis in recent publications has been reported as 11–31% [21, 22]. In our cohort study, 77% of infants had simple gastroschisis, in other words almost 1 in 4 patients had complex gastroschisis. Researchers have proved that the only factor that has been consistently shown to predict poorer outcomes of this anomaly is the presence of complex gastroschisis [23, 24]. The results we obtained in our study show the same. Also, the presence of complex gastroschisis could lead to prolonged duration of total parenteral nutrition, ventilation support, and hospital stay. On the other hand, in our study, as well in some others, mortality did not differ significantly between simple and complex gastroschisis [9, 10, 22]. Some previous researches, on contrary, claim that intestinal complications are associated with higher mortality, as high as 28% [10, 11].

We also try to investigate possible relationship between intra-abdominal and extra-abdominal bowel dilatation with poor outcome. Some studies have shown that antenatal bowel dilatation (bowel diameter ≥ 18 mm) and in particular intra-abdominal bowel dilatation (IABD) is a useful predictor for impending necrosis or atresia and for bad outcome [25, 26]. On the other hand, one study shows [12] that 19% of complex patients never had IABD and the other one shows [27] that 75% never had extra-abdominal bowel dilatation (EABD). Therefore, the absence of bowel dilatation cannot fully exclude complex patients with gastroschisis. However, combined IABD/EABD or IABD/collapsed extra-abdominal bowel is highly suggestive to complex gastroschisis [28].

Neonates with gastroschisis have delayed beginning of enteral feeding and prolonged time to achieve full enteral feeding (FEF), possibly due to bowel exposure to amniotic fluid. The research done by Yang et al. shows that IABD is associated with prolonged time to achieve full enteral feeding (FEF) and prolonged length of hospital stay (LHS) [25]. On the other hand, systematic review of isolated gastroschisis reported by Helen Carnaghan et al. [12] does not support those results; this study data on contrary show that neither EABD nor IABD could be predictors of increased poor neonatal outcomes [29]. However, it is proved that if the IABD and collapsed extra-abdominal bowel or both IABD/EABD are identified earlier than 30 weeks of gestation that could be more accurate predictor of poor outcome. Our study has shown that antenatal bowel dilation does not predict the poor outcome in infants with gastroschisis.

A PubMed literature search revealed fetal gastroschisis cases with intrauterine eviscerated bowel or stomach perforation in five reports [25, 27, 28, 30, 31]. There was one case with gastric perforation identified in prenatal period [28] and the other one where the gastric perforation was diagnosed during surgical repair of complex gastroschisis [27]. Two cases of gastroschisis had bowel perforation and intestinal atresia at the same time [25, 31].

The prenatal sonographic findings of bowel or gastric perforation are variable. According to literature, prenatal sonographic findings depend on the extent of meconium leakage, time when the bowel or gastric perforation occurred, the underlying bowel disorder, the stage of the disease, and the site of perforation [32]. The mechanism of gastric and bowel perforation in gastroschisis is multifactorial. Firstly, an amniotic fluid has got toxic effect on the muscle cells of bowel and stomach. Secondly, the amniotic fluid exerts negative effects on the vascular structures of mesentery causing mesenteric shortening which then leads to bowel ischemia. Besides, the lack of blood supply may be additionally caused by previously occurred vascular insult, as well as by constriction of the abdominal wall defect [33, 34]. All this could result in muscle layer thinning and interruption. Furthermore, if the perforation occurs, chemical irritation caused by dissipated meconium leads to an inflammatory reaction which initiates bowel mural thickening (causing stenosis) and adhesions creation (causing external bowel obstruction).

Grundy et al. presented a case of an infant with gastroschisis and intrauterine bowel perforation. The suspicion of fetal bowel perforation was indicated by the presence of calcifications on the surface of the extra-abdominal bowel as well as by the presence of the extra-abdominal intramesenteric pseudocyst. Unfortunately, the neonate died third day after birth [27]. Another case was presented by Haberman et al.: a neonate with gastroschisis associated with bowel

atresia who developed a terminal ileum perforation. The echogenic material spillage at the margin of a bowel loop near the site of the abdominal wall defect led to diagnosis of an acute intrauterine bowel perforation. The perforation has been identified proximal to an atretic segment of ileum. Finally, the patient was treated by resection of the 14 cm of bowel and ileostomy, which were followed by primary fascial repair. The operation outcome was favorable [28]. Furthermore, a case of child with gastroschisis and fetal eviscerated gastric perforation was reported by Tseng and Chou. The antenatal sonography identified a mural thickening of the triple layered gastric segment, a concave deformity of the inner layer, and a small nodule on the outer surface. Firstly, the small perforation over the greater curvature of the stomach was repaired and then staged operations were performed in the aim to reduce the exposure of the bowel loops out of the abdominal cavity [31]. Next case was published by Yang et al.: a patient where the gastric perforation was diagnosed during surgical repair of complex gastroschisis (associated with colon atresia) [25]. Marinović et al. reported case of gastroschisis with gastric perforation and intestinal stenosis in male newborn. Prenatal sonographic findings were inconclusive. Large gastric perforation was diagnosed during surgical repair of gastroschisis [30].

Having diagnosed some of above-mentioned factors prenatally may lead to consideration of an early delivery with the aim to salvage necrotic bowel, although these antenatal findings may indicate that the bowel damage has already occurred. On the other hand, early delivery is associated with prolonged time to achieve a full enteral feeding (FEF) and prolonged length of hospital stay (LHS), suggesting that elective delivery earlier than 37 weeks of gestation is not beneficial.

Closing gastroschisis is rare, but potentially extremely complicated type of this anomaly. Houben et al. [35] published a research with the largest series of infants born with various stages of closing gastroschisis where 6% of infants present with closing abdominal ring. Recent literature shows low survival rate of an infant with closing gastroschisis [36–39]. In our research one patient (6.66%) presented with closing gastroschisis. Identifying progressive intra-abdominal bowel dilatation using prenatal ultrasonography could be indicative of a presence of closing abdominal ring complication. If there is a suspicion of a closing ring, early delivery must be urgently considered [37].

There are many different methods of surgical treatment of gastroschisis. Reducing the evaporative and thermal loss is crucial primary goal. This could be accomplished by primary closure or staged closure using a silastic bag [15]. We found that the only factor that has been shown to predict poorer outcomes of gastroschisis is the presence of complex gastroschisis. Therefore, the strategy of surgical treatment should be focused on management of gastroschisis-associated conditions such as perforation, necrosis, stenosis, atresia, and short bowel syndrome. Our experience confirms the safety of an early restoration of bowel continuity and primary fascial closure. We found that much better outcome is associated with this way of treatment. Others have reported both early and late primary anastomosis as the safe options for treatment of gastroschisis associated with atresia [40]. By experience, surgeons may identify which patients have fascial defects more amenable to primary closure [30]. Our study favored primary closure because it is associated with significant reduction in length of hospital stay, total parenteral

nutrition, and days with ventilation support. On the other hand, primary closure may cause abdominal hypertension and abdominal compartment syndrome which then could lead to an ischemia and necrosis of the bowel, renal failure, respiratory distress, and sepsis [41]. Abdominal hypertension is defined as prolonged or repeated increase in intraperitoneal pressure above 12 mmHg [42]. In fact, when the bowels are reduced into the non-sufficiently developed abdominal cavity, the raise of intraperitoneal pressure leads to compression of the blood vessels causing mesenteric ischemia and bowel necrosis. This kind of ischemia occurs very fast because the bowels in gastroschisis have got, in most cases, primarily lower perfusion than the bowels of a healthy infant [43]. Besides, an increased intra-abdominal pressure reduces the blood flow in big veins leading to diminished heart preload which then causes lower cardiac output and global hypoperfusion. This has an influence on renal blood flow making the renal hypoperfusion, anuria, and renal failure. We identified two patients in our study who received primary fascial repair and had abdominal compartment syndrome (**Figure 5**). So, it is very important that surgeon considers many different parameters when making the decision regarding the way of treatment of various cases of gastroschisis. In case when the primary closure without risk of abdominal compartment syndrome is not possible, surgeon should perform stage closure using a silastic bag which use becomes routine in many healthcare centers around the world. The criterion which strictly indicates that the silastic bag treatment should be performed is the presence of antenatal type of gastroschisis. Regarding to the duration of the exposure of the eviscerated bowels to amniotic fluid and the degree of abdominal cavity development, Moore classified gastroschisis into antenatal and prenatal types [44]. In antenatal type, the abdominal wall defect appears in early pregnancy so the bowels are exposed to negative influence of the aminotic fluid for a long time. Postnatally, the bowels are covered with gelatinous matrix, with a lot of adhesions and shortened mesentery. This type is also characterized by non-sufficiently developed abdominal cavity and the fascial defect which tends to become smaller and more tight during the intrauterine development. The closing of the fascial defect leads to an intrauterine bowel ischemia, which causes thickening of the intestinal wall, creating of the intestinal peel, stenosis, necrosis, and perforation. On the other hand, surgeon is not allowed to apply silastic bag if there is a possibility that tight fascial defect

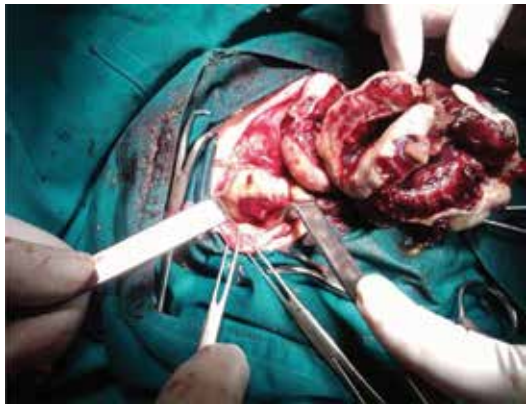

Figure 5. Massive necrosis of the bowel due to abdominal compartment syndrome.

Figure 6. Necrosis of the bowel placed into silastic bag.

could compromise eviscerated organs' blood flow. In that case, it is very important that surgeon performs an urgent fasciotomy before placing the eviscerated organs into silastic bag. The bad evaluation of fascial defect size and skipping the urgent fasciotomy may lead to bowel ischemia and necrosis. In our study, we identified two patients who had developed gangrene of the bowels placed in the silastic bag without having fasciotomy previously performed (**Figure 6**). On contrary, in prenatal type of gastroschisis, the abdominal wall defect appears later in pregnancy, so the bowels are not as damaged as in antenatal type, and the abdominal cavity is much more developed. This type of gastroschisis could be treated by the primary closure.

Finally, the length of hospital stay in patients with complex gastroschisis is in most cases based on additional intestinal complications they have, so it is often prolonged, regardless to way of closure [9].

5. Conclusions

The only factor that has been shown to predict poorer outcomes of gastroschisis is the presence of complex gastroschisis. Therefore, the strategy of surgical treatment should be focused on the management of gastroschisis-associated conditions such as perforation, necrosis, stenosis, atresia, and short bowel syndrome. Our experience confirms the safety of an early restoration of bowel continuity and primary fascial closure. We found that much better outcome is associated with this way of treatment. More researches should be focused on finding of complex gastroschisis predictors, improvement of prenatal diagnosis, and postnatal management.

Current available evidence suggests that antenatal bowel dilatation is not associated with increased risk of adverse perinatal outcome in infants with gastroschisis. Also, the absence of bowel dilatation cannot fully exclude complex patients. However, a randomized controlled trial is urgently needed.

Author details

Vesna Milojković Marinović*, Blagoje Grujić, Aleksandra Stojanović, Dalibor Sabbagh and Petar Rašić

*Address all correspondence to: vesnamilojkovic@yahoo.com

Department of Neonatal Surgery, Institute for Mother and Child Health Care of Serbia "Dr. Vukan Čupić", Belgrade, Serbia

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Chapter 12

Congenital Abdominal Anomalies

Ples Liana and Anca Lesnic

Additional information is available at the end of the chapter

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Abstract

Introduction: Abdominal anomalies that appear during intrauterine life are complex due to many organs that are affected. In cases, the ultrasound appearance is a cystic image with different content and the differential diagnosis is often difficult. Body—research methods: the organs affected by abdominal congenital anomalies involve the gastrointestinal tract (stomach, duodenum, small bowel or colon, and gall bladder), the kidney and urinary tract, the peritoneal cavity (ascites), suprarenal glands, and tumors of the reproductive system (especially the ovaries). In order to identify the affected structures, it is mandatory to know the normal aspect of the abdominal content at different gestational ages. The diagnosis may be very difficult, but its accuracy is important, considering the need of further counseling the couple. In minor conditions, without chromosomal anomalies or associations, the outcome is usually good, and there are even possibilities of in utero treatment. In severe conditions, with poor outcome, the couple can choose to terminate the pregnancy, after counseling is provided. Conclusion: abdominal congenital anomalies are common findings in ultrasound screenings for anomalies in all the trimesters of pregnancy and their recognition is important for subsequent management.

Keywords: gastrointestinal anomalies, cystic anomalies, congenital anomalies of the kidney and urinary tract

1. Introduction

The chapter will be structured on four main sections: the normal ultrasonographic appearance of the fetal abdominal cavity and abdominal wall, the absence of the normal abdominal structures, abnormal structures present in the abdomen (cysts, tumors, etc.), and abdominal wall anomalies.

Abdominal anomalies that appear during intrauterine life are complex due to the number of different organs that are affected. In most cases, the ultrasound appearance is of a cystic image with different content, and the differential diagnosis is often difficult.

2. Congenital anomalies overview

Congenital anomalies of the abdominal contents involve organs of the gastrointestinal tract, kidneys and urinary tract, suprarenal glands, and genital organs (mainly the ovaries).

Anomalies in the fetal abdomen are diagnosed either by the lack of visualization of normal structures or evidence of abnormal images during the anomalies screening ultrasound examination. Therefore, obtaining and documenting standard normal images of the abdomen is of crucial importance.

This chapter is structured in 4 subsections:

2.1. Normal aspect of the fetal abdomen.

2.2. Anomalies consisting of absent structures.

2.3. Abnormal structures present in the abdomen: cystic or echoic masses.

2.4. Abdominal wall anomalies.

2.1. Normal ultrasound images of the abdomen

At the midtrimester routine ultrasound scan, there are a couple of images that must be obtained according to ISUOG guidelines [1], images that can rule out most of the abdominal pathological conditions.

First step of the examination should be visceral situs assessment, by demonstrating the position of the stomach, liver veins, abdominal aorta, and superior cava vein as seen in **Figures 1** and **2**.

The abdominal transverse section at the umbilical vein–portal sinus is the level for abdominal circumference measurement and a standard image to identify some important structures:

- fetal stomach-an anechoic structure of bean-like form. It can be seen from 9 weeks, but at 14 weeks, the different parts of the stomach can be seen and gastric peristalsis can be detected

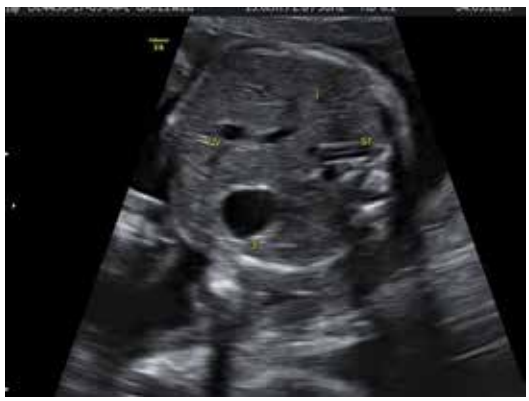

Figure 1. Transverse section of the fetal abdomen—the structures that can be seen are: stomach (s), umbilical vein (uv), liver (l), and suprarenal gland (sr).

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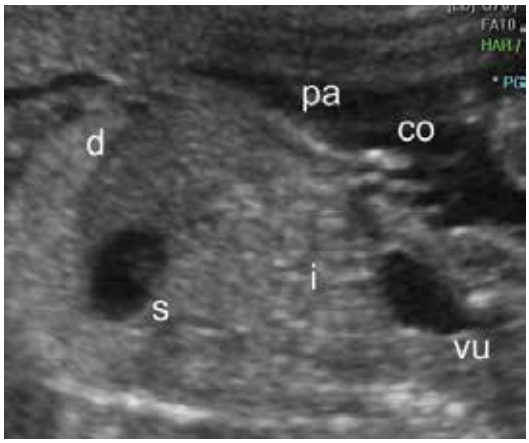

Figure 2. Sagittal section of the fetal abdomen—the continuity of the anterior abdominal wall is obvious (pa), the cord insertion (co), stomach (s), urinary bladder (vu), diaphragm (d), and bowel (i).

after 16 weeks of gestation. Nomograms of stomach size have been imagined at different gestational age [2]. Hyperechoic mass of uncertain origin may be seen inside the stomach and may disappear at the following examinations without pathological significance [3].

- fetal liver is an hypoechogenic structure that occupies the section on the right of the stomach.
- gall bladder is an ovoid, hypoechoic structure on the right and under the intrahepatic part of the umbilical vein.
- the umbilical vein has a caudal trajectory, penetrates the liver and connects with the left portal vein. Actually, the umbilical vein is the left portal vein, because the right portal vein regresses at 6–7 weeks.
- the anterior abdominal—skin, subcutaneous cellular tissue, and muscles.

The sagittal section at the abdominal level is essential for assessing the integrity of the anterior abdominal wall, because the insertion of the umbilical cord and the wall above and below the insertion can be visualized. Differentiating between the internal structures of the abdomen can be difficult, because the liver and intestinal loops have similar echogenicity. Between 8 and 10 weeks of gestation, the physiological gut herniation can be visualized by ultrasound, as a hyperechoic mass at the base of the umbilical cord. Reintegration occurs between 10 and 12 weeks and it is complete at approximately 11 weeks and 5 days.

At a lower transverse section of the abdomen, the kidneys, small bowel, and colon can be seen as the following:

- the kidneys are located on both sides of the spine; their adult similar shape can be recognized from 12 weeks but the medular/cortical differentiation is obvious starting from 15 weeks of gestation. The fluid filled structure of the calyces is a useful landmark to identify the kidneys. Corticomedullary differentiation (CMD) is determined according to echogenicity of the cortex and the medulla, considering that during the prenatal period, the

normal renal cortex is as echogenic as the liver or spleen and that the normal renal medulla is relatively hypoechogenic, which leads to a well-defined CMD [4].

- the small bowel is visible as a uniform, echogenic mass that can be differentiated from the colon by its central layout, aspect, and peristaltic changes, until the third trimester when its aspect is of round anechoic image with peristalsis (large intestinal loops filled with meconium) [5].
- the colon appears as a tubular structure located at the periphery of the abdomen, meanwhile the small intestine is centrally placed. The haustration of the wall serves to differentiate from other anechoic or hypoechoic structures. Meconium production begins at 16 weeks of pregnancy, giving the ultrasound-like appearance of the intestinal wall.

The echogenicity of the colon is established in comparison to other structures such as the liver or bladder:

- grade 0: the abdomen is uniformly homogeneous and the colon cannot be visualized.
- grade 1: the colon is hypoechogenic, isoechoic with the stomach and the bladder, haustrations being present.
- grade 2: the colon's echogenicity is higher than the bladder, but lower than the liver and occurs after 29 weeks.
- grade 3: echogenicity is similar to the liver's and occurs after 34 weeks.

Coronal or sagittal section of the fetal abdomen allows the visualization of the urinary bladder. It can be identified starting at 11–12 weeks of gestation as an anechoic mass with a thin wall, delineated by two umbilical arteries.

2.2. Absence of normal abdominal structures

The most common condition is the nonvisualization of the stomach, kidneys, or urinary bladder.

Nonvisualization of the gall bladder occurs in rare chromosomal diseases, mucoviscidosis, and in 20% of the fetuses with biliary atresia [6].

Absent stomach or small stomach can be associated with mechanical or functional absence of stomach filling:

- absent or reduced fetal swallowing: facial clefts, neuromuscular conditions, infections, SNC conditions, and fetal hydrops.
- mechanical obstruction or compression: esophageal atresia, diaphragmatic hernia, and thoracic tumors.
- reduced amniotic fluid production: oligohydramnios of any cause.

2.2.1. Esophageal atresia

There are five types of esophageal atresia, but the most common one after de Jong is the type with esophageal stump and trachea-esophageal connection below the interruption. In such cases, it is important to look after other indirect signs, like polyhydramnios and small for gestational age. Many of the anomalies are nonisolated [7]. Still, 44% of the anomalies are not diagnosed during the prenatal period [7].

Esophageal atresia is a condition defined by the lack of continuity between the proximal and the distal esophagus. The missing portion is the middle one and the main cause is poor blood flow. The anomaly appears during the 8th week of pregnancy when the primitive intestine fails to divide forming the trachea anteriorly and esophagus posteriorly. According to de Jong, in 90% of cases, esotracheal fistulae are associated. There are five types of esophageal atresia considering the anatomical location of the defect and the existence of the tracheoesophageal fistula [7]:

- type A: without fistula
- type B: proximal fistula
- type C: distal fistula (88% of cases)
- type D: double fistula, proximal, and distal
- type E: existing fistula without concomitant atresia

The incidence of this anomaly is 1:3500 live born and usually is nonisolated, being associated with CNS anomalies, VACTERL association, T21, T18, diaphragmatic hernia, and abdominal wall anomalies. [7]. Twenty percent of cases of the associations are with chromosomal anomalies (trisomy 13, 18, 21) [8] and cardiac defects may be present in 50% of cases. VACTERL syndrome is comprised of vertebral defects, ventricular septal defect, anal atresia, esotracheal fistula, renal anomalies, radial aplasia, and single umbilical artery [9].

Ultrasound diagnosis of esophageal atresia can be missed in pregnancy according to Brandberg and 44% of the cases cannot be diagnosed.

The prenatal diagnosis of esophageal atresia is difficult due to the absence of specific signs. The rate of detection varies between 8 and 24% [10, 11], and the lack of detection is due in 85% of cases to the tracheoesophageal fistulae association.

Prenatal esophageal atresia must be suspected if polyhydramnios is present after the 25th week of gestation and if the gastric pouch is absent. Sometimes, gastric secretions are sufficient to distend the gastric pouch, and make the diagnosis more difficult; if an esotracheal fistula is present, the gastric pouch may appear normal. Sometimes, the distal dilated portion of the esophagus may be observed as a hypoechoic area in the mediastinum, behind the heart (blind pouch aspect). Although the sign has a great diagnostic value, it is rarely present before 25 weeks of gestation [8, 12, 13]. The detection rate is improved if an antenatal MRI is performed.

The differential ultrasound diagnosis can be made with other conditions with absent stomach, the most frequent are:

- facial cleft;
- congenital diaphragmatic hernia;
- neuromuscular conditions [9].

The risk of association with other anomalies, chromosomal and nonchromosomal, is high rising to 30–40% of cases: trisomy 21 and 18, VACTERL association. Perinatal approach implies karyotype analysis when the diagnosis is made. The birth should take place in a tertiary center with a neonatal intensive department considering the high risk of fetal hypotrophy (40% of cases) and prematurity (due to polyhydramnios). Surgical reconstruction of the esophagus is possible. The prognosis depends on the association with other congenital anomalies and on the gestational age at birth. After 32 weeks of gestation, if the prenatal diagnosis is achieved, reflux and aspiration pneumonia can be prevented and the survival rates are over 95%. Long time prognosis is affected by the high rate of postoperative complications [9]. The postoperative mortality is approximately 9%, with a intrauterine fetal mortality of 22%. Retrospective studies have shown a neonatal mortality of 75%.

2.2.2. Absence of the kidney in the renal fossa

It can be caused by renal agenesis or ectopic kidney. True isolated renal agenesis is confirmed by the absence of renal artery and is associated with oligoamnios if it is bilateral. Unilateral renal agenesis can be isolated but association as VACTERL is common [14]. Failing to visualize the urinary bladder can be caused more frequently by bilateral renal agenesis or exstrophy.

2.2.3. Renal agenesis

It is defined as bilateral absence of kidneys with an incidence variable from 1 to 3/10000 births and it is more frequent in male fetuses—**Figures 3** and **4**. Renal agenesis can be sporadic (due to teratogens or diabetes mellitus), isolated, or part of syndrome association, the most frequent found being:

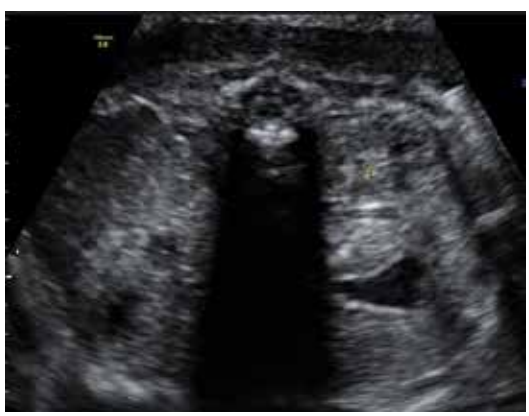

Figure 3. Renal agenesis—transverse abdominal section—no renal structure on the right side.

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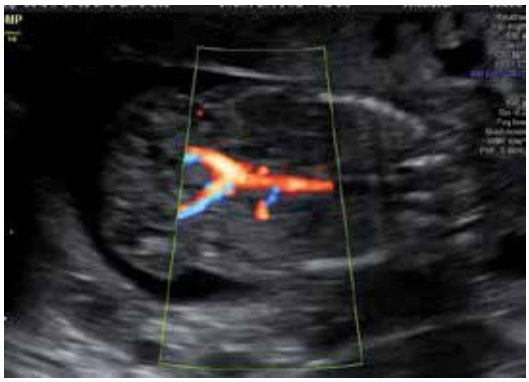

Figure 4. Unilateral renal agenesis—coronal section depicting only one renal artery.

- Cat's eye syndrome, characterized by iris coloboma, anal atresia, preauricular tags, and renal anomalies.
- 4p-Syndrome is characterized by multiple heterotopies of cells (in adrenals, brain, pancreas, and skin), renal agenesis, cardiac, facial, and genital anomalies.
- Fraser syndrome with: cryptophthalmos, syndactyly, auditory canal atresia, cleft palate, renal agenesis, and genital anomalies.
- a very severe syndrome: cerebro-oculo-facio-skeletal syndrome, characterized by: microcephaly, microphthalmia, narrow palpebral fissures, high nasal bridge, large ears, micrognathia, kyphosis, scoliosis, flexion contraction of the extremities, and rocker-bottom foot.
- in some cases, Müllerian duct anomalies can be associated.

Oligohydramnios is a constant finding in bilateral renal agenesis, and it can be seen from 14 weeks of gestation. "Potter syndrome" associates the following abnormalities:

- pulmonary hypoplasia.
- typical face—low set ears, epicanthus, parrot-beak nose, and receding chin.
- abnormal position of the hand and foot and bowed legs, clubbed feet, hip dislocation.
- intrauterine growth retardation.
- absence of urinary bladder visualization.

Ultrasound diagnosis of bilateral renal agenesis is based on three main elements:

- oligohydramnios.
- bilateral absence of the fetal kidney (sometimes the adrenal glands can be confused with the kidneys therefore the visualization of the normal cortical and medular structures is useful for exclusion).
- absence of the urinary bladder. If the urinary bladder is present the bilateral adrenal agenesis is excluded.

The differential diagnosis should include other anomalies of the kidney, associated with oligohydramnios as polycystic kidney disease, multicystic kidneys, etc.

When bilateral renal agenesis is suspected, a detailed examination of the fetal anatomy should be performed considering the high risk of other anomalies association [15]:

- Cardiovascular malformations (14%): tetralogy of Falloch, ventricular septal defect, atrial septal defect, hypoplastic left ventricle, coarctation of the aorta, dextrocardia, single ventricle, transposition of the great vessels, total anomalous pulmonary venous drainage, tricuspid atresia, and hypoplastic aorta.
- Musculoskeletal malformations (40%): absent radius and fibula, digital anomalies, lumbar hemivertebrae, cleft palate, sacral agenesis, and diaphragmatic hernia.
- Central nervous system malformations (11%) include hydrocephaly, microcephaly, meningocele, cephaloceles, holoprosencephaly, and iniencephaly.
- Gastrointestinal malformations (19%): duodenal atresia, imperforate anus, esotracheal fistula, intestinal malrotations, absent stomach or gallbladder, and omphalocele.
- Single umbilical artery.

The prognosis is usually lethal due to the association of pulmonary hypoplasia and growth retardation, the fetuses die in utero or in the first days of life.

2.2.4. Bladder exstrophy

Bladder exstrophy as well as cloacal exstrophy arise from the abnormal growth of the caudal fold, resulting in a anterior abdominal wall defect. The absence of the anterior abdominal wall and the anterior bladder wall will expose the posterior bladder wall to the amniotic fluid. Small defects result in epispadias, but a larger one might expose the posterior bladder wall. The incidence of bladder exstrophy is 1:30,000 births, with male fetuses being more affected [16]. These anomalies are frequently sporadic, although familial transmissions have been reported [16].

Positive and differential ultrasonographic diagnosis of bladder exstrophy should be suspected whenever the bladder cannot be visualized, even though the amniotic fluid volume is normal (the cycle of the bladder filling is 15 min)—**Figure 5**. Others ultrasound signs useful are:

- a solid hyperechoic mass that comes in close contact with the umbilical arteries.
- the absence of the bladder within the fetal pelvis.
- normal volume of the amniotic fluid.
- genital ambiguity (duplication and division of the penis).

Bladder exstrophy must be differentiated from gastroschisis and omphalocele. In those conditions, despite the abdominal wall defects, the bladder is still present within the fetal pelvis [17]. The risk of association with chromosomal and nonchromosomal syndromes is low. Perinatal counseling depends on the association with other anomalies. If the prenatal diagnosis of bladder exstrophy is made, therapeutic abortion must be offered as an option.

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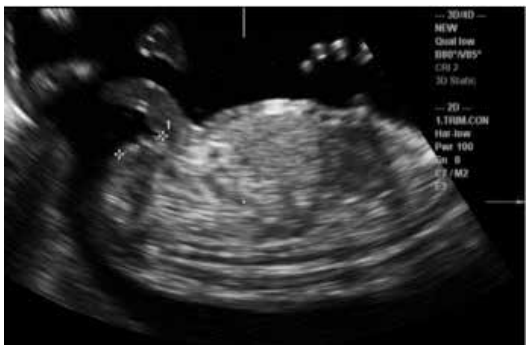

Figure 5. Bladder exstrophy—no urinary bladder can be seen.

The prognosis depends on the grade of urinary incontinence and the associated genital anomalies [17] with a survival rate of 80% in the cases where surgery interventions are needed to reconstruct the bladder wall and the genitalia. Although, it has been suggested that in the case of genital ambiguity, the sex should be deemed female, later follow-up has shown that the patients, male or female, can lead a normal life with a normal IQ and in some cases, corrective and fertility surgery can improve the quality of life.

2.3. Abnormal structures present in the abdomen: cystic or hypoechoic masses

The presence of cystic lesions in the fetal abdomen can have many underlying conditions. The diagnosis can be made upon their appearance: unique or multiple, the situs of the abnormal structure, and its relations with the abdominal viscera, the aspect of the wall and content. In most cases, the correct prenatal diagnosis of these structures is difficult to make and their origin can be determined only after birth.

Single cystic masses can be:

- megacystis,
- ovarian cysts,
- intestinal cysts (mesenteric or duplication intestinal cysts),
- choledocal cysts,
- hepatic cysts,
- kidney solitary cyst.

Multiple cystic lesions can be more frequent:

- double bubble image in duodenal atresia,
- bowel dilatations in obstruction conditions,
- multiple intestinal cysts,

- bowel volvulus,
- polycystic kidney,
- hydronephrosis,
- dilated megaureter in uretero-pelvic junction obstruction,

Other complex aspects involving hypo and hyperechoic structures can be found in:

- ascites,
- meconium peritonitis,
- liver calcification.

The differential diagnosis of the cystic abdominal proliferations includes:

- mesenteric cysts,
- omental cysts,
- choledochal cysts,
- renal cysts,
- intestinal obstruction,
- intestinal duplication,
- meconium peritonitis-related cysts,
- anterior meningomyelocele,
- ovarian cysts,
- hydrometrocolpos,
- megacystis,
- the persistence of the cloaca.

2.3.1. Duodenal atresia

It is defined as the obstruction of the bowel produced by a degenerated middle segment of the duodenum. It can be also extrinsic due to a malformed annular pancreas or fibrous peritoneal bands that cause compression. The most frequent affected segments are the 2nd and the 3rd segment of the duodenum. With an incidence is 1:10,000 births, it is the second main cause of small bowel obstruction [18].

The diagnosis is suspected in the presence of polyhydramnios and it is based on the "double bubble" sign (**Figure 6**) formed by the stomach and the proximal part of the duodenum, both appearing dilated. This sign may be present from 19 weeks, but usually it is seen in the second part of the pregnancy or even later due to the fetal capacity of swallowing small amounts

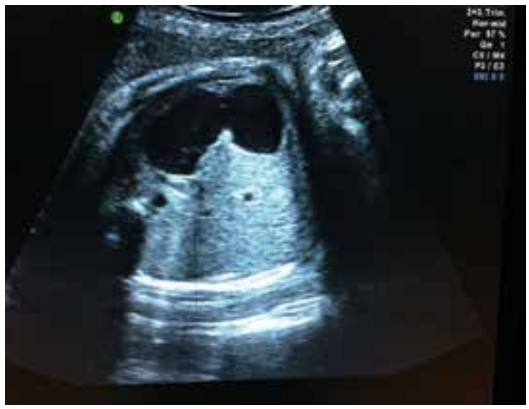

Figure 6. Duodenal atresia—double bubble sign.

of liquid and delaying the dilatation of the intestine. Sometimes, the only consistent sign at repeated scans is a dilated stomach. Differential ultrasonographic diagnosis should be made with other cystic structures present in the upper or inferior abdomen:

- persistent right umbilical vein or varicose veins pertaining to the umbilical vein.
- choledocal cyst.
- hepatic cyst.
- intestinal duplication cyst.
- ovarian cysts.
- kidney cyst or multicystic dysplastic kidney.
- mesenteric cysts.
- urachal cyst.
- ureterocele.
- pyelectasis.

Duodenal atresia has a high risk (62%) of association with chromosomal anomalies and associated anomalies mainly with Down syndrome. Duodenal atresia is a sporadic anomaly, but it has been demonstrated that it can be transmitted in an autosomal recessive manner. Almost half of the fetuses with duodenal atresia manifest other anomalies: skeletal defects (vertebral and rib abnormalities, sacral agenesis, esotracheal fistula, intestinal malrotation, Meckel's diverticulum, and anorectal atresia), renal and cardiac defects. Because of the close vicinity with the Vater Ampulla, in 1% of cases biliary duct anomalies are present. Gall bladder atresia is impossible to diagnose before birth, but it can be suspected, if duodenal atresia is present and the gall bladder cannot be visualized [18].

The prognosis of isolated duodenal atresia is favorable, the rate of survival after corrective surgery is over 95%. The incidence of early postoperative mortality is between 3 and 5%, and the long term postoperative mortality rate is 6%. Considering the high risk of chromosomal anomalies association, the karyotype analysis is mandatory whenever duodenal atresia diagnosis is made prenatally, and also a careful examination of the fetus anatomy. Polyhydramnios can cause preterm birth and although vaginal delivery is allowed, it must take place in a tertiary unit to assure proper care for the neonate.

2.3.2. Intestinal obstruction

Intestinal obstruction is defined by the total or partial intestinal obstruction, which can occur in an intrinsic or extrinsic manner. The intrinsic lesions are caused by intestine stenosis or atresia. In the case of atresia, the two intestinal segments can be completely separated or tied by a fibrous band. In the case of intestinal stenosis, the two segments can be separated by a septum or a central diaphragm or the intestinal lumen is very narrow. "Apple-peel" atresia is characterized by the absence of an important intestinal segment that can include the distal duodenum, the entire jejunum, or the proximal ileum—**Figure 7**. Conditions that can produce extrinsic obstruction are most frequently represented by:

- intestinal malrotations with volvulus,
- peritoneal adherences,
- meconium ileus.
- Hirschsprung's disease.

The intestinal areas affected in the order of frequency are: the distal ileum (35%), the proximal jejunum (30%), distal jejunum (20%), proximal ileum (15%), or it can be multicentric in approximately 5% of cases. Anorectal atresia results from an abnormal cloacal division in the 9 weeks of gestation [5]. The incidence of intestinal obstruction is 1:2000 births. In half of the cases, obstruction of the small intestine is present, and the other half is made up by anorectal atresia.

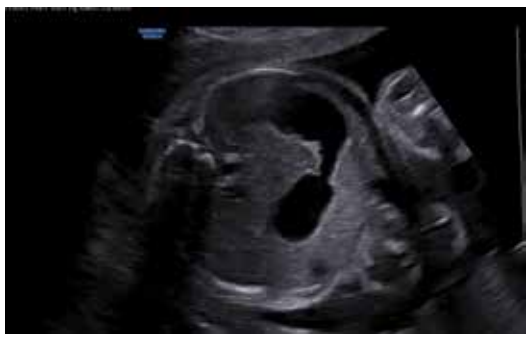

Figure 7. Duodenal stenosis—in utero image.

Intestinal obstruction is usually sporadic, but it can have a genetic transmission when the affected areas are multiple. Anorectal atresia is associated in 80% of cases with vertebral defects, genitourinary, cardiac and other gastrointestinal abnormalities. The association with chromosomal or other anomalies is rare.

Ultrasound diagnosis is usually possible beyond 25 weeks of gestation, due to the slowly dilation progression. The size of the intestinal lumen does not exceed 2–7 mm. The jejunum and ileum obstructions aspect is of dilations of the intestinal loops with active peristalsis. The fetal abdomen is fully distended and the majority of cases also present polyhydramnios, especially in the case of proximal obstructions. Similar images of the fetal abdomen can be found in Hirschsprung's disease. Transitory ascites or meconium peritonitis can appear when intestinal perforations occur [5]. When intestinal obstruction is diagnosed, the work-up to exclude other intestinal tract anomalies, ovarian cysts, mesenteric cysts, or intestinal duplication cysts is mandatory. Anorectal atresia is difficult to diagnose prenatally due to the great distension of the proximal bowel and the normal amount of amniotic fluid. Occasionally, calcification of the fetal meconium may be present within the fetal pelvis.

The prognosis depends on the type and location of the obstructed site and on the association of other anomalies. Considering that polyhydramnios that can occur, preterm births are common and the birth should take place in a tertiary unit. After birth, the affected babies develop emesis and abdominal distention, and can require immediate surgery repair. For isolated obstructions, requiring small resections of the intestine, the survival rates are over 95%. The resection of a large intestinal segment can lead to a lethal syndrome—short gut syndrome.

2.3.3. Hirschsprung's disease

It is caused by the congenital absence of intramural parasympathetic ganglia of the colon. The deficiency is caused by the lack in neuroblast migration from the neural crest, which occurs between the 6th and the 12th week of development. Also, the degeneration of the already migrated neuroblasts, which can occur before or after birth, may be involved. The incidence is approximately 1:3000 births. This disease is usually sporadic, but in 5% of cases there is a familial transmission. In a small number of cases, Hirschsprung's disease is associated with Down syndrome.

Ultrasound diagnosis can be suspected in the presence of the dilatation of the intestinal lumen produced by abnormal peristaltic movements. At the ultrasound scan, images are similar to those found in anorectal atresia, in which the colon is also affected. Similarly, when the small intestine loops are affected, the images are of an obstruction with dilated intestinal loops and polyhydramnios. The prognosis depends on the postnatal postoperative evolution, which aims to resect the affected intestinal segment, and can include a temporary colostoma with a neonatal mortality rate of 20%. Considering the prematurity risk due to associated polyhydramnios and the need for postnatal surgery, the birth must take place in a tertiary unit, but cesarean birth is not mandatory.

2.3.4. Choledochal cysts

They are defined as cystic dilatations of the common bile duct; they are rare and are usually of unknown etiology. The diagnosis is made in the presence of a transonic image located in

the upper right abdominal quadrant. The differential diagnosis includes intestinal duplication cysts, hepatic cysts, situs inversus, and duodenal atresia. The absence of polyhydramnios and the presence of intestinal peristalsis are useful for excluding intestinal obstruction. Common complications that intervene after birth are: biliary cirrhosis, hypertension, lithiasis, and rarely—adenocarcinoma. The complications can be prevented by early postnatal diagnosis and surgical resection. Surgical mortality rate is about 10% [19].

2.3.5. Mesenteric and omentum cysts

They are usually an accumulation of lymphatic fluid produced by lymphatic hamartomas or blockage of the lymphatic drainage. Ultrasound diagnosis can be suspected in the presence of a hypoechoic lesion located usually on the midline. The cysts can vary in size, their content can be unilocular or multilocular, or filled with echoic masses with solid content caused by secondary hemorrhage. The cysts can be filled with serous, hemorrhagic, or chylous fluid.

The prognosis of the cyst depends on the possible complications: intestinal obstruction, torsion, and hemorrhage. Malignant transformation of the cysts is rare. Prenatally, the cysts require drainage by puncture, only when they are of important size and can cause compression and secondary hydrops. After birth, the management is surgical but a complete resection of the cysts is difficult because of the close vicinity with large vessels and because of the 20% rate of recurrence.

2.3.6. Hepatic cysts

Hepatic cysts are a rare finding in the prenatal life. Usually, they are located in the right hepatic lobe and can produce obstruction of the intrahepatic biliary system. Their ultrasound aspect is of a unilocular anechoic round structure. Even after birth, they are asymptomatic and complications like infections and hemorrhage rarely occur. In approximately 30% of cases, hepatic cysts are associated with polycystic renal disease [19].

2.3.7. Duplication intestinal cysts

Duplication intestinal cysts are rare but located throughout the entire gastrointestinal tract. They appear in the form of tubular-like structures of variable sizes, and can occur singularly or associated with renal malformations, adenomatous cystic lung malformations, and lung sequestration. The thickening of the cystic wall and the peristaltic movements make the diagnostic process easier. The surgical excision of the cysts is the only therapeutic choice.

2.3.8. Ovarian cysts

Ovarian cysts are the most frequent fetal tumors and they are a relatively frequent finding during fetal autopsy (approximately 1/3 of fetuses). The cysts are usually asymptomatic and small. Ovarian fetal cysts are hormone-dependent (influenced by the human chorionic gonadotropin hormone, estrogens, and placenta hormones) and appear after 25 weeks of gestation [20].

Ovarian cysts (**Figure 8**) appear as anechoic round images located laterally to the urinary bladder. They are unilateral and unilocular and appear most frequently in isoimmunization-affected fetuses or those coming from pregnancies associated with diabetes, probably due to placental hyperplasia.

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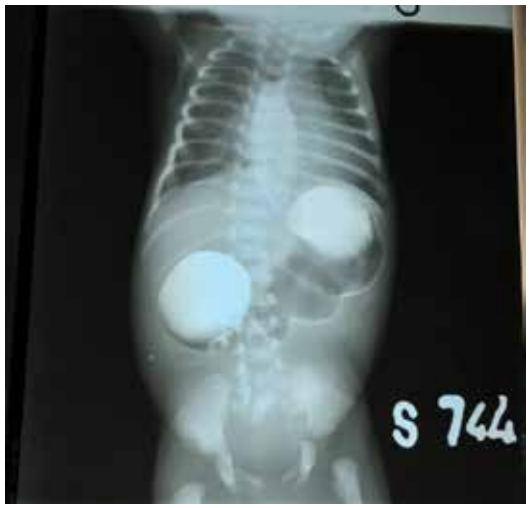

Figure 8. Duodenal stenosis—same case after birth.

The clear majority of the ovarian cysts is benign and resolves spontaneously after birth. The differential diagnosis has to be made with hydrocolpos, a condition that manifests itself as a hypoechoic or hyperechoic pelvic mass in a female fetus [20]. The prognosis is usually good but complications may appear like: torsion of the cysts, ascites, intracystic hemorrhage, rupture of the cysts, or cyst infarction. In such cases, the inner aspect of the cyst can change and speckles or hyperechoic structures inside the cyst can appear. When the cysts are large, intestinal compression could induce polyhydramnios. In such cases, cyst puncture and amniodrainage should be considered. There is no need for cesarean section, but when the risk of premature birth is high due to polyhydramnios, birth should take place in a tertiary unit.

2.3.9. Congenital hydronephrosis

It is defined by a dilatation of the renal pelvis and calyceal system that exceeds the normal size according to the age of gestation (anteroposterior diameter of the renal pelvis over 4 mm at 20 weeks and over 7 mm at 32 weeks)—**Figures 9** and **10**. The most frequent cause is the ureteropelvic junction obstruction. When dilatation of the ureter occurs, the obstruction is lower usually at the vesicoureteral junction [21]. It is more common in males than in females, with a sex ratio of 5:1. Ureteropelvic junction obstruction is usually sporadic, but can also be inherited.

Anatomic causes that produce ureteropelvic junction obstruction are: fibrous adhesions, bands, kinks, ureteral valves, aberrant lower pole vessels, abnormal ureteral insertion, and unusual shapes of the pyeloureteral outlet. They can be associated with urinary anomalies and extraurinary anomalies: vesicoureteral reflux, bilateral ureteral duplication, bilateral obstructed megaureter, contralateral nonfunctioning kidney, contralateral renal agenesis, Hirschsprung's disease, cardiovascular abnormalities, neural tube defects, sagittal synostosis, mandibular hypoplasia, esophageal atresia and distal fistula, imperforate anus, syndactyly, congenital hip dislocation, and adrenogenital syndrome.

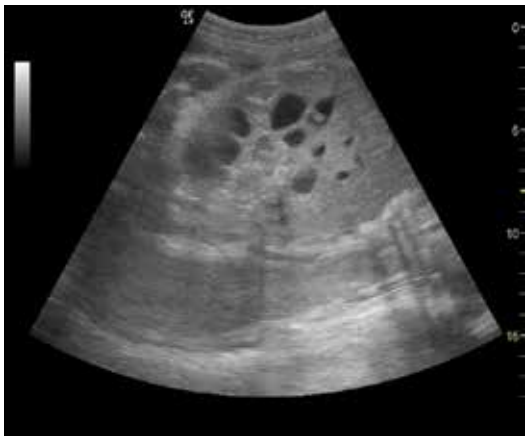

Figure 9. Intestinal obstruction—small bowel dilatations above the obstruction level.

Ultrasound diagnosis is based on the evidence of the dilated renal pelvis and on the measurement of the anteroposterior diameter of the dilatation on transverse abdominal section. Former criteria of hydronephrosis dilatation included also the ratio between the maximum transverse pelvic diameter and the renal diameter at the same level with ratios above 50% being the cut-off for hydronephrosis. Most UPJ obstructions are unilateral and bladder should fill normally. In case of severe oligohydramnios, association of unilateral hydronephrosis contralateral renal agenesis or dysplasia should be suspected. Differential diagnosis includes multicystic dysplastic kidneys, polycystic kidneys, and other condition associated with anechoic abdominal masses [22].

The prognosis of ureteropelvic obstruction is generally good, but requires serial ultrasound scans to evaluate the progress of the dilatation. In most cases, the surgery is not needed, but the postsurgery mortality is absent [23].

Concerning the prenatal management, there is no need for premature intervention and vaginal birth is preferred (**Figures 11** and **12**).

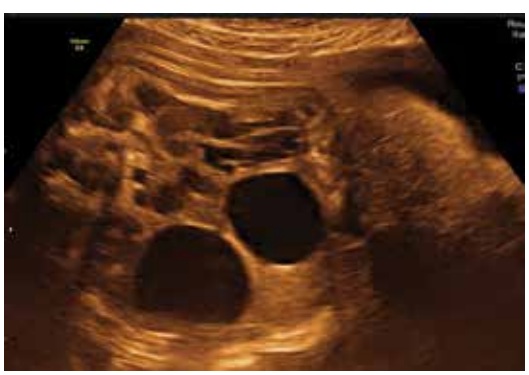

Figure 10. Ovarian cyst—two anechoic round structures in the fetal pelvis with no Doppler signal.

2.3.10. Multicystic kidney disease

It is a congenital disorder characterized by cystic lesions that correspond primarily to dilated collecting tubules. The disease can be bilateral, unilateral, or segmental and it is known also as Potter's type II syndrome, cystic kidney disease, and multicystic dysplastic kidneys.

It can be isolated or associated with urinary or extraurinary disorders such as: malrotations, ureteropelvic junction obstruction, horseshoe kidney, cardiovascular malformations, CNS abnormalities (anencephaly, hydrocephalus, iniencephaly, spina bifida, occipital meningocele), diaphragmatic hernia, cleft palate, microphthalmia, duodenal stenosis and imperforate anus, esotracheal fistula, and bilateral absence of radius and thumb. Association with liver cysts or pancreatic cysts is not characteristic for Potter II syndrome [24].

Ultrasound diagnosis of multicystic kidneys (**Figure 11**) is made in the presence of an enlarged unilateral or bilateral kidney with multiple round anechoic structures peripheral located and variable in size. In some cases, the kidneys can be small but the renal sinus cannot be identified. Oligohydramnios is a common association, but in some cases, when the lesion is unilateral or the obstruction is incomplete, amniotic fluid may have normal volume.

Differential diagnosis includes infantile polycystic kidney disease, single cyst, ureteropelvic junction obstruction, Wilms tumor and hamartoma that has undergone necrosis, but can be difficult to diagnose prenatally.

The prognosis of bilateral disease is poor and termination of pregnancy can be offered. Unilateral isolated disease prognosis can be favorable, but delivery should take place in a tertiary unit (**Figures 13** and **14**).

2.3.11. Autosomal dominant polycystic kidney disease (ADPKD)

Adult polycystic kidney disease (APKD) is an autosomal dominant condition characterized by the presence of multiple cysts of variable size in the renal parenchyma. The cysts can replace the parenchyma and are produced by the dilatation of the collecting tubules and other tubular segments

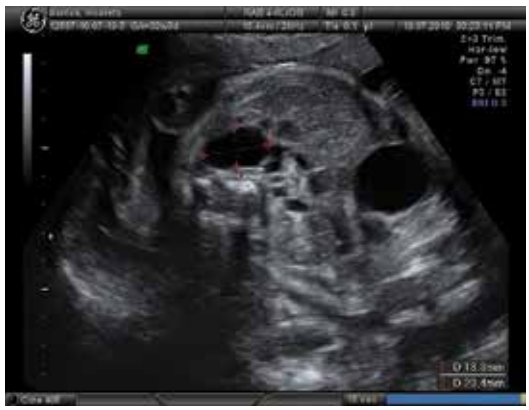

Figure 11. Hydronephrosis—significant dilatation of the renal pelvis and reduced thickens of the renal functional tissue.

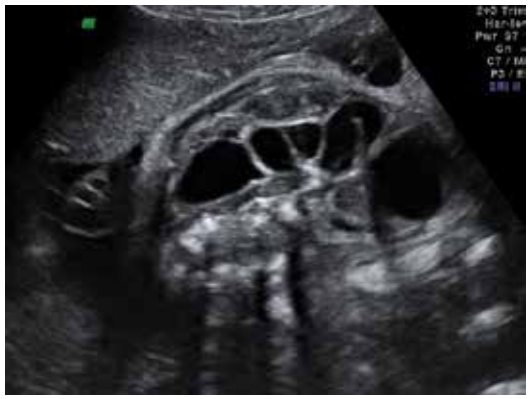

Figure 12. Ureteral dilatation consecutive to uretro-vesical obstruction.

of the nephrons. Potter's type III polycystic is one of the entities responsible for ADPKD in which cysts of variable sizes (some up to several centimeters) coexists with normal renal structure. Being an autosomal dominant disease, the risk of transmission to the off springs of the altered gene on chromosome 16 is 1/2 pregnancies. APKD is one of the most common genetic disorders and the third most prevalent cause of chronic renal failure [25]. Epigenetic factors and penetrance of the gene determine the variability in symptoms, the disease manifesting late in the fourth decade. Intrauterine manifestation of the disease is not uncommon [26]. APKD is associated with cysts affecting other organs: liver, pancreas, spleen, lungs, testes, ovaries, and epididymis.

Prenatal diagnosis is difficult and often late due to the nonspecific appearance of the kidneys; only a few of these diagnoses can be recognized in the prenatal period, by family history, amniotic fluid volume, associated abnormalities, and genetic testing [4].

Ultrasound diagnosis of the APKD can be suspected in the presence of moderately enlarged hyperechogenic kidneys, with increased corticomedullary differentiation (CMD), in association with a normal amount of amniotic fluid. The diagnosis is usually late and should prompt investigation of both parents.

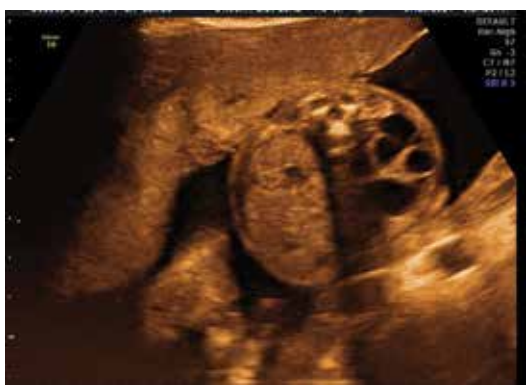

Figure 13. Multicystic kidney—multiple anechoic round structures occupying the whole renal aria with no remaining normal renal structure.

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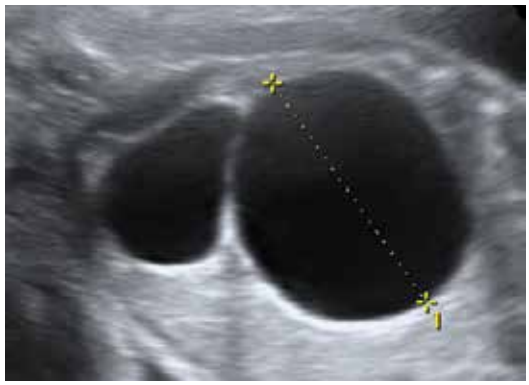

Figure 14. Giant kidney cyst.

The prognosis depends on other associated anomalies. The parents must be informed that the immediate outcome can be good, but the natural history of the disease includes the following: from completely asymptomatic to lower abdominal pain, renal enlargement, renal insufficiency, uremia and hypertension, with a mean age of onset of symptoms in the fourth decade of life.

Obstetrical management is based on the gestational age at diagnosis; in the first trimester, pregnancy termination can be offered. Family members should undergo ultrasound examination as well. The fetus must be thoroughly scanned to exclude other anomalies. Otherwise, the obstetrical attitude is not altered and vaginal birth is the first choice (**Figure 15**).

2.3.12. Infantile polycystic kidney disease

Infantile polycystic kidney disease (IPKD) is an autosomal recessive disorder characterized by bilateral and symmetrical enlargement of the kidneys. The disease is known also as polycystic kidney disease type I, infantile polycystic disease of the liver and kidney. Unlike the adult polycystic kidney disease, there is no renal parenchyma, only dilated collecting tubules [27]. As a recessive autosomal inherited condition, the risk of transmission is 25%. The disease is always bilateral. Other anomalies that can be associated: liver cysts, biliary duct hyperplasia, and dilatation of the biliary tree and portal hypertension.

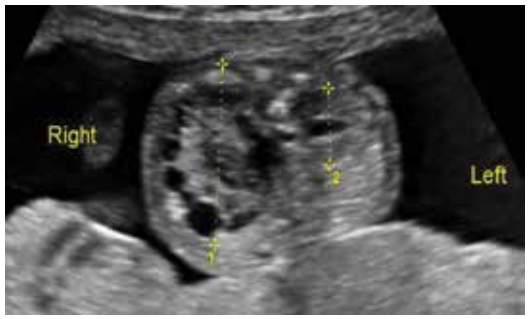

Figure 15. Autosomal polycystic kidney disease.

Ultrasound diagnosis is based on three elements:

- bilaterally enlarged kidneys of typical hyperechogenic texture.
- oligohydramnios.
- absent fetal bladder.

The disease can be diagnosed late in pregnancy or may progress gradually during pregnancy; therefore, repeated scans are mandatory.

The prognosis depends on the clinical variety of IPKD, which can vary from mild to severe with intrauterine death. After birth, the most important complications are respiratory, as a consequence of the pulmonary hypoplasia. Death later in life is the result of renal failure.

The management depends on the diagnosis age; if the diagnosis is made before viability, termination of pregnancy should be offered to the parents. Also in cases with severe oligohydramnios and absent bladder, the termination of pregnancy can be offered even in the third trimester.

2.3.13. Megacystis

It represents an enlarged urinary bladder usually due to a bladder outlet obstruction [lower urinary tract obstruction (LUTO)], which may appear also in nonobstructive conditions (megacystis-microcolon-intestinal hypoperistalsis syndrome). It can be detected from the first trimester scan in about 1 in 1500 pregnancies [28].

Prognosis, management, prediction of resolution, and postnatal outcome depend on the subsequent cause. Fetal lower urinary tract obstruction (LUTO) has an incidence of 2.2/10000 births and it is usually diagnosed during the late first or early second trimester of pregnancy [28, 29]. The most common condition in the LUTO spectrum includes urethral valves, urethral atresia, and urethral stenosis.

2.3.14. Posterior urethral valves

It is a condition that causes lower urinary tract obstruction due to a membrane-like structure in the posterior urethra of male fetuses. The disease is usually sporadic, and has a heterogeneous embryologic origin. Young type I syndrome valves seem to result from an exaggerated development of the urethrovaginal folds with an abnormal insertion of the distal end of the Wolffian ducts. Other valves, like in Young type III, develop because of abnormal canalization of the urogenital membrane [30]. Distention of the bladder (megacystis) leads to vesicoureteral reflux and hydronephrosis and can cause renal dysplasia [30].

Posterior urethral valves can be associated with other anomalies of the urinary tract (sequence) megacystis, megaureter, hydronephrosis, paraureteral diverticula, and dilatation of proximal urethra, cryptorchidism, and hypospadias. There are also extraurinary anomalies that can be associated: tracheal hypoplasia, patent ductus arteriosus, total anomalous pulmonary vein drainage, mitral stenosis, scoliosis, skeletal anomalies in lower extremities, and imperforate anus. The most frequent chromosomal abnormalities that can be associated are: trisomies 18 and 13, del 2q, and 69 XXY.

Ultrasound diagnosis can be made in the presence of megacystis, hydroureter, and hydronephrosis in a male infant. In female fetus, lower urinary tract obstruction includes agenesis of the urethra, megacystis-microcolon-intestinal hypoperistalsis syndrome, and variants of the caudal regression syndrome. When the rupture of the megacystis intervenes, urine can extravasate into the peritoneal cavity. Oligohydramnios can also occur.

The differential diagnosis is difficult in prenatal life, and includes ureteropelvic junction obstruction, ureterovesical junction obstruction, primary megaureter, and massive vesicoureteral reflux, absence of the urethra or detrusor hypertrophy.

Prognosis depends on the renal reserve, which can be difficult to assess prenatally. Another factor that can influence the outcome is the timing of the occurrence of urinary obstruction, and this is a critical factor: the earlier its appearance–the worse the prognosis. Complications include: pneumomediastinum and pneumothorax, related to pulmonary hypoplasia, associated congenital anomalies, renal failure, and surgical complications after decompressive surgery. Termination of pregnancy can be offered if the prognosis is poor and if other anomalies are associated. In utero vesicoamniotic shunts are possible, but the results at 2 years of life are not very encouraging [31].

2.3.15. Meconium peritonitis

Intestinal perforation in fetuses during pregnancy can lead to a sterile, chemical, and localized type of peritonitis. At the site of the perforation, a reactive process of calcification and fibrosis occurs in order to stop the progression. The etiology is in over 50% of cases due to intestinal stenosis, atresia, or meconium ileus. Other cited situations are volvulus or Meckel's diverticulitis. Meconium ileus is associated with cystic fibrosis and results from the blockage of the distal ileum with compacted meconium. The incidence is 1:3000 births.

The diagnosis is suggested by the dilatation of the intestinal loops or the presence of hyperechoic areas situated in the abdomen of the fetus. Over 80% of the fetuses that developed meconium peritonitis also have intra-abdominal calcifications. Ascites is an important sign of intestinal peritonitis. Other ultrasonographic signs suggesting meconium peritonitis include: polyhydramnios, meconial pseudocysts, thickening of the abdominal wall or pleural effusions.

The differential diagnosis of hyperechoic abdominal masses include: intra-amniotic hemorrhage, early ascites, fetal hypoxia, meconium peritonitis, and cystic fibrosis.

Meconium ileus and hyperechoic images of the intestinal loops at 16–18 weeks of gestation can be present in over 75% of cystic fibrosis affected fetuses. The incidence of cystic fibrosis in fetuses diagnosed before birth with intestinal obstruction is approximately 10%, consequently when other causes of intestinal blockage have been excluded, a genetic cystic fibrosis test is recommended.

The prognosis is poor in this case; approximately, 50% of fetuses suffering from meconium peritonitis pass away in the neonatal period.

2.3.16. Liver calcifications

Most of them are idiopathic, but can be associated with congenital infections and chromosomal anomalies. The incidence rate is 1:2000 fetuses, especially in the 3rd trimester. The

ultrasonographic image is of hyperechoic nodules situated in the liver parenchyma or liver capsule. The diagnosis is easy in the presence of solitary or multiple hyperechoic images (size between 1 and 2 mm) situated in the liver parenchyma or capsule. The prognosis depends on the association with infections or chromosomal anomalies. Isolated calcifications do not have pathological significance.

2.4. Abdominal wall anomalies

The evaluation is the integrity of the abdominal wall is part of routine midtrimester scan, although it can be performed starting with the first trimester examination. Conditions as: oligoamnios, placenta, or uterine wall proximity, excessive movement of the fetus can obstruct the proper visualization of the abdominal anterior wall. It is very important that the integrity of the abdominal wall is assessed by showing the insertion of the umbilical cord and visualization of the bladder in the pelvis, so that that bladder and cloacal exstrophy can be excluded.

The abdominal wall anomalies will be discussed separately in a subsequent chapter.

Author details

Ples Liana[1]* and Anca Lesnic[2]

*Address all correspondence to: plesliana@gmail.com

1 UMF Carol Davila, Bucharest, Romania

2 Bucur Maternity, Bucharest, Romania

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Chapter 13

Renal Anomalies

Alexandru Cristian Comanescu, Florentina Tanase, Maria Cristina Comanescu, Razvan Cosmin Pana, Madalina Barbu and Nicolae Cernea

Additional information is available at the end of the chapter

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Abstract

This chapter is dedicated to the main renal anomalies detectable by ultrasound. Anomalies of the lower urinary tract will be addressed in a separate chapter. The anomalies presented are renal agenesis, renal development variants, autosomal recessive polycystic kidney disease, multicystic dysplastic kidney disease, autosomal dominant polycystic kidney disease, obstructive cystic dysplasia, pelvis dilatation, renal tumors, and nonchromosomal syndromes associated with renal anomalies. All chapters are structured similar into definition, incidence, pathology, ultrasound findings, differential diagnosis, and clinical facts.

Keywords: kidney, anomaly, ultrasound

1. Introduction

The present chapter addresses the main renal anomalies. It will be structured on nine subjects made to help the reader orientate easily when facing an anomaly in everyday practice. Information regarding the moment an anomaly is visible has taken into account midrange ultrasound machines that are responsible for most of the anomaly screening.

Kidneys are visible at 12–14 weeks of gestational age, easier with transvaginal examination, and the renal architecture is seen first at 16–18 weeks. Current protocols advise documenting the presence of the normal kidneys at the second and third trimester ultrasound. A special attention must be given not to confuse them with "lying-down" adrenal structures. We recommend using both transversal and longitudinal views; coronal views are helpful in the diagnosis of the horseshoe kidneys. Color Doppler ultrasound can be used to identify the renal

Weeks of gestation	Fetal renal mean longitudinal length (cm) (±SD)
16	1.7 (0.3)
17	1.8 (0.1)
18	2.0 (0.0)
19	2.3 (0.3)
20	2.1 (0.1)
21	2.1 (0.1)
22	2.4 (0.3)
23	2.5 (0.3)
24	2.8 (0.1)
25	2.9 (0.2)
26	2.8 (0.1)
27	3.0 (0.1)
28	3.3 (0.3)
29	3.5 (0.2)
30	3.4 (0.3)
31	3.6 (0.1)
32	3.7 (0.2)
33	3.7 (0.2)
34	3.8 (0.2)
35	3.9 (0.3)
36	4.1 (0.3)
37	4.3 (0.3)
38	4.2 (0.3)
39	4.2 (0.2)
40	4.3 (0.2)
41	4.1 (0.2)

Table 1. Mean renal length by gestational age.

arteries. Normal measurements for renal length are shown in **Table 1** [1]. The renal circumference to abdominal circumference is about one-third. The anterior-posterior renal pelvis is usually less than 4 mm before 22 weeks and less than 7 mm in the third trimester.

2. Renal agenesis

Definition: this chapter will address only bilateral renal agenesis, a condition defined as the absence of both kidneys which is invariably lethal.

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Incidence: 1:2000–1:5000.

Pathology: it results from failure of development of the ureteric bud. The consequence for the pregnancy is Potter sequence: oligohydramnios, Potter face, clubbed hands and feet, and pulmonary hypoplasia which leads to death in the cases that reach birth [2].

Ultrasound findings: we notice severe oligohydramnios and fail to see the kidneys and the bladder. Sometimes, lying-down adrenals may be confused with kidneys in the conditions of poor visibility associated with low amniotic fluid/absence of amniotic fluid. Color Doppler interrogation fails to demonstrate the renal arteries. A small thorax is noticed, especially if we take the time to measure the heart/chest ratio.

Differential diagnosis:

- PROM (patient history and the presence of kidneys and bladder point us the right diagnosis).
- Severe IUGR (kidneys are present, and there are abnormal Doppler values).

Clinical facts:

- Risk of chromosomal anomalies is low (though there have been described cases of trisomy 7, 10, 21, 22).
- It may be part of a nonchromosomal syndrome (COF syndrome, VACTERL).
- Oligohydramnios is an associated sign only after 16 weeks.
- You should always examine carefully not to confuse adrenal glands with kidneys; keep in mind that adrenal arteries can also mimic renal arteries, so Doppler is not always a solution.
- Bilateral agenesis is always lethal (one-third stillbirth, the rest die at birth from pulmonary hypoplasia) (**Figure 1**).

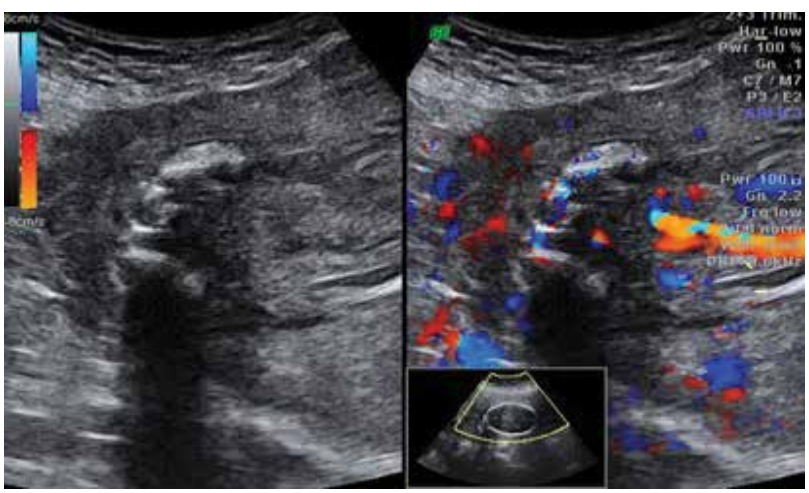

Figure 1. Renal agenesis (absence of renal arteries).

3. Renal development variants

3.1. Unilateral agenesis

Definition: one kidney does not form resulting one present kidney and one renal artery.

Incidence: 1:1000 [2].

Pathology: failure of development of only one ureteric bud with normal development on the other side.

Ultrasound findings: we notice an empty renal fossa on axial view; this view should be completed with longitudinal and coronal views. The contralateral kidney is increased in size (>95 percentile)—compensatory hypertrophy. The use of color Doppler shows only one renal artery. Some structures may mimic the second kidney—one is the adrenal gland, and the other is the colon.

Differential diagnosis: an empty renal fossa may be present in:

- Pelvic kidney.
- Unilateral renal agenesis.
- Crossed renal ectopia.
- Horseshoe kidney (graph).

Clinical facts:

- Careful scanning of the fetal abdomen (do not confuse with renal ectopia/do not confuse kidney with adrenal glands).
- Isolated unilateral kidney has good prognosis and associates rarely with chromosomal anomalies (**Figure 2**).

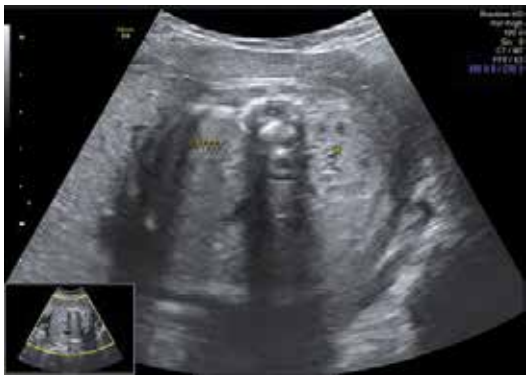

Figure 2. Unilateral renal agenesis.

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3.2. Pelvic kidney

Definition: the presence of one kidney in the pelvis; the most common location for ectopic kidney.

Incidence: 1:700–1:1200 [2–4].

Pathology: the kidney forms normally but fails to ascend to the lumbar area. This normally happens between 6 and 10 weeks of gestational age.

Ultrasound findings: the first thing we notice is an empty renal fossa; careful scanning reveals the kidney adjacent to the bladder. The normally positioned kidney shows no compensatory hypertrophy. Amniotic fluid is within a normal range. The use of color Doppler can be helpful—sometimes, you can follow the renal artery to the ectopic kidney, but sometimes a pelvic kidney can have vascularization from the iliac arteries.

Differential diagnosis: empty renal fossa (see above).

Clinical facts:

- Pelvic kidney should be the first thing to search in an empty renal fossa.
- Visualization can sometimes be difficult due to bowel loops or interposed iliac wing.
- May be associated with genital, gastrointestinal, or cardiac anomalies.
- Risk of chromosomal anomalies is low and so is the risk of nonchromosomal syndromes.
- May be a family group so parents should be scanned.
- Vesicoureteral reflux is frequently present so postnatal ultrasound monitoring is recommended (**Figure 3**).

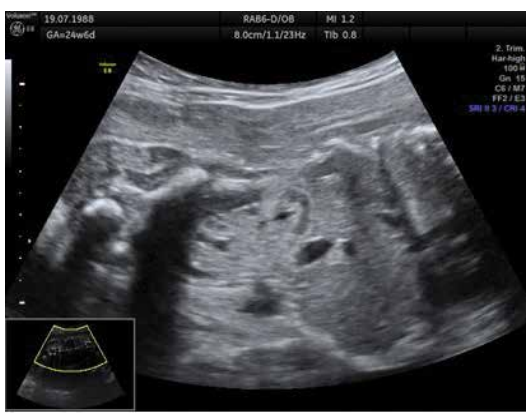

Figure 3. Pelvic kidney.

3.3. Horseshoe kidney

Definition: the kidneys are fused in their lower poles, with equal amount of renal tissue bilaterally. The fused portion may be renal parenchyma or fibrous tissue.

Incidence: 1:400.

Pathology: the fusion takes place before the ascent of the kidney which is partially impeded by the emergency of the inferior mesenteric arteries, causing also alteration of the kidneys' axis.

Ultrasound findings: on the standard axial scan, we can see renal tissue in front of the descending aorta. On coronal sections we can see the kidneys fused in the region of the inferior poles (other variants are possible but extremely rare). We also notice a medial rotation of the inferior poles and a lower position than normal kidneys.

Differential diagnosis: includes empty renal fossa (see above), but also severe oligoamnios may suggest pathology due to lack of visibility.

Clinical facts:

- It is frequently associated with hydronephrosis and genital anomalies.
- 33% of cases have CNS and cardiac or skeletal malformations [5].
- Risk of chromosomal anomalies—horseshoe kidney may be found in fetuses with Turner's syndrome or trisomy 18.
- Risk of nonchromosomal syndrome (caudal regression syndrome, otocephaly, Oro-facial digital syndrome).
- Recurrence risk—low in isolated forms.
- Careful anatomy scan to exclude other anomalies.
- Karyotyping should be offered (especially if other anomalies or soft markers are present).
- Postnatal monitoring for vesicoureteral reflux, hydronephrosis, and urinary tract infections is recommended.
- Prognosis is considered good in isolated forms (**Figure 4**).

3.4. Crossed renal ectopia

Definition: both kidneys are on the same side of the abdomen; a significant number (95%) are fused.

Incidence: 1:7000.

Ultrasound findings: at the anatomy scan, we notice one empty renal fossa and one abnormally large, frequently bilobed contralateral kidney. Statistically, it is more likely to find the kidney/kidneys on the right side. Color Doppler study shows two renal arteries on the same side (one in the normal position and one lower).

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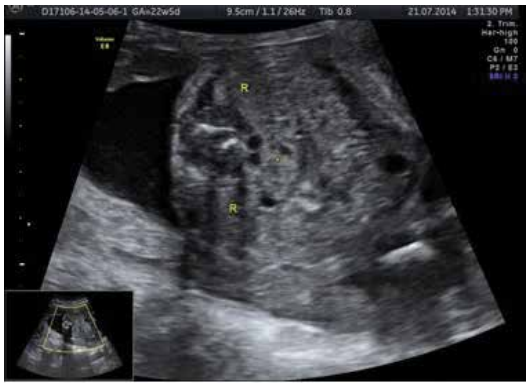

Figure 4. Horseshoe kidney.

Differential diagnosis: empty renal fossa (see above).

Clinical facts:

- May be associated with renal anomalies, spina bifida, and sacral agenesis, so attentive evaluation of the spine should be conducted.
- As all renal development variants, it may be associated with infections, obstructions, and vesicoureteral reflux so postnatal monitoring is recommended.
- Postnatal evaluation of genital organs—uterine anomalies may be associated.

4. Autosomal recessive polycystic kidney disease (Potter type I)

Definition: autosomal recessive polycystic kidney disease (ARPKD) is a bilateral renal anomaly caused by a gene disorder.

Incidence: 1:20,000–1:45,000.

Pathology: the PKHD1 gene on chromosome p21 [6] is generally accepted as a primary cause though the specific mechanism is not completely understood. Mutations are specific for individual families. The anomaly is characterized by convoluted tubes and collecting ducts often associated with liver fibrosis [4].

Ultrasound findings: ARPKD is characterized by kidney enlargement (>2SD above the mean for that gestational age) [4], increased echogenicity (resulting from the interference of the microcysts) [3], absent bladder, and oligoamnios (present from 16 weeks).

Differential diagnosis:

- Autosomal dominant polycystic kidney disease (ADPKD)—normal quantity of amniotic fluid and a normal bladder.
- Trisomy 13 (holoprosencephaly, polydactyly, facial anomalies).

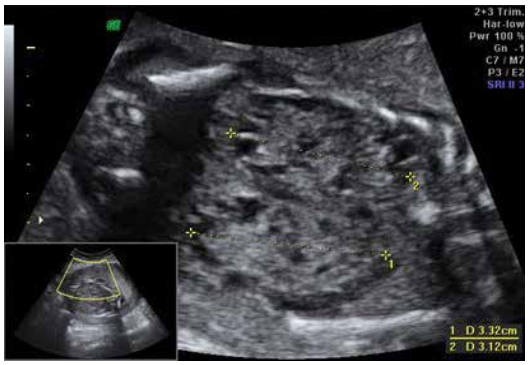

Figure 5. Autosomal recessive polycystic kidney disease.

Clinical facts:

- Not associated with chromosomal anomalies.
- Enlarged, hyperechogenic kidneys may be present in many syndromes (Meckel-Gruber, Bardet-Biedl, Beckwith-Wiedmann, Perlman, Elejade).
- Most cases are diagnosed by 24 weeks, but you must keep in mind that kidneys may look normal until 20 weeks.
- ARPKD is classified in perinatal, neonatal, infantile, and juvenile form.
- Cases diagnosed in utero end with stillbirth or neonatal death.
- Thirty to fifty percent die in the neonatal period.
- Juvenile form has less renal involvement but marked hepatic fibrosis.
- Survivors develop systemic hypertension (75%) and portal hypertension (44%).
- Recurrence risk is 25%.
- When diagnosed prenatally, termination should be offered (**Figure 5**).

5. Multicystic dysplastic kidney disease (Potter type II)

Definition: Multicystic dysplastic kidney (MCDK) presents with unilateral/bilateral enlarged kidneys with parenchyma replaced by multiple, noncommunicating cysts [3].

Incidence: 1:1000–1:5000; more common in males (2:1), but females have a worse prognosis (twice more likely to have bilateral forms and four times more likely to have aneuploidy).

Pathology: in normal kidney embryology, the ureteric bud signals the metanephros to form nephrons. Early ureter obstruction or atresia prevents the signaling so the metanephric tissue does not form nephrons, resulting in dysplastic cystic tissue. Segmental/partial MCDK may result from a duplex ureter [2].

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Ultrasound findings:

Unilateral (75–80%): the diagnostic is made in the presence of multiple cyst structure in the renal fossa, significantly larger than normal kidneys. The bladder is normal. Amniotic fluid is within the normal range [3].

Bilateral (20%): both kidneys are multicystic; the bladder cannot be visualized, and severe oligoamnios is associated.

Partial (rare): in rare cases of duplex kidney, only part of the kidney may be involved, more frequently the superior pole.

Differential diagnosis:

- Hydronephrosis (distended calyces appear as cysts, but at attentive scrutiny communication with the renal pelvis can be proved).
- Obstructive cystic dysplasia (more normal renal tissue visible).
- Ureteral dilatation.

Clinical facts:

- Risk of chromosomal anomalies is relatively low in unilateral forms (2–4%).
- The risk for nonchromosomal syndromes is about 5–10% (branchio-oto-renal syndrome, cerebro-reno-digital syndrome, VACTERL).
- Careful examination of the contralateral kidney (40% have an associated anomaly).
- Genetic counseling and karyotyping are advised if associated anomalies are present.
- Antenatal kidney monitoring is recommended.
- Conservative management is standard as most cases involute in the first years of life.
- Postnatal ultrasound evaluation is recommended every 6 months (**Figure 6**).

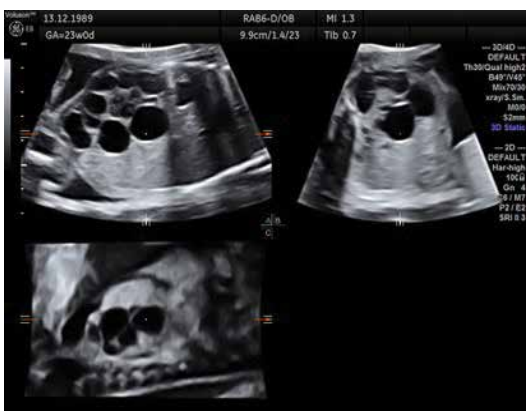

Figure 6. Multicystic kidney (unilateral).

6. Autosomal dominant polycystic kidney disease (Potter type III)

Definition: ADPKD is a bilateral renal anomaly where cysts arise from all areas of the nephron or collecting ducts. It commonly appears in adults but can rarely be seen prenatally, especially when screening is targeted to families at risk.

Incidence: 1:1000.

Pathology: the genetic mechanism involves two genes PKD1 and PKD2 on chromosome 16. The condition is associated with multiple renal cysts, hypertension, and renal failure. Cysts are also present in the liver, spleen, and pancreas.

Ultrasound findings: the kidneys are hyperechoic, in some cases only in the cortical region. Amniotic fluid and the bladder are usually normal.

Differential diagnosis: ARPKD (autosomal recessive polycystic kidney disease). Normal fluid, bladder, and family history help us make the difference.

Clinical facts:

- Once diagnosed, serial monitoring is recommended.
- Examination of parent's kidneys is indicated due to the autosomal dominant nature of the disease.
- The disease manifests in the third to fifth decade, most patients needing dialysis and transplant.
- Normal ultrasound cannot exclude the disease later in life!

7. Obstructive cystic dysplasia (Potter type IV)

Definition: obstructive cystic dysplasia results from early and severe obstruction of the collecting system causing the formation of renal cysts [5].

Pathology: most cases result from early urethral obstruction, but vesicourethral junction obstruction and upper urinary tract obstruction are also a possible cause. Obstruction leads to ascension of fluid in the upper tract, with fluid retention in the nephron, with secondary cyst formation, and with a decrease in the number of normal nephrons.

Ultrasound findings: sonographic examination reveals renal macrocysts and signs of urinary tract obstruction (hydronephrosis, hydroureter, bladder distension). In cases of urethral obstruction, thickening of the bladder wall and severe oligoamnios are met.

Differential diagnosis:

- MCDK.
- Hydronephrosis.
- ARPKD.

Clinical facts:

- Risk of chromosomal anomalies (5–10%).
- Risk of nonchromosomal syndromes may be found in VACTERL, cerebro-reno-digital syndrome, and tuberous sclerosis.
- Look for renal cysts when urinary tract obstruction is diagnosed.
- Unilateral: renal cysts + hydronephrosis/hydroureter.
- Bilateral: oligoamnios + distended bladder + bilateral renal cysts.
- Perform careful follow-up.
- Amniocentesis is indicated when associated anomalies are present.
- May be impossible to differentiate from MCDK.
- Termination should be offered for bilateral form.

8. Pelvis dilatation

Definition: the dilatation of the pelvis is the most common anomaly detected by ultrasound. It can present as a mild pelviectasis or as hydronephrosis. Though numbers may vary in different sources, generally values are around these figures:

- Mild pelviectasis [2]: above 4 mm in the second trimester and above 7 mm in the third trimester.
- Hydronephrosis [4]: above 7 mm between 16 and 20 weeks and above 10 mm after 20 weeks.

Limits of normal size for gestational age have also been described [2]:

- 3 mm in the first trimester.
- 4 mm between 14 and 22 weeks.
- 5 mm between 22 and 32 weeks.
- 7 mm after 32 weeks.
- Above 10 mm always pathology.

Incidence: 1–5:500 newborns.

Pathology: mild pelviectasis has been associated with aneuploidy (minor marker), especially trisomy 21. The mechanism for unilateral hydronephrosis may be obstruction of the ureteropelvic junction, vesicoureteral reflux, and obstruction of the vesicourethral junction. Bilateral hydronephrosis may be caused by bilateral vesicoureteral reflux or by urethral obstruction.

Ultrasound findings: renal scanning reveals a dilated renal pelvis above the cutoff for the respective gestational age. Frequently, when hydronephrosis is installed, the calyces are also

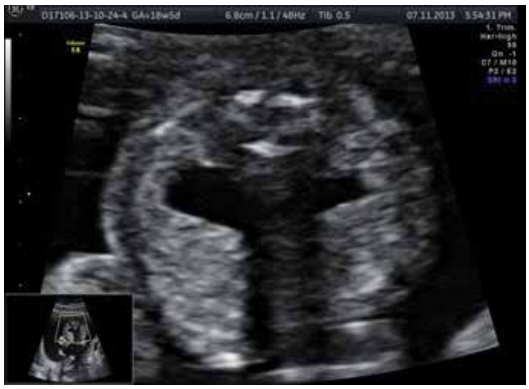

Figure 7. Bilateral hydronephrosis.

dilated. Sometimes, the dilatation is isolated (as in ureteropelvic junction stenosis) or includes dilatation of the ureters. In rare cases dilatation may lead to urinoma (only in cases of severe obstruction). Amniotic fluid is usually normal and in one-third of the cases may even be increased (impaired concentration ability).

Clinical facts:

- Risk of chromosomal anomalies is low, though mild pelviectasis has been associated with trisomy 21.
- Risk of nonchromosomal syndromes (VACTERL, Schinzel-Giedion syndrome, camptomelic dysplasia).
- In the presence of mild pelviectasis, screening for T21 markers is recommended.
- Eighty percent of mild pelviectasis resolve antenatally, and half of the rest resolve postnatally [2].
- Pelviectasis that is slowly progressing to hydronephrosis usually has an underlying pathology that would have to be addressed postnatally.
- Even with hydronephrosis the prognosis is excellent if there is no renal impairment.
- Poor prognosis may appear in cases of bilateral renal pathology or associated anomalies (syndromic or not).
- Postnatal following is recommended with scans and evaluation of the renal function.
- Prenatal intervention is rarely needed (**Figure 7**).

9. Renal tumors

Definition: renal tumors in the fetus are more commonly mesoblastic nephroma (a benign tumor) with rare occurrence of Wilms' tumor (which is malignant).

Pathology: mesoblastic nephroma is a benign mesenchymal tumor with spindle-shaped cells. It is frequently associated with polyhydramnios through mechanisms that are not yet fully understood; polyuria caused by hypercalcemia and bowel obstruction by mass effect are among the most accepted theories.

Ultrasound findings: examination usually reveals a tumor/mass that occupies part or the entire kidney. Mesoblastic nephromas have ill-defined margins and may present on color Doppler ultrasound as a vascular mass. When there are arteriovenous shunts, fetus may present hydrops.

Differential diagnosis:

- Adrenal mass (tumor or hemorrhage).
- Crossed fused ectopia.
- Renal collecting system duplication.

Clinical facts:

- Risk of chromosomal anomalies is very low.
- Risk of nonchromosomal anomalies: Wilms' tumor may be associated with Beckwith-Wiedemann or Denys-Drash syndrome [5].
- The first sign may be polyhydramnios.
- Tumor may have rapid growth.
- You should look for Beckwith-Wiedmann signs.
- May have a–v shunts and hydrops, or cardiac failure may appear.
- Surgical removal of the tumor or nephrectomy is indicated in the neonatal period (**Figure 8**).

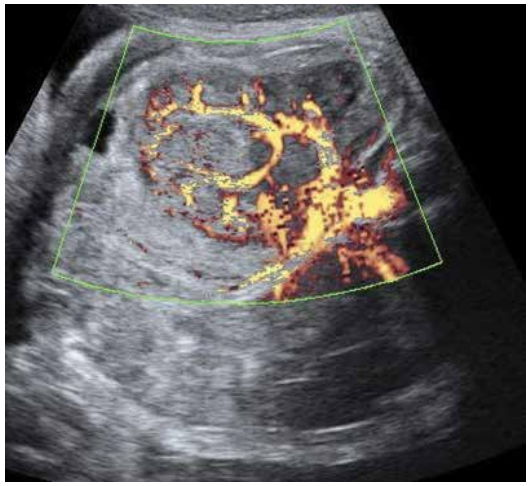

Figure 8. Nephroblastoma.

10. Nonchromosomal syndromes associated with renal anomalies

Nonchromosomal syndromes associated with abnormal kidneys on ultrasound that have been mentioned throughout this chapter have been included in **Table 2**.

Syndrome	Short description of the syndrome
COF skeletal syndrome	Renal agenesis + microcephaly, micrognathia, and joint contractures
VACTERL	Renal agenesis + vertebral anomalies, anal atresia, CHD, tracheoesophageal fistula, and limb anomalies
Meckel-Gruber syndrome	Polycystic kidney + cephalocele, microcephaly, and polydactyly
Bardet-Biedl syndrome	Polycystic kidney + polydactyly and genital anomalies
Beckwith-Wiedmann syndrome	Polycystic kidney + macroglossia, omphalocele, and hemihypertrophy
Perlman syndrome	Polycystic kidney + diaphragmatic hernia, macrosomia, cleft palate, and dextrocardia
Elejade syndrome	Polycystic kidney + omphalocele, corpus callosum agenesis, macrosomia, craniosynostosis, and skeletal dysplasia
Brachio-oto-renal syndrome	Multicystic kidney + preauricular tags and brachial cleft fistulas
Cerebro-reno-digital syndrome	Multicystic kidney + digital and limb anomalies and CNS malformations
Schinzel-Giedion syndrome	Hydronephrosis + midface retraction, skull anomalies, talipes, and cardiac anomalies
Camptomelic dysplasia	Hydronephrosis + bowed tibiae/femurs, scapular hypoplasia, micrognathia, and sex reversal in males
Denis-Drash syndrome	Nephroblastoma + ambiguous genitalia and diaphragmatic hernia (rare)

Table 2. Nonchromosomal syndromes associated with renal anomalies.

Author details

Alexandru Cristian Comanescu*, Florentina Tanase, Maria Cristina Comanescu, Razvan Cosmin Pana, Madalina Barbu and Nicolae Cernea

*Address all correspondence to: aleodor77@gmail.com

University of Medicine and Pharmacy, Craiova, Romania

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Chapter 14

Congenital Anomalies of Urinary Tract and Anomalies of Fetal Genitalia

Sidonia Maria Sandulescu, Ramona Mircea Vicol, Adela Serban, Andreea Veliscu Carp and Vaduva Cristian

Additional information is available at the end of the chapter

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Abstract

Congenital anomalies of the kidney, urinary tract and genitalia anomalies are among the most frequent types of congenital malformations. Many can be diagnosed by means of ultrasound examination during pregnancy. Some will be discovered after birth. Kidney and urinary malformations represent 20% of all birth defects, appearing in 3–7 cases at 1000 live births. Environmental factors (maternal diabetes or intrauterine exposure to angiotensin-converting enzyme inhibitors) and genetic factors (inherited types of diseases) seem to be among causes that lead to the disturbance of normal nephrogenesis and generate anomalies of the reno-urinary tract. It is very important to diagnose and differentiate between the abnormalities incompatible with life and those that are asymptomatic in the newborn. The former requires interruption of pregnancy, whereas the latter could lead to saving the renal function if diagnosed antenatally. In many cases, the congenital anomalies of the urinary and genital tract may remain asymptomatic for a long time, even up until adulthood, and can be at times the only manifestation of a complex systemic disease. Some can manifest in more than one member in the family. This is the reason why the accurate genetic characterization is needed; it can help give not only the patient but also her family the appropriate genetic counseling, and also, in some cases, the management may prevent severe complications.

Keywords: genital, urinary, kidney, anomalies, fetal, malformation

1. Introduction

The congenital anomalies of the urinary tract include a large number of diseases caused by anomalies in the morphogenesis of the urinary system. These anomalies include obstructive

and nonobstructive dilatation of the urinary tract that can be associated with alterations in the number, size and/or position of the kidneys [1, 2].

We will discuss the congenital anomalies of the urinary and genital tract, with a short review of kidney abnormalities. These malformations may coexist within the same case, and this is due to their common embryonic origin [3].

The reno-urinary anomalies occur more frequently in males than in females, the ratio being 2.5:1 (M-F), and there are many cases with family aggregation. The incidence is 3–4 at 1000 lives or 1–5% of all pregnancies [4, 5]. If including all cases detected at post-mortem fetal autopsies, the prevalence of these malformations is much higher [2].

2. Congenital anomalies of urinary tract

2.1. Relevant embryology

The urogenital system is represented by two major components: the urinary system and the genital system. Embryological and fetal kidneys, genital tract and the urinary system develop from intermediate mesoderm. The rhythm of growth and development of the collector tubes differs greatly during pregnancy. Until 15 weeks of gestation, the rhythm of development is very rapid and later decreases [1, 2].

The urinary tract is almost entirely developed from the intermediate mesoderm. The evolution implies different stages in development: pronephros, mesonephros and metanephros. These stages will appear successively in the craniocaudal direction and coexist over time. Intermediate mesoderm is divided in the upper cervical and thoracic region, resulting in nephrotomes [2, 3].

The mesonephric duct will give rise to the ureteral bud after the formation of the pronephros. This, after 15 generations of divisions, will lead to the formation of the ureter, the calves, the collector tubes and the kidney pelvis. The lack of formation or agenesis of the pronephros or of the mesonephric duct can lead to the total or partial absence of the kidney or to other anomalies of the reno-urinary tract [4, 5].

CAKUT (congenital anomalies of kidney and urinary tract) may be part of multi-organ processes in single-gene disorders, with dominant or recessive inheritance, as we can find in Fraser syndrome, the branchiootorenal syndrome, Kallmann syndrome, Ehlers-Danlos syndrome and others [5, 6].

The genitalia differentiation, which leads to female or male gender, starts at 7–8 weeks of pregnancy and finalizes at 12–13 weeks. Every fetus will develop female characteristics, because at the beginning of gestational period, the Mullerian and Wolffian structures coexist. If the Mullerian structure will suffer atrophy, due to testosterone and anti-Mullerian hormone effects, male sex structures will develop from the Wolffian structure, and the fetus will

become a male. In the opposite circumstance, the fetus will become a female. In conclusion, from the embryological point of view, an individual could be a female if the masculine features will not develop [7, 8].

2.2. Classification

Congenital urinary abnormalities are often associated with the kidney anomalies, and there is a wide range of malformations resulting from disorders in the normal development process [9].

Malformations of renal parenchyma may occur due to the abnormal nephron development—in cases of renal dysplasia, renal agenesis and renal polycystic disease. The migration abnormalities of kidney embryo buds are found in renal ectopy and in the mismatched malformations [10].

Abnormalities in the development of the urinary tract system cause duplicated collective systems, posterior urethral valves and obstructions of the pyeloureteral junction. Defects may be unilateral or bilateral, and several types of defects may be associated [1–3, 6, 7].

The anomalies of the urinary system can be divided into nephropathies and uropathies:

a. Nephropathy involves the renal parenchyma and refers to multicystic kidney disease (MCDK), renal dysplasia disease, renal agenesis defect, congenital polycystic kidney disease and other anomalies (nephromegaly, trisomy 13, Meckel syndrome, Beckwith-Wiedemann syndrome) [6–8].

b. Uropathies represent the pathology of the urinary tract, and by the site of the defect, they can be pyeloureteral and ureterovesical, or they can refer to the vesicoureteral reflux and to the posterior urethral valve. Many authors also consider here the urachal fistula, the urachal cyst and the exstrophy of the urinary bladder [10–12].

For a better understanding of urinary tract abnormalities, we will summarize the classification of kidney malformations that may accompany these anomalies:

I. Anomalies in number

a. *Complete bilateral renal agenesis* is a rare condition, not compatible with extrauterine life. The physical appearance of the babies is very characteristic (the so-called Potter syndrome). The absence of the kidneys may be suspected before conventional postmortem autopsy. Fetal ultrasound examination is very difficult, due to the absence of amniotic fluid.

b. *Unilateral renal agenesis* or the 'congenital solitary kidney' is probably the most difficult diagnosis of renal malformations. There is a consensus in terms of a definitive diagnosis, autopsy being the only conclusive method.

c. *Renal aplasia*—there is a fetal bud, but it does not develop into a normal functioning organ. The pelvis and ureter are usually absent or are rudimentary.

d. *Supernumerary kidney* is the rarest anomaly and consists of a third kidney with excretory cavities and its own vascularity, completely separated from the other kidney [1–8].

II. Renal size abnormalities

a. *Renal hypoplasia*. There are small congenital kidneys, located next to the median line and excretory cavities. The renal function is normal or low.

b. *Kidney hyperplasia*. There is a large kidney, after ruling out any other cause [5–7].

III. Kidney's shape abnormalities

a. *Lobular kidney*. There is a persistence of fetal lobulation.

b. *Kidney fusion*. There are bilateral symmetrical or asymmetrical mergers or unilateral asymmetry.

c. *The kidney in the horseshoe*. In 90% of the cases, kidneys join at the lower pole through a parenchymal or fibrous bridge.

d. *Bilateral asymmetric mergers*. One of the kidneys is smaller than the other.

e. *Unilateral asymmetric fusions*. There is a single kidney mass with a crossed ectopic kidney, known as 'the sigmoid kidney', usually located in the pelvis [7–10].

VI. Renal position abnormalities

a. *Ectopic kidney*. A birth defect given by an abnormal (unilateral or bilateral) kidney position. The ectopic kidney is more often located on the left side. There are several ectopic kidney types: the caudal (lumbar, iliac, sacral) kidney, the cranial kidney and the crossed kidney.

b. *Renal dystopia*. Initially, in embryonic life, the hill and pelvis are located in the anterior part, and then they undergo a rotation around the longitudinal axis, until they reach the median side [1–4, 7].

V. Multicystic renal dysplasia

These are large and hyperechogenic kidneys, including renal ciliopathies. These conditions may be divided into autosomal dominant diseases and autosomal recessive disorders, including the polycystic kidney disease, renal dysplasia, glomerulocystic kidney disease (trisomy 13 and trisomy 18, Beemer syndrome), multicystic dysplastic kidneys (MCDK), medullary cystic dysplasia (Meckel-Gruber and Beckwith-Wiedemann syndromes, as well as congenital infections) [10–13].

2.3. Diagnosis

Nowadays, the fetal bladder and kidneys may be visualized starting with 11 weeks (by transvaginal echography) or 12 weeks (by means of transabdominal echography). The fetal bladder and kidneys are located near the spine, having an elliptical shape [1, 2].

In the first trimester of pregnancy, the kidneys appear as an ovoid structure located on both sides of the spine (**Figure 1**) [1–4].

Renal urine production begins during week 9 of embryonic life, making it possible to visualize the bladder, as a fluid collection in the fetal pelvis. The bladder appears spherical and transonic and is located between the iliac bone centers of ossification, in the lower pelvis. It can be visualized starting with the ninth week of pregnancy, and the umbilical arteries can be visualized laterally next to the bladder. Beyond the first trimester, the bladder will fill and empty in an intermittent manner, every 25–30 minutes, due to the influence of hormonal factors on the bladder (**Figure 2**) [2, 3].

Normal ureters cannot be visualized by means of echography. The ratio of renal circumference to abdominal circumference is 0.27–0.30 and remains constant during pregnancy [8].

Evaluation of the urinary tract also requires the evaluation of the amniotic fluid volume. After the 14th week of intrauterine life, the amniotic fluid comes mainly from the production of fetal urine and only one-third of its quantity comes from the pulmonary fluid [2, 5].

For a correct diagnosis, the clinician has to perform a complete examination in all of the three planes, the coronal, the sagittal and the longitudinal plane, using 2D grayscale and color Doppler. The examination should be complete. Sometimes, the ultrasound examination has to be completed by another screening method. Due to the association between renal malformations and other congenital defects or chromosomal anomalies, performing an invasive diagnosis method may be required [14].

The renal pelvic dilatation (RPD) is the most common of the abnormalities that can be detected during antenatal ultrasonography and is probably the most frequent sign of a reno-urinary

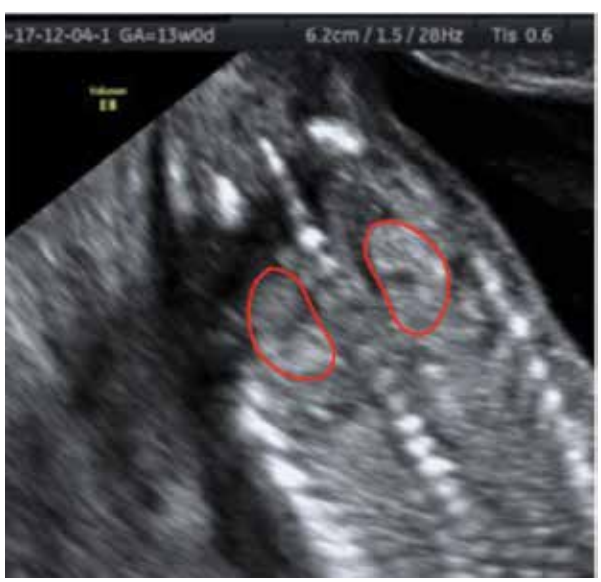

Figure 1. Fetal kidneys in the first trimester of pregnancy.

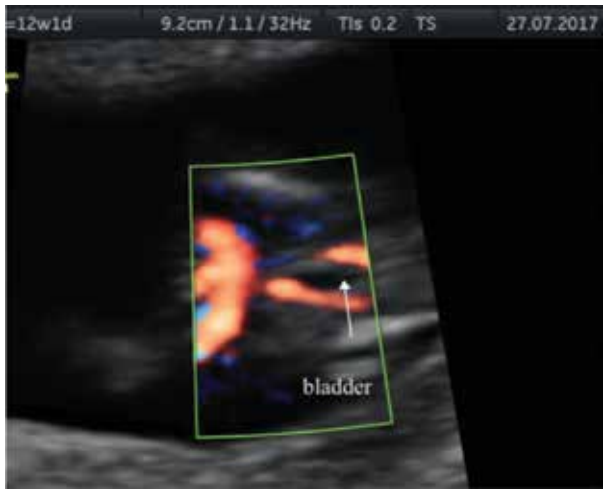

Figure 2. The bladder in the first trimester of pregnancy.

anomaly. The diagnosis of the RPD is based on an increased anteroposterior diameter of the renal pelvis in the transverse plane, and the value allows classification: severe, moderate or mild RPD. Normal values of anteroposterior diameter of the kidney pelvis are up to 4 mm at week 16 of pregnancy, less than 7 mm at 28 weeks of pregnancy and less than 10 mm postnatal [15].

In many cases a transient dilatation occurs. This situation is caused by narrowing or natural folds of the urinary tract that may occur during the early stages of development. Transient dilatation is usually less than 6 mm in the second trimester and less than 8 mm in the third trimester. It usually resolves spontaneously or disappear postnatally [16].

- Many authors concluded that for an accurate diagnosis, the assessment of the renal and urinary function may be performed by ultrasound [5, 6]. The following statements gained acceptance:
- The amount of amniotic fluid is an indirect indicator of the kidney function.
- The bladder filling indicates the normal functioning of at least one kidney.
- The absence of the bladder filling may indicate renal agenesis and bilateral ureteral obstruction.
- The bladder distension may hide a urethral reflux problem.
- The ureteral dilatation may be caused by a lower obstruction of the inferior urinary tract.
- The echogenicity of renal parenchyma cannot be considered for the renal function assessment.
- The increasing rebound pressure in the renal artery may cause renal function [5–12].

2.4. Uropathies

Uropathies are the most common reno-urinary abnormalities diagnosed during the prenatal period and may be caused by obstructive or nonobstructive factors [10–13]. The most common

urinary malformations encountered in children are vesicoureteral reflux (VUR), obstructive megaureter, posterior urethral valve and megacystis [11].

Fetal hydronephrosis may result in a number of conditions, like pelvic or vesicoureteral junction obstruction, posterior urethral valves, vesicoureteral reflux, pelvic-ureteric junction obstruction and other rare congenital anomalies [12, 13]. A clear definition of hydronephrosis would be that it is a dilatation of the calyces and the renal pelvis of over 10 mm or more than 50% of the anteroposterior diameter of the kidney. This dilatation of the urinary system may occur at the upper urethral segment, ureters, bladder or kidney pelvis. Pyelectasis is the dilatation of the renal pelvis only (**Figure 3**) [6, 15].

By some authors, the clinician can diagnose hydronephrosis if the renal pelvic AP diameter is increased over 4 mm in the second trimester and 7 mm in the third trimester [3, 11, 15] (**Figure 4**). A renal pelvic AP diameter > 15 mm is strongly associated with a pathology of the urinary tract that requires treatment after birth. However, in the majority of cases, the renal pelvis is mildly or moderately dilated, and no cause is identified [16].

There is no clear consensus on the follow-up and management of mild or moderate hydronephrosis observed on antenatal ultrasound, although it is generally accepted that a postnatal assessment should be performed if the AP diameter of the renal pelvis exceeds 10 mm at any point in gestation [17].

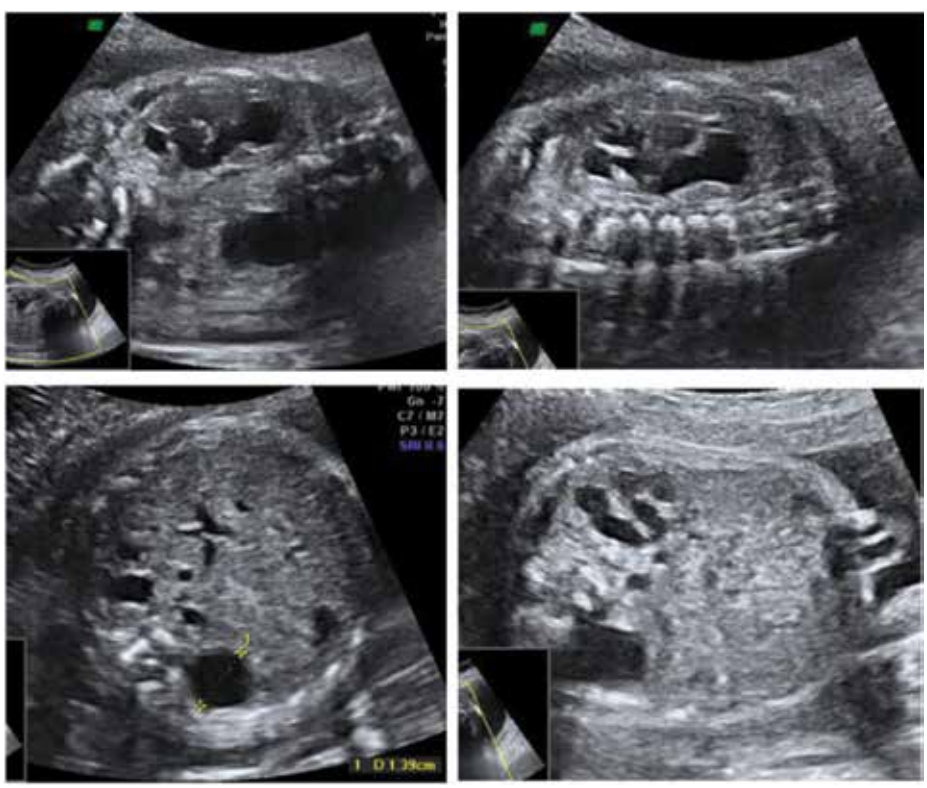

Figure 3. Second trimester: different aspects in hydronephrosis cases.

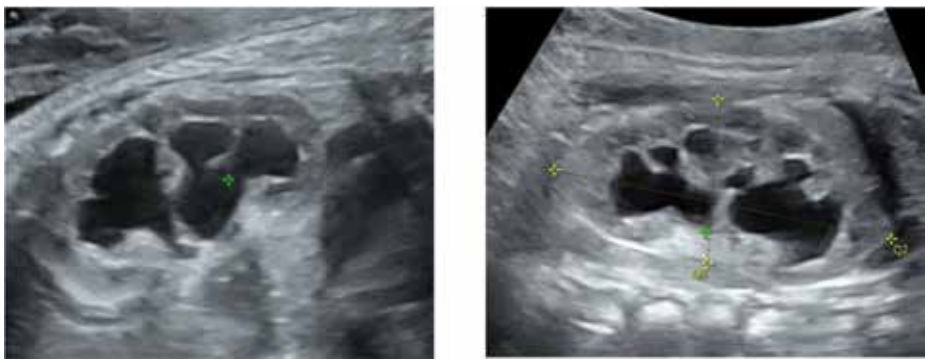

Figure 4. Hydronephrosis in the third trimester of pregnancy.

Many studies show that a right or left prenatal AP renal pelvic diameter > 4 mm is associated with a higher risk of postnatal hydronephrosis compared with a right and left prenatal AP renal pelvic diameter ≤ 4 mm [15, 16]. Male neonates have a higher risk of postnatal hydronephrosis than females. These results can assist in establishing the appropriate follow-up method and evaluation of fetuses with renal pelvic dilatation [18, 19].

2.5. Ureteral malformations

In medical practice many abnormalities can occur, like:

- Number abnormalities
- Structure abnormalities
- Calibration abnormalities
- Vesicoureteral reflux (VUR)
- Abnormalities of the pyeloureteral junction
- Position and opening abnormalities [1, 2, 14]

a. Ureteral abnormalities

- Ureteral agenesis is accompanied by the absence of the ipsilateral kidney. It may be uni- or bilateral, the latter being incompatible with life.
- Incomplete ureteral duplication (ureter fissus or ureter bifid)—a double-sided pyeloureteral system: the ureters bend before opening into the bladder through a single orifice.
- Complete ureteral duplication (duplex ureter)—a double-sided pyeloureteral collection system: the ureters open through separate boreholes in the bladder, one in orthoposition and the other in the ectopic position (**Figure 5**) [15–17].

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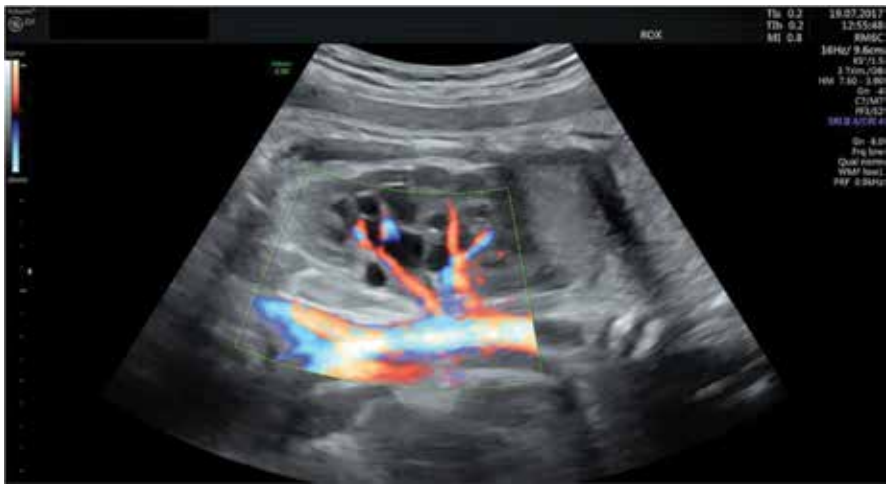

Figure 5. Coronal section and high-definition power color Doppler, in a supernumerary kidney cases. Visualization of the double renal artery.

b. The ureteropelvic junction obstruction

Obstruction of the ureterobladder junction (obstructive megaureter) or obstruction on pyeloureteral junction is one of the most common causes of hydronephrosis found in children, its incidence being 1 case in 1000–2000 newborns. In this situation, hydronephrosis may be caused by an abnormal shape of the ureteral junction—the existence of the ureteral valves and the mucosal fold at this level. Like many other abnormalities, this pathology occurs much more frequently in males, usually unilaterally and especially on the left side [10, 14].

The ultrasound diagnosis is based on the observation of the increase of the anteroposterior diameter of the kidney, a degree of kidney pyelectasis. If the obstruction is unilateral and the filling of the bladder is normal, the normal amount of amniotic fluid will be preserved. When the damage is bilateral, the oligoamnios/oligohydramnios may appear.

In most cases this condition does not produce symptoms after birth; in 10–15% of the cases, it regresses spontaneously, but sometimes repeated evaluation is needed [1–8].

c. Obstruction of the ureterobladder junction

This condition is the cause of approximately 5–10% of all cases of dilatation of the urinary tract. Ultrasound diagnosis is based on dilated urethra, with renal pelvis dilatation and normal bladder image. The cause of the disease is the dysfunction of the lower ureter, the outcome is favorable and the pathologic aspects disappear postnatally in many cases [16] (**Figure 6**).

The normal ureter size in children is up to 5 mm. Normal ureter cannot be detected during prenatal ultrasound examination. It can only be detected if it is dilated to a size greater than 7 mm and is observed like a translucent structure. The dilated ureter should be differentiated from full intestinal loops. Pathological dilatation of the ureter is more common in male patients, usually appearing to be unilateral (**Figure 7**) [15–17].

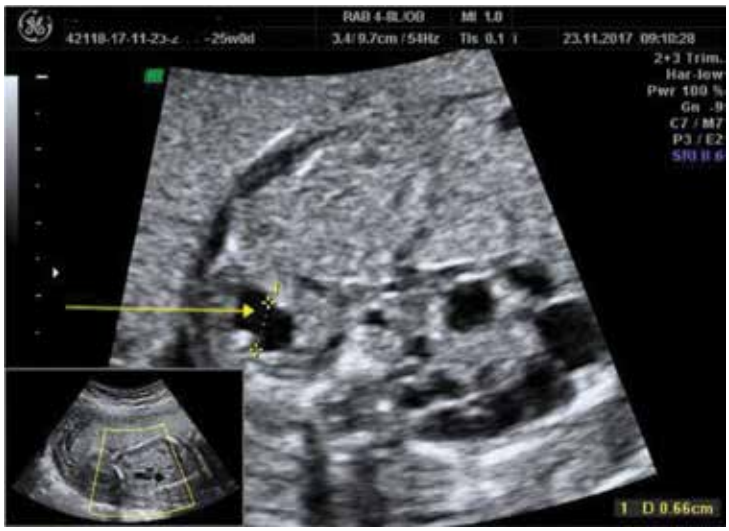

Figure 6. Contralateral pyelectasis in a unilateral MCDK case.

The dilatation of the ureter may be partial or total, and this pathology can be classified into the following conditions:

- Obstructive-type megaureter
- Reflux-type megaureter
- Megaureter without reflux and without obstruction
- Obstructive- and reflux-type megaureter

d. Vesicoureteral reflux

Vesicoureteral reflux (VUR) is characterized by the return of urine from the bladder to the kidney which often causes hydronephrosis and sometimes even abnormalities in kidney development (renal dysplasia). Causes include transient obstruction of bladder discharge, delayed maturation of the vesicoureteral junction and high bladder evacuation pressure. Patients with vesicoureteral reflux have a high risk of pyelonephritis, hypertension and progressive renal failure. Vesicoureteral reflux is represented by the retrograde passage of urine from the bladder to the ureter and subsequently to the kidneys, due to the incompetence of antireflux mechanisms [17, 19, 20].

This condition is usually easy to diagnose prenatally, when visualizing renal pelvis and calyces dilatations that vary in size, associated with unilateral or bilateral ureteral dilatations. RVU reveals a nonprogressive hydronephrosis with normal amniotic fluid index [10–13, 18].

VUR classification:

- Grade I reflux: reflux is only present in the ureter that has various degrees of dilatation.

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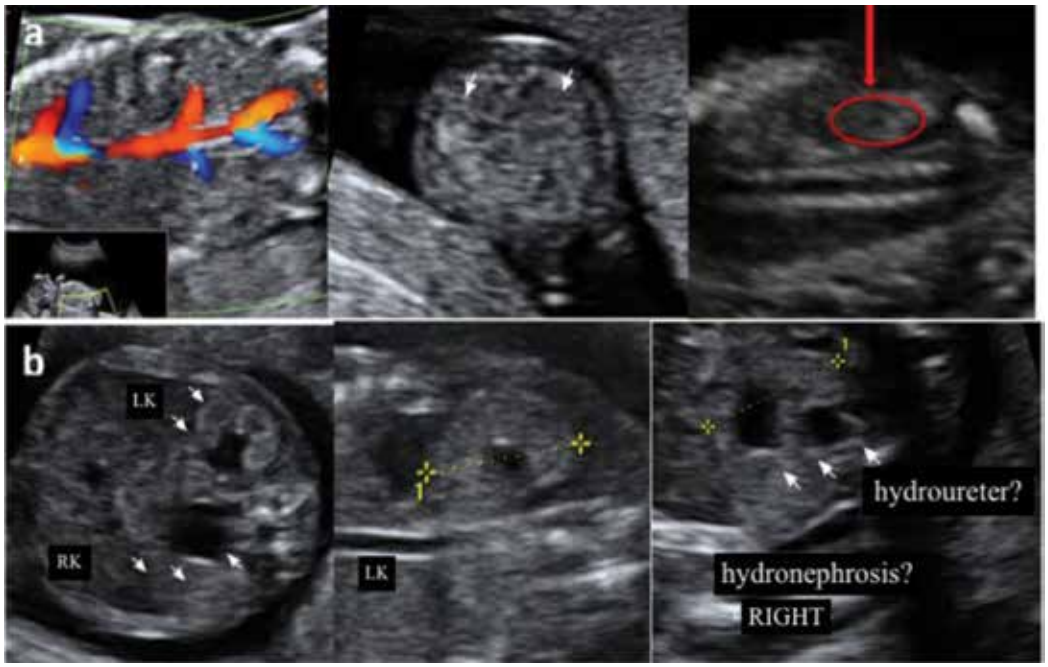

Figure 7. (a) First trimester: both renal arteries visualized in color Doppler, normal kidney images on both sides of the cross section and a kidney highlighted in the coronal section. (b) Second trimester (same case): asymmetrical bilateral pyelectasis, left kidney longitudinal diameter and hydroureter on the right side.

- Grade II reflux: reflux reaches the renal pelvis, without dilatation of the collector system, the papillae being normal.
- Grade III reflux: moderate dilatation of the ureter, with or without sinusitis; moderate dilatation of the collector system.
- Grade IV reflux: moderate dilatation of the ureter with or without sinuosity; moderate dilatation of the collector system; calyces are flattened but with the impression of the papilla still visible.
- Grade V reflux: severe dilatation with ureter sinuosity and marked dilatation of the collector system; reflux in the parenchyma, with parenchymal thinning [10–15, 18].
- The prognosis is good. The prenatal diagnosis is important. Forty percent of the newborns develop severe kidney damage [2].

e. Ureterocele

As many other kidney abnormalities, ureterocele is more common in male patients. This pathology appears as a thin wall cyst or sept on the bladder wall [1, 16]. In many cases the diagnosis may be omitted when the bladder is full, the filling masking the cyst. There have been described cases of ureterocele shed in the urethra. This phenomenon may lead to acute obstruction of the lower urinary tract [1, 2]. The prognosis is favorable, but its evolution must be assessed postnatally, by residual renal function testing and reflux tests (**Figure 8**) [20].

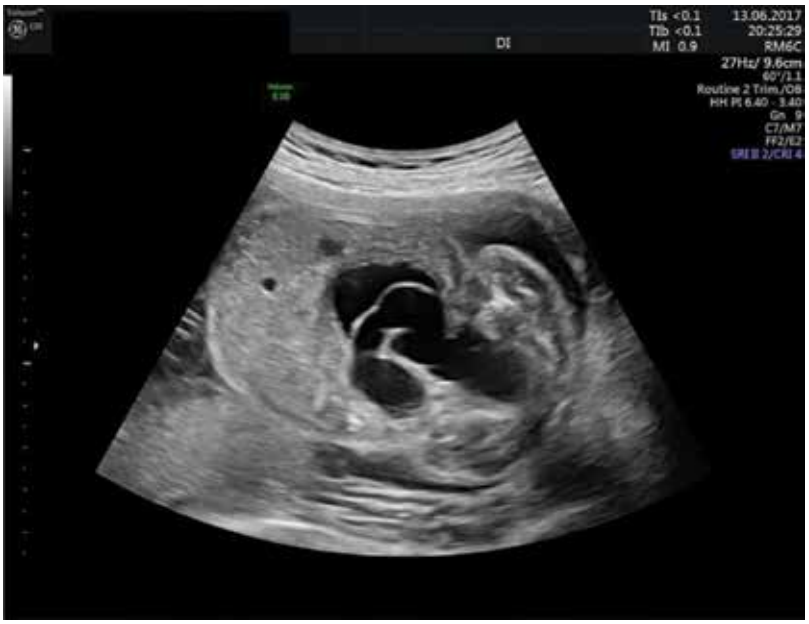

Figure 8. Ureterocele and hydroureter.

3. Bladder anomalies

The bladder is a very important element in antenatal fetal examination. Clinicians may suspect anomalies of the bladder when not visualized on prenatal examination or when enlarged. From the pathological point of view, we may encounter various anomalies as well:

a. Megacystis is a neurodysplastic disease, due to the anomaly of innervation. This leads to bladder dilatation (over 7 cm in diameter). It may be associated with small, short and dilated bowels, as well as a low-caliber colon. At ultrasound, the striking signs are polyhydramnios, enlarged ureters and kidneys [17].

b. Congenital bladder diverticulitis. A septum can be observed.

c. Bladder exstrophy. It is commonly associated with other urogenital malformations and is constantly accompanied by epispadias. This pathology is characterized by many anomalies and lesions, such as:

- Abdominal anterior wall injuries: inguinal hernia is common.
- Lesion of pelvic bones: shortening and defects of rotation of pubic bones.
- Lesions of the genitalia: micropenis and cryptorchidism appear in boys; in girls, the vagina is short and has various degrees of stenosis, the clitoris is bifid and the small labia are divergent.
- The anterior bladder wall is absent, and the posterior wall is the submuscular segment of the anterior abdominal wall.

- The bladder mucosa is exposed to the external environment, with the ureteric holes and the inner urethra opening visible.
- Vesicoureteral reflux is present in all cases.
- Some patients have rectal prolapse and anal incontinence; this phenomenon is due to the malposition of sphincter structures [1–4, 15–17, 19, 20].

4. Urethral malformations

The most common obstructive cause of the lower urinary tract is the posterior urethral valve (PUV). PUV is due to the existence of membranes in the posterior urethra. Echography shows dilated bladder and urethral dilatation, giving a classic echographic sign—'the keyhole sign'. Dystriation of ureters and troughs also occurs [14]. In advanced forms, oligohydramnios-associated pulmonary hypoplasia and urinary ascites may also appear. These fetuses require prenatal intervention to avoid kidney damage. Some authors tried to demonstrate that creating a vesicoamniotic passage may lead to a better outcome, but this has not yet been fully demonstrated [16].

In the prenatal life, other malformations may be seen:

1. Urethral agenesis (absence of urethra) is a rare malformation, incompatible with life unless an alternative communication between the bladder and amniotic sac exists. The urine is discharged through abnormal communication with other organs (between bladder and bowels or by umbilical fistula).
2. Congenital structures.
3. Rear urethral valves: mucosal lining located in the posterior urethra originating from the seminal colonic and insertion on the anterior wall of the urethra [14–17].
4. Epispadias: abnormality characterized by opening the urethra on the dorsal face of the penis at variable distance of the gland, dorsal curvature of the penis and foreskin abnormalities. There are many forms of epispadias:
   - Balanic: distal incomplete defect.
   - Penian: incomplete proximal defect.
   - Penopubian: a complete defect, often associated with bladder exstrophy. In this situation, a distinct pathological condition appears: the exstrophy-epispadias complex [19].
   - Hypospadias: the anomaly is characterized by opening the urethra on the ventral side of the penis, at any level between the gland and the perineum, causing a ventral penis (chord). Patients with hypospadias have often abnormalities of the foreskin and cryptorchidic scrotum, inguinal hernia and hydrocele. Studies have shown a higher presence of hypospadias in patients with fetal growth restriction (**Figures 9** and **10**) [19]

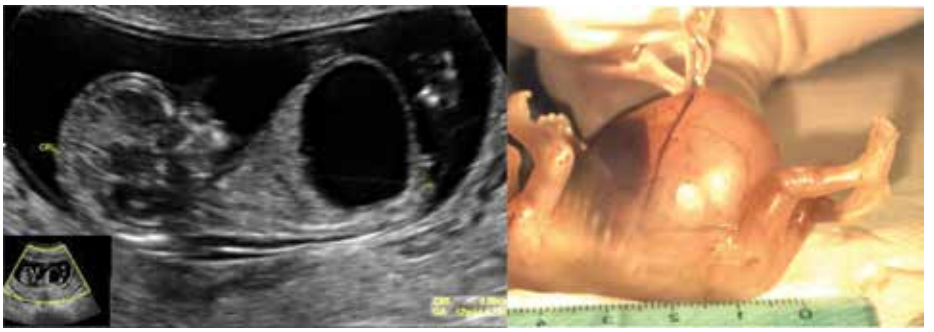

Figure 9. Isolated megacystis: the right-side image is the sagittal plane of the fetus and the CRL (crown-rump length) measurement; the left-side image (same case) is the pathological specimen after medical termination of pregnancy.

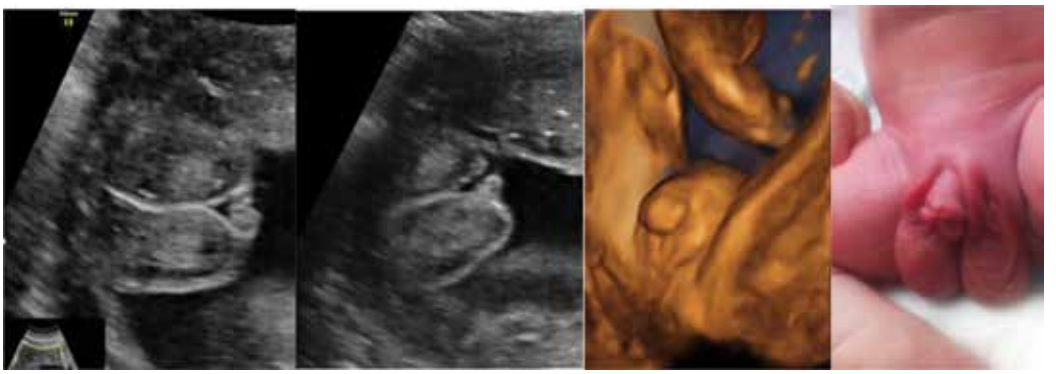

Figure 10. Grade III hypospadias (perineal) is the most severe form, with the opening of the urethra at the penoscrotal junction.

The diagnosis of hypospadias with prenatal ultrasound is based on several important criteria:

- A blunter bulbous tip to the penile shaft rather than the normal.
- A 'tulip' sign formed by the ventral-bent penis located between the two scrotal folds.
- Abnormal curvature of the penis.
- A short penile shaft.
- Ventral deflection of the urinary stream which can be studied by color Doppler [20].

5. Evolution and treatment

Renal pelvic dilatation is commonly seen during antenatal ultrasound examinations, and its management remains a clinical dilemma. Although it is proven that severe antenatal hydronephrosis requires postnatal clinical and ultrasound evaluation, there is no consensus on the

follow-up and management of mild or moderate hydronephrosis observed during antenatal ultrasound examinations [15]. The prenatal diagnosis may improve the prognosis and the outcome of the fetus. An early diagnosis and treatment of urinary obstruction may prevent the renal damage or loss of renal function [5, 21].

Most of the cases will spontaneously resolve after delivery. Thus, some assurance should be given. Many studies suggest follow-up when the AP diameter is 4–7 mm and antibiotic therapy when the AP diameter is greater than 7 mm [14, 18].

The postnatal assessment of fetal hydronephrosis may be invasive and lengthy [6–8]. Thus, the risks and the inconvenience of a protracted evaluation need to be weighed against the probability that milder degrees of renal pelvic dilatation will decrease without resulting in any renal damage [17].

6. Congenital genital anomalies

The spectrum of congenital genital malformation is very broad, and the diagnosis is usually difficult. A reliable classification reveals four main types of genital anomalies:

1. True hermaphroditism: an individual has both ovarian and testicular tissues.
2. Male pseudohermaphroditism.
3. Female pseudohermaphroditism: adrenogenital syndrome or congenital adrenal hyperplasia. The main feature is clitoris hypertrophy.
4. Gonadal dysgenesis [5, 19, 20].

Fetal gender abnormality is diagnosed by ultrasound or by finding a discrepancy between fetal phenotype and sex chromosomes. The ultrasound diagnosis is late, usually accessible in the second or third trimesters [5, 20–24].

I. Male genital malformations

Due to improved ultrasound technology and increased experience in this area, the fetal sex can be established with high accuracy beyond 13 weeks of pregnancy [5]. Determination of fetal sex is based on the 'sagittal sign'. During the first trimester, in the sagittal plane, the penis is oriented upwards and the clitoris downwards. In the third trimester, the genitalia can be described with high accuracy [21].

Penian malformations (abnormal phallic structure)

1. Micropenis or penian hypoplasia
2. Penian agenesis
3. Megalopenia or hyperplasia of the penis [1–3, 22]

Testicular malformations.

1. Number abnormalities

- Anorchia (or anorchism): the absence of both testicles in the presence of a normal male phenotype (46XY)
- Monorchism (or monorchidism): the absence of a testicle
- Polyorchism: the presence of more than two testicles
- Testicular fusion: the fusion of the two testicles in the same scrotum [2, 5, 20–24]

2. Development abnormalities

- Microorchidism: small, hypoplastic testicles.
- Macroorchidism may be secondary to contralateral testicular damage and may be bilateral in congenital syndromes (fragile X syndrome) or other disorders (hypophysis adenoma, aromatase deficiency).
- Cystic dysplasia of the testicle: benign, congenital tumor, frequently associated with other testicular malformations [5, 20–24].

3. Migration abnormalities

- Cryptorchidism: the process of descensus testis is affected by anatomical and mechanical factors, such as a poor connection between the gubernaculum and testis and endocrine factors (**Figure 11**) [5, 22].

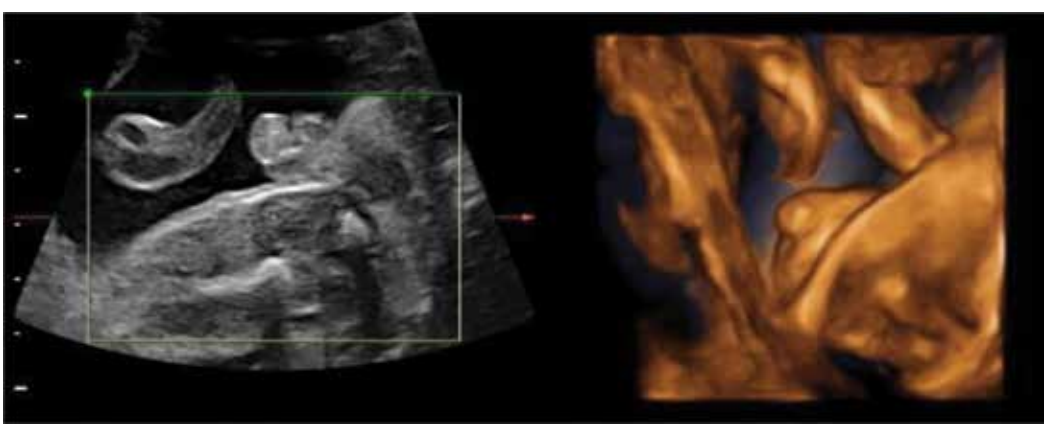

Figure 11. Hypospadias: the left-side image is the 'tulip sign' in 2D conventional ultrasound; the right-side image is a 3D reconstruction, surface rendering technique.

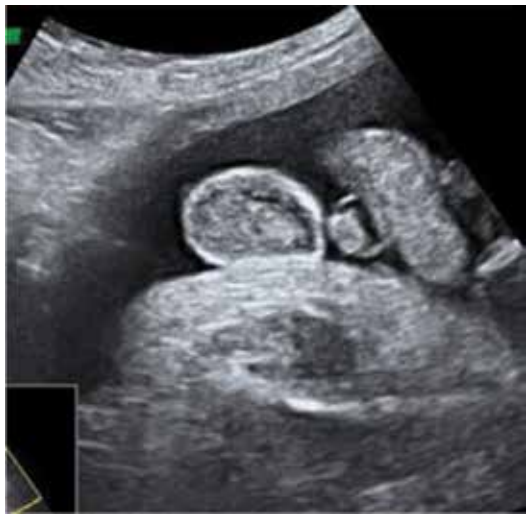

Figure 12. Unilateral cryptorchidism (in association with penian anomaly).

Classification:

- Intraabdominal: above or at the internal inguinal opening
- Intracanalicular: in the inguinal canal, between the inguinal inlet and the external groove
- Extracanalicular:
- Suprapubian: just above the external inguinal opening above the pubic symphysis level
- Infrapubian: in retroscrotal space, inferior to pubic symphysis [1, 5] (**Figure 12**)
- Ectopic testis: migration is normal to the level of the inguinal external hole, but the testicle follows an abnormal tract. Possible localizations are between aponeurosis of external oblique muscle and subcutaneous or femoral, etc. [24].

It is recommended that information about the fetal abnormalities, postnatal and prenatal options of treatment and prognosis should be presented to the parents by a multidisciplinary team that includes neonatologists, urologists, perinatologists and medical geneticists with expertise in this field [5].

7. Female genital malformations

7.1. Ovarian cysts

Ovarian cysts are the most frequently abdominal tumors that may be seen in female fetuses and newborns. The incidence of fetal ovarian cysts has increased lately, due to the improvement

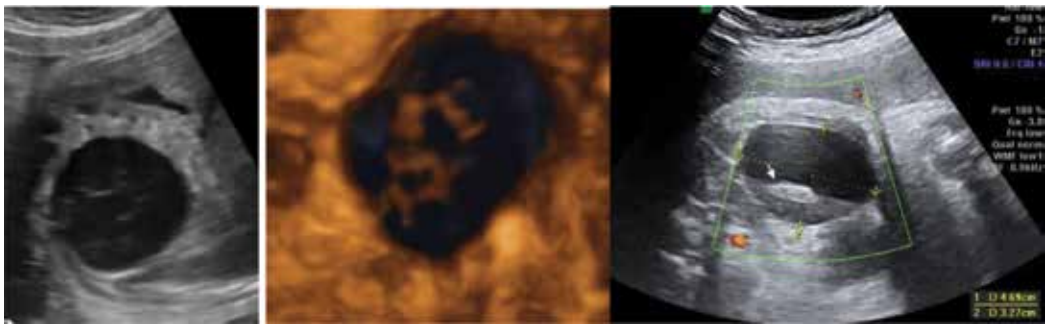

Figure 13. Fetal ovarian cyst: 2D and 3D surface rendering images. The evolution of the case led to the typical 'fluid–fluid' level aspect, due to the intracystic hemorrhage.

of ultrasound technology and due to the increase in the incidence of pregnancies that require hormonal treatment during the gestation period [2].

These ovarian tumors may be uni- or bilateral, sometimes multiple, and their appearance is as anechoic structures, thin-walled and having various sizes [5, 21–24]. Some authors described cases with solid tumors, teratomas or hemorrhagic cysts. To increase the accuracy of the diagnosis, MRI examination may be required (magnetic resonance imaging (MRI)) [22].

Fetal ovarian cysts have usually a good outcome; most of them progress to spontaneous resolution in the postnatal period. The most frequent complication of cysts is ovarian torsion. Other complications may be intracystic hemorrhage, rupture, dystocia during birth, etc. There are no guidelines for monitoring and treatment of this condition. The non-invasive monitoring by ultrasound seems to be the best approach in prenatal life [1, 5, 19–25] (**Figure 13**).

7.2. Hydrocolpos

Hydrocolpos is the accumulation of fluid in the vagina. When the fluid is observed on the vagina and the uterine body, the condition is called hydrometrocolpos. These diseases are caused by the persistence of the urogenital sinus or cloaca malformations [23]. The presence of a cystic mass in the presacral area, containing an anechoic fluid (suggesting urine) or sediment content, should guide the clinician to a diagnosis of urogenital sinus persistence [1, 2, 25].

8. Conclusions

The ultrasound diagnosis of renal and urinary tract abnormalities is generally based on the exclusion criteria, by comparison with the normal imaging one. In most cases, kidney or urinary tract abnormalities are diagnosed considering the appearance of amniotic fluid abnormalities, visualization of kidney size abnormalities or dilated appearance of the urinary tract. Congenital kidney abnormalities are often associated with the urinary tract malformation, and there is a wide range of anomalies resulting from disorders in the development process. It is important to differentiate abnormalities incompatible with life (as they require interruption of pregnancy) and asymptomatic/paucisymptomatic diseases in the postnatal life.

The genitalia anomalies must be treated by a multidisciplinary team that includes neonatologists, endocrinologists, urologists, perinatologists and medical geneticists with expertise in this field.

Conflict of interest

We have no conflict of interest.

Author details

Sidonia Maria Sandulescu[1]*, Ramona Mircea Vicol[2,3], Adela Serban[2,3], Andreea Veliscu Carp[2,4] and Vaduva Cristian[1,5]

*Address all correspondence to: ssidoniam@yahoo.com

1 University of Medicine and Pharmacy, Craiova, Romania

2 University of Medicine and Pharmacy, Bucharest, Romania

3 INSMC Alessandrescu-Rusescu, Bucharest, Romania

4 Clinical Hospital of Obstetrics and Gynecology Panait Sarbu, Bucharest, Romania

5 County Clinical Emergency Hospital of Craiova, Craiova, Romania

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Chapter 15

The Antenatal Detection of Fetal Limb Anomalies

Iuliana Ceausu, Dominic Iliescu, Cristian Poalelungi,
Cristian Posea, Nicolae Bacalbasa,
Dragos Dobritoiu and Liana Ples

Additional information is available at the end of the chapter

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Abstract

The etiology of fetal limb abnormalities is very complex, involving different risk factors: chromosomal abnormalities, gene disorders, intrauterine factors, maternal diseases, or exposure to different risk factors. The prevalence of fetal limb anomalies is reported to be approximately 6 in 10,000 live births, and the impairments of the upper limbs seem to present a higher incidence in comparison to the inferior limbs, more often are affected unilaterally and on the right side in comparison to the left side, some being isolate or may associate other anomalies, as a part of an underlying syndrome. According to the current guidelines, the assessment of the fetal limbs should be performed in the late first and early second trimester. Three-dimensional ultrasound provides a better understanding of the fetal anomaly for the parents and helps a better counseling, and it is used to confirm the anomalies detected by the conventional ultrasound. In cases of treatable anomalies, a multidisciplinary approach involving an obstetrician, geneticist, neonatologist, pediatrician, and pediatric orthopedic surgeon is essential to improve the postnatal outcome. Ultrasound examination and genetic counseling for the parents has an important benefit since some conditions present a genetic inheritance, and the recurrence rate in further pregnancies is very high.

Keywords: fetal limbs, malformations, fetal syndrome, ultrasonography, 3D ultrasound, matero-fetal medicine

1. Current recommendations

The evaluation of musculoskeletal system and limbs is a part of the routine fetal ultrasound (US) examination, especially during the first- and second-trimester (ST) screening.

Its assessment is significantly more difficult in the third trimester, as the fetal dimensions and movements frequently alter the visualization of some segments, situated far from the transducer or behind other fetal bony structures.

In the last decades, the 11–13 weeks +6 days of US genetic scan has become an important tool for fetal anatomy assessment. It includes almost all segments of the fetal body and also the upper and lower extremities. The second-trimester anomaly scan remained the standard morphologic evaluation, an audit for the early scan, and a baseline for future US evaluations and interpretation of the fetal development. Still, between the guidelines issued by the major societies, there is a wide variation of the parameters proposed as a minimum for limb evaluation (**Table 1**).

Systematic and careful examination of the extremities is important, at any time. Congenital anomalies may affect one or more limbs and may affect any segment.

Usually, these limb anomalies are isolated, but detection of any of them should be followed by a detailed examination of the rest of the fetal anatomy. In many cases with aneuploidy and genetic syndromes, limb defects are present.

Limb segments included in the protocol recommendations	ISUOG [1]	NHS (UK) [2]	ACOG, AIUM, ACR, SRU [3–5]
Upper and lower limb presence	x	x	x
Femur diaphysis length (measurement)	x	x	x
Metacarpal and metatarsal bones/presence of the hands and feet	x	x	—
Digit count	—	—	—
Fetal movement	x	—	—

ISUOG: International Society of Ultrasound in Obstetrics and Gynecology; NHS, UK: National Health Service in the United Kingdom; ACOG: American College of Obstetricians and Gynecologists; AIUM: American Institute of Ultrasound in Medicine; ACR: American College of Radiology; SRU: Society of Radiologists in Ultrasound.

Table 1. Recommendation for fetal limb evaluation on prenatal ultrasound.

2. Development

The fetal skeleton starts to develop early during gestation. The appendicular and axial skeletons undergo a programmed pattern of endochondral ossification during which a cartilage template is replaced by the bone. In contrast, the calvarium and portions of the clavicle and pubis ossify via membranous ossification, whereby mesenchymal cells differentiate directly into osteoblasts [6].

Limb buds begin to develop during the fourth to fifth gestational week (GW) as clusters of mesenchymal cells covered by the ectoderm, but before the end of the seventh GW, the anatomy

of the embryonic pole is difficult to observe. The upper limb development precedes the lower limbs in bud appearance, differentiation, individualization, movements, and final size. The process starts from proximal to distal, with the humerus and femur first, then ulna and radius, tibia and fibula, metacarpal and metatarsal bones, and lastly phalanges [7]. Then, the mandible, maxilla, and clavicles ossification centers appear at 8 weeks of gestation; appendicular skeleton, ilium, and scapula by 12 weeks; and metacarpals and metatarsals by 12–16 GW [6].

3. First-trimester assessment

During the so-called nuchal or genetic scan, a morphologic evaluation is recommended. Nuchal translucency (NT) assessment is more sensitive at an earlier gestation, 11–12 weeks of gestational age, but the optimal moment of the first-trimester anomaly scan is reported after 12 GW [8–11]. Regardless of scan timing, the fetus needs to be assessed in all planes: longitudinal, axial, and coronal. The examination may be performed transabdominal, and if necessary transvaginal, and a combination of the two approaches might give the best results [12]. In our experience, the completion of the basic protocol regarding the assessment of the fetal skeleton rarely requires an increased gestational age or the transvaginal approach, but we should keep in mind that the imaging of the fingers and feet was reported consistently and is achieved only after 12 GW [13]. Still, there was an important and constant technological progress in ultrasound capabilities since the respective researches that enables the operators to use modern systems and high-resolution probes for an earlier and a better visualization of fetal anatomy and especially the echogenic structures.

The exam should detect both upper limbs, which are often found in front of the fetal thorax or face, in semiflected position. The lower limbs are generally flexed at the hip at this gestation. The fingers are relatively easy to assess in the first trimester as number and position, including the thumb, because they frequently lie in the same ultrasound plane. Feet can also be identified, but the number of toes may be difficult to assess because of their small size. The tendency of the ankles to have an inward position may result in an overdiagnosis of clubfoot in the first trimester. The proximal long bones—femur and humerus—can be seen and measured at the first-trimester scan, although their dimensions are not part of the routine biometry at this developmental stage.

The performance of the routine first-trimester anomaly scan was reported satisfactory in a recent study [14], where all the examinations were performed transabdominal and the vast majority of limb abnormalities detected prenatally were identified in the first trimester (82%). In the respective group, 77.8% of the total limb abnormalities were diagnosed prenatally and 63.9% on the first-trimester scan.

These encouraging results followed a previous large screening study regarding the results of routine fetal anomaly evaluation at the time of genetic scan [15], where only one third of the skeletal abnormalities were diagnosed (34.12%). In the respective group, all cases of body stalk anomaly were diagnosed, but none of those with unilateral or bilateral talipes,

club or claw hand, and digital defects. The correct diagnosis was made in the majority of cases of a missing hand or foot (77.8%), or polydactyly (60%), and half of the lethal skeletal dysplasia (50%) and isolated shortening of one of the long bones (50%). The only case of ectrodactyly was missed, and arthrogryposis was not suspected during the first-trimester scan.

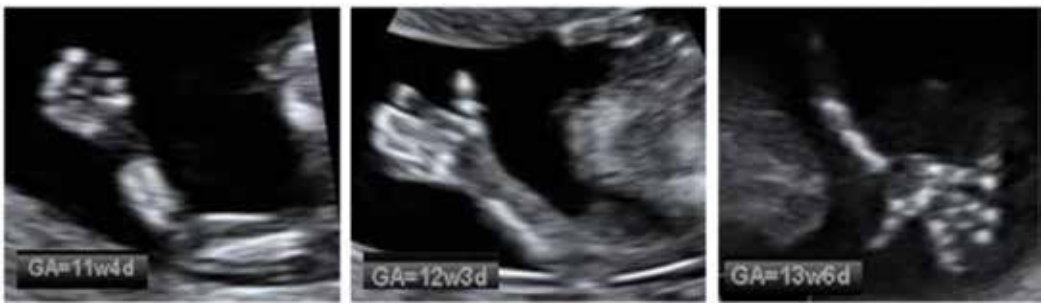

Figure 1. Normal aspects of fetal hand in the late first trimester.

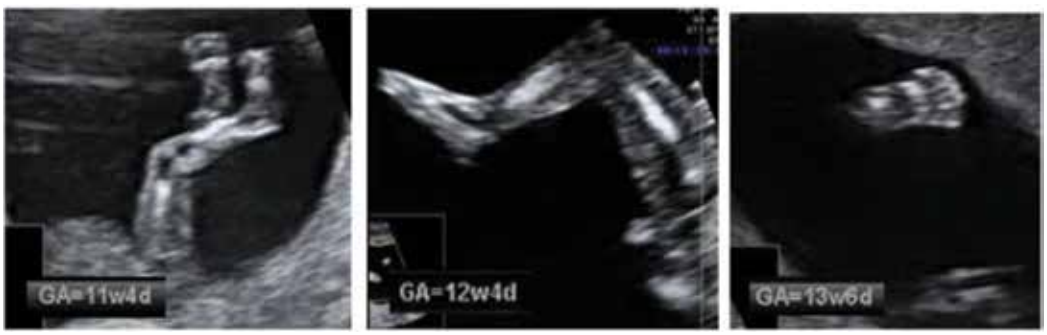

Figure 2. Normal aspects of fetal foot in the late first trimester.

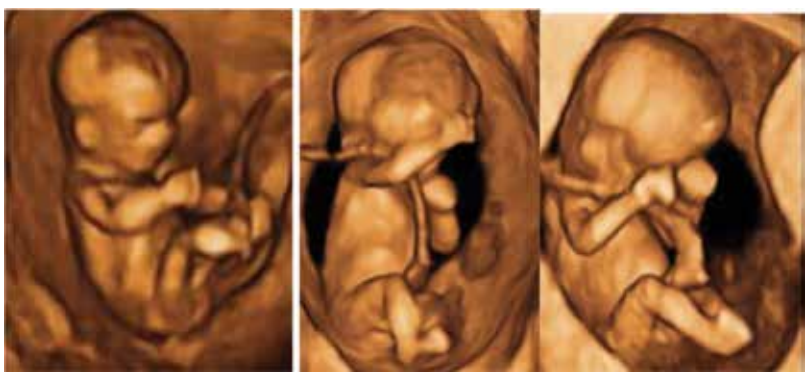

Figure 3. The whole fetus, imaged by 3D static ultrasound (surface rendering mode). The harmonious development and relationship between limbs' segments are easy to asses.

It was suggested that a systemic sequential approach scanning from proximal to distal until the entire limb is observed, and the strict operational training and audit and the use of high-resolution ultrasound machines may improve the early diagnosis of limb defects [14].

As for the most frequent limb anomalies diagnosed early in pregnancy, not only transverse limb reduction defects [14] but also radial aplasia and club hand [16] were proposed in different studies.

An abnormal nuchal translucency may accompany major skeletal abnormalities [17] and sometimes may be the only early sign in conditions with discrete if any early features [18–20]. Narrowing of the thorax with secondary mediastinal compression and abnormal cutaneous collagen deposition were discussed as possible causes (**Figures 1–3**).

4. Second-trimester assessment

Most of the authors agree that the fetal anatomy may readily be assessed at 20–24 WG, because:

- The pregnant uterus is completely lifted up in the maternal abdomen.
- The fetus may present favorable positions and axis for scan.
- The fetus is also enough developed to be seen, leading to good results if scanning for anomalies.

Some important studies underlined a statistically significant difference being able to perform a complete fetal morphology scan if US is performed at 18 to 19 + 6 (in 76% of cases) versus 20 to 22 + 6 weeks of gestation (in 90% of cases) [21–24]. However, with the improved technological capabilities of the ultrasound equipment, the gestational age for confidently assessment is constantly lowering. On the other hand, due to absorption of sound phenomenon, the visualization of the skeleton is easier than for other fetal systems (e.g., the cardiovascular system). Also, the skeletal system is already completely developed, unlike other structures (e.g., central nervous system components, as the corpus callosum or vermis). Therefore, the fetal skeletal evaluation may be proposed and successfully performed in the routine early second-trimester scan (**Figures 4–7**).

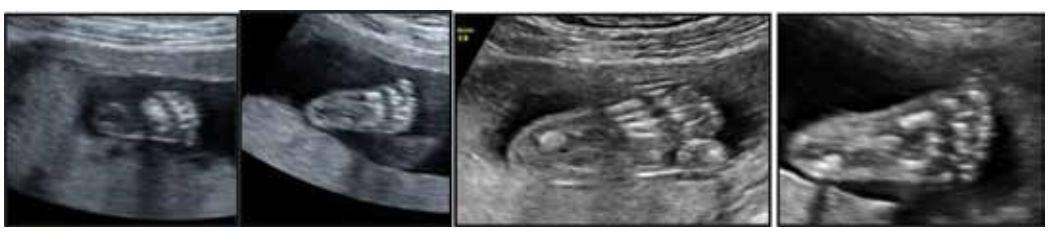

Figure 4. 2D conventional US images of normal feet at 17 weeks of amenorrhea (WA) and at 23 WA. The normal position of the toe is readily observed. In many cases, numbering the digits is possible.

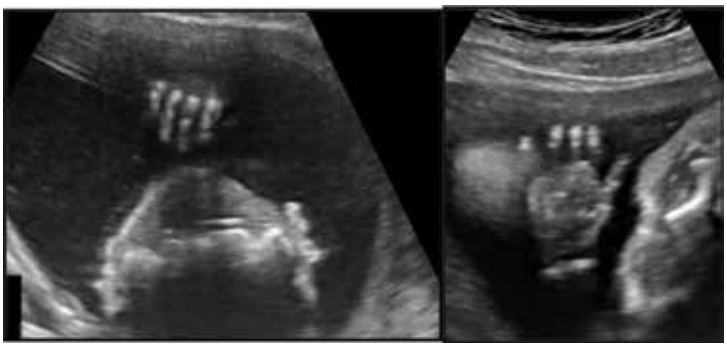

Figure 5. 2D conventional US images of normal fetal hands in midtrimester. Similarly, numbering the fingers is possible and, in certain cases, even the phalanges. As seen, in most cases, the thumb lies in a different plane than the other four fingers. Due to hand anatomy, thumb visualization may not be simultaneous than the other fingers. Yet, confirming the presence of the opposable finger is considered important, due to the prehension function of the hand.

Figure 6. Hands and foot, imaged by 3D static ultrasound (surface rendering mode). Using this technique, the demonstration of the extremities is easier, despite the different spatial arrangement of the thumb.

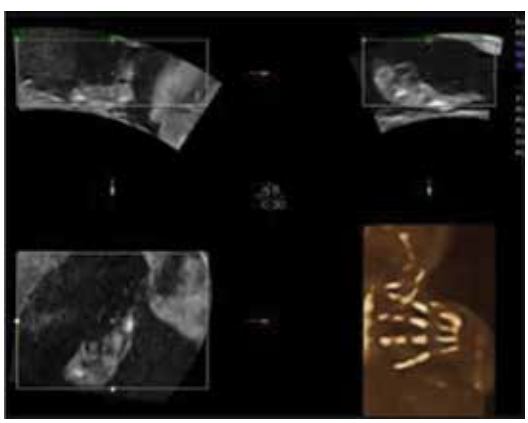

Figure 7. Hand imaged by 3D static ultrasound (skeletal mode). The technique makes the confirmation of the normal number of phalanges of each finger easier.

5. Third-trimester assessment

Later in the second trimester and in the third trimester, despite the increase in the size of the fetus, morphological examination of the limbs is more difficult because:

- the fetal position is maintained for longer periods, due to the reduced mobility;
- the limb's segments have a complete flexion, and the proximal limb's position is maintained toward the fetal axis;
- the amniotic fluid volume decreases, especially at term; and
- the bone ossification increases, impairing the visualization of the underlying structures.

In certain cases, in the late second and third trimester, the secondary anatomy changes due to functional disturbances (some forms of skeletal dysplasia, fetal tumors, segmental deformations secondary to compression in oligohydramnios, multiple pregnancies, or other pathologies) become evident. Thus, even in cases with a normal morphological examination in the second trimester, the examination of the upper and lower members should be attempted in the third trimester. The commendation is stronger if such conditions are suspected.

In the third trimester, the evaluation of the fetal well-being includes the limbs and hand movements, as part of the Manning classical biophysical profile.

6. Literature

Historically, the sensitivity of prenatal ultrasound for detection of musculoskeletal and limb anomalies has been low. In 1991, Levi published a series of 16,072 pregnant women with prenatal ultrasound and found a 45.32% sensitivity for detection of any type of anomaly, with a 23.26% sensitivity for detection of limb and skeletal anomalies [25]. In 1992, Stoll found a 15% sensitivity for isolated anomalies and 48% sensitivity for multiple anomalies for the second-trimester prenatal ultrasounds [26]. The most meaningful result of these early studies is the high specificity of scanning in terms of skeletal abnormalities [25, 26]. This is important, because conditions with high false-positive rates can mislead parents and clinicians in their decisions and recommendations.

Detection of major anomalies has improved over time as a result of improvements in technology and skills, although detection of limb anomalies remained low. The Eurofetus study, in 1999, showed an overall sensitivity for detection of any anomaly to be 61%, with identification of musculoskeletal anomalies much lower and similar to the findings of Levi et al. at 18% [27].

It seems that detection of proximal limb reduction defects is better (23–50%) than detection of hand or finger limb reduction defects (0–8%) [28]. The 2005 EUROCAT study of 4366 fetuses with different anomalies reported a prenatal detection rate for both upper and lower limb reduction defects of 34% [29]. In a more recent study, a higher prenatal detection rate was found for limb reduction defects with associated malformations (49%), if compared to isolated limb reduction defects (25%) [30]. Pajkrt et al. also found a high detection rate for fetuses with short or absent radii and/or ulnae associated with aneuploidy or genetic syndromes (70%) [31]. In another large study, Gray et al. found that 31% of upper extremity anomalies were detected prenatally; however, only 18% were correctly diagnosed [32]. The missed malformations were also located distally (hand and fingers).

The difficulties in detection of upper extremity anomalies may be related to the current guidelines. They mandate only a cursory examination of the upper and lower limbs during the standard second-trimester (ST) examination. This may contribute to the high false-negative rate [33].

7. Technique

The standard examination includes measurements of fetal biometry, in order to estimate the gestational age and fetal weight. It includes the biparietal diameter (BPD), the head circumference (HC), the abdominal circumference (AC), and the femur length (FL) [34]. The measurements of the humerus length (HL) and the transcerebellar diameter (TCD) are optional in many settings. Yet, the fetal biometry may be completed with other segment measurements, as Jeanty proposed over three decades ago [35]. Benefits of such an approach are investigated recently [36]. For almost all fetal structures, nomograms were created, in order to accurately estimate the gestational age.

For limbs examination is recommended to start the sweep proximally. The long bones must be measured in their entirety ("end to end") in a parallel plane to the probe. The examination aims to confirm the normal mineralization and the absence of fractures. The "shortening" diagnosis is allowed only if a previous scan certifies gestational age (preferably, a first-trimester scan).

The forearm and lower leg contain two long bones. In routine examination their presence and normality should be confirmed. If differences between them are suspected or in the presence of other anomalies, all measurements and comparison with the standard data for the gestational age should be done. At the elbow, the ulna is located medially to the radius and has a much higher extremity in relation with humerus. At the wrist, its position depends on the degree of rotation of the forearm.

The image of the foot is obtained in a transverse section to show the heel, the sole, and toes. The position of the big toe with respect to the other toes can be evaluated readily. The length of the foot is not a part of the routine examination, but is important in assessment of skeletal dysplasias and in cases of short femur. If the dimensions of foot remain in normal range for the gestational age and the femur is short, the femur/foot length ratio will be significantly decreased (0.9). In fetuses with constitutionally short femur, this ratio will remain normal.

The ideal window for visualizing the fetal hands is at the late first and early second trimester, when the fingers tend to be extended and abducted. US examinations will be less accurate later in pregnancy, due to fetal position and flexed digits [37]. By some authors, the use of three-dimensional (3D) and 4D US, as well as fetal MRI, improves detection of hand anomalies [32, 37–42]. However, the technique is not currently recommended for routine use by The American College of Obstetricians and Gynecologists [3, 33].

8. Types of limb abnormalities

The most common types of limb anomalies include abnormal number of digits (the higher frequency having polydactyly), abnormal hand/foot position, limb reduction defects, and arthrogryposis. It seems that unilateral limb defects are rarer.

Abnormal hand position is defined as clenched hands or overlapping digits. Arthrogryposis is defined as fetal joint contractures and rigidity.

Counting the fingers is not part of routine scan. Polydactyly is more common in some ethnic groups, such as African Americans. It may occur isolated or may affect both hands and feet.

In amniotic band syndrome, fingers can be missing. This is due to the arrest in development and not as a primary defect in the blastulation process.

In some rare syndromes such as ectrodactyly-ectodermal dysplasia-cleft syndrome (EEC syndrome), missing fingers occur in association with complex malformations. EEC syndrome is a rare form of ectodermal dysplasia. It is an autosomal dominant disorder, inherited as a genetic trait. EEC includes also vesicoureteral reflux, recurrent urinary tract infections, obstruction of the nasolacrimal duct, decreased pigmentation of the hair and skin, missing or abnormal teeth, enamel hypoplasia, absent punctae in the lower eyelids, and photophobia. Occasional, cognitive impairment, kidney anomalies, and conductive hearing loss may appear.

In the development of fetal limbs the free movement itself has a very important role. This is favored by the proximity of fluid in the uterine cavity. The limbs should move freely within each joint. Normal movement assures the normal positions of the hip, knee, elbow, ankle, and wrist joints.

Apparition of abnormal angulation of the ankle joint (ankle clubbing, talipes equinovarus) is frequent, with a prevalence of 1 in 100 live births. The best image is to get a coronal section of the ankle, in which the extended ankle straight along is seen, in a normal spatial relationship with the lower leg. In ankle clubbing, the ankle deviates medially. In the third trimester, especially when the amniotic fluid decreases, a slight subjective angulation of the ankle is common. The key feature for ruling out a true clubbing is the normal shape of the foot. Unilateral ankle clubbing is usually an isolated defect. Bilateral clubbing should be investigated for chromosomal anomalies and genetic syndromes.

The wrist is very flexible and the position of the fingers is also variable. Thus, the examination can find them in a wide variety of positions. In late second trimester and third trimester, the resting position is fisting. The hand can be stimulated to open, showing all four fingers and the thumb. Due to the anatomy of the hand, the thumb is visible in a different plane from the rest of the fingers. Due to this particular context, the diagnosis of abnormal hand position is more difficult than in distal limb.

9. Rationale of screening

All limb anomalies, other than isolated polydactyly, have an increased risk for associated nonskeletal malformations, aneuploidy, stillbirth, neonatal neurodevelopmental delay, and pregnancy termination [43]. This information influences the guiding of evaluation and management, the counseling of parents, and the delivery planning.

The abnormal number of fingers or abnormal position of fingers (Campylodactyly or clinodactyly) is associated with an increased risk of an underlying fetal syndrome.

An image of "sandal gap" anomaly has a weak association with trisomy 21.

The shortening of the humerus seems to have a slightly better predictive value than shortening of the femur in screening for aneuploidies, especially for trisomy 21.

In skeletal dysplasias, the shortening or fracture of long bones is a criterion for diagnosis. The site and the type of shortening are important in establishing an accurate diagnosis (**Table 2**).

Limbs segments	Proximal	Midsegments	Distal segments
Term*	(Humerus/femur)	(Radius and ulna/tibia and Fibula)	(Hand and foot)
Normal (N)**	N	N	N
Rhizomelia	Short	N	N
Mesomelia	N	Short	N
Acromelia	N	N	Short
Micromelia	Short	Short	Short

*The term does not include the malformation, fractures, or absence of the bones.

**Normal measurements is related to an accurate gestational age, ideally established in the first trimester of pregnancy.

Table 2. Terminology in long bone abnormalities.

The upper limb anomalies (and especially radial hypoplasia or aplasia) are phenotypical features of a number of syndromes.

The primary advantage of prenatal diagnosis of upper extremity anomalies is the opportunity for more refined prenatal counseling [44]. Parents are given the chance to discuss their child's diagnosis with a variety of specialists and to receive genetic counseling. For treatable anomalies, a team may be assembled to prepare for postnatal care. Some families will consider pregnancy termination for major untreatable anomalies, and several studies have shown higher rates of pregnancy termination after early prenatal diagnosis of major untreatable anomalies [25, 28, 29, 45].

10. Personal experience

We selected from our archive several suggestive cases of limb abnormalities (**Figures 8–19**):

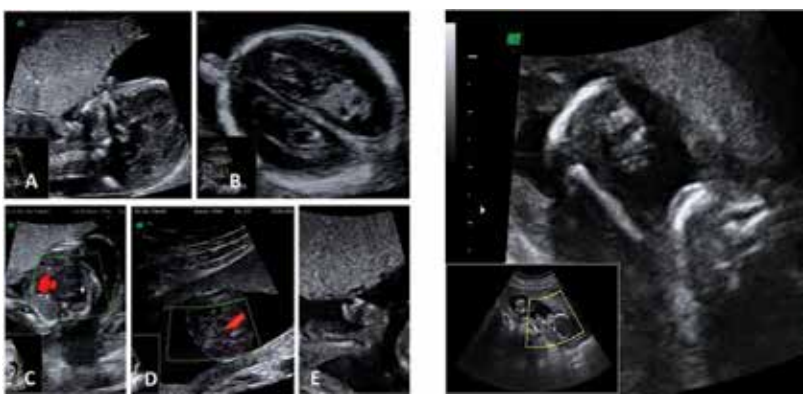

Figure 8. Trisomy 18, diagnosed in early pregnancy. The left image composite shows (A) the abnormal facial profile, the nuchal edema, and the absent nasal bone; (B) multiple choroid plexus cysts; (C) axial plane of the fetal thorax with dextroposition of the fetal heart and presence of the stomach in the thorax, both suggesting diaphragmatic hernia; (D) single umbilical artery crossing lateral to the fetal bladder; and (E) skeletal abnormality and persistent malposition of the fetal arm. In the right-hand image—a detail: the radial aplasia, very characteristic for the syndrome.

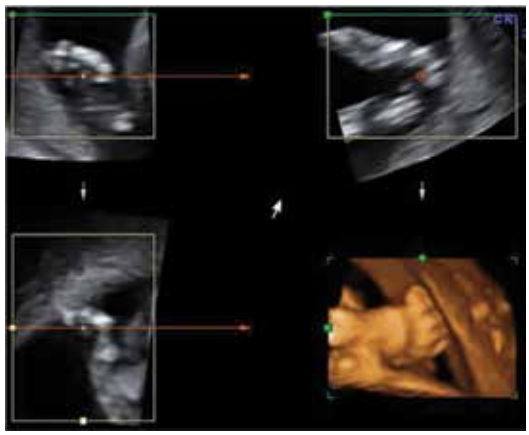

Figure 9. 3D ultrasound images (surface rendering mode), applied in a case of polydactyly. The case was scanned in the first trimester, and the volume was acquired by means of transvaginal scan.

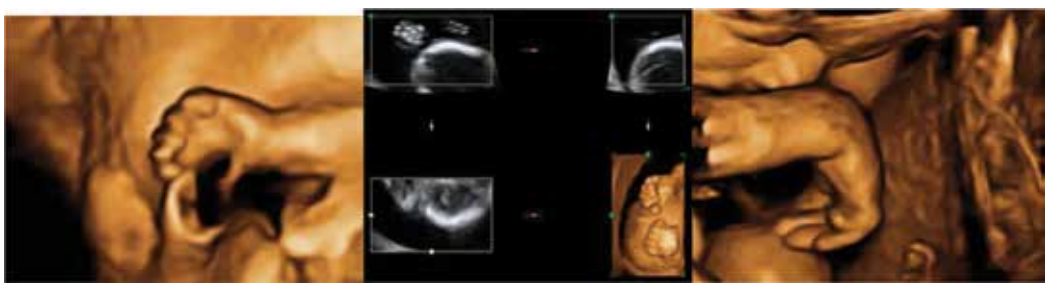

Figure 10. 3D ultrasound images (surface rendering mode), applied in cases of polydactyly in the second trimester; the volume datasets were acquired by means of transabdominal scan. The images were used in the parental counseling process.

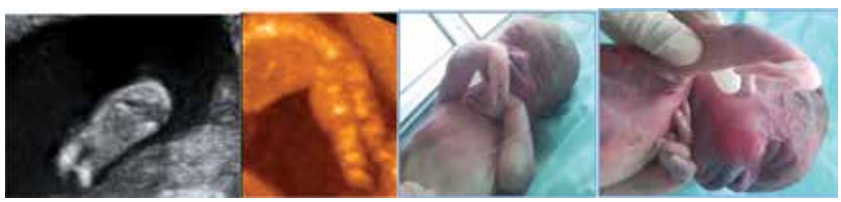

Figure 11. Ectrodactyly: conventional 2D ultrasound, 3D ultrasound skeletal mode, and pathological specimen correlated.

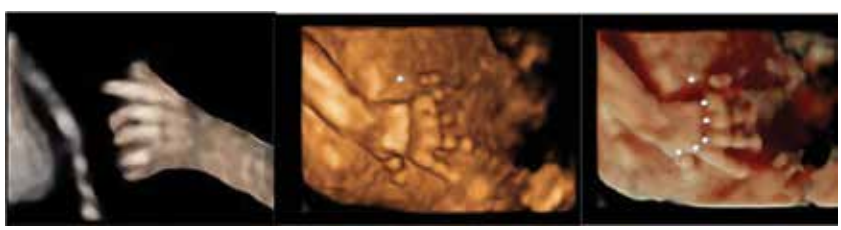

Figure 12. Unilateral postaxial polydactyly type I. Different techniques for acquiring the 3D volume datasets: surface rendering, skeletal mode, and HD life. The case evolved with spontaneous amputation in utero (reproduced with permission of authors) [39].

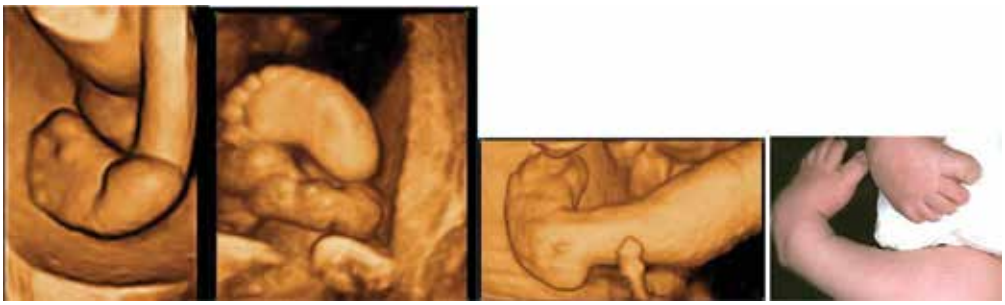

Figure 13. Different cases of clubfoot.

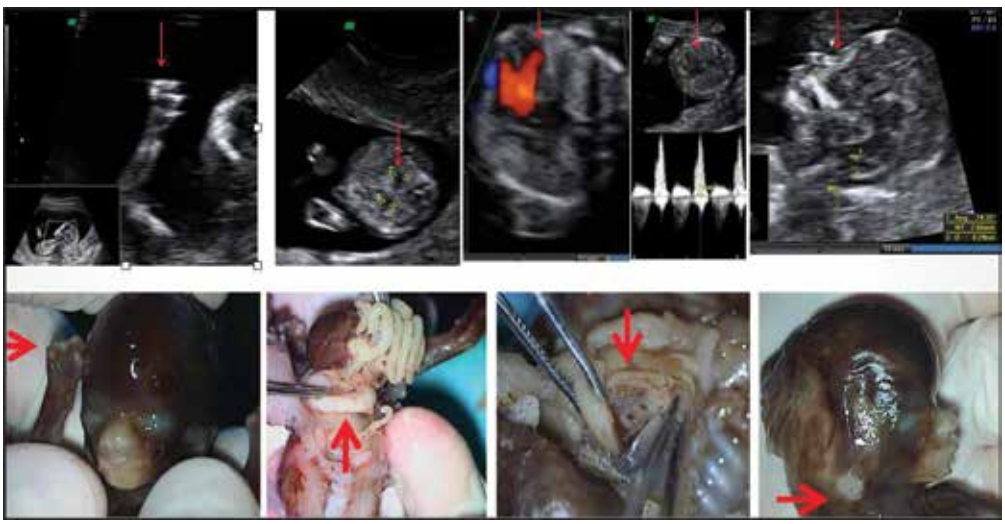

Figure 14. A paucisymptomatic case of trisomy 18, diagnosed in the late first trimester. The upper row demonstrated the ultrasound features: club hand, bilateral pyelectasis, atrioventricular defect, abnormal spectral Doppler at the tricuspid valve interrogation, and unremarkable profile. All these features were compared with the pathological specimen details. The added information were horseshoe kidneys and low set years.

Figure 15. Persistent abnormal hand position. The ultrasound and pathologic data are displayed (the thumb overlapping finger 2). In this case trisomy 13 was diagnosed. The fetus had multiple-associated congenital malformations.

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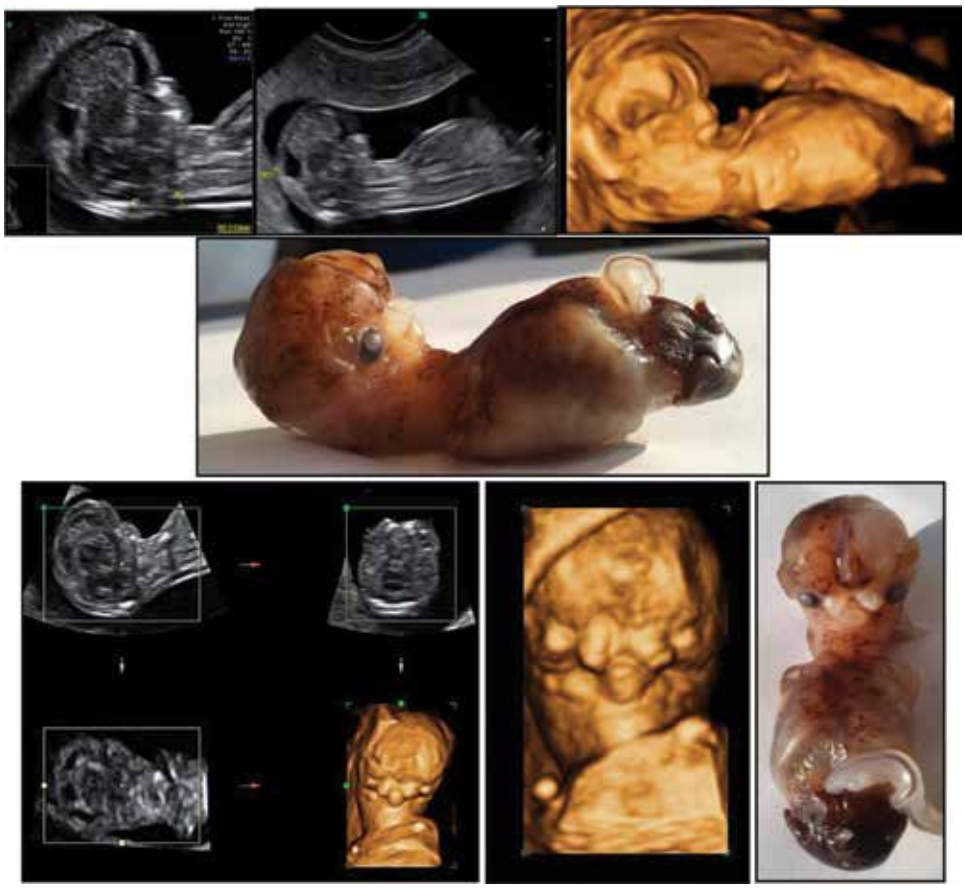

Figure 16. A rare case of complex severe facial malformation, in association with tetraamelia. The 2D conventional ultrasound, the 3D static surface rendering mode, and the pathologic data are correlated.

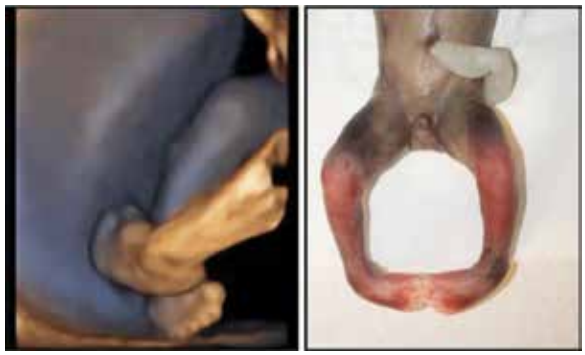

Figure 17. Bilateral clubfoot (genu varum), seen prenatally and post abortion.

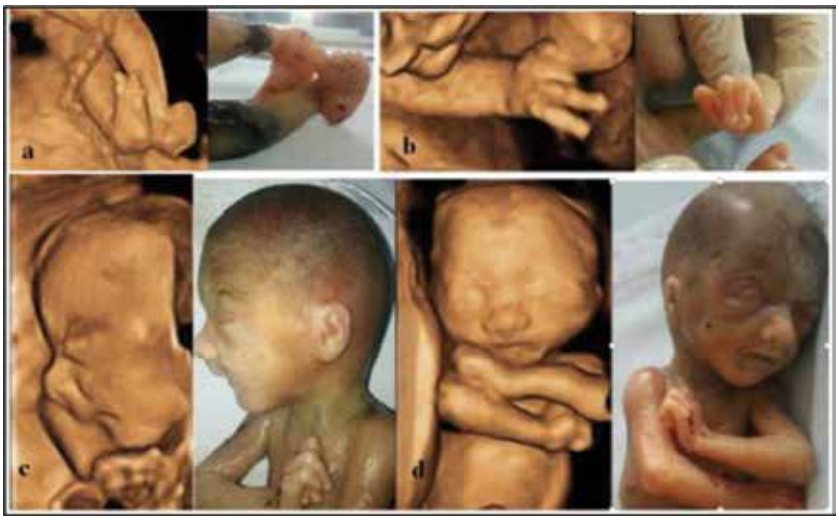

Figure 18. A case of fetal akinesia deformation sequence. The fetus had a complete normal 12 weeks of scan. The mother self-presented for decreased active fetal movements. The matching details obtained by means of volumetric ultrasound and pathology can be observed: Abnormal feet position[a], campylodactyly [b], ulnar deviation of the hands [c], multiple joints contracture (arthrogryposis) [b, c, d], short neck, facial anomalies, hypertelorism, telecanthus, posterior angulation of the ears, and small mouth [c, d].

Figure 19. Abnormal position of the hand, with camptodactyly and overlapping fingers.

Author details

Iuliana Ceausu[1]*, Dominic Iliescu[2], Cristian Poalelungi[1], Cristian Posea[1], Nicolae Bacalbasa[1], Dragos Dobritoiu[1] and Liana Ples[3]

*Address all correspondence to: iulianaceausu2004@yahoo.com

1 Department of Obstetrics–Gynecology, University of Medicine and Pharmacy "Carol Davila," "Dr. I. Cantacuzino" Hospital, Bucharest, Romania

2 Department of Obstetrics–Gynecology, University of Medicine and Pharmacy, Craiova, Romania

3 Department of Obstetrics–Gynecology, University of Medicine and Pharmacy "Carol Davila," "Sf. Ioan" Emergency Hospital, Bucharest, Romania

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Chapter 16

Abnormalities of the Placenta

Roxana Cristina Drăgușin, Maria Șorop-Florea,
Ciprian Laurențiu Pătru, Lucian Zorilă,
Cristian Marinaș, Bogdan Virgiliu Șorop,
Răzvan Căpitănescu and Dominic Gabriel Iliescu

Additional information is available at the end of the chapter

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Abstract

The placenta is considered an important organ that evolves with the implantation of the blastocyst throughout the pregnancy. The placenta has an essential role in functions such as nutrition, excretion, and immunologic and endocrine function. The normal placenta is a round- or oval-shaped organ that attaches to the uterine wall and has roughly 22 cm in diameter and a thickness of about 2–2.5 cm and weighs about one sixth of the fetal birth weight. Thus, a normal development of the placenta is important for an uneventful embryonic and fetal development. Consequently, the placenta abnormalities can range from structural anomalies, to function disorders, to site of implantation abnormalities.

Keywords: placenta, abnormalities, percreta, praevia, choriocarcinoma

1. Introduction

The placenta is a crucial feto-maternal organ with both embryonic (chorion frondosum) and maternal (decidua basalis) components. The development of the placenta begins with the implantation of the blastocyst into the maternal uterus, and it evolves throughout the pregnancy. At the end of the first trimester of pregnancy, the maternal blood supply to the placenta is complete. The placenta has numerous and complex, developmentally essential functions such as nutrition, excretion, and immunologic and endocrine function. The normal placenta is a round- or oval-shaped organ that attaches to the uterine wall and has roughly 22 cm in diameter. The placenta thickness is about 2–2.5 cm and weighs about one sixth of the fetal birth weight [1]. Thus, a normal development of the placenta is important for an uneventful

embryonic and fetal development. Consequently, the placenta abnormalities can range from structural anomalies, to function disorders, to site of implantation abnormalities [1].

2. Placenta accreta, placenta increta, and placenta percreta

Abnormal placental implantation (accreta, increta, and percreta) is described using a general clinical term, respectively, morbidly adherent placenta (MAP) [2] or "abnormal invasive placenta" (AIP). If not diagnosed before delivery, MAP can lead to catastrophic postpartum hemorrhage, with life-threatening complications. Risk factors include increased maternal age, previous Cesarean delivery or myomectomy, multiparity, and previous intrauterine maneuvers (such as hysteroscopy and multiple dilatation and curettage [3]). The reported incidence ranges from 1:2500–1:7000 pregnancy in 2007 [4] to 1:533 deliveries in 2017 [3]. When the placental villi attach to the myometrium rather than the decidua, it is called placenta accreta; when the chorionic villi penetrate the myometrium, it is called placenta increta (e.g., **Figure 1**), whereas placenta percreta extends into the uterine serosa or adjacent organs (e.g., **Figure 2**). Placenta increta and placenta percreta are rare disorders, which represent <20% of the cases of placenta accreta [5]. These varieties can lead to more severe maternal complications (60% maternal morbidity [6], 7–10% maternal mortality [7]). The most important measure in decreasing these potentially fatal complications is the prenatal ultrasound diagnosis. In many cases, the patient's history is highly relevant. The key feature for early first-trimester diagnosis of MAP is an abnormal neovascularization in the ill-defined placental-myometrial junction detected in a color or power Doppler (2D or 3D) image [8], similar to the flow observed in an invasive mole, arteriovenous malformation, or retained products of conception. Other aspects can include focal or diffuse irregular lacunar lakes with turbulent flow typified by a high velocity (PSV, >15 cm/s) [9]. A higher number of lakes increase the risk of a presenting placenta accreta. The complete loss or disruption of the echolucent myometrial zone between the placenta and bladder is highly suggestive for MAP. When using color Doppler examination, the sensitivity and specificity of

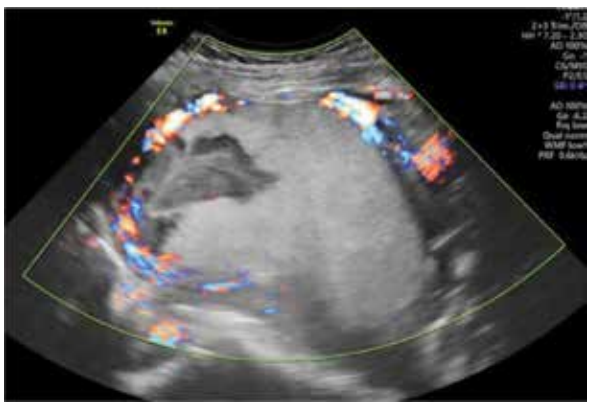

Figure 1. Ultrasound color Doppler image of a case of placenta increta diagnosed in the early second trimester of pregnancy, associated with fetal demise. The surgical termination of pregnancy was performed under laparoscopic guidance, with no complications.

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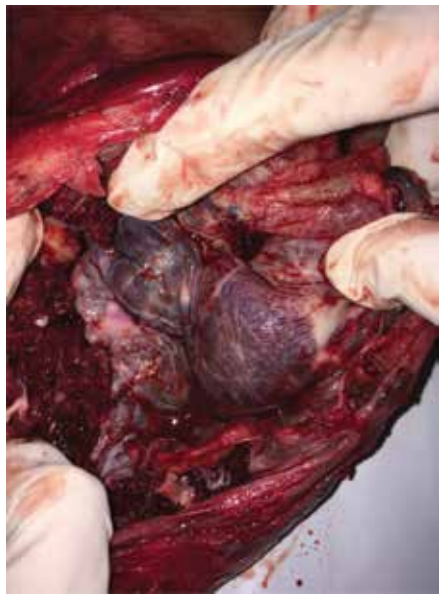

Figure 2. Image of the uterus occupied by placenta percreta after postpartum hysterectomy due to important hemorrhagic complications.

the ultrasound scan can be as high as 80–90% and, respectively, 98% [10]. Magnetic resonance imaging can add accuracy to MAP diagnosis when assessing the lateral extension and penetration depth of the placenta. However, a majority of cases of MAP are diagnosed during the third stage of labor or during Cesarean section [9], and about 21% of cases of MAP are responsible for peripartum hysterectomy [11]. Overall, in suspected cases with this type of placental pathology, the best approach includes a multidisciplinary team with early planning for antepartum and intrapartum management, preferable than late planning [12]. Some groups recommend delivery at 34–35 weeks by performing preterm Cesarean section with the placenta left in situ [13]. Other several adjuvant techniques have been proposed, as methotrexate treatment and/or placement of internal iliac artery balloon catheters, for occlusion and/or arterial embolization [14]. The goal of the conservative approach of MAP is the attempt of gradual resorption of the placenta or delayed delivery of the placenta [15]. A good prognosis of MAP pathology is feasible, with improving maternal and fetal outcome, if diagnosis is timely and there is adequate preparation of the delivery. These are essential keys in the management of such cases [16].

3. Placenta praevia

This type of obstetric pathology was firstly described in 1685 by Paul Portal, a French physician [17], as a major cause of hemorrhage, with a potentially life threat to the mother and the fetus. It was defined as the placenta that overlies entirely or partially the internal cervical os of the uterus. In complete praevia, the internal os is completely covered by the placenta (e.g., **Figure 3**). Placenta praevia is divided into *partial praevia* (a portion of the internal os is covered by the placenta),

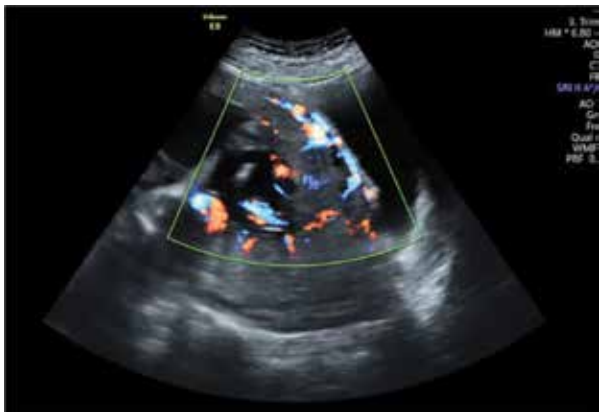

Figure 3. Ultrasound image of complete placenta praevia percreta in a patient with a previous Cesarean section (color Doppler examination showing the penetration of the placenta into the bladder).

marginal praevia or praevia maginalis (the edge of the placenta extends to the edge of the cervical os), and *low-lying placenta* defined as within 2 cm of the cervical os, without covering it [2]. The reported incidence of the condition is 1 in 200–250 pregnancies [1]. Among the risk factors, there are prior Caesarean delivery, previous abortion, prior intrauterine surgery, smoking, multifetal gestation, increase in parity, and increased maternal age. The risk for placenta praevia is 12 times higher in women with history of placenta praevia in a previous pregnancy. Some studies demonstrated an increased rate of placental insufficiency in women with placenta praevia [18]. However, in a retrospective study of women with a complete or partial praevia, no fetal growth restriction was diagnosed [19]. The placenta location must be recorded during the ultrasound scan in the first- and early second-trimester pregnancies. If the placenta is significantly low, an additional ultrasound scan at the beginning of the third trimester allows the final diagnosis. Patients should be aware that nothing can be done to prevent placenta praevia. The appropriate delivery in placenta praevia is by Cesarean section, as dilation of the cervix causes separation of the placenta, leading to bleeding from the opened vessels. Still, in cases of a low-lying placenta, as the bleeding morbidity has proven to be limited, a vaginal delivery remains an option [1]. Every hospital must have a suitable protocol or algorithm for the management of placenta praevia, as this is a condition with high maternal and fetal morbidity and mortality [20].

4. Vasa praevia

Vasa praevia is a rare condition, in which the fetal blood vessels traverse the lower uterine segment in advance of the presenting part, unsupported by either the umbilical cord or placental tissue (e.g., **Figure 4**). This pathologic structure can cause fetal blood loss, with significant neonatal morbidity or death in case of spontaneous rupture of membranes or amniotomy. Also, fetal heart decelerations and bradycardia can occur if compression of these vessels appears, due to the presenting part [20]. This condition is encountered in 1:2500–5000 pregnancies [21]. The prenatal diagnosis is made with a high accuracy by ultrasound, with a sensitivity of 100% and a specificity

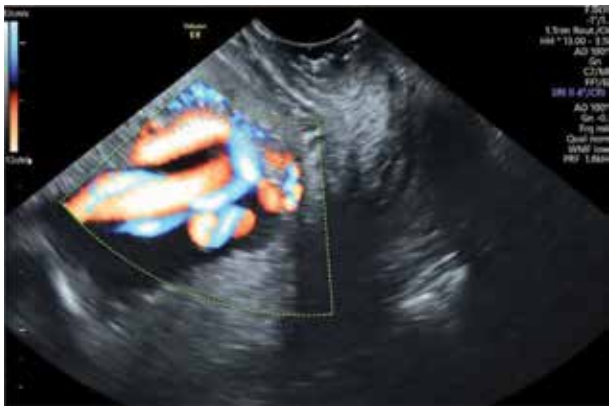

Figure 4. Ultrasound color Doppler image showing vasa praevia.

of 99–99.8%, if transvaginal color Doppler examination is used [20]. If unrecognized before the onset of labor, the fetal mortality rate ranges between 22.5 and 100% [22]. To improve the prenatal diagnosis, the prenatal ultrasound form should include a standard evaluation of the umbilical cord insertion site. However, some researchers demonstrated that general screening for vasa praevia is not cost-effective and is not advised [23]. There are recent reports of two main associations: velamentous insertions and vessels crossing between lobes in succenturiate or bilobate placentas [24]. Besides these strong risk factors, others include placenta praevia and conception by assisted reproductive technologies. If diagnosed with vasa praevia, elective Cesarean delivery should be proposed at 35–36 weeks [25]. Others prefer a scheduled Cesarean section at 37–38 weeks or when fetal lung maturation has been confirmed [26, 27]. The Canadian guidelines for the management of prenatally diagnosed vasa praevia include elective Cesarean section prior to the onset of labor. Also, as premature delivery is most likely, consideration should be given to administration of corticosteroids at 28–32 weeks (to promote fetal lung maturation), and hospitalization at about 30–32 weeks is advisable. Continuous electronic fetal heart rate monitoring and a rapid biochemical test for fetal hemoglobin can be considered, and if any of the above tests are abnormal, emergency Cesarean section should be performed [28]. Overall, physicians must be vigilant whenever amniotomy is performed as not all cases of vasa praevia are diagnosed antenatally. Any case of suspicion should benefit of immediate delivery, to avoid fetal shock or demise [22].

5. Placenta variants

5.1. Bilobed placenta

Bilobed placenta (placenta bilobate, bipartite placenta, placenta duplex) is a placental morphological anomaly that refers to a placenta separated into two roughly equal-sized lobes, separated by membranes (e.g., **Figure 5**). If there are more than two lobes, then the placenta is called a multilobed placenta. The estimated incidence is 2–8% of placentas [29]. The pathology of this type of placenta is considered to be a result of a localized placental atrophy, as a result of poor decidualization or vascularization of a part of the uterus (dynamic placentation theory) [30]. Also, the

genetic origin has been considered, as the risk of a bipartite placenta is greater in a woman with already a history of bipartite placenta. Frequent association with a velamentous insertion of the cord is reported, as the umbilical cord may insert in either lobe or in between the lobes. The diagnosis of bilobed placenta is made by ultrasound assessment when two separate placental discs of nearly equal size are noted. In cases of bilobed placenta, there is no increased risk of fetal anomalies. However, this type of placental abnormality can be associated with first-trimester bleeding, polyhydramnios, abruption, and retained placenta. Also, it can increase the incidence of vasa praevia with a high incidence of hemorrhage. Taking all these risk factors into consideration, a bilobed placenta does not have any unfavorable short-term or long-term pregnancy outcomes.

5.2. Circumvallate placenta

Circumvallate placenta represents one type of an extrachorial placenta, defined as an annularly shaped placenta with raised edges composed of a double fold of chorion, amnion, degenerated decidua, and fibrin deposits [1]. Pathologically, the basal plate is larger than the chorion frondosum [31]. The incidence of circumvallate placenta has been reported in 0.5–18% of placentae examined after delivery [32, 33]. There is an increased risk of vaginal bleeding at the beginning of the first trimester and also a risk of premature rupture of the membranes, preterm delivery, placental insufficiency, and placental abruption [34, 35]. The pregnancy outcome can be very poor. Prenatally, during the ultrasound scan, circumvallate placenta can be suspected as a peripheral rim of chorionic tissue appearing as an echodense ridge (placental shelf), with a "tire sign" appearance on the 3D exam [36]. However, the diagnosis is made most often after delivery, by inspection of the placenta. If circumvallate placenta is suspected antenatally, the pregnancy should be classified as a high-risk pregnancy, and special precautions should be considered, to prevent preterm labor. A high association between circumvallate placenta and a single umbilical artery [37] and no relationship between the amniotic band syndrome or limb body wall complex and circumvallate placenta have been reported [31]. Thus, the condition carries no risk of fetal deformity. Circummarginate placenta is another type of extrachorial placenta, with no clinical significance, where the transition from membranous to villous chorion is flat [1].

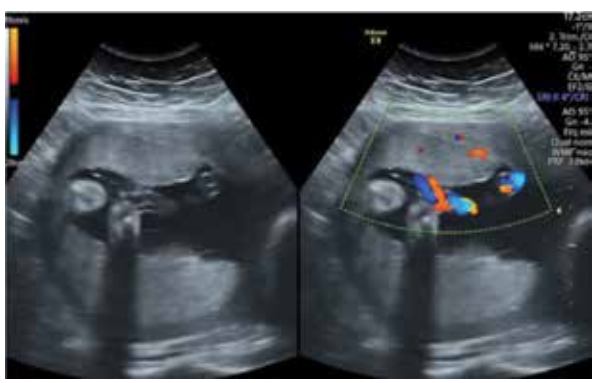

Figure 5. Ultrasound image (gray scale and color Doppler) of a bilobed placenta, showing the two lobes of the placenta and the umbilical cord insertion in one of the lobes.

5.3. Placenta membranacea

Placenta membranacea is an extremely uncommon variation in placental morphology, in which the placenta develops as a thin structure, occupying the entire periphery of the chorion. This type of placental abnormality is classified as *diffuse placenta membranacea* (with chorionic villi covering the fetal membranes completely) and *partial placenta membranacea* [1]. The estimated incidence is 1:20,000–1:40,000 pregnancies [38], with an association of abnormal placental adherence in up to 30% of cases [38]. The ultrasound assessment is useful, but being an extremely rare variant, there are no reports of its sensibility and specificity. The common symptom of this type of placental pathology is vaginal bleeding in the second or third trimester (often painless) or during labor. Complications such as antepartum hemorrhage, second-trimester miscarriages, fetal demise, and postpartum hemorrhage have been reported in pregnancy with placenta membranacea [39]. Placenta praevia and placenta accrete or intrauterine growth restriction can also be associated with this condition, worsening the maternal and fetal prognosis [30, 40].

5.4. Succenturiate placenta

In succenturiate placenta a smaller accessory placental lobe develops in the membranes, apart from the main disc of the placenta. There can be more than one succenturiate lobe, and it is a smaller variant of a bilobed placenta. In placenta supuria the communicating membranes do not have vessels [1]. As risk factors, advanced maternal age, in vitro fertilization, primiparity, proteinuria in the first trimester of pregnancy, and implantation over leiomyomas or in areas of previous surgery have been cited in the literature [1]. This condition can be diagnosed in 5% of pregnancies, by ultrasound scan as a smaller separate lobe similar to the main placental lobe. Caution should be considered in identifying any connecting vessels, especially vasa praevia. Differential diagnosis may also include focal myometrial contraction and iso-echoic hematoma from a placental abruption. Complications may appear as there is an increased risk of vasa praevia and postpartum hemorrhage, due to retained placental tissue.

6. Chronic intervillositis

Chronic intervillositis, also known as massive chronic intervillositis or chronic histiocytic intervillositis, is an exceptionally rare placental anomaly, defined by inflammatory placental lesions [1], mainly diffuse histiocytic infiltrate in intervillous space [41]. Among risk factors, maternal diabetes, maternal hypertension, intravenous drug abuse, preeclampsia, and systemic lupus erythematosus are mentioned. This condition has a perinatal mortality of 80%, due to an associated risk of recurrent spontaneous abortion [42], fetal growth restriction [43], and fetal death. The recurrence rate is considered to be above 60%.

7. Placental mesenchymal dysplasia

Placental mesenchymal dysplasia is a rare vascular anomaly of the placenta characterized by mesenchymal stem villous hyperplasia [1]. The ultrasound diagnosis includes placentomegaly

and a "grape-like" placental appearance, both mistaken clinically and macroscopically for a partial hydatidiform molar pregnancy [44]. The differential diagnosis is important, because it may result in termination of pregnancy. Still, the final diagnosis is made by means of placental histology. The disorder also has been reported to be associated with both intrauterine growth restriction (IUGR) and fetal death [45]. In many cases, the cause of fetal death is fetal vascular obstructive pathology, causing longstanding, severe fetal hypoxia, due to chorionic vessel thrombosis [46]. Beckwith-Wiedemann syndrome has been linked to placental mesenchymal dysplasia. Invasive testing is advisable to confirm a normal karyotype and exclude partial molar pregnancy [47].

8. Diabetic placenta

The placenta represents a natural selective barrier between maternal and fetal blood circulations, and it is highly sensitive to the hyperglycemic environment. Consequently, adaptive changes of the structure and function appear. The histological findings are typical: villous immaturity, villous fibrinoid necrosis, chorioangiosis, and increased angiogenesis [48]. Chronic fetal hypoxia can occur due to placental changes associated with inflammation and oxidative stress. Potential intrauterine complications are growth restriction, premature labor, preeclampsia, risk of oxygen deprivation, low neonate body temperature, low blood sugar levels at birth, and stillbirth [49].

9. Placental chorioangioma

Chorioangioma is a benign vascular tumor, found in approximately 1% of all pregnancies [50]. It was firstly described in 1798 by Clarke [51]. This pathology is a malformation of the primitive angioblastic tissue of the placenta perfused by the fetal circulation. It is rarely clinically significant and is usually discovered incidentally. Most of the chorioangiomas have small

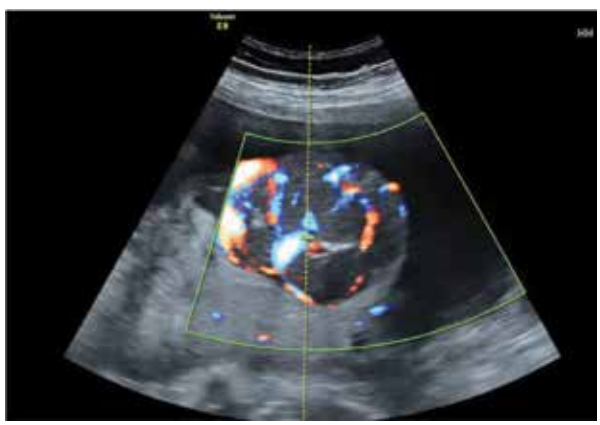

Figure 6. Ultrasound color Doppler image of a chorioangioma diagnosed in the second trimester of pregnancy.

dimensions. However, large chorioangiomas have been associated with a range of fetal conditions (fetal anemia, thrombocytopenia, hydrops, hydramnios, intrauterine growth retardation), including prematurity and stillbirth [1]. Also, large tumors can degenerate in necrosis, calcification, hyalinization, or myxomatous degeneration. Typically, on the ultrasound, a chorioangioma is located near the insertion of the cord into the amniotic cavity, as a hypoechoic, rounded mass with usually anechoic cystic areas with low resistance pulsatile flow (e.g., **Figure 6**) [52]. In rare cases the tumors are pedunculated. As differential diagnosis, subamniotic hematoma, partial hydatidiform mole, submucosal uterine fibroid, placenta teratoma, and atypical placental venous lake should be considered [53].

10. Placental infections

Most infections arise from several infective agents that may cross into the placenta from the maternal circulation [1]. These kinds of infections can be associated with a variety of developmental effects, from virtually insignificant to major maternal and fetal developmental complications. Placental examination by a pathologist should be considered in every case of preterm delivery, fetal tachycardia, maternal signs of endomyometritis (e.g., fever, uterine tenderness, leukocytosis, tachycardia), neonatal intensive care unit admission, malodorous placenta, retained placenta or postpartum hemorrhage, and stillbirth [54]. However, a specific infectious agent is rarely diagnosed by placental examination. Still, the placental histology may confirm the clinical diagnosis of an infectious etiology in some cases of nonreassuring fetal heart rate patterns or neonatal morbidity/mortality. The most common placental infections are:

- Malaria: characterized by the pigment-laden maternal red blood cells and macrophages aggregate in the intervillous space [55].
- Cytomegalovirus is the most common congenital viral infection, mostly subclinical at birth in cases of intrauterine growth restriction and stillbirths [56]. The classic histopathological finding in the placenta includes viral inclusions. These may be detected only if using immunohistochemistry techniques.
- Herpes simplex virus: the histopathological features of the placenta may include lymphoplasmacytic villitis. The demonstration of the virus by immunohistochemistry or by molecular techniques allows the diagnosis, since the above findings are nonspecific [57].
- *Listeria monocytogenes* is characterized by acute villitis, with abscess formation and fetal central nervous system damage [58].
- Streptococcal infection: both group B and group A streptococci can produce placental infection.
- Syphilis: *Treponema pallidum* infections determine a chronic villitis (plasma cells, mixed acute and chronic infiltrate).

- Toxoplasmosis implies a risk of placental colonization, depending on the volume of uteroplacental blood flow, on the maternal immunocompetence, and parasitemia. Placental infection, described by granulomatous villitis, cysts, plasma cell deciduitis, villous sclerosis, and chorionic vascular thrombosis, is more common with advancing gestational age at the time of maternal parasitemia [59].
- *Chlamydia psittaci*: can infect the placenta and can cause significant feto-maternal morbidity and mortality by an intense, acute intervillositis, perivillous fibrin deposition with villous necrosis, and large irregular basophilic intracytoplasmic inclusions within the syncytiotrophoblast [60, 61].

11. Placental membranes

The fetal membranes (chorion, amnion) represent the interface between the fetal graft and the maternal host [1]. Infection may also pass the fetal membranes, especially in the area overlying the cervix. It provides direct access to pathogens, ascending from the vagina and the cervix [62]. Less commonly, infectious agents enter the uterus as a result of invasive procedures (e.g., amniocentesis, fetoscopy, cordocentesis, and chorionic villus sampling) or via the fallopian tubes from an infectious process in the peritoneal cavity.

11.1. Chorioamnionitis

Chorioamnionitis is the most frequent histopathological result of ascending transcervical infection and occurs with both symptomatic and silent infections [63]. The histologic diagnosis of chorioamnionitis is allowed if the inflammatory infiltrate involves either or both the chorion and the amnion. The acute chorioamnionitis is more common than the chronic form [64]. As clinical symptoms, chorioamnionitis is characterized by maternal fever, tachycardia, uterine tenderness, or foul-smelling amniotic fluid. However, cultures of the amniotic fluid or membranes fail to document the bacterial infection in 25–30% of placentas with histologic chorioamnionitis [65]. The infection of the membranes is often polymicrobial, with the most commonly seen bacteria: *Streptococcus* sp., *Escherichia coli*, *Ureaplasma* sp., *Fusobacterium* sp., *Mycoplasma* sp., and anaerobes [63]. The correct diagnosis and treatment of chorioamnionitis are paramount, as it is an important cause of perinatal and maternal morbidity and mortality [66]. The major pathological consequences of chorioamnionitis may include premature rupture of membranes, preterm labor, prolonged labor, premature delivery, fetal and newborn infection, and endomyometritis.

12. Gestational trophoblastic disease.

12.1. Hydatidiform mole

Hydatidiform mole (HM), called also a *molar pregnancy*, represents a subcategory of gestational trophoblastic disease. The origin of the entity is the gestational tissue. The character

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of HM is usually benign, but it has a known potential to become malignant and invasive. The incidence of a HM is 1:1000–2000 [67]. Risk factors include extremes of maternal age (greater than 35 years old and less than 20 years old), a previous molar pregnancy, women with previous spontaneous abortions or infertility, dietary factors, and smoking [68]. The HM can be a *complete mole*, with the absence of the fetus, or a *partial mole* with an abnormal fetus or a fetal demise; rarely, a mole coexists with a normal pregnancy. In complete HM, 90% of cases the karyotype are 46XX diploid, while in partial HM, the karyotype is usually triploid 69XX [1]. The histopathological event of HM is considered to be a proliferation of the villous trophoblast, accompanied by swelling of the chorionic villi, resulting in high levels of human chorionic gonadotrophin (hCG) production (e.g., **Figure 7**) [68]. The location of the HM is the uterine cavity, with exceptionally rare cases located in the fallopian tubes or ovaries. Clinically, the most common symptom is the vaginal bleeding in the first trimester. Sometimes an association of hyperemesis (severe nausea and vomiting) or passage of vaginal tissue described as "grape-like clusters" or "vesicles" can be encountered. If not early diagnosed, other significant complications may appear, such as hyperthyroidism, including tachycardia and tremors and preeclampsia. Usually, on a physical exam, there is a uterine size discrepancy compared with the amenorrhea period, the uterus being larger in complete mole and smaller in partial mole [69]. The ultrasound exam finding is a heterogeneous mass in the uterine cavity, with multiple anechoic spaces

Figure 7. Image of post-hysterectomy uterus invaded by a hydatidiform mole in a 48-year-old patient.

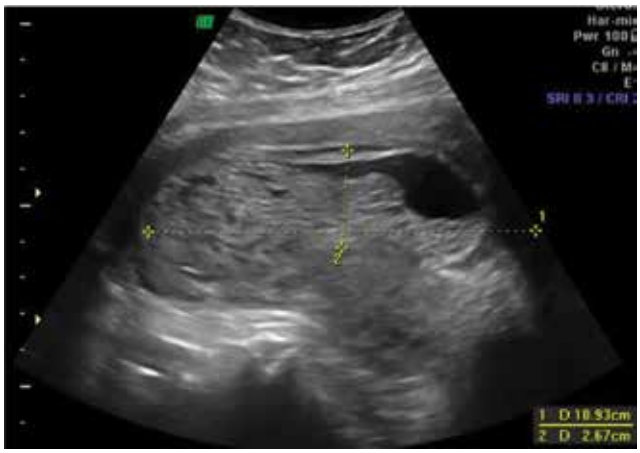

Figure 8. Ultrasound image of the case of hydatidiform mole.

(e.g., **Figure 8**). The "snow storm" or "bunch of grapes" appearance is no longer seen with nowadays equipment. In complete moles the embryo is absent, and no amniotic fluid is present [70]. In the first trimester, the diagnosis of complete mole can be difficult; bilateral theca lutein cyst may be seen [71]. In partial mole, the molar placenta may not always be seen; the amniotic cavity is either empty or contains a well-formed but growth-retarded fetus, either dead or alive, with hydropic degeneration of fetal parts [72]. Occasionally, the differential diagnosis between partial moles, complete moles, and missed abortion [73] may be difficult. In molar pregnancy the first step after the diagnosis is the chest X-ray to determine metastasis. Computer tomography and magnetic resonance imaging can add valuable additional information for the final diagnosis. After careful counseling of the patient, including genetic testing, the best treatment option remains suction and curettage for evacuation. Hysterectomy, however, is an option if preservation of the fertility is not necessary. When hCG levels remain elevated after a proper evacuation of the uterine cavity, a gynecology oncology consultation is required to guide the therapy and consider chemotherapy [68].

12.2. Choriocarcinoma

Choriocarcinoma is a rare aggressive tumor, with highly malignant potential and widespread dissemination metastases [74]. It is considered part of the spectrum of gestational trophoblastic disease and is called *gestational* choriocarcinoma. The high mortality is due to lack of early diagnosis and appropriate chemotherapy [75]. Approximately 5% of cases of complete HM can be complicated with choriocarcinoma. Only about half the cases of choriocarcinoma arise from a complete HM. The imaging diagnosis of choriocarcinoma includes a discrete, central, infiltrative mass enlarging the uterus, with a possible invasion of the myometrium and beyond (e.g., **Figures 9** and **10**). The ovaries may be enlarged, due to cysts secondary to increased levels of hCG [76]. If choriocarcinoma arises from a complete HM, the prognosis is usually favorable after proper chemotherapy. On the contrary, other cases of choriocarcinoma have a less favorable prognosis.

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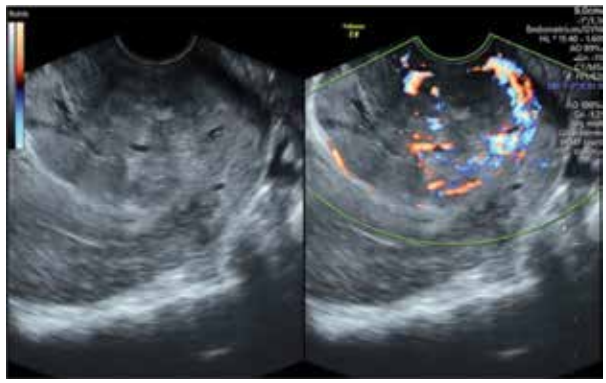

Figure 9. Ultrasound image in gray and color Doppler scale showing a rare case of choriocarcinoma of the cervix with intense vascularization.

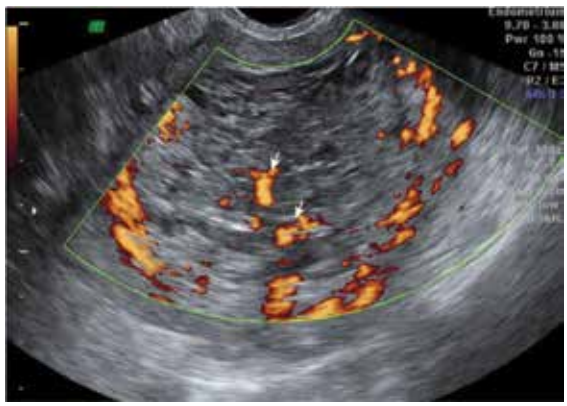

Figure 10. Ultrasound image in gray and color Doppler scale showing a case of choriocarcinoma with invasion of the myometrium and beyond.

Author details

Roxana Cristina Drăgușin[1]*, Maria Șorop-Florea[1], Ciprian Laurențiu Pătru[1], Lucian Zorilă[1], Cristian Marinaș[2], Bogdan Virgiliu Șorop[3], Răzvan Căpitănescu[1] and Dominic Gabriel Iliescu[1]

*Address all correspondence to: roxy_dimieru@yahoo.com

1 Department of Obstetrics and Gynaecology, University of Medicine and Pharmacy, Craiova, Romania

2 Department of Anatomy, University of Medicine and Pharmacy, Craiova, Romania

3 Department of Obstetrics and Gynaecology, University of Medicine and Pharmacy, Timișoara, Romania

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Chapter 17

Abnormalities of the Umbilical Cord

Sidonia Catalina Vrabie, Liliana Novac,
Maria Magdalena Manolea,
Lorena Anda Dijmarescu, Marius Novac and
Mirela Anisoara Siminel

Additional information is available at the end of the chapter

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Abstract

Abnormalities of the umbilical cord, related to morphology, placental insertion, number of vessels and primary tumors, can influence the perinatal outcome and may be associated with other fetal anomalies and aneuploidies. The chapter investigates the most important congenital anomalies of this structure. Single umbilical artery appears to be associated with ventricular septal defects and conotruncal anomalies, hydronephrosis, dysplastic kidneys, esophageal atresia, spina bifida, holoprosencephaly, diaphragmatic hernia, and cystic hygromas. Velamentous insertion of the cord can be associated with trisomy 21, spina bifida, ventricular septal defects, and esophageal atresia. A hypoplastic umbilical artery has an artery-to-artery diameter difference of more than 50%; described anomalies include trisomy 21, polyhydramnios, congenital heart disease, and fetal growth restriction. Pseudocysts are more common than true cysts, and they are strongly associated with chromosomal defects and other congenital anomalies, especially omphalocele, hydrops, and trisomy 18. Other benign masses are teratomas, angiomyxomas, and patent urachus. Alterations in morphology and ultrastructure of the umbilical cord should extend the investigation, since there are associations with chromosomal anomalies.

Keywords: umbilical cord, prenatal ultrasound, congenital anomalies, fetal malformations, outcome

1. Introduction

Umbilical cord makes stable interconnection between fetal well-being and placenta at the fetomaternal interface level. The prenatal ultrasonographic assessment of the umbilical cord offers the possibility to investigate the morphologic characteristics during fetal life, from early to late gestation.

The umbilical cord structure can be demonstrated by conventional real-time ultrasound and the umbilical blood flow patterns can be analyzed by color (power) and pulsed Doppler ultrasound, which relate to its functionality [1]. Second trimester scan is able to assess four characteristics of the umbilical cord: measurement of umbilical cord area, evaluation of the number of vessels, assessment of placental umbilical cord insertion site, and determination of the coiling pattern [2].

Abnormalities of the umbilical cord related to morphology, placental insertion, number of vessels, and primary tumors can influence the perinatal outcome and may be associated with other fetal anomalies and aneuploidies. Many of these conditions are being diagnosed in utero as prenatal ultrasound becomes more sophisticated nowadays.

Using ultrasound, we can depict various congenital abnormalities of the umbilical cord, including cysts, pseudocysts, umbilical vein varix, persistent right umbilical vein, angiomyxomas, aneurysm, single umbilical artery (SUA), velamentous insertion, and teratomas.

2. Abnormal number of vessels

Sometimes, during pregnancy, changes in the number of umbilical vessels may occur. Abnormal number of umbilical cord vessels includes: two-vessel cord (single umbilical artery), four-vessel cord (two veins and two arteries, one vein and three arteries), five and more vessels cord (numerous variations in conjoined twins), umbilical cord that does not keep the same number of vessels at the fetal and placental extremity [3].

2.1. Single umbilical artery

It seems that the first descriptions of the single umbilical artery were made in 1543 by Vesalius in De Humani Corporis [4]. It may be diagnosed with the finding of two vessels on a cross-section of the cord or a vessel seen on only one side of the fetal bladder. These anomalies appear to be more common when the left umbilical artery is absent and may be associated with aneuploid fetuses and renal anomalies in euploid fetuses. Atresia, aplasia, or agenesis of one artery can lead to single umbilical artery syndrome [5].

Single umbilical artery (SUA) is the most common abnormality of the umbilical cord.

There are three theories about the absence of umbilical artery pathogenesis: (1) primary agenesis of an umbilical artery; (2) atrophy or secondary atresia of the previously normally developed umbilical artery; and (3) persistence of the original allantoic artery of the body stalk [6]. It is suggested that from the embryological point of view, the second theory would be a reasonable explanation [7].

In single umbilical artery pregnancies, chromosomal abnormalities were found in 8–11% of fetuses, more commonly trisomy 13 and 18 and less frequently trisomy 21 [8], intrauterine growth restriction (IUGR), preterm birth, placental anomalies, and perinatal mortality [9, 10].

In rare cases, both umbilical arteries are missing and the one arterial vessel is, in fact, a persistent vitelline artery, which branches off the abdominal aorta. [11]. This persistent vitelline artery appears to be associated with serious developmental defects and was classified as type II single umbilical artery (type II SUA) by Blackburn and Cooley. This anomaly accounts for 1.5% cases of single umbilical artery [12]. According to the same authors, the most common form of single umbilical artery (98%) is type I that has one artery and one vein (left), whereas type II SUA has a frequency of 1.5%. Very rare forms are type III with one artery and two veins (left and persistent right umbilical vein) and type IV with one artery and one vein (right).

There is an increased incidence of severe malformations associated with type II SUA with the implication of the caudal body wall (sirenomelia, omphalocele-exstrophy-imperforate anus-spinal defects) and urorectal like exstrophy of the bladder, anal atresia, or urogenital agenesis [13].

Among pregnancies with single umbilical artery associated with various malformations, two-thirds of deaths occur before birth. Regarding the other third of postnatal deaths, an increased incidence of fetal growth restriction and small placental size was found [14].

If no additional chromosomal or structural abnormalities occur, single umbilical artery is defined as an isolated SUA (iSUA) [10], and more than 90% of cases with SUA exhibit an isolated anomaly but without increasing the risk of chromosomal abnormalities [15]. Regarding adverse pregnancy outcomes and perinatal complications, studies show discordant results. A meta-analysis suggests that there is no significant association between iSUA and pregnancy outcomes [16, 17], while another meta-analysis suggests that iSUA is associated with a significant increase in adverse perinatal outcomes [18].

Single umbilical artery can be diagnosed in the first trimester using color Doppler and high-definition ultrasound with a low pulse repetition frequency (PRF) and a high color gain. Visualization of the umbilical arteries is preferable at the level of the fetal urinary bladder (**Figure 1**) by demonstrating the cord's perivesical course [19].

In conclusion, the easiest way to assess the number of arteries by ultrasound is by identifying the intra-abdominal portion of the umbilical artery alongside the bladder with color Doppler and/or by visualizing the cross-section of a free-floating loop of umbilical cord (**Figure 2**) [20]. In a 1991 study, Nyberg's group concluded that prenatal sonography alone was reliable in detecting any associated anomalies. They also recommended no management modification in cases with no concurrent anomalies [7]. The visualization of that anomaly should prompt a detailed sonographic assessment of the cardiovascular and genitourinary systems [3].

Fetal anomalies most commonly associated with single umbilical artery include several anomalies like ventricular septal defects, hydronephrosis, cleft lip, ventral wall defects, esophageal atresia, spina bifida, hydrocephaly, holoprosencephaly, diaphragmatic hernia, cystic hygromas, and polydactyly or syndactyly. In these cases, fetal echocardiography and karyotype analysis should be considered. Usually, there are no specific fetal abnormalities to be associated with the single umbilical artery. In fact, the single umbilical artery is often found in cases with healthy neonates, with a normal size and development at term. Although, to be sure that the infant has no hidden anomalies, the pediatrician should be notified of its existence to

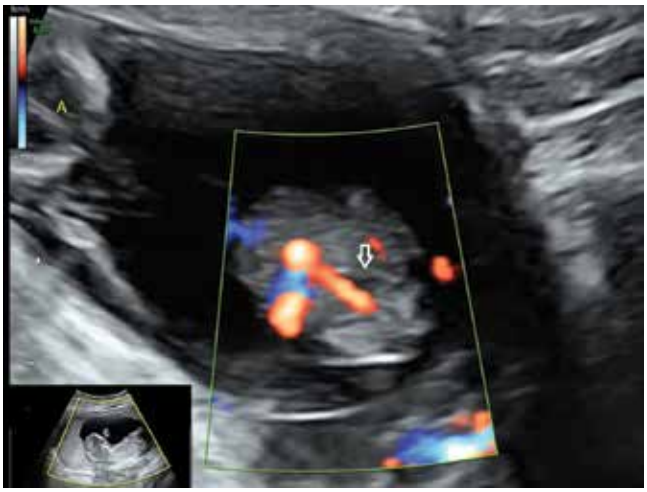

Figure 1. Visualization of the umbilical arteries at the level of the fetal urinary bladder.

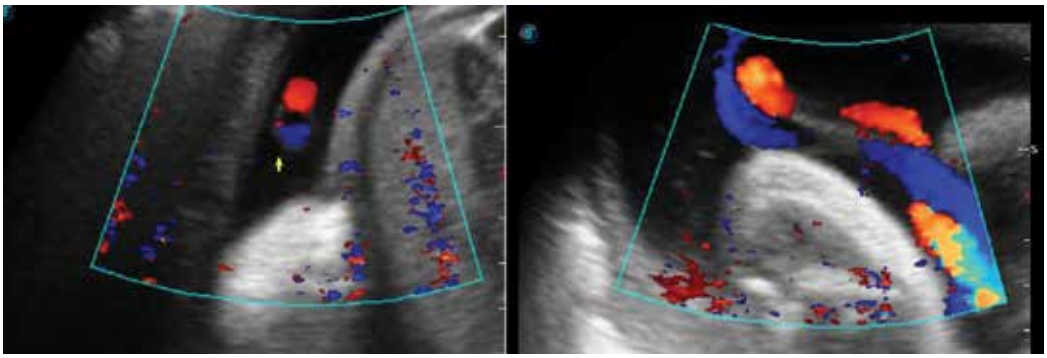

Figure 2. Color Doppler visualization of a free-floating loop of umbilical cord.

have a more detailed physical examination [11, 21]. Ultrasound views of the heart described in FMF's recommendations (minimum four-chamber view, outflow tract, and three-vessel view) can detect 66% of the heart malformations associated with single umbilical artery. The undiagnosed ones are minor and have a favorable outcome [22].

Nonisolated SUA requests invasive testing with chromosomal microarray because the risk of syndromes and chromosomal anomalies are substantially increased (**Figure 3**). Isolated SUA with a normal insertion of the cord does not require special precautions during labor. In these cases, the long-term outcome for children is the same as for children born with three vessels in the umbilical cord [23].

2.2. Persistent right umbilical vein

Unusual persistence of the right umbilical vein with left vein umbilical regression will lead to alteration in the development of embryonic vasculature, knowing that in the normal

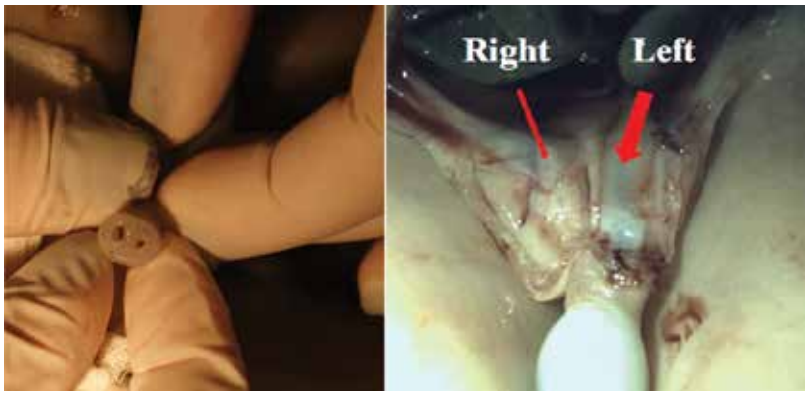

Figure 3. SUA at necropsy.

fetus, the right umbilical vein disappears by the seventh week of gestation. This condition does not alter the formation of ductus venosus, the distribution of blood to the fetus remaining normal [24]. First-trimester folic acid deficiency, teratogens such as retinoic acid or early obstruction of the left umbilical vein from external pressure or occlusion are considered etiologic factors [25].

The ultrasound diagnosis is made in the transverse section of the fetal abdomen. Umbilical vein is abnormally connected to the right portal vein instead to the left portal vein, and fetal gallbladder is located between the umbilical vein and the stomach [26] (**Figures 4** and **5**).

It is associated with congenital anomalies: cardiac anomalies, trisomy 18, abdominal visceral situs inversus, total anomalous pulmonary venous connection, urinary tract malformation like unilateral renal agenesis, umbilical vein varix, skeletal malformations, and others [27].

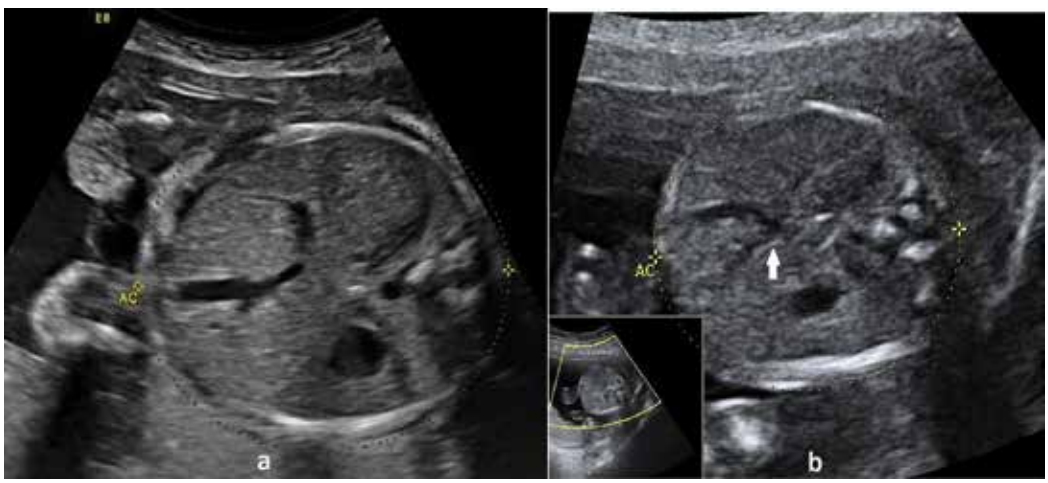

Figure 4. Persistent right umbilical vein: (**a**) Normal section of abdominal circumference and (**b**) section of abdominal circumference with persistent right umbilical vein view.

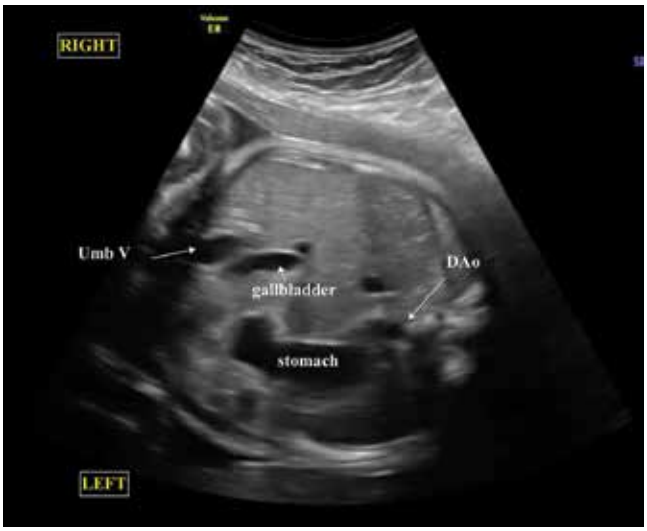

Figure 5. Persistent right umbilical vein (*Dao,* descending aorta).

2.3. Four-vessel umbilical cord

Five percent of umbilical cords exhibit a four-vessel structure due to the persistence of small vitelline arteries, which follow the normal twisting of the main umbilical arteries. [28].

Four umbilical vessels view is an abnormal situation that has been reported to be associated with major congenital anomalies [29]. The presence of three umbilical arteries is the most common situation of four-vessel cord, although in the specialty literature have been reported a few cases of cord with two umbilical veins and two umbilical arteries [30].

3. Abnormal course or connection of vessels

The insertion of umbilical cord can be located following the chorionic plate vessels using color Doppler technique. The placental insertion of the UC is better observed by ultrasound in the first trimester. Later when gestational age increases, visualization becomes difficult, especially when the placenta is posterior. The evaluation of fetal circulation is done by examining the umbilical arteries. The umbilical vascular evaluation provides information on the circulation at the fetomaternal interface level, giving the possibility of early detection of risk to the fetus [19].

3.1. Velamentous insertion of the cord

The umbilical cord insertion is located on the placental mass in about 99% of cases, into the central portion of the placenta. The velamentous insertion is the condition in which the umbilical vessels are configured between amnion and chorion before reaching the placenta on the chorioamniotic membranes [31]. That abnormal insertion occurs when the cord implants in the trophoblast anterior to the decidua capsularis or when placental tissue grows laterally,

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leaving an area which becomes atrophic. The umbilical cord inserts into the chorion leave at a point away from the placental mass and appears as membranous umbilical vessels at the placental insertion site (velamentous vessels are not protected by Wharton's jelly), the rest of the cord is usually normal. This type of pathological insertion of the cord occurs in 1–2% of singleton pregnancies. In multiple pregnancies, the incidence of velamentous cord insertion is 10-fold higher than in singleton pregnancies [32] (**Figure 6**).

Heinonen et al. [33] in this aberrant attachment, such as at the margins or to the membranes, found an association with higher maternal serum human chorionic gonadotropin (hCG) and lower maternal serum alpha-fetoprotein (AFP). However, until further data is available, no specific recommendations can be made.

Prenatal identification of these pregnancies is an important issue. There is a higher risk for an adverse perinatal outcome like intrauterine growth retardation, preterm birth, placental abruption, vasa previa, low Apgar scores at 1 and 5 min, neonatal death, congenital anomalies, and fetal bleeding [34]. Associated anomalies include trisomy 21, spina bifida, ventricular septal defects, esophageal atresia, obstructive uropathies, congenital hip dislocation, and asymmetrical head shape. It has been noted that a higher rate of deformations occur instead of malformations or disruptions [34]. Velamentous insertion associated with vasa previa appears to have an increased rate of congenital malformations. Also, 13% cases of single umbilical artery are associated with velamentous insertion [14].

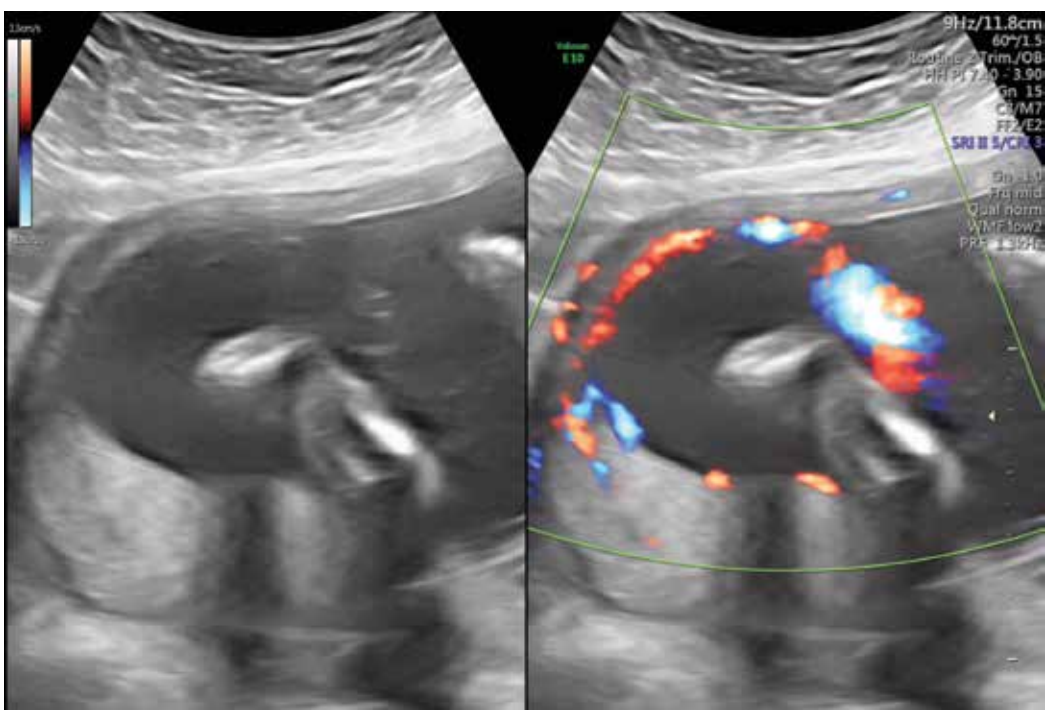

Figure 6. Velamentous cord insertion.

Vasa previa

It is important to be aware that velamentous cord insertion is associated with an increased rate of vasa previa. Vasa previa is a form of velamentous cord insertion in which velamentous vessels pass through the fetal membranes of the lower uterine segment and incidence is estimated to be 0.04% [35]. These fetal vessels may break when membrane rupture occurs and the result is fetal exsanguination. Intrapartum diagnosis is very difficult in this case [36].

4. Abnormal structure or configuration of vessels

4.1. Hypoplastic umbilical artery

A hypoplastic umbilical artery has a smaller diameter than the contralateral artery, showing by ultrasonography an artery-to-artery diameter difference of more than 50% [37] (**Figure 7**).

It seems that the hypoplastic umbilical artery represents a mild form of the single umbilical artery. Described anomalies include trisomy 21, polyhydramnios, congenital heart disease, stillbirth, trisomies, and fetal growth restriction. The presence of discordant umbilical arteries is a sign of different umbilical artery blood flow indices and of placental disease [38]. This condition increases the risk of IUGR, placental infarction, umbilical cord hematoma, and abnormal umbilical cord insertion. It is also known that the fetal prognosis is better for hypoplastic umbilical arteries compared with SUA syndrome [37].

Karyotyping is not indicated in isolated hypoplastic umbilical artery because there is no evidence of increased risk of chromosomal defects.

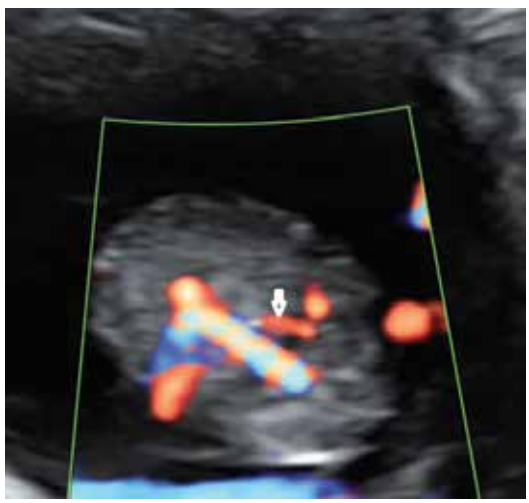

Figure 7. Hypoplastic umbilical artery.

4.2. Umbilical vein varix

Umbilical vein varix is a rare condition which occurs in the intrahepatic portion of the umbilical vein presents an incidence of 2.8:1000 [39]. Ultrasound scan usually discovers a circular vessel dilation ≥ 9 mm, 59 or more than 50% over the diameter of the intrahepatic UV [40]. The condition is associated with chromosomal anomalies in up to 12% of cases, especially trisomy 21and poor fetal outcome with emergent cesarean delivery [41].

Complete follow-up includes karyotyping, regular fetal testing, and third trimester interval growth studies [42]. Because the incidence is very low, the clinical significance remains controversial.

4.3. Umbilical artery aneurysm

Umbilical artery aneurysm is an extremely rare vascular anomaly usually associated with high risk of fetal aneuploidy, IUGR, and fetal demise. Fetal demise is a result of compression of the dilated artery on the umbilical vein, thrombus formation, or due to associated fetal anomaly like trisomy 18 [43]. This condition is a vascular anomaly which appears as an anechoic cyst close to cord insertion with a hyperechogenic rim in which color flow and spectral Doppler examinations show nonpulsatile and turbulent blood flow within the artery [44].

It is important to consider karyotype analysis given the high incidence of aneuploidy associated with umbilical artery aneurysm.

Tumors of the Umbilical Cord

4.4. Cord cysts

Cord cysts have no clinical relevance and develop from the remnants of the allantois or the omphalomesenteric duct. The finding of an isolated umbilical cord cystic mass should lead to further detailed sonographic evaluation and karyotype testing should be done when IUGR or other anomalies are found [45]. The majority of first-trimester cysts are transient ultrasound findings that have no influence on pregnancy outcome [46]. The prognosis of persistent cysts appears to be similar to that of second-trimester cysts [47].

Several studies concluded that morphologic features of cord cyst (single, multiple) correlate with fetal abnormalities like abdominal wall defects and patent urachus [48].

Umbilical cord cysts are classified as true cysts or pseudocysts. True cysts have an incidence of 3.4% in first trimester of pregnancy and have no clinical significance, and are sometimes associated with fetal structural anomalies and aneuploidy [45]. True cysts are derived from the embryological remnants of either the allantois or the omphalomesenteric duct, are located typically toward the fetal insertion of the cord and range from 4 to 60 mm in size [49].

The exact cause of umbilical cyst is not known, but it is thought to be due to raised hydrostatic pressure in the umbilical vessels (**Figure 8**).

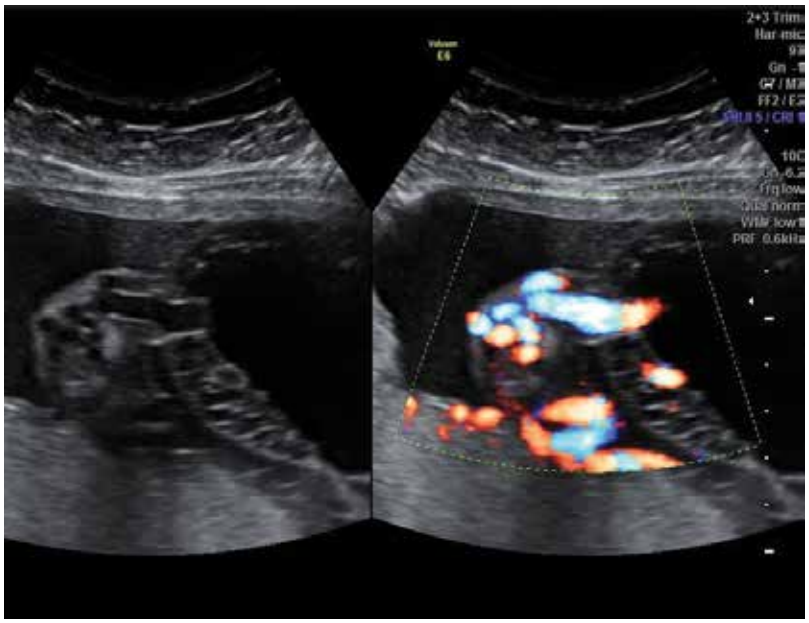

Figure 8. Large umbilical cyst in the second trimester.

Pseudocysts are more common than true cysts and can be located anywhere along the cord; they have no epithelial lining and represent localized edema and liquefaction of Wharton's jelly (known as Wharton jelly cysts). It is rarely possible to differentiate between true cysts and pseudocysts on ultrasound imaging [50]. But differentiation between the two entities is not very important because both are associated with anomalies. Pseudocysts are more common than true cysts and they are strongly associated with chromosomal defects and other congenital anomalies, especially omphalocele, hydrops, and trisomy 18 [51]. Usually, ultrasonography monitoring is sufficient, invasive tests not being typically needed. A higher risk of fetal anomalies is associated with the following: detection of cysts in the second or third trimester, persistence after the first trimester, large size, and location near fetal or placental end. Also, trisomy 18, 13, and 21 are known to be associated, in such cases, chromosomal analysis may be warranted [52].

They might be associated with omphalocele, Meckel's diverticulum, patent urachus, and hydronephrosis. False cysts are most commonly found at the fetal end of the cord, do not have an epithelial lining and might be associated with omphalocele, patent urachus, and chromosomal anomalies [53]. Twenty percent of cord cysts, no matter what type they are, are associated with structural or chromosomal anomalies [54].

When the umbilical cyst is detected antenatally, especially in second or third trimesters, it is recommended a detailed ultrasonographic examination of the fetus, and it should be carefully looked for any associated defects. In case of any suspicion should be done the karyotyping analysis.

4.5. Umbilical cord teratomas

They are rare benign lesions, only 12 cases reported in the literature, which may lead to adverse fetal outcomes. These tumors are the only true neoplasms of the umbilical cord which

have a very polymorphic presentation and should be evaluated when the lesion contains calcifications [55].

It can also be associated with severe fetal anomalies such as anencephaly, intestinal anomalies, and abdominal wall defects. The outcome in extragonadal teratomas can be affected by the presence of associated anomalies and surgical complications after correction of the congenital malformations [56].

Angiomyxomas are benign solid masses which may be associated with fetal demise. Associated complications are premature delivery, cardiovascular anomalies, nonimmune hydrops fetalis, hydatidiform mole, polyhydramnios, and stillbirth [57]. The management of pregnancy with angiomyxoma in the third trimester is not well defined.

5. Patent urachus

Urachus represents a vestigial structure formed by the bladder dome and the obliterated umbilical arteries. Patent urachus represents 10–15% of all urachal anomalies in the literature [58] and may lead to urination through umbilicus and infections. It is a rare condition because urachal lumen typically closes at week 17 post-conception [59]. Alterations in the morphology of the umbilical cord should extend the investigation, since there are associations with chromosomal anomalies. It has been associated with bladder exstrophy and anterior abdominal wall defects.

6. Congenital hernia of the umbilical cord

Congenital hernia of the umbilical cord (CHUC) is a rare congenital entity recognized as a distinct entity since the 1920s but is often misdiagnosed as a small omphalocele. During the first 5th–6th week of gestation, the bowel herniates into the developing umbilical cord and withdraws into the abdominal cavity until the 10th–12th week of gestation [60]. Return of

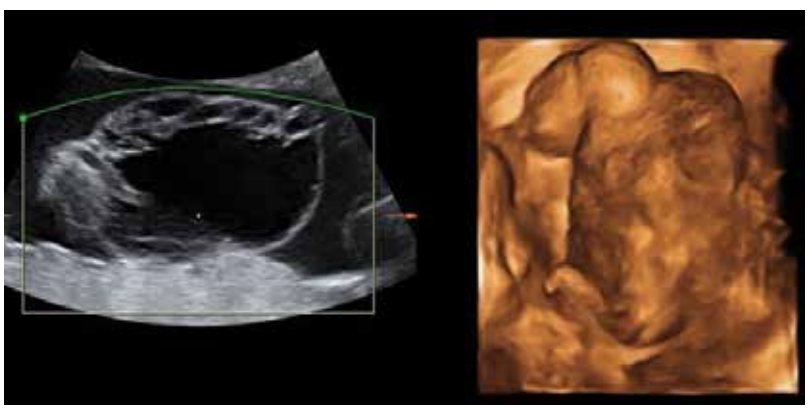

Figure 9. Large umbilical cyst 3D view.

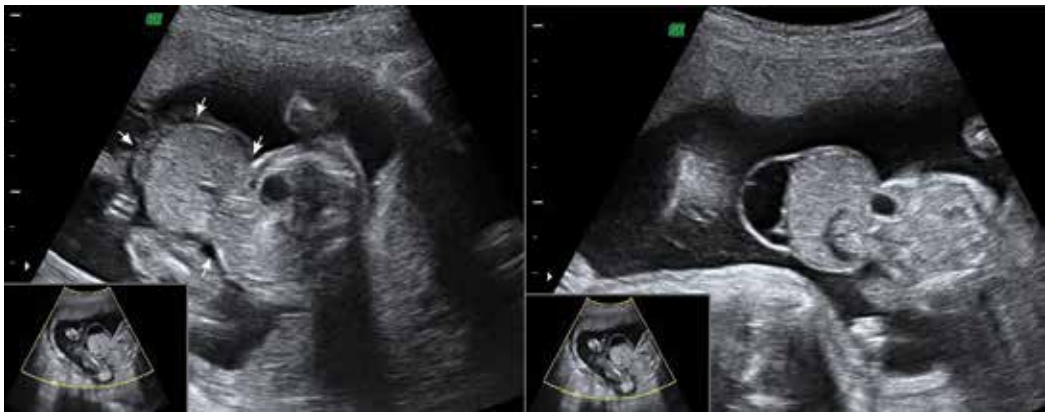

Figure 10. Congenital hernia of the umbilical cord.

physiologically herniated bowel or failed closure of umbilical ring (**Figures 8** and **9**). A review of the literature described associated malformations like pulmonary stenosis, cleft lip and palate, ear tag, small and large bowel atresia and stenosis, short bowel syndrome, tetralogy of Fallot, Meckel's diverticulum, persistent cloaca, and congenital glaucoma [61] (**Figure 10**).

7. Congenital umbilical arteriovenous malformation

The literature reported extremely rare cases of congenital umbilical arteriovenous malformation, less than 10 cases communicated in literature because congenital arteriovenous malformations are found most commonly in the brain, liver, and extremities. Congenital umbilical arteriovenous malformation is congenital lesions presented as a multitude of arteries and veins connected by a fistula. This condition can be asymptomatic but can also lead to congestive heart failure and massive hemorrhagic shock [62].

8. Conclusion

Invasive (diagnostic and therapeutic) procedures implying the puncture of the umbilical circulation are widely guided by ultrasound. Therefore, perinatal management may be enhanced by a prenatal ultrasonographic depiction of the morphology of the umbilical cord. In early pregnancy should be undertaken targeted examination because many details of cord development become difficult to identify on ultrasound with increasing gestational age. It is known also the association with structural (especially cardiovascular) and chromosomal anomalies, and for that further extended investigation should be needed in case of detection of abnormalities in the number, structure, or course of cord vessels. Most cases with isolated congenital anomalies of UC have a favorable outcome. Particular attention should be paid to umbilical cord insertions, both fetal and placental one. In apparently isolated single umbilical

artery, further ultrasound scans during the late pregnancy and continuous fetal-heart-rate monitoring during labor should be offered. The single umbilical artery assumes an additional risk and the parents should be advised of the need for extra surveillance; they have to be also aware regarding the possibility of detection of some possible associated abnormality only after delivery.

Author details

Sidonia Catalina Vrabie[1]*, Liliana Novac[1], Maria Magdalena Manolea[1], Lorena Anda Dijmarescu[1], Marius Novac[2] and Mirela Anisoara Siminel[3]

*Address all correspondence to: sidocatalina@yahoo.com

1 Department of Obstetrics and Gynecology, University of Medicine and Pharmacy, Craiova, Romania

2 Department of Anesthesiology and Intensive Care, University of Medicine and Pharmacy, Craiova, Romania

3 Department of Neonatology, University of Medicine and Pharmacy, Craiova, Romania

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Section 2

Fetal Chromosomal Anomalies

Chapter 18

Prenatal Biochemical and Ultrasound Markers in Chromosomal Anomalies

Eusebiu Vlad Gorduza,
Demetra Gabriela Socolov and
Răzvan Vladimir Socolov

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.73604

Abstract

The unbalanced chromosomal anomalies generate an abnormal pattern of development and usually determine miscarriage. The most frequent prenatal chromosomal anomalies are X monosomy, trisomies of chromosomes 21, 18, 13, 16, 8, triploidy and tetraploidy. Identification of chromosomal anomalies can be done by prenatal screening and diagnosis. Prenatal screening is biochemical, sonographic or molecular (detection of fetal DNA in maternal blood). Biochemical screening can be done in the first or second trimester. First-trimester screening is based on the detection in maternal serum of beta-hCG (β-hCG) and pregnancy-associated plasma protein-A (PAPP-A). Biochemical screening in the second trimester requires the detection of alpha-fetoprotein (aFP) hGC, unconjugated estriol (μE) and inhibin A. The sonographic examination can be used in the first or second trimesters. In the first trimester, an ultrasound can identify soft markers like nuchal translucency, nasal bone and ductus venous flow. In the second trimester the sonographic examination can identify congenital anomalies or different soft markers. Prenatal chromosomal diagnosis requires an invasive procedure to obtain embryonic or fetal material. Such procedures are represented by chorionic villus sampling amniocentesis or cordocentesis. The fetal cells are used for cell cultures (in cytogenetic methods) or for molecular analyses (FISH, QF-PCR, MLPA, array-CGH).

Keywords: chromosomal anomalies, chromosomal syndromes, prenatal screening, biochemical screening, ultra-sonographic screening

1. Introduction

Chromosomal anomalies represent large genomic modifications that could be identified using light microscope. Apart from these characteristics, many chromosomal anomalies produce severe changes in the phenotypes of carriers that induce a high rate of miscarriage (>50% of spontaneous abortions are produced by a chromosomal anomaly) and chromosomal disorders in neonates and infants (global incidence in newborns is 1%). Early identification of chromosomal anomalies during the prenatal period has become the purpose of prenatal screening and diagnosis. Prenatal screening allows discovery of pregnancies at risk using non-invasive methods that do not harm the pregnant woman and fetus. An abnormal prenatal screening imposes the confirmation by using a prenatal diagnosis method. Prenatal screening methods could be biochemical, ultra-sonographic and genomic. Biochemical methods imply detection of some serum constituents in maternal blood like hCG, β-hCG, aFP, μE3, PAPP-A, and so on. Ultra-sonographic methods imply the use of ultrasound for the assessment of morphologic features of the fetus. Genomic prenatal screening allows the detection of free fetal DNA in maternal blood. Prenatal diagnosis imposes the use of the invasive methods that allow the harvesting of these fetal cells (trophoblastic cells, amniotic cells or blood cells). The major inconvenience of invasive methods is the risk of miscarriage or fetal damage. Fetal cells could be used for cytogenetic or molecular genetics investigations that allow a prenatal diagnosis [1].

2. Chromosomal anomalies

Chromosomal anomalies are produced by genomic or chromosomal mutations. Chromosomal anomalies could be numerical and structural. Numerical chromosomal anomalies produce an important genomic imbalance and the phenotype of carriers is severely affected. Numerical chromosomal anomalies are represented by aneuploidies (trisomies, monosomies, etc.) and polyploidies (triploidy and tetraploidy). These are generated by errors during meiosis, fertilization or first mitosis of embryo. The most common error is chromosomal non-disjunction during the first meiosis that generates an aneuploidy (trisomy or monosomy) and is associated with advanced maternal age. Structural chromosomal anomalies are generated by changes of structure of one or multiple chromosomes and could be divided into unbalanced and balanced anomalies. Unbalanced structural chromosomal anomalies are characterized by absence (partial monosomy) or supplementary (partial trisomy) chromosomal segment(s) and produce a genomic imbalance that induces an abnormal phenotype. Balanced chromosomal anomalies are characterized by changes in the position of some chromosomal segments, but the quantity of genetic material remains unchanged. The phenotype of carriers is usually normal, but they could present a malsegregation of derivative chromosomes during meiosis that generates formation of gametes with genomic imbalances. Fertilizing such gametes results in embryos with unbalanced chromosomal anomalies [1].

Unbalanced chromosomal anomalies produce a severe modification of phenotype and generate chromosomal diseases. The majority of such anomalies do not permit survival of the embryo and the pregnancy ends in miscarriage. Other anomalies—gonosomal trisomies (XXX, XXY, XYY), some autosomal trisomies (21, 18, 13), some cases with X monosomy, some partial monosomies or partial trisomies—are compatible with life, but children have a chromosomal disease [1].

The epidemiological studies showed that the frequency of chromosomal anomalies will be reduced during pregnancy, from 1/4 at conception to 1/100 at birth (**Table 1**). The aneuploidies are the most frequent of these anomalies. The most common chromosomal disorders are Down syndrome (trisomy 21—**Figure 1**, birth prevalence 1/700–1/800) [2, 3], Klinefelter syndrome (trisomy XXY—**Figure 2**, birth prevalence 1/1000), triplo X syndrome (trisomy X—**Figure 3**, birth prevalence 1/1000), Turner syndrome (monosomy X—**Figure 4**, birth prevalence 1/2000 girls), Edwards syndrome (trisomy 18—**Figure 5**, birth prevalence 1/6500) and Patau syndrome (trisomy 13—**Figure 6**, birth prevalence 1/12,500). The risk of a couple having an affected child with a major trisomy (13, 18 and 21) is associated with advancing maternal age. In the last decade, the age of women at first pregnancy increases such that the birth prevalence for trisomy 21 in the USA has increased from 1 in 740 in 1974 to 1 in 504 by 1997 [4, 5].

The majority of chromosomal disorders has a high lethality rate during pregnancy and thus in the first trimester there are a significant number of fetuses affected than at full term. For example, in the case of trisomy 21, there is a 40% fetal loss between 12 weeks and full term and a 30% fetal loss between 16 weeks and full term. For trisomies 13 or 18, the loss is more important with an 80% fetal loss between 12 weeks and full term and a 40% fetal loss between 16 weeks and full term [6].

The incidence of the main chromosomal disorders in neonates is present in **Table 2**.

For trisomy 21, the risk at 12 weeks of gestation is 1/1000 for a woman aged 20 years and 1/250 for a woman aged 35 years. The risk of delivering an affected baby with Down syndrome is 1/1500 for a woman aged 20 years and 1/350 for a woman aged 35 years. For trisomy 18, the risk at 12 weeks of gestation is 1/2500 (for a woman aged 20 years) and 1/600 (for a woman aged 35 years) [7].

Ontogenetic period/ disorder	Incidence of chromosomal anomalies
1. gametes	10-25%
2. biochemical miscarriages	unknown, probably 33-67%
3. spontaneous miscarriages during first trimester of pregnancy	50-70%
4. intrauterine death	5% - 10%
5. newborns	1%
6. severe congenital anomalies	4%
7. plurimalformative syndromes	5,5%

Table 1. Incidence of chromosomal anomalies in prenatal and perinatal period (adapted from Gorduza [1]).

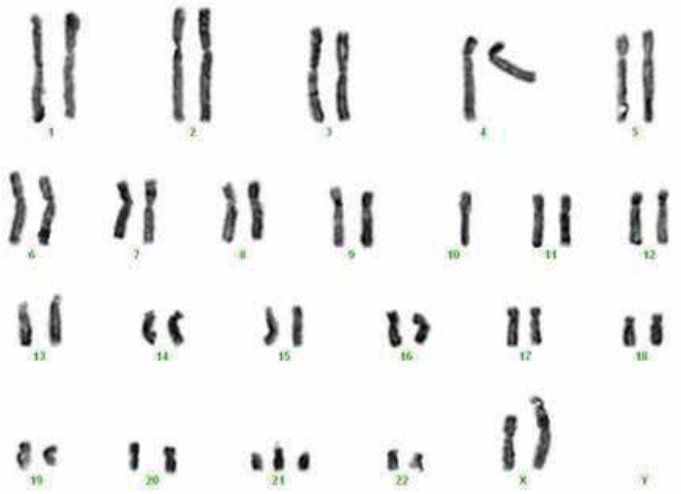

Figure 1. Trisomy 21 (collection of cytogenetic laboratory, "Grigore T. Popa" University of Medicine and Pharmacy Iaşi, Romania).

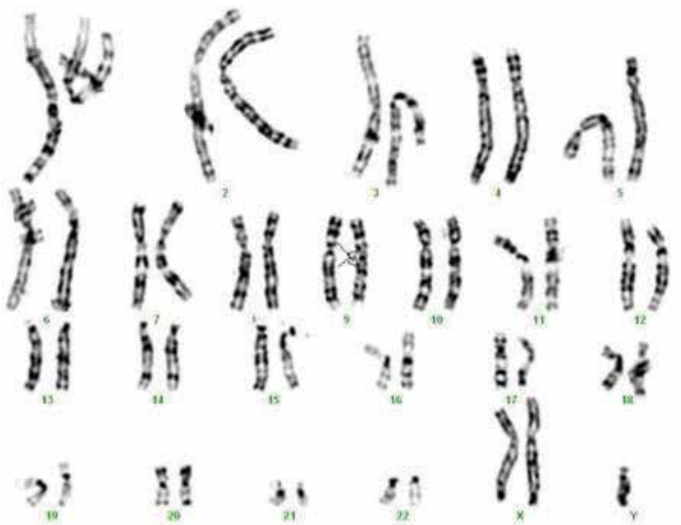

Figure 2. Trisomy XXY (collection of cytogenetic laboratory, "Grigore T. Popa" University of Medicine and Pharmacy Iaşi, Romania).

The risk of delivering an affected baby with Edwards syndrome is 1/18,000 for a woman aged 20 years and 1/4000 for a woman aged 35 years. For trisomy 13, the risk at 12 weeks of gestation is 1/8000 (for a woman aged 20 years) and 1/1800 (for a woman aged 35 years). The risk of delivering an affected baby with Patau syndrome is 1/42,000 for a woman aged 20 years and 1/10,000 for a woman aged 35 years [7].

http://dx.doi.org/10.5772/intechopen.73604

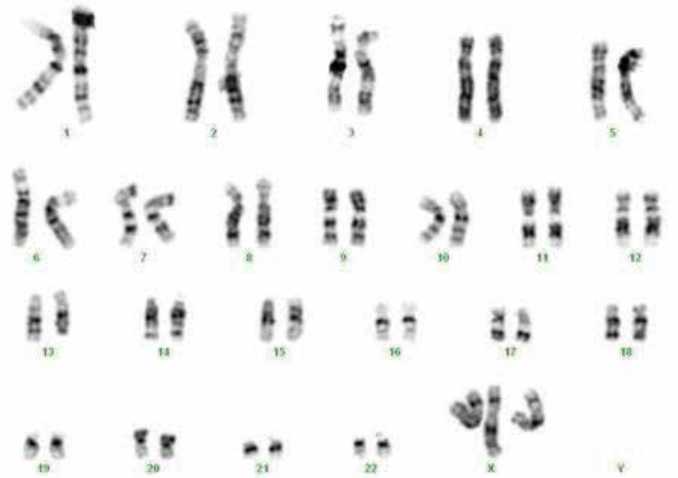

Figure 3. Trisomy X (collection of cytogenetic laboratory, "Grigore T. Popa" University of Medicine and Pharmacy Iaşi, Romania).

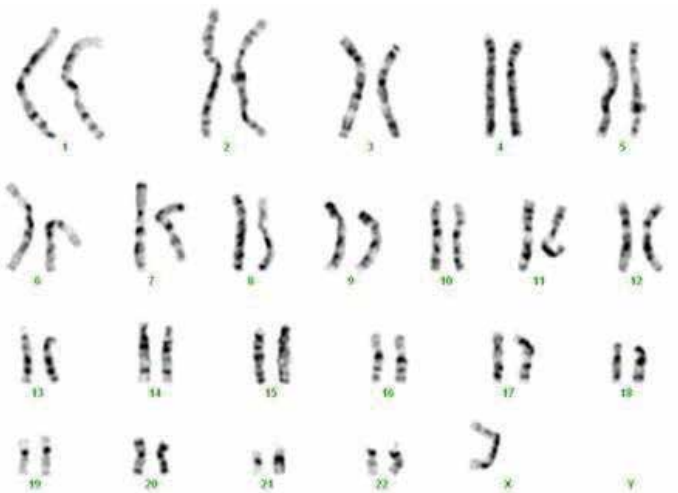

Figure 4. Monosomy X (collection of cytogenetic laboratory, "Grigore T. Popa" University of Medicine and Pharmacy Iaşi, Romania).

In the case of gonosomal aneuploidies the risks are not correlated with advanced maternal age, and with the exception of monosomy X, the chromosomal anomaly does not modify the viability of the fetus. In monosomy X, the prevalence of anomaly is about 1/1500 at 12 weeks of gestation and 1/4000 at 40 weeks. For the gonosomal trisomies (47,XXX, 47,XXY and 47,XYY), the overall prevalence of 1/500 does not decrease with gestation [7].

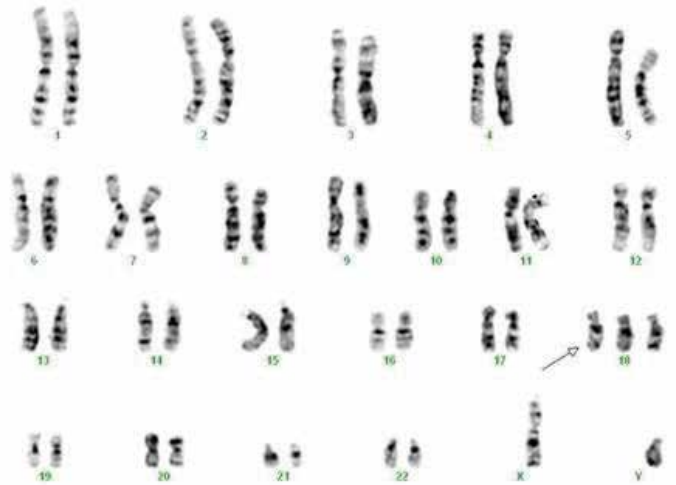

Figure 5. Trisomy 18 (collection of cytogenetic laboratory, "Grigore T. Popa" University of Medicine and Pharmacy Iaşi, Romania).

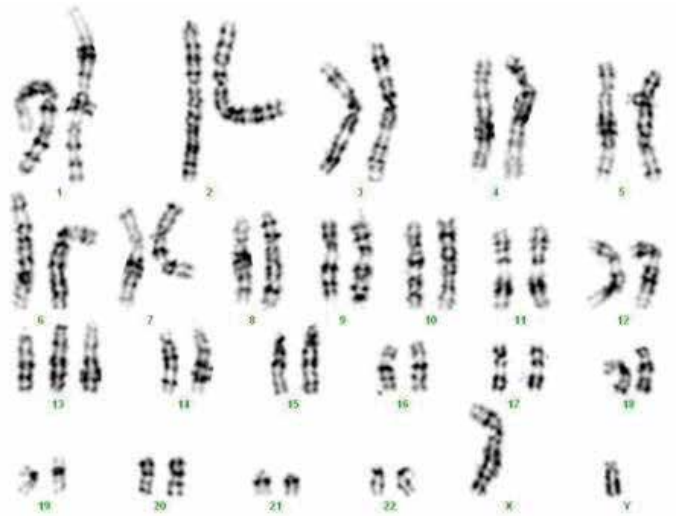

Figure 6. Trisomy 13 (collection of cytogenetic laboratory, "Grigore T. Popa" University of Medicine and Pharmacy Iaşi, Romania).

Triploidy is unrelated to maternal age and the prevalence is about 1/2000 at 12 weeks, but the majority of affected fetuses die by 20 weeks and the born babies are mosaics 46/69 [7].

The birth of a child is an important event in the life of every family and represents the end of a long period of uncertainty generated by fear that the future child will be abnormal. The high incidence of chromosomal anomalies during prenatal life and the severity of phenotype of chromosomal anomalies that allow survival, imposed the development of methods of prenatal

Autosomal trisomies	13 –Patau syndrome 18 –Edward syndrome 21 –Down syndrome	0.08‰ 0.15‰ 1.2‰	Global 1.4‰
Triploidies			0.02‰
Gonosomal aneuploidies in boys	47,XXY –Klinefelter syndrome 47,XYY –double Y syndrome other	1 ‰ 1 ‰ 0.74‰	Global 2.75‰
Gonosomal aneuploidies in girls	monosomy X –Turner syndrome 47,XXX –triplo X syndrome other	0.3‰ 1.1‰ 0.37‰	Global 1.8‰
Unbalanced structural chromosomal anomalies			0.7‰
Unbalanced chromosomal anomalies (numerical and structural)			4‰ (1/250)
Balanced structural chromosomal anomalies	Reciprocal translocations Robertsonian translocations Inversions	2.5‰ 1‰ 0.8‰	Global 4.3‰

Table 2. Incidence of chromosomal anomalies in neonates (adapted from Gorduza [1]).

screening and diagnosis. Different such methods were developed during the last decades and now it is possible to discover the chromosomal pathology of the embryo in a couple at risk.

3. Methods of prenatal screening and diagnosis

The main procedures of prenatal screening are biochemical screening and ultrasound that allow the identification of pregnancies with increased genetic risk. The prenatal screening methods were introduced in medical practice in the1980s, based on the association between incidence of trisomy 21 (Down syndrome) and advanced maternal age. A decade later both the maternal serum biochemistry and detailed ultra-sonographic examination in the second trimester were developed and allowed the identification of high-risk pregnancies. In the 1990s, the prenatal screening shifted to first trimester by a combination of maternal age, fetal nuchal translucency (NT) thickness and maternal serum-free β-hCG and PAPP-A. In the last 10 years, the prenatal screening methods changed again by the introduction of genomic screening that searches free fetal DNA in maternal blood [8].

The prenatal diagnosis imposes the obtaining of embryonic or fetal cells by using invasive methods like chorionic villus sampling (CVS), amniocentesis or cordocentesis. All these methods present risks for spontaneous miscarriages, obstetrical hemorrhages and fetal damages. The embrionar or fetal cells are used for cytogenetic or molecular diagnosis.

3.1. Biochemical screening

Biochemical screening is based on the determination of maternal serum markers that are associated with an increased risk of chromosomal diseases. Biochemical screening could be

applied during the first or the second trimester of pregnancy. The presence of a fetal aneuploidy is associated with changes of maternal serum concentrations of some fetoplacental products: aFP, free ß-hCG, inhibin A, μE3 and PAPP-A. In normal pregnancies, aFP concentration in maternal serum increases from 11.3 ng/ml in the 8th week of gestation to 250 ng/ml in the 32nd week of pregnancy. After that, it then declines slightly until term. In normal pregnancies, hCG in the maternal serum increases in first trimester of pregnancy and reaches a peak in weeks 7–9 (100.000 IU/ml). After that, it reduces continuously until around 20 weeks of pregnancies, when reduction is stopped and plasma levels remain constant until term. In normal pregnancies, inhibin A increases from the 6th week of pregnancy to the 9th week of pregnancy and reaches a peak (~550 pg/ml). After that, the values decline continuously to the 14th week of pregnancy. In normal pregnancies, μE3 is first detectable at 9 weeks of gestation (0.05 ng/ml) and after that it increases continuously to about 30 ng/ml at term. In normal pregnancies, PAPP-A is first detected in maternal serum after 4 weeks of pregnancies. PAPP-A concentration increases exponentially in the first trimester. After that, the rise occurs slowly, but it continues until delivery [9–12].

In biochemical screening, the measured concentration of the markers is converted into a multiple of the median (MoM) of unaffected pregnancies at the same gestation. The Gaussian distributions of log10 (MoM) in trisomy 21 and unaffected pregnancies are then derived, and the ratio of the heights of the distributions at a particular MoM represents the likelihood ratio for a trisomy [7].

3.1.1. First-trimester prenatal screening

During the first trimester of pregnancy, different serological components present variations, but only free β-hCG and PAPP-A were associated with the presence of a trisomy 21. Other serological marker could be ADAM-12.

3.1.1.1. Human chorionic gonadotropin

The first attempts of using the hCG in detection of trisomy 21 in the first trimester of pregnancy gave controversial results. Use of total hCG in the first-trimester screening is inadequate because this marker becomes elevated only after 11 weeks of gestation [13]. In opposition, β-hCG is substantially elevated at 8–14 weeks of gestation in trisomy 21 pregnancies [14]. At a 5% false positive rate, the association between β-hCG and maternal age allows the detection of 42–46% of cases with trisomy 21 [15, 16].

3.1.1.2. Pregnancy-associated plasma protein-a

Pregnancy-associated plasma protein-A (PAPP-A) is produced by placental trophoblasts, but its function still unclear. The level of maternal serum PAPP-A is low during the first trimester in pregnancies with trisomy 21 and thus this marker could be used in prenatal screening of first trimester [17]. By using a protocol that associates PAPP-A in combination with maternal age, at a 5% false positive rate, the detection rate of cases with trisomy 21 ranges from 48 to 52%. After 15 weeks of gestation, the efficacy of this marker is low and its use in second-trimester screening is without benefits [15, 16].

3.1.1.3. Other biochemical markers

The serum marker used in second-trimester screening (aFP, μE3 and inhibin-A [INH-A]) shows minimal differences in trisomy 21 pregnancies and thus could not be used in first-trimester screening [14].

ADAM 12 is a glycoprotein synthesized by the placenta and secreted through pregnancy. ADAM 12 presents proteolytic functions and has a low level in first-trimester cases with trisomy 21 or trisomy 18. This reduction is more pronounced in earlier gestation, with best results at around 8–10 weeks. ADAM 12 in combination with PAPP-A (both measured at 8–9 weeks), nuchal translucency (NT) and free β-hCG measured at 12 weeks allow a detection rate of 97% at a 5% false positive rate and thus could be the best protocol for prenatal screening in the first trimester of pregnancy [18, 19].

3.1.1.4. Screening of other aneuploidies

The screening of other aneuploidies in the first trimester of pregnancy is also possible and has a good rate of detection. Low maternal serum PAPP-A was identified in trisomy 18, trisomy 13, triploidy and monosomy X. Low levels of free β-hCG were discovered in trisomy 18, trisomy 13 and in some cases of triploidy [20–23]. However, all these disorders have a high rate of spontaneous miscarriages (minimum 80%) and any conversion of the observed detection rates to true detection rates is, therefore, associated with a substantial degree of uncertainty [13].

3.1.2. Second-trimester prenatal screening

Second-trimester serum markers are represented by alpha-fetoprotein, human chorionic gonadotropin, unconjugated estriol and inhibin-A.

Screening for aneuploidies was initially focused on the second trimester of pregnancy and demonstrated a substantial improvement in detection rates of trisomy 21, compared with screening using only maternal age. At a false positive rate of 5%, the detection rate improves from 30% in screening by maternal age alone to 60–65% by combining maternal age with serum AFP and free ß-hCG (double test), 65–70% with the addition of μE (triple test) and 70–75% with the addition of inhibin A (quadruple test). In the case of hCG, it is better to search for free ß-hCG than total hCG [24–27].

3.1.2.1. Alpha-fetoprotein

The first report concerning the association between low level of maternal serum alpha-fetoprotein and fetal trisomy 21 was made in 1984, by Merkatz et al. [9]. At a risk cut-off of 1:270 for trisomy 21 (equivalent to the maternal age of 35), using this parameter alone would allow the detection of 55% of cases with trisomy 21 [28, 29].

The aFP is produced by fetal liver, but its biological functions and the reason why the aFP level is lower in Down syndrome pregnancies remain unclear. Placentas of affected pregnancies show a high level of aFP suggesting a defect in the secretion of AFP into the maternal circulation [30].

3.1.2.2. Human chorionic gonadotropin

In 1987, Bogart et al. showed that human chorionic gonadotropin (hCG) levels are generally higher in the maternal serum of women with Down syndrome pregnancies. They noted that hCG appeared to be superior to aFP in detecting fetal chromosome abnormalities, and association of maternal age with hCG as the screening method allows the identification of about 60% of pregnancies with trisomy 21 [31].

hCG is a glycoprotein produced by the placenta, composed of two subunits: α and β. Maternal serum contains intact hCG but also free α, free β and degradation products. At 8–10 weeks of gestation, intact hCG and free β-hCG show peak concentrations. Similar high levels of these compounds are found during the second trimester of pregnancy [32].

The anomalies of the placenta, characterized by disturbance in fluid homeostasis, like fetal hydrops and/or a cystic placenta, are associated with high levels of hCG in maternal serum. Such anomalies are present in hydropic Down syndrome, triploidy, Turner syndrome or other causes of hydrops fetalis. Even in the absence of hydrops, in cases with trisomy 21, there is a fluid accumulation that causes enlarged nuchal translucency and thickening and this could be related to the increase of hCG [33–35].

3.1.2.3. Unconjugated estriol

The presence of a low level of estriol in maternal urine in the case of a pregnancy with trisomy 21 was first reported by Jørgansen and Trolle [36]. Other studies confirmed this particularity and μE3 could be used as a marker in the prenatal screening of Down syndrome [37, 38].

The placenta uses 16 alpha-hydroxydehydroepiandrosterone sulfate (DHEAS) as the precursor of μE3. In Down syndrome pregnancies, both μE3 and DHEAS present lower levels in different tissues, including placenta [39]. During the second trimester the concentration of μE3 rises quickly and this marker can identify pregnancies with a small or underdeveloped fetus at the time of screening [27].

3.1.2.4. Inhibin-A

The possible application of inhibin in Down syndrome prenatal screening was suggested by Van Lith et al. [10]. Inhibin is a glycoprotein synthesized by gonads and placenta. The functional protein is dimeric with two subunits, α and β. The subunit α could be coupled with two different β subunits (βA or βB) and forms inhibin-A or inhibin-B. Inhibin-A (INH-A) is increased in pregnancies with trisomy 21 and presents an interdependent secretion with hCG. INH-A allows a good distinction between affected and unaffected pregnancies, alone or in combination with hCG [40–42]. INH-A has not got variations in relation with gestational age and thus the accuracy of testing is better by comparison with other serological markers [43].

3.1.2.5. Multiple marker screening in the second trimester of pregnancy

Second-trimester serum screening could be applied between 14 and 22 weeks of gestation, but usually it is carried out at 15–18 weeks of pregnancy. The serum markers could be combined in different ways but the most commonly used tests are double test (association between aFP

and hCG), triple test (association between aFP, μE3 and hCG), and quadruple test (association between aFP, μE3, hCG and INH-A) [42, 44, 45]. The values obtained by these tests are combined based on a multivariate Gaussian model and finally a risk algorithm is obtained [46].

A very important parameter is the age of gestation and this must be established using an ultrasound determination of gestational age (best results with crown-rump measurement between 8 and 11 weeks) [47]. The risk algorithm must include other variables like maternal weight, ethnicity, maternal diseases (diabetes, systemic lupus erythematosus), multiple gestation, smoking, in vitro fertilization, sex of the fetus or maternal rhesus blood type [48–56]. In unaffected twins' pregnancy, the concentrations of maternal serum markers are twofold higher than that seen in unaffected singleton pregnancies and thus the algorithm needs an adjustment by using a "pseudo-risk" [51].

3.1.2.6. Screening of other aneuploidies

In case of a pregnancy with trisomy 18, all serum markers (aFP, μE3, hCG and INH-A) for the second trimester are characterized by low concentrations [57]. The risks are calculated using a multivariate normal model and the detection rates for this aneuploidy are similar to those of trisomy 21 screening [58]. For other autosomal trisomies (13, 16, 20) and for triploidy different protocols for the second-trimester biochemical screening were tried but without specific features [27].

Among the sex chromosome aneuploidies, only one presents a bad prognosis: monosomy X with fetal hydrops. In this case, the biochemical prenatal screening shows an association between low aFP and μE3 and elevated hCG and INH-A. In pregnancies with monosomy X without hydrops, all serological markers are lower than normal concentrations [59].

3.2. Ultrasound screening

Ultrasound examination represents a good tool for the detection of morphological abnormalities in fetuses with chromosomal aberrations. In aneuploidies we could identify structural defects and non-structural findings (sonographic markers). Sonographic markers of fetal aneuploidy (SMFAs) are insignificant by themselves because they are nonspecific and often transient [60]. The sensitivity of sonography for detecting these abnormalities varies with a number of factors: type of chromosomal abnormality, gestational age, quality of the sonography and the experience of the sonographer. During the first trimester only the SMFA could be identified in pregnancies with aneuploid fetuses. During the second trimester, major/structural abnormalities could be observed in 20% of fetuses with trisomy 21 and in the majority of fetuses with trisomies 18 and 13. By combining SMFA and structural defects, the sonography allows the identification of 50% of fetuses with trisomy 21, 80% of fetuses with trisomy 18 and 90% of fetuses with trisomy 13 [61, 62].

3.2.1. First-trimester screening

During the first trimester of pregnancy many sonographic markers of fetal aneuploidy were described, but the most used are nuchal translucency and nasal bone (NB). Also, some major congenital anomalies could be identified but usually such changes are diagnosed during the second trimester of pregnancy.

3.2.1.1. Nuchal translucency

Nuchal translucency (NT) was introduced in medical practice in the 1990s and it is the sonographic appearance of a subcutaneous collection of fluid in the region of fetal neck [63]. Using a fixed cut-off for the NT measurement of 3 mm, it was possible to identify 64% of chromosomally abnormal cases, while only 4.1% of normal fetuses showed similar NT values [64]. It was proved that cut-off value was variable depending on gestational age, and it developed a Gaussian model for the NT variable that allowed this test to be readily combined with other markers [65].

The measurement of fetal NT thickness is done at the 11–14th week of gestation. This sonographic scan has been combined with maternal age to provide an effective method of screening for trisomy 21—at 5% false positive rate, about 75% of trisomic pregnancies can be identified by this method [63].

The explanations of NT are multiple but the most plausible are cardiovascular defects which cause over-perfusion of the head and neck and abnormal or delayed development of the lymphatic system. Thus, NT marker could be associated also with other chromosomal anomalies that produce fluid accumulation in the neck region. Also, NT can be a transient phenomenon that appears in a normal fetus and it spontaneously resolves in the second trimester [66].

3.2.1.2. Nasal bone

Cicero et al. were the first who evaluated the absence of the nasal bone (NB) in pregnancies and showed that it was present in 73% of trisomy 21 fetuses versus 0.5% of unaffected fetuses. They concluded that in trisomy 21, the absence of the nasal bone is not related to the nuchal translucency thickness, and thus both sonographic markers could be combined to provide an effective method of early screening for trisomy 21 [67]. This combined screening allows an increase of sensitivity from about 57 to 86% at a fixed false positive rate of about 1%. If the biochemical screening in the first trimester is added, a sensitivity of more than 90% could probably be achieved at a false positive rate of 1% [5, 67]. The analysis of nasal bone in aneuploidy versus euploidy, made by Kagan et al., showed that the nasal bone was absent in 2.6% of the euploid fetuses, in 59.8% with trisomy 21, 52.8% with trisomy 18, 45.0% with trisomy 13 and in none of the fetuses with Turner syndrome [68]. In contrast, Cicero et al. indicated that trisomy 21 was associated with the absence of nasal bone in 68.8% of cases, trisomy 18 in 54.8% of cases, trisomy 13 in 34.2% of cases, monosomy X in 10.9% of cases, gonosomal aneuploidies (XXX, XXY, XYY) in 5% of cases and other types of autosomal aneuploidies in 16.7% of cases, but none of the 19 cases with triploidy presented the absence of nasal bone [69].

3.2.1.3. Other sonographic markers in the first trimester

Another potential marker for trisomy 21 in the first trimester of pregnancy is tricuspid regurgitation (TR) observed by pulsed wave Doppler ultra-sonography. Falcon et al. indicated a tricuspid regurgitation in 67.5% of fetuses with trisomy 21, 33.3% of fetuses with trisomy 18 and only 4.4% of euploid fetuses [70]. Kagan et al. reported this anomaly in 55.5% of fetuses with trisomy 21, 33.3% of fetuses with trisomy 18, 30% of fetuses with trisomy 13, 37.5% of fetuses with monosomy X and only 0.9% of euploid fetuses. The free β-hCG and PAPP-A present

an independent variation in relation with tricuspid regurgitation and by combining all these parameters it would be expected to achieve a detection rate of 95% at a 5% false positive rate or 90% at a 2% false positive rate [71].

Borrell et al. measured the pulsatility index for veins and found an abnormal blood flow through the ductus venosus (DV) in the Down fetus. ***They indicated that with a 4–5% false positive rate, the detection rate for trisomy 21 is 65–75%. The use of this marker in association with NT increased the detection rate to 75–80%. Combining these two markers with serum biochemical markers measured at 10 weeks provided a detection rate of 92% at a 5% false positive rate [72].

Abele et al. analyzed retrospectively the NB, TR and DV. For normal children NB was identified in 2.0% of cases, TR was identified in 1.7% of cases and DV was identified in 3.5% of cases. In opposition, in cases with trisomy 21, NB was identified in 61.3% of cases, TR was identified in 61.3% of cases and DV was identified in 60.2% of cases. The normal children presented at least one of the markers in 5.9% of cases while more than 95% of the fetuses with trisomy 21 presented minimum 1 of these markers. The use of such combined prenatal screening (maternal age + NT + NB + TR + DV) during the first trimester could offer a detection rate of 95% with 1.5% false positive rate at a risk cut-off of 1:50 [73].

The assessment of each of these ultrasound markers can be incorporated into first-trimester combined screening by maternal age, fetal NT and serum-free ß-hCG and PAPP-A, resulting in the improvement of the performance of screening with an increase in detection rate from 93 to 96% and a decrease in false positive rate to 2.5% [68, 71, 74].

3.2.2. Second-trimester screening

During the second trimester of pregnancy different sonographic markers could be identified, as well as major congenital anomalies. The most common markers in the second trimester are nuchal thickening, hyperechoic bowel, shortened extremities, renal pyelectasis, echogenic intracardiac foci (EIF) and choroid plexus cysts. The discovery of such a marker is important especially in cases with trisomy 21 because many cases with Down syndrome do not present major congenital anomalies. In other aneuploidies and also in triploidy, usually the visceral anomalies are common, and identification of a congenital defect imposes an invasive procedure, followed by a chromosomal diagnosis [62].

3.2.2.1. Trisomy 13

Trisomy 13 is a severe disorder, characterized by the presence of different malformations in the brain (holoprosencephaly, agenesis of the corpus callosum, Dandy-Walker malformation, vermian agenesis and neural tube defects), face (cyclopia, hypotelorism, cleft lip and palate), kidneys (renal cystic dysplasia and hydronephrosis) and heart (aterial septal defect, ventricular septal defect and patent ductus arteriosus). Also, cystic hygroma, polydactyly and club or rocker-bottom feet could be identified. All these anomalies can be observed easily by ultrasound examination in the second trimester of pregnancy. Also in the cases of trisomy 13 some sonographic markers can be discovered, but they are nonspecific. Such markers

are intrauterine growth restriction (IUGR), mild dilatation of the lateral cerebral ventricles, hyperechoic bowel and echogenic intracardiac foci. The most commonly identified marker is echogenic intracardiac foci. A specific association that can be considered is the one between echogenic intracardiac foci and the hypoplastic left side of the heart [62].

3.2.2.2. Trisomy 18

Trisomy 18 is a severe disorder characterized by a lot of congenital anomalies that could be identified by ultrasound examination during the second trimester of pregnancy. These anomalies involve the central nervous system (hydrocephalus, spina bifida, vermian agenesis), lymphatic system (cystic hygroma, nonimmune hydrops), cardiovascular malformations (ventricular and atrial septal defects, patent ductus arteriosus and polyvalvular disease), thorax and abdomen (diaphragmatic hernia, tracheoesophageal fistula, omphalocele), genitourinary system and skeletal system (clenched hands, club feet, radial aplasia, limb shortening). Also, the ultrasound examination shows an intrauterine growth restriction associated with polyhydramnios [75, 76].

Some subtle anomalies discovered by ultrasound examination were considered markers for trisomy 18. Such anomalies are choroid plexus cysts, brachycephaly, "strawberry-shaped" head and single umbilical artery [62]. Choroid plexus cysts are a relatively common variant during the second trimester. It is transient, and if the karyotype is normal it does not have an adverse outcome. The median prevalence of choroid plexus cysts in the general population has been reported as 1–2%. The importance of this marker is limited. Snijders et al. discovered only two cases of chromosomal anomalies in a cohort of 107 fetuses with isolated choroid plexus cysts who had karyotyping. On the other hand, the same authors found no chromosomal anomaly among the 174 children with choroid plexus cysts who did not have amniocentesis [77]. However, Nyberg et al. noted that choroid plexus cysts are observed in 30–40% of fetuses with trisomy 18 before 20 weeks, but usually this marker was associated with other major anomalies specific to trisomy 18 [62]. The presence of isolated choroid plexus cysts is associated with higher likelihood ratios for trisomy 18. Thus, Ghidini et al. [78] found a likelihood ratio of 7.1 and Yoder et al. [79] found a likelihood ratio of 13.8 for trisomy 18 in the presence of isolated choroid plexus cysts. Nyberg et al. concluded that fetal karyotyping should be offered only in cases when all the following conditions are met: maternal age at delivery is over 36 years, the biochemical risk for trisomy 18 is more than 1/3000 and choroid plexus cysts are large. However, the detection of isolated choroid plexus cysts imposes an ultrasound follow-up that can show other abnormalities that were previously missed [62].

3.2.2.3. Trisomy 21

During the second trimester of pregnancy, congenital anomalies in trisomy 21 fetuses are not frequently discovered. Before 20 weeks, the detection of such anomalies in trisomy 21 is around 16% and this value reflects the low sensitivity of sonography for detection of cardiac defects. The most frequent anomalies are cardiac defects, hydrops, cystic hygroma and duodenal atresia associated with esophageal atresia [62]. However, a sonographic scan at

24 weeks of gestation performed by a competent specialist could discover around 50% of congenital anomalies (including subtle ventricular septal defects) in trisomy 21 fetuses [80].

The markers for trisomy 21 in the second trimester of gestation are nuchal thickening, hyperechoic bowel, shortened limbs, pyelectasis, echogenic intracardiac foci, widened pelvic angle, shortened frontal lobes, clinodactyly, pericardial effusion, right–left disproportion of the heart and small ears [81, 82].

Each marker taken alone has a low sensitivity, but the presence of more than one marker is detected in minimum half of the pregnancies with trisomy 21. The presence of only one marker is discovered in around 22.6% of fetuses with trisomy 21 but also in 11% of normal fetuses. In opposition, identification of more than two markers is present in one-third of pregnancies with trisomy 21, while only 2% of normal pregnancies show such a characteristic. The risk for trisomy 21 is twofold higher if one marker is detected, but the risk becomes 10-fold higher when two markers are present and gets more than 100-fold when three markers are identified. The search of these markers is widely referred to as a "genetic sonogram". The results of a genetic sonogram depend on gestational age, quality of the apparatus and competence of the sonographer and the type of marker, but the minimum sensitivity of this method is around 60% [62]. The big inconvenience of this screening is the high false positive rate associated with the use of multiple sonographic markers that generates anxiety among low-risk patients and imposes an invasive procedure to deny the presence of trisomy 21 [83].

To improve the use of sonographic markers in detection of trisomy 21, Bromley et al. proposed a scoring index, and amniocentesis is offered only to those with a score of 2 or higher. A major congenital anomaly, nuchal thickening and an age bigger than 40 years are noted with 2 points each. Hyperechoic bowel, shortened femur, shortened humerus, pyelectasis, echogenic intracardiac foci and age between 35 and 40 years are noted with 1 point. The authors showed that a score ≥ 2 is associated with 75.5% of 21 trisomic pregnancies, while in normal pregnancies such a score is discovered in only 5.7% of cases [84]. An improvement of sonographic screening is the combination of this with biochemical screening, because the sonographic features are independent of biochemical analytes [85].

3.2.2.4. Nuchal thickening

Redundant skin on the neck is a clinical feature of infants with trisomy 21 and it was first reported by Benacerraf et al. as nuchal thickening during the second trimester [86]. Nuchal thickening is one of the most important markers of trisomy 21 during the second trimester. The sensitivity of this criterion is 20–40%. First, a threshold ≥6 mm after 15 weeks of pregnancy was associated with a high risk of trisomy 21, but now a nuchal thickening of greater than 5 mm up to 20 weeks is considered an adequate value [87]. The normal nuchal thickness varies with gestational age. Thus, the better choice is the use of multiple-of-the-median data, comparing the nuchal measurement with the expected measurement. In these conditions, the calculation of likelihood ratios would permit integration with maternal serum biochemical markers for a combined risk [88].

3.2.2.5. Hyperechoic bowel

Hyperechoic bowel is detected with increased frequency in cases with aneuploidy (including trisomy 21) but it is nonspecific and could be observed also in about 0.5% of normal fetuses. In addition, this marker was identified also in other disorders like bowel atresia, congenital infection, meconium ileus secondary and cystic fibrosis. The presence of hyperechoic bowel also represents a risk factor for intrauterine growth retardation, fetal death and placenta-related complications [62]. To standardize this feature, a scale with three values was proposed: grade 1—mildly diffuse echogenic, grade 2—moderately focal echogenic and grade 3—very echogenic (like in a bone). The echogenicity of normal bowel increases with transducer frequency, and to minimize the subjectivity, is preferable to take in consideration only the cases with moderate and markedly hyperechoic bowel. In these situations, the risk for fetal aneuploidy is high, but the sensitivity remains acceptable [89].

3.2.2.6. Skeletal abnormalities

Skeletal abnormalities in trisomy 21 that could be identified in the second trimester of gestation are limb shortening, clinodactyly and widened pelvic angle. The last two are difficult to detect and for this reason are not commonly used in screening protocols [62]. A slightly rhizomelic short stature is characteristic for trisomy 21, with both shortening of femur and shortening of humerus. These features can be detected in some cases with trisomy 21 during the second trimester [90], but a shortened humerus is a slightly more specific indicator than a shortened femur. These markers vary with gestational age, ethnic group and fetal gender. The practical use of these parameters is based on the comparison of measurement of humerus and femur length with expected length of these bones. Optimal results were obtained by using a multiple-of-the median data and corresponding likelihood ratios rather than a single cut-off. However, in a simplified manner a single cut-off of 0.91 multiples of the median for a short femur and 0.89 for a short humerus could be used [62, 90].

3.2.2.7. Renal pyelectasis

Mild pyelectasis (hydronephrosis) is associated with high risk for aneuploidy (especially for trisomy 21). This marker was also detected in about 3% of normal fetuses. The interpretation of this feature is very subjective because its prevalence varies with gestational age and it is influenced also by maternal hydration and degree of fetal bladder distension. Renal pyelectasis is measured as the fluid-filled renal pelvis in an anterior–posterior dimension. The threshold for a positive finding is a dimension ≥3. At this threshold, the risk of trisomy 21 is 1.6-fold over the baseline risk [62, 91].

3.2.2.8. Echogenic Intracardiac foci

Echogenic intracardiac foci (EIF) are marker that are found in 3–4% of normal fetuses, with a three times bigger prevalence in Asian populations [92]. The evaluation of EIF is very subjective and depends on resolution of the sonographic equipment, technique, thoroughness of the examination, the sonographer's experience and fetal position. In normal fetuses, it typically

disappears during the third trimester of pregnancy [93]. The EIF is not an efficient marker for detection of trisomy 21 because it occurs only in 16% of fetuses with this anomaly and the false positive rate is 17%. In contrast, EIF is present in 29% of those with trisomy 13% [94, 95]. The likelihood ratio of EIF in trisomy 21 has been estimated in the range of 1.8–4.2 [62]. Usually, the EIF is detected in the left ventricle, but right-sided or bilateral EIF had an approximately twofold greater risk of aneuploidy compared with left-sided foci [96].

3.2.2.9. Mild ventricular dilatation

The lateral cerebral ventricles normally show a mean diameter of 6.1 ± 1.3 mm. The presence of ventriculomegaly is suspected when diameter reaches 10 mm and such change has been associated with trisomy 21 (and also with other aneuploidies) [97]. The prevalence of this marker in trisomy 21 fetuses varies between 2.8 and 5% [98–100]. On the other hand, van der Hof et al. showed that mild ventriculomegaly is present in 0.15% of euploid fetuses compared with 1.4% of the fetuses with trisomy 21, with a likelihood of aneuploidy 9 times greater in aneuploid fetuses versus normal fetuses [101].

3.3. Prenatal diagnosis methods

The prenatal diagnosis is based on the chromosomal or molecular analyses of embryonic or fetal cells obtained using an invasive method.

3.3.1. Invasive methods to obtain embryo-fetal cells

The methods for obtaining embryonic or fetal cells are chorionic villus sampling, amniocentesis and cordocentesis.

Chorionic villus sampling (CVS) is a method that allows prenatal diagnosis in the first trimester of pregnancy, typically at 10–12 weeks of gestation. It is done transabdominal or transcervical, under ultrasound guidance. The samples obtained contain trophoblast cells (derived from fetus) and maternal decidua cells. The last must be removed before analysis. The major advantages of this technique are reduced maternal risk generated by termination of pregnancy and a limited emotional trauma on the patient. The risks of this method are injury of the embryo (especially limb abnormalities in early procedures), miscarriage, bleeding or embryonic infection [102, 103]. The risk of miscarriage after performing chorionic villus sampling was initially estimated at 2–3%. Recent data disproves this risk, showing that the real risk is about 0.22% [104].

Amniocentesis is performed from the 16th week of gestation (rarely sooner) and involves the transabdominal extraction of 10–20 ml of amniotic fluid, under ultrasound guidance. The method has a low risk of miscarriage and other incidents. The risk of miscarriage was initially estimated at 1%, but recent data disproves this risk, showing that the real risk is about 0.11%. There is also a risk of amniotic fluid leakage and some rare complications (placental hemorrhage, intra-amniotic infection, abdominal wall hematoma and fetal lesion). A major disadvantage of this method is that it provides the final results of prenatal diagnosis in the second half of the pregnancy [103–105].

Cordocentesis is a method that consists of transabdominal or transvaginal puncture of the umbilical cord under ultrasound guidance in order to obtain small amounts of fetal blood. The method is performed after week 20 of pregnancy and has a reduced applicability in the diagnosis of chromosomal diseases. It is usually used to diagnose fetal blood diseases. Risk of fetal loss is high, about 3%. The major advantage of the diagnosis of chromosomal disorders is associated with the best results of blood cells culture in comparison with amniotic or chorionic cells [106].

3.3.2. Methods of prenatal diagnosis

The biological material obtained via invasive prenatal diagnosis methods can be used for cytogenetic or molecular assays.

3.3.2.1. Cytogenetic techniques

Cytogenetic techniques require dividing cells. They can be applied directly or after a cell culture.

3.3.2.1.1. First trimester cytogenetic analyses

In the case of trophoblast cells, obtained by chorionic villi sampling, the analysis can be done directly because the rate of division of placental tissue is high. However, even in the case of chorionic tissue, the cell culture is preferable because after harvest the quality is better and the cell number is high. Direct analysis of dividing cytotrophoblast cells is provided after uniform staining or after a chromosome banding procedure. The major advantages of this method are rapid final results (2/3 days) and absence of maternal cell contamination [103, 107].

The culture of chorionic villus cells is done in a special medium, after fragmentation of trophoblast tissue. The culture allows the formation of cell colonies adhering to the surface of the flask culture. At the end of 12–14 days, the cell division is blocked and chromosomal preparations are made. The chromosomes are banded using an R banding protocol because it does not require an aging period. The metaphases are analyzed on an optical microscope in direct illumination, using an immersion objective [103, 107].

The main advantage of cytogenetic diagnosis in the first trimester of pregnancy is achieving final results quickly, which decreases the time of uncertainty, the psychological distress of the parents and allows the end of pregnancy in the first trimester, when methods are easier and less traumatic [103, 107].

The main disadvantages of the chromosomal analysis in cells obtained by CVS are reduced number of mitosis and poor quality of chromosomal preparations which reduces resolution, allowing only the identification of numeric chromosomal abnormalities and those structural abnormalities of large dimensions. Another inconvenience is the possible detection of chromosomal mosaics. This could be real or confined to placenta. The inconsistencies can be explained by possible contamination with maternal cells, a chromosomal abnormality that occurs during the culture or the real existence of a placental mosaicism. In these cases, the karyotype must be

repeated after amniocentesis or cordocentesis to determine real fetal chromosomal formula. Another problem associated with CVS is the failure of culture that requires the repeat of CVS or the application of amniocentesis in the second trimester of gestation [103, 107].

3.3.2.1.2. Second-trimester cytogenetic analyses

Fetal karyotype analysis, using cells obtained by amniocentesis, requires a step of 10–14-day cell culture. Culture technique and processing steps are similar to those used in the case of trophoblastic cells. Amniotic cultures can be done in situ (allow differentiation between mosaics and pseudomosaics) or in culture flasks. In the last case, at the end of the cultures, the separation of cells from the vessel is obtained using an enzymatic treatment. The contamination with maternal cells is insignificant and the quality of prepared chromosomes is better in comparison with chorionic villus cells [103, 107].

3.3.2.2. Molecular techniques

Molecular techniques for prenatal diagnosis of chromosomal disorders were introduced in the medical practice in the last 25 years with the aim of improving the resolution of chromosomal detection and to eliminate the major inconvenient of classic cytogenetic techniques—the requirement of cell culture. Such techniques are fluorescence in situ hybridization (FISH), quantitative fluorescent polymerase chain reaction (QF-PCR), multiplex ligation probe amplification (MLPA) and array-comparative genome hybridization (CHG).

3.3.2.2.1. Fish

FISH technique allows a hybridization between a fluorescent probe and a complementary DNA sequence present on the target chromosome. In prenatal diagnosis this method has been developed in order to identify the aneuploidy of chromosomes 21, 18, 13, X and Y (the most common chromosomal abnormalities) (**Figure 7**). The probes for chromosomes 13 and 21 are locus specific while the rest are centromeric. The method is done on uncultivated interphasic amniocytes. The final results are obtained in 24–48 hours after amniocentesis which allows maternal anxiety relief [108–110]. The results are obtained after the evaluation of minimum 50 cells. The main advantages are faster results, high specificity and sensibility (close to 100%) and the absence of cell culture. The inconvenients are impossibility of detection of blood contamination, bad quantification of chromosomal mosaics and impossibility of detection of structural abnormalities of chromosomes investigated. FISH can be done also for the evaluation and elucidation of uncommon structural abnormalities: microdeletion syndromes, cryptic or subtle duplications and translocations, complex rearrangements and marker chromosomes [111].

3.3.2.2.2. QF-PCR

QF-PCR method allows the detection of major prenatal numerical chromosome disorders within 24–48 hours. The method identifies polymorphic chromosomal specific repeat sequences (short tandem repeats—STRs) that are amplified by the PCR using fluorescent

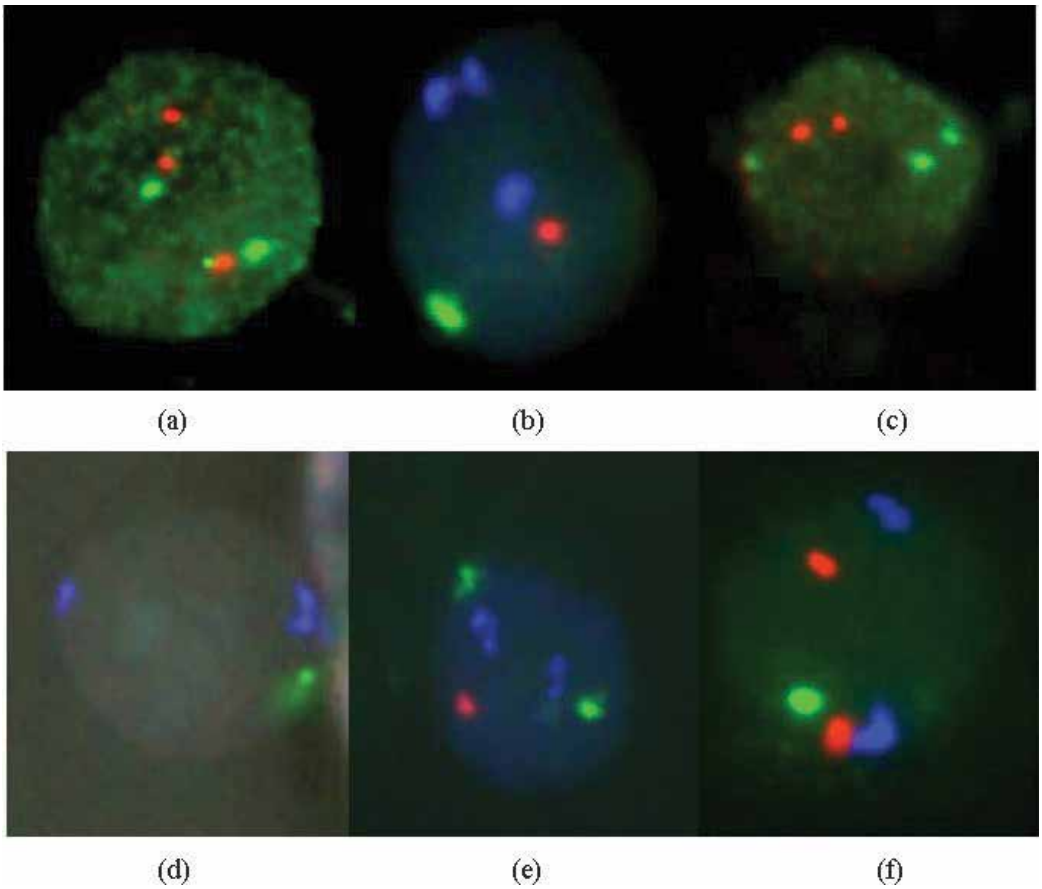

Figure 7. Aneuploidies detected using FISH method. (a) Trisomy 21; (b) Trisomy 13; (c) Trisomy 18; (d) Monosomy X; (e) Trisomy XXY; (f) Trisomy XYY (collection of prenatal diagnosis laboratory of "Cuza Vodă" obstetrics and gynecology hospital, Iaşi, Romania).

primers. The amplification is observed and quantified using a genetic analyzer and appropriate software. In a normal case, two peaks of fluorescence activity were obtained that reflect a normal heterozygous fetus (1:1 diallelic normal ration). Trisomic samples demonstrate either three peaks with a ratio of 1:1:1 (trisomic triallelic) or two peaks with a ratio of 2:1 (trisomic diallelic) for each informative probe. For each chromosome four or more polymorphic STR markers are analyzed, and thus only few fetal samples will remain uninformative. By comparison with FISH, QF-PCR can detect mosaicisms that have a rate of 20–30% and also identify the maternal cell contamination. The main advantage of QF-PCR is that it is considerably more cost-effective particularly when larger sample numbers are processed [111]. The main limitation of assay is the impossibility to detect triploidy [112].

3.3.2.2.3. MLPA

MLPA is a PCR-based method used for quantification of the copy numbers of specific sequences of DNA. This method uses a two-part probe of unique length that, when hybridized

to adjacent target sequences on genomic DNA, can be joined together by the DNA ligase. This permits the amplification of all target sites, using a single primer pair that is complementary to the two free ends which are common to all probes. The PCR products are run on a capillary electrophoresis system and MLPA allows relative quantification of up to 50 different target sequences in one reaction. MLPA is a fast method (final results in 2–3 days) and it is less labor intensive and cheaper compared to karyotyping and FISH. The main domain of application of MLPA in prenatal diagnosis is the detection of most common aneuploidies (of chromosomes 21, 18, 13, X and Y) but this technique has some inconvenients associated with the impossibility of detection of triploidy, mosaicisms and maternal contamination. Other applications concern the cases with multiple congenital anomalies and intrauterine growth retardation detected by ultra-sonography. In these situations, using subtelomere probes or specific probes for some specific syndromes (velocardiofacial, Williams, Wolf-Hirschhorn, Prader-Willi, etc.), MLPA could confirm the presence of some subtle unbalanced structural chromosomal anomalies. MLPA can also be used to determine the origin of marker chromosomes, frequently discovered in chromosomal prenatal diagnosis [113, 114].

3.3.2.2.4. Array-CGH

Array CGH is a method that can detect simultaneously sub-microscopic copy number changes across the whole genome, thus overcoming the limitations of karyotyping and locus-specific techniques. Array CGH has become an important tool for clinical diagnostics and gene-identification studies and is having a great impact on the understanding of pathologies, the counseling of families and patient management. Different types of array CGH platforms at an increasingly higher resolution have been developed, differing mainly in the type of the interrogating probes and in their coverage of the genome. The microarray consists of thousands of unlabeled different probes (particular to a specific DNA sequence) fixed on a glass slide or a silicon chip, arranged in orderly rows in the form of a network with a specific density ("DNA chip"). The two samples of DNA (genomic DNA extracted from patient and reference sample) are fragmented and labeled with different fluorochromes (Cy3—green for patient and Cy5—red for test sample), mixed in equal amounts, denatured and co-hybridized on the microarray. The chips are scanned with a microarray scanner and the images obtained are analyzed using a programme that determines the intensities of emissions of both red and green fluorochrome for each spot on the network and calculates their report. This ratio is in proportion to the number of copies of the patient's genome DNA and test sample. If the intensities of the two fluorochromes are equal to a spot (ratio Cy3/Cy5 = 1, or $\log_2 = 0$), this region of the patient's DNA is interpreted as normal. If there is a deletion, the test sample hybridizes preferentially to DNA control, and the ratio Cy3/Cy5 will be smaller than 1 (ex. 1:2, $\log_2 = -1$). On the other hand, if there is a duplication, the patient DNA will hybridize preferentially, and the ratio Cy3/Cy5 will be greater than 1 (ex. 3:2, $\log_2 = 0.58$.) [115].

The application of array CGH eliminates the majority of fetal chromosomal analysis inconveniences: the long period of waiting for the final result, the possible failures of culture, the poor quality of chromosomal preparations and the reduced number of chromosomal bands. The method uses genomic DNA from fetal cells and can be applied on cells in interphase or division. The sensitivity of method is higher than the standard karyotype, and thus array-CGH allows the detection of all unbalanced chromosomal abnormalities (excepting polyploidy), even the smallest

such subtelomeric rearrangements. In the prenatal diagnosis, "targeted" arrays are commonly used, containing genomic clones for subtelomeric regions and those that are frequently involved in microdeletion/microduplication syndromes. The major advantage of array-CGH is the very high resolution, this technique allowing the detection of genomic changes of 50–100 kb. The main inconvenient is the possibility of detecting copy number variants (CNVs) with unknown clinical consequences. In this case, with limited possibility of fetal phenotype investigation, the evaluation of functional consequences of genomic changes is very difficult. A CNV discovered in these conditions is most probably pathogen if it is de novo, has a size >1 Mb, contains a deletion rather than a duplication and involves a gene-rich area [116–118].

Nowadays, in developed countries, the array-CGH represents the first option in the prenatal genetic investigation of fetuses with multiple congenital anomalies detected by ultra-sonography.

4. The combined use of biochemical and ultrasound prenatal screening

Each method used in prenatal screening has some inconvenients that can be limited by using a combination of multiple assays. Biochemical and ultrasound screening can be done at the same time or at different times. The first method is called concurrent and the second sequential. The sequential protocol can offer the results when all analyses are complete—non-disclosure method—or at the time when each analysis is finished—step-wise method [119].

The biochemical screening in the first trimester is based on the detection of PAPP-A and ß-hCG. The PAPP-A has a different discriminatory power in a different week of gestation with a decline from the 10th to 13th week. For a predicted detection rate with 5% false positive rate the combination of PAPP-A and ß-hCG has a detection rate of 72% in 10th week, 65% in 11th week, 57% in 12th week and 51% in 13th week. By using a combination between double test (PAPP-A and ß-hCG) with detection of aFP and μE during second trimester, the detection rate increases to 78% (with PAPP-A measured in the 10th week), 72% (with PAPP-A measured in the 11th week), 66% (with PAPP-A measured in the 12th week) and 61% (with PAPP-A measured in 13th week) [119].

Nuchal translucency (NT) is independent for gestational age and its screening can be done at 11–13 weeks, with a detection rate of 73% for a 5% false positive rate. By combining biochemical screening in the first trimester with sonographic examination, the detection rate can increase. The best solution is to apply the biochemical screening in weeks 10–12 and the sonographic examination 1 week later. Using this protocol, the detection rate is 92% with double test done in the 10th week, 89% with double test done in the 11th week and 87% with double test done in the 12th week [119].

The best results are obtained using a non-disclosure protocol that combined NT with double test in the first trimester and detection of aFP and μE in the second trimester. This test, called integrated test, generates a detection rate of 93% (with PAPP-A measured in the 10th week), 92% (with PAPP-A measured in the 11th week), 91% (with PAPP-A measured in the 12th week) and 90% (with PAPP-A measured in the 13th week) for a 5% false positive rate. The use of such an algorithm has the inconvenience of having to wait a long time because the final

results are done during the second trimester which increases the anxiety of the couple and limits its reproductive options [119, 120].

5. Conclusions

The chromosomal disorders have an important impact on the health of future infants. For this reason, in the last decade, important efforts were made to improve the prenatal screening and diagnosis. The prenatal screening uses non-invasive methods that allow the detection of pregnancies with risk of chromosomal anomalies. These methods can be done in the first or second trimesters of pregnancy. The first-trimester screening methods are biochemical and sonographic. Biochemical screening for first trimester uses the detection of PAPP-A and β-hCG in the maternal serum. Sonographic examination in the first trimester allows the detection of some markers—nuchal translucency, absence of the nasal bone, tricuspid regurgitation or abnormal blood flow through the ductus venosus—that are associated with high risk for aneuploidy. The prenatal screening during the second trimester of pregnancy can be done by biochemical or sonographic examinations as well. The biochemical screening is based on the detection of aFP, hCG (or β-hCG), μE and inhibin A in maternal serum. The sonographic examinations in the second trimester can identify some structural defects (cardiac, cerebral, renal, etc.) but more frequent are the sonographic markers like nuchal thickening, hyperechoic bowel, shortened limbs, pyelectasis, echogenic intracardiac foci, widened pelvic angle, and so on. The best choice for prenatal screening of aneuploidies is the use of combined biochemical (in the first and second trimesters) and sonographic examination. Such protocol has a detection rate higher than 90% at 5% false positive rate. The prenatal diagnosis requires an invasive procedure (chorionic villus sampling, amniocentesis, cordocentesis) to obtain fetal material. The fetal cells can be used for cytogenetic or molecular analyses. The cytogenetic analyses (fetal karyotype) require a long-time cell culture and have a limited resolution but have the advantage of diagnosis of all chromosomal anomalies. Some molecular analyses (FISH, QF-PCR, MLPA) are targeted methods and can identify only specific anomalies, such as aneuploidies of chromosomes 21, 18, 13 X and Y. Array-CGH (molecular karyotype) eliminates the major inconvenience of karyotype (long-time culture and limited resolution) but is expensive and thus it's use remains prohibitive in countries with limited economical resources. However, the implementation of prenatal screening and diagnosis allows many couples the opportunity to take an informed decision in relation to their baby's future.

Author details

Eusebiu Vlad Gorduza[1]*, Demetra Gabriela Socolov[2] and Răzvan Vladimir Socolov[2]

*Address all correspondence to: vgord@mail.com

1 Medical Genetics Department, "Grigore T. Popa" University of Medicine and Pharmacy, Iaşi, Romania

2 Obstetrics and Gynecology Department, "Grigore T. Popa" University of Medicine and Pharmacy, Iaşi, Romania

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Chapter 19

Genomic Testing for Prenatal Clinical Evaluation of Congenital Anomalies

Gorazd Rudolf, Luca Lovrečić, Aleš Maver, Marija Volk and Borut Peterlin

Additional information is available at the end of the chapter

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Abstract

Congenital anomalies occur in about 2–3% of liveborn and 20% of stillborn infants. They constitute a serious public health and epidemiological problem. The etiology of congenital anomalies is complex; they can result from genetic factors, environmental factors, or a combination of both. It is estimated that genetic factors represent an important cause of congenital anomalies and may be due to different genetic mechanisms: aneuploidies, deletions and duplications of DNA segments, and single gene disorders. Due to the genetic complexity, the targeted prenatal genetic diagnostics of congenital anomalies is usually problematic and challenging. In recent years new diagnostic algorithms for prenatal genetic testing are being developed with the advent of new genomic technologies, like molecular karyotyping and next-generation sequencing. These technologies offer testing options that exceed conventional karyotyping and targeted molecular genetic testing with better diagnostic yield. In this chapter, an overview of the conventional genetic diagnostic approach and the use of new genomic technologies in the diagnostic algorithm of prenatally detected congenital anomalies are discussed.

Keywords: congenital anomalies, epidemiology, etiology, conventional karyotyping, molecular karyotyping, next-generation sequencing, prenatal diagnostics

1. Introduction

Congenital anomalies (CAs) occur in about 2–3% of liveborn and 20% of stillborn infants. They are an important cause of neonatal mortality, children morbidity, and long-term disability and

so constitute a serious public health and epidemiological problem [1]. A significant proportion of CAs is detected before birth by routine ultrasound examination and other screening techniques [2]. Prenatal identification of CAs can have significant emotional and psychological consequences for parents and affected babies [2]. Therefore, it is imperative to make the right diagnosis as soon and as accurate as possible. Genetic testing in prenatal period is an area with very sensitive and ethically challenging situations [3]. Determining a genetic diagnosis prenatally permits parents to make informative reproductive decisions and to be counseled about possible fetal outcomes [4]. It adds important information for current pregnancy in the terms of full phenotype beyond ultrasonographically detected abnormalities on the one hand and postnatal prognosis on the other [3]. Consequently, it is important to use appropriate genetic testing approach to obtain a specific diagnosis.

In recent years new diagnostic algorithms for prenatal genetic testing are being developed with the advent of new genomic technologies, like molecular karyotyping (comparative genomic hybridization) and next-generation sequencing (NGS). These technologies offer testing options that exceed conventional karyotyping of the fetus and provide better diagnostic yield. Despite the evidence of important additional diagnostic yield of new technologies in the etiology of CAs, they have not been systematically implemented in clinical prenatal diagnostic algorithms in several national healthcare systems.

2. The epidemiology and etiology of CA

A CA is defined as any structural anomaly present at birth. Major CAs are anomalies that have medical, surgical, or cosmetic significance and occur in about 2–3% of liveborn and 20% of stillborn infants [1]. Thus, CAs are more prevalent that many chronic childhood diseases, such as autism, pediatric cancers, and type 1 diabetes, are an important cause of neonatal mortality, children morbidity, and long-term disability [1, 5]. Therefore, they represent an important public health and epidemiological problem.

CAs can be isolated or present in a characteristic pattern affecting one or more organ systems.

The overall prevalence of most major CAs does not vary much across ethnic groups [6, 7]. However, the risk for different types of anomalies is variable and may be related to genetic susceptibilities and also to cultural and social differences that can influence exposures (e.g., neural tube defects due to a dietary deficiency of folic acid) [6, 7]. The prevalence of most major birth defects over time has remained constant, but some have shown a significant increase such as gastroschisis [6, 7].

The etiology of CAs is complex. CAs can be the result of genetic factors, environmental factors, or a combination of both [8, 9], although the underlying etiology often remains unknown. It is estimated that genetic factors represent an important cause of CAs and may result from different genetic mechanisms: the most common are aneuploidies, deletions, and duplications of DNA segments (collectively known as CNV), and single gene disorders [8, 9]. Some disorders have an

epigenetic basis; genes can be silenced or activated by modifications that may depend on the parent of origin or other influences [4].

With the traditional diagnostic approach using conventional karyotyping and direct molecular genetic testing, the etiology of CAs remains undiagnosed in 65–70%, including cases with multifactorial or polygenic etiology (e.g., isolated neural tube defects or cleft palate), 15–25% is thought to be genetic or genomic—chromosomal in 10–15% and monogenic in 10%—and 10% is thought to be due to environmental factors [4]. Although most CAs are isolated and sporadic; the genetic contribution has long been recognized, and specific genes involved are increasingly being identified. However, the majority of isolated CAs are thought to be caused by a complex interplay of genetic and environmental factors and follow the so-called multifactorial or polygenic inheritance [4, 8, 9]. On the other hand, multiple CAs are often part of a syndrome, of chromosomal or monogenic etiology.

In the prenatal settings, the frequency of chromosomal abnormalities depends on many factors: the gestational age, type of the anomaly, the number of anomalies, and the combination of anomalies identified [10]. In retrospective series, chromosomal abnormalities were found in 2–18% of cases when isolated and in 18–35% when multiple CAs were prenatally detected on ultrasound [10, 11]. Chromosomal abnormalities are more common in spontaneous abortions (50%) than in stillbirths (6–13%) [12].

Due to the frequency, morbidity and lethality CAs pose an important public healthcare problem. For the planning of preventive healthcare measures, it is very important to determine the epidemiology and etiology of CAs.

The following chapters give an overview of the conventional genetic diagnostic approach and the use of new genomic technologies in the prenatal genetic diagnosis of CAs.

3. Conventional genetic diagnostic approach

Currently fetal karyotyping and targeted genetic testing are still most commonly used in the genetic diagnostic evaluation of high-risk pregnancies including morphologically abnormal fetus detected by ultrasound examination and positive result of the screening test or due to parental chromosome rearrangement or genetic disorder with a known pathogenic variant. Despite the recent shift of genetic diagnostics toward genomic approach, the conventional diagnostic approach encompassing the karyotyping and targeted molecular genetic testing is worth noting.

3.1. Karyotyping

To identify possible genetic causes underlying ultrasonographically detected CAs or positive result of the screening test (nuchal translucency, combined screening test, triple/quadruple hormone test), a full chromosome analysis has been widely used and regarded as the gold

standard from the late 1990s to about 2010. A diagnostic yield of classical karyotype is more than 18% in fetuses presenting with isolated or multiple CAs [10].

As chromosome analysis is subjective and experience-dependent [13], its insufficiencies have been complemented by fluorescent in situ hybridization (FISH) analysis, where a DNA-specific fluorescent probe is hybridized to the complementary sequence in a cell preparation. In contrast to conventional chromosome analysis, FISH can be used to study cultured or direct cell preparations (metaphase/interphase FISH). FISH allows for the detection of repetitive regions like satellites in the acrocentric chromosome or variable length of pericentromeric heterochromatin not covered by genomic methods [13]. Currently, FISH analysis is a valuable tool for the identification of the origin of the marker chromosome composed of heterochromatin [14] and complex chromosome rearrangements and mechanism of the chromosome rearrangement [15, 16]. Locus-specific fluorescent probes detect subtelomere and interstitial submicroscopic chromosomal rearrangements associated with clinically recognizable phenotypes with diagnostic yield of 3–6% for chromosome abnormalities [17]. However, screening with FISH for tandem duplications seems to be of limited value.

FISH is a more targeted approach, because it requires prior knowledge of chromosome region of interest but has limited utility as a first-tier investigation [18].

Chromosome analysis may also be considered as a quantitative method, which can accurately detect the proportion of the mosaicism. As many as 0.16% of cases with low-level yet clinically significant chromosome mosaicism would be undetected by array CGH method [18]. In addition, in mosaic cases with two abnormal cell lines resulting in a no-net gain or loss (i.e., 45,X/47, XXX) array, CGH would return to normal result [18].

Different types of mosaicism can be found in prenatal diagnostics, like confined placental mosaicism (CPM), true fetal mosaicism, and clonal expansion because of in vitro cultivation [20]. CPM is found in about 1–2% of chorionic villi samples, and certain chromosome trisomies are typically found, like trisomy of chromosome 2, 7, or 16 [19].

Over the last decades, chromosome analysis has been the cornerstone in prenatal genetic diagnosis. In fetuses with multiple CA, there is a chance of more than 18% to detect a chromosomal abnormality [11], while a chance for a chromosomal aberration in cases with an isolated CA is not well determined [20, 21].

There are some pros to why fetal karyotyping remains in the everyday genetic practice. The chromosome analysis assesses the number (aneuploidies) and the structure of chromosomes (chromosome rearrangements) in a single assay (i.e., free trisomy 21 versus unbalanced Robertsonian translocation involving chromosome 21 or balanced reciprocal translocations) [18].

However, because of its low resolution, the need for cell cultivation, which is time-consuming and artifact prone, and the inability to detect complex abnormalities, the chromosome analysis is placed behind other high-throughput genomic investigations [19].

Currently, karyotyping remains the investigation of choice for low-risk pregnancies with normal fetal morphology, like advanced maternal age with increased risk for trisomy 21 [22].

3.2. Targeted molecular genetic testing

As mentioned above, about 10% of CAs is thought to be associated with monogenic disease [4]. Ultrasound examination can detect many fetal structural abnormalities, from the early anatomic survey in the first trimester to morphology and biometry in the second trimester and monitoring of the fetal growth in the third trimester. In addition to ultrasound, fetal magnetic resonance is now widely used to improve imaging of the central nervous system structures [23].

The conventional genetic approach using targeted molecular methods, like Sanger or PCR, is useful (enables) in the diagnostics of cases with ultrasonographically well-defined phenotypes associated with specific diagnostic hypothesis in genetically homogenous CA (e.g., TAR, achondroplasia) and is the method of choice for prenatal testing in cases of familial monogenic condition with known pathogenic variant [24]. In cases with poorly defined phenotype and genetically heterogeneous CAs (many genes responsible for the same phenotype), this approach rarely warrants the diagnosis.

While the conventional genetic diagnostic approach is time-consuming, labor-intensive, and with limited diagnostic yield, the new genomic approaches and technologies, like molecular karyotyping and next-generation sequencing, offer new possibilities to establish specific prenatal genetic diagnosis in high-risk pregnancies.

3.3. Molecular karyotyping

Growing knowledge and important technical evolution in the last two decades enabled us, in the clinical context, to detect and interpret smaller and smaller genomic imbalances. The classical karyotyping has been replaced first by comparative genomic hybridization and soon thereafter with array-based CGH (aCGH). It is becoming widely applied in the prenatal setting, where it is recommended by many professional societies for routine prenatal diagnostic testing in fetuses with ultrasound anomalies [25].

The comparative genomic hybridization using microarrays (aCGH) is based on competitive hybridization of short segments of whole genome DNA to preprepared probes (short sequences of DNA), spotted on a glass slide in a precise grid (microarray). The DNA of a patient and reference sample DNA are both digested with restriction enzymes to generate short fragments and after that labeled with two different fluorescent dyes. Both patient and reference DNAs are combined and hybridized to the same microarray, thereby competing for the same probes. A specialized scanner measures signal intensities and dedicated software links signals to specific genomic regions (**Figure 1**). When there is a deletion in the patient, we see it as a predominance of reference DNA in that genomic region. As a result, a relative log ratio of patient's signal compared to reference signal gives a curve with negative values. Despite enabling the detection of progressively smaller genomic imbalances, one needs to be aware of the limitations—the technique will not detect low-level mosaicism, triploidy, balanced translocations, and point mutations.

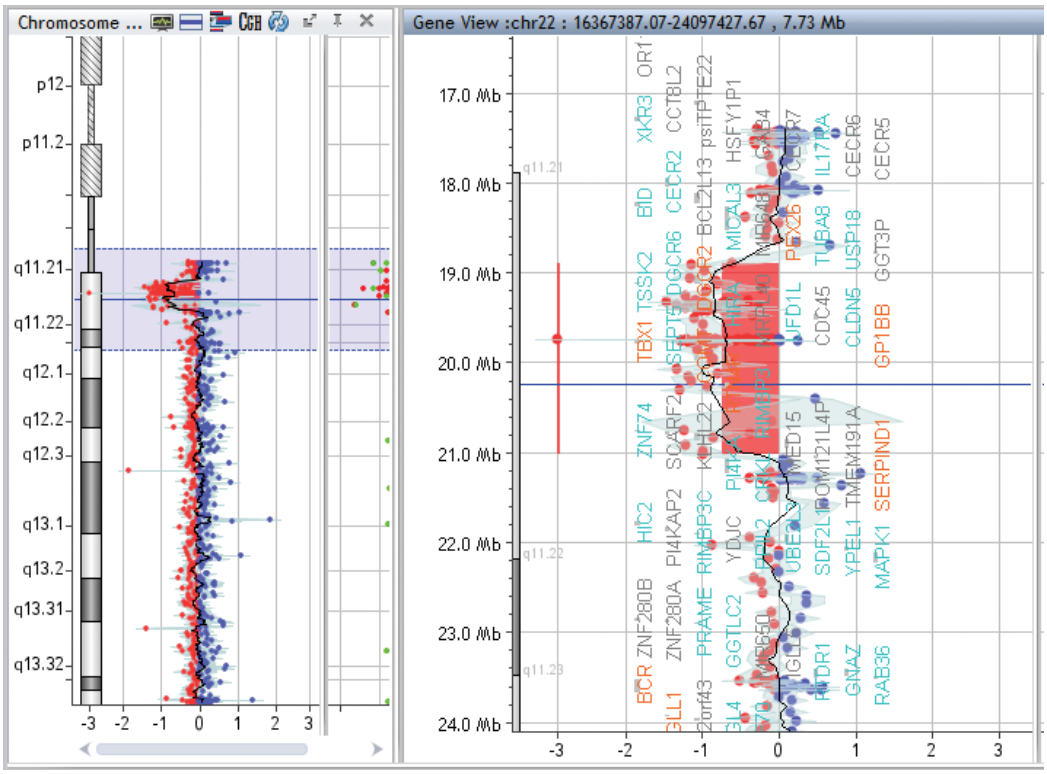

Figure 1. Array CGH results in a prenatal case showing typical 22q11.2 deletion. The left side of the figure shows the whole chromosome 22; the right side shows magnified region 22q11.

After performing several large prospective and retrospective studies, it is estimated that this technique offers a 5–10% increase in detection of clinically relevant copy number variation in fetuses with ultrasound anomalies (compared to conventional karyotyping) [3, 26–28].

In the first years, the technology has been used only in fetuses with multiple congenital anomalies where the yield of pathogenic CNVs was reported to be up to 20%. With the broader use, gained experience, and numerous data on normal variation, molecular karyotyping has been introduced in different prenatal situations. It is also used in the cases of isolated congenital anomalies, increased nuchal translucency only, or positive maternal serum screening. In some countries, all prenatal genetic testing is performed with molecular karyotyping, if the invasive approach has been employed [29]. Namely, a systematic review and meta-analysis of 17 evaluated studies demonstrated additional 5% of clinically relevant CNVs over conventional karyotype in the group of fetuses with isolated increased nuchal translucency NT > 3.5 mm. Even more, a copy number abnormality was identified in 1.7% of fetuses with a normal ultrasonographic examination result with an indication for invasive testing being advanced maternal age or positive aneuploidy screening test [28, 30].

Last but not least, molecular karyotyping has two additional benefits over classical karyotype. As it does not need dividing cells, it can be performed directly from the prenatal sample,

speeding up the whole process and giving results in a few days. Even more, only a small amount of DNA is needed, and therefore, it can be easily performed even on those samples with an insufficient amount of material.

The abovementioned added diagnostic yield of microarrays over conventional karyotyping provides evidence that molecular karyotyping should be used as a method of choice for the analysis of potential genetic causes of fetal congenital anomalies. Consistent with this is the ACOG committee opinion which states that molecular karyotyping is recommended instead of a conventional karyotype when there is one or more ultrasonographically identified CAs in the fetus [31].

However, there are still some limitations in prenatal settings, such as the possibility of detecting variants of unknown significance (VOUS), CNV in susceptibility loci, and secondary findings.

The identification of a variant of unknown significance (VOUS) still occurs in 0.3–1% of prenatal cases, despite the wide use of the technology and diverse population data from pre- and postnatal testing. The percentage depends on the resolution and type of the platform used [28, 32]. Currently, there are no guidelines on how to deal with VOUS findings in the prenatal settings. Different practices exist between laboratories. Parental samples can be obtained at the same time as the prenatal sample, so that they are accessible if there is a need to test the origin of certain VOUS identified in the fetus. On the other hand, they can be collected later in those cases that need additional testing. The management of pregnancy is significantly influenced by knowing if specific CNV is de novo or inherited. Some laboratories report all VOUS findings; others only report such CNV when it occurs de novo and taking into account the size and location of the identified CNV.

Yet again, different approaches can be employed when discussing detection and reporting of secondary findings and CNV in susceptibility loci—some laboratories report all such findings, whereas others have specific national or internal guidelines and lists of specific variants that are reported and those that are not reported in prenatal settings [29, 33]. It is important to emphasize the need for informative pretest genetic counseling, where these situations are discussed with future parents.

Generally, it is well accepted that CNVs in susceptibility loci with higher penetrance are reported as such in the context of prenatal genetic testing. A clear difference between such findings and other known fully penetrant microdeletion/microduplication syndromes must be presented to the pregnant couple.

3.4. Next-generation sequencing

Although microarray analysis has increased the diagnostic yield in comparison to conventional karyotyping, a considerable proportion of fetuses with multiple CAs have a normal karyotype and also a normal microarray result and thus remain without a definitive diagnosis. Determining the cause of CAs in those cases is, during the prenatal period, usually very challenging and frustrating. Genetic testing can be a long process, and the quick turnaround

required for prenatal testing limits this process. Additionally, there is often an incomplete presentation of characteristic phenotypes. So targeted gene sequencing is limited by poorly defined phenotype, genetic heterogeneity, and a limited time period during pregnancy.

When CAs are associated with genetic changes in multiple genes, then sequencing the panel of genes using next-generation sequencing (NGS) should be considered a method of choice. The next-generation sequencing approach is based on parallel sequencing of multiple DNA fragments in a single reaction. This enables high-throughput sequencing of large segments of human genome in a cost-efficient manner (**Figure 2**).

While this approach is widely used in postnatal settings, its use is more limited prenatally, for reasons similar to that of Sanger sequencing. The limitation of gene panel (gene targets)-based approaches is in their dependence on correct diagnostic hypothesis and the long time to reach a diagnosis in case appropriate panel is not selected or cannot be selected due to a nonspecific clinical presentation. These issues can be addressed by using either mendeliome sequencing or whole exome sequencing, which use NGS to sequence the coding exons of genes associated with Mendelian diseases or all genes in the human genome, respectively. Mendeliome and exome sequencing are achieved by capturing exonic sequences using exon-specific probes. In

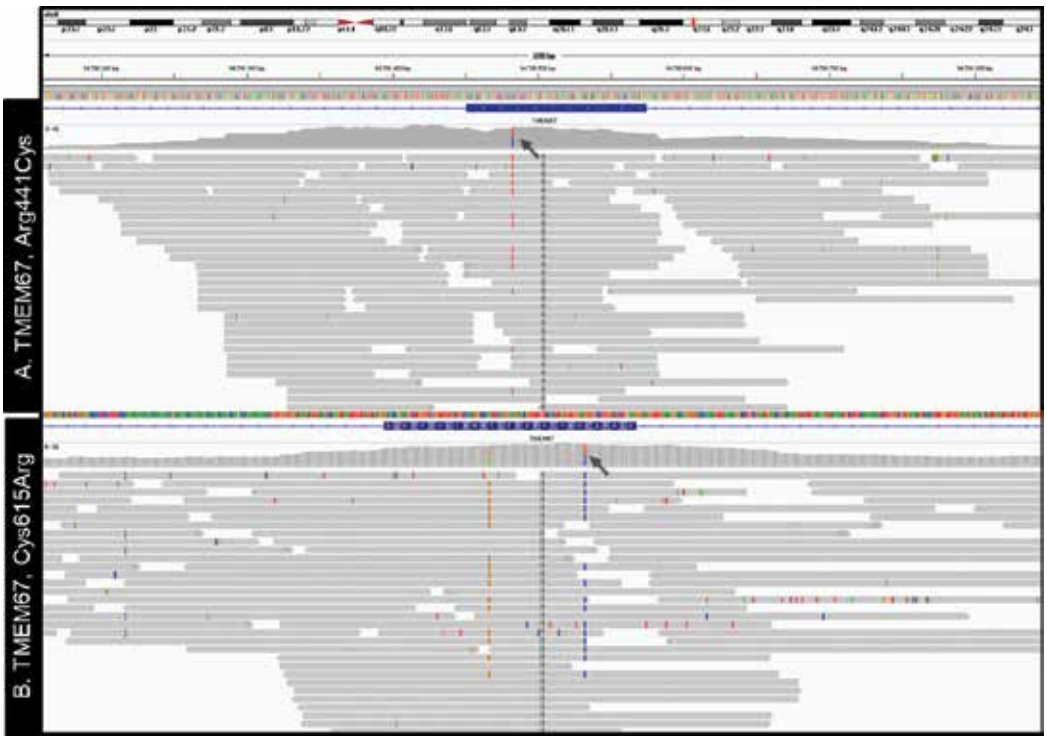

Figure 2. Two causative variants are shown identified by next-generation sequencing (clinical exome sequencing) in a fetus with Joubert syndrome. Part A depicts variant Cys615Arg and part B depicts variant Arg441Cys, both in TMEM67 gene. Both variants have previously been reported as pathogenic, and segregation analysis has shown them to be present in the compound heterozygous form, clarifying the cause in this case.

this way, exonic sequences of the human genome are enriched in the sample, making it possible to focus sequencing on those regions. The principle benefit of this approach is that rather than performing multiple separate gene panel tests for identification of monogenic causes of CAs, a single genetic test is performed, and then results for any gene panel can be inspected depending on the observed clinical signs and symptoms [34]. This makes such an approach significantly faster and without the need for cascading numerous laboratory tests in the case of negative results. Such an approach is also robust in cases with nonspecific clinical presentation without a clear diagnostic hypothesis and in cases that were misdiagnosed.

Current reports have consistently shown the benefit of using exome sequencing in the diagnosis of fetal CA. The current evidence suggests that a genomic abnormality may be identified in up to 20–30% of fetuses with multiple CA and with normal standard genetic results. While initial reports have shown a modest added benefit of exome sequencing in multiple CAs [35], later studies showed considerably higher yields. In a study by Drury et al., exome sequencing could resolve additional 21% cases of pregnancies with multiple congenital anomalies, abnormal ultrasound findings, and a normal microarray result [36]. Even higher diagnostic yields were reported in more selected series of cases—a recent report has shown a positive yield of 47% in fetuses with high suspicion of an underlying genetic disorder and a negative microarray and/or targeted tests [37]. Similarly, Alamillo and colleagues reported a relatively high positive yield in patients with prenatal ultrasound anomalies [38]. These cases illustrate the potentially important role of this new technology in the routine prenatal diagnostics of CAs.

Several studies have now shown that exome sequencing can also be used to detect structural variants and a variety of other pathologic variants apart from simple single-nucleotide variants [39]. This property makes exome sequencing an efficient test for structural and point variation. Despite this, molecular karyotyping is still considered the method of choice in prenatal diagnostics, predominantly because of lower costs and well-established evidence of sensitivity and specificity in the prenatal setting. With the reduction of the price of exome sequencing and with increasing evidence supporting its sensitivity, we expect that next-generation sequencing will ultimately be used for detection of structural and point mutations in a single test. Exome sequencing is, however, a method of choice in multiple CAs cases with normal results of molecular karyotyping and strong clinical suspicion of a monogenic etiology. Accordingly, American College of Medical Genetics has released a policy statement suggesting that WES can be used in the clinical assessment of "a fetus with a likely genetic disorder in which specific genetic tests, including targeted sequencing tests, available for that phenotype have failed to arrive at a diagnosis." However, the statement stresses the limitations of the use of this technology in the prenatal setting, including long turnaround times and high rates of false positives, false negatives, and VOUS [40].

Despite several benefits outlined above, there are additional challenges associated with NGS-based approaches, particularly in the prenatal diagnostic practice. Exome sequencing is a demanding diagnostic test, requiring a complex set of laboratory, bioinformatic, and interpretative steps before a clinical report may be issued. For this reason, its turnaround time usually ranges from several weeks to several months. To address this issue, there is an incentive to offer urgent exome sequencing service and thus offer provision of clinical reports within less

than a month's time. This significantly increases the utility of this test in prenatal diagnosis. Sequencing of parental samples along with the fetal sample may also be used to facilitate the timely interpretation of the sequencing results. Furthermore, we believe that limiting the set of reported variants to known and clear pathogenicity is also an option in order to limit the complexity of the analysis only to clinically actionable and conclusive results. Furthermore, as in other genome-wide analysis approaches, NGS-based diagnostics inherently raise the issues of incidental findings and variants of uncertain clinical significance. Due to limited time and other specificities in prenatal diagnostics, several approaches should be employed to address these issues. These include (1) limiting the gene target to genes with overlapping clinical symptoms and signs and (2) limiting the reported variants to definitely pathogenic and likely pathogenic variant classes. Furthermore, efficient collaboration within a multidisciplinary team is often crucial in clarifying the clinical relevance of identified variants. Opting for this approach, it is possible to utilize diagnostic advantages of NGS-based approaches while reducing the chance of encountering uncertain and unsolicited findings. Nevertheless, extensive genetic counseling should be offered to patients while stressing the possibility of identification of VUS findings and incidental findings.

4. Proposed workflow

The goal of prenatal genetic testing in fetuses with CAs is to determine if there is a genetic etiology and consequently enabling well-informed genetic counseling to the parents about the prognosis, reproductive options, obstetric and pediatric management, and recurrence risks.

Different approaches of prenatal genetic diagnostics are used. Despite known evidence of important additional diagnostic yield of new genomic technologies to the etiology of CAs, most countries still use the traditional genetic diagnostic approach. Hereinafter we present a diagnostic workflow that is currently in use at our institution (**Figure 3**). It incorporates the use of new genomic technologies and is focused on the expected diagnostic yield and limited diagnostic time frame.

When fetal CAs are detected on an ultrasound examination, we offer an invasive procedure for diagnostic genetic testing.

In cases when specific chromosomal disorder (e.g., double bubble and trisomy 21) or monogenic syndrome is strongly suspected on the initial evaluation and single gene testing is straightforward (e.g., achondroplasia), we exclude common aneuploidies (trisomy 13, 18, and 21, and aneuploidies of sex chromosomes) first, using quantitative fluorescence-polymerase chain reaction (QF-PCR), and proceed with single gene testing, respectively.

When the specific clinical diagnosis is not apparent, we use a genomic approach for the detection of genetic etiology of CAs. Because aneuploidies represent the commonest genetic etiology of CAs, we first opt for QF-PCR to exclude the aneuploidies mentioned above.

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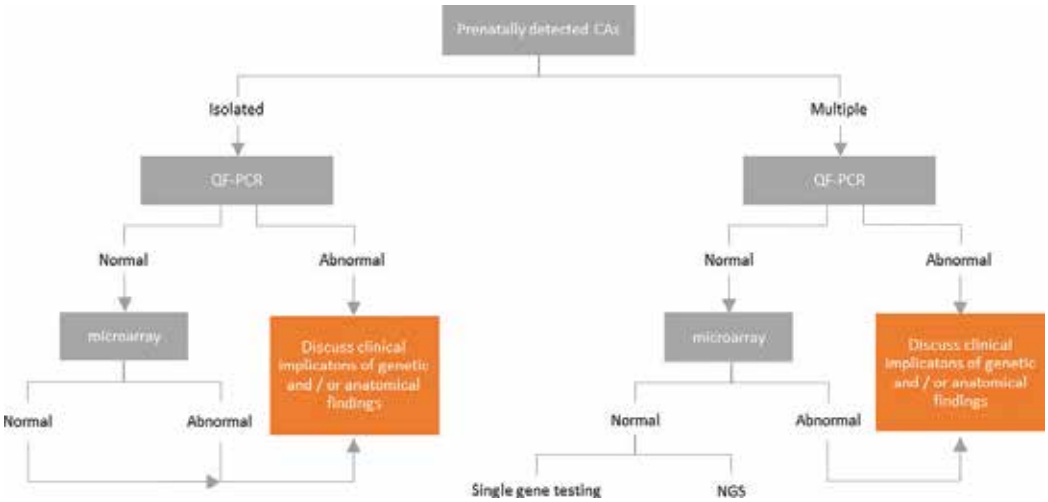

Figure 3. Diagnostic algorithm for the prenatal genetic diagnostics of CAs. CAs, congenital anomalies; QF-PCR, quantitative fluorescence-polymerase chain reaction; NGS, next-generation sequencing.

If the results are normal we proceed with molecular karyotyping instead of a conventional karyotype as studies showed that this approach allows for the highest diagnostic yield. We use this approach whether the anomaly appears to be isolated or multiple anomalies are detected.

In fetuses with normal results of molecular karyotyping, with multiple CAs, and a strong clinical indication for monogenic etiology, we proceed with WES; our approach involves sequencing the fetus as well as the biological parents (so-called trio sequencing), which increases the diagnostic yield by filtering out thousands of uninformative genomic variants as well as shortens the analysis turnaround time (less than 3 weeks at our institution).

In cases when CAs are lethal or have unfavorable prognosis, the parents often decide to terminate the pregnancy, but for the purpose of genetic counseling, it is still important to obtain the diagnosis. Accordingly, we shift the diagnostic process after the termination of the pregnancy. Thorough dysmorphological and pathohistological evaluation may give additional information on the specific phenotype and thus enables a more direct diagnostic approach in the aborted fetus. Otherwise, we use the diagnostic approach similar to the approach during the pregnancy.

Different medical specialists are involved in the process of prenatal diagnosis of CAs. The role of a clinical geneticist in the whole pathway of genetic diagnostics of a pregnancy with CAs in a close collaboration with other medical specialists (obstetricians, surgeons, radiologists, pathologists, etc.) and a multidisciplinary approach is undisputed due to all the complexities of prenatal diagnostics of CAs, their clinical presentation and phenotype evaluation, choice of the right genetic testing strategies, interpretation of genetic testing results, and their communication to patients and families.

5. Conclusions

With the advent of new genetic genomic technologies in the prenatal settings, the diagnostic yield in the etiology of CAs can be significantly improved. This has important consequences for the patients, as it enables the identification of the cause of CAs and, consequently, their prevention, as well as understanding the genetic epidemiology of CAs and designing optimal professional and cost-effective diagnostic algorithms for the diagnostics of CAs.

With the implementation of new genomic technologies in the diagnostic algorithm, approximately 50% of the genetic etiology of prenatally detected CAs can be explained. Therefore, we suggest a timely implementation of these technologies in prenatal diagnostics of CAs.

Author details

Gorazd Rudolf*, Luca Lovrečić, Aleš Maver, Marija Volk and Borut Peterlin

*Address all correspondence to: gorazd.img@gmail.com

Clinical Institute of Medical Genetics, UMC, Ljubljana, Slovenia

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Chapter 20

Congenital Heart Disease: Genetic Aspect and Prenatal and Postnatal Counseling

Amal Zubani, Irfan Asra and Amjad Kouatli

Additional information is available at the end of the chapter

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Abstract

Cardiac malformation present at birth is an important component of pediatric cardiovascular disease. The etiology of congenital heart disease is multifaceted including environmental, genetic and stochastic factors. With the advancement of cardiac diagnostic and therapeutic techniques in the past decade, with relatively low morbidity and mortality, has led to more and more children with congenital heart disease living to adulthood. Therefore the role of prenatal and postnatal genetic counseling becomes even more paramount as there is a higher likelihood of these patients living to adulthood and having families of their own. Prenatal counseling allows for the expectant parents to understand the full ramifications of continuing the pregnancy and possible events after birth. It is a multidisciplinary approach to help parents reach an informed decision on how to best to proceed with the pregnancy. After the birth of the child with congenital heart defects, the course is significantly dependent on the type of cardiac lesion. Postnatally, if the lesion is amenable to surgery, therapeutics intervention is offered. The postnatal counseling session includes the possibility of performing advanced genetic testing to help determine the hereditary potential of the cardiac defect in future offspring.

Keywords: congenital heart disease, genetic syndromes, recurrence, counseling, genetic testing

1. Introduction

Congenital heart diseases (CHD) are the most common major fetal structural defects and leading cause of neonatal morbidity and mortality among birth defects. The medical and surgical management of these children has continued to progress rapidly such that, most of these patients now survive to adulthood. The estimated incidence of moderate and severe forms of CHD is 6 per 1000 live births [1]. However, fetuses with heart disease show unique diagnostic,

therapeutic and sometimes ethical challenges. Treatment of the fetuses with CHD may expose the mother to significant risks, which may compete with the welfare of the mother [2, 3].

Advances in the field of prenatal imaging, and increasing experience in fetal cardiology and echocardiography over the last two decades has allowed for most heart defects to be well defined as early as the second trimester [4]. Pediatric cardiologists specializing in fetal medicine, play a critical role in help making an accurate diagnosis. In addition, these specialized physicians will be critical in providing prenatal counseling to help guide parents to understand the diagnosis and in the decision-making process. This counseling will give parents information about the fetus' heart defect and its expected outcomes. Fetal echocardiography has evolved since its inception, which now can provide precise details of cardiac structural and hemodynamic aberration in fetuses with CHD. During pregnancy, the sequential use of this modality can predict the evolution of disease in utero and transition to postnatal life. Such an approach allows for detailed prenatal counseling and detection of fetuses at high risk for morbidity and mortality. This allows for appropriate planning and postnatal management [5, 6]. Most CHD is well tolerated in utero, and does not present hemodynamic risks immediately. After birth, many of these babies, with simple cardiac lesion do not require specialized delivery care. However, some high-risk fetuses may develop hemodynamic instability soon after birth and may require immediate intervention [5]. With such infants it is highly recommended that these children be born at centers where a pediatric cardiac team and intensive care personnel are available to make appropriate therapeutics decisions and intervention, without delay.

Is the availability of a perinatal diagnosis of CHD is associated with improved surgical outcomes and less neonatal mortality? Some studies report a positive impact on outcomes while others showing no difference in outcomes compared to babies diagnosed with CHD after birth [7–19]. A recent meta-analysis evaluating the differences in pre-operative mortality rates between newborns with and without a prenatal diagnosis found that prenatal diagnosis of critical CHD improves neonatal pre-operative survival, and newborns with a postnatal diagnosis were more likely to die of cardiovascular compromise prior to planned cardiac surgery [20].

The etiology of CHD is multifaceted including environmental, genetic, and stochastic factors [21, 22]. Knowing the basis of the CHD will aid in the counseling of parents and help them to attain a complete understanding of the fetuses cardiac defect [23]. Although it will not change the course or management option, but it will allow for familial planning and future pregnancies.

2. Genetic syndromes

Genetic syndromes are defined as a consistent pattern of malformation caused by a genetic alteration. A malformation syndrome consists of multiple structural defects that are thought to be due to a single cause, even if the suspected cause has not yet been identified [24].

2.1. Noonan's syndrome

The Noonan phenotype includes characteristic facies (ptosis, hypertelorism, low set ears, and low posterior hairline), short stature, webbed neck and cardiac anomalies. Noonan syndrome occurs in I per 1000 to 1 per 2500 live births diagnosed clinically [25–27]. Cardiac anomalies are present in 80% of individuals [28]. In 70–80% of cases, the lesion is pulmonary stenosis, usually due to

dysplastic pulmonary valve leaflets [25]. In 20–30% of affected individuals, the cardiac anomaly is in the form of a cardiomyopathy, which may be present at birth or develop later [25, 29].

Most of the cases of Noonan syndrome are sporadic, although families with a pattern of autosomal dominant inheritance are well known. Mutation in the gene PTPN11 on the chromosome locus 12q24.1 was noted in 45% of cases. Gelb et al. demonstrated a positive association between those with PTPN11 mutations and pulmonary stenosis [30]. Maternal transmission of the gene is three times more common than paternal transmission [28]. Prenatal testing can be established by chorionic villus sampling or amniocentesis, fetal ultrasound can show increased nuchal translucency, increased nuchal thickening, pleural effusions and generalized hydrops [31]. Developmental delays are always present, and intellectual disability is typically in the range of moderate mental retardation [28, 29]. Diagnosis in newborn baby may be difficult unless the cardiac lesion is severe, with either significant pulmonary stenosis or severe cardiomyopathy. The diagnosis can only be confirmed genetically if there is an affected parent with a recognized mutation [25, 27, 30].

2.2. Turner's syndrome

The classical Turner's syndrome phenotype includes short stature, webbed neck, renal anomalies, congenital lymphedema, ovarian dysgenesis and cardiac anomalies. In many, the features are sufficiently subtle to be overlooked until the teenage years. The prevalence of Turner's syndrome is 1 in 2500 female births [32]. The phenotype depends on whether the X chromosome is absent (45, X in almost 50% of patient) or structurally abnormal [33].

The most common presentation is spontaneous abortion with hydrops or lymphatic malformation in the neck or mediastinum. Cardiac anomalies are present in 30% of patients with Tuner Syndrome, bicuspid aortic valve (30%), coarctation of the aorta (10%) and hypoplastic left heart syndrome (HLHS); partial anomalous pulmonary venous connection is also associated with this syndrome. Aortic root dilatation is present in 5–10% of cases, associated with aortic root dissection in later life, this finding is mostly related to decreased numbers of smooth muscle and elastic fibers in the vascular walls [32]. Gotzsche et al. demonstrated a correlation between the precise karyotype and the form of congenital heart disease; 38% of patients with X0 had aortic valve anomalies and coarctation of the aorta, compared with 11% of individuals with mosaic X0 [34].

Fetuses with Turner's syndrome have been shown to have small hearts in 90% of the cases. Significant myocardial hypoplasia is thought to be associated with the high incidence of fetal death [32]. Neonatal diagnosis may be difficult but should be considered in females presenting with left-sided heart anomalies or lymphedema.

2.3. William's syndrome

The phenotype of Williams' syndrome is variable, but includes characteristic facies (flared eyebrows, bright stellate irides and wide mouth), specific personality and cognitive features, and infantile hypercalcaemia in addition to cardiac anomalies. The prevalence is 1 in 10,000–20,000. Children with Williams's syndrome can be diagnosed at different ages and present with a broad range of clinical features [35]. Early in life, feeding disorders and growth retardation are common. Hypercalcemia is seen in 15% of infants and usually resolves over

time [36]. Cardiac anomalies are present in 55–80% of individuals with William's syndrome, which typically include supravalvar aortic stenosis and/or supravalvar pulmonary stenosis [37, 38]. The degree of the cardiovascular involvement and the relative involvement of the pulmonic or aortic vessels varies widely. By 1 year of age 41% of the pulmonary lesions will have improved, whereas 73% of the aortic lesions will have progressed [38].

Approximately 90% of patients with the clinical diagnosis of Williams's syndrome have a deletion at chromosome 7q11.23, which can be detected by fluorescence in situ hybridization (FISH), multiplex ligation- dependent probe amplification (MLPA) and microarray technologies. The gene mapping to this region has been defined and includes the gene ELN, whose product is elastin. The deletion of this gene results in the connective tissue abnormalities associated with the CHD of Williams' individuals [39, 40]. Prenatal genetic testing can be performed on Chorionic villus sampling or amniotic fluid samples in the few pregnancies considered to be at increased risk. Neonatal diagnosis is challenging, and full features become more apparent with time. William's syndrome is transmitted in an autosomal dominant manner. Most cases are de novo occurrence and recurrence risks are 50% if a parent is affected but otherwise low (<5%) [41, 42].

2.4. 22q11 deletion syndrome (DiGeorge syndrome, velocardiofacial syndrome, conotruncal anomaly face syndrome)

Molecular studies demonstrate that the vast majority of patients with clinical diagnosis of DiGeorge, velocardiofacial, conotruncal anomaly face syndromes share a common genetic cause, namely a 22q11.2 deletion [43–45]. The prevalence is 1 in 4000 to 6000 live births, but the severity of the phenotype is variable and in some the features may go unrecognized [46]. CHD are estimated to occur in 75–80% of patients with a 22q11.2 deletion. The most common CHDs associated with 22q11.2 deletion include tetralogy of Fallot (TOF) and aortic arch anomalies. Other conotruncal lesions include pulmonary atresia with ventricular septal defect (VSD), and truncus arteriosus [47, 48]. In cases of truncus arteriosus, the truncal valve tends to be more dysplastic when the 22q11 deletion is present [49].

Identifying the cardiac patient with a 22q11.2 deletion early in life can provide substantial benefits to the child and family. Currently, it is recommended that infant with interrupted aortic arch type B, truncus arteriosus, TOF and isolated aortic arch anomalies undergo testing for a 22q11.2 deletion [22]. Prenatal diagnosis can be performed using FISH technology on samples obtained from chorionic villus sampling or amniocentesis if cardiac defects are present. Non-cardiac lesions are not easily diagnosed but, absent fetal thymus has been reported [50]. Many children initially present without cardiac symptoms in the form of recurrent infections. This may point to an underlying immunodeficiency associated with 22q11.2 deletion [51]. The risk of recurrence is in 50% as this is transmitted in an autosomal dominant inheritance if either parent carries the deletion. If neither parent carries the deletion, there may still be germline mosaicism, but the risk of recurrence is small (1%) [22, 48].

2.5. CHARGE syndrome

The CHARGE syndrome was previously referred as an association, however this was resolved after the discovery of causative mutations in chromodomain helicase DNA-binding gene7 (CHD7) on chromosome 8q12.1 [52, 53]. The phenotype is described by its acronym:

colobomata (79%), heart defects (85%), choanal atresia (57%), growth and developmental retardation (100%), Genital hypoplasia (34%) and Ear anomalies (91%). Additional problems include renal anomalies, facial clefts and esophageal atresia [54]. CHD has been always been part of the core phenotype.

The frequency of the CHD range from 74–92% in CHD7 mutation-positive cases [55, 56], as compared to 71% in CHD7 mutation- negative individuals in one report [55]. A wide range of CHD has been reported in CHARGE syndrome, including conotruncal and aortic arch anomalies consistently over represented in clinical series [56]. The frequency of the CHARGE syndrome has been reported to range from 1 per 10,000 to 1 per 15,000 live births, although one population-based study estimated a frequency of 1 in 8500 live births [57]. Most of the cases of CHARGE syndrome are sporadic in occurrence, but autosomal dominant inheritance and germline mosaicism, have now been confirmed by molecular testing [55].

2.6. VACTERL association

The phenotype is described by its acronym: Vertebral defects, Anorectal anomalies, Cardiac anomalies, Tracheoesophageal fistula with Esophageal atresia, and Renal and upper Limb anomalies. A general diagnostic guideline requires three or more defects to establish the diagnosis [58]. It is usually a sporadic occurrence of unknown cause. In rare cases an association can occur in trisomy 18 [59], or trisomy 21 [60]. A cardiac anomaly is present in at least 73% of affected individuals and includes atrial septal defect (ASD), VSD, double-outlet right ventricle, TOF and dextrocardia [58].

No definitive prenatal testing is available, but the diagnosis should be considered if antenatal ultrasound demonstrates a vertebral anomaly, absence of the fetal stomach and a cardiac anomaly with or without polyhydramnios. The management involves a multidisciplinary approach [61]. VACTERL has a low recurrence risk of 2–3%, although there are rare reports of familial cases, including one of a mother and son, both with typical features [62].

2.7. Alagille syndrome

Alagille syndrome was originally defined as the presence of bile duct paucity on liver biopsy in conjunction with three of the following five findings: cholestasis, congenital heart disease, skeletal or ocular abnormalities or typical facial features which give the face an inverted triangle appearance (broad forehead, deep set eyes, rounded tip and pear like shape of the nose and pointed chin) [63, 64]. Alagille syndrome is an autosomal dominant condition with high penetrance (94%) and variable expressivity, which is the result of mutations or deletions in the JAG-1 gene (locus 20p11.2). De novo mutations occur in 50–60% of cases [65, 66]. Alagille syndrome is now recognized to be a genetically heterogeneous disorder. Approximately 5% of the patients with a chromosomal deletion involving one copy of the entire JAG1 gene, whereas most will have various intragenic JAG1 mutations [67].

The prevalence is 1 in 70,000 to 100,000 live births [68]. Cardiovascular anomalies are present 90% of the cases [68]. The most common cardiac lesion is pulmonary artery branch stenosis (PABS), tetralogy of Fallot (in up to 10% of cases), pulmonary stenosis and coarctation of the aorta [69]. If the mutation or deletion is identified in a parent, prenatal diagnosis is available

on samples from chorionic villus sampling or amniocentesis. It is, however, not possible to predict the severity of the phenotype in an identified fetus [69]. The diagnosis needs to be considered in a baby with a cardiac defect and prolonged jaundice, and with at least three of the recognized features [61]. Alagille syndrome has a mortality rate around 10–20%. The risk of recurrence is low in the absence of a positive family history, but it is 50% if there is an affected parent [61, 68].

2.8. Holt-Oram syndrome

The phenotype is characterized by the bilateral, asymmetrical upper limb anomalies of variable severity and is estimated to occur in 1 per 100,000 live births. There is a variation in the severity of the phenotype even within a family, and in some the upper limb anomalies may be so mild that X-ray can only diagnose them. A thumb anomaly is usually present [70]. Approximately 75% of the patients diagnosed with Holt-Oram syndrome have CHD. Atrial septal defects (secundum type) are present in 58% of these patients, in addition 28% have VSD. Up to 40% have conduction defects including a long PR interval, sinus bradycardia, atrial fibrillation and complete heart block [71]. Other types of congenital heart diseases in the form of total anomalous pulmonary venous drainage, TOF and truncus arteriosus have been associated with this syndrome [72]. There appears to be a correlation between the severity of the upper limb anomaly and the cardiac lesion [73].

Holt-Oram syndrome is an autosomal dominant condition with 100% penetrance and variable expression. New mutations make up 30–40% of the inheritance pattern. The affected gene is TBX5 on chromosome locus 12q24 [74]. The diagnosis should be considered prenatally when a cardiac lesion occurs in the presence of an upper limb anomaly. The risk to the offspring of an affected individual is 50% [61].

2.9. Trisomy 21 (Down's syndrome)

The most familiar syndrome to cardiologists is Down's syndrome is trisomy 21 in which there is a complete extra copy of chromosome 21 in 94% of cases. Less commonly, partial trisomy of chromosome 21(6% overall), is present owing to a chromosomal translocation or mosaicism. Common findings include: hypotonia, global developmental delays and moderate intellectual disability, microbrachycephaly, small ears, mouth and nose, protruding tongue, up-slanting eyes with epicanthal folds, transverse palmar creases, and sparse hair. Skeletal anomalies include fifth finger clinodactyly, brachydactyly, a gap between first and second toes, atlantoaxial instability, hypoplastic pelvis, and joint laxity. Additional problems involve the visual, auditory, endocrine, hematologic, reproductive, and gastrointestinal systems. Almost half of live born Down's syndrome individuals have a CHD, approximately 40% of whom have a complete atrioventricular septal defect (also known as atrioventricular canal defect or endocardial cushion defect) [75]. The association of Down syndrome and atrioventricular septal defects is underscored by the fact that approximately 75% of patients with a complete atrioventricular septal defect have Down syndrome. Other common CHDs include secundum atrial septal defect, conoventricular and muscular ventricular septal defect, tetralogy of Fallot (with and without atrioventricular septal defect), and hemodynamically significant patent ductus arteriosus [75]. The overall prevalence of Down syndrome is 1 in 700 live births [76].

The risk of conceiving a child with aneuploidy (an extra chromosome), including Down's syndrome increases with maternal age. Overall survival has improved, although prenatally diagnosed CHDs and/or growth retardation may predict a poorer outcome [77]. The largest survey study to date reported that the frequency of CHDs in patients with Down syndrome mosaicism was similar to the complete trisomy 21 comparison group (~42 and 50%) [78]. Prenatal screening programs providing risk figures for Down's syndrome in individual pregnancies are widely available. Definitive testing involves an invasive procedure, either chorionic villus sampling or amniocentesis, and a rapid result can be obtained by FISH. The diagnosis is suspected clinically and confirmed by karyotyping. The risk of recurrence is about 1% for women aged 39 or less [61].

2.10. Trisomy 18 (Edward's syndrome)

It is a rare syndrome with a prevalence of 1 in 6000, and a male to female ratio of 1:4. Majority of this syndrome is caused by maternal meiotic non-disjunction. Greater than 90% of cases have trisomy 18, the remainder having trisomy 18-mosaicism or partial trisomy of 18q. All cases have cardiac anomalies: mal-aligned VSD is the most common finding; ASD and patent ductus arteriosus are also common findings in these patients. Polyvalvular dysplasia, usually without stenosis or regurgitation, is usually present [79, 80]. Karyotyping is indicated if prenatal screening detected structural anomalies on ultrasound. The risk of recurrence is low, at around 1 in 200 [61].

3. Counseling

3.1. Prenatal

The process of prenatal counseling and its recommendations, should be based on the best available current evidenced-based practice. This process may require more than one consultation due to its emotional nature of the situation and complexity of information being delivered. Any prenatal counseling should include the suspected cardiac diagnosis in detail based on the fetal ultrasound findings. The purpose of this is to give the most accurate and up to date information about the prognosis and outcome of the pregnancy and fetus. This will allow the parents to make the best-informed decision for them and the fetus.

In regards to the screening ultrasound, all relevant information available needs to be given prior to the examination. Ideally, all prescreening information should be made available to the referring hospital. It needs to be emphasized that not all cardiac defects can be detected in the initial ultrasound examination [81, 82]. Whenever a cardiac abnormalities is detected this will require prompt referral for specialist examination. The general screening detection rates for congenital heart disease (CHD) vary between 14–45% [83]. A standard 4-chamber view can detect 40–50% of major CHD [84], while a 4-chamber view and outflow tract detects 70–80% of major CHD [85]. In dedicated fetal cardiac centers the diagnostic accuracy is close to 100% [86, 87]. Thereafter a referral for specialized echocardiography and cardiology consultation should be done. If there are suspected cardiac abnormalities on the screening fetal ultrasound, there should be minimal time delay in referring the mother for a fetal echocardiogram

and cardiology consultation. Delays in referral for further evaluation increase parental stress [88], and may prohibit the option of early termination of pregnancy. At the referral center, before the scan, the physician should make sure that the parents have consented to the examination and understand why they have been referred. A detailed review of past maternal history, including health wellbeing, previous pregnancies outcomes and similar conditions in the family need to be determined. In addition, any previous genetic screening has been performed or suspected in the family.

Ideally, the parents should be counseled by a pediatric cardiologist specialized in fetal cardiology, once the fetal echocardiogram is complete. The counselor needs to have full knowledge of the anatomy, physiology, gestational age, and association with extra-cardiac malformations and its natural history. In addition, the discussion should include the short and long-term management and possible outcomes. If possible a multidisciplinary meeting with the parents should be conducted. This conversation should include the most accurate information and include prenatal and postnatal management. Ideally this discussion should include fetal cardiologist, obstetrician, neonatologist, geneticist, pediatric cardiac surgeon and a psychologist or social worker. In addition to the physicians, a fetal nurse coordinator or midwife should be involved from the first counseling visit to delivery of the baby or termination of the pregnancy. This is to provide continuous support and ongoing resources for follow up with the family [89]. There is little research on performing prenatal counseling for CHD or determining the most effective strategies for providing family support. Therefore, it is important that counselors have good communication skills, show empathy, and be perceptive in assessing how the information is being received. The counselor must assess parental understanding and emotional status throughout the discussion.

A structured explanation focused on assessing the parents understanding is very important at this stage. Highlights of the counseling of session needs to repeated and the expected parent should be made to verbalize understanding in their own words. This may need to be repeated to ensure complete understanding of the situation and implication for treatment and intervention. Throughout this process, the counselor needs to assess and give feedback to the treating team on how the information is being received. Particularly at the first visit, the initial shock and grief reactions to an abnormal finding may inhibit the parents' ability to retain information. Therefore, it maybe necessary to repeat information on subsequent encounters and assess understanding. A common issue that complicates counseling in today technological age, is the access and availability of the vast amount of information on the Internet. At time such recourses can be beneficial, but more often than not, this information is misleading, biased and inappropriate for the precise circumstances. Unfortunately, none of this information is subject to review and can be a source of major confusion for the parent [90].

Complications of the cardiac abnormality and its progression in utero, and the results of surgery or any intervention also figure in to the discussion. There is a need to describe possible poor outcomes, so that they have been informed of all possible scenarios, even though unlikely to happen. This information allows the parents to decide how best to proceed with knowledge of the worst-case scenario [91]. One of the most important points which needs to be mentioned during the consultation is that the risk of intrauterine death is low in fetuses with CHD who are in sinus rhythm with good myocardial function [89]. Characterization of the cardiac defect and its association with genetic syndrome or not will guide the counselor on how best to give

the information to the parent [92]. The parent should be counseled after each scan, and should be given enough time for questions and follow up information [89]. If the amniocentesis detects a chromosomal abnormality, advance cytogenetic testing may be warranted. These testing include FISH, chromosomal microarray and whole exome sequencing [93]. The next step in the counseling, should mention the possibility of chorionic villus sampling or amniocentesis, as this knowledge may help determine prognosis and guide postnatal care. The finding of an associated chromosomal abnormality may also strongly influence decisions about pregnancy termination [94, 95]. Whatever the parental decision is made, the counselor should express full support.

In the final step, the counselor needs to identify and discuss the prenatal options and parental decision-making. This stage is crucial, because the counselor will be discussing the management options with the parents in regards to the outcome of the pregnancy. The management options include: pregnancy continuation, pregnancy termination (if legally allowed) and prenatal intervention if available [96].

If the decision is to continue with the pregnancy, there will be further decisions to be made as to where the infant will to be delivered, mode of delivery and the need for postnatal care and intervention [97]. Delivery at a tertiary care facility with access to pediatric cardiac care is recommended for ductal-dependent lesions and any heart defect that is expected to require neonatal and surgical interventions. Transfer is usually between 30 and 34 weeks gestation to allow the mother to become familiar with the new obstetrician and hospital in the time of her delivery. At the same time, it can be useful to have parent meet the surgeon. The fetus can be delivered at the local hospital, depending on the nursery's comfort level in dealing with such newborns. However, continued communications between the referral hospitals is vital for optimal outcome [98]. Delivery after 39 weeks is typically recommended because of high morbidity, and mortality has been reported in babies born before 36 weeks. Particularly in those with extracardiac and genetic abnormalities [99]. Parents should be counseled that IUGR is associated with increased morbidity after cardiac surgery [100]. Similarly, lower weight (<2.5 kg) is associated with higher mortality after cardiac surgery [101]. Mode of delivery is not typically altered in the setting of fetal CHD, and high rates of vaginal delivery can be achieved [102]. Cesarean section is almost never indicated for cardiac reasons and should be avoided if possible if the cardiac malformation is associated with a high mortality [103]. When the parents make an informed decision to continue the pregnancy, it may be useful for them to meet and speak with parents who have had a child with similar cardiac abnormalities. This will allow for them to have a better understanding of what is to be expected of the journey ahead.

If the decision is to terminate the pregnancy, parents should be counseled and supported fully, as this can cause guilt and emotional stress. Counselor should appreciate the mixed feelings of the parents when it comes to such decisions. It is very important to highlight that termination of pregnancy is never recommended nor absolutely indicated in any circumstances. Termination of pregnancy is a legal option in most of the developed world, but the gestational age limit is variable. In general, it is allowed up to 24 weeks of gestation in most countries all over the world, but late termination, even up to term, can be obtained in some countries like the United States of America for fetal malformations. The counselor must be able to discuss the options of termination of pregnancy and its risks, regardless of their personnel beliefs. The earlier the diagnosis of fetal malformation can be reached (possible from as early as 12 weeks of gestation) the more safely termination of pregnancy can be accomplished. This will create

the least amount of physical and emotional trauma for the mother and family [90, 96, 104]. In one center experience, over 2000 sets of parents were counseled, half of them chose termination and the other half continued with pregnancy. Those who accepted termination of pregnancy recovered from it and with time ended up as normal healthy family. However, many of those who continued with the pregnancy, eventually lost the affected child, which was associated with increase grief and agony. In addition, break- down of the whole family unit after many years was reported [90].

Outcomes in terms of rate of termination, after prenatal diagnosis of heart defects vary between countries and even between centers within the same country [105, 106]. The reason for this may be due to differences in social/religious elements and in the local laws and practices. Termination rates are greatly influenced by the gestational age at the time of diagnosis [107], by the presence of the chromosomal abnormalities and other extracardiac malformations [25]. Severity of the cardiac malformation also influences the termination rate like hypoplastic left heart syndrome [81, 105].

Intrauterine interventions may be available for some cardiac malformations like Balloon aortic and pulmonary valvuloplasty. Currently there is a conflict between American College of Obstetricians and Gynecologists and the American Academy of Pediatrics (AAP) regarding the issue of fetal interventions [108]. The AAP favors fetal intervention if available, and puts less weight in maternal decision that is recommended for fetal benefits. This approach may place the mother at greater risks and decrease autonomy [96, 109]. If the intervention considered are questionable and carry a high risks to the mother, it is prudent to respect the mothers autonomy and giving her priority [96], until further research and consensuses are definitive in this regards.

In case of multiple pregnancies with one fetus with a serious congenital anomaly need to be highlighted in this step of the counseling. These risks and benefits of continuing or terminating the pregnancy of affected twin needs to be considered and balanced. The expectant parents need to understand that the death of the normal twin can occur if the twin pregnancy is continued. This is particularly true when there is a monochorionic twin pregnancy [96, 110].

The prenatal counseling should discuss the anticipated postnatal course, intervention and outcome/survival. In most cases, the infant born with cardiac malformation will require immediate medical and/or surgical intervention. Medical intervention to ensure patency of the ductus arteriosus will include starting Prostaglandin for duct-dependent lesions for either pulmonary blood flow (e.g., severe TOF or pulmonary atresia) or systemic blood flow (e.g., HLHS, interrupted aortic arch). Once these patients are stable medically, they may require cardiac catheterization and/or surgical repair. Parents should be counseled on what to expect in the delivery room. Management will vary, depending on the severity of the cardiac defect. Decision such as, where the baby will be admitted and how much time they will have the baby, will be decided prior to the delivery date. Parent should be made aware that the postnatal cardiac diagnosis might be modified after birth. Emphasis on the possibility of modification of the postnatal course, including change in the interventions and length of stay needs to be discussed. Helping the parents understand and deal with changes that may occur and be contrary to what they might have been told [98].

The outcomes and long-term survival (20 years) are profoundly dependent on the type of defect in babies born with CHD. Majority of these babies, approximately 85% are expected

to reach adult age. For example, infants with simple CHD such as VSD or ASD have survival rate of 95%, whereas moderate severity such as TOF reach 90%, and complex CHD such as single ventricle reach 80%.) [111]. A follow up study of 1000 Fontan patients by d'Udekem et al. showed 97% 10-year survival rate [112]. Although there are relatively good survival many of these patient may manifest other complications, including dysrhythmias, need for pacemaker and thromboembolic events [98]. Parents have to be informed about that there is an increased risk of neurodevelopmental delay in children with cardiac malformations. The severity of cardiac defect correlates with the degree of developmental delay [113]. In a recent meta-analysis, fetuses with severe cardiac malformation showed signs of impaired fetal cerebral development as shown by fetal MRI or ultrasound. However, correlations of fetal brain findings with neurodevelopmental outcome have been inconclusive and more long-term data are needed [114].

3.2. Postnatal

The advancement of cardiac diagnostic and therapeutic techniques in the past decade, with relatively low morbidity and mortality, has led to more and more children with congenital heart disease living to adulthood. Therefore, the role of genetic counseling becomes even more paramount as there is a higher likelihood of these patients living to reproduce and that they may have families of their own [22]. It is very important to help elucidate the genetic basis for patients' congenital cardiac malformation for the reason mentioned, as there may be important reproductive risks that the families need to know about [22, 115, 116]. Recent analysis indicate that adults now constitute roughly two-thirds of the congenital heart disease population, representing a nearly 60% increase in congenital heart disease among adult patients since the year 2000 [115, 116]. The greatest increase in congenital heart disease survival has occurred among the 18-year old to 40-year-old demographic, which has clear implications for heritability [116].

One of the obstacles, in performing genetic testing in patients with congenital heart disease is that there are no standardized recommendations or protocols incorporating, newer genetic testing technologies at present. The literature is sparse with guidelines, and there is evidence that there is under use even of those modalities of testing that are available [22, 115]. However, there has been an emphasis from the American Heart Association in the recent past, in obtaining genetic testing in these patients [117].

3.2.1. Genetics in congenital heart disease

Cardiac malformation present at birth are an important component of pediatric cardiovascular disease. Defects can range from simple ventricular septal defects to complicated cyanotic lesions, requiring complex interventions shortly after birth. With the possibility of myriad of presentations, it begets one to ask, what is the percentage of pediatric cardiac defects are a result of a genetic anomaly. CHD is estimated that the prevalence of cardiac malformation at birth ranges from 4 to 10 live born infants per 1000. The true incidence, perhaps maybe higher as there are silent cardiac malformations that are only found later on in life [115]. As most calculations do not include bicuspid aortic valves, mitral valve prolapse and conduction problems, such as prolonged QT syndrome and complete atrioventricular block [115, 116]. The care of the pediatric patient with cardiac malformation is multifaceted, ranging from simple reassurance and observation to advanced surgeries and

interventional techniques shortly after birth. The primary focus of treatment of the patient with cardiac malformation is diagnosis and best course of treatment. However an important and integral part of the care of these patients is to have genetic counseling with their parents in regards to possible etiologies of the congenital heart disease. In the past, it was believed that the recurrence of congenital cardiovascular malformations in the same family was low, with expert quoting recurrence rate of only 3–5%. However currently it is known that for a family with autosomal-dominant 22q 11 deletion syndrome, the risk is up to 50% with a variable phenotypic expression [117, 118].

Etiology of some cardiac malformation that are known to have genetic components, where they make up approximately 5–17% are part of a genetic syndrome. Environmental factors need to be considered and a detailed family history needs to be elicited [119]. The role of the primary care giver is paramount, in detecting possible associated cardiac genetic syndromes. When genetic syndromes are a possibility, intervention requires referral to a genetic counselor for accurate diagnosis and possible future pregnancy. Since approximately, 75% of currently known cardiac malformations have no identifiable cause or underlying condition, the necessity for genetic counseling may appear unwarranted. However with the advent of advanced genetic testing such as whole exome sequencing, once unrecognized features are now being associated with syndromes [120–123]. Postnatal, the purpose of the genetic evaluation is to help establish a diagnosis and educate the family about future risk recurrence and expected outcomes. Parents need to be counseled and educated on both the numeric risk and the variable expressivity that makes predicting severity difficult.

3.2.2. Genetic evaluation of congenital heart disease

The role of genetic evaluation in patients with cardiac malformations, as patients live longer is becoming increasingly important. In the past, where genetic testing was limited to research laboratories, in today clinical practice this is no longer the case. The current clinical practice allows for the physician to obtain chromosomal analysis and request FISH testing when looking for specific deletions [22, 121–123]. The yields of these testing becomes higher when a genetic counselor is consulted prior to obtaining specific test. However even with the advancement on genetic testing, not all patients with congenital heart disease will be identified to have a genetic cause. The recommend approach for newly diagnosed patients with cardiac malformations includes the routine evaluation of all available relatives for a potential genetic contribution [22], and obtaining an accurate and complete medical history and documenting and extended pedigree. If from the information a syndrome if recognized, then evaluation and counseling of other family members becomes extremely important. Depending on the suspected diagnosis or syndrome, other consultation will need to be obtained such neurology, ophthalmology, and others subspecialties.

Cytogenetic testing should be obtained in the following situations (from AHA Scientific Statement):

1. Any child or infant with the phenotype of a recognizable chromosomal syndrome (e.g., Trisomy 21 or 18)

2. Because not all chromosomal abnormalities result in a clinically recognizable syndrome, any infant or child with congenital heart disease combined with (a) dysmorphic features (b) growth retardation that cannot be explained by the heart defect (c) developmental delay or mental retardation or (d) multiple congenital anomalies.
3. Infant or children with a family history of multiple miscarriage and/or sibling with birth defects
4. If major cardiac and/or other visceral organ malformations are documented by prenatal ultrasound and/or fetal echocardiogram.

   Review of the literature shows that chromosome abnormalities were present in 12% of patients with TOF, 26% in tetralogy of Fallot/pulmonary atresia, 44% in interrupted aortic arch, 12% in truncus arteriosus, 5% in double outlet right ventricle, and 60% in absent pulmonary valve. With certain cardiac defect, chromosomal analysis should be considered. In patients with conotruncal defects or interrupted aortic arch, FISH should be used looking for 22q11 deletion. Also analysis of the 8p region should be included [124].

3.2.3. Types of genetic testing

3.2.3.1. Karyotype

Prior to the advent of advanced cytogenetic testing, the standard chromosomal analysis (i.e., karyotype) was widely used. Chromosome testing using standard metaphase karyotype is the traditional method and remains standard for the detection of aneuploidy (Trisomy 13, 18 and 21 and Turners 45 XO) and detecting gross changes such translocation and duplications [22, 117, 125]. A more sensitive karyotype is also available, which allows for the visualizations of greater number of bands. However, standard karyotype has an estimated 3% detection rate for pathogenic chromosome abnormalities. Conventional chromosome analysis detects well-known chromosome aneuploidies in about 10% of cases of CHDs [126]. with the advent and feasibility of newer technology, karyotype maybe used less and become replaced.

3.2.3.2. Florescence in situ hybridization (FISH)

More advanced cytogenetic techniques such as FISH and chromosome microarray are required to diagnose more subtle structural abnormalities, such as microdeletions, tiny duplications and/or subtle translocations. This technology can be used to detect small deletions and duplications in chromosomes that cannot be detected with standard analysis as it looks specifically at the one area of the chromosome. A final FISH analysis will report on how many chromosomes of a certain type are present, in addition confirm suspected rearrangements. FISH technology uses probes of DNA that have been labeled with a fluorescent dye, that bind to complementary parts of a DNA, when it is heated. These probes are able to attach to their complementary DNA sequence [127]. The classic examples that uses this technology is the diagnosis of DiGeorge Syndrome with 22q11 deletion and William Syndrome with 7q11.23 deletion. The drawback of fluorescence in situ hybridization (FISH) lies in its targeted approach to detect chromosomal defects, rather than a genome-wide screening method like microarrays [128].

3.2.3.3. Chromosome microarray

Chromosomal microarray (CMA) testing looks for extra (duplicated) or missing (deleted) chromosomal segments, sometimes called copy number variants (CNVs). It refers to a microchip-based testing platform that allows high-volume, automated analysis of many pieces of DNA at once. CMA chips use labels or probes that bond to specific chromosome regions [129]. The resolution of conventional karyotype analysis is limited to 5 Mb or larger genomic imbalances. Chromosome Microarray Analysis (CMA) is a routine technique in clinical molecular testing nowadays, which contains two types of arrays: oligonucleotide arrays and Single Nucleotide Polymorphism arrays (SNP arrays). Computer analysis is used to compare a patient's genetic material to that of a reference sample. A difference between a patient's DNA and the reference sample is called a variant. These include chromosomal microdeletions and micro-duplications that are too small, abnormalities of chromosome number like the trisomies. In addition other variants include unbalanced rearrangements of chromosome structure such as translocations and triploidies.

Both the arrays could detect genome-wide CNVs. Moreover, SNP arrays can detect mosaicism, triploid, loss of heterozygosity and uniparental disomy. In 2010, the American College of Medical Genetics issued practice guidelines for CMA, and pointed out that CMA was recommended as a first-tier test for postnatal patients with multiple congenital anomalies, intellectual disabilities/developmental delay (ID/DD) and autism spectrum disorders [127, 129]. Recently, CMA has been successfully applied to detect CNVs in patients with CHD, which confirmed the relationship between chromosome microdeletion/microduplication and CHD [128].

3.2.3.4. Whole exome sequencing

Whole exome sequencing is part of next-generation sequencing. With this technology, it is now possible to sequence large amounts of DNA that provide genetic code for making proteins, which are called exons. All the exons in a genome are referred to as the exome, hence this method of sequencing them is known as whole exome sequencing, which allows for the identification of variations in the protein-coding region. It is known that most mutations that cause disease states, occur in these regions. Therefore, the use of this technology allows an efficient way to detect possible disease-causing mutations [130]. Whole exome sequencing has been successfully applied to patients with CHD. Many de novo mutations involved in cardiac related genes to the developing heart have been detected. [22, 130, 131]. This finding helped better elucidate understanding of overall CHD and its developmental pathways. However, more research needs to be done to determine a causal relation and best therapeutic interventions in these cohort of patient studied [130].

3.2.4. Preimplantation genetic diagnosis

In the current era of in vitro fertilization, preimplantation genetic diagnosis is possible. PGD provides chromosomal and mutational analysis of blastocyst that results from in vitro fertilization before implantation [22]. In assisted reproductive technology, PGD is becoming a

treatment option for some inherited disorders. The application of PGD can be used in some conditions present at birth, in addition to prevent carrier states that may or may not present later on in life. Holt-Oram syndrome (HOS) was the first heart disease in which PDG was used successfully [125, 132]. The features of HOS include ASD and cardiac conduction disorder, which has a variable penetrance. Currently there is no treatment prospect as it may manifest later on in life. Clinical manifestations may be extremely variable, and may not be present at birth, or present subtly as a sinus bradycardia, as the only clinical sign. So PGD may provide a treatment option to prevent offspring with this genetic diagnosis [117, 125, 132].

3.2.5. Impact on patients and families

The identification of genetic cause in congenital heart disease can prove to be very beneficial. Firstly is allows for the physician to be confident of the diagnosis and explain the mechanism of disease and other prognostic factors.[1] When the cardiac malformation is part of a genetic syndrome, it allows for the care team to look for other associated anomalies in other organ system. A genetic basis for disease may also necessitate evaluation into other family members [22, 117]. This will help further characterize the extent of the disease in the family and monitor risks and assess ability to pass on to future offspring [117]. Patients and families need to be made aware of both the numeric risk, as in Marfan and William Syndrome, an affected person has a 50% risk. However when the cardiac malformation has variable expressivity, predicting severity becomes extremely difficult [118].

4. Conclusion

Since approximately, 75% of congenital heart diseases have no identifiable cause or underlying condition, the notion of formal genetic evaluation may appear unwarranted [123]. However with the development and feasibility of genetic evaluations improving, more and more cardiac malformation are being linked to underlying genetic anomalies. Therefore the need to look for a genetic link become more crucial, as more patient with congenital heart disease live into adult age, it is very important that families understand their recurrence risk [120–122]. Unfortunately genetic counseling is not an integral or compulsory part of the treatment plan for families at many centers. Too many times, parents are exhausted from the complex interventional procedures and surgeries and its subsequent complications, the need for such counseling is forgotten and pushed aside [22, 117]. There are likely to be approximately 400 genes involved in the causation of congenital heart disease, many of which are yet to be identified [119]. Therefore the role of genetic counselors, with specialized skills in cardiovascular genetics is of utmost importance in the adult patient with congenital heart disease. Such genetic counselors play a crucial role in providing accurate recurrence risk, facilitating appropriate genetic testing, interpreting of results and appropriate subspecialty referrals. Phenotypic heterogeneity and incomplete penetrance complicate our understanding of the genesis of congenital heart disease. However it seems more likely than ever that our gaps in understanding the causes of congenital heart disease are primarily genetic and that the mechanism are multifactorial [117].

It is know that the prenatal diagnosis of moderate to severe CHD is associated with improved outcomes and reduction in the morbidity in select cardiac defects. Prior knowledge of the cardiac lesion allows, the delivery room team to be prepared with appropriate resources to help minimize hypoxemia and metabolic acidosis. The likely need of invasive ventilation can be assed prior to delivery. Therefore the prenatal counseling allows for an accurate diagnosis of the cardiac defect, with parents educated on the possible interventions and expected outcomes after birth. Counseling and the availability of a multidisciplinary team will give the expectant parents support and allows for them to make informed decision before and after delivery.

Conflict of interest

None.

Author details

Amal Zubani*, Irfan Asra and Amjad Kouatli

*Address all correspondence to: azubani@kfshrc.edu.sa

King Faisal Specialist Hospital and Research Center 'Gen.-Org.', Jeddah, Saudi Arabia

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Chapter 21

Prenatal Genetic Counseling in Congenital Anomalies

Mihaela Amelia Dobrescu, Florin Burada,
Mihai Gabriel Cucu, Anca Lelia Riza, Gratiela Chelu,
Razvan Mihail Plesea, Adela Cucu,
Alina Liliana Cimpoeru and Mihai Ioana

Additional information is available at the end of the chapter

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Abstract

The impact of genetic variability on embryogenesis and fetus development established medical genetics as essential for the prevention of congenital anomalies, early detection and appropriate management. Advances in ultrasonography equipment and technique allow early detection of many congenital malformations. In addition, genetic testing can be performed in a prenatal setting on a variety of biological samples obtained by invasive and noninvasive procedures: chorionic villus sampling, amniocentesis, cordocentesis, or maternal blood collection (i.e., cell free fetal DNA). In the past, only a small percentage of congenital anomalies had a readily identifiable etiology; genetic diagnostic procedures can provide at least some of the answers for the remaining unsolved cases. Undoubtedly, the need for appropriate case management and counseling justifies the importance of uncovering the underlying genetic cause of birth defects. In this chapter, we will focus on genetic counseling in congenital anomalies, including isolated congenital anomalies and preimplantation genetic diagnosis. Genetic counseling provides information and support, assisting parents in making informed decisions. Through this process, parents learn about the risk of having a newborn with a congenital malformation and the nature of the disorder and its natural history, are advised on available testing for that particular case, and discuss options for risk management and family planning.

Keywords: congenital anomalies, genetic counseling

1. Rationale for prenatal genetic counseling

Congenital anomalies are a major cause of stillbirths and neonatal mortality. Taking into consideration that in 2004 WHO estimated an incidence of about 7% in newborns, congenital anomalies are a major cause of morbidity and mortality worldwide.

Congenital anomalies can be caused by *chromosome abnormalities, single-gene defects, multifactorial inheritance*, or *epigenetic or nongenetic factors*. It is notable that in up to 50% of all cases no apparent identifiable cause can be found. Any microscopically detectable autosomal imbalance, such as trisomy, duplication, deletion, or monosomy, will result in severe structural and developmental abnormality, most of which are lethal conditions. Single-gene defects have been associated with congenital abnormalities that might involve one or more organs and systems with or without an obvious underlying embryological relationship. Multifactorial inheritance accounts for the majority of congenital abnormalities, including isolated malformations, in which genetic factors can clearly be involved.

It should be noted that although malformations are always thought to be congenital, not all congenital abnormalities are "literally" malformations. Anomalies due to an intrinsic, genetic (chromosomal aberration and gene mutation), or multifactorial factor represent approximately 45% of all congenital abnormalities. These are considered primary congenital malformations. Anomalies resulting from the action of an extrinsic factor—chemical, physical, biological agents, and possibly maternal condition—add up 5% of the congenital anomalies identified and are considered secondary congenital anomalies. For the remaining 50% of these abnormalities, the cause is unknown and therefore cannot be included in this classification [1].

The impact of genetic variability on embryogenesis and fetus development established medical genetics as essential for the prevention of congenital anomalies, early detection, and appropriate management. In the past, when dealing with congenital malformations, medical professionals had to face two major issues: a late detection of the anomaly and the lack of an identifiable cause. The act of disease prevention back then was virtually impossible.

Though, in the last decade of rapidly progressing genomic technologies, genetic diagnosis tools became widely accessible, playing an important role in both clinical practice and research. The completion of the Human Genome Project has contributed greatly to our understanding of the molecular basis of genetic disorders.

The importance of determining the genetic cause of birth defects lies in the need for appropriate case management and genetic counseling. Genetic counseling is meant to assist parents in making informed decisions. Through counseling, parents learn about the risk of having a newborn with a congenital malformation and the nature of the disorder and its natural history, are advised on available testing for that particular case, and discuss options for risk management and family planning.

All attempts must be made to arrive at as precise a diagnosis as possible by evaluating gestational history for environmental factors, family history for genetic factors, and patient anatomy for clues to embryologic etiopathogenic mechanisms. Evaluating family history for genetic factors, gestational history for environmental factors, and patient phenotype for information on embryologic mechanisms is mandatory to arrive at as precise a diagnosis as possible.

Genetic counseling may be hampered by the inaccurate recording of the above mentioned and the inherent uncertainty in interpreting them. Given the incompleteness of available data and the difficulty in interpretation, genetic counseling has a demanding and potentially difficult mission.

1.1. Prenatal genetic counseling—when and how

Genetic counseling is a complex medical act, which aims to help families, individuals, and couples to better understand the familial, medical, psychological, and reproductive consequences of the genetic contribution to specific health conditions. It can be offered both pre- and postnatally.

Fortunately, most babies are born healthy. However, in some pregnancies, a risk for birth defects or other genetic problems may be identified. Geneticists and genetic counselors provide prenatal genetic counseling services for individuals, couples, or families with a concern about the health of their unborn baby.

Prenatal counselling manages cases with risks by understanding prenatal screening and testing options. Increased chance of having a child with a birth defect or genetic condition makes the genetic consultations a necessity. The purpose of genetic counseling is to allow informed decision-making by communicating accurate and complete information and presenting objective diagnostic and therapeutic options [2]. To achieve its goal, information transfer must be made in a clear but neutral way, using simple language, respecting ethical and cultural values.

Pretest counseling. At this stage, the couple will be informed on the objectives of the counseling session regarding the suspicion of congenital anomaly for the pregnancy.

The genetic counselor/geneticist will lay down the alternatives the couple has for following up the pregnancy and explain the possibility and alternatives for testing for identifying the cause of the congenital anomalies identified. The geneticist must take into consideration that accepting to be tested may be influenced by psychosocial factors, such as ethnicity, sociodemographic status, and the presence of the partner during the counseling session [3].

If the couple expresses the desire for prenatal diagnosis, the counselor must present the objectives, benefits, risks, limitations, costs, and alternatives for each of the available screening and/or diagnosis techniques. The patient has the right to accept or refuse a given recommendation. At all times, it must be clear that testing is optional.

The counseling must go beyond making an informed choice for testing and what this step entails, but also preparing the couple for possible outcomes dictated by a positive or negative result.

Posttest counseling. Posttest counseling must explain thoroughly the significance of the result, the meaning of a positive or negative result, and go over the limitations of each test. It must

also suggest other possible confirmatory or complementary tests or alternatives [2] and unconditionally support the patient's options, respecting the autonomy of his/her choice.

One of the most encumbering tasks of genetic counseling is presenting a family with the fact that their child has a genetic condition or birth defect. Most of the test results face the couple with a termination/no-termination decision.

As part of the informed decision-making process, the couple must be informed in detail on the clinical presentation and prognosis of the disorder identified. This is often problematic in chromosomal disorders: (1) genotypic variability—the phenotype will vary depending on the extent of the genetic defect and (2) phenotypic variability—the evolution of a case can vary greatly, even between carriers of the same type of anomaly.

1.2. "Why did it happen? Will it happen again? What can be done?"

These questions are perhaps among the most frequent during the counseling session and we will try to answer them briefly below. The probability reoccurrence is called "recurrence risk." Recurrence risk assessment and counseling is based on a combination of theoretic risk assessment and empiric data. Families and patients should be informed on the assumptions involved and the limitations of such estimates.

This chapter is focused on genetic counseling in congenital anomalies, caused by chromosomal, monogenic, or plurifactorial anomalies, as well as on preimplantation genetic diagnosis.

2. Genetic counseling in chromosomal congenital anomalies

Carrier and aneuploidy screening and diagnostic testing have expanded intensely over the past two decades [2], which is justifiable given the estimate of 5.3% of the neonates affected by a genetic disorder. Despite ultrasound and biochemistry reasons for recommending a prenatal diagnosis, genetic testing in pregnancy is optional. Decisions about undergoing testing should be expressed, consented, and based on individual patient's values and needs and guided by the geneticist during counseling sessions.

Congenital anomalies can be caused by chromosomal, monogenic, and multifactorial disorders [4]; out of which, chromosomal anomalies have a significant impact given their combined frequency of 1 in 153 pregnancies [5] and the reserved prognosis for many of them.

Aneuploidies are the most frequent chromosomal anomalies. Aneuploidies are numerical disorders (**Figure 1**)—the number of chromosomes differs to the normal state, called euploidy. Any of the chromosomes, autosomes, or heterosomes can be affected. Aneuploidies can be complete, involving the whole chromosome, or partial. From a single fertilized egg, more populations of cells of different genotypes can develop—this abnormal situation is called mosaicism. Due to their high incidence, three complete trisomies bear significance for the prenatal diagnosis: trisomy 21 (T21—Down syndrome), 18 (T18—Edwards syndrome), and 13 (T13—Patau syndrome).

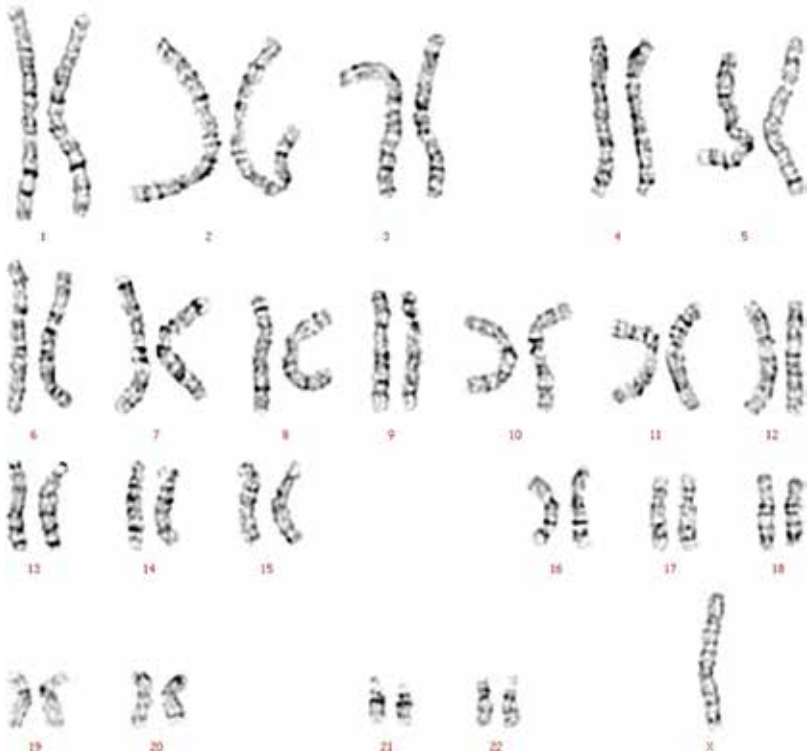

Figure 1. Karyotype 45,X—monosomy X.

Other chromosomal anomalies are structural, such as deletions, duplications, inversions, insertions, translocations, etc. (**Figures 2** and **3**). They are rare and require different diagnosis strategies, counseling, and management of the case.

Possible alternatives for screening ("Prenatal Biochemical and Ultrasound Markers in Chromosomal Anomalies") and diagnosis ("Genomic Testing for Prenatal Clinical Evaluation of Congenital Anomalies") are presented in detail in different chapters, due to their marked importance in genetic testing and counseling.

In the current section, we aim to cover several genetic counseling concepts in a few hypothetical situations of congenital anomaly with underlying chromosomal cause. Pre- and posttesting counseling are a prerequisite of all genetic counseling, but the genetic consult comprises also of a detailed assessment of medical history, psychosocial assessment, and family history, which we are not focusing on here [3, 6, 7].

The possible mechanism by which the chromosomal anomalies occur is usually due to errors in the cell division cycles: nondisjunction in the maternal meiotic division I, and, less frequently, paternal origin [8] or meiosis II [9].

The etiology is mostly unclear, but the probability of chromosomal anomalies increases with maternal age [4], and this is one of the most common etiological factors. Predisposition to

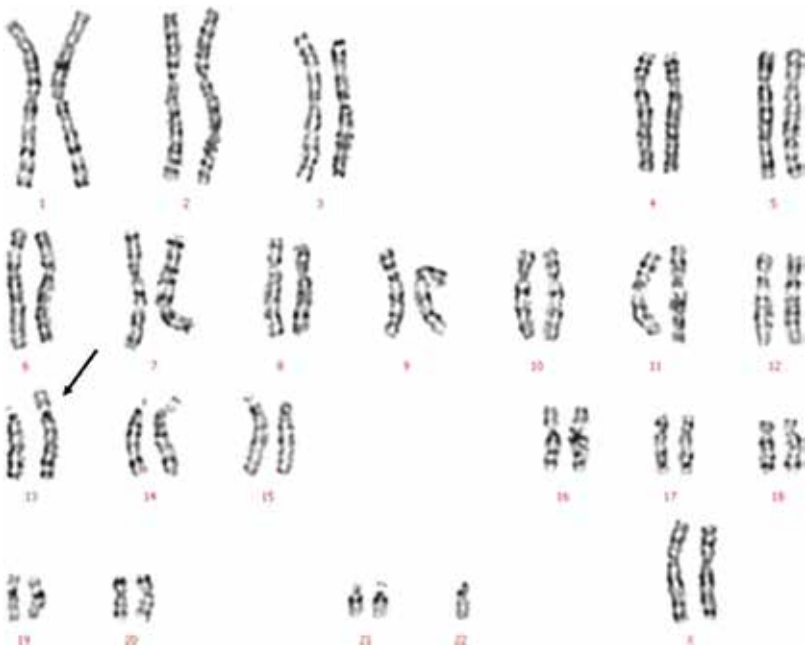

Figure 2. Karyotype 45,XX,rob(13;22)(q10;q10)—Robertsonian translocation.

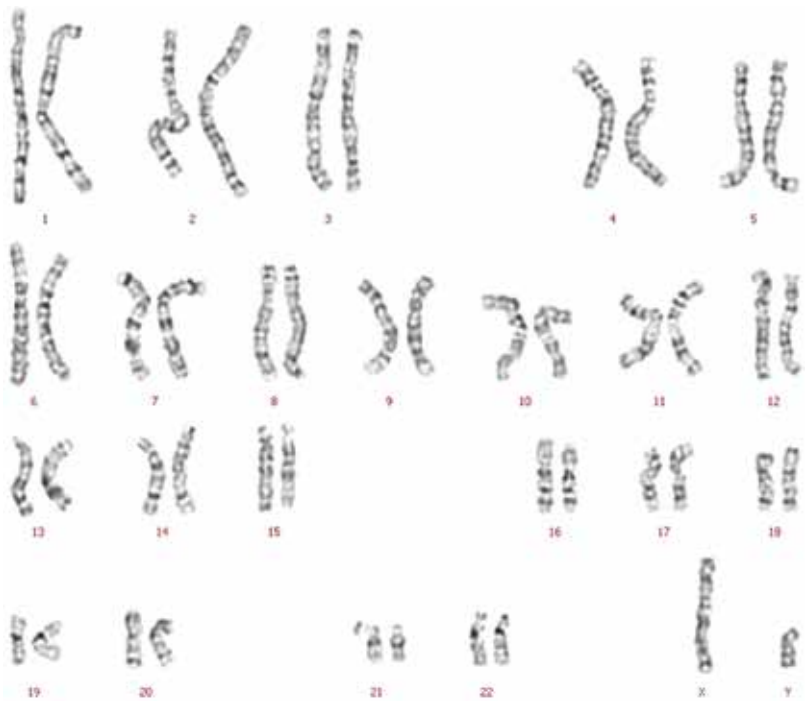

Figure 3. Karyotype 46,XY,t(1;15)(p36.3;q26.1)—reciprocal translocation.

oocyte aneuploidy is also seen in young women, gene expression alteration due to environmental factors and the influence of follicle-stimulating hormone (FSH) being possible culprits [10]. It is yet uncertain if the paternal age contributes to the risk of aneuploidy, if at all [11]. The contribution of different occupational or environmental factors is insufficiently documented.

Aneuploidies are most frequent causes of mental retardation and pregnancy loss [9]. It comes as no surprise that the chance of reoccurrence is one of the most relevant aspects of genetic counseling.

(a) Complete chromosomal, especially autosomal trisomies, when parents are not carriers of translocations

Recurrence risk in the absence of parent translocations follows the empirical risk—the risk measured in the general population, generally evaluated around 1% for the most common trisomy [12] and increases with age for trisomy 21. For other trisomies, the recurrence risk seems lower. Recurrence rates are rather difficult to estimate in sexual aneuploidies. Subjects with Down syndrome are generally infertile, but they have a significant risk of aneuploidy recurrence in their offspring [13].

(b) Chromosomal trisomies with one of the parents being a carrier of a chromosome 21 translocation

Down syndrome translocations are present in less than 4% of the cases. Translocations can occur de novo. For transmitted translocations, the recurrence risk depended on the affected parent: for instance, depending on the involved translocated chromosomes, if the mother is the balanced carrier, the risk is to that of the father, without any known reason for the discrepancy. A balanced translocation t(21,21) has 100% recurrence risk [14].

(c) Mosaicism

Generally, mosaicism cases have the lowest frequency contributions to the total of the trisomies. Mosaicism can occur de novo in the offspring, but parental germ line mosaicism contributes to the recurrence risk [15]. Reduced mosaic [16], meaning low percentage of modified cell lines, or partial trisomy [17], equivalent with duplication, generally has a better prognosis by comparison with a homogenous complete trisomy, but this is not a rule [18].

The couple must be informed that there is no prophylaxis or treatment to correct the aneuploidy, but genetic counseling can provide the support for medically informed decisions to guide the management of the case.

If the couple wishes to keep a pregnancy with chromosomal disorder, they must be informed on the obstetrical complications that may arise, the life expectancy, and the natural history of the disease neonatally and into adulthood.

A trisomy prenatal case, especially 13 or 18, may present with different obstetrical challenges: miscarriage and stillbirth are more frequent than compared to the general population. Structural anomalies of the fetuses lead to a negative prognosis after birth and low life expectancy [19].

Screening and diagnosis limitations for trisomy 13 lead to underdiagnosis of this aneuploidy. Genetic counseling should bring into discussion the viable fetuses in the second trimester (60% of the cases), when life expectancy is very hard to predict and there is no longer the alternative to terminate the pregnancy. It is crucial to inform the parents on the neonatal procedures for resuscitation, possibilities to correct certain defects so that the couple is prepared to face the trauma of having a child with lethal defect [20].

For trisomy 18, only 10% of the neonates survive longer than 1 year. Diagnosing this trisomy though genetic testing is essential for decision-making during the neonatal life, where critical emergency interventions and choosing invasive treatments are often required [21].

Trisomy 21 has a life expectancy of almost 60 years. Following up, the patient asks for collaborations with multiple medical specialties: cardiological, ENT, ophthalmology, endocrinology, to assess possible complications. During their pediatric life, other interventions are generally symptomatic and similar to their euploid peers [22]. The parents must be prepared though through genetic counseling for the possible difficulties due to motor and cognitive delay. Support in the patient's lifestyle can also come from nongovernmental associations and patient support groups, e.g., Down Syndrome International (https://ds-int.org/down-syndrome-your-country).

3. Congenital anomalies in monogenic diseases

Very often, genetic congenital anomalies are part of the clinical presentation of monogenic diseases; 7.5% of isolated or syndromic congenital anomalies are caused by monogenic disorders. Congenital anomalies can become obvious prenatally or at birth, and at times, they are noticeable only in later development, but in all cases, it happens between conception and birth.

The diagnosis of a monogenic disease is often established based on a conclusive family history, clinical examination, and pedigree pattern and confirmed through genetic testing.

With a known diagnosis, the risk of recurrence will be estimated according to the inheritance pattern of the disease. When definite diagnosis is not available, all attempts should be made to associate the clinical picture with a specific disease. If successful, precise genetic counseling can be offered. Situations when diagnosis cannot be demonstrated before birth are difficult to manage—the counselor will advise the couple when there is a lack of crucial medical information.

Should screening identify congenital anomalies during intrauterine life, couples will be faced with a pressing situation, as anomaly finding does not necessarily imply certain diagnosis. In this case, establishing the diagnosis should be aimed for whenever possible, as the first step in genetic counseling.

There are situations with a known diagnosis and known disease-causing mutation that allow prenatal diagnosis testing. Prenatal invasive diagnosis for monogenic disease running in the family, depending on its severity, should and will be recommended. If diagnosis can be readily

established, then the recurrence risk can be calculated. Probability of inheritance based on Mendel's principles and conditional probability (also known as Bayesian analysis, based on Bayes' theorem on probability) are used to calculate genetic risk [1].

The risk of expressing a monogenic disease is dependent not only on the pattern of inheritance, but also on other factors such as the incidence of the disease, the presence of other affected members, the penetrance and variable expressivity, ethnicity, and the influence of environmental factors.

3.1. Autosomal dominant inheritance

An autosomal dominant disease is a condition expressed in both heterozygous, carrying one copy, and homozygous individuals, carrying two copies one from each parent. The disease is caused by a single gene defect located on an autosome. The affected individuals are usually heterozygous, and the homozygous genotype is associated with more severe features or can be lethal. Females and males exhibit the trait in approximately equal proportions and severity of clinical signs is similar between the two sexes. Both sexes are equally likely to transmit the mutation to their offspring. Mostly, the affected offsprings are descendants of an affected heterozygous and a normal parent. On average, half of the children will be heterozygous and express the disease and half will not. Rarely, homozygous are seen in autosomal dominant diseases. This status can be due to a higher frequency of a gene with mild effects, late onset (e.g. Huntington disease) or when both parents are affected (e.g. achondroplasia). Unusually, an affected homozygous parent will transmit the disease to all of his children. On the pedigree, a vertical transmission pattern is observed (**Figure 4**), and the disease phenotype is usually seen in one generation after another. The disease does not skip generations: if an individual has an autosomal disease, in most of the cases, one parent must also have it [1, 2].

Frequently, autosomal dominant disorders involve different organs and systems of the body; however, dominant conditions affecting one organ have been described (e.g., congenital cataract). The capacity of a single gene to affect unrelated organs is called *pleiotropy* (e.g., Marfan syndrome can affect the skeletal, ocular, and cardiovascular systems; some affected individuals have all features, whereas others may have almost none). In addition, the clinical features in autosomal dominant disorders can show remarkable variation between patients, even between the members of the same family. This difference between individuals is referred to as *variable expressivity* (e.g., in autosomal dominant polycystic kidney disease, some affected individuals develop renal failure in early adulthood, whereas others have just a few renal cysts that do not significantly influence renal function). Occasionally, the heterozygous and homozygous individuals express identical phenotype (complete dominance) [2, 23].

Sometimes, a dominant mutation is inherited, but the condition it determines is not expressed. In these cases, the gene has *reduced (incomplete)penetrance.* The term penetrance is used in monogenic inheritance to indicate the probability of a gene to influence the phenotype. A number of autosomal dominant diseases show an incomplete penetrance (e.g., polydactyly), meaning that a person has the mutation but shows no evidence of a disease. A gene is *completely penetrant* if each individual who inherited the mutation expresses clinical features (e.g., neurofibromatosis type I) [3].

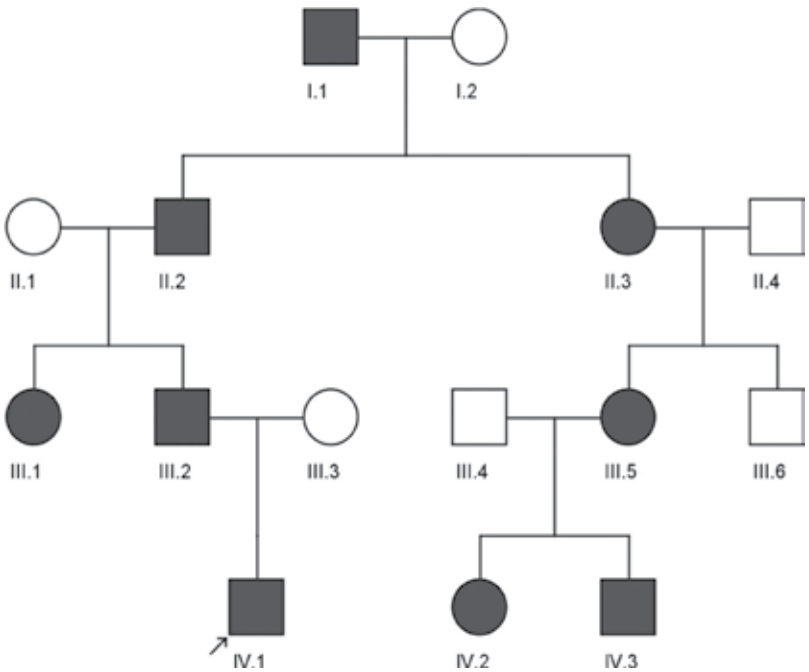

Figure 4. Autosomal dominant inheritance.

Often, known autosomal dominant conditions are seen in a person without an affected parent. The condition seems to be isolated and no clinical features are detected among other family members. In these cases, the disease can be attributed to a "*de novo" mutation* and the recurrence risk for siblings is very low. The mutation is found only in a gamete and the mutated gene is transmitted by one of the healthy parents. The percent of cases caused by de novo mutations is influenced by the severity of clinical features or the capability of reproduction. Osteogenesis imperfecta type II is exclusively caused by new mutations, the condition being perinatally lethal. Also, more than 80% of cases with achondroplasia are due to new mutations, and the proportion is significantly lower in polycystic kidney disease. In this case, it is important to know the family history to distinguish isolated cases and rule out incomplete penetrance or variation in expression. The detection of a specific mutation in a proband allows direct testing of the parents to exclude a disease with expression variability. Also, the detection of a specific mutation can help predict the severity of clinical features in some diseases [24].

Germline mosaicism is another mechanism documented in a number of autosomal dominant diseases such as tuberous sclerosis or osteogenesis imperfecta. Germline mosaicism, also known as gonadal mosaicism, is a condition in which the precursor (germ line) cells to egg and sperm cells are a mixture (mosaic) of two or more genetically different cell lines [1, 2]. The parents do not exhibit any clinical features because the somatic cells are not affected; only a proportion of eggs or sperm cells are carriers of the mutation. Two or more children are affected when there is no family history of disease. This condition is associated with increased recurrence risk for future offspring of a mosaic parent. Because mutation is a rare event, it is unlikely that this would be due to multiple mutations in the same family.

3.2. Autosomal recessive inheritance

An autosomal recessive disease is a condition expressed only in homozygous individuals with both mutant alleles. The parents of such homozygotes must be at least heterozygous for the disease allele and are usually referred to as carriers for that disorder (**Figure 5**). In most cases, the *loss-of-function* mutation is a process in which mutant allele reduces or removes the function of an enzyme. In the heterozygous state, the normal allele can compensate the mutant one, and in homozygotes or compound homozygotes with both mutant alleles, the disease occurs [1, 2, 4].

When two carrier parents of the mutant allele are matting, there is a 50% chance for each of them to transmit either the wild-type or the mutant allele. Thus, each of them has a 50% chance to transmit the mutant allele and further 25% of offspring may be homozygous affected. This also means that 50% of the cases the offspring will get one wild-type allele and one mutant allele, resulting in a carrier. If a parent is affected by a recessive disorder and the other is heterozygous there is a 50% chance that the disorder will be transmitted to children, depending on which allele the partner contributes with. All children are carriers when a parent is affected by an autosomal recessive disorder and the other is homozygous wild-type [1, 4].

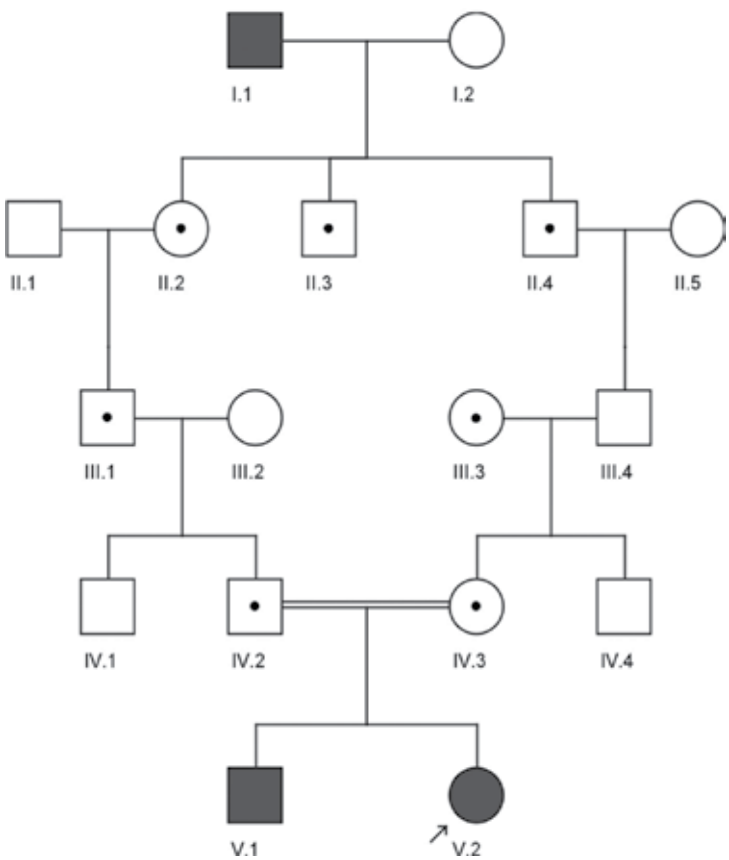

Figure 5. Autosomal recessive inheritance.

Consanguinity is referred to as a couple who have at least a common ancestor, meaning that they are relatives. Finding out that an individual with a genetic disorder is the result of a consanguineous couple is strong evidence for a recessive condition, although not certainty, because there is a greater chance that the parents would have inherited the mutant allele from their common ancestor and passed it down, than the possibility of finding a similar mutation in two unrelated individuals in the general population. In fact, this is true for very rare mutations (e.g., alkaptonuria or xeroderma pigmentosum). In contrast for common autosomal recessive disorders (e.g., cystic fibrosis), the incidence in general population is not significantly lower than in consanguineous marriages. Meaning that the rarer the mutation is in the general population, the more likely that the parents are related (consanguinity) [5].

There are specific recessive disorders for which it is not uncommon that two affected individuals will have children together. Such is the case for individuals with deafness or visual impairment who will benefit from the same social facilities or will be educated together. If the disorder is caused by the same mutation, then all their children would be affected; however, there are studies that show that normal children are born from these couples. The most common explanation is that the parents are homozygous for different genes, both causing deafness, and so the children are heterozygous for both mutations, also known as double heterozygote. This type of genetic heterogeneity is called *locus heterogeneity.* Heterogeneity can also be found in the same locus, as it would be the case of an affected individual who is heterozygote for both alleles, making him/her a *compound heterozygote*. Most affected individuals with recessive autosomal inherited disorders are compound heterozygotes, unless that specific mutation is rather common in the general population (as is the case with cystic fibrosis), or he/she is the result of a consanguinity marriage [1].

Another method of assessing recurrence risk is by calculating the genotype frequency, knowing the allele frequency. This is not as straightforward as it would seem because there is the matter of allele distribution in heterozygotes and homozygotes. This can be done by using the *Hardy-Weinberg Law*, but the population used on has to meet some criteria such as: (a) the population is large and the mattings are random; (b) there is no significant rate of new mutations; (c) there is no selection for any genotype; and (d) there is no significant migration disturbing the endogenous population allele frequency [6].

The presence of both homologous from a pair or chromosomal regions in an offspring coming from the same parent is called *uniparental disomy*. The uniparental disomy can be caused by an error in meiosis resulting in two different chromosomes coming from the same parent, which is called heterodisomy, or by an error in meiosis II, which will result in identical chromosomes transmitted from the same parent called isodisomy. This abnormality has been reported to be a rare cause for cystic fibrosis, in families where only one parent is heterozygote and the offspring takes both homologous chromosomes with the mutant allele from that parent [1, 4].

3.3. Sex-linked inheritance

This type of inheritance is linked to the genes found on the sex chromosomes. Inheritance patterns for the genes found on X chromosome relates to X-linked inheritance, while for the genes located on Y chromosomes, it is called holandric or Y-linked inheritance. The genes positioned on the X and Y chromosomes are unequally transmitted to males and females.

X-inactivation is a normal process, which appears in the early development of the embryo. The result is that most of the genes on one of the two X chromosomes in females are inactivated in each cell, ensuring the fact that, similar to males, females have only one functional X chromosome. One of the two chromosomes is randomly inactivated, meaning that approximately half of the cells in females have a functional X chromosome of maternal origin and the other half have the paternal one functional. This process interferes with both dominant and recessive X-linked inheritance as detailed below [5].

3.3.1. X-linked dominant inheritance

X-linked dominant inheritance is caused by a dominant mutant allele located on the X chromosome. Hemizygous males and both homozygous and heterozygous females are affected. Males are more likely to be severely affected given the fact that in females one of the X chromosomes will be inactivated (X-inactivation), unless the females are homozygous for that allele.

Affected heterozygote offsprings of both sexes have a 50% chance to inherit the mutant allele from an affected mother, which is similar in the autosomal dominant inheritance too (**Figure 6**). The difference between the autosomal and X-linked dominant inheritance refers to affected males. All daughters of an affected male will also be affected by inheriting the X chromosome with the mutant allele, whereas male offsprings will inherit the Y chromosome, thus avoiding the disorder. Affected females are twice more frequent than affected males, although females tend to have milder phenotypic manifestations. One example of an X-linked dominant inheritance disorder is the hypophosphatemic rickets [1, 2, 4].

In some cases, affected males with an X-linked dominant disorder are rarely seen, for example, Rett syndrome and incontinentia pigmenti. This is due to the fact that the presence of the mutant allele in male hemizygotes will result in an early embryonic development stop. In other cases, it seems that only females are affected because males are "speared." An example of a disorder that spares male hemizygotes is X-linked females—limited epilepsy and cognitive impairment. Females appear to be healthy at birth, yet they develop the affection from the second year of life, while males are unaffected their whole life. This disorder is caused by a loss of functional mechanism in the protocadherin gene 19, which is expressed in the neurons. The explanation for this particular case would be that random X-inactivation makes a mosaic expression of this gene in the cells of the central nervous system, which disrupts communications between neurons. In males, the brain is spared this miscommunication between neurons by seemingly a different protocadherin, which compensates the loss of the first [6].

3.3.2. X-linked recessive inheritance

X-linked recessive inheritance is caused by a recessive mutant gene located on the X chromosome. Almost all affected individuals are males (hemizygotes), while homozygotes affected females are rarely seen. The clinical features seen in females are mainly due to non-random X-inactivation [4].

All daughters of an affected male (hemizygous) will be carriers (heterozygotes) for a specific disorder, whereas the sons will inherit the Y chromosomes from the father and thus will be

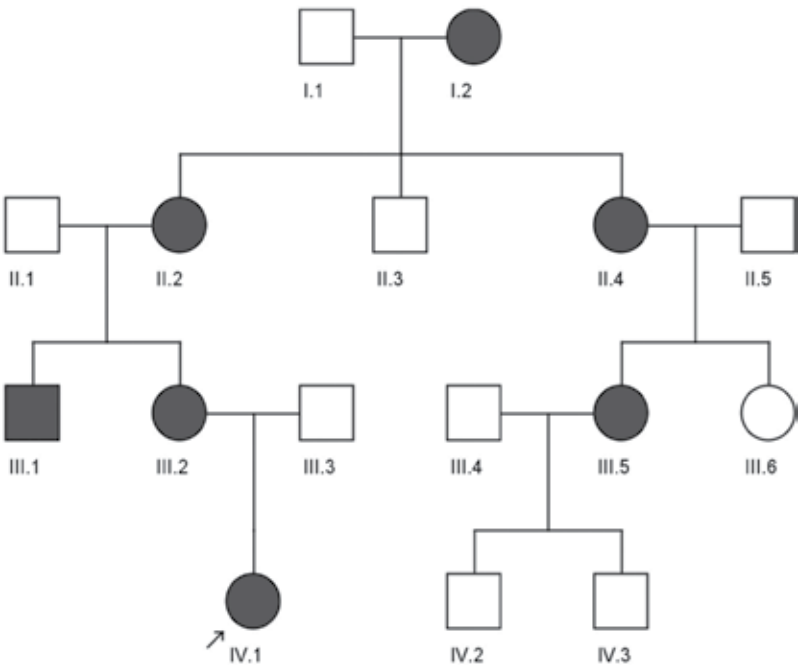

Figure 6. X-linked dominant inheritance.

unaffected by the disorder. For a female carrying the mutation, there is a 50% chance to transmit the mutant X chromosome to the offspring, as a result 50% of the daughters will be carriers and 50% of the sons will be affected (**Figure 7**). For a female to be affected means to inherit the mutant allele from each parent, which is very unlikely to happen, or another option is the presence of only one X chromosome (monosomy X) on which the mutation is present, making her a hemizygous for the allele, like in the case of males. A commonly known X-linked recessive disorder is hemophilia A caused by deficiency of factor VIII, a protein involved in clotting [1, 2, 6].

Sometimes, the females can express the phenotype. The most common situation is represented by a carrier female showing phenotypic features, phenomenon known as *manifesting heterozygote.* This manifestation is due to X-inactivation, which is not random anymore; rather, it has become unbalanced or skewed. The skewed X-inactivation can be both advantageous when the inactivated X chromosome in all or most cell lines and tissues is the one with the mutation and deleterious when inactivation occurs on the X chromosome containing the wild-type allele. This unbalance can be created through chance alone by selecting mostly one of the X chromosomes, rather than the other, or through different mechanisms like cytogenetic abnormalities (translocation) or removal of the cells containing the mutant allele [6].

The *germline mosaicism (gonadal mosaicism)* is an important mechanism in assessment of X-linked recessive inheritance risk and it was also seen in autosomal dominant inheritance. Because both male and female gametogenesis can be affected, it should be taken into account when the recurrence risk is assessed in apparently sporadically appeared X-linked disorders like Duchenne muscular dystrophy [1].

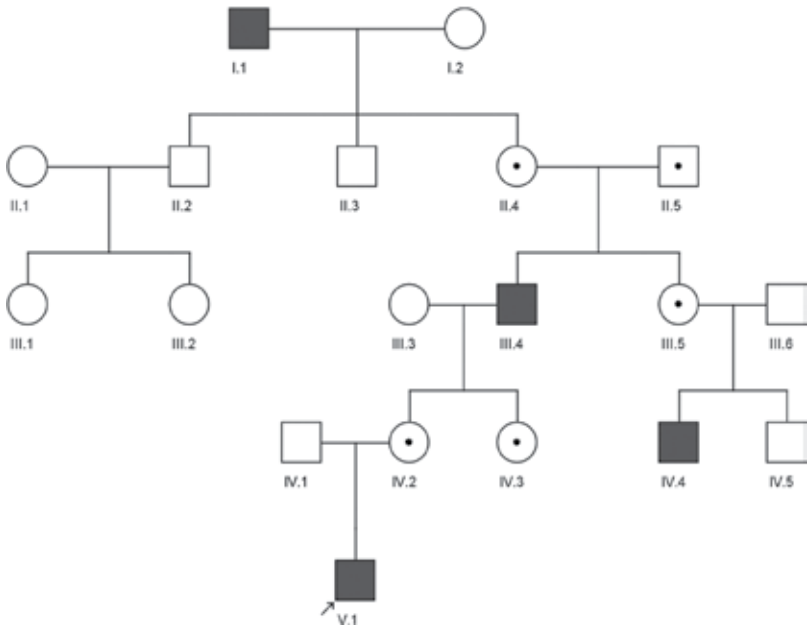

Figure 7. X-linked recessive inheritance.

3.3.3. Y-linked inheritance

Y-linked inheritance also known as holandric inheritance is caused by genes located on the Y chromosome. This is a rather straightforward type of inheritance as only males have Y chromosome, meaning that a male will transmit the mutant allele and thus the disorder to all his male descendants and none of his female ones.

4. Genetic counseling in multifactorial congenital anomalies

Multifactorial heredity describes a trait whose manifestations are determined by the activity of one or more genes in combination with environmental factors that can trigger, accelerate, or exacerbate the pathological process. Multifactorial diseases present a specific familial disposition, the incidence for close relatives of the affected individual being about 2–4%, unlike diseases determined by the mutations of a single gene (25–50%) [7].

These types of pathologies are classified into two main categories: (1) common diseases of adulthood (coronary disease, hypertension, diabetes, asthma, schizophrenia, etc.), having a prevalence of around 1–5%, and (2) isolated congenital abnormalities of the childhood (e.g. neural tube defects, cleft lip and anterior palate, congenital anomalies of the heart, varus equina), with an incidence of approximately 1–8% in newborns [25].

Congenital anomalies, also referred to as congenital abnormalities, congenital malformations, congenital disorders, or birth defects, are conditions of prenatal origin that describe developmental

disorders of the embryo and fetus, potentially impacting its health and development [26]. There is a wide array of anomalies including structural and functional conditions that can fall under these headings [3].

Congenital anomalies are affecting 1–6% of pregnancies worldwide, making them a leading cause of morbidity and mortality in early life [8, 9, 27, 28]. In high-income countries, a quarter of the infant deaths is due to these anomalies [10, 29, 30]. Mortality in children under 5 years old escalates to 3.3 million [28].

These anomalies can occur in isolation (isolated congenital anomalies) or as a group of defects (multiple congenital anomalies). However, there is no generally accepted system of classification, or even an agreed definition of what constitutes a congenital anomaly [3].

Improvements in the sensitivity and availability of prenatal screening have helped decrease the number of children born with congenital anomalies [8, 31]. Even so, when the event arises, the diagnosis and the discussions around pregnancy termination create significant emotional distress [32]. Moreover, parents who have lost a child to a congenital anomaly or families with a pre-existing condition will be very concerned about the risk of recurrence in future pregnancies [11].

The role of genetic counseling is to provide guidance and support to the families being affected by these conditions [12, 24], yet the etiology of most congenital anomalies is multifactorial or unknown [33] and so an exact evaluation of the recurrence risk is hard to make for most anomaly groups and subtypes. There are a few population-based studies that offer some information concerning the recurrence risk [13, 14, 34]. All three studies conducted in the 1990s found that a congenital anomaly has twice the risk of occurrence in a future pregnancy if it has already been present, and the risk rises 5- to 12-fold if the same anomaly is present in the subsequent pregnancy [13, 14, 34]. These studies have also limitations, due to small sample size, lack or outdated classification, rendering them less useful. There is also more accurate data available in a recent article [3] that shows that for similar anomalies the recurrence risk for isolated congenital anomalies is 20-fold higher, while for dissimilar anomalies, the recurrence risk is 1.3-fold higher. Also, it was concluded in the article that the absolute recurrence risk varies between 1 in 20 and 1 in 30 [3].

General recurrence risk. Under these conditions, a number of general principles must be respected for genetic counseling. The empirical risk represents a medium risk for the respective disease in the population of which the proband (index case) is, and so it is possible that in the studied family the average risk is not the same as the real risk.

The overall empirical risk of recurrent fracture or progression for isolated congenital malformations with a frequency of 1–1000 newborns is about 2.5% for common diseases; at a frequency of 1–100, the risk is about 10%.

The risk of recurrence of the condition is influenced by a number of factors:

- The degree of kinship with the proband (index case). The risk of recurrence to first-degree relatives is much higher than for other people in the family; for example, the descendants and siblings of a proband with oral cleft have a risk of 3.15 and 2.79%, respectively, and the second- and third-degree relatives have much lower risks, 0.47 and 0.27%, respectively.

- The presence of a more severe condition in the proband. If the proband has a unilateral oral cleft, the risk to siblings is 1.9%, and if the proband has bilateral oral cleft, the risk rises to 6.6%.
- The presence in the family of several affected individuals. In the case of labia, if two siblings are affected, the risk for the next birth is 10%; if a parent and child are affected, then the risk for another affected child is 14%.
- Sex of the proband. The risk increases if in the family there are sick individuals of a certain sex at which the illness is normally less frequent (i.e., developmental dysplasia of the hip in boys and pyloric stenosis in girls).
- Consanguinity increases the risk of recurrence because the risk genes are inherited from both sides.

If for certain isolated congenital anomalies there is no information on the empirical risk in a given population, the risks may be recalculated based on the population frequency and the severity of the condition, as well as the number of affected individuals.

Recurrence risks per pathology. Regarding *congenital anomalies of the heart*, the recurrence risk is greater on the horizontal line (brotherhood) than on the vertical line for first-degree relatives and it revolves around 2–4%, whereas for second-degree relatives, the risk is reduced, becoming similar to that of the general population [35]. On the other hand, though, if the affected parent is the mother, the recurrence risk is significantly higher than the one for which the father would have been the carrier of the anomaly.

Cleft lip when associated or not with anterior palate represents the most common facial congenital anomaly, being present in over 20% of the cases and also having a positive family history.

At birth, the fact that the child has an affected mother and that she has another affected child increases the prevalence. The recurrence risk for patients that have first-degree relatives with this disease is 32 times greater than in the general population for cleft lip and anterior palate and 56 times greater for anterior palate alone, even though patients with cleft lip have a high familial recurrence of almost 4%.

In regard to *neural tube defects*, recent studies have pointed that if the proband would be the first affected child in the family then the recurrence risk for the following children would be 3.15%, whereas for the second affected sibling, the risk for recurrence would be around 10–11.76%. Some studies also showed that the risk is higher for female children and for the first and last siblings of a mother.

Congenital hip dislocation has a 5% recurrence risk if an affected sibling is already present. An increased risk of male probing according to sex ratio (8 males per 1 affected female) is encountered in people affected by this congenital anomaly.

Varus equina seems to be twice as frequent in girls as in boys, while in families that have one child with this condition, the occurrence risk for the following children is 30 times higher than that of the general population being approximately 7.3%.

The indirect setting, based on family history, of an increased individual risk of the disease will allow for the direct determination by molecular tests of genetic risk factors, possibly specific medical actions of early diagnosis.

To summarize, genetic counseling in isolated congenital anomalies relies on information gathered from population-based studies, on new and future discoveries related to the etiology of these disorders, and other factors such as the degree of kinship with the proband, presence of a more severe condition, more than one individual affected in the same family, or consanguinity for calculating the recurrence risk for the respective condition.

Genetic counseling is about guidance and support for the patient and the patient's family, so a great deal of attention must also be directed toward careful wording when explaining the risk and decisions that need to be made.

5. Preimplantation genetic diagnosis (PGD)

Preimplantation genetic diagnosis is a multistep procedure that analyzes the genetic material from a single or several cells, with the purpose to avoid a pregnancy affected by a specific disease. The biological samples were obtained during assisted reproductive treatment (ART) by the biopsy of oocyte polar bodies or embryos. PGD requires a multidisciplinary and highly experienced team in ART and genomic evaluation at single-cell level [15, 16].

Indications for PGD. Usually, PGD is provided to couples at risk of conceiving abnormal offspring with monogenic or chromosomal disorders. Thus, PGD is suitable for couples where one member is affected by a dominant disorder or both are known carriers of mutant alleles for a recessive disease, or one of them carries a balanced chromosome rearrangement that predisposes him/her to transmit and unbalanced chromosomal abnormality, often deletion or duplication [16, 17]. The presence of a gene mutation or chromosomal abnormality in a member or members of a family must be identified before PGD to allow the detection of a particular genetic abnormality before implantation and further the transmission of a specific disorder to children. Only normal embryos are transferred to the uterus to initiate the pregnancy knowing that the embryo is not a carrier for a specific abnormality, thus decreasing the risk of having an offspring affected by a specific genetic disorder. Many of these diseases are associated with an early death or severe mental and congenital abnormalities. The monogenic diseases diagnosed through PGD include autosomal recessive conditions (e.g., β-thalassemia, cystic fibrosis, spinal muscular atrophy, and sickle cell disease), autosomal dominant conditions (Huntington's disease, myotonic dystrophy, and Charcot-Marie-Tooth disease), or X-linked recessive conditions (fragile X syndrome, Duchenne muscular dystrophy, and hemophilia) [18].

PGD is also available to help parents in creating embryos that are human leucocyte antigen (HLA) compatible with a child affected by a severe blood disease, thus the selected sibling serving as a donor. PGD is an appropriate choice for carrier couples who also have infertility problems and plan to use assisted reproductive treatment anyway or for couples with an ethical or religious objection to pregnancy termination. PGD can also be used for the detection of a variety of cancer predispositions (e.g., familial breast cancer) [19, 20].

Biopsy procedures and genetic analysis technique. Genetic testing can be performed using biological samples obtained by one of the following: polar body, cleavage-stage embryo, or blastocyst biopsy [15, 16].

Polar body biopsy. First and second polar bodies are haploid cells produced in the first and, respectively, second meiotic division of oogenesis. The genetic evaluation of both polar bodies is required to precisely establish the genetic status of the oocyte. Because polar bodies are not a part of the zygote, this technique is mainly performed in some countries where embryo biopsy is unauthorized by law. Polar body analysis only provides data about mutations or aneuploidies of maternal origins. The chromosome abnormalities occurring postmeiotically (e.g., mosaicism and polyploidy), limited amount of genetic material, and doubling the number of samples for analysis have made the need to perform this type of biopsy questionable [36, 21].

Cleavage-stage embryo biopsy. Cleavage-stage biopsy is usually performed on day 3 when early embryo consists of approximately 6–10 cells. At this stage, the cells are still totipotent and are not yet adhering to one another, allowing the extraction of a single blastomere for genetic testing. Limited amount of genetic material and high rates of mosaicism observed in early embryos can lead to misdiagnosis at this stage. The biopsy of two blastomeres was associated with deleterious effects on embryo development and is recommended to be avoided [22, 37].

Blastocyst biopsy. The embryo reaches the blastocyst stage on day 5 or 6 after fertilization. The blastocyst contains about 100 cells and comprises the outer trophectoderm and inner cell mass. During blastocyst biopsy, 5–10 trophectoderm cells are retrieved; thus, more material for genetic diagnosis is available. The ethical and safety considerations related to early embryo biopsy are overcome somewhat because the trophectoderm cells will differentiate into trophoblast cells and further go on to form placenta and other extraembryonic tissues, and not participate to form the embryo [15, 23]. Recent studies showed that this type of biopsy has no effect on reproductive capacity of a blastocyst [16, 24]. However, only about 40–50% of preimplantation embryos will reach this stage in vitro. Because the time to obtain a genetic diagnosis is very limited to perform a fresh embryo transfer, mostly frozen embryo transfer is performed after vitrification [15, 16, 36].

Genetic analysis techniques. After the biological material is available for biopsy, the genetic analysis can be performed. The evaluation is based on only a single cell or very limited genetic material. For fresh embryo transfer, the genetic diagnosis must be done within 24–36 h. The single-gene mutations are detected using molecular genetic methods (PCR, PCR-multiplex, RTqPCR, whole genome amplification, or even next-generation sequencing) and chromosomal abnormalities (e.g., translocation and aneuploidies) by cytogenetic techniques (FISH, array CGH, and SNP array) [16, 25].

The embryo testing using genetic methods with the aim to detect *de novo* chromosomal aneuploidies is known as preimplantation genetic screening (PGS) [26]. PGS analyzes whether a single cell or a small number of cells biopsied from a preimplantation embryo is euploid before transferring it to the uterus. PGS is not PGD, being mainly offered to couples with advanced maternal age, recurrent implantation failure or recurrent miscarriages, and other conditions associated with high risk for aneuploid embryos in order to increase the success rate of IVF (~30%). PGS can be performed using FISH, multiplex quantitative PCR, or chromosomal microarrays [16, 27, 28].

Genetic counseling. A clinical genetic consultation provided by a geneticist with practice in ART is required to the couples before starting PGD treatment. Its purpose is to confirm the genetic diagnosis, to evaluate the reproductive status of the couple, and to provide information about the disease, mode of inheritance, recurrence risk, genetic testing, and reproductive options, including PGD [38].

Genetic counseling by a qualified geneticist or a certified genetic counselor is recommended to the couples to receive support and appropriate information in a nondirective manner and with no pressure, allowing them to make the best choice. Family history, reason for PGD, what is PGD, alternative reproductive options and side effects of treatment, the limitations of testing, success rates (about 30%), and possible outcome options should be discussed, including an unsuccessful cycle [29, 30].

Also, a multiple birth should be considered when ART is used. Thus, the couple should understand and consider the physical, psychological, and financial impact of treatment [31].

An important part of genetic counseling is to establish the reason for choosing PGD. In most cases, the couples choose PGD to avoid termination of pregnancy due to a genetic disease or to know earliest that the pregnancy is unaffected by a specific genetic abnormality [17]. Other reasons for PGD include a previously affected child or a loss of a child, recurrent abortions, or infertility. When parents are carriers for a recessive disorder, more embryos may be carriers for a mutant allele. The couple must be informed about the genetic status of the embryos and in the absence of a clinical feature in carriers, these can be considered for transfer to increase the number of available embryos. The issue of genetic testing of children for carrier status should be discussed prior to offering prenatal diagnosis to confirm the PGD result.

Sex selection is not allowed by law in many countries, while in others, it is allowed. Except some recessive X-linked disorders where females may have a mild phenotype, in these cases, the female embryos should be excluded for transfer, and the parents should be able to choose not to know the sex of their embryos.

After implantation, a new contact with a geneticist is required. Occasionally, when PGD is used, a misdiagnosis can occur; therefore, prenatal diagnosis should be offered. Prenatal diagnosis requires an invasive testing (chorionic villus sampling and amniocentesis) associated with the risk of losing the pregnancy, and many of them may refuse the confirmatory test [29].

The postnatal confirmatory diagnosis from blood is in contrast to recommendations for testing in childhood, which specify that unless there are clinical benefits to testing minors, testing for carrier or late disease conditions should be delayed until the child is old enough to understand the implications and be part of the decision making. In most cases, a successful PGD cycle will result in an ongoing pregnancy and a healthy live born infant. However, a follow-up after birth is recommended.

6. Ethical considerations

Biomedical ethics is based on applying various principles in order to create a framework of moral analysis that allows the practitioner to make an optimal decision in agreement with the patients' wishes/needs and their point of view.

Medical genetics is one of the medical fields in which, from the very beginning, sensitive ethical issues have been raised; their importance subsequently became more and more undeniable due to technological advances and discoveries in the field (see Human Genome Project, Next Generation Sequence, and Whole Genome/Exome Sequencing).

Of all the areas of genetics, prenatal diagnosis raises the most fervent debates and, consequently, ethical dilemmas. It is one of the chapters that are hard to fit in an accurate guide for the clinician, sufficient enough to use and make sure he has done or said what is needed to ensure that the health of the patient and family is protected.

The particularity of this field is derived from the existence of two entities whose rights must be taken into account: on one hand, the "patient," the unborn fetus at different stages of development at the time of the diagnosis request, and on the other hand, the mother/couple requesting the diagnosis. Although the phrase"on one hand and … on the other side" might seem inappropriate, it still reflects reality, because not always the rights of the patient are on the same side as those of the parents. And here lies the first dilemma: autonomy vs. benefit.

6.1. Ethical principles and prenatal counseling

In order to improve medical practice in medical genetics and implicitly in prenatal genetic diagnosis, a set of essential ethical principles was developed to support a clinical decision [32, 35]:

1. Respecting the autonomy of a person referring to the right of a patient to make his/her own decision without any constraint but at the same time informed by a genetic counseling in a nonlinear and impartial manner, without prejudices.
2. The "do not harm" obligation and the "doing good" duty reflect on the degree of necessity of the two desires. Obviously, it is desirable to do well (benefit), but in this process, it is much more important to avoid mistakes before getting the right benefit (e.g., presymptomatic testing for early-onset diseases) [33].
3. Confidentiality protects the patient's genetic data from various other parts. The data could be provided only with the patient's consent and only if the doctor considers them relevant. However, the doctor may not respect confidentiality if the genetic data are relevant for the relatives and the patient is not able to properly inform them about familial medical conditions.
4. Equal access to patients for care and treatment: this concept is the most difficult to apply due to the insufficient resources.

Prenatal diagnosis (PD), and here we will only refer to invasive PD, involves a genetic test that allows the diagnosis of a fetus with a serious genetic disorder (and there is an issue of what "serious" means in the opinion of specialists), followed by communication of the data to parents. The purpose of prenatal genetic testing is exclusively medical and testing criteria should be clearly established [34].

When PD is recommended, the couple will be informed, regardless of their perspective on abortion because sometimes it can be useful for psychological and medical training for the

birth of a child with a congenital anomaly [34]. However, PD is a voluntary decision of the couple who will decide if the suspected condition requires diagnosis testing or termination of the pregnancy.

The distinctiveness of PD consists in this one-sided decision of the pregnant woman whose sentence affects both herself and the unborn child; if a woman is able to make an independent and well-considered decision, she must have the necessary knowledge to act in the context that PD does not only give information about a potential termination of a pregnancy but also it provides information that will prepare the parents for the birth of an affected child.

For this purpose, pretesting counseling is vital, and it will determine not only the risk of the fetus being affected, but also the chances of it being normal, it will inform about the conditions that can be diagnosed and their consequences not only on the fetus but also on the care/treatment options. Furthermore, it will also provide counseling regarding the limits of the test, the possibility of an irrelevant or unexpected result, and the couple's options after testing.

If a PD is established, the physician should discuss with the pregnant woman about all the possible aspects of the clinical features, including the heterogeneity of the clinical manifestations. The informed choice of the pregnant woman/couple in the diagnosis of a fetus with congenital malformations will be respected and protected without prejudice, giving importance and priority to the family and sociocultural background in which the couple and the future malformed child will spend their lives.

In the case of PD without medical indication, when the testing is only based on pregnancy/couple's anxiety, it will be done but with a low priority in allocating resources compared to PD associated with medical reasons. The practice of PD testing with the intention of selecting the child's sex (except for X-linked diseases) is not permitted, as well as the testing of paternity (excepting the pregnancy after an incest or rape) [34].

Particularly, the evolution of technology with the implementation of NGS in PD complicates the ethical aspects because, although genetic diagnosis has been improved, the method has some limitations, some of them common with those of the usual methods of PD [35]:

1. Diagnosing a disease for which there is no treatment.
2. Neither the severity of the clinical manifestations nor the progression of the disease can always be predicted only by conducting a genetic test.
3. There are not yet genetic tests established for all genetic diseases.
4. The results require a complex interpretation because the test provides a lot of data.
5. No test is 100% safe; the safety is dependent on the disease and the used method.
6. Laboratory errors sometimes do occur.
7. Not all pathogenic variants could be detected and interpreted.
8. The cost of the method is very expensive and not all the patients have financial resources.

In conclusion, ethical aspects surrounding PD are multiple and demanding for both the physician and parents, but using the qualified knowledge of a professional, exposed with much tact and patience, the couple will correctly understand the implications of the problem and their possible solutions/the lack of solutions and will take the best decision based on these aspects and according to their own convictions.

Author details

Mihaela Amelia Dobrescu*, Florin Burada*, Mihai Gabriel Cucu, Anca Lelia Riza, Gratiela Chelu, Razvan Mihail Plesea, Adela Cucu, Alina Liliana Cimpoeru and Mihai Ioana

*Address all correspondence to: amelia_dobrescu@yahoo.com and florinburada2000@yahoo.com

Medical Genetics Regional Center (CRGM), Dolj, Human Genomics Laboratory, University of Medicine and Pharmacy of Craiova, Craiova, Romania

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Section 3

The Delivery in Congenital Anomalies

Chapter 22

Management of Pregnancy and Delivery in Prenatally Diagnosed Congenital Anomalies

Diana Ramasauskaite

Additional information is available at the end of the chapter

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Abstract

Prenatal diagnosis of congenital anomalies provides valuable information and allows proper management of pregnancy and delivery. The common congenital anomalies are cardiovascular anomalies, congenital anomalies of the central nervous system, fetal thoracic anomalies, abdominal wall defects, kidney and urinary tract defects, and esophageal, gastrointestinal, and anorectal abnormalities. Different defects require particular assessment, evaluation and care. Pregnancy management mainly includes detection of the malformations, genetic assessment, ultrasound follow-ups and evaluation of fetal well-being as well as performing various invasive or non-invasive procedures. Managing delivery is also highly important and fetal anomaly specific. The main aspects of delivery management discussed in this chapter are delivery place, timing, route and delivery room care.

Keywords: congenital anomalies, management, pregnancy, delivery

1. Introduction

Prenatal diagnosis of congenital anomalies provides parents an opportunity to obtain prognostic information prior to birth, learn about treatment options before and after delivery, reach decisions concerning the management approach that is best for their family (e.g., whether to terminate pregnancy or undergo in utero intervention, if available; nonintervention), and plan for specific needs at birth [1].

2. Cardiovascular anomalies

Identification and management of fetal cardiac abnormalities are important because congenital anomalies are the leading cause of infant death and congenital heart disease accounts for 30–50% of these deaths [1]. The best time for evaluating the fetal heart anatomy is 18–22 weeks of gestation, because the fetal cardiac anatomy can be visualized well at this stage of pregnancy, a complete fetal anatomic survey can be performed, and there is time for further evaluation (e.g., echocardiogram, chromosomal microarray), if indicated, while the fetus is still periviable [2]. After 30 weeks of gestation, it can be difficult to obtain good images as the fetus becomes more crowded within the amniotic cavity. Fetal arrhythmias, myocarditis, cardiomyopathy, heart failure, valvular insufficiency or obstruction and cardiac tumors have variable onset. Fetal echocardiography should be performed in fetuses at a higher risk of congenital heart disease (**Table 1**).

Indications with higher risk profile (estimated >2% absolute risk)	**Indications with lower risk profile (estimated >1 and <2% absolute risk)**
- Maternal pregestational diabetes mellitus or diabetes mellitus diagnosed in the first trimester	- Maternal medications (anticonvulsants, lithium, vitamin A, paroxetine, NSAIDs in first/second trimester)
- Maternal phenylketonuria (uncontrolled)	- Congenital heart disease in second-degree relative of fetus.
- Maternal autoantibodies (SSA/SSB), especially if a previous child had SSA/SSB-related heart disease	- Fetal abnormality of the umbilical cord or placenta (e.g., single umbilical artery, agenesis of the ductus venosus)
- Maternal cardiac teratogens (e.g., thalidomide, angiotensin-converting enzyme [ACE] inhibitor, retinoic acid, nonsteroidal anti-inflammatory drugs [NSAIDs] in the third trimester)	- Fetal intra-abdominal venous anomaly
- Maternal first trimester rubella infection	
- Maternal infection with suspicion of fetal myocarditis because of poor contractility or effusions on standard four-chamber cardiac examination (e.g., coxsackie virus, adenovirus, cytomegalovirus)	
- Pregnancy conceived by assisted reproduction technology (ART)	
- Congenital heart disease in first-degree relative of fetus (maternal, paternal or sibling)	
- Disorder of first- or second-degree relative with Mendelian inheritance with congenital heart disease association (e.g., Noonan, tuberous sclerosis, Holt-Oram, velocardiofacial [DiGeorge] syndrome/22q11 deletion, Alagille syndrome, Williams syndrome)	
- Fetal cardiac abnormality (structural, functional, arrhythmia) suspected on obstetrical ultrasound	
- Fetal noncardiac abnormality suspected on obstetrical ultrasound	
- Fetal chromosome testing reveals a genetic mutation, deletion, rearrangement, or aneuploidy	
- Fetal tachycardia or bradycardia or frequent or persistent irregular heart rhythm	
- Fetal increased nuchal translucency >95 percentile (≥3 mm) on first trimester ultrasound	
- Monochorionic twinning	
- Fetal hydrops or effusions	

Table 1. Indications for fetal echocardiography [2].

2.1. Pregnancy management

When a fetal cardiac abnormality is detected, additional evaluation and follow-up are indicated.

- Assessment for extracardiac anomalies. The extracardiac abnormalities are detected in 20–40% of all fetal cardiac anomalies [1, 3]; the cardiac anomalies are part of numerous fetal syndromes [4]. A systematic review and meta-analysis of studies of prenatal ultrasound and magnetic resonance imaging (MRI) found that brain abnormalities, delay in head growth, and brain-sparing were observed in subgroups of fetuses with congenital heart disease [5] However, the prognostic significance of these findings was unclear.

- Genetic assessment. Fetal genetic assessment is indicated because chromosome abnormalities are common in fetuses with cardiac defects, even when isolated [6]. Forty-one percent of fetuses with prenatally diagnosed structural cardiac defects had an abnormal karyotype [7]. The incidence in infants of congenital heart disease about 15% [6], it is higher because of in utero mortality in many cases, such as the lethal autosomal trisomies (e.g., trisomy 9 or 16). The risk of fetal aneuploidy varies depending on the malformation. For example (risk percent, [2]): atrioventricular septal defect (46–73%), truncus arteriosus (19–78%), double-outlet right ventricle/conotruncal malformations (6–43%), coarctation/arch interruption (5–37%), tricuspid valve dysplasia (including Ebstein malformation, 4–16%), tetralogy of Fallot (7–39 percent), hypoplastic left heart syndrome (HLHS, 4–9%), pulmonic stenosis/atresia with intact septum (1–12%), and transposition of great arteries (0%).

- Ultrasound follow-up. The necessity, timing, and frequency of serial assessment should be guided by the nature and severity of the lesion, presence of heart failure, anticipated timing and mechanism of progression, and the options available for prenatal and postpartum intervention [2]. At least one follow-up examination early in the third trimester is reasonable in order to look for abnormalities that progressed in severity or may not have been detectable earlier in gestation and have peripartum clinical implications. Some causes of progressive fetal cardiac dysfunction include worsening valvular insufficiency or obstruction, increasing obstruction to blood flow in the great arteries, and development or worsening of myocarditis or cardiomyopathy, arrhythmias, or cardiac tumors [2]. Intrauterine fetal growth restriction is more prevalent in these fetuses with congenital heart disease [8].

- Referral to a pediatric cardiologist. The purpose is to educate the patient about the suspected diagnosis and discuss management options before and after delivery, including the preferred site for delivery [1].

- Evaluation of fetal well-being. Fetuses with cardiac structural anomalies, functional disorders, or arrhythmias that have the potential to compromise tissue oxygen delivery are generally followed with antepartum testing, with intervention if results are abnormal. In one retrospective cohort study, fetuses with a genetic syndrome, extracardiac anomaly, or severe valvular regurgitation were at increased risk for fetal demise: 15/197 (7.6%) fetuses with one or more of these risk factors died in utero versus 3/270 (1%) fetuses without any of these risk factors [9]. Six of the 22 fetal deaths occurred at 20–23 weeks and 16 occurred

at 26–41 weeks (including three deaths at 37, 39, and 41 weeks). However, there is no strong evidence of the value of this practice and antepartum fetal testing with the nonstress test, biophysical profile, or fetal movement count has not been tested specifically in this clinical setting. The type of test depends on the underlying abnormality; for example, the biophysical profile is particularly useful in fetuses with arrhythmias and provides an opportunity to monitor for development or progression of hydrops in any fetus with severely altered hemodynamics.

- Fetal therapy. Transplacental medical therapy can improve the prognosis of some fetal arrhythmias [1]. Invasive in utero cardiac intervention (aortic or pulmonary balloon valvuloplasty, atrial needle septoplasty) may improve the prognosis of some lesions, such as HLHS or severe valvular abnormalities (severe mitral regurgitation, aortic stenosis, pulmonary atresia). Current evidence on the effectiveness of prenatal intervention for CHD derives mostly from case reports and a few larger series; although the results of the meta-analysis are encouraging in terms of perinatal survival, they should be interpreted with caution when comparing with procedures performed after delivery [10].

2.2. Delivery management

- Delivery place. Delivery should be planned at a facility with the appropriate level of care for the mother and neonate. Neonates with ductal-dependent lesions and most with critical cardiac lesions should be delivered at a facility with a level III NICU and pediatric cardiology expertise. If this is not feasible, transport arrangements should be established in advance of delivery [1].

Specialized delivery room care is recommended for fetuses with:	- d-transposition of the great arteries - sustained or uncontrolled tachyarrhythmias with heart failure or hydrops fetalis
Specialized delivery room care planning is reasonable for fetuses with:	- hypoplastic left heart syndrome (HLHS) with restrictive or intact atrial septum and abnormal pulmonary vein flow (pulmonary vein forward/reversed flow ratio < 3) or abnormal hyperoxia test in the third trimester - complete heart block and low ventricular rate, cardiac dysfunction, or hydrops fetalis
Specialized delivery room care planning may be considered in fetuses with:	- tetralogy of Fallot with absent pulmonary valve - Ebstein anomaly with hydrops fetalis - total anomalous pulmonary venous return, obstructed
Specialized delivery room care is not needed for fetuses with:	- mild tetralogy of Fallot, ventricular septal defect, atrioventricular septal defect - shunt lesions - most ductal-dependent lesions, but initiation of prostaglandin E1 may be indicated in neonatal intensive care unit - controlled arrhythmias

Table 2. Need for specialized delivery room care in specific anomalies.

- Timing and route. Cesarean delivery is performed for standard obstetrical indications, as there is no evidence that route of delivery of fetuses with congenital heart disease affects outcome [11]. Based on observational data, induction of labor or scheduled cesarean before 39 weeks of gestation is not recommended in the absence of standard maternal or fetal concerns about well-being, as even early term delivery has been associated with worse outcomes after neonatal cardiac surgery [2, 12]. One exception may be single ventricle defects, where earlier delivery may be beneficial [13].
- Delivery room care. Risk assessment for anticipated compromise in the delivery room or during the first few days of life is disease-specific (**Table 2**, [2]).

3. Congenital anomalies of the central nervous system (CNS)

Malformations of the central nervous system (CNS) are among the most common types of major congenital anomalies. Ultrasound examination is an effective modality for prenatal diagnosis of these anomalies. Poor timing of the examination, rather than poor sensitivity, can be an important factor in failing to detect a CNS abnormality [14]. Ideally, pregnancies at increased risk of fetal CNS anomalies and those with suspicious findings on a basic examination should undergo fetal neurosonography performed by clinicians with expertise in this area. Magnetic resonance imaging (MRI) is an option for further evaluation in cases of diagnostic uncertainty when additional information will influence subsequent management of the pregnancy [15].

3.1. Holoprosencephaly

Holoprosencephaly is a fetal anomaly that cannot be altered or treated. Elective termination of pregnancy is recommended if the diagnosis is made early (till 22–24 weeks of gestation under the pregnancy termination law in different countries). Because approximately 30–50% of fetuses with this anomaly have chromosomal abnormalities, prenatal karyotype is recommended. A family history (the familial recurrences have been reported), the history of current pregnancy (exposure to ethanol, salicylates) should be obtained, the evaluation for cytomegalovirus should be done. If the parents choose the conservative management, there is no fetal intervention for this condition and the cesarean delivery should be considered only for maternal indications [16].

3.2. Agenesis of the corpus callosum

During routine screening for fetal anomalies at 20–22 weeks of gestation, the two most important clues that the corpus callosum needs further assessment to exclude a callosal abnormality are (1) non-visualization of the cavum septi pellucidi and (2) ventriculomegaly (lateral ventricles measuring >10 mm). The cause of this anomaly may be genetic, infectious (TORCH infections and Zika virus), vascular, or toxic (alcohol—fetal alcohol syndrome). Callosal dysgenesis

was isolated in only 24% of the fetuses, and isolated callosal abnormalities are associated with normal neurodevelopmental outcome in approximately two-thirds of fetuses [17].

3.2.1. Pregnancy management

- Genetic assessment. Genetic factors are most common. Among the genetic causes, "syndromic" diagnosis is made in 30–45% of cases and a monogenic cause can be identified in 20–35%. Over 200 genetic syndromes, many of which may have variable phenotype, include disorder of the corpus callosum as a feature.
- Magnetic resonance imaging (MRI) is most helpful after the 20th week of gestation, since about 20% of apparently isolated cases diagnosed by ultrasound have associated CNS anomalies on MRI [18].
- Evaluation of fetal well-being. If an isolated agenesis of corpus callosum is detected and the chromosomes are normal, the usual standard pregnancy management should be recommended.

3.2.2. Delivery management

Vaginal delivery is recommended unless is significant hydrocephalus with macrocephaly. Delivery prior to term is not advisable [16].

3.3. Dandy-Walker malformation

'Isolated' Dandy-Walker malformation (DWM) in the light of recent literature, which has demonstrated a potential good clinical and intellectual outcome of fetuses presenting with DWM characterized by partial vermian agenesis and absence of associated anatomical anomalies [19].

3.3.1. Pregnancy management

- Assessment for associated CNS and extra-CNS anomalies. The presence of the additional anomalies adversely affects survival and prognosis for the infant and child with DWM. The risk of associated intracranial anomalies appears to be 20–60%, and in this situation, the mental retardation and perinatal mortality are increased [16].
- Genetic assessment. In the syndromic form of DWM, malformations of the heart, face, limbs, or gastrointestinal or genitourinary system may be present. DWM may occur as part of a Mendelian disorder (e.g., Meckel syndrome), a chromosomal aneuploidy (e.g., 45X, triploidy), environmental exposures (e.g., rubella, alcohol), a multifactorial etiology (e.g., congenital heart defect, neural tube defects), or as a sporadic defect (e.g., holoprosencephaly).
- Evaluation of fetal well-being. The option for elective termination of pregnancy is offered for parents if the diagnosis of DWM with associated CNS anomalies is made early. If the diagnosis is made in the third trimester, conservative management is recommended. In

most cases, the cyst, ventricular dilatation, and cisterna magna enlargement occur slowly, rarely severe or rapidly increasing ventriculomegaly needs for obstetrical intervention [16]. There is no fetal intervention for DWM.

3.3.2. Delivery management

The cesarean delivery should be considered only for maternal indications.

3.4. Anencephaly

3.4.1. Pregnancy management

Anencephaly is the most common neural tube defect (NTD) [20]. The anencephalic fetus can be definitively identified by the 12th postmenstrual week by TVS; although in some cases, this diagnosis has been made as early as 9–10 postmenstrual weeks [21]. Early diagnosis can be made if the cranium is examined carefully at the time of nuchal translucency measurement [22].

Up to 75% of anencephalic infants are stillborn. Liveborn infants generally die within hours but occasionally survive for a few days or weeks. There are no neurosurgical management options. In most developed countries where abortion is legal, these pregnancies are interrupted earlier [23]. Because of their poor prognosis, anencephalic infants have been considered as potential organ donors for transplantation. The clinical cases reported that anencephalic infants are not good candidates for organ donation because they do not generally meet criteria for brain death until their clinical condition has declined to the point where the solid organs are damaged [24]. Polyhydramnios develops in up to 50% of the cases during the second and third trimester due to decreased fetal swallowing, but is not present during the first trimester [20].

Prevention is the most important aspect of management of anencephaly. Periconceptional folic acid supplementation is recommended for all women who are pregnant or who may become pregnant. Higher doses of folic acid supplements are usually recommended for women who are taking anticonvulsant drugs or who have had a previous pregnancy affected by a NTD.

3.4.2. Management of labor

Because polyhydramnios is often associated with this condition, the rate of premature labor is increasing. Labor and delivery are frequently associated with an unstable fetal position, dystocia of labor, placental abruption, and postpartum hemorrhage. The cesarean delivery should be considered only for maternal indications.

3.5. Exencephaly

Exencephaly has been detected as early as the 10th postmenstrual week. In the second trimester, the usual appearance of the cranium encasing the brain is lost. The exposed brain has

a heterogeneous appearance and is not covered by the cranium. Although the cranial vault is absent, the fetal facial bones can be clearly visualized. Maternal serum alpha-fetoprotein levels are highly elevated.

3.5.1. Pregnancy management

Exencephaly is a lethal condition, the termination of pregnancy should be recommended for parents. Typically, exencephaly is not associated with chromosomal abnormalities, but, because of the severity of the defect, a chromosome analysis should be performed to permit accurate genetic counseling [16].

3.5.2. Delivery management

The cesarean delivery should be considered only for maternal indications. There are no indications for resuscitation of the newborn.

3.6. Encephalocele

3.6.1. Pregnancy management

Encephalocele can be diagnosed at 11–14 weeks during sonographic screening for aneuploidy.

- Genetic assessment. Cephalocele usually occurs as an isolated lesion, but may be a part of a syndrome such as Meckel (or Meckel-Gruber) or Walker-Warburg syndrome in a small percentage of cases. Both syndromes are autosomal recessive.
- Assessment for associated anomalies. Detailed sonography or MRI should be performed to verify the diagnosis and to search for associated anomalies.

Obstetrical management depends on the size of defect, the gestational age at diagnosis, and the presence or absence of associated anomalies. Prognosis depends on (1) the presence and amount of brain in the herniated sac (this is the most important consideration) and (2) the presence or absence of hydrocephalus, microcephaly, and other anomalies. If the encephalocele is diagnosed at less than 22–24 weeks of gestation, the termination of the pregnancy can be offered to the parents. If the pregnancy is not terminated, the consultations of neurosurgeon, neonatologist, and medical genetics are recommended [16].

Fetuses with neural tube defects or central nervous system abnormalities typically remain active; however, the quality of fetal movement is often different from that in normal fetuses [20]. The fetus with an encephalocele did not respond to repeated vibroacoustic stimulation (VAS) with a movement or fetal heart rate (FHR) acceleration [25].

3.6.2. Delivery management

When diagnosed prenatally, vaginal delivery may be safe if the lesion is relatively small. Large encephaloceles require cesarean section. Neonates with encephalocele should be delivered at

a facility with a level III NICU. Surgical treatment is appropriate in most cases unless the encephalocele is massive and there is severe microcephaly or other lethal anomalies. The procedure basically consists of removing the overlying sac and closing the defect including the dural defect [26]. In patients with basal encephaloceles or cerebrospinal fluid (CSF) leakage, prompt closure is important to reduce the risk of infection. Patients with hydrocephalus usually undergo ventriculoperitoneal shunt placement prior to encephalocele repair to prevent postoperative CSF leaks.

3.7. Iniencephaly

3.7.1. Pregnancy management

Iniencephaly is a rare, lethal developmental anomaly. Associated malformations occur in up to 84% of cases and include hydrocephaly, microcephaly, ventricular atresia, holoprosencephaly, polymicrogyria, agenesis of the cerebellar vermis, occipital encephalocele, diaphragmatic hernia, thoracic cage deformities, urinary tract anomalies, cleft lip and palate, omphalocele, and polyhydramnios [20]. The sonographic diagnosis has been made as early as 12.5–13 postmenstrual weeks. Detailed sonography or MRI should be performed to verify the diagnosis and to search for associated anomalies. If the iniencephaly is diagnosed at less than 22–24 weeks of gestation, the termination of the pregnancy can be offered to the parents.

3.7.2. Delivery management

The presence of the hyperextended fetal head might cause dystocia. There is no indication for aggressive resuscitation of neonates [16].

3.8. Spinal dysraphism and the Arnold-Chiari malformation

3.8.1. Pregnancy management

Assessment for other abnormalities should be performed by the detailed sonography. Associated brain abnormalities include hydrocephaly, relative microcephaly, agenesis of the corpus callosum, and diastematomyelia. Non-CNS anomalies consist of congenital scoliosis or kyphosis and hip deformities [20]. There is a high prevalence of genetic abnormalities among fetuses with NTDs, especially in the presence of other congenital anomalies so microarray should be offered. The diagnostic sensitivity of prenatal sonography for detection of myelomeningocele in a high risk population is about 97–98% with 100% specificity [27]. Determining the site and extent of the spinal lesion is important because these features correlate with neurologic outcome; more severe neurologic dysfunction is associated with higher and larger lesions. Sonographic diagnosis of open spina bifida typically occurs during the second trimester of the pregnancy.

When the diagnosis of NTD is confirmed, the parents should be offered the opportunity to discuss the long-term prognosis for a child with multidisciplinary team (neonatologist,

medical geneticist, pediatric neurologist, pediatric neurosurgeon, pediatric urologist, pediatric orthopedic surgeon). Long-term prognosis is related to the location of the NTD—the lower the defect, the better the prognosis [16]. In fetuses with myelomeningoceles, higher and larger lesions on MRI were significantly associated with full-time wheelchair use. High lesion level was associated with dysphagia. The absence of a covering membrane was associated with scoliosis and high-risk bladder dysfunction [28]. If the diagnosis is at less than 22–24 weeks of gestation, the opportunity of pregnancy termination can be offered to the parents. During prenatal counseling, discussion with the parents includes the natural history of myelomeningocele and the prenatal management decisions, including termination of the pregnancy, pursuit of additional prenatal testing, choice of delivery setting, and, when applicable, the possibility of fetal surgery. The postnatal management choices are also discussed, including surgical closure of the defect and possible need for ventriculoperitoneal shunt placement. Longitudinal follow-up after prenatal diagnosis of myelomeningocele suggests that approximately 60–70% of pregnancies end in termination or fetal demise [29, 30].

- Fetal intervention. Fetal surgery for myelomeningocele can arrest leakage of spinal fluid from the back and might therefore prevent or reverse herniation of the hindbrain (Chiari II malformation) and hydrocephalus [31]. Prenatal surgery for myelomeningocele reduced the need for shunting and improved motor outcomes at 30 months but was associated with maternal and fetal risks [32]. These benefits occurred despite a higher risk of preterm delivery and pulmonary complications among infants undergoing fetal surgery and of obstetrical complications, including placental abruption, dehiscence of the hysterotomy site, and maternal transfusion at delivery [32, 33]. Because fetal surgery is associated with risks of fetal and maternal complications, the family should be informed about the option of prenatal surgery, including the uncertainty regarding whether the risks of the procedure are outweighed by the potential benefits, particularly since long-term outcomes are not clearly known. Women with pregnancies complicated by fetal myelomeningocele who meet established criteria for in utero repair should be counseled in a nondirective fashion regarding all management options, including the possibility of open maternal-fetal surgery. Maternal-fetal surgery for myelomeningocele repair should be offered only to carefully selected patients at facilities with an appropriate level of personnel and resources [34].

3.8.2. Delivery management

For infants with a prenatal diagnosis of myelomeningocele who do not undergo fetal intervention, delivery should occur at a center with a level III NICU, pediatric neurosurgery services, and other personnel experienced in the neonatal management of these infants. Latex-free gloves and equipment should be used during delivery and subsequent care of the infant because patients with myelomeningocele are at risk for developing life-threatening latex allergy.

Term delivery is preferable, but increasing ventriculomegaly with macrocephaly on prenatal ultrasound may necessitate preterm delivery. Fetuses presenting in the breech position are

typically delivered by cesarean section. The optimal route of delivery of a fetus presenting in the vertex position is controversial. Vaginal delivery is reasonable if the head is normal size, the meningocele is unlikely to cause dystocia, and there are no obstetrical indications for cesarean [35].

3.9. Fetal cerebral ventriculomegaly

3.9.1. Pregnancy management

Fetal cerebral ventriculomegaly is a relatively common finding on second trimester obstetrical ultrasound examination. Many cases are associated with other abnormal findings, but in some fetuses, ventriculomegaly is the only abnormality [36]. Most children with isolated, mild ventriculomegaly have a normal outcome. The risk of abnormal outcome increases with the severity of ventriculomegaly, progression of ventriculomegaly, and presence of other anomalies. After ventriculomegaly is identified, further management involves identifying whether additional abnormalities (CNS and non-CNS) are present, diagnostic evaluation for the most common causes of ventriculomegaly, and counseling patients about the prognosis and potential pregnancy interventions. If the etiology of ventriculomegaly has been determined (e.g., trisomy, CMV) or associated malformations are identified, the parents can be given more specific information. Before viability, pregnancy termination is an option and should be offered.

- Assessment for associated CNS and extra-CNS anomalies. Associated abnormalities have been reported in 10–76% of cases [36, 37]. Identification of these abnormalities helps in determining the cause of ventriculomegaly and the prognosis. Fetal MRI can be used to identify underlying CNS abnormalities not detected by sonography. Because CNS infection can result in ventriculomegaly, it is important to look for characteristic sonographic findings of fetal infection, such as intracerebral and periventricular calcifications, hepatic calcifications, hepatosplenomegaly, ascites, and polyhydramnios.
- Evaluation for infection. Tests for CMV infection, toxoplasmosis, Zika virus infection, and lymphocytic choriomeningitis virus infection should be recommended. Sporadic cases of ventriculomegaly associated with other viruses have also been reported (mumps enterovirus 71 (EV71), parainfluenza virus type 3, parvovirus B19) [36]. PCR for CMV and toxoplasmosis should also be obtained when amniocentesis is performed. If the patient declines amniocentesis or karyotyping has been done previously, maternal serology is used to identify an infectious etiology. However, serology is neither as sensitive nor as specific as PCR on amniotic fluid, thus amniotic fluid PCR is the preferred method of evaluation for infection [36].
- Genetic assessment. Fetuses with apparently isolated mild ventriculomegaly in 4.7% were found to have an abnormal karyotype [38]. The risk is higher with severe ventriculomegaly or associated abnormalities.
- Follow-up evaluation. Follow-up ultrasound examinations are obtained to look for regression or progression of ventriculomegaly and to re-evaluate for anomalies. Early isolated

mild ventriculomegaly may resolve by the third trimester; progression occurs in 16% of cases and has been associated with a worse outcome [36, 39]. Follow-up ultrasounds have detected fetal abnormalities not detected on the initial scan in 13% of cases [36]. Therefore, at least one additional detailed ultrasound examination should be performed between 28 and 34 weeks of gestation to look for CNS and non-CNS abnormalities and regression or progression of dilatation. Antepartum fetal testing has no proven benefit in pregnancies with isolated fetal ventriculomegaly in the absence of other findings, such as intrauterine growth restriction or oligohydramnios.

- Fetal intervention. Intrauterine treatment with ventriculoamniotic shunting was performed in the 1980s. The expert consensus at that time was that these results did not represent an improvement in outcome over expectant management, which led to a de facto moratorium on such procedures [40]. At present, however, such procedures are investigational [36].

3.9.2. Delivery management

Ventriculomegaly may or may not be accompanied by macrocephaly. Most infants with ventriculomegaly have a normal head circumference (HC), there is no increased risk of cephalopelvic disproportion, and cesarean delivery is not required except for standard obstetric complications. When the HC exceeds 40 cm, abdominal delivery should be considered.

Cephalocentesis, which almost always results in fetal death, is rarely used to decompress the head, allow vaginal delivery, and avoid maternal morbidity from cesarean delivery, in cases in which the neurological prognosis is so dismal (trisomy 13 or 18 or lethal co-existent anomalies) [41].

4. Fetal thoracic anomalies

4.1. Congenital diaphragmatic hernia

4.1.1. Pregnancy management

Over the past 20 years, prenatal detection of congenital diaphragmatic hernia (CDH) has improved worldwide, reaching up to 60% in Europe. Pulmonary hypoplasia and persistent pulmonary hypertension are the two main determinants of neonatal mortality and morbidity, so new tools have been focused on their evaluation. Fetal surgery for severe cases requires proper evaluation of the prognosis of fetuses with CDH [42]. After CDH is identified, further management involves referral to a tertiary center for confirmation of the diagnosis, assessment of severity and associated anatomic and genetic abnormalities, multidisciplinary counseling about options and prognosis, and planning further management. Management may be expectant with prenatal referral to a center with expertise in caring for these infants, termination of pregnancy, or fetal intervention [43]. The mean gestational age at diagnosis is about 24 weeks. Polyhydramnios may be present due to esophageal compression. Hydrops fetalis can occur from mediastinal shift and compression of the great vessels.

- Assessment for associated anomalies. Ultrafast fetal MRI to look for associated abnormalities and liver herniation and to estimate lung volumes and fetal echocardiography should be performed.

CDH can be an isolated anomaly, part of a syndrome, or nonsyndromic but associated with other abnormalities. Approximately 50–70% of cases of CDH are isolated. Pulmonary hypoplasia, intestinal malrotation, and cardiac dextroposition are due to the hemodynamic or mechanical consequences of CDH; thus, they are usually considered part of the CDH sequence and do not negate the designation 'isolated CDH.' The other 30–50% of cases are called 'complex', 'nonisolated', or 'syndromic' CDH (CDH+) because they are associated with additional abnormalities, including major structural malformations, chromosomal abnormalities, and/or single gene disorders. Malformations occur in all major organ systems, with no specific pattern [43]. An underlying syndrome is present in approximately 10% of CDH cases occurring with associated anomalies [43]. CDH is a prominent finding in the Fryns phenotype; facial dysmorphology, distal digital hypoplasia, and cardiac/renal/brain anomalies can also occur. CDH and diaphragmatic eventration are also an occasional component of many other syndromes, including Apert, Killian/Teschler-Nicola (Pallister-Killian), CHARGE, Coffin-Siris, Goltz, Perlman, Swyer, Brachmann-Cornelia De Lange, Goldenhar sequence, Beckwith Wiedemann, Simpson-Golabi-Behmel, Donnai-Barrow, Mathew-Wood, Jarcho-Levin, Fraser, Stickler, Pierre Robin, and others [43, 44].

Associated anomalies are most common with bilateral CDH and in stillborn infants with CDH, where the prevalence is as high as 95% [43]. Anomalies in stillborn infants with CDH primarily consist of neural tube defects (anencephaly, myelomeningocele, hydrocephalus, and encephaloceles) and cardiac defects (ventriculoseptal defects, vascular rings, and coarctation of the aorta) [45].

- Genetic assessment. Chromosomal anomalies are identified in 10–20% of prenatally identified cases; the most common diagnoses include trisomies 18, 13, and 21 [43, 46]. Other karyotype abnormalities, such as monosomy X, tetrasomy 12 p (isochromosome 12p), partial trisomy 5, partial trisomy 20, and polyploidies, have also been reported [43, 47].
- Evaluation of prognostic factors for survival. Prognosis is worse in the setting of an abnormal chromosomal microarray, severe associated anomalies, right-sided defect, liver herniation, and lower fetal lung volume [43, 48]. The lung area to head circumference ratio (LHR) is more predictive of morbidity than mortality. A large defect is more likely to result in pulmonary hypoplasia and death than a small defect. The size of the defect is not measurable prenatally, so the presence of liver herniation and fetal lung volume measurements serves as a proxy for defect size [43]. Several other clinical findings for survival have not been confirmed (early gestational age at diagnosis, severe mediastinal shift, polyhydramnios, a small lung-thorax transverse area ratio, left ventricle/right ventricle index, left heart hypoplasia, and the stomach in the chest) [43].

Liver herniation is the most reliable prenatal predictor of postnatal survival. A systematic review of studies that used ultrasound or MRI to evaluate outcome of fetuses with liver herniation included 710 fetuses and reported significantly higher survival rate in fetuses without

herniation (74% versus 45% with herniation) [49]. Ultrafast fetal MRI using rapid HASTE technique is the most powerful tool to accurately demonstrate liver herniation [50]. Ultrasound can be useful; in particular, color flow Doppler can visualize bowing of the ductus venosus to the left of the midline or coursing of the portal branches or hepatic veins to the lateral segment of the left lobe above the diaphragm; however, ultrasound has not always accurately demonstrated liver herniation in the fetus with left-sided CDH [43, 50].

Absolute or relative fetal lung volume appears to be useful for predicting survival, but the optimum equation has not been determined [43, 51]. Several small studies have suggested that postnatal survival is poor when fetal lung volume measured by MRI is less than about 30% of expected lung volume for gestational age and especially when <15% [43]. Lung volume can also be assessed using 3D sonography, but MRI may be more reliable.

Right- versus left-sided lesion. Right-sided CDH have a poorer outcome than that reported for fetuses with left-sided CDH with similar lung size before birth [52].

Lung area to head circumference ratio (LHR) is an estimate of contralateral lung size and mediastinal shift at the level of the atria on transverse scan of the fetal thorax. Although there is a significant correlation between LHR and survival, the lower limit of LHR compatible with survival is dropping, so the test is less predictive than in the past [43, 53]. LHR is now more indicative of morbidity than mortality [43]. In left CDH, the LHR is calculated using a two-dimensional perpendicular linear measurement of right lung area (in square millimeters) divided by the head circumference (in millimeters) to minimize lung size differences owing to gestational age [43]. Measurement of fetal lung volume is much more useful than LHR in fetuses without liver herniation [54]. Because lung growth is four times greater than head growth during pregnancy [55], some experts suggest that the LHR should be expressed as a function of gestational age (observed [O]/expected [E] LHR). The O/E LHR can be calculated using a formula specifically developed for this measuring technique and has been validated in fetuses with unilateral isolated CDH in terms of both mortality and morbidity [53]. An online calculator is available (www.totaltrial.eu). O/E LHR is considered extreme if <15%, severe at 15–25%, moderate at 26–35%, and mild if 36–45% [44].

- Fetal interventions. Fetal endoscopic tracheal occlusion (FETO) is an investigational procedure for treatment of isolated severe congenital diaphragmatic hernia to prevent or reverse pulmonary hypoplasia and restore adequate lung growth for neonatal survival. The rationale for this approach is that the dynamics of fetal lung fluid can dramatically affect lung growth [43]. Under normal circumstances, the lungs are net producers of amniotic fluid with lung liquid volume and intratracheal pressure maintained at constant values by fetal laryngeal mechanisms [43]. Prenatal tracheal occlusion (TO) obstructs the normal egress of lung fluid during pulmonary development, increasing transpulmonic pressure and resulting in large fluid-filled lungs. Lack of lung expansion 2 and 7 days after TO is a poor prognostic sign and may indicate that the occlusion is inadequate [56]. Techniques to achieve minimally invasive fetoscopic reversible fetal TO have been developed to decrease the risks of preterm labor and restore surfactant deficiency [43]. A percutaneous

procedure under local anesthesia, with fetal pain relief and immobilization, is possible [57]. Fetal TO in severe CDH is associated with a high incidence of PPROM and preterm delivery but a substantial improvement in survival. Smaller and fewer trocars were utilized in another study, resulting in a lower rate of preterm rupture of membranes and preterm delivery [58].

Important factors in offering prenatal therapy continue to be, first and foremost, determining which fetuses have a poor prognosis. The optimal timing, duration, and release of occlusion in humans are not known. The Eurofetus group has had early success with fetal TO [59]. The insertion of the balloon at 26–28 weeks for severe cases and 30–32 weeks for moderate cases is recommended. Ideally, the occlusion is reversed before delivery at 34 weeks, usually by fetoscopy or ultrasound-guided puncture.

The FETO Consortium subsequently reported the outcome of 210 consecutive procedures [57]. Compared with the outcome of expectantly managed cases enrolled in their registry, FETO increased survival in severe cases with left CDH from 24–49% and right CDH from 0–35% ($p < 0.001$) [57]. However, at least 10 deaths attributed to difficulty with balloon removal before or at the time of emergent delivery have been reported [60]. The Eurofetus consortium also noted that preterm delivery, usually due to premature rupture of membranes, is a common complication and occurred in 17% of cases within 3 weeks of the procedure [43]. FETO has resulted in few clinical side effects on the developing trachea, except in very early occlusions and complications arising at the time of removal [43]. Neonates have tracheomegaly, which does not seem to have a clinical impact other than a barking cough on effort. The Tracheal Occlusion to Accelerate Lung Growth (TOTAL) trial is ongoing in Europe and feasibility studies for FETO are ongoing at several North American fetal centers [43].

- Follow-up assessment. There are no data from well-designed studies on which to base recommendations for antepartum obstetrical management. The intrauterine risk of fetal demise is 2–8%, but higher when other anomalies are present [43]. Twice-weekly nonstress testing or biophysical profile testing at 33–34 weeks should be offered [43]. Ultrasound examinations at 28, 30, 32, and 34–35 weeks of gestation to assess fetal growth and amniotic fluid volume. Polyhydramnios may develop at 28–32 weeks if fetal swallowing is impaired, and oligohydramnios may develop if the fetus is compromised later in gestation. Signs of secondary complications, such as particulate meconium in fluid, dilated stomach in chest, effusions, or ascites, may lead us to deliver the fetus preterm. Fetal growth restriction or oligohydramnios may also lead us to deliver the fetus early. Antenatal glucocorticoids are given, if appropriate, to decrease morbidity from preterm delivery as for standard indication [43].

4.1.2. Delivery management

The optimal mode and gestational age for delivery of an infant diagnosed prenatally with CDH is uncertain [43]. A planned induction of labor between 38 and 39 weeks of gestation is suggested so that the fetus is monitored from the earliest stage of labor and so pediatric

surgery and neonatology services are prepared to care for the infant. The fetal lung maturity prior to delivery should not be assessed [43]. Up to 50% of cases require extracorporeal membrane oxygenation (ECMO); therefore, the delivery at a tertiary center with ECMO capability is recommended [43]. Cesarean delivery is performed for standard obstetrical indications [43].

4.2. Congenital pulmonary airway malformation

4.2.1. Pregnancy management

Prenatal diagnosis of congenital pulmonary airway malformation (CPAM) has increased with widespread use of prenatal ultrasonography and magnetic resonance (MR) imaging. When CPAM is diagnosed, the quantitative evaluation helps predict the prenatal course of the disease and should include the following [61]:

1. Congenital pulmonary airway malformation volume ratio (CVR)—Obtained by calculating the volume of the lung mass using the formula for the volume of an oval and normalizing it by gestational age. To normalize by gestational age, the lung mass volume should be divided by the head circumference. CVR = height x anteroposterior diameter x transverse diameter x 0.52 (constant)/head circumference.
2. Mass-to-thorax ratio (MTR)—The ratio between the transverse diameter of the mass and the transverse diameter of the thorax. It is measured on an axial image of the chest, where the four-chamber view of the heart is present.
3. Observed to expected lung-to-head ratio (o/e LHR)—Initially described as a predictor of outcome in congenital diaphragmatic hernia.

The prenatal course depends on the gestational age, size of the mass, amount of mediastinal shift, fetal hemodynamics, and associated anomalies, more than the type of lesion [61]. About 50% of masses persist to delivery [62]. Fifteen percent of these masses decrease in size during the late second and the third trimesters; the majority have a relative decrease in size due to normal fetal thoracic growth, but a few increase in size [61]. It is difficult to predict at the time of the initial ultrasound whether lesions will regress, stabilize, or continue to grow and lead to significant problems, including hydrops, need for surgical intervention or postnatal respiratory assistance, or death. The use of CVR, MTR, and, to a lesser degree, o/e LHR helps better identify patients at risk [61, 63]. A CVR >1.6 is predictive of risk for hydrops, respiratory distress at birth, and probable need for early surgery [61], whereas a CVR <0.91 at presentation predicts a favorable outcome so follow-up examinations can be less frequent [61, 63]. A MTR <0.51 suggests the fetus is at low risk for developing complications [61, 63]. In the absence of hydrops, the prognosis is good with reported live birth rates ≥95% [61].

- Assessment for associated anomalies. A comprehensive fetal survey, including fetal echocardiography, should be performed as 10–20% of fetuses with CPAM have associated congenital abnormalities, such as esophageal atresia with tracheoesophageal fistula, bilateral

renal agenesis or dysgenesis, intestinal atresia, other pulmonary malformations, and diaphragmatic, cardiac, central nervous system, and bony anomalies [61]. Fetal echocardiography is recommended in all patients at time of diagnosis to rule out congenital cardiac anomalies.

- Follow-up assessment. All patients should have serial prenatal follow-up examinations every 1 to 4 weeks to assess change in size of the lung mass, change in CVR, and development of polyhydramnios and hydrops [61]. The frequency depends on the gestational age and CVR. Closer follow-up should be performed in those patients at high risk of developing hydrops (CVR ≥1.6, age < 26 weeks), whereas the interval between examinations can be lengthened if the CPAM is very small, CVR is <0.91 [63]. The presence of hydrops is a sign for impending fetal demise and thus it is an indication for fetal intervention [61]. The recommendation of proceeding with fetal intervention is based on results from small case series showing good survival (>90%) if hydrops resolves [61].

For fetuses greater than 32–34 weeks of age, early delivery with immediate postnatal resection is a reasonable option [61]. Ex utero intrapartum therapy (EXIT) has been used to stabilize fetuses with large lesions expected to have difficulty breathing at delivery [64].

For gestations between 20 and 32 weeks, several interventions with the goal of improving fetal hemodynamics and preventing lung hypoplasia have been described and appear to improve survival [61]. Drainage procedures are used for CPAMS with dominant cysts, while solid masses are treated by resection or ablation. Karyotype analysis is recommended prior to initiating fetal therapy [61]. All of the following interventions should be considered investigational.

Antenatal corticosteroids are the only medical treatment of CPAM. They are used primarily for treatment of microcystic CPAM, since these masses cannot be managed by minimally invasive procedures, but have been used for macrocystic disease, as well [61]. In uncontrolled studies, maternal steroid administration appeared to reverse hydrops and improve outcome [61]. Multiple courses of antenatal betamethasone for high-risk fetal CPAMs often result in favorable short-term outcomes without the need for open fetal resection. The fetuses who did not respond to a first course of steroids stabilized or improved (e.g., reduction in lesion size, resolving hydrops) after receiving two to four courses of therapy [65]. The median interval between the first and second courses of steroids was about 2 weeks (range 1–6 weeks) [61].

- Fetal intervention. Successful fetal surgery depends on surgical experience, optimal maternal anesthesia, uterine relaxation, hysterotomy, fetal exposure, and intraoperative fetal monitoring.

4.2.2. Drainage procedures

- Thoracentesis—For fetuses with large pleural effusions, thoracentesis to prevent pulmonary hypoplasia is possible, but rapid reaccumulation of fluid limits its usefulness [61]. The fluid should be sent for cell count to exclude an infectious etiology [61].

- Cyst aspiration should decompress a large macrocyst and reverse the mediastinal shift. Although fluid reaccumulation is common and limits its usefulness [61].
- Thoracoamniotic shunt provides a therapeutic option for select fetuses with large macrocystic lung lesions or pleural effusion at risk for hydrops and/or pulmonary hypoplasia. Survival following shunting depends on gestational age at birth, reduction in mass size, and hydrops resolution [66]. Complications include displacement or malfunction of the catheter, thrombus occlusion of the catheter, fatal fetal hemorrhage, procedure-related abruptio placentae, premature rupture of membranes, and preterm labor [61].

4.2.3. Surgical resection

For solid or mixed solid/cystic CPAM with a large solid component, in-utero open resection has been successfully performed. Following resection, hydrops resolves over 1 to 2 weeks with reversal of the mediastinal shift over 3 weeks [61]. Maternal-fetal surgery requiring hysterotomy appears to be associated with an increased risk of premature labor, premature rupture of membranes, and subsequent pregnancy (uterine dehiscence or rupture) [61]. Percutaneous laser ablation of solid CPAM has been reported in only a few case reports and further research is warranted [61].

4.2.4. Sclerotherapy

A single study described fetal sclerotherapy in three patients under 26 weeks with CPAM and hydrops, severe mediastinal shift, and polyhydramnios [67]. Sclerotherapy was performed with percutaneous injection of Ethamolin (ethanolamine oleate) or Polidocanol (aethoxysklerol) into the mass under ultrasound guidance using a 22-gauge needle [61]. Resolution of hydrops and of the mass effect was observed in all cases. The patients were delivered at term without complications. Further studies are indicated to assess the risks and benefits of this innovative technique [67].

4.2.5. Delivery management

If the lung mass has resolved or is small with no mediastinal shift or hydrops, CPAM itself is not an indication for early delivery or cesarean delivery [61]. Neonatal respiratory problems would be unlikely, but the delivery should be recommended in a tertiary care center. For fetuses with large masses that cause mediastinal shift and/or hydrops, delivery should be planned for a tertiary care center with an intensive care nursery capable of resuscitation of a neonate with respiratory difficulties, including capability of extracorporeal membrane oxygenation (ECMO), and with pediatric surgeons experienced in care of these infants [61]. If hydrops develops after 32 weeks of gestation, early delivery is recommended, possibly with the use of EXIT [61]. In EXIT, the fetus is partially delivered and intubated without clamping the umbilical cord. Uteroplacental blood flow and gas exchange are maintained by using inhalational agents to provide uterine relaxation and amnioinfusion to maintain uterine volume. This provides time for resection of the lung mass prior to complete delivery of the infant

in rare instances or, more often, cannulation for extracorporeal membrane circulation, thus creating a controlled situation for delayed removal of the CPAM. Overall fetal survival of 90% has been reported [61].

4.3. Bronchopulmonary sequestration

4.3.1. Pregnancy management

Bronchopulmonary sequestration (BPS) is usually a small lesion and decreases in size in late gestation in about 75% of cases [68].

- Assessment of additional anomalies and genetic evaluation. When a lung mass is first identified, thorough assessment for additional anomalies is necessary. Intralobar sequestration is not associated with an increased risk of additional anomalies [68]. Extralobar BPS is associated with anomalies in up to two-thirds of cases [68]. These anomalies include chest wall and vertebral anomalies hindgut duplications, diaphragmatic hernia, congenital heart disease, and renal and intracranial abnormalities [68]. The incidence of chromosomal abnormalities is not increased above baseline in fetuses with BPS alone [68]. Karyotype analysis is recommended prior to initiating fetal therapy.

Parents should be counseled about the possible course of the BPS during pregnancy. At initial presentation in the early midtrimester, it is difficult to accurately predict what the outcome will be for an individual fetus, but some predictions are possible, e.g., a large BPS with hydrops in the second trimester is likely to do poorly [68].

- Follow-up assessment. All patients should have serial prenatal follow-up examinations to assess change in size of the lung mass and development of hydrops [68]. The frequency depends on the size of the lesion. The larger lesions should be followed more closely. The presence of hydrops is a sign of impending fetal demise and an indication for fetal intervention [68]. This recommendation is based on results from small case series showing higher survival rates if hydrops resolves [68]. Because hydrops is uncommon, fetal intervention is rarely required and is warranted only in cases where the fetus is severely compromised and remote from term. For fetuses greater than 32–34 weeks of age, early delivery with immediate postnatal resection is a reasonable option [68].

For gestations between 20 and 32 weeks, several interventions with the goal of improving fetal hemodynamics and preventing lung hypoplasia have been described and appear to improve survival [69]. These interventions should only be undertaken at centers experienced in fetal surgery. Prenatal intervention requires extensive counseling to the parents on the potential risks versus benefits of surgery.

- Fetal intervention. If the BPS is solid with a large pleural effusion, thoracentesis to prevent pulmonary hypoplasia is possible, but rapid reaccumulation of fluid limits its usefulness. It can be used as a temporizing maneuver to provide prognostic information about the possible result from placement of a thoracoamniotic shunt [68]. The fluid should be sent for cell

count to exclude an infectious etiology [68]. Complications of shunts include displacement or malfunction of the catheter, thrombus occlusion of the catheter, fatal fetal hemorrhage, procedure-related abruptio placentae, premature rupture of membranes, and preterm labor [68]. There is also a risk of trauma to the fetal chest wall, especially if the procedure is performed before 20 weeks [68].

- In-utero open resection, percutaneous laser ablation of the feeding vessel has been successfully performed in several small studies [68]. Percutaneous ultrasound-guided fetal sclerotherapy has also been described [68]. Sometimes two procedures were necessary.

4.3.2. Delivery management

If the lung mass has resolved or is small with no mediastinal shift or hydrops, BPS itself is not an indication for early delivery or cesarean delivery [68]. Neonatal respiratory problems would be unlikely. For fetuses with large masses that cause mediastinal shift and/or hydrops, delivery should be planned for a tertiary care center with an intensive care nursery capable of resuscitation of a neonate with respiratory difficulties, including capability of extracorporeal membrane oxygenation (ECMO), and with pediatric surgeons experienced in care of these infants [68]. If hydrops develops after 32 weeks of gestation, early delivery is recommended, possibly with the use of EXIT. In EXIT, the fetus is partially delivered and intubated without clamping the umbilical cord. Uteroplacental blood flow and gas exchange are maintained by using inhalational agents to provide uterine relaxation and amnioinfusion to maintain uterine volume. This provides time for initiating extracorporeal membrane circulation to stabilize the infant, thus creating a controlled situation before resection of BPS in another operating room [68].

4.4. Congenital lobar emphysema

Congenital lobar emphysema (CLE) is a rare congenital malformation and sometimes is detected by prenatal ultrasonography. Lung lesions have increased echogenicity and/or a cystic appearance and usually can be differentiated from other congenital lung lesions [70]. A chest mass may even disappear on prenatal ultrasound and become apparent again on postnatal evaluation [70]. Predictors of severe respiratory distress or mortality include polyhydramnios, fetal hydrops, and lung to thorax transverse area ratio (L/T value) of less than 0.25 [70]. Approximately 25% of cases present at birth, 50% by 1 month of age, and nearly all by 6 months of age. Infants typically have tachypnea and increased work of breathing and often have cyanosis. Recurrent pneumonia or poor feeding with failure to thrive are less frequent presentations that may occur in milder forms [70].

4.5. Pulmonary agenesis

Any fetus with suspected bilateral pulmonary agenesis should have a detailed sonographic assessment to confirm the diagnosis. If the diagnosis is made till periviable pregnancy, the pregnancy termination is an option. If the diagnosis is made at a later gestational age, the delivery should be planned without monitoring for fetal distress [16].

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5. Congenital abdominal wall defects

5.1. Gastroschisis

5.1.1. Pregnancy management

There is wide variability in the antenatal management of gastroschisis due to a lack of high-quality evidence to guide clinical practice [71].

- Assessment of associated anomalies. Associated gastrointestinal anomalies and problems (e.g., malrotation, atresia, stenosis, perforation, necrosis, volvulus) occur in up to 25% of cases [72] and may be related to vascular disruption caused by herniated bowel. Disruption of the superior mesenteric artery, for example, may lead to volvulus or to "apple peel" jejunal-ileal lesions. Meckel's diverticulum and gallbladder atresia also occur, but are less common. Bladder herniation has been reported in 6% of cases, with bowel or urinary tract dilation [73]. Most cases have no extraintestinal abnormalities, approximately 10% of gastroschisis cases were associated with major unrelated defects, approximately 2% of cases were part of a recognized syndrome, and cardiac anomalies were detected in 2–3% of cases [74]. Oligohydramnios is the most common amniotic fluid abnormality, but polyhydramnios may occur, particularly in fetuses with reduced bowel motility or obstruction [73].
- Genetic assessment. The prevalence of chromosomal abnormalities in fetuses with isolated gastroschisis is not increased above the baseline population risk, so invasive fetal genetic testing is not routinely offered. The fetal genetic evaluation is suggested if nongastrointestinal structural abnormalities are identified on ultrasound examination. Chromosome abnormalities were detected in 1.2% of the total cases, which included isolated and nonisolated, and the most frequent abnormalities were trisomy 18, trisomy 13, sex chromosome anomalies, and trisomy 21 [73].
- Follow-up assessment. The most common pregnancy complications associated with gastroschisis include development of growth restriction (30–60% of cases), intrauterine fetal demise (3–6%), spontaneous preterm birth (30%), and bowel dilation and wall thickening (common, frequency depends on diagnostic criteria) [73]. The mechanisms causing these adverse outcomes in gastroschisis are unclear. Therefore, pregnancy monitoring is empiric and typically includes serial ultrasound examinations for assessment of fetal growth and fetal bowel abnormality and standard tests for antepartum fetal surveillance [73].
- Assessment of fetal growth and amniotic fluid volume—serial ultrasound examinations every 3 weeks for assessment of fetal growth and amniotic fluid volume (AFV). If growth arrest or oligohydramnios is diagnosed, umbilical artery Doppler flow is evaluated [73]. A systematic error of birth weight underestimation when using the Hadlock formulas in fetuses affected with gastroschisis was found [75]. Siemer and colleagues developed a specific formula for estimating fetal weight in fetuses with abdominal wall defects using

the biparietal diameter, occipitofrontal diameter, and femur length measurements [76]. Oligohydramnios may be related to fetal growth restriction and is a risk factor for cord compression and its sequelae. Polyhydramnios is less common, but an important finding because it is often caused by dysfunction of the gastrointestinal tract due to bowel atresia [73].

- Assessment of fetal bowel. Gastric dilatation, bowel dilatation, and bowel wall thickening have been considered poor prognostic signs by several investigators [73]. If these significant changes are observed prior to 34 weeks, a course of glucocorticoids is suggested for fetal maturation [73].
- Antepartum fetal surveillance. Fetal growth restriction and amniotic fluid abnormalities are commonly accepted indications for increased antepartum fetal surveillance. The precise timing and frequency of testing is arbitrary [73].

5.1.2. Delivery management

Gastroschisis increases the risk of preterm delivery; delivery should occur in a facility with appropriate resources for caring for these neonates. Gastroschisis alone is not an indication for preterm intervention or cesarean delivery [73].

The decision on timing of delivery is based on a combination of factors, including gestational age, ultrasound findings (fetal growth profile, AFV, appearance of fetal bowel), and fetal testing results (NST, BPP, umbilical cord Doppler if fetal growth restriction is present). In the absence of standard obstetric indications for abdominal delivery, a trial of labor rather than scheduled cesarean birth for most patients is suggested. Cesarean delivery is reasonable if the liver is significantly herniated because of the theoretic risk of dystocia and trauma. Delivery of pregnancies complicated by fetal gastroschisis at 37 or 38 weeks of gestation is suggested to minimize neonatal morbidity and mortality and avoid the possibility of term (39–40 weeks) stillbirth; however, there is no consensus on the optimum timing of delivery of these pregnancies [73].

5.2. Omphalocele

5.2.1. Pregnancy management

Omphalocele and gastroschisis are the most common fetal abdominal wall defects. By the end of the first trimester (11–14 weeks), almost all omphaloceles can be detected by prenatal ultrasound examination [77].

- Genetic assessment. Multiple chromosomal abnormalities have been reported among fetuses with omphalocele. As many as 60% of omphaloceles not containing liver are associated with fetal aneuploidy, particularly trisomy 18 or 13 [77, 78]. Fetal genetic studies should be offered if omphalocele or related body wall defects are identified prenatally, because of the high risk of aneuploidy. It is reasonable to offer amniocentesis for genetic testing for Beckwith-Wiedemann syndrome, but this testing is complicated and should be discussed

with a geneticist [77]. There is a 10–20% risk of Beckwith-Wiedemann syndrome in fetuses with apparently isolated omphalocele on ultrasound.

- Assessment of associated anomalies. Associated abnormalities that occur with increased frequency in these fetuses include additional gastrointestinal abnormalities, cardiac defects (up to 50% of cases), genitourinary anomalies, orofacial clefts, neural tube defects, defects of the diaphragm, polyhydramnios, and growth restriction. Associated syndromes are best categorized by upper, middle, and lower midline omphalocele defects. Omphalocele has been associated with several syndromes, including Pentalogy of Cantrell (upper midline defect), amniotic band sequence, schisis association (at least two of the following defects: neural tube defect, oral cleft, omphalocele, diaphragmatic hernia); lower midline defects are associated with OEIS syndrome (omphalocele, exstrophy of the bladder, imperforate anus, spinal defects), Shprintzen syndrome, Carpenter syndrome, Goltz syndrome, Marshall-Smith syndrome, Meckel-Gruber syndrome, otopalatodigital type II syndrome, CHARGE (coloboma, heart defect, atresia choanae, retarded growth and development, genital abnormality, and ear abnormality) syndrome, and Beckwith-Wiedemann syndrome (hallmark features: macroglossia, gigantism, omphalocele) [77].
- Follow-up obstetrical care. The serial ultrasound examination every 3–4 weeks to evaluate fetal growth is recommended. When growth is appropriate and amniotic fluid volume is normal, weekly nonstress testing or biophysical profile monitoring at 32 weeks of gestation to assess fetal well-being are recommended, as these pregnancies appear to be at increased risk of late fetal death [79]. Fetal growth restriction and preterm delivery are not uncommon in pregnancies complicated by an omphalocele, particularly with associated abnormalities [77]. Nonreassuring fetal testing and/or cessation of fetal growth at or near term is an indication for early delivery. A systematic error of birth weight underestimation in fetuses affected with omphalocele was found, the same situation as discussed in fetuses with gastroschisis. Intrauterine growth restriction in fetuses with abdominal wall defects is predictive of an increased risk of adverse neonatal outcome [77].

5.2.2. Delivery management

Delivery should be planning at a tertiary care center. In the absence of standard indications for early delivery, it is reasonable to await spontaneous labor or achieve 39 weeks of gestation. Preterm birth offers no advantage to affected neonates and is associated with increased morbidity and mortality. There is no evidence that cesarean delivery improves outcome in uncomplicated omphalocele; surgery should be reserved for usual obstetric indications [77]. However, some pediatric surgeons have recommended cesarean delivery for fetuses with giant omphaloceles (defined as an omphalocele containing >75% of the liver and defect greater than 5 cm) in an attempt to avoid dystocia, rupture, infection, and hemorrhage [80]. Visceral trauma has also been reported after cesarean delivery [77].

5.3. Bladder exstrophy

Often the diagnosis of bladder exstrophy is made by prenatal ultrasound and, in some cases, may be confirmed by MRI. In the event that a prenatal diagnosis is not made, the diagnosis

should be clinically apparent and recognizable at birth in the delivery room [81]. If a prenatal diagnosis is not made, the diagnosis of bladder exstrophy should be clinically recognizable at delivery. A careful physical examination will differentiate bladder exstrophy from other congenital anomalies that involve abdominal wall defects, such as omphalocele, gastroschisis, and cloacal exstrophy.

Following the prenatal diagnosis of bladder exstrophy, prenatal care includes the following [16, 81]:

1. Education and counseling of the parents, touring the neonatal intensive care unit, meeting the pediatric urologic care team, and allowing the expectant parent(s) the opportunity to interact with other families with a child with bladder exstrophy.
2. Preparation for delivery. In many tertiary centers, one option for planning initial surgical management is an induced vaginal delivery that is scheduled in late gestation with coordination with an on-site pediatric urology service. This approach facilitates bladder closure within 72 hours of life.

The cesarean delivery should be reserved for obstetrical complications.

5.4. Body stalk anomaly and cloacal exstrophy

- Body stalk anomaly (also called limb-body wall complex) is a massively disfiguring and generally lethal malformation of the thorax and/or abdomen, often associated with limb defects. The intrathoracic and abdominal organs lie outside the abdominal cavity and are contained within a sac composed of amnioperitoneal membrane attached directly to the placenta. The umbilical cord may be totally absent or extremely shortened. Severe kyphoscoliosis is often present. Termination of pregnancy is usually offered since the abnormality is generally considered lethal [82]. However, repair has been performed in rare cases [82]. If the pregnancy is continued, vaginal delivery is recommended given the highly lethal nature of this disease, assuming there are no maternal contraindications to vaginal delivery. In this setting, the patient should be extensively counseled on the likelihood of neonatal demise, as well as the severe morbidity associated with a successful repair [82, 83].
- Cloacal exstrophy. The accuracy of sonographic diagnosis appears to be less than 25% due to the rarity of the disorder and the wide spectrum of anatomic variants, which depend upon the degree of cloacal septation completed. Fetal genetic studies during the initial evaluation can be useful, although cloacal exstrophy has not been reported to be associated with specific aneuploidies. The chromosomal findings, which will include gender, may influence the decision to terminate the pregnancy, perform a cesarean delivery for fetal indications, or initiate a series of corrective operations in the newborn period [41]. Although there are no studies of the optimum route of delivery for this rare disorder, cesarean delivery is generally reserved for standard obstetric indications. The umbilical cord should be clamped or ligated carefully to avoid injury to proximate structures. At delivery,

saline-soaked sterile dressings should be applied over the exposed bladder and bowel mucosa and covered with plastic wrap to minimize insensible fluid and heat loss. Survival rates of 80–100% have been reported, but quality of life (e.g., bowel, urinary, and sexual function) is a concern [82].

6. Congenital anomalies of the kidney and urinary tract

6.1. Pregnancy management

Congenital anomalies of the kidney and urinary tract (CAKUT) constitute approximately 20–30% of all anomalies identified in the prenatal period [84]. Defects can be bilateral or unilateral, and different defects often coexist in an individual child. In general, the optimal timing recommended for a screening antenatal ultrasound is between 16 and 20 weeks of gestation because of the following factors at this gestational age. Counseling of families with fetuses with CAKUT should be universally available. If the fetal prognosis is poor, as determined by severe bilateral disease, bilateral RA, oligohydramnios, or unfavorable amniotic fluid analysis, legal termination, if possible, can be offered. In all other cases, continued counseling throughout the pregnancy including discussion of postnatal management is required. In particular, discussion with parents regarding their wishes on the level of support given to offspring with severe oligohydramnios, who are at risk for lung hypoplasia that may be incompatible with life, is helpful in establishing guidelines for initial postnatal care [84].

- Assessment of amniotic fluid volume and analysis of biochemical markers are used to evaluate fetal renal function. By 20 weeks of gestation, fetal urine accounts for more than 90% of the amniotic fluid volume. Thus, a decrease in amniotic fluid volume (oligohydramnios) at or beyond the 20th week of gestation is an excellent predictor of abnormal fetal renal function and CAKUT [84]. Severe oligohydramnios due to CAKUT either involves both kidneys or occurs in a solitary kidney in the fetus. Bilateral renal agenesis (RA) or severe dysgenesis, bilateral ureteric obstruction, or obstruction of the bladder outlet or urethra can result in severe oligohydramnios as early as 18 weeks of gestation. Because an adequate amniotic fluid volume is critical for lung development, severe oligohydramnios due to abnormal fetal renal function in the second trimester can result in lung hypoplasia, a potentially fatal disorder.
- Assessment for additional anomalies. Potter's syndrome consists of a typical facial appearance characterized by pseudoepicanthus, recessed chin, posteriorly rotated, flattened ears and flattened nose, decreased fetal movement, musculoskeletal features including clubfoot and clubhand, hip dislocation and joint contractures, and pulmonary hypoplasia.
- Analysis of amniotic fluid. Although oligohydramnios is the most reliable predictor of abnormal fetal renal function, its absence does not assure normal fetal renal function.

Because amniotic fluid is predominantly composed of fetal urine, measurement of biochemical markers contained in amniotic fluid (fetal urine) can be used to assess fetal renal function [84].

- Follow-up assessment. Repeat antenatal ultrasound examinations are performed to help guide management decisions. The timing is dependent on findings on the initial examination. Fetuses with second trimester hydronephrosis (RPD >4 mm) should undergo repeat testing in the third trimester to assess progression and select those who will benefit most from postnatal testing. A repeat examination 2–3 weeks later in fetuses with bilateral involvement (or an affected solitary kidney) and at 32–34 weeks of gestation in those with unilateral involvement is recommended [85].
- In utero intervention. Although there have been case series of antenatal surgery in fetuses with severe hydronephrosis and oligohydramnios, this intervention has not been shown to improve renal outcome. These procedures may increase the amount of amniotic fluid, thus potentially improving lung development and survival rate. In these rare cases, the procedure should only be performed in select centers with expertise and in infants with severe bilateral hydronephrosis, absent of severe renal parenchymal or cystic disease, favorable urinary electrolyte levels and osmolality, and normal karyotype [84]. Data are limited on whether percutaneous vesicoamniotic shunting compared with conservative observation in fetuses with lower urinary tract obstruction improves survival and renal outcome. The percutaneous vesicoamniotic shunting should not be routinely performed in fetuses with lower urinary tract obstruction [85].

6.2. Delivery management

Cesarean delivery should be reserved for obstetrical indications. The time of delivery depends on the fetal well-being and amniotic fluid volume.

7. Esophageal, gastrointestinal, and anorectal atresia

7.1. Pregnancy management

Prenatal sonographic diagnosis of gastrointestinal atresia is challenging since obstruction may not become evident sonographically until the late second trimester, after the typical time of a fetal anatomic survey (18–20 weeks of gestation). It can also be difficult to differentiate dilated small bowel loops from colon or megaureters sonographically [86]. It is unclear whether prenatal diagnosis of esophageal, gastrointestinal, or anorectal atresia improves the prognosis. However, early prenatal diagnosis provides an opportunity for parental counseling and preparation, screening for associated anomalies, and the option for pregnancy termination or delivery at a setting with appropriate personnel and facilities for newborn care [86].

- Indications for magnetic resonance imaging. MRI may be used to confirm or clarify suspected gastrointestinal abnormalities on ultrasound examination if this information is important for managing the pregnancy. Fetal bowel is well visualized by MRI and easily differentiated from adjacent liver, spleen, kidneys, bladder, and gallbladder. Meconium is also well visualized [87]. The normal esophagus, stomach, and duodenum should always be filled with T2 hyperintense fluid (amniotic fluid).
- Assessment of additional anomalies and follow-up assessment. Many of these pregnancies are complicated by polyhydramnios. After diagnosis, the performance of periodic ultrasound examinations to look for any change in the appearance of the atresia or associated anomalies and to assess interval fetal growth and amniotic fluid volume is recommended. Nonstress tests or biophysical profiles are indicated in pregnancies in which the risk of antepartum fetal demise is increased, such as a fetal anomaly associated with growth restriction [86].

7.2. Delivery management

Atresia alone is not an indication for cesarean delivery in the absence of a standard obstetric indication. However, if the abdominal circumference is much larger than the head circumference, cesarean delivery should be considered due to the risk of fetal abdominal dystocia. Delivery should be planned at a center that has an appropriate level of neonatal support.

Author details

Diana Ramasauskaite

Address all correspondence to: diana.ramasauskaite@mf.vu.lt

Vilnius University, Faculty of Medicine, Institute of Clinical medicine, Clinic of Obstetrics and Gynaecology, Vilnius, Lithuania

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Chapter 23

The Neonate with Minor Dysmorphisms

Simona Vlădăreanu, Mihaela Boț, Costin Berceanu, Claudia Mehedințu and Simona Popescu

Additional information is available at the end of the chapter

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Abstract

Congenital anomalies are present in at least 10% of all neonatal intensive care unit admissions, of whom many have an underlying genetic condition. About 50–60% of human congenital anomalies are of unknown etiology, and approximately one- third are caused by genetic factors. A smaller percentage of birth defects are the result of chromosomal aberrations and gene mutations. Around 1 in 40 or 2.5% of all newborns have a malformation at birth. This may be an isolated malformation or may occur together with other malformations and/or dysmorphic features as part of a malformation syndrome. Around 4000 malformation syndromes have now been delineated. Many are associated with medical problems and making a specific syndrome diagnosis can influence immediate medical management. However, the infant with dysmorphism often does not have a major malformation, and may simply have an appearance that is unusual compared with the general population and of unaffected close relatives. The chapter intends to provide semnificative data concerning the approach and management of a dysmorphic neonate, mainly when there are minor anomalies and will offer all those relevant data and try to establish a protocol guide for the approach of the dimorphic neonate.

Keywords: congenital, anomalies, neonate, dysmorphic, syndrome

1. Introduction

Dysmorphology is the branch of clinical genetics that attempts to interpret the human growth patterns and structural defects.

Often, the neonatologist has the opportunity to be the first to identify a congenital anomaly in the neonates. Thus, the presence of a neonatal dysmorphic syndrome (be it major or minor) must be shared with the parents, something that may certainly cause feelings of anxiety.

Addressing the diagnosis of a dysmorphic newborn is similar to the diagnosis of systemic diseases – it relies on analyzing the family history and on performing a meticulous examination of signs and expressions, in an effort to identify a syndrome [1].

The steps to be taken after identifying a neonatal dysmorphism are to confirm the diagnosis through cytogenetic testing via molecular techniques (in order to confirm/exclude a genetic etiology), followed by family counseling by the neonatologist-geneticist team.

After many years spent 'looking after little patients', we hereby discuss a number of anomalies and abnormal physical characteristics, isolated or associated, together with the genetic syndromes in which they can be included.

Since the neonatologists are the first to evaluate the neonates, they must be familiar with various major and minor dysmorphisms. The diagnosis of a syndrome depends on good clinical skills, knowledge of phenotypic features of various syndromes and the experience of the examiner.

Dysmorphism [1] is a morphological anomaly of a structure, a deviation from the norm, and can be classified as major or minor. Major abnormalities may be surgical, medical or cosmetic, and they may be markers for other malformations too. Minor anomalies do not have significant surgical or cosmetic importance, though many genetic syndromes can be recognized based on basis of minor anomalies.

2. Mechanisms of occurrence

Anomalies may occur through three mechanisms [2], each having different implications for the diagnosis:

- ***The malformative mechanism*** causes structural defects, resulting from an inherently abnormal development process, a primary error in morphogenesis. Malformations include congenital heart, lips, and palate abnormalities. These types of malformations are most commonly associated with a genetic disease or a genetic predisposition.
    - The malformation sequence results from a single primary malformation, as is the case with lumbar neural tube defects.
    - Malformative syndrome results from several different biological errors during morphogenesis.
- ***The deforming mechanism*** is an anomaly resulting from the action of prenatal mechanical forces on normal fetal structures. The femur, the fingers (that become overlapped) and the head (that grows into an unusual shape) can be affected. Deformations are rarely genetic, and the recurrence risk is usually low.
- ***The disruptive mechanism*** causes structural defects resulting from the destruction or interruption of normal intrinsic tissue, such as limbs reduction in amniotic band sequence or certain types of intestinal atresia due to vascular insufficiency [3]. The anomalies are rarely caused by a genetic condition and unlikely to occur in a future pregnancy.

Other terms used to describe the congenital anomalies are:

- Dysplasia, which is an abnormal cellular organization within a tissue, causing structural abnormalities (for example changes in bone structure and cartilage in skeletal dysplasia).
- Association, which is a group of abnormalities that occurs more frequently than expected, but which do not have a predictable pattern or a unique etiology.

3. Incidence

The incidence of congenital abnormalities is approximately 10% of total admissions in neonatal intensive care units (NICUs). Many of them have underlying genetic syndromes. Worldwide, around 7.9 million children (6% of births worldwide) are born with congenital anomalies [4] annually.

Minor anomalies, the subject of this chapter, appear to be isolated more frequently. About 15% of neonates are diagnosed with one minor anomaly (**Table 1**). About 71% of them are found in head, neck and hands. Among neonates diagnosed with an isolated minor anomaly, 3% have a major associated abnormality.

Affected segment	Minor anomaly diagnosed
Head and throat	• Asymmetric crying facies
	• Aplasia cutis congenital
	• Mild micrognathia
	• Flat nasal bridge
	• Upturned nose
	• Large fontanel
Eyes	• Brushfield spots
	• Inner epicanthal folds
	• Telecanthus and hypertelorism
	• Slanting of palpebral fissures
Ear	• Lack of helical fold
	• Posteriorly rotated pinna
	• Preauricular with or without auricular skin tags
	• Auricular (preauricular) pit or sinus
	• Small pinna
	• Folding of helix
	• Darwinian tubercle
	• Crushed (crinkled) ear
	• Asymmetric ear sizes
	• Low-set ears

Affected segment	Minor anomaly diagnosed
Skin	• Dimpling over bones
	• Capillary hemangioma (face, posterior neck)
	• Mongolian spots (African Americans, Asians)
	• Sacral dimple
	• Pigmented nevi
	• Redundant skin
	• Cutis marmorata
	• Café au lait spot
Hand	• Simian creases
	• Bridged upper palmar creases
	• Clinodactyly of the fifth finger
	• Hyperextensibility of thumbs
	• Single flexion crease of fifth digit (hypoplasia of middle phalanx)
	• Partial cutaneous syndactyly
	• Polydactyly
	• Short, broad thumb
	• Narrow, hyperconvex nails
	• Hypoplastic nails
	• Camptodactyly
	• Shortened fourth digit
Leg	• Partial syndactyly of second and third toes
	• Asymmetric toe length
	• Clinodactyly of second toe
	• Overlapping toes
	• Nail hypoplasia
	• Wide gap between hallux and second toe
	• Deep plantar crease between hallux and second toe
Others	• Mild calcaneovalgus
	• Hydrocele
	• Shawl scrotum
	• Hypospadias
	• Hypoplasia of labia majora

Table 1. Minor anomalies seen in various systems.

0.8% of neonates have two minor anomalies associated, and 11% of them have a major associated abnormality.

The presence of three or more minor abnormalities is rare (about 0.5%), and in most cases (90%), neonates also associate a major malformation.

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4. Classification

4.1. Minor head and throat anomalies

4.1.1. Asymmetric crying facies

Asymmetric crying facies (ACF) is a minor abnormality, characterized by lowering the corner of the mouth on the unaffected side when crying or sketching a grimace. This is caused by the congenital absence of the anguli oris depressant muscle. The ACF neonates show both nasolabial folds with normal, symmetrical depth and do have the normal ability to lift their forehead and close both eyes. This anomaly must be distinguished from facial nerve paralysis, which is less common [5]. In 20–70% of cases, ACF is associated with other congenital abnormalities, the most common being head/neck, cardiovascular, musculoskeletal, genitourinary and gastrointestinal.

Once this anomaly has been identified, genetic testing is recommended (FISH test or chromosomal microarray comparative genomic hybridization) because ACF is especially associated with 22q11 deletion syndrome (also known as velocardiofacial or DiGeorge syndrome). In this syndrome, the facial dysmorphism coexist with structural heart anomalies, long fingers/limbs, thymus aplasia/hypoplasia and kidney abnormalities. The postnatal follow-up protocol recommends close monitoring of growth and development, evaluation of thyroid and parathyroid function, immunological, hearing and ophthalmic evaluation, echocardiography, renal ultrasonography and the treatment of possibly associated anomalies [6].

4.1.2. Aplasia cutis congenita

Aplasia cutis congenita (ACC) is the congenital absence of the skin, and may occur on any part of the body. It affects the scalp in 70–80% of the cases (**Figure 1**), either as solitary lesions or associated with skull and dura mater defects [2, 7]. Aplasia cutis congenita is a rare anomaly in neonates. Over 500 cases have been reported since the first description, by Cordon in 1767. Due to the unreported cases, their real incidence is unknown. An estimate of the incidence is about 3 out of 10,000 births [8].

Figure 1. Aplasia cutis congenita.

The pathophysiological mechanism of aplasia cutis congenita is unclear; some theories suggest the involvement of factors such as obstetrical trauma, intrauterine infections with varicella zoster or herpes virus, as well as teratogenic agents, such as cocaine and methimazole [7, 9].

When this anomaly is confirmed, a series of additional investigations are required to determine if there are also other associated malformations that describe a genetic syndrome.

Adams-Oliver's syndrome includes (alongside ACC and limb defects) cutis marmorata telangiectatica congenita, central nervous system abnormalities and cardiovascular abnormalities. To diagnose this genetic syndrome, cerebral and spine (MRI) imaging, limb radiographs, echocardiography and genetic tests with genes ARHGAP31, DOCK6, RBPJ, EOGT [7, 10] sequencing are required. Adams-Oliver Syndrome can be transmitted either autosomal dominant or autosomal recessive. ACC has also been associated with trisomy 13 [11].

ACC may evolve with complications (local infection, meningitis, bleeding and superior sagittal sinus thrombosis). The mortality rate lies between 20 and 50% and depends on the size of the lesion and its association with other malformations.

4.1.2.1. Management

Small sized ACC, located laterally to the median line, is usually a unique congenital anomaly and does not require further evaluation. In sizeable defects, located on the median line, with a membranous appearance that raises the suspicion of a simultaneously damage of the skull and dura mater, cerebral and spinal MRI are recommended. A subjacent neural tube defect must be confirmed or excluded. Treatment for ACC is usually conservative [7].

4.1.2.2. Prognosis

The outcome is usually very good, small defects evolving toward healing within a few weeks through progressive epithelization and atrophic, hairless scarring [8]. In rare cases, hemorrhage and local infections may appear. Large defects of the scalp can be surgically repaired using autologous or biological grafts.

If aplasia cutis congenita is associated with other anomalies, the outcome depends on their severity.

Deep and small defects of the scalp and skull close spontaneously during the first year of life. Larger-sized defects require surgical correction.

Scalp defects that interest the skull and dura mater can be complicated by sagittal sinus thrombosis and are associated with a mortality rate greater than 50%.

4.1.3. Mild micrognathia

Micrognathia is a rather frequent clinical craniofacial abnormality, caused by congenital mandibular hypoplasia (**Figure 2**). It is usually associated with a deficient gonial angle, ascending ramus, and mandibular corpus.

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Figure 2. Mild micrognathia associated with retrognathia.

It can appear as a minor and isolated abnormality, or may be severe, as part of a genetic syndrome, frequently causing postnatal complications.

Congenital mandibular hypoplasia occurs either through intrauterine deformation or malformative mechanisms, as a result of a primary intrinsic growth disorder [12, 13].

The mandible is formed from the neural crest, beginning with the onset of the 4th week of gestation, the cells migrating to the upcoming region of the head and neck and with the initiation of the formation of the gill arches. From the first branching arch, two prominences develop, the mandibular and the maxillary one. The mandibular protrusion will form the mandible, and the jaw will form the jaw bone, the zygomatic bone and the squamous part of the temporal bone.

It is likely that congenital mandibular hypoplasia results from poor or insufficient development of the neural crest, or by means of altered migration process to the first branch of the gill, during the 4th week of gestation.

The diagnosis of micrognathia in neonates requires a careful clinical evaluation, to identify other associated craniofacial abnormalities, such as cleft palate or the coexistence of other congenital anomalies. The maxillary, the zygomatic bone, the temporal bone, the cranial vault and the cervical spine represent the other anatomical regions that can be affected.

In the clear majority of cases that include, among the first clinical signs – micrognathia, the diagnosis of genetic syndromes can be suspected on clinical examination. Subsequently, the case requires confirmation by genetic testing, as in deletion syndrome 22q11 cases.

Approximately 60 syndromes associated with micrognathia have been described, such as [12]:

Aneuploidic syndromic

- Trisomy 9
- Trisomy 13
- Trisomy 18

Non Aneuploidic syndromic

- Fryns syndrome
- Goldenhar syndrome (hemifacial microsomia)
- Hydrolethalus syndrome
- Lethal multiple pterygium syndrome
- Nager syndrome
- Pena Shokeir syndrome
- Pierre Robin sequence
- Seckel syndrome
- Smith Lemli Opitz syndrome
- Stickler syndrome
- TAR syndrome
- Treacher Collins syndrome (mandibulofacial dysostosis)

Micrognathia can result in a malocclusion (poor bite), where the teeth and jaws do not line up properly, or in more severe cases, in difficulties in breathing or swallowing. Underdeveloped mandibles can also cause severe psychological and functional impact in the growing of the child, and may be associated with life-threatening complications such as obstructive sleep apnea [12].

4.2. Minor eye anomalies

Although there is a wide variety of ocular morphology (in terms of gender, ethnicity and age), a careful analysis of some dysmorphological entities and objective measurements during the clinical examination can help diagnose some features outside of the normal standards, which may help identifying a syndrome.

4.2.1. Brushfield spots

Brushfield spots are white, yellow-colored spots on the anterior surface of the iris or small white-gray areas around the pupil.

Brushfield spots are observed in 20% of normal neonates, regardless of the color of their eyes. 85% of people with blue eyes show these spots (**Figure 3**).

They are also very common (80%) in the iris of children with trisomy 21. In children with Down syndrome and brown eyes, these spots are visible in 15–17% of cases only, being masked by normal pigmented cells. In cases with black eyes, they cannot be identified.

Brushfield spots should be differentiated from normal stromal condensation called "Kunkmann Wolffian bodies", which are light-colored, located peripherally in the iris and are not considered to be ocular dysmorphisms.

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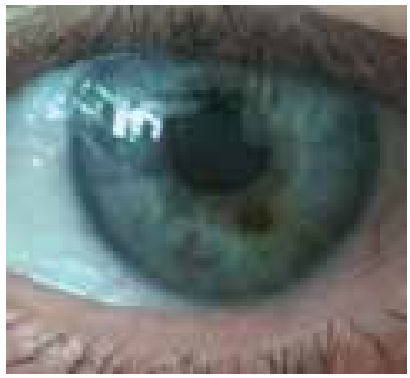

Figure 3. Brushfield spot.

4.2.2. Inner epicanthal fold

Epicanthal fold represents the oblique or vertical skin fold [14], which starts from the upper eyelid to the lower eyelid, covering the inner corner of the eye and it is most frequently bilateral (**Figure 4**). This feature is also named plica palpebronasalis or the historically Mongolian fold.

These skin folds appear through the excessive development of the skin across the nasal bridge. This excess skin presents a certain tension determined by the ectopic orbicularis oculi muscle fibers and connective tissue [15], leading to residual horizontal skin over the nasal bridge.

One of the main facial features that is often closely associated with the epicanthic fold is the elevation of the nasal bridge [16].

Factors influencing this facial trait are: geographical ancestry, age and certain pathological conditions such as blepharophimosis, palpebral ptosis.

The epicanthic fold may be an isolated congenital anomaly, or it may be a manifestation of other syndromes [17, 18]. Approximately 60% of people with Down syndrome have this fold, named "the Mongoloid fold" by John Langdon Down. In Zellweger's syndrome, epicanthic folds are present and prominent [19]. Other pathological conditions that highlight this epicanthic fold are the fetal alcohol syndrome, phenylketonuria, Turner syndrome and Smith-Lemli-Opitz syndrome.

Figure 4. Inner epicanthal fold.

Four types of epicanthic folds [20] have been identified:

1. Epicanthus tarsalis: the fold is most prominent along the upper eyelid - the normal anatomical variant of the Asian eyelid
2. Epicanthus inversus: the fold is most prominent along lower eyelid - associated with blepharophimosis syndrome
3. Epicanthus palpebralis: involves both upper and lower eyelids
4. Epicanthus superciliaris: the fold originates from the brow and follows down to the lacrimal sac

The evolution of epicanthic folds is favorable: a mild degree of epicanthus disappears most frequently with further development of the nose and massive facial bone [20, 21].

Surgical correction is only occasionally required. One of the surgical indications is in the case of epicanthus inversus, which does not resolve on its own with further growth and development of the face [15].

4.2.3. Telecanthus and hypertelorism

Telecanthus is the increased distance between the medial canthi of both eyes, with normal interpupillary distance. This condition is different to hypertelorism, which refers to an increased distance between the orbits [22].

Telecanthus may appear secondary to obstetrical traumas such as naso-orbito-ethmoidal fractures, and it may be an ethnic marker. It could also represent the expression of sinus or orbital tumors, or it may be associated with syndromes such as:

- Sinus polyps – Kartagener syndrome
- Down syndrome
- Turner syndrome
- Klinefelter syndrome
- Fetal alcohol syndrome
- Cri du chat syndrome
- Dubowitz syndrome
- Noonan syndrome
- SHORT syndrome

Hypertelorism is a clinical sign in a wide range of affections and syndromes such as:

- Edwards syndrome
- 1q21.1 duplication syndrome

- Basal cell nevus syndrome
- DiGeorge syndrome
- Loeys-Dietz syndrome
- Apert syndrome
- Neurofibromatosis
- Leopard syndrome
- Crouzon syndrome
- Wolf-Hirschhorn syndrome
- Andersen-Tawil syndrome
- Waardenburg syndrome
- Cri du chat syndrome

Since hypertelorism is a facial dysmorphism associated with a large and diverse number of congenital disorders and syndromes, the mechanism of hypertelorism is heterogeneous.

A number of theories have attempted to pinpoint this anomaly, such as: the early ossification of the lower wings of the sphenoid, the increasing width of the ethmoid sinuses, the formation and abnormal development of the skull, which can be seen in syndromes such as Apert and Crouzon [22].

4.2.4. Slanting of palpebral fissures

In the normal eye, the eyelids are generally positioned so that the lateral canthus is about 1 mm higher than the medial canthus. The palpebral slant is the direction of the slant of a line that goes from the outer corner of the eye to the inner corner.

The upper or lower slant of the palpebral fissure can be a genetic or ethnic feature (Asian population), but there are a number of conditions and syndromes manifested through this anomaly, isolated or in association with others, such as the Treacher Collins syndrome, Franceschetti (oculo-mandibulo-facial) syndrome, Down syndrome, fetal alcohol syndrome or other genetic disorders.

The identification of an abnormal slant of the palpebral fissure requires a thorough medical examination with an analysis of family history, a physical exam to detect other associated disorders/abnormalities and paraclinical investigations (karyotype), enzyme assays and metabolic studies [23].

4.3. Minor ear anomalies

The incidence of ear malformations is approximately 1 in 3800 newborns [24] and accounts for 50% of all ENT (Ear, Nose, and Throat) malformations. The most common malformations are unilateral and localized in the outer and middle ear.

Auricular malformations in newborns may be genetic (associated with syndromes or not, with family history, spontaneous mutations) or intrauterine (acquired by deformation mechanisms).

External ear malformations may involve the orientation, position, size, and external configuration of the pinna. The absence of the external ear can be identified (anotia).

4.3.1. Preauricular and auricular ear tags and pits

Auricular and preauricular ear tags and pits (**Figures 5** and **6**) are frequent findings on routine neonatal physical examinations, occurring at a frequency of 1 in 12,500 births [25]. The incidence of spontaneous formation of external ear pits in the non-syndromic population ranges between 0.3 and 1.3%, it equally affects both sexes and it has no race predilection. The incidence of unilateral preauricular sinus is 1.3% and that of bilateral preauricular sinus is 0.3%. The rate of genetic transmission of bilateral preauricular sinus was higher in children with a parent with this condition, compared to the cases of unilateral preauricular sinus.

The ear begins to develop in the 6th week of gestation, from the first and second branchial arches. A series of 6 mesenchymal proliferations is formed, known as hillocks of His, which subsequently fuse to form the definitive auricle. The first three hillocks are derived from the first branchial arch and form the tragus, crus of the helix and helix, and the other three hillocks are derived from the second arch and form the antihelix, scapha, and the lobule.

Auricular fistulas may be caused by faulty or incomplete fusion of the hillocks or by localized folding of the ectoderm. Genetic tests suggest that preauricular fistula appears due to an abnormality in chromosome 8q11.1-q13.3 [25].

Preauricular tags may be caused by supernumerary development of the first 3 hillocks of the first branchial arch.

Auricular fistulas are small, pigmented, benign congenital formations [26], located in the tegument and auricular and periauricular soft tissues, anywhere along a line drawn from the tragus to the angle of the mouth. They were first described by Van Heusinger in 1864.

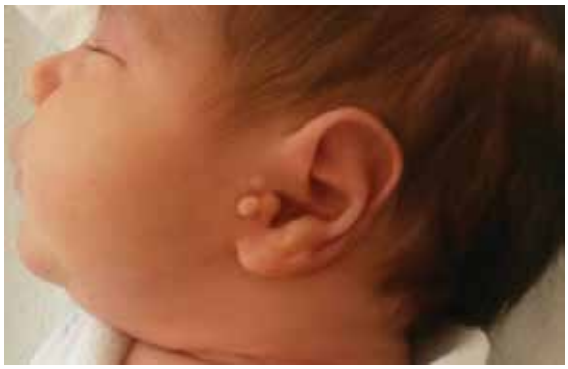

Figure 5. Preauricular tag.

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Figure 6. Preauricular tag.

Auricular fistulas are small pits/openings, located anywhere at the anterior margin of the auricle, from crus of the helix to helix, and are lined by squamous epithelium.

These auricular abnormalities can be found in isolation or as part of a genetic syndrome. All newborns will need a hearing assessment later because outer ear abnormalities can be associated with additional abnormalities such as shape abnormalities (helical ear pits), asymmetry, posterior angulation, small size, absent tragus, and narrow external auditory meatus [26], middle or inner ear malformations, and with progressive hearing loss.

These patients should be examined for any other malformations in an attempt to include the anomaly in a genetic syndrome such as [2, 26–29]:

- **Craniofacial microsomia**: association of auricular nodules with other external ear abnormalities, progressive hearing loss, palatoschisis, maxillary and/ or mandibular hypoplasia and renal abnormalities. These children require audiological assessment and renal ultrasonography, and from the point of view of genetic diagnosis, karyotype testing.
- **Branchio-oto renal syndrome (BOR)**: the association of auricular fistulae with other outer ear abnormalities, renal abnormalities and Brachial cleft fistulae. These children require auditory and renal echography, and from the point of view of genetic diagnosis, EYA1, SIX5, SIX1 sequencing is required.
- **Beckwith-Wiedemann syndrome**: auricular fistulae associated with ear lobe asymmetry
- **Oculo-auriculo-vertebral dysplasia (Goldhar Syndrome)**: associates auricular nodules, upper eyelid coloboma, outer ear deformities and vertebral abnormalities
- **Chromosome arm 11q duplication syndrome**: Preauricular tags or pits
- **Chromosome arm 4p deletion syndrome**: Preauricular dimples or skin tags
- **Chromosome arm 5p deletion syndrome**: Preauricular tags

De novo appearance of these auricular abnormalities associated with those on the face and neck may be related to the use of propylthiouracil in early pregnancy to treat maternal hyperthyroidism [30].

When auricular fistulae and nodules are isolated, no further evaluation is required for these children [2].

Most cases with typical location of auricular and preauricular fistulas are asymptomatic and do not require surgery. They can retain epithelial and sebum debris, and can evolve to subcutaneous cysts or infection. This may in turn lead to cellulitis or abscess, and may require aspiration of the collection if the antibiotic therapy is not responding. In cases of recurrent cyst infection, surgical excision of the cyst and the fistula tract is indicated. A preauricular fistulae may vary in length, may have a sinuous tract or may be extensively branched. If there are auricular fistulas and subcutaneous cysts, they adhere to the auricular perichondritis. Thus, complete elimination of the fistula or cyst should also include a portion of the auricular perichondritis at the base of the lesion [26]. Auricular and preauricular nodules can be excised for esthetic reasons.

4.3.2. Microtia

Microtia is a congenital anomaly characterized by the underdevelopment of the outer ear, while anotia is the complete absence of the ear. Because microtia and anotia have the same origin, they can be described as microtia-anotia [31].

Microtia can be unilateral or bilateral and its frequency is of approximately 1–3 to every 10,000 births [32]. In the case of unilateral microtia, the right ear is most frequently affected [31].

Etiologically, the administration of the teratogenic agent called isotretinoin (Accutane®) during pregnancy may lead to these congenital auricular abnormalities (anotia/microtia).

The pathogenesis of microtia is heterogeneous, and there have been indications of unique genetic mutations or its presence as a family trait [33].

Microtia has a broad spectrum of phenotypic aspects, from the uncomplicated hereditary one, (which is transmitted as a dominant feature, and it is most often harmless), to severe, complicated forms of hearing loss. From a clinical point of view, four grades of microtia have been described:

- **Grade I:** A less than complete development of the external ear with identifiable structures and a small but present external ear canal
- **Grade II:** A partially developed ear (usually the top portion is underdeveloped) with a stenotic external ear canal producing a conductive hearing loss
- **Grade III**: the most common form of microtia: Absence of the external ear with a small peanut-like vestige structure and an absence of the external ear canal and ear drum.
- **Grade IV:** Absence of the total ear or anotia.

Isolated microtia is relatively common, but it can be found in newborns in association with other facial dysmorphisms, such as hemifacial microsomia, Goldenhar syndrome or Treacher

Collins syndrome [34], jaw deformities, vertebral anomalies [35], heart defects, limb abnormalities, renal abnormalities and holoprosencephaly [32, 36].

Auricular atresia is the underdevelopment of the middle ear and auditory canal, and it occurs relatively frequently in conjunction with microtia, since newborns with microtia have no external opening to the ear canal, although the cochlea and the other internal ear structures are usually present. The degree of microtia usually correlates to the grade of underdevelopment of the middle ear [37, 38].

The assessment of newborns and infants with microtia-anotia should include a thorough clinical examination for the detection of associated structural defects, pediatric audiological test, multi-disciplinary consultation with the genetic specialist, pediatric otolaryngologist, and pediatric plastic surgeon.

4.3.2.1. Management

A minor anomaly does not require surgical correction. When the auricle is very deformed or absent (grades III and IV), reconstruction is often required for esthetic reasons. Most reconstructive interventions are recommended after the age of 6–10 years old, when the ear pavilion has 80% of the size of an adult ear.

The management of a microtia case associated with an auditory meatus defect is performed by long term periodic audiological monitoring, especially if there is an atresia of the auditory meatus, with the possible placement of an amplification device, especially in the case of the bilateral forms [39].

The surgical procedure for restoring the pinna is complex and is performed in several stages, with esthetic results that vary greatly, as the outer ear structure is difficult to duplicate [40]. A plastic surgical alternative is the use of a synthetic prosthetic pinna or a pinna obtained via the three-dimensional printing technology, but the research is still underway [41].

4.3.3. Macrotia

Macrotia refers to an oversized or enlarged but well-developed auricle without any other malformations of the ear (**Figure 7**). The most exaggerated portion of the ear is the scaphoid fossa. The condition is usually bilateral and symmetric.

Generally, it has an autosomal dominant pattern of transmission and an unknown pathogenesis [42].

Macrotia is commonly associated with the following syndromes:

- Marfan Syndrome: large auricle with dropped, floppy cartilage
- Fragile X-syndrome: macrotia with floppy cartilage, associated with mild or profound X-linked retardation [43].
- Cerebro-oculo-facial-skeletal syndrome (COFS): macrotia associated with neurogenic arthrogryposis, microcephaly, micro-ophthalmia.

- Variant of De Lange type 2 syndrome [44]: characterized by macrotia associated with severe microcephaly, mild mental retardation, muscular hypotonia and dysmorphic faces (flat profile, mild ptosis, short nose with a large tip and anteverted nares, narrow mouth, retrognathism).

4.3.3.1. Management

Otoplasty can improve the shape, position and proportion of the ear. It is a reconstructive surgery procedure that attempts to harmonize the ratio between ear and face.

4.4. Minor skin anomalies

4.4.1. Capillary hemangioma

It is a congenital vascular abnormality which consists of an agglomeration of neo-formation capillary vessels, manifested in the form of variable reddish-purple patches (**Figures 8** and **9**). These patches are mainly located on the face, neck and lips, but they can appear on any area of the body. They are diagnosed by clinical inspection.

Capillary hemangiomas occur only in the layers of the skin, and they do not develop in depth. They generally appear within a few weeks after birth, but they may appear in infants too and most frequently disappear spontaneously in 1–2 years. A special form of this anomaly is the 'birthmark', the clinical form that appears on the nape or covers a portion of the face and has a violet color [45, 46].

4.4.1.1. Management

Capillary hemangiomas are prone to irritation and ulceration. Each lesion must be evaluated individually, and the practitioner may opt to treat it selecting an alternative therapeutic route.

Figure 7. Bilateral macrotia with abnormal shape of the auricle.

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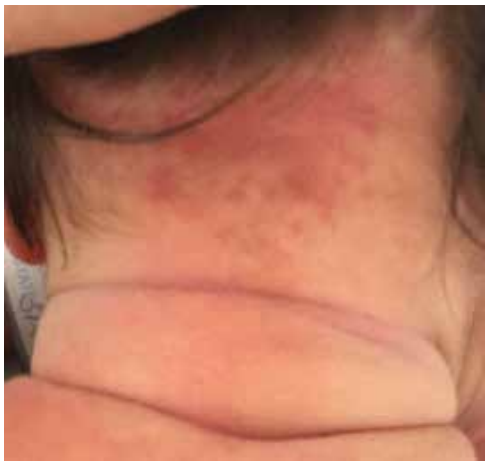

Figure 8. Capilary hemangioma – Posterior neck.

The treatment can be surgical and dermatological-medical and may consist of the surgical excision of hemangiomas, laser pulses, cryosurgery and systemic administration of glucocorticoids. Oral propranolol may be administered in order to reduce the size of hemangiomas may be a therapeutic option [47].

4.4.2. Mongolian spots (Africans, Americans, Asians)

Mongolian Spots, also known as Mongolian Blue Spots or congenital dermal melanocytosis, represent a congenital condition characterized by the presence of smooth spots, irregular-shaped with wavy borders, dark blue to brown, with a normal skin texture [48]. They may be present from birth or may appear within the first few weeks of life during the neonatal period.

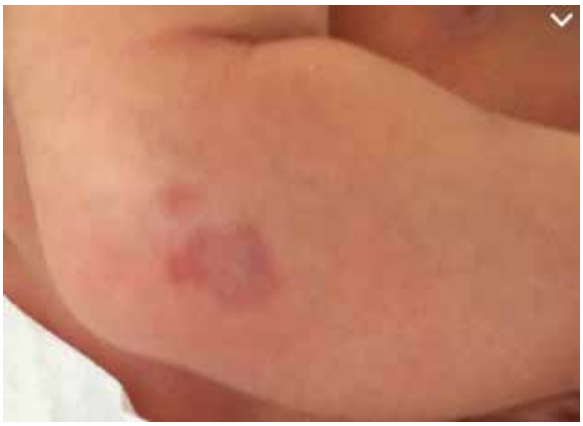

Figure 9. Capilary hemangioma – Forearm.

Mongoloid Spots represent an agglomeration of dermal melanocytes and is not a clinical sign associated with a disease or syndrome.

Depending on the location of melanocytes on the surface of the skin, the coloration of the Mongoloid Spots change. If they are superficially located, the color of the spots is brown, and the deeper they are, the color tends more and more to have a blue shade [48, 49].

Mongoloid Spots are most commonly diagnosed at birth due to specific coloration and localization, and no additional investigation methods are required. They are found with a frequency of 90% in the black population and the Native Americans, in about 80% of Asian infants, 70% of Hispanic individuals and in a reduced proportion of 5–10% of Caucasian children [48, 49]. Incidence is lower in preterm infants compared to full-term infants, and in terms of gender distribution, the incidence is higher in boys.

Most spots are located on the buttocks, lumbosacral (**Figure 10**), deltoid and dorsal region, on the limbs and in rare cases on the face or on the occipital region. There may be single or multiple spots, ranging in size from 1 to 2 cm to tens of cm [50].

4.4.2.1. Management

No treatment is recommended, as Mongoloid spots generally disappear spontaneously at the age of 1–4 years, most frequently in the first year of life. If they do not disappear until puberty, they remain permanent, a situation that occurs in approximately 5% of cases [51].

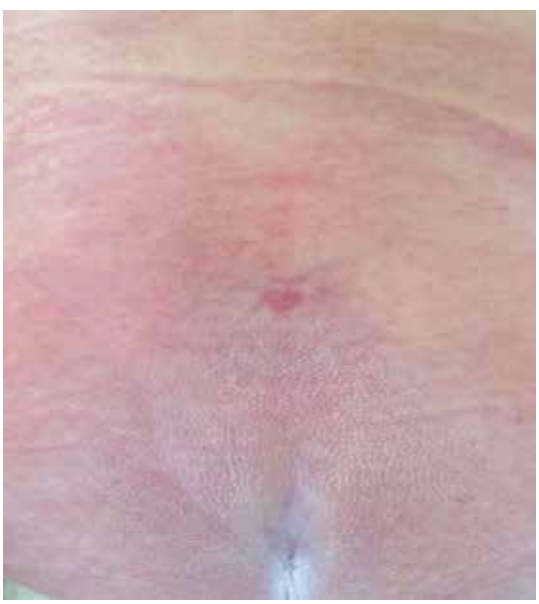

Figure 10. Mongoloid spot – Lumbosacral region.

4.4.3. Cutis marmorata telangiectatica congenita

Cutis marmorata telangiectatica congenita is a rare congenital vascular disorder that manifests itself by affecting the blood vessels of the skin by alternating a vascular network with a vasodilation and vasoconstriction process which gives the skin a marbled appearance. It is accentuated by cold temperatures, but it does not disappear when exposed to warmer temperatures [52].

It should not be confused with Cutis Marmorata, which is a normal, adaptive, physiological response of the newborn to exposure to low temperatures. This disorder is due to a neurological and vascular immature system, it varies between the constriction and dilation of blood vessels, and it occurs most frequently in the hands and feet.

Very few cases of cutis marmorata telangiectatica congenita have been reported worldwide - less than 100 cases [53], but in reality it is more common than that. Mild forms are not that rare, but they are not reported [54].

The pathophysiological mechanisms are still unclear, with most cases occurring sporadically, although rare cases were reported in some families. Studies indicate the primary involvement of capillaries, venules and veins, and possibly arterioles and lymphatic vessels.

The hypothetical mechanisms that have been proposed are environmental factors, peripheral neural dysfunctions, failure of the development of mesodermic vessels in an early embryonic stage and autosomal dominant inheritance with incomplete penetrance [52, 55].

Diagnosis: skin manifestations may be associated with the asymmetry of extremities, macrocephaly, glaucoma, cutaneous atrophy, chronic skin ulcerations, neurological anomalies, vascular anomalies (nevus flammeus, Sturge–Weber syndrome, Klippel-Trénauna syndrome, Adams Oliver syndrome), psychomotor and /or mental retardation [56].

Management: in general, there is no treatment for this condition, but the associated anomalies can be treated. In the case of limb asymmetry, without motor dysfunction, there is the possibility of inserting an "elevation" device for the shorter leg during early childhood. Laser therapy has not been successful in the treatment of this vascular skin disorder, possibly due to many dilated capillaries and veins in the deep layers of the skin.

Prognosis: the prognosis is favorable in most cases, when patients experience an isolated cutaneous abnormality. In most cases, the marbled appearance regresses spontaneously during the first year of life due to the normal maturation process, with the thickening of the epidermis and dermis. In fewer cases, lesions can continue for up to 10 years or throughout the patient's life.

4.4.4. Pigmentary nevi

Pigmentary nevi, also known as melanocytic nevi, are benign neoplasms present from birth - congenital melanocytic nevi may develop throughout life.

Pigmentary nevi appear with a high frequency as uniform, beige, brown or skin-color formations, sometimes protruding, circular or oval, with regular, smooth, well-defined margins, of 6 mm in diameter [57, 58].

Histopathologically, they are cellular (melanocyte) benign clusters that change very little in life, have a slow growth, and never invade the surrounding tissues. The number of nevi is influenced both genetically - the family history is very important - and from the sun exposure of the infant [59].

Congenital pigmentary nevi over 20 cm in diameter have an increased risk of malignancy.

Pigmentary nevi are commonly diagnosed clinically or using the dermatoscope.

The management of pigmentary nevi depends on the type of nevus and the degree of uncertainty of the diagnosis. Benign ones require nothing else than monitoring after the neonatal period [60, 61], while those with special characteristics - asymmetry, uneven, irregular margins, color variations, diameter > 6 mm - very rare cases, require biopsy with histopathology, immunohistochemistry and electron microscopy [57, 62].

4.5. Minor hand anomalies

4.5.1. Camptodactyly

Camptodactyly is the irreversible flexion of one or both interphalangeal joints at the level of one or more fingers, being most frequently a congenital condition.

It can be diagnosed antenatally [63–65] "in utero" or postnatally, being a clinically obvious deformity, which subsequently requires imaging investigations. An abnormal insertion of lumbrical and flexor digitorum tendons of the hand is often noted.

Camptodactyly may occur sporadically, de novo or by autosomal dominant inheritance.

It may be an isolated clinical manifestation or clinical expression in syndromes such as Trisomy 18 and 13, Freeman Sheldon Syndrome, Pena Shokeir Syndrome, CACP Syndrome (Camptodactyly, Arthropathy, Coxa vara, Pericarditis), arthrogryposis [63, 65–67].

4.5.2. Clinodactyly

Clinodactyly is a congenital malformation consisting of the lateral deflection of the fingers by affecting the first interphalangeal joint, which interests any finger, especially the pollex and the auricular fingers (the fifth finger), (**Figure 11**).

Clinodactyly is a descriptive term, which refers to a radial angulation at a common interphalangeal joint in radio-ulnar or palmar planes, and can often be a normal anatomical variant.

The incidence varies, ranging between 1 and 18%, as it is most frequently under-reported.

Clinodactyly may be a very common isolated clinical manifestation in the context of a family history [68] - with autosomal recessive inheritance, but it may also occur in several syndromes, in association with other locomotor abnormalities or in other organs and systems.

Clinodactyly is seen in over 60% of children with Down syndrome [63], Klinefelter syndrome, trisomy 18, Turner syndrome, Cornelia de Lange Syndrome, Feingold Syndrome, Roberts Syndrome, Russell-Silver Syndrome or Fanconi Syndrome. It may also be a clinical manifestation associated with other abnormalities such as macrodystrophia lipomatosa and brachydactyly type A3.

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Figure 11. Clinodactily of the fifth finger.

Considering the presence of this sign in multiple chromosomal anomalies, some authors consider it a "soft sign", if detected in an antenatal ultrasound scan.

If the clinodactyly is isolated, it has an excellent prognosis.

Usually, the treatment is not necessary. If necessary - because of emotional stress due to esthetic reasons or the impairment of the fine hand movements - the treatment is surgical [69]. For surgery, preoperative radiographs of the pollex are performed, establishing the size of the graft and the degree of angulation necessary to restore the normal function of the distal phalange.

4.5.3. Polydactyly

It is one of the most common congenital abnormalities of upper limbs, seen in all ethnicities, and it refers to the presence of additional fingers, being usually bilateral [70]. Most often, polydactyly affects the upper and lower limbs synchronously. Supernumerary fingers do not usually have adequate muscle connections [71, 72].

The classification of this condition is based on the location of the additional fingers, the polydactyly being:

- Postaxial (duplicated finger V),
- Mesoaxial/central (duplication of fingers II, III, IV),
- Preaxial (duplicated thumb),
- Mixed.

Polydactyly may appear isolated, de novo, sometimes autosomal dominant inherited or may be associated with syndromes [73, 74] such as Bardet-Biedl Syndrome, Carpenter Syndrome, Elis-Van Creveld Syndrome, Fanconi Syndrome, Greig Syndrome, Holt-Oram Syndrome, Meckel-Gruber

Syndrome, Pallister-Hall Syndrome, Smith-Lemil-Opitz Syndrome, Trisomy 13, Trisomy 18, Short Rib Polydactyly Syndrome Type I (Saldino-Noonan Type) (Majewski type), Trisomy 21, Townes-Brocks Syndrome.

Usually, polydactyly is diagnosed antenatally, but if it is postnatally discovered, it requires paraclinical investigations in order to be included in one of the genetic syndromes, except for cases of family history. The investigations are performed using imaging techniques (MRI, CT scan, ultrasound examination), followed by genetic consultation in case of association with other malformations. The most commonly associated malformations are syndactyly, hypoplasia or aplasia of long bones, hydrocephalus, microcephaly, spina bifida, ventricular septal defect, atrial septal defect, esophageal atresia, duodenal atresia, anal imperfection, abdominal wall defects, renal agenesis, polycystic kidney disease, hydronephrosis, diaphragmatic hernia, anophthalmia, cheilopalatoschisis.

In the case of isolated polydactyly, no treatment is required. If this anomaly affects the mobility and gross/fine movements of the fingers/hands, the treatment is always surgical.

4.6. Minor foot anomalies

4.6.1. Partial syndactyly of the second and third toe

Syndactyly is one of the most common congenital limb malformations involving the fusion of two or more fingers due to the failure of separation process during the development of limbs in the first trimester. In the lower limbs, the most common location is between the second and the third finger [75].

It is a heterogeneous clinical phenotype, as it may be: unilateral or bilateral, symmetrical or asymmetrical, partial or complete, cutaneous or bony, involving only the phalanges and/ or metatarsal bone, or may extend to tarsal bones or even the calf bones.

Partial syndactyly of the second and third toe may appear as a clinically isolated phenotype (the most common is zygodactyly) [75] or may be associated with syndromes such as:

- Pfeiffer syndrome [76–79] - type V acrocephalopolysyndactyly has as its etiology a dominant autosomal genetic defect in which mutations occur in the FGFR1 gene (fibroblast growth factor receptor 1) and in the FGFR2 gene (fibroblast growth factor receptor 2). In this syndrome, the partial syndactyly of the second and third toe is accompanied by other malformations such as craniosynostosis, facial hypoplasia, hypertelorism, brachydactyly.
- Carpenter syndrome - type II acrocephalopolysyndactyly is an autosomal recessive genetic disorder in which mutations occur in RAB23, a hydrolysis involved in transmembrane regulation [80]. Carpenter syndrome associates, besides partial syndactyly and polydactyly, with auricular, cardiac and genital abnormalities.
- Smith-Lemli-Opitz syndrome is an autosomal recessive genetic disorder of cholesterol biosynthesis [81]. This syndrome associates with syndactyly and microcephaly, micrognathia, genital malformations, auricular malformations, autism spectrum disorders.

Partial syndactyly of the second and third toe does not affect the motor function, and therefore does not require correction.

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4.6.2. Dysplastic nails

Insufficient development of nails [82] may occur in isolation or in many genetic malformations such as:

- Simpson-Golabi-Behmel Syndrome (Bulldog Syndrome). The most common etiology of this syndrome is the mutations in the GPC3 gene to chromosome X [83]. Nail hypoplasia is accompanied by other clinical manifestations such as macrosomia, hypertelorism, polydactyly, macrostomia, macroglossia.
- Fetal Alcohol Syndrome [84]. Prenatal exposure to alcohol causes numerous fetal malformations, including nail dysplasia accompanied by: microcephaly, facial hirsutism, short palpebral fissures.
- Fryns Syndrome. This syndrome is a genetic disorder inherited in an autosomal recessive manner, in which dysplastic nails occur along with other minor and major malformations such as diaphragmatic hernia, hirsutism, distal phalangeal hypoplasia, Dandy-Walker malformation, agenesis of corpus callosum.

4.6.3. Phalanx anomalies: digital deformities

The small bones and soft tissues of the feet can be affected by systemic disorders, and frequently, the findings are quite unique and virtually help diagnose some genetic or metabolic disorders [85]. Sometimes the changes in the structural bones of the feet, metacarpals and metatarsals, or the phalangeal units are so astonishing that they ensure the diagnosis of peculiar and rare syndromes.

There are many disorders – some genetic, some neoplastic, some inflammatory – which sometimes produce extraordinary changes in the patient's feet. In some cases, phalanx abnormalities occur as a result of the sucking of the finger by the fetus, causing elongation and hypertrophy (**Figures 12** and **13**).

Figure 12. Phalanx anomalies.

Figure 13. Phalanx anomalies.

A small listing includes synovial chondromatosis, fibrous dysplasia, tumoral calcinosis, Maffucci syndrome, Ollier's disease, hereditary multiple osteocartilaginous exostosis, type 1 neurofibromatosis, pigmented villonodular synovitis, hyperparathyroidism, or gout.

Author details

Simona Vlădăreanu[1]*, Mihaela Boț[1], Costin Berceanu[2], Claudia Mehedințu[1] and Simona Popescu[1]

*Address all correspondence to: simconst69@gmail.com

1 University of Medicine and Pharmacy "Carol Davila", Bucharest, Romania

2 University of Medicine and Pharmacy of Craiova, Romania

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Nowadays, nobody can imagine practicing obstetrics without using obstetrical ultrasound. Working in the prenatal diagnosis field requires dedication, patience, skills, experience, caution, and empathy.

The concept of this book was guided by the desire to provide some help to the ultrasound operators. On a daily basis, they are confronted with the challenging task of ruling out or suspecting/confirming the diagnosis of fetal anomalies, either structural or chromosomal.

The chapters of this book contain objective and exhaustive updated reviews of the pertinent literature, so that the reader would have a wide reference basis on each subject. Yet, many authors scan the fetus themselves or are directly involved with managing pregnancies with structural malformations or chromosomal anomalies. They kindly shared their personal experience and lessons learned over the years.

This book is beneficial for all the professionals working in the prenatal diagnosis.

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