IntechOpen

Childbirth

Edited by Miljana Z. Jovandaric and Svetlana J. Milenkovic

Childbirth

Edited by Miljana Z. Jovandaric and Svetlana J. Milenkovic

Published in London, United Kingdom







IntechOpen






Supporting open minds since 2005

Childbirth
http://dx.doi.org/10.5772/intechopen.83156
Edited by Miljana Z. Jovandaric and Svetlana J. Milenkovic

Contributors
Asher Ornoy, Liza Weinstein-Fudim, Zivanit Ergaz, Miljana Z. Z Jovandaric, Svetlana J. Milenkovic, Matilde Fernández Fernández-Arroyo, Niaz Mustafa Kamal, Melaku Desta, Zalka Drglin, Iffath Abbasi Hoskins, Donald Morrish, Rosemary Ogu, Omosivie Maduka, Radim J. Sram, Milos Veleminsky, Jr., Milos Veleminsky

First published in London, United Kingdom, 2020 by IntechOpen
IntechOpen is the global imprint of INTECHOPEN LIMITED, registered in England and Wales, registration number: 11086078, 7th floor, 10 Lower Thames Street, London, EC3R 6AF, United Kingdom
Printed in Croatia

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library

Additional hard and PDF copies can be obtained from orders@intechopen.com

Childbirth
Edited by Miljana Z. Jovandaric and Svetlana J. Milenkovic
p. cm.
Print ISBN 978-1-78985-961-4
Online ISBN 978-1-78985-962-1
eBook (PDF) ISBN 978-1-83962-779-8

Meet the editors

Miljana Z. Jovandaric was born in 1963 in Serbia. She graduated from the Faculty of Medicine in Belgrade in 1989 and completed a specialization in Pediatrics at the University Children's Hospital, Belgrade, in 1999. She completed her specialization in Neonatology in 2003. She defended her master's thesis "Analysis of lipid infants in women suffering from gestational diabetes mellitus (GDM)," in 2006 and her doctoral dissertation "Effect of hypoxia on electrolyte and lipid levels in term newborns," in 2018, at the School of Medicine, University of Belgrade, Serbia. She is author and co-author of 74 scientific papers presented at national and international conferences and published in journals. Dr. Jovandaric is currently head of the Department of Sick Newborns at the Clinic for Gynecology and Obstetrics, Department of Neonatology, Clinical Center of Serbia, Belgrade.

Svetlana J. Milenkovic was born in 1960 in Serbia. She graduated from the Faculty of Medicine - University of Belgrade in 1983, and completed a specialization in Pediatrics in 1992 at the Institute for Mother and Child Health in Belgrade. She completed her specialization in Neonatology in 2008. She defended her master's thesis, "The influence of external and genetic factors on the age menarche and pubertal development," in 1998 and her doctoral dissertation "Association of leptin and adiponectin levels with somatic and metabolic parameters in discordant twins," in 2017 at the University of Belgrade. She is the author of papers published at expert meetings and medical journals. Dr. Milenkovic currently works at the Department of Neonatology at the Clinic of Gynecology and Obstetrics, Clinical Center of Serbia.

Contents

Preface XIII

Chapter 1 1
Methods for Prenatal Sex Determination and Their Importance in Understanding and Prevention of Gender-Related Birth Defects
by Asher Ornoy, Liza Weinstein-Fudim and Zivanit Ergaz

Chapter 2 23
Influences the Aeromath in the Way of Ending Births
by Radim J. Sram, Milos Veleminsky, Jr and Milos Veleminsky

Chapter 3 39
Placenta Abruption and Delivery Method
by Miljana Z. Jovandaric and Svetlana J. Milenkovic

Chapter 4 47
Childbirth Education: Comparative Analysis
by Matilde Fernández Fernández-Arroyo

Chapter 5 63
Consanguinity Marriage Increases Risk of Newborn's Congenital Anomalies in Sulaimani City
by Niaz Mustafa Kamal

Chapter 6 73
Low Birth Weight and Adverse Perinatal Outcomes
by Melaku Desta

Chapter 7 89
Towards Salutogenetic Birth Space
by Zalka Drglin

Chapter 8 109
Induction of Labor: Review of Pros, Cons, and Controversies
by Donald Morrish and Iffath Abbasi Hoskins

Chapter 9 119
Preventing Maternal Mortality during Childbirth: The Scourge of Delivery with Unskilled Birth Attendants
by Omosivie Maduka and Rosemary Ogu

Preface

Childbirth, also known as labor and delivery, is the ending of pregnancy where one or more babies leaves a woman's uterus by passing through the vagina or by Caesarean section. The most common way of childbirth is a vaginal delivery. Each year, complications from pregnancy and childbirth result in about 500,000 maternal deaths, and 7 million women have serious long-term problems and 50 million women have negative health outcomes following delivery. Most of these occur in the developing world. Specific complications include obstructed labor, postpartum bleeding, eclampsia, and postpartum infection. Complications in the baby may include lack of oxygen at birth, birth trauma, prematurity, and infections.

The first chapter by Asher Ornoy, Liza Weinstein- Fudim, and Zivanit Ergaz describes the needs for accurate sex determination and the methods that can be used. We should note that today there are many biological processes that are gender dependent, but many of these gender-specific processes are still unknown, especially in teratology. A better understanding of these gender-related effects will enable us to find more appropriate methods of treatment and prevention.

The second chapter by Radim J. Sram, Milos Veleminsky, Jr., and Milos Veleminsky examines the effects of air pollution on children in the Czech Republic. The authors describe the impact of increased concentrations of carcinogenic polycyclic aromatic hydrocarbons on fetal growth, expressed as intrauterine growth retardation, and the impact of air pollution on respiratory morbidity and neurodevelopment in children.

Dr. Miljana, Z. Jovandaric, and Svetlana J. Milenkovic in the third chapter discuss placental abruption as a significant contributor to maternal mortality worldwide. Placental abruption must be considered whenever bleeding is encountered in the second half of pregnancy, since it is a significant cause of third-trimester bleeding associated with fetal and maternal morbidity and mortality.

The fourth chapter by Matilde Fernández Fernández-Arroyo discusses prenatal education programs to increase maternal and child health. Today no one knows the most effective educational approach. The author analyzes different programs and explains their conceptual approaches and methodologies, helping professionals and researchers improve the quality of programs.

The fifth chapter by Niaz Mustafa Kamal talks about how consanguineous marriage may cause the transfer of two recessive defective mechanisms, one from the mother and one from the father, to offspring, which may cause the appearance of congenital anomalies. This study aims to determine the role of consanguineous marriage in congenital anomalies and their types in Sulaimani city, Iraq. This is a retrospective case-control study based on hospital records. Consanguineous marriage is referred to as a marital union among close biological kin. In clinical genetics, it is called the relationship by marriage between first and second cousins. Consanguineous marriage is most common in the Middle East and among Islamic populations. Rates of consanguineous marriage in different countries are dependent on different factors

like education level, religion, local tradition, and socio-economic status. Studies over several decades have shown that there is a high correlation between consanguineous marriage and inherited congenital malformations.

The sixth chapter by Melaku Desta highlights the prevalence of low birth weight, its predictors, and adverse perinatal outcomes, and possible prevention modalities. Socio-demographic, obstetric (previous abortion, hypertensive disorder, antenatal visits, and prematurity), and nutritional factors increase the risk of low birth weight. Low birth weight neonates are associated with adverse perinatal and childhood outcomes, such as low Apgar score, neonatal death, malnutrition, and academic and mental disorders. Improving the care of women who have previous or recent morbidities, hypertensive disorders of pregnancy, and premature births is a priority. The authors recommend incorporating mental health in the prenatal visit, improving the care of high-risk pregnant women, and community-based kangaroo mother care practice.

The seventh chapter by Zalka Drglin describes how we can improve the birth space to protect normal physiological birth. The space where childbirth takes place, including the persons in this space, affects a woman's well-being (she can either feel safe, connected, and relaxed, or scared, strained, and endangered) and the way she responds as an incarnate being as well as influences the course of childbirth. The birth space can have two different types of effects: pathogenic, which are experienced by the woman giving birth as dangerous or even hostile, and salutogenic, having "birthing shelter" characteristics. Modern findings of different disciplines (physiology, architecture, neuroscience, social and evolutionary anthropology, culturology) contribute to our understanding of the complexity of childbirth, and the needs of the woman and her baby, and lead to maternity hospitals being designed as places of support for the holistic health of both. The chapter presents basic recommendations for transforming maternity hospitals into salutogenic birth places.

The eighth chapter by Dr. Donald Morrish and Dr. Iffath Abbasi Hoskins discusses birth inductions and how they have increased over the years, while improvements in perinatal outcomes have not occurred. Induction delivery may result in increased risks for mother and baby, due to factors such as gestational age, Bishop cervix score, and the methods used. Failed birth inductions resulting in increased cesarean sections may be due to unripe cervixes, decreased Pitocin use, or incorrect patient choice. Medically indicated induction of labor (IOL) does not require waiting for the gestational age (GA) to reach 39 weeks. Non-medically indicated IOL prior to 39 weeks GA may result in neonatal morbidity. Patients at 39 weeks GA can be induced electively and need not wait for natural labor. Cervical ripening methods include vaginal, oral, or IV medications, and can be administered as outpatient rather than in hospitals, in order to reduce financial and time constraints. Ethical issues regarding indications, GA, agent choice, location of cervical ripening, and failed induction can have an impact on healthcare resources.

The ninth chapter by Omosivie Maduka and Rosemary Ogu refers to the health of women during pregnancy, childbirth, and the postpartum period. While motherhood is often a positive and fulfilling experience, for too many women it is associated with suffering, ill health, and even death. Maternal mortality is the death of a woman during pregnancy and within 42 days of delivery irrespective of GA and site of birth. Maternal mortality ratio is the number of maternal deaths per 100,000 live births, while maternal mortality rate is the number of maternal deaths per 100,000 women of reproductive age. The maternal mortality ratio is a key performance

indicator for efforts to improve the health and safety of mothers before, during, and after childbirth per country worldwide. Of all maternal deaths, 94 percent occur in developing countries. In settings with weak health systems and suboptimal service delivery more and more women continue to utilize traditional birth attendants during childbirth. Traditional birth attendants are unskilled and unable to prevent or treat the complications during pregnancy or childbirth that lead to maternal deaths. This chapter utilizes qualitative research methodology and discusses the challenges of preventing maternal deaths in a setting where women routinely utilize traditional birth attendants. It also examines the reasons for the persistence of traditional birth attendants.

I hope this book will shed light on some of the fascinating aspects of childbirth. I would like to thank all the contributing authors for their patience and cooperation during the process of creating this book. In addition, I would like to express my sincere appreciation and gratitude to the personnel at IntechOpen publishing, especially Ms. Rozmari Marijan who offered me great help throughout the processing of this book.

Miljana Z. Jovandaric and Svetlana J. Milenkovic
Department of Neonatology,
Clinic for Gynecology and Obstetrics Clinical Center of Serbia,
Belgrade, Serbia

Chapter 1

Methods for Prenatal Sex Determination and Their Importance in Understanding and Prevention of Gender-Related Birth Defects

Asher Ornoy, Liza Weinstein-Fudim and Zivanit Ergaz

Abstract

Various hormones, chemicals, and teratogenic agents exhibit gender-related effects in utero as well as postnatally. Among such gender-specific teratogens are endocrine disruptors, especially phthalates that affect male gonads, diabetes-induced oxidative stress with more deleterious effects on male offspring, procarbazine-induced cleft palate affecting more male fetal rats compared to females, and VPA-induced autism-like behavior that affects differently males than females. Hence, there are many needs for the accurate determination of genetic gender. In newborn animals, the morphological methods that exist for sex determination (i.e., anogenital distance) are generally inaccurate. Hence, an accurate and simple method for the prenatal and early postnatal assessment of the genetic sex, prior to reliable evaluation from the external genitalia, is of utmost importance. Indeed, several methods have been developed for accurate assessment of genetic sex, which are discussed in this chapter. Findings from studies in our laboratory have shown that the method described by McFarlan et al. for the assessment of genetic sex in adult mice by PCR of Sly/Xlr genes can be reliably used for the genetic sex determination of any tissue, including embryos and fetuses, with an accuracy of about 100%.

Keywords: sex determination, sex differentiation, androgens, gender-related teratogenesis, methods for sex assessment

1. Introduction

The ability to accurately assess the genetic sex in tissues, embryos, fetuses, and newborns is crucial in animal models when gender has specific impacts on development and morbidity or whenever genetic and environmental effects are gender-related or gender-specific. For the human, gender assessment is crucial in all cases of ambiguous genitalia and intersex where the proper definition of the sex is of diagnostic and/or therapeutic importance.

Female and male embryos are morphologically and anatomically indistinguishable until the development of internal and external genitalia and secondary sex characteristics appear. In mice, for example, sexual differentiation starts around

prenatal day 11.5 when the male-determining gene Sry is expressed in the bipotential genital ridge and induces testes-specific gene expression. In the lack of Sry expression, female-determining gene expression is activated [1].

There are two basic phases of sexual development in mammals: sex determination at fertilization and sex differentiation that is associated with sex determination but may be influenced by a variety of internal factors (mainly hormones and their receptors) and external factors (hormones, endocrine disruptors, and a variety of environmental chemicals) [2]. We will therefore briefly describe in this chapter first the development of the sex organs and then in more details the teratogenic effects that are gender-specific and the different methods that are used for the discrimination between genders, assessing the genetic sex.

2. Development of the reproductive system

2.1 Development of internal genitalia

The reproductive system consists of the gonads, internal sex organs, and external genitalia [3]. In all mammals the initial stages of the development of reproductive organs are dimorphic (indifferent) since the precursor organs are similar in both genders [4]. During early development, both male and female primordial sex organs develop in every embryo, and with the advancement in development, depending on the genetic sex determined at fertilization and on endocrine function of the sex steroids, one of the two internal sex organs will regress and become nonfunctional. Hence, sex determination is genetically programmed during fertilization, but sex differentiation, the second phase of sexual development, is hormone-dependent [5]. SHH, FGF, and TGF signals are involved in the first phase, while androgen-dependent signaling and androgen receptors are mainly involved in the second phase [1–5].

In the human embryo, similarly to other mammals, there is initial development of an indifferent gonad, and both the Wolffian duct (mesonephric duct) and the Mullerian (paramesonephric) duct develop bilaterally in the primitive genital ridges. The presence of the Y chromosome (Sry) determines the persistence and further development of the Wolffian duct and derivatives, while its absence will cause regression (degeneration) of the Wolffian duct. The gonads will differentiate toward testes that will start secreting sex steroid hormones (androgens secreted by the interstitial [Leydig] cells of the testis), as well as the anti-Mullerian hormone secreted by the Sertoli cells that will induce regression of the Mullerian ducts [6, 7]. In the absence of the Sry, the Mullerian ducts will continue their differentiation to uterus and fallopian tubes, the gonad will be female, and the Wolffian duct will regress. In the human embryo, the gender-specific morphologic differentiation of the reproductive organs occurs during weeks 7–10 of gestation (5–8 postfertilization) with the establishment of endocrine function of the gonads [3]. The development of the external genitalia in the area of the urogenital sinus occurs slightly later.

2.2 Development of the gonads

The gonadal primordia appear in the human embryo around the fourth–fifth week postfertilization (weeks 6–7 of pregnancy), initially without the germ cells (gametes). The germ cells, apparently originating from the dorsal part of yolk sac epithelium that is later incorporated into the gut, migrate in the primitive hindgut into the dorsal mesentery alongside nerve fibers [3, 8] to the gonads. They start to invade the gonad during the fifth week postfertilization [9]. Migration of primordial germ cells may

continue up to postfertilization week 14. The molecular basis for the formation and migration of the germ cells is poorly understood [9]. The male gonad starts its morphologic differentiation before the female gonad, occurring during the end of week 6 postfertilization, at which time it also starts to secrete its hormones [3, 10].

2.3 Development of external genitalia

The first phase of the differentiation of external genitalia occurs during the fifth postfertilization week as an "indifferent stage" where the cloacal folds and genital tubercle, the area of future development of external genitalia, are similar in male and female embryos (ambisexual stage that extend to 9–10 weeks postfertilization). There are androgen-independent and androgen-dependent phases of development within the cloacal folds that unite and enlarge to form the genital tubercle which is located cranial to the urogenital opening (ostium) and composed of mesoderm of the urogenital sinus. The final development of the external genitalia is largely affected by environmental factors (i.e., endocrine disruptors) [11]. Sonic hedgehog (SHH) regulates the early development of the external genitalia. Under the influence of androgens (5-dihydrotestosterone), the genial fold will fuse to form the scrotum in the male. Androgen deficiency will induce the development of female external genitalia even in genetic males [10–12]. The inability to transform testosterone to 5-dihydrotestosterone, i.e., 5α-reductase deficiency and sometimes 17β-hydroxysteroid dehydrogenase deficiency, may lead in genetic males to the formation of female genitalia [11, 13].

3. The importance of sex identification in biology and in teratology

Teratogens might be gender-specific and might cause lethality or congenital malformations that are dependent on embryonic sex. Possible gender-specific effect of teratogens is not always established because in most studies embryonic and fetal genetic sex is not determined. The ability to determine fetal sex will allow a better understanding of the possible gender-related effects of teratogens and their mechanism of action.

It is important that sex identification techniques will be noninvasive and when needed will be performed even on highly degraded noninvasive samples such as feces and hair or different organs from which some tissue can be spared [14]. Nongenetic methods to determine fetal and neonatal sex were proven to be to a large extent inaccurate. Evaluation of anogenital distance difference is subjective, has an overlap zone, and is accurate only in about 50% of the cases [15]. Although Barr bodies were detected in the amnion and liver cells of rat embryos and fetuses during days 12.5–20.5, this cannot serve for accurate sex determination since they were detected in a relatively small proportion of subjects and in both sexes. They were detected in 20–50% in the amnion and 10–51% in the liver of females. Moreover, they were also detected in a very small proportion of males: 0–7% in the amnion and 0–8% in the liver [16]. Hence, genetic methods for the detection of gender-related genes and/or chromosomal studies are the most reliable methods.

4. Gender-related effects in biology and in teratology

4.1 Gender-related teratogenic effects

Gender-related biological effects have been shown at early stages of development. Schwartz et al. [17] examined the effect of the sex hormones—estradiol (E2)

and testosterone—on the modeling of cultured fetal mouse long bones separated according to their sex. They reported specific sex-dependent response of fetal mouse long bones to E2 and testosterone, bones from female fetuses responding to E2 and from male fetuses responding to testosterone. In a subsequent study, the authors described similar gender-specific effect of testosterone on growth plate chondrocytes in culture (see **Table 1**) [18].

Exposures to substances, such as cigarettes, cocaine, and alcohol, have been implicated as causes of developmental problems, but only few studies have investigated the gender aspect of their teratogenicity.

Bahado-Singh et al. [19] reviewed data from the Center for Disease Control and Prevention, USA, for 2006, covering more than 2 million births from 19 reporting states. They found that first trimester cigarette smoking increased the risk of cleft lip and cleft palate only in males, OR 1.431 (95% CI 1.241, 1.651), while male gender also appeared to be an independent risk factor for some types of congenital anomalies [19]. A strong association between male gender and the presence of cleft lip and/or palate (OR = 3.51; 95% CI 2.83–4.37) was also found by Strange et al. [20].

Male gender as a gestational risk factor was also reported by Radin et al. [21] who investigated the effect of preconception intake of low-dose aspirin (LDA) on male live birth. They followed two groups of women with prior pregnancy loss: one group was treated with daily intake of LDA, and the second group was treated with placebo. They detected a low proportion of males at birth in the placebo group (44%) that may be related to a disordered inflammatory milieu that is harmful for

Substance	Teratogenic effect	References
Human studies		
Cigarette smoking	Increased risk for cleft lip and cleft palate in males	Bahado-Singh et al. [19], Strange et al. [20]
Cocaine	High risk for attention and inhibitory control problems, emotional modulation difficulties, health risk behaviors, and antisocial behavior in males	Bennett et al. [22, 23]
Alcohol	Fetal alcohol syndrome disorder is more prevalent in young boys	Thanh et al. [24]
	Childhood mental health problems are more prevalent in girls	Sayal et al. [25]
Endocrine disruptors	Exposure to endocrine disruptors, especially substances with estrogenic or antiandrogenic affects, such as 2-ethylhexyl phthalate and bisphenol A, might adversely affect embryonic sex organ development	Lambrot et al.
Rodent studies		
Alcohol	Impaired social recognition memory in a sexually dimorphic manner in prenatally exposed mice	Kelly et al. [26]
Procarbazine	Cleft palate and micrognathia were significantly more frequently in the male fetuses	Malek et al. [27]
VPA	Mice exposed to VPA during pregnancy demonstrated gender-dependent changes in social behavior, oxidative stress markers, and gene expression	Ornoy et al. [28, 30]
Endocrine disruptors	Exposure to endocrine disruptors, especially substances with estrogenic or antiandrogenic effects, such as 2-ethylhexyl phthalate and bisphenol A, might adversely affect embryonic sex organ development	Lambrot et al. [28], Rouiller-Fabre et al. [29]

Table 1.
Reported gender-related teratogenic effects in human and rodents.

male conception or survival. Preconception low-dose aspirin increased male live birth (first tertile: 48% male in LDA vs. 52% in placebo, intention-to-treat relative risk (ITT RR) ratio = 0.97, 95% CI: 0.70–1.35; second tertile: 57% male in LDA vs. 43% in placebo, ITT RR = 1.36, 95% CI: 0.98–1.90; third tertile: 53% male in LDA vs. 35% in placebo, ITT RR = 1.70, 95% CI: 1.13–2.57; P interaction = 0.03). Their results suggest that maternal inflammation may be hazardous to the conceptus or survival of male embryos.

Long-term gender differences between males and females exposed to illicit substances during pregnancy were also detected in neurodevelopmental studies. Bennett et al. [22] reported that males prenatally exposed to cocaine, especially if raised in high-risk environments, appeared to be at greater risk for attention and inhibitory control problems, emotional modulation difficulties, health risk behaviors, and antisocial behavior. Similarly, exposed males had mild cognitive deficit manifested by lower IQ scores and more difficulty with abstract/visual reasoning tasks than exposed females [23].

Thanh et al. [24] estimated the prevalence of fetal alcohol syndrome disorder among patients recorded at Alberta provincial health databases. They found that fetal alcohol spectrum disorder (FASD) was more prevalent in young boys than in young girls (on average 12.9 out of 1000 male births compared to 10.4 out of 1000 female births); however, there were no sex difference in the rate of FASD diagnosis when the children were diagnosed later in life.

In contrast, in a prospective, population-based study, Sayal et al. [25] investigated the relationship between maternal self-reports of the amount and frequency of alcohol use during the first trimester of pregnancy and the presence of clinically significant mental health (behavioral and emotional) problems at 4 and 6.5 years (parental report: n = 9086 and 8046, respectively) and at 7.7–9 years (teacher report: n = 5648). They reported an association between low levels of alcohol consumption in the first trimester (1 glass per week) and clinically significant childhood mental health problems, more prevalent in girls. This pattern was replicated with both parent and teacher data collected at two later time points, suggesting that the association persisted into middle childhood.

Sex-dependent neurodevelopmental effect of prenatal alcohol exposure was also described in rodent studies; Kelly et al. [26] exposed rats to ethanol during the prenatal and early postnatal periods. Ethanol exposure during development impaired social recognition memory in a sexually dimorphic manner; male rats showed a deficit in social recognition memory impaired in all variations of the test, while females had deficit only when the task was more challenging. They suggested that the deficit in ethanol-exposed females may be related to changes in oxytocin receptors in the amygdala.

Procarbazine is an alkylating antineoplastic substance used for the treatment of Hodgkin's lymphoma and brain cancers. Malek et al. [27] investigated the sex-related differences of procarbazine teratogenicity treatment in rats exposed to this substance during pregnancy. They reported that procarbazine induced clefts of the secondary palate in 90% of the fetuses. Gender-specific analysis of the results obtained from the fetuses of the procarbazine-exposed group showed that cleft palates were present in all males (100%) but only in 78.5% of female fetuses. Furthermore, micrognathia was observed significantly more frequently in the male fetuses. The authors suggested that these may be attributed to sex-related differences in the critical period for organogenesis.

Another example is the increased risk of oxidative stress-related congenital malformations in male infants of nondiabetic women compared to females [19].

Endocrine disruptors: It is well documented for years that prenatal exposure to endocrine disruptors, especially substances with estrogenic or antiandrogenic

affects, might adversely affect embryonic sex organ development [28, 29]. Indeed, there are many experimental animal studies showing the effects of these agents on the gonads and on the internal and external genitalia. Of special concern are the effects of substances with estrogenic effects on the development of the testes. For example, Lambrot et al. [28] studied the possible effects of phthalates, which are known to reduce testosterone secretion in the fetal rat, on first trimester human fetal testes in culture. They found that mono-2-ethylhexyl phthalate decreased the expression of the mRNA of anti-Mullerian hormone by the Sertoli cells and increased the apoptosis of the germ cells [28]. Later, the same group [29] reported that bisphenol A decreased the production of testosterone in the human fetal testis.

Valproic acid (VPA): Valproic acid is a highly teratogenic anticonvulsant that may also induce autistic-like behavior in human and in rodents. It is therefore used for the experimental induction of autistic-like behavior in mice and rats. Prenatal or early postnatal administration of valproic acid in mice or rats is known to induce neurobehavioral deficits. The affected animals (either offspring of the VPA-treated dams or the animals following early postnatal injection of VPA) will exhibit autistic-like behavioral changes and increased oxidative stress in their brains [30, 31]. We injected 4-day-old mice with 300 mg/kg of VPA and performed neurobehavioral studies during postnatal days 50–60. On day 60 we euthanized the animals and carried out biochemical and molecular studies on the prefrontal cortex. VPA induced changes in the redox potential and gene expression in relation to treatment and gender. VPA-induced oxidative stress was manifested by increased lipid peroxidation and activity of antioxidant enzymes and upregulation of antioxidant gene expression. There were significant differences between males and females, oxidative stress markers being more prominent in females. VPA also induced gender-dependent changes in the expression of many genes related to brain function. In addition there were behavioral changes typical of autistic-like behavior, but female mice were better than males in social behavior while they were poorer in learning [30, 32].

4.2 Sex-associated genetic disorders

Diseases associated with X chromosome, such as fragile X, Duchenne muscular dystrophy, and Rett syndrome, are more common in males than in females due to the X-linked inheritance pattern. Therefore in the last decades, the use of gender selection due to preimplantation genetic diagnosis has been significantly increased. These procedures test the polar bodies of eggs or cells from preimplantation embryos following IVF, to diagnose the sex of the embryo or the specific disorder in those affected and select for implantation those that are not, thus preventing the transmission of X-linked genetic disorders [33]. For example, in a case control study by Ye et al. [34], the authors described preimplantation gender selection of embryos of women whose first child was diagnosed with Duchenne muscular dystrophy. Sex-specific selection of female embryos after in vitro fertilization was developed for prevention of the disease in the patient's future children. However since about 10% of the women carriers for the Duchenne muscular dystrophy gene are symptomatic due to the pattern of X chromosome inactivation, a preimplantation gene analysis by PCR can nowadays allow the birth of normal offspring, both male and female. However, as this can only be done when the mutation is known, it is not feasible for some of the X-linked diseases, in which sexing is still important to prevent morbidity [35].

Nonmedical gender selection is merely performed to satisfy the parent's desire to breed a specific sex. In many countries gender selection of nonmedical purpose is prohibited for ethical reasons.

4.3 Discussion

Teratogens might be gender-specific and might cause lethality or congenital malformations that are dependent on embryonic sex. Possible gender-specific effect of teratogens is not always established because in most studies embryonic and fetal genetic sex is not determined. The paucity of data relating teratogenic effects to gender seems to result from the difficulties in the accurate anatomical assessment of sex in fetuses or newborns.

Indeed, most studies that investigated the teratogenic effects of drugs or teratogenic substances in pregnancy did not look for gender differences. Although gender is sometimes included as a covariate for the statistical analysis, generally, the biological differences between males and females are barely taken as a factor in such analyses. The ability to easily identify fetal sex will allow a better understanding of the possible gender-related effects of teratogens.

As stated above, there are many hereditary diseases that are gender-specific. The importance of sex identification in these cases was described above. These data emphasize that gender, being male or female, is an important factor that can influence both the vulnerability and the adaptive response of the fetus to prenatal teratogenic exposure or, in cases of sex-associated genetic disorders, to enable choosing the normal embryos.

We will therefore describe the existing methods of sex determination including those developed for clinical purposes and those mainly used for research purposes.

5. Methods for sex determination

5.1 Preconception sperm

Evaluation and controlling the sex of the embryo prior to conception by separation of the X and Y sperm may have an uttermost importance for prevention of X-linked diseases. Preselection of the desired sex sperm can reduce the number of animals used in research of diseases that are either gender associated or have different manifestations in each gender. Among humans, it allows the prevention of pregnancies with X-linked diseases. The different methods of sperm selection are based on the difference between the X and the Y chromosomes. The X chromosome is bigger and has increased DNA content than the Y chromosome. Additionally, the X chromosome has a negative charge, while the Y chromosome has a positive charge. The different sperms also have different antigens, and the Y chromosome swims in a straighter path. Methods for sperm separation should be safe and should not affect the chromatin integrity. The methods include flow cytometry, swim up, percoll and albumin gradient centrifugation, sephadex columns, and presence of H-Y antigen (see **Table 2**) [36].

At present, only flow cytometry was proven to effectively sort X and Y sperm. This method can use either fresh or frozen-thawed sperm. The greater amount of DNA in the X sperm allows sperm separation by this method [37]. The X chromosome has 2.8% more DNA than the Y chromosome. When a DNA-specific fluorochrome is used, the absorbed and then emitted light signal band of wavelengths varies according to the DNA content, so that the sperm can be sorted by flow cytometry instrument. Variations in the sperm head size, shape, and number of vacuoles may affect the sorting process. Only motile sperm can be used, and the multiple processing steps decrease the number of sperm available for assisted reproduction [38]. A risk of cytotoxicity by oxidative stress was shown in semen from horses [39]. When boars' semen was evaluated, the fluorescent dye (Hoechst)

	Method	Feasibility	Reference
Human studies			
Preconception sperm separation	Flow cytometry	Safe, about 85% accuracy, higher accuracy when sorting for X than from Y chromosome, can be used to prevent X-linked diseases	Bianco et al. [33], Hendriksen [35], Karabinus et al. [36]
	Sperm motility	Low accuracy, not in use for sex determination	Ericsson et al. [42]
	Gradient and centrifugation	Low accuracy, not in use for sex determination	Pearson et al. [43], Esmaeilpour et al. [44]
Barr bodies	Diagnosis of the inactivated X chromosome by light microscopy	Low accuracy, not in use for sex determination	Miller [46], Sharma et al. [47]
Chromosomal analysis	Karyotype	High accuracy, widely used in utero from amniotic fluid, chorionic villous sampling; postdelivery from blood for genetic evaluation	Gadd [48], Nadler et al. [49], Borrell et al. [50]
Ultrasonography	Ultrasonography	Safe, highly used, cost-effective and accurate	Grande et al. [51], Manzanares et al. [54]
Genetic methods	Sry and the Zfy genes	By FISH or PCR analysis	Cho [61]
	Cell-free DNA in maternal blood	Safe, can be done from 10 weeks gestation, diagnosis by PCR analysis, 98% accuracy	Koumbaris et al. [62], Ordonez et al. [63]
	Amelogenin gene	Based on deletion in intron 1 on chromosome X compared to the Y and analyzed by PCR, commercial kit, easy to use, low accuracy. Used in forensic medicine	Chowdhury et al. [68], von Wurmb-Schwark et al. [69]
	The TriXY method	Amplicons of known X and Y single nucleotide polymorphism (SNP), analyzed by PCR. Can be used in various tissues including hair shafts. High accuracy. Used in forensic medicine	Madel et al. [72]
	Y short tandem repeat (STR)	Y-STR can be used to determine sex by PCR and discriminate between paternal genealogical relationships. Can be used in various tissues, about 90% accuracy, used in forensic medicine	Pilli et al. [70], Delfin [71]
Animal studies			
Preconception sperm separation	Flow cytometry	Safe, a risk of oxidative stress was shown in horses' semen in vitro, about 90% accuracy, used in agriculture with normal offspring	Balao da Silva et al. [37], Spinaci [38] et al., Moore et al. [39], Gonzalez-Marin et al. [40], Tubman et al. [41]
	Immunological sperm sexing	Low accuracy, not in use for sex determination	Yadav et al. [34]
Barr bodies	Diagnosis of the inactivated X chromosome by light microscopy	Low accuracy, not in use for sex determination	Lyon et al. [45]

	Method	Feasibility	Reference
Physical examination	Anogenital distance	Inaccurate, cannot be used during pregnancy, valid in fetuses near term and offspring	Greenham [15], Griffith et al. [52]
	External genitalia score	High accuracy, cannot be used during pregnancy, valid in fetuses near term and offspring	Murdaugh [53]
Ultrasonography	Ultrasonography	Safe, no side effects, successfully used in large animals. Accuracy decreases with litter size	Aurich et al. [55], Quintela [56], Gil [57]
Genetic methods	Multiplex PCR	By two-step PCR analysis, the Sry gene sequence and internal control sequences, high accuracy	Yano [58], Prantner et al. [59], Kunieda et al. [60]
	Simplex PCR	Amplification of homologous genes on the X and Y chromosome that have an intron of different lengths, high accuracy	McFarlane et al. [1], Fontanesi et al. [64], Chuma et al. [65], Clapcote et al. [66], Tunster et al. [67]
	Cell-free DNA in maternal blood	Safe, PCR analysis among horses: 85% accuracy	Aurich et al. [55]

Table 2.
Studies assessing gender in human and animals.

decreased the rate of live spermatozoa; however, the sorting process did not affect the number of live spermatozoa or formed blastocysts [40].

This method is used in order to affect fetal sex among humans [38]. In a large cohort study of 4993 couples, it reached about 87% accuracy when sorting for X sperm and 74% when sorting for Y sperm. Sperm was used in various assisted reproduction methods including intrauterine insemination (IUI), in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), and frozen embryo transfer. Following sperm sorting, the pregnancy rate for female sex was 93.5%, while for male sex the pregnancy rate was 85.3%.

Sperm sorting by flow cytometry technology is commercially used in animals. It was first used in rabbits and now mostly in bovines. Commercially bovine semen is available, and in 2017 this technique was used in 15 countries [41]. The analysis of sorted bovine sperm by the flow cytometry method (SexedULTRA™) by evaluating motility, DNA fragmentation rate, and plasma membrane and acrosome (a body containing enzymes on the sperm head derived from the Golgi apparatus) integrity showed that the semen quality was not affected by the sorting process [42]. The calves produced following flow cytometry selection did not vary from controls in prenatal and postnatal death rate and in anthropometric parameters. None of the offsprings had gross anatomical abnormalities [43]. When used for assisted reproduction in humans, the rate of major congenital anomalies was not statistically indistinguishable from the general population [38].

The progressive sperm motility of the Y sperm was used by Ericsson et al. [44] to divide human sperm according to sex. This method selected a population of spermatozoa that were mainly (85%) but not totally Y sperm. Since the slower fraction contained, beside X sperm, also non-motile and abnormal sperm, it could not be used for X sperm selection.

Immunological sperm sexing method was offered as one of the choices to separate X- and Y-chromosome-bearing sperm. It is based on the development of antibodies to antigens and proteins that are differently expressed between genders. The anti-H-Y antibody was not suitable since it did not preferentially adhere to the

Y sperm. Other proteins differentially expressed between sexes were also found inappropriate due to the low levels of membrane proteins of the sperm [36].

The X and Y sperm can also be separated by the use of albumin gradient [45], the PureSperm centrifugation method, and a combination of both [46]. However none of the methods is valid due to their inaccuracy.

5.2 The Barr body

Based on the Lyon hypothesis, all but one X chromosome is randomly inactivated early in embryogenesis, after implantation. The end result is that, when evaluated, female cells have one Barr body, while the male cell has none. In 1948 Barr et al. proved, first in cats and then in humans, that female and not male cells consist of deeply stained body in the nucleus. Since the correct number of human chromosomes was only found in 1956, this method allowed indirect evidence on the human sex, especially in complicated cases like neonates with ambiguous genitalia. The origin of the Barr body was established by Lyon [47], who claimed that the Barr body is a heteropyknotic material (pyknosis-irreversible condensation of chromatin in the nucleus) originating from the X chromosome that is randomly inactivated and can be from either maternal or paternal origin in the same species.

This method was used to differentiate between female and male embryos and fetuses at the stage when anatomical discrimination is not feasible. Although it also allowed the use of discarded tissues which is especially important in embryos who have limited amount of tissue material, it cannot be trusted. Barr bodies were detected in the amnion and liver cells of rat embryos and fetuses during days 12.5–20.5, in a relatively small proportion of subjects and in both sexes. They were detected in 20–50% in the amnion and 10–51% in the liver of females. Moreover, they were also detected in a very small proportion of males: 0–7% in the amnion and 0–8% in the liver [16].

The Barr body had a tremendous importance when it was discovered, when there were no other ways to assess the sex of animals and humans. This test may be misleading in cases of abnormalities of sex chromosomes like in XO women (Turner) or XXY males (Klinefelter) [48]. This method is no more feasible in clinical research due to its limitations and the discovery of much more accurate methods like chromosomal analysis which is generally one of the simplest and very accurate ways for gender detection.

Lately Barr body became a marker in some malignancies since it was found that Barr body disappearance happens in some malignant cells [49]. The X chromosome has tumor suppressor genes, and the disappearance of the Barr body results in misregulation of the centromere-associated heterochromatin and epigenetic instability.

5.3 Chromosomal analysis

It was developed only in 1956 and became of clinical use slightly later. Chromosomal analysis by light microscopy is feasible during the metaphase of cell division. This discovery allowed the diagnosis of the origin of many of the known syndromes, and when intrauterine chromosomal analysis of fetal origin cells by amniocentesis was established in 1965, prenatal genetic evaluation of the developing fetus was allowed [50, 51]. The understanding of the mammalian genome and the development of more accurate, easily used, and cheap methods for genetic evaluation improved the understanding of diseases. Microarray genetic methods are now commonly used for prenatal evaluation of fetuses [52, 53].

5.4 Physical (anatomical) examination

As described earlier, until the appearance of sexual characteristics, male and female embryos are morphologically indistinguishable [1]. Different methods have been developed, especially in rodents, for accurate sex determination after the appearance of gender-related sexual characteristics.

Farris et al. showed in 1942 that in the newborn rat, sex can be distinguished based on the larger genital papilla of the male and its longer distance from the anus. The female rat did not have nipples up to postnatal days (PND) 8–15. The average anogenital distance (AGD) at PND 1 was 2.8 mm in the male and 1.2 mm in the female [54]. This method, which was found feasible in pups, was also feasible right after delivery. Greenham et al. [15] evaluated the method in albino mice pups on the first 3 days of life. Sex was verified at 3 weeks by visual examination. They found 14.5% sexing error in the females and 1.8% sexing errors in the males. When pups with non-determined AGD (1.6–2.1 mm) were excluded, the mistake rate dropped to 2.1% in females and 6.3% in males. They concluded that accurate sex discrimination cannot be reached at this age group by this method.

Lately Murdaugh et al. [55] offered a method of prenatal sex discrimination in mouse fetuses on 16.5–18 gestational day (GD) based on morphological features of the external genitalia. They based their method on the development of three areas from caudal to rostral: the scrotal/labial swelling, the preputial swelling, and the distal glans. By evaluating the urethral plate which is located between the glans and the base of the tubercle, they found two major criteria: the urethral seam in males or meatus in females (which will later be the vaginal opening) and the shape of the meatus. They found, following verification by PCR of Sry from the tail tissue, that sexing was successful when experienced raters evaluated fixed and unfixed fetuses and also from photographs. The seam vs. meatus at GD 17 was the most accurate method with 96% accuracy. Evaluation of the prepuce attachment to the genital folds (92.5%) and the shape of the area of the ventral midline where the prepuce swellings meet (62%) increased the accuracy to 99.5%. Raters with no experience performed best when evaluating the genital shape (93% accuracy). Full evaluation increased their accuracy rate to 95%. However, morphological sex discrimination does not give 100% accuracy. Although this method can be used while performing an experiment, it is not practical for tissues that were kept for further investigations.

Ultrasonography: Prediction of the fetal sex by ultrasonography is based on the assessment of the external genitalia. Among humans it is safe and cost-effective and was shown lately to be accurate even in the first trimester [56]. It is successfully used in animals including horses [57], cows [58], and other large animals. In multiple pregnancies the method is less accurate. Gil et al. found in canine pregnancy that the accuracy was 100% when there were up to two fetuses but decreased with the litter size [59]. This method is not in use in small animals where there are several fetuses in each litter.

5.5 Genetic methods

Genetic sex determination methods are not related to subjective physical examination, are accurate, require small samples, and do not necessitate the evaluation of a specific tissue, and any organ can be used. Their applicability depends on the specific methods. Successful assays are simple, need small amount of tissue, and are accurate during the entire pregnancy. Measuring the activity of X chromosome-linked enzymes [60] or RNA-based PCRs is complicated by the presence of some gene products only at certain developmental stages [61]. However, this problem is not present when the test is based on DNA (see **Table 2**).

5.6 The Sry and the Zfy genes

The Sry and the Zfy genes are located on the mammalian Y chromosome and were detected by simple PCR analysis in mammalian tissues including preimplantation embryos [62]. Their FISH analysis in gonadal tissue of male and female hermaphrodite patients was in agreement with chromosomal analysis [63]. Since it is characteristic to male gender, it can be used for sex determination.

Lately, molecular analysis of free fetal DNA extracted from maternal plasma became a safe noninvasive approach to fetal sex determination. Fetal cell-free DNA can be found in maternal blood at about 10 week's gestation [64]. The Sry sequence can be detected in the maternal plasma by real-time PCR [65].

However, determining the Y chromosome genes Sry and Zfy may be misleading since female genetic sex is concluded based on the absence of a PCR amplicon. To overcome this, some studies evaluated both genes and/or evaluated autosomal genes as internal control.

Multiplex PCR: Multiplex PCR simultaneously amplifies a Y chromosome gene (e.g., Sry) in combination with an endogenous control gene to confirm that the inability to amplify the Y chromosome gene is a true negative for that gene.

Simplex PCR: Simplex PCR assays for the determination of the genetic sex in mice amplify homologous genes on the X and Y chromosome that have an intron of different lengths. Determination of two primers is complicated; simple PCR using orthologous genes on sex chromosomes which requires only one set of primer is therefore preferential.

To determine the sex of European rabbits and hares, Fontanesi et al. [66] used the simplex PCR. By co-amplification of the orthologous sexual chromosome genes zinc finger protein (ZFX) and Zfy genes, they used the same pair of PCR primers. The method was based on the analysis of a point mutation that differentiates the size of the ZFX and the Zfy genes. They used the hair, muscle, and ear tissue [66].

Chuma and Nakatsuji [67] used the Uba1 and Ube1y1 genes on the X and Y chromosomes, respectively. Primers were designed to cover deleted regions within the Ube1y1 gene, resulting in two amplification products in males, a small and large amplicon, but only the larger product in females [67].

Clapcote and Roder [68] used as an alternative method a single set of primers to amplify the X chromosomal gene Kdm5c (synonyms: Jarid1d, Smcy) and the Y chromosomal gene Kdm5d (synonyms: Jarid1d, Smcy), resulting in two amplicons in the male and one in the female [68] . However, in both cases, the size differences of the amplicons were relatively small, 19 bp for Uba1/Ube1y1 and 29 bp for Kdm5c/Kdm5d resulting in difficulties in accurately determining the sex while assessing the results by gel electrophoresis.

Tunster [69] offered to amplify the two-copy Y-linked Rbm31y and the single-copy X-linked Rbm31x. Their sequence alignment identified a high degree of sequence homology and revealed an 84 bp deletion in Rbm31x compared with Rbm31y. The analysis revealed a 269 and 353 bp products in male samples and only the 269 bp product in female samples [69]. However, since the accurate analysis depends on the difference between one and two products and in the common product there is no size difference, it may sometimes be hard to interpret.

To overcome the small size difference, qPCR with melting point analysis was used by Prantner et al. [61] to determine the sex of mice blastocysts demonstrating that this method, although technically complicated, is accurate in all the stages of the pregnancy since DNA, which does not change during the pregnancy, was evaluated. They used the primer pair previously used by Chuma and Nakatsuji [67] that amplified the portion of the X chromosome gene Kdm5c (synonyms: Jarid1c, Smcx)

and the corresponding Y chromosome gene Kdm5d (synonyms: Jarid1d, Smcy). The different sizes of the fragments (X 331 bp, Y 302 bp) resulted in distinguishable melting curves of the qPCR product. Following temperature increment of the PCR product, the dsDNA was denaturized, resulting in two melting points in the male and one in the female [61].

A single PCR probe of the pseudoautosomal genes Xlr and Sly was offered by McFarlane et al. [1] for sex determination with the advantage of a larger difference of 405 bases between genders. This method uses lysate, does not need DNA purification [1], and can be carried out in any laboratory that is equipped for basic molecular studies. The accuracy of the method was proven in tail tissue among different adult mouse strains.

By using the method published by McFarlane et al., we evaluated liver tissue that was collected from newborns of the outbred ICR CD1 mice. The method was verified by evaluating liver tissue from 60-day-old male and female mice with known sex. To further verify the offspring male genetic sex, we also determined the Zfy gene by PCR analysis.

The genetic sex was accurately determined in all the adult mice by Sly/Xlr genes and in 91% by Zfy gene (**Figure 1**). In the genomic DNA samples from the newborn mice, the sex was identified easily by both Sly/Xlr and Zfy in most samples. However, Sly/Xlr (97.5%) appeared slightly superior to the Zfy (94.9%) gene. In about 7% of the samples, we could not assess the sex from Sly/Xlr or Zfy after the first run and had to repeat the analysis. This allowed accurate determination of the genetic sex from both genes in all samples, except one where the DNA was inappropriate for study. Hence, the method described by McFarlane et al. [1] for sexing mice by PCR using a single primer pair for both sexes (Sly/Xlr) seems simple and accurate, as the differentiation between genders is determined by a size difference between the amplicons. If the data is not clear in the first PCR, then a second PCR will enable accuracy of almost 100% of the cases. Hence, there seems to be no need to carry out concomitant studies on the Zfy gene (see **Figures 1** and **2**). It should be noted that other investigators have also shown that this method can also be applied to younger fetuses and embryos and to any tissue.

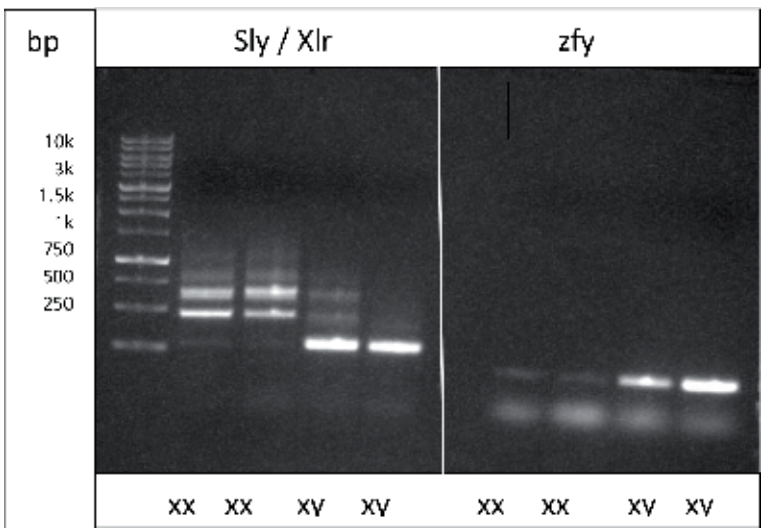

Figure 1.
Mice sex determination using Sly/Xlr and Zfy genes. PCR sex determination results. Sly/Xlr: 280 bp product in males, 685 bp and approximately 480 and 660 bp products in females. Zfy: clear product in males, almost no visible DNA product in females.

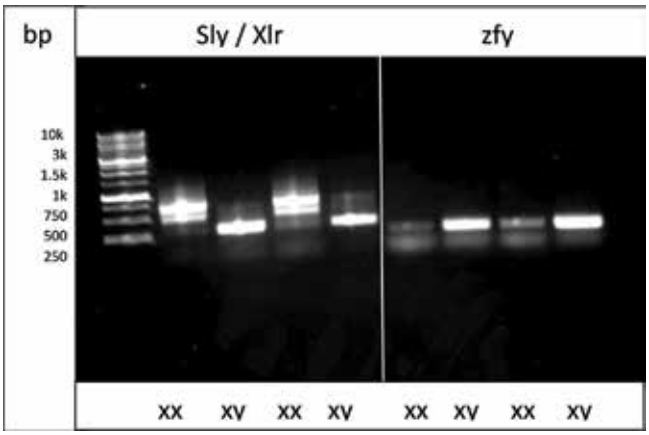

Figure 2.
Determination of the sex of newborn mice using Sly/Xlr and Zfy genes PCR sex determination results. Sly/Xlr: 280 bp product in males, 685 bp and approximately 480 and 660 bp products in females. Zfy: clear product in males, almost no visible DNA product in females.

5.7 Sex analysis in forensic medicine

The amelogenin gene which is found on both X and Y chromosomes is in common use for sex discrimination in forensic medicine. A 6 bp deletion in intron 1 on chromosome X compared to the Y chromosome can be detected by using a pair of PCR primers. It can be used in various tissues including long-lasting remnant tissues like dental pulp [70]. However, mutations and deletions in the amelogenin Y were reported to result in amplification failure. Additionally low DNA quality and quantity necessitated alternative molecular genetic assays [71].

DNA can be recovered from highly degraded tissues as happens in archeology or forensic medicine. The petrous bone was found suitable for short tandem repeat (STR) typing via electrophoresis. This method compares DNA loci from multiple samples. The probes that attach to special areas on the DNA measure the number of repeats of a special unit whose length can be detected by PCR analysis. The difference in autosomal repeated units can be used to discriminate between related and unrelated people, while Y-STR can be used to determine sex, and discriminate between paternal genealogical relationships [72]. Y-STR was used to differentiate between the assailant and victim in males and for proving male sexual harassment in females. Even small samples of vaginal and rectal swabs up to 72 hours post the insult were suitable for evaluation. This method can also prove multiple assailants and be used for matching with a reference sample [73].

The TriXY-Homogeneous genetic sexing [74] is another method that can use ancient DNA specimens from archeological excavations and hair shafts. This method uses three amplicons of known X and Y single nucleotide polymorphism (SNP) markers: one on the X chromosome and two on the Y chromosome detected by PCR. The different melting temperatures of the PCR products were used to discriminate between sexes.

5.8 Discussion

An ideal method for sex identification would be accurate, simple, and cheap, enabling its use in most laboratories. In addition, it should also be able as much as possible to be used for all animals as well as tissues and/or cells. We have described all available methods currently used for the identification of sex. It seems that the

most reliable and accurate methods are the determination of chromosomes and molecular determination of genes related to the sex chromosomes and/or gender.

For chromosomal analysis, we need viable cells that are able to divide, and if this is not possible, these methods cannot be used. On the other hand, genetic methods are reliable and do not need living cells, and it is easy to obtain DNA for these studies even in very ancient and nonviable tissues. These methods are therefore the most accepted ones.

As stated above, there are many methods for the genetic sex determination of tissues, generally using genes that are on the X or Y chromosome. Each of these methods has its advantages and disadvantages. Of all methods, the method described by McFarlane et al. [1] using the Sly/Xlr genes seems to be the simplest and most accurate one. As reported above, we used this method for the successful identification of sex in newborn mice and found it superior to the method using the detection of the male gene Zfy. Hence, this method can be used on embryonic and fetal tissues as well as isolated DNA obtained from any tissue.

6. Conclusions

Reliable and easy to perform sex determination methods are important for many medical and biological reasons, especially in situations where the physical examination is unable to be accurate. Hence, many methods have been developed to serve the purpose of accurate sex determination. In this chapter we described the main needs for the accurate sex determination and the methods that can be used. We should note that today there are many biological processes that are gender-dependent, but many of these gender-specific processes are still unknown, especially in teratology. A better understanding of these gender-related effects will enable us to find more appropriate ways for treatment and even for prevention.

Acknowledgements

This review was funded by the Irving Harris Foundation, Chicago, USA.

Conflict of interest

No potential conflict of interest is reported by the authors.

Author details

Asher Ornoy*, Liza Weinstein-Fudim and Zivanit Ergaz
Laboratory of Teratology, Department of Medical Neurobiology Canada Israel Medical Research Institute, Hebrew University Hadassah Medical School, Jerusalem, Israel

*Address all correspondence to: ornoy@cc.huji.ac.il

References

[1] McFarlane L, Truong V, Palmer JS, Wilhelm D. Novel PCR assay for determining the genetic sex of mice. Sexual Development. 2013;**7**(4):207-211

[2] Biason-Lauber A. Human sex development: From basic science to clinical practice and Back. Pediatric Endocrinology Reviews. 2017;**15**(1):8-20

[3] Gondos B. Development of the reproductive organs. Annals of Clinical and Laboratory Science. 1985;**15**(5):363-373

[4] Murashima A, Kishigami S, Thomson A, Yamada G. Androgens and mammalian male reproductive tract development. Biochimica et Biophysica Acta. 2015;**1849**(2):163-170

[5] Eid W, Biason-Lauber A. Why boys will be boys and girls will be girls: Human sex development and its defects. Birth Defects Research Part C, Embryo Today. 2016;**108**(4):365-379

[6] Rey RA, Grinspon RP. Normal male sexual differentiation and aetiology of disorders of sex development. Best Practice & Research Clinical Endocrinology & Metabolism. 2011;**25**(2):221-238

[7] Josso N, Rey R, Picard JY. Testicular anti-Mullerian hormone: Clinical applications in DSD. Seminars in Reproductive Medicine. 2012;**30**(5):364-373

[8] Mollgard K, Jespersen A, Lutterodt MC, Yding Andersen C, Hoyer PE, Byskov AG. Human primordial germ cells migrate along nerve fibers and Schwann cells from the dorsal hind gut mesentery to the gonadal ridge. Molecular Human Reproduction. 2010;**16**(9):621-631

[9] Mamsen LS, Brochner CB, Byskov AG, Mollgard K. The migration and loss of human primordial germ stem cells from the hind gut epithelium towards the gonadal ridge. The International Journal of Developmental Biology. 2012;**56**(10-12):771-778

[10] Biason-Lauber A. Control of sex development. Best Practice & Research Clinical Endocrinology & Metabolism. 2010;**24**(2):163-186

[11] Blaschko SD, Cunha GR, Baskin LS. Molecular mechanisms of external genitalia development. Differentiation. 2012;**84**(3):261-268

[12] Yamada G, Suzuki K, Haraguchi R, Miyagawa S, Satoh Y, Kamimura M, et al. Molecular genetic cascades for external genitalia formation: An emerging organogenesis program. Developmental Dynamics. 2006;**235**(7):1738-1752

[13] Wilson JD, Rivarola MA, Mendonca BB, Warne GL, Josso N, Drop SL, et al. Advice on the management of ambiguous genitalia to a young endocrinologist from experienced clinicians. Seminars in Reproductive Medicine. 2012;**30**(5):339-350

[14] Hrovatin K, Kunej T. Genetic sex determination assays in 53 mammalian species: Literature analysis and guidelines for reporting standardization. Ecology and Evolution. 2018;**8**(2):1009-1018

[15] Greenham LW, Greenham V. Sexing mouse pups. Laboratory Animals. 1977;**11**(3):181-184

[16] Kajii T, Farias E, Gardner LI. Sex chromatin in embryonic rat liver. Experimental Cell Research. 1968;**50**(2):435-440

[17] Schwartz Z, Soskolne WA, Neubauer T, Goldstein M, Adi S, Ornoy A. Direct and sex-specific

enhancement of bone formation and calcification by sex steroids in fetal mice long bone in vitro (biochemical and morphometric study). Endocrinology. 1991;**129**(3):1167-1174

[18] Schwartz Z, Nasatzky E, Ornoy A, Brooks BP, Soskolne WA, Boyan BD. Gender-specific, maturation-dependent effects of testosterone on chondrocytes in culture. Endocrinology. 1994;**134**(4):1640-1647

[19] Bahado-Singh RO, Schenone M, Cordoba M, Shieh WS, Maulik D, Kruger M, et al. Male gender significantly increases risk of oxidative stress related congenital anomalies in the non-diabetic population. The Journal of Maternal-Fetal & Neonatal Medicine. 2011;**24**(5):687-691

[20] Martelli DR, Coletta RD, Oliveira EA, Swerts MS, Rodrigues LA, Oliveira MC, et al. Association between maternal smoking, gender, and cleft lip and palate. Brazilian Journal of Otorhinolaryngology. 2015;**81**(5):514-519

[21] Radin RG, Mumford SL, Silver RM, Lesher LL, Galai N, Faraggi D, et al. Sex ratio following preconception low-dose aspirin in women with prior pregnancy loss. The Journal of Clinical Investigation. 2015;**125**(9):3619-3626

[22] Bennett DS, Bendersky M, Lewis M. Children's intellectual and emotional-behavioral adjustment at 4 years as a function of cocaine exposure, maternal characteristics, and environmental risk. Developmental Psychology. 2002;**38**(5):648-658

[23] Bennett DS, Bendersky M, Lewis M. Children's cognitive ability from 4 to 9 years old as a function of prenatal cocaine exposure, environmental risk, and maternal verbal intelligence. Developmental Psychology. 2008;**44**(4):919-928

[24] Thanh NX, Jonsson E, Salmon A, Sebastianski M. Incidence and prevalence of fetal alcohol spectrum disorder by sex and age group in Alberta, Canada. Journal of Population Therapeutics and Clinical Pharmacology. 2014;**21**(3):e395-e404

[25] Sayal K, Heron J, Golding J, Emond A. Prenatal alcohol exposure and gender differences in childhood mental health problems: A longitudinal population-based study. Pediatrics. 2007;**119**(2):e426-e434

[26] Kelly SJ, Leggett DC, Cronise K. Sexually dimorphic effects of alcohol exposure during development on the processing of social cues. Alcohol and Alcoholism. 2009;**44**(6):555-560

[27] Malek FA, Moritz KU, Fanghanel J, Bienengraber V. Sex-related differences in procarbazine-induced cleft palate and microgenia and the anti-teratogenic effect of prenatal folic acid supplementation in rats. Annals of Anatomy. 2003;**185**(5):465-470

[28] Lambrot R, Muczynski V, Lecureuil C, Angenard G, Coffigny H, Pairault C, et al. Phthalates impair germ cell development in the human fetal testis in vitro without change in testosterone production. Environmental Health Perspectives. 2009;**117**(1):32-37

[29] Rouiller-Fabre V, Habert R, Livera G. Effects of endocrine disruptors on the human fetal testis. Annales d'endocrinologie. 2014;**75**(2):54-57

[30] Ornoy A, Weinstein-Fudim L, Tfilin M, Ergaz Z, Yanai J, Szyf M, et al. S-Adenosyl methionine prevents ASD like behaviors triggered by early postnatal valproic acid exposure in very young mice. Neurotoxicology and Teratology. 2019;**71**:64-74

[31] Rodier PM, Ingram JL, Tisdale B, Nelson S, Romano J. Embryological origin for autism: Developmental

anomalies of the cranial nerve motor nuclei. The Journal of Comparative Neurology. 1996;**370**(2):247-261

[32] Ornoy A, Weistein-Fudim L, Ergaz Z, Yanai J, Turgeman G. Gender differences in the expression of nervous system genes in a mouse model of valproic acid-induced autism-like behavior is corrected by S-adenosyl methionine. Birth Defects Research. 2018;**11**:791

[33] Ravitsky V, Nguyen MT, Birko S, Kleiderman E, Laberge AM, Knoppers BM. Pre-implantation genetic diagnosis: The road forward in Canada. Journal of Obstetrics and Gynaecology Canada. 2019;**41**(1):68-71

[34] Ye Y, Yu P, Yong J, Zhang T, Wei X, Qi M, et al. Preimplantational genetic diagnosis and mutation detection in a family with duplication mutation of DMD gene. Gynecologic and Obstetric Investigation. 2014;**78**(4):272-278

[35] Bianco B, Christofolini DM, Conceicao GS, Barbosa CP. Preimplantation genetic diagnosis associated to Duchenne muscular dystrophy. Einstein. 2017;**15**(4):489-491

[36] Yadav SK, Gangwar DK, Singh J, Tikadar CK, Khanna VV, Saini S, et al. An immunological approach of sperm sexing and different methods for identification of X- and Y-chromosome bearing sperm. Veterinary World. 2017;**10**(5):498-504

[37] Hendriksen PJ. Do X and Y spermatozoa differ in proteins? Theriogenology. 1999;**52**(8):1295-1307

[38] Karabinus DS, Marazzo DP, Stern HJ, Potter DA, Opanga CI, Cole ML, et al. The effectiveness of flow cytometric sorting of human sperm (MicroSort(R)) for influencing a child's sex. Reproductive Biology and Endocrinology. 2014;**12**:106

[39] Balao da Silva CM, Ortega-Ferrusola C, Morrell JM, Rodriguez Martinez H, Pena FJ. Flow cytometric chromosomal sex sorting of stallion spermatozoa induces oxidative stress on mitochondria and genomic DNA. Reproduction in Domestic Animals. 2016;**51**(1):18-25

[40] Spinaci M, De Ambrogi M, Volpe S, Penazzi P, Galeati G, Seren E. Assessment of some morphofunctional characteristics of flow-cytometrically sorted and stained boar spermatozoa. Veterinary Research Communications. 2005;**29**(Suppl 2): 207-209

[41] Moore SG, Hasler JF. A 100-year review: Reproductive technologies in dairy science. Journal of Dairy Science. 2017;**100**(12):10314-10331

[42] Gonzalez-Marin C, Gongora CE, Gilligan TB, Evans KM, Moreno JF, Vishwanath R. In vitro sperm quality and DNA integrity of SexedULTRA™ sex-sorted sperm compared to non-sorted bovine sperm. Theriogenology. 2018;**114**:40-45

[43] Tubman LM, Brink Z, Suh TK, Seidel GE Jr. Characteristics of calves produced with sperm sexed by flow cytometry/cell sorting. Journal of Animal Science. 2004;**82**(4):1029-1036

[44] Ericsson RJ, Langevin CN, Nishino M. Isolation of fractions rich in human Y sperm. Nature. 1973;**246**(5433):421-424

[45] Pearson PL, Bobrow M, Vosa CG. Technique for identifying Y chromosomes in human interphase nuclei. Nature. 1970;**226**(5240):78-80

[46] Esmaeilpour T, Elyasi L, Bahmanpour S, Ghannadi A, Monabbati A, Dehghani F, et al. Effect of combined density gradient centrifugation on X- and Y- sperm separation and chromatin integrity. Iranian Journal of Reproductive Medicine. 2012;**10**(5):435-440

[47] Lyon MF. Gene action in the X-chromosome of the mouse (*Mus musculus* L.). Nature. 1961;**190**:372-373

[48] Miller FA. Your true and proper gender: The Barr body as a good enough science of sex. Studies in History and Philosophy of Biological and Biomedical Sciences. 2006;**37**(3):459-483

[49] Sharma D, Koshy G, Gupta S, Sharma B, Grover S. Deciphering the role of the Barr body in malignancy: An insight into head and neck cancer. Sultan Qaboos University Medical Journal. 2017;**17**(4):e389-ee97

[50] Gadd RL. The volume of the liquor amnii. Proceedings of the Royal Society of Medicine. 1966;**59**(11 Part 1):1131-1133

[51] Nadler HL, Gerbie AB. Role of amniocentesis in the intrauterine detection of genetic disorders. The New England Journal of Medicine. 1970;**282**(11):596-599

[52] Borrell A, Grande M, Pauta M, Rodriguez-Revenga L, Figueras F. Chromosomal microarray analysis in fetuses with growth restriction and normal karyotype: A systematic review and meta-analysis. Fetal Diagnosis and Therapy. 2018;**44**(1):1-9

[53] Grande M, Jansen FA, Blumenfeld YJ, Fisher A, Odibo AO, Haak MC, et al. Genomic microarray in fetuses with increased nuchal translucency and normal karyotype: A systematic review and meta-analysis. Ultrasound in Obstetrics & Gynecology. 2015;**46**(6):650-658

[54] Griffith JQ, Farris EJ. The Rat in Laboratory Investigation. Philadelphia: JB Lippincott Company; 1942

[55] Murdaugh LB, Mendoza-Romero HN, Fish EW, Parnell SE. A novel method for determining sex in late term gestational mice based on the external genitalia. PLoS One. 2018;**13**(4):e0194767

[56] Manzanares S, Benitez A, Naveiro-Fuentes M, Lopez-Criado MS, Sanchez-Gila M. Accuracy of fetal sex determination on ultrasound examination in the first trimester of pregnancy. Journal of Clinical Ultrasound. 2016;**44**(5):272-277

[57] Aurich C, Schneider J. Sex determination in horses-current status and future perspectives. Animal Reproduction Science. 2014;**146**(1-2):34-41

[58] Quintela LA, Becerra JJ, Perez-Marin CC, Barrio M, Cainzos J, Prieto A, et al. Fetal gender determination by first-trimester ultrasound in dairy cows under routine herd management in Northwest Spain. Animal Reproduction Science. 2011;**125**(1-4):13-19

[59] Gil EM, Garcia DA, Giannico AT, Froes TR. Use of B-mode ultrasonography for fetal sex determination in dogs. Theriogenology. 2015;**84**(6):875-879

[60] Yano T. Sexing of in vitro-fertilized preimplantation mouse embryos by the PCR method. The Japanese Journal of Human Genetics. 1993;**38**(3):277-288

[61] Prantner AM, Ord T, Medvedev S, Gerton GL. High-throughput sexing of mouse blastocysts by real-time PCR using dissociation curves. Molecular Reproduction and Development. 2016;**83**(1):6-7

[62] Kunieda T, Xian M, Kobayashi E, Imamichi T, Moriwaki K, Toyoda Y. Sexing of mouse preimplantation embryos by detection of Y chromosome-specific sequences using polymerase chain reaction. Biology of Reproduction. 1992;**46**(4):692-697

[63] Cho NH, Han SW, Ha MJ. Sry gene detection in gonads of intersex patients

using FISH. Journal of Korean Medical Science. 1997;**12**(3):204-209

[64] Koumbaris G, Kypri E, Tsangaras K, Achilleos A, Mina P, Neofytou M, et al. Cell-free DNA analysis of targeted genomic regions in maternal plasma for non-invasive prenatal testing of trisomy 21, trisomy 18, trisomy 13, and fetal sex. Clinical Chemistry. 2016;**62**(6):848-855

[65] Ordonez E, Rueda L, Canadas MP, Fuster C, Cirigliano V. Evaluation of sample stability and automated DNA extraction for fetal sex determination using cell-free fetal DNA in maternal plasma. BioMed Research International. 2013;**2013**:195363

[66] Fontanesi L, Tazzoli M, Pecchioli E, Hauffe HC, Robinson TJ, Russo V. Sexing European rabbits (*Oryctolagus cuniculus*), European brown hares (*Lepus europaeus*) and mountain hares (*Lepus timidus*) with ZFX and ZFY loci. Molecular Ecology Resources. 2008;**8**(6):1294-1296

[67] Chuma S, Nakatsuji N. Autonomous transition into meiosis of mouse fetal germ cells in vitro and its inhibition by gp130-mediated signaling. Developmental Biology. 2001;**229**(2):468-479

[68] Clapcote SJ, Roder JC. Simplex PCR assay for sex determination in mice. BioTechniques. 2005;**33**(5). 702, 704, 706 p

[69] Tunster SJ. Genetic sex determination of mice by simplex PCR. Biology of Sex Differences. 2017;**8**(1):31

[70] Chowdhury RM, Singhvi A, Bagul N, Bhatia S, Singh G, Goswami S. Sex determination by amplification of amelogenin gene from dental pulp tissue by polymerase chain reaction. Indian Journal of Dental Research. 2018;**29**(4):470-476

[71] von Wurmb-Schwark N, Bosinski H, Ritz-Timme S. What do the X and Y chromosomes tell us about sex and gender in forensic case analysis? Journal of Forensic and Legal Medicine. 2007;**14**(1):27-30

[72] Pilli E, Vai S, Caruso MG, D'Errico G, Berti A, Caramelli D. Neither femur nor tooth: Petrous bone for identifying archaeological bone samples via forensic approach. Forensic Science International. 2018;**283**:144-149

[73] Delfin FC, Madrid BJ, Tan MP, De Ungria MC. Y-STR analysis for detection and objective confirmation of child sexual abuse. International Journal of Legal Medicine. 2005;**119**(3):158-163

[74] Madel MB, Niederstatter H, Parson W. TriXY-homogeneous genetic sexing of highly degraded forensic samples including hair shafts. Forensic Science International Genetics. 2016;**25**:166-174

Chapter 2

Influences the Aeromath in the Way of Ending Births

Radim J. Sram, Milos Veleminsky, Jr and Milos Veleminsky

Abstract

Air pollution represents a significant health problem in the Czech Republic (CR). Originally, the most polluted region was Northern Bohemia, later Northern Moravia. These specific conditions were used to study the impact of air pollution to children in those two regions. In Northern Bohemia, the impact of the increased concentrations of carcinogenic polycyclic aromatic hydrocarbons (c-PAHs) to fetal growth was observed, expressed as intrauterine growth retardation and impact of air pollution to respiratory morbidity and neurodevelopment in children. In Northern Moravia was studied the effect of air pollution to the morbidity of preschool children; to asthma bronchiale—gene expression, children susceptibility to benzo[a]pyrene (B[a]P); to genetic damage in newborns; concentrations of PAHs in the urine of mothers and newborns, content of PAHs in human breast milk and diet.

Keywords: air pollution, polycyclic aromatic hydrocarbons, pregnancy outcome, respiratory morbidity, neurodevelopment, genetic damage, oxidative stress

1. Introduction

Health impact of air pollution to children was studied in heavily polluted parts of the Czech Republic during the last 30 years. The research program analyzed these effects in the region of Northern Bohemia, later in Northern Moravia, using Southern Bohemia as the control region.

It is generally accepted that exposure to air pollution has negative effects on human health, increasing risk of mortality and morbidity from respiratory and cardiovascular diseases [1]. WHO [2] recognized air pollution and particulate matter (PM) in polluted air as a proven human carcinogen. Another human carcinogen in the polluted air is benzo[a]pyrene (B[a]P) from polycyclic aromatic hydrocarbons (PAHs) [3]. According to WHO, air polluted by B[a]P concentrations higher than 1.0 ng/m^3 induces DNA damage [4]. Study on city policemen exposed personally to B[a]P over 1.0 ng/m^3 proved increased genomic frequency of translocations [5], micronuclei [6], and DNA fragmentation in sperm [7].

2. Northern Bohemia

The Northern Bohemia brown coal basin comprises four mining districts located in the northwestern region of the Czech Republic (CR) (**Figure 1**). The coal in this region contains usually 1–3% of sulfur and is surface-mined from open-pits. It has

Figure 1.
Map of the Czech Republic with the locations of molecular epidemiology studies.

been used especially for coal-fired power plants and local heating. The combustion of this coal together with the heavy industrialization made this region in previous decades one of the most polluted regions in Europe (called together with a similar pollution on the other side of the border with Germany and Poland "Black Triangle") [8].

Exploratory analysis of the health consequences of environmental pollution in this region prior 1989 suggested shorter life expectancy for males and females (2 years vs. CR), increased frequency of congenital anomalies (5.5–7 vs. 2% in CR), increased frequency of newborns with lower birth weight (<2500 g, 8–9 vs. 4.5% in CR), and increased respiratory morbidity in preschool children (2.90 vs. 0.54 in CR, number of cases/100 children) [9, 10].

After major political changes in the Czechoslovakia in November 1989, a new research program, the Teplice Program, was developed to evaluate the short-term and long-term health impact of air pollution on population. As a model district, the mining district of Teplice was selected, and as a control district, the district of Prachatice in Southern Bohemia was selected with some of the cleanest air in the Czech Republic. The Teplice district had 127,500 inhabitants and an area of 469 km^2, and a large part of the area has been devastated by the strip mining of coal and associated industrialization. District of Prachatice had 51,500 inhabitants and an area of 1375 km^2, and 52% of it is covered by forests. For example, in 1993, the average PM10 (<10 μm) concentrations in Teplice were 76 vs. 38 $\mu g/m^3$, and in Prachatice, PM2.5 concentrations were 64 vs. 32 $\mu g/m^3$ and B[a]P was 3.7 vs. 2.5 ng/m^3, respectively [11].

The Teplice Program was initiated by the Czech Ministry of Environment in 1990, and the research program was prepared in collaboration with US Environmental Protection Agency (US EPA) [12].

2.1 Pregnancy outcome

Initially, a relationship between PM and fetal growth was observed by analyzing data collected during the first 2 years of this study in the highly polluted district of Teplice [13]. When mothers were exposed to PM10 levels >40 $\mu g/m^3$ or PM2.5 >37 $\mu g/m^3$ during the first month of gestation, increased risk of intrauterine growth retardation (IUGR) was observed in their children. For each 10 $\mu g/m^3$ increase

in PM10, the adjusted odds ratio (AOR) of IUGR was 1.25 (95% CI, 1.08–1.56); a similar but weaker association was also observed for PM2.5. This was the first study indicating that exposure to PM10 and PM2.5 affects the fetal growth already in the first months of gestation. But similar association for the risk of IUGR and exposure to sulfur dioxide, nitrous oxides, or ozone was not observed.

Dejmek et al. [14] examined the impact of PM10, PM2.5, and PAHs on IUGR in all single births that occurred in the Teplice and Prachatice districts during the 4-year period from April 1994 through March 1998, which included 3349 pregnancies in the Teplice cohort and 1505 pregnancies in the Prachatice cohort. Compared with exposure to the mean PM10 of <40 μg/m^3 during the first month of gestation, the AOR was 1.44 (95% CI, 1.03–2.02) for the medium-exposure group (PM10 40–<50 μg/m^3) and 2.14 (95% CI, 1.42–3.23) for PM10 of ≥50 μg/m^3. Using a continuous exposure, the AOR of IUGR was 1.19 (CI, 1.06–1.33) per 10 μg/m^3 increase of PM10 in the first gestational month. Dejmek et al. [14] further analyzed in both districts the association between carcinogenic PAHs and IUGR. In the district of Teplice, a significant increase of IUGR was observed related to exposures of carcinogenic PAHs (c-PAHs) (benz[*a*]anthracene, benzo[*b*]fluoranthene, benzo[*k*]fluoranthene, benzo[*g*,*h*,*i*]perylene, benzo[*a*]pyrene (B[a]P), chrysene, dibenz[*a*,*h*]anthracene, and indeno[1,2,3-*c*,*d*]pyrene) above 15 ng/m^3, which corresponds to 2.8 ng/m^3 of B[a]P. Similarly as with PM10 and PM2.5, the effect was specific for the first gestational month. Using a continuous measure of exposure, a 10 ng/m^3 increase in c-PAH level was associated with an AOR of 1.22 (95% CI, 1.07–1.39). The association between c-PAHs and IUGR was also observed in Prachatice, where such effect was not seen for PM10. Again, the only consistent association between c-PAHs and IUGR was observed in the first gestational month.

The results by Dejmek et al. [13, 14] suggest that the first month was the most sensitive period for the effect of air pollutants. Data by Dejmek et al. [14] imply a critical role of PAHs. It is possible that c-PAHs are responsible for the biologic activity of complex mixtures adsorbed to respirable air particles that can result in IUGR.

The results by Dejmek et al. [14] support the hypothesis that the increased IUGR risk is related to c-PAHs. Based on this hypothesis, the association of particles with IUGR risk in Teplice is related to the high correlation of c-PAHs and PM in this area [14]. This finding is consistent with the idea of a primary role for c-PAHs in fetal growth modulation.

Support for the role of PAH in reproductive effects is the findings from many of the biomarker studies [15]. PAH-DNA adduct levels in placentas of nonsmoking mothers were associated with exposure to c-PAHs, and DNA adducts in placentas of IUGR infants were significantly increased [15].

Thus, the first gestational month seems to be the critical period for the association of pollution with fetal growth. The timing of this association is in agreement with the current hypothesis that IUGR pathogenesis is triggered by an abnormal reaction between trophoblast and uterine tissues in the first week of pregnancy [16]. Fine particles and c-PAH levels were associated with IUGR risk. Reduced fetal growth is an important predictor of neonatal morbidity and mortality. Barker [17] showed a relationship between some serious adult risks (viz., non-insulin-dependent diabetes, hypertension, and coronary heart disease) and impaired growth in the prenatal and early postnatal period. He implied that higher exposure to pollutants during the early stages of intrauterine life may be responsible for diseases in the middle age.

2.2 Respiratory morbidity

Stratified random sample of 1492 mother-infant pairs from the "Pregnancy Outcome Study" was recruited to "Immune Biomarker Study," and samples of

maternal and cord blood were collected at delivery. Later, these children were contacted by pediatric nurses for follow-up at the age of 3 and 4.5 years. Pediatricians and pediatric nurses administered the questionnaires to the family and abstracted the children's medical records. In 2005 the medical records of these children up to the age of 6 years were abstracted; the study continued with 1007 children. The study continued each year until the children born in 1998 reached the age of 10 years. The data covering the period from birth to 10 years were available for 960 children, i.e., 245 boys and 269 girls in the Teplice district and 227 boys and 219 girls in the Prachatice district. Respiratory infections were reported using International Codes of Diseases -10 (ICD-10 codes) [18].

Morbidity differed between children from Teplice town, Teplice district, and Prachatice. Comparing Teplice town vs. Prachatice, at the age 0–2 years, in the Teplice town, incidence of laryngitis, tracheitis, influenza, pneumonia, and otitis media was higher; at the age 2–6 years, laryngitis, tracheitis, and influenza; and at the age 6–10 years, laryngitis, tracheitis, and influenza. Similar differences in the respiratory morbidity were observed between Teplice town and Teplice district for laryngitis, tracheitis, and influenza at the age 0–6 years and bronchitis, laryngitis, tracheitis, and influenza at the age 6–10 years. The prevalence of allergies at the age of 6 years diagnosed as wheezing was higher in the Teplice district (OR 2.0, 95% CI 1.1–3.4), but allergic rhinitis was higher in the Prachatice district (OR 2.7, 95% CI 1.7–4.2) [18].

When this cohort (N = 1105) was followed at the age of 3 years for the impact of air pollution to the children height, indoor coal use was associated with reduced height at age 36 months, adjusted for anthropometric and sociodemographic factors: 1.34 cm for boys and 1.30 for girls [19]. Baker et al. [20] studied in this subcohort (N = 452) incidence of lower respiratory illness (LRI). Maternal prenatal smoking and coal home heating increased significantly the risk for LRI in the first 3 years (RR = 2.77 (95% CI, 1.45–5.37) and RR = 2.52 (95% CI, 1.31–4.85), respectively).

2.3 Neurobehavioral studies

In the mining districts of Northern Bohemia, the first studies on a possible impact of air pollution to children's neurodevelopment started. Symptoms of minimal brain dysfunction (MBD) were analyzed in 5080 children in the second class from the districts of Usti nad Labem, Teplice, and Jablonec nad Nisou. Examination implied increased disturbance of intellect as well as behavioral changes [21]. From polluted districts, 4.8% of children visited special schools, and 10% of children in normal schools were diagnosed with MBD symptoms. Therefore, it may be postulated that the children living in this polluted region are at greater risk for learning disorders than other children in the Czech Republic. Sram [10] hypothesized that in utero exposure to environmental chemicals causes functional changes in the nervous system expressed as developmental disorders or other behavioral dysfunctions. This idea was later confirmed by studies from the USA, Poland, China, and Spain [22]. According to the Czech Statistical Institute [10], in 1988 mental illness was diagnosed in children of age 7–15 years in 4.09% in mining districts vs. 2% in the Czech Republic.

Neurobehavioral functions were assessed using neurobehavioral evaluation system (NES2, computerized assessment battery) [23] in 2nd-, 4th- and 8th-grade students from Teplice and Prachatice (2nd-grade cohort N = 772, 4th-grade cohort N = 322, 7th-grade cohort N = 470 children). Teachers reported that significantly more 2nd-grade children from Teplice (26.6%) than from Prachatice (12.9%) had been referred for clinical assessment of learning and behavioral problems. Similar

results were observed in the 4th-grade children, 27.3% from Teplice and 13.0% from Prachatice, as well as in 7th-grade children, 25.6% from Teplice and 13.1% from Prachatice. Those neurobehavioral studies really indicate poorer performance on neurobehavioral tests and high prevalence of learning disabilities in children from the air polluted mining district [24].

3. Northern Moravia

The Moravian-Silesian Region (MSR) is a heavily populated, industrial area situated in the easternmost part of the Czech Republic, covering 5428 km^2 with 1.21 million inhabitants [25]. Since the second half of the eighteenth century, the region has been characterized by coal mining, the processing of coal, and metallurgy. Currently, the most important industries are metallurgy, steel and coke production, coal mining, and power generation.

The MSR population is exposed to high concentrations of PM2.5 which exceed the EU standard of 25 μg/m^3/year. Similarly, the concentrations of B[a]P in the MSR are several times higher than the EU standard of 1 ng/m^3/year. In the district of Ostrava Radvanice-Bartovice (R&B), the concentrations of B[a]P reached the highest in the Czech Republic. Comparing air pollution between 2010 and 2017, it appears that concentrations of PM2.5 decreased in the MSR, but surprisingly, there is no change in the concentration of B[a]P in Ostrava Radvanice-Bartovice [26].

To verify the impact of air pollution on the health of the population in MSR, we analyzed the morbidity of children in three studies: (1) morbidity in children; (2) asthma bronchiale in children; and (3) impact of air pollution on the genome of newborns.

3.1 Child morbidity in the city of Ostrava

The morbidity in the city of Ostrava was studied in 10 pediatric districts in children born from 2001 to 2004 up to 5 years of age (N = 1888) [27]. The pediatricians abstracted medical records in ICD-10 codes. Comparing the detailed age-specific morbidity of 1655 children born and living in the district of Ostrava Radvanice-Bartovice (R&B) vs. children in other parts of Ostrava, a significantly higher incidence of acute illness was observed. Children from R&B experienced a higher incidence of acute respiratory disease in the first year of life (**Figure 2**) and a higher prevalence of asthma bronchiale (37.1%, N = 170) compared to other parts of Ostrava (10.2–13.2%, N = 1287) [27]. From birth until the age of 5 years, the incidences of pneumonia, tonsillitis, viral infections, and intestinal infectious diseases were also several times higher in children living in the district of Ostrava Radvanice-Bartovice. As Hertz-Picciotto et al. [28] proposed, prenatal exposure to PAHs may alter lymphocyte immunophenotypic distribution in cord blood and change immunoglobulin E levels in the cord serum. We may hypothesize that high concentrations of PAHs affect maturation of the immune system, and children from a more polluted region, therefore, suffer from higher respiratory morbidity, especially in their first year of life.

3.2 Asthma bronchiale in children

This study evaluated the impact of air pollution on gene expression in children and analyzed if there is any specific effect on the origin and development of asthma bronchiale. Specifically, we compared gene expression profiles in the leukocytes of asthmatic children with those in children without asthma,

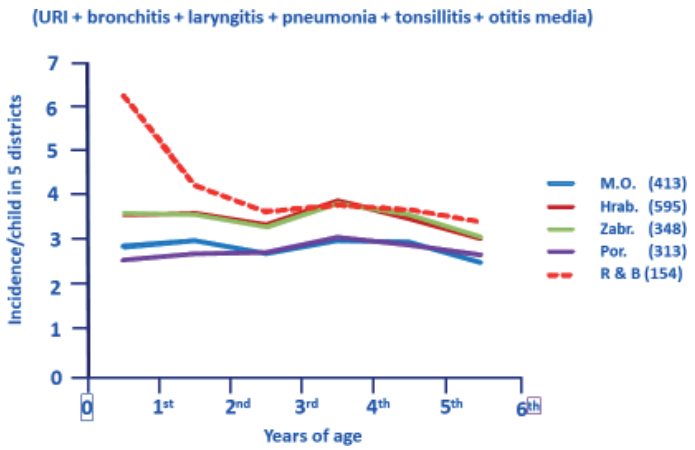

Figure 2.
Children respiratory morbidity in the city of Ostrava.

using Illumina HumanHT-12 BeadChip. The study included a group of 200 children—100 asthmatic and 100 healthy children—aged 6–15 years living in the district of Ostrava Radvanice-Bartovice and a control group of 200 children–100 asthmatic and 100 healthy children-living in the district of Prachatice (Southern Bohemia) [29].

Comparing the first signs of asthma bronchiale (e.g., wheezing), the prevalence in Ostrava was approximately 60% of the cases diagnosed up to the age of 3.5 years, while in Prachatice it was only 25%.

Gene expression was analyzed in 368 samples, and RNA was hybridized on whole genome chips with more than 20,000 coding genes per chip. Samples were evaluated according to locality and disease (i.e., Ostrava-asthma, Ostrava-control, Prachatice-asthma, and Prachatice-control). Differences in gene expression were checked by the statistical tests, t-test and ANOVA. When children were compared, according to locality and the change in the gene expression >1.5, 64 deregulated genes were observed. When Ostrava-asthma children were compared with Ostrava-control, 12 deregulated genes were observed. Comparing Prachatice-asthma children with Prachatice-control, 17 deregulated genes were observed. Using Venn diagrams, genes that were specific to asthma in Ostrava and to Prachatice were found to differ completely, while no gene was observed in both localities. Effects were further observed for the MAPK signaling pathway ($P < 0.01$, 1.5-fold) in Ostrava and for the cytokine-cytokine receptor interaction pathway ($P < 0.01$, 1.5-fold) in Prachatice.

Selected genes were verified using the qPCR method. For asthmatic children from Prachatice, the results showed an increased expression of the genes *SIGLEC8*, *CLC*, *CCL23*, and *CACNG6* (relationship of the presence of eosinophils and eosinophilic inflammation is related to the allergic type of asthma) corresponding to the allergic phenotype. For asthmatic children from Ostrava, increased gene expression corresponded to the non-allergic phenotypes *DEFA4* (relationship to the presence of neutrophils), *AHSP* (stabilization of hemoglobin), and *HBG2* (part of fetal hemoglobin, with a higher affinity to oxygen). We may check if the increased expression of the genes *HBG2* and *AHSP* is related to hypoxia in Ostrava children or if it is related to changes in hematopoiesis. The significant difference in the gene expression was observed comparing children from Ostrava and Prachatice, which is probably related to the dissimilarity of air pollution between these two regions, especially different concentrations of B[a]P exposure.

This study is unique because it is the first time when whole genome microarrays were used to analyze the relationship between air pollution and asthma bronchiale. The results suggest the distinct phenotype of asthma in children living in the polluted Ostrava region (non-allergic type) compared to children living in Prachatice (allergic type).

Rossnerova et al. [30] studied DNA methylation in the same children. They observed a methylation pattern in 58 CpG sites was significantly different in children from Ostrava compared to children in Prachatice. The methylation of all of these 58 CpG sites was lower in children from Ostrava which indicates a higher gene expression than the control Prachatice region. The patterns of methylation in asthmatic children also differed similarly between both regions.

We may conclude that studying gene expression and DNA methylation in children is a new approach that could allow to better understand the effects of air pollution on human health, as well as to better evaluate the significance of induced changes to the morbidity of children as well as morbidity in adulthood [29].

Choi et al. [31] studied on the same cohort of asthmatic children the effect of 95 candidate genes to contribute to the variability of children susceptibility to ambient B[a]P on doctor-diagnosed asthma. DNA was isolated from sputum. During the period of investigation, B[a]P concentrations in Ostrava were 7.8 vs. 1.1 ng/m^3 in Prachatice. Vulnerability to asthma appears to differ according to single nucleotide polymorphisms (SNP) of genotypes *CTLA4*, *STAT4*, and *CYP2E1.* The highest tertile of B[a]P ambient concentration range (>6.3 ng/m^3) is associated with a significantly elevated odds of asthma diagnosis. Children with those high-risk genotype are at even elevated risk only when the ambient B[a]P level reaches >6.3 ng/m^3. The present study provides first direct evidence of quantified airborne concentration of B[a]P and its risk on asthma and allergies to children.

Choi et al. [32] investigated air pollution-associated risks of childhood asthma among lean, overweight, and obese children within a heavy polluted city (Ostrava) vs. background air quality region (Southern Bohemia). They postulated that (1) airborne PAHs are correlated with biomarkers of oxidative stress (i.e., lipid peroxidation 15-F2 t-IsoP, DNA oxidation 8-oxodG, and protein oxidation carbonyl); (2) PAH exposures pose different risks of asthma among overweight/obese (OV/OB) girls than boys; and (3) oxidant stress biomarkers are associated with sexually dimorphic susceptibility to asthma per unit PAH exposure. The adolescent (>12 years) OV/OB girls were associated with the highest adjusted odds of the asthma (AOR = 15.4; 95% CI, 2.9–29.1; $P < 0.001$). B[a]P exposure was associated with a large leap in the odds of asthma among the OV/OB adolescents, particularly the girls, after adjusting for 15-F2 t-IsoP and carbonyls. Choi et al. [32] demonstrated for the first time that OV/OB girls might represent the most vulnerable subgroup to airborne B[a]P.

Choi et al. [33] explored molecular signatures and respiratory networks underlying childhood exposure to ambient B[a]P and asthma. Contemporaneous B[a]P concentration, gene expression, and DNA methylation data were analyzed against asthma diagnosis. An elevated B[a]P concentration induced epigenetic supression of NF-kB (Nuclear factor kappa-B) inflammation, decreased Natural Killer T (NKT) cells and activated anti-inflammatory IL10-secreting CD8+ T effective memory cells. B[a]P was positively correlated with an increased expression of a heme biosynthesis gene, *ALAS2*, which, in turn, appears to promote concurrent increase of neutrophilic metamyelocyte and mature CD71^{low} erythroid cells. In the urban asthma cases, erythroid-specific master transcription regulator gene (*GATA1*), glutathione transferase genes (*GSTM1* and *GSTM3*) and eosinophil marker (*ILSRA*) were simultaneously activated. In children with atopic march onset and diversity, B[a]P exposure enhanced heme biosynthesis, which might

reflect host compensatory mechanism to generate more erythrocytes following B[a]P and other PAH exposure. This comprehensive multiscale network analysis of a large cohort of transcriptomics and epigenetic data in asthma uncovers the global landscape of molecular interactions in asthma as well as the detailed local regulatory circuits in B[a]P-induced asthma.

3.3 Impact of air pollution on the genome of newborns

In the Czech Republic, the Moravian-Silesian Region is the region most polluted by PM2.5 and c-PAHs, as B[a]P is emitted by heavy industry and local heating systems. Accordingly, the impact of air pollution on newborns was studied in two districts: the exposed district of Karvina (MSR, Northern Moravia) and the control district of Ceske Budejovice (Southern Bohemia). This project was very complex, analyzing the concentrations of PAHs in (i) its impact on biomarkers of genetic damage as DNA adducts and gene expression and biomarkers of oxidative stress (8-oxodG adducts and lipid peroxidation); (ii) the urine of mothers and newborns; (iii) the breast milk of mothers; and (iv) ambient air and the diet of mothers. The samples were collected in hospitals in Ceske Budejovice and Karvina. The samples were collected from the normal deliveries (38–41 weeks+) of nonsmoking mothers and their newborns in the summer and winter season to account for differences in air pollution. The samples included venous blood and urine from 99 mothers (summer) and 100 mothers (winter) in Ceske Budejovice, a locality with relatively clean air, and 70 mothers (summer) and 73 mothers (winter) in Karvina, a locality with high air pollution. In addition, cord blood and urine samples were taken from 99 newborns (summer) and 100 newborns (winter) in Ceske Budejovice and from 71 newborns (summer) and 74 newborns (winter) in Karvina. c-PAHs bound to PM2.5 were collected by a high volume air sampler (model ECO-HVS3000, Ecotech, Australia) on Pallflex membrane filters (EMFAB, TX40HI20-WW) for 2 months during the period of biological sample collection [34].

The concentration of PM2.5 was higher in Karvina than in Ceske Budejovice in the summer of 2013 (mean ± SD: 20.41 ± 6.28 vs. 9.45 ± 3.62 $\mu g/m^3$, $P < 0.001$) and in the winter of 2014 (mean ± SD: 53.67 ± 19.76 vs. 27.96 ± 12.34 $\mu g/m^3$, $P < 0.001$). Similarly, the concentration of B[a]P was higher in Karvina than in Ceske Budejovice in the summer of 2013 (mean ± SD: 1.16 ± 0.91 vs. 0.16 ± 0.26 ng/m^3, $P < 0.001$) and in the winter of 2014 (5.36 ± 3.64 vs. 1.45 ± 1.19 ng/m^3, $P < 0.001$). The concentrations of air pollutants were higher in the winter season than in the summer season for both locations [35].

DNA adducts were determined in the umbilical cord blood by 32P-postlabeling method [36]. DNA adducts were analyzed as total adducts and B[a]P-like adducts. Both categories were significantly higher in Karvina than in Ceske Budejovice (e.g., in winter total DNA adducts in the cord blood were 2.76 ± 1.11 in Karvina vs. 2.32 ± 0.90 adducts/10^8 in Ceske Budejovice ($P < 0.001$); B[a]P-like DNA adducts were 0.72 ± 0.28 vs. 0.62 ± 0.28 adducts/10^8, respectively ($P < 0.001$)) [37].

Oxidative DNA damage was measured as levels of 8-oxodG (8-oxo-7,8-dihydro-2′-deoxyguanosine) [38]. Levels of 8-oxodG in newborns were more elevated in the Karvina samples than in the Ceske Budejovice samples (mean ± SD: 5.70 ± 2.94 vs. 4.23 ± 1.51 nmol/mmol creatinine, $P < 0.001$, respectively). This is in agreement with the fact that the concentration of air pollutants was higher in Karvina than in Ceske Budejovice. These results indicate that, in newborns, 8-oxodG levels tend to increase as air pollutant concentrations increase in the winter season [34].

Blood plasma 15-F2t-isoprostane levels (15-F2t-IsoP), a marker for lipid peroxidation, were analyzed using immunoassay kits from the Cayman Chemical Company (Ann Arbor, MI, USA) [39]. Lipid peroxidation in newborn winter

samples in Karvina was significantly higher compared to that in summer samples (15-F2t-IsoP, mean ± SD: 104.26 ± 38.18 vs. 64.24 ± 26.75 pg/ml plasma, $P < 0.001$, respectively).

When we separately analyzed the impact of air pollution on oxidative stress in newborns in the polluted region of Karvina, the results of multivariate regression analysis showed PM2.5 concentrations to be a significant predictor for 8-oxodG levels. Exposure to PM2.5 and B[a]P was shown to be a significant predictor of the induction of lipid peroxidation [35].

Honkova et al. [40] analyzed whole genome expression in cord blood of leukocytes of 202 newborns from the districts of Karvina and Ceske Budejovice. They aimed to identify differentially expressed genes and pathways in relation to locality and concentration of air pollutants. A pathway analysis revealed a deregulation of processes associated with cell growth, apoptosis or cellular homeostasis, immune response-related processes, or oxidative stress response. They did not find the direct effect of PM2.5 and B[a]P exposure on gene expression of newborns from Karvina; therefore, they assumed that the locality rather than air pollution levels might be a driving force of gene expression modulation. It seems likely that a common environment and complex lifestyle variables mediate long-term effects on gene expression at delivery.

3.4 PAH metabolism in urine of mothers and newborns

For the urine of mothers and newborns, monohydroxylated metabolites of PAHs (OH-PAHs) were analyzed [41]. While the content of ΣOH-PAHs in mothers' urine collected in the summer period was comparable in both Karvina and Ceske Budejovice, in the winter period, the samples from the Karvina region showed 1.5 times higher amounts of exposure markers. The amounts of ΣOH-PAHs in newborns' urine samples from highly industrialized Karvina in the winter season were 1.5 times higher than in the summer season collected in the same locality and 3.3 times higher when compared with the less polluted locality of Ceske Budejovice. This was probably related to the air pollution caused by heavy industry and local heating (**Figure 3**).

In all samples, the highest concentrations of 2-hydroxynaphthalene (2-OH-NAP) was observed. Recently Nie et al. [42] indicated that prenatal exposure to naphthalene decreased birth weight and birth head circumference. Detected concentrations of 2-OH-NAP in urine of mothers from Karvina corresponded to similar level in Taiyuan in China.

3.5 Analysis of PAHs in human breast milk and diet

Twenty-four PAHs were analyzed in the human breast milk samples [43]. The results of this unique study focused on a critical assessment of the impact of atmospheric pollution by PAHs in Karvina and Ceske Budejovice within summer and winter on the contamination of breast milk collected from mothers who reside there. As regards c-PAHs, B[a]P was detected only in 19 of analyzed samples and made about 0.4% of the total PAH amount. Comparing the data from winter and summer, in both residential areas, higher concentrations were measured in samples collected in the winter period. Also in the highly industrialized locality with heavily contaminated air, PAH amounts in milk were higher than in the control locality, but the PAH profiles were very similar. The most frequently detected compounds in both areas and seasons were noncarcinogenic phenanthrene, fluorene, fluoranthene, and pyrene. Therefore, the PAH metabolites in breast milk do not represent a significant health risk.

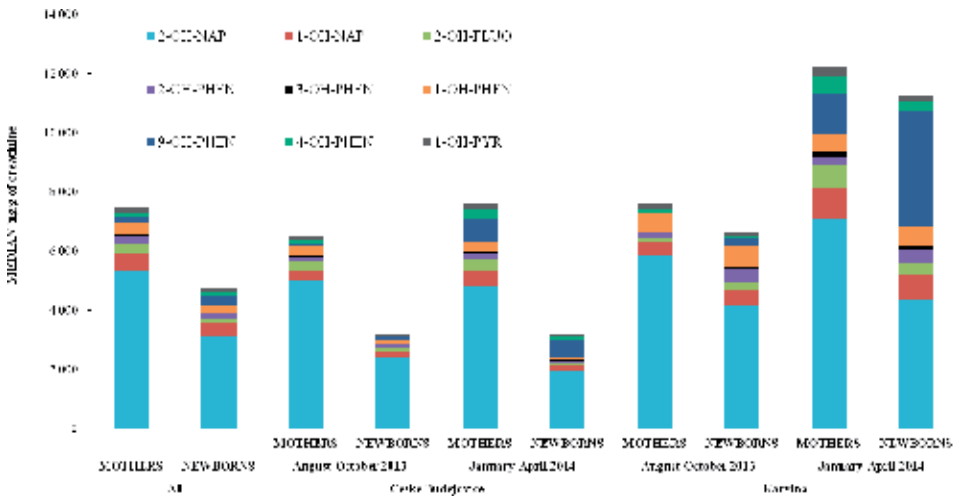

Figure 3.
Concentrations (ng/g creatinine) of detected OH-PAHs in the urine samples of mothers and newborns.

The contribution of ingestion to the total intake is quite variable for individual PAHs, and in summer, between 50 and 95% of the total intake was made, while in winter in the heavily air-contaminated industrialized locality, the inhalation is unambiguously the dominant pathway. Adverse pregnancy outcomes may be affected by lifestyle. The effect of smoking as well as passive smoking is already known [44]. It is understood in the Czech population that pregnant mothers should not smoke. This habit is also affected by education and social standards. Pavlikova et al. [45] studied in those two cohorts of mothers from Karvina and Ceske Budejovice the quality of diet. It showed the low nutritional quality of food consumed: recommended daily intake of vegetables in Karvina was 15.9 vs. 22.8% in Ceske Budejovice and fruits 35.5 vs. 61.8%, respectively. The milk and dairy product intake in both cohorts was sufficient only in 30% of days. (Real samples analyzed for the diet of mothers, 10 in summer 2013 and 10 in winter 2014, 1/4 of daily food intake, were collected for 7 days and 2 weeks before the expected term of delivery in each location). The quality of the diet of mothers and intake of vegetables were negatively correlated with the DNA adduct levels of newborns [46]. These results confirm that sufficient intake of antioxidants may improve the detoxification mechanism of PAHs in pregnant mothers [29].

3.6 Child morbidity in Karvina vs. Ceske Budejovice

Postnatal development and morbidity were compared from birth until the age of 2 years in children born and living in the districts of Karvina and Ceske Budejovice [47]. Maternal consent for the study was obtained during the admission of mothers at the departments of obstetrics in Ceske Budejovice and Karvina. Postnatal follow-up was successfully performed on 178 children (out of 216) registered in 48 pediatric offices in Ceske Budejovice and on 126 children (out of 148) registered in 28 pediatric offices in Karvina. All pediatric offices were visited to provide lists of children, who were selected to the cohort as newborns, as well as the pediatric and maternal questionnaire. The questionnaires were completed for 178 children in Ceske Budejovice and 126 children in Karvina. When postnatal growth and development of children (body weight, length, and head circumference at 3, 6, 12, and 18 months) were compared, there were no differences between children in the two localities. For the analyses of child morbidity, the diagnoses of diseases

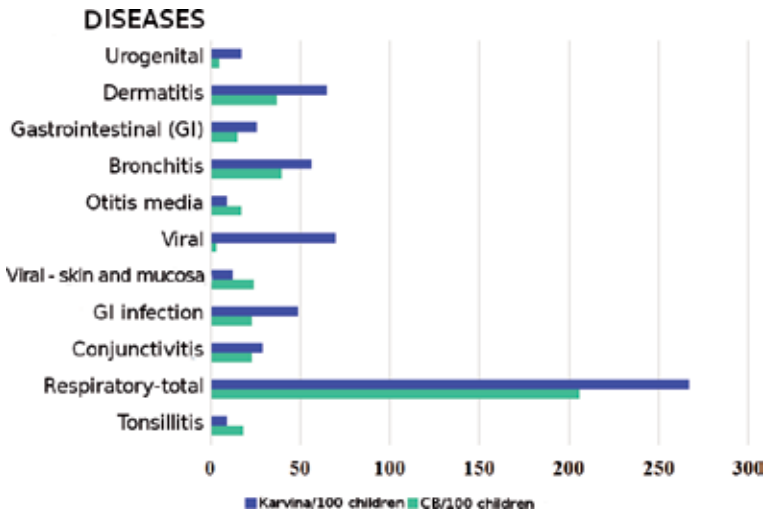

Figure 4.
Morbidity in children up to 2 years of age in the districts of Karvina and Ceske Budejovice.

affecting children (presented in the ICD-10) were grouped into 20 classes. The five most frequent illnesses in the first 24 months of life were gastrointestinal infections, dermatitis, tonsillitis, viral infections of the skin and mucous membranes, and viral diseases. The lowest incidence was in the first 6 months. Differences between the incidences of the disease, based on the season that children were born in, were negligible. The highest incidence was observed with the group of diagnoses related to upper respiratory infections (J00, J01, J02, J04, J05, and J06). When expressed as the incidence for 100 children, the incidence of urogenital diseases, dermatitis, viral diseases, and infections of the gastrointestinal system and upper respiratory infections was statistically significantly higher in children living in Karvina than in children living in Ceske Budejovice (**Figure 4**). Considering other studies on child morbidity, it may be concluded that the above findings are due to Karvina's more polluted environment.

4. Conclusions

Impact of air pollution to children health was studied in the Czech Republic in two heavily polluted regions: Northern Bohemia and Northern Moravia.

Studies in the Northern Bohemia proved the effect of PAHs to pregnancy outcomes as IUGR, increased respiratory morbidity, and behavioral changes.

Studies in the Northern Moravia observed the impact of air pollution to respiratory morbidity in preschool children, effect of B[a]P to asthma bronchiale in children, increased DNA adducts and oxidative damage in newborns, increased monohydroxylated metabolites of PAHs in urine, increased noncarcinogenic PAHs in breast milk, and low nutritional quality of pregnant mothers.

It should be understood that the present level of air pollution—standard EU 1 ng B[a]P/m^3/year was exceeded in the Czech Republic in the year 2017 for 62% of population—will affect the health status of the Czech population already in the next decades. We can assume that functional changes in newborns will be seen as an increased morbidity for cardiovascular diseases in the middle age, i.e., approx. After the next 50 years, the increased load of mutations in genetic material will be transferred to the genetic material of future generations. All these results and new

information should stimulate to decrease the present air pollution and to prevent future morbidity and the economic load for such morbidity.

Acknowledgements

This work was supported by the ERDF/ESF project "Healthy Aging in Industrial Environment HAIE"(No.CZ.02.1.01/0.0/0.0/16_019/0000798).

Author details

Radim J. Sram[1*], Milos Veleminsky, Jr[2] and Milos Veleminsky[2]

1 Institute of Experimental Medicine AS CR, Prague, Czech Republic

2 University of South Bohemia, Ceske Budejovice, Czech Republic

*Address all correspondence to: radim.sram@iem.cas.cz

References

[1] Dockery DW, Pope CA, Xu X, Spengler JD, Ware JH, Fay ME, et al. An association between air pollution and mortality in six U.S. cities. The New England Journal of Medicine. 1993;**329**:1753-1759

[2] WHO. IARC monographs on the evaluation of carcinogenic risks to humans. In: Outdoor Air Pollution. Vol. 109. Lyon, France: International Agency for Research on Cancer; 2016

[3] WHO. IARC monographs on the evaluation of carcinogenic risks to humans. In: Chemical Agents and Related Occupations. Vol. 100F. Lyon, France: International Agency for Research on Cancer; 2012

[4] Choi H, Harrison R, Komulainen H, Deldago Saborit JM. Polycyclic aromatic hydrocarbons. In: WHO Guidelines for Indoor Air Quality: Selected Pollutants. WHO Regional Office for Europe, Denmark. 2010. pp. 289-345

[5] Sram RJ, Beskid O, Rossnerova A, Rossner P, Lnenickova Z, Milcová A, et al. Environmental exposure to carcinogenic polycyclic aromatic hydrocarbons—The interpretation of cytogenetic analysis by FISH. Toxicology Letters. 2007;**30**:12-20

[6] Rossnerova A, Spatova M, Rossner P Jr, Solansky I, Sram RJ. The impact of air pollution on the levels of micronuclei measured by automated image analysis. Mutation Research. 2009;**669**:42-47

[7] Rubes J, Rybar P, Prinosilova P, Veznik Z, Chvátalova I, Solansky I, et al. Genetic polymorphisms influence the susceptibility of men to sperm DNA damage associated with exposure to air pollution. Mutation Research. 2010;**683**:9-15

[8] Moldan B, Schnoor L. Czechoslovakia restoring a critically ill environment. Environmental Science & Technology. 1992;**26**:14-21

[9] Sram RJ, Roznickova I, Albrecht V, Berankova A, Machovska E. Monitoring congenital anomalies in population exposed to environmental mutagens. In: Kappas A, editor. Mechanisms of Environmental Mutagenesis-Carcinogenesis. New York: Plenum Press; 1990. pp. 255-266

[10] Sram RJ. New ethical problems related to environmental pollution. In: Sram RJ, Bulyzhenkov V, Prilipko L, Christen Y, editors. Ethical Issues of Molecular Genetics in Psychiatry. Berlin-Heidelberg: Springer Verlag; 1991. pp. 94-105

[11] Benes I, Skorkovsky J, Novak J, Sram RJ. The development of air pollution in Teplice, Prachatice and Prague in the last thirteen years (In Czech). Air Pollution Protection. 2007;**5-6**:9-10

[12] Sram RJ, Benes I, Binkova B, Dejmek J, Horstman D, Kotesovec F, et al. Teplice program—The impact of air pollution on human health. Environmental Health Perspectives. 1996;**104**(Suppl. 4):699-714

[13] Dejmek J, Selevan SG, Benes I, Solansky I, Sram RJ. Fetal growth and maternal exposure to particulate matter during pregnancy. Environmental Health Perspectives. 1999;**107**:475-480

[14] Dejmek J, Solansky I, Benes I, Lenicek J, Sram RJ. The impact of polycyclic aromatic hydrocarbons and fine particles on pregnancy outcome. Environmental Health Perspectives. 2000;**108**:1159-1164

[15] Sram RJ, Binkova B, Rossner P, Rubes J, Topinka J, Dejmek J. Adverse reproductive outcomes from exposure

to environmental mutagens. Mutation Research. 1999;**428**:203-215

[16] Duvekot JJ, Cheriex EC, Pieters FA, Peeters LL. Severely impaired fetal growth is preceded by maternal hemodynamic maladaptation in very early pregnancy. Acta Obstetricia et Gynecologica Scandinavica. 1995;**74**:693-697

[17] Barker DJ. Intrauterine programming of adult disease. Molecular Medicine Today. 1995;**1**:418-423

[18] Dostal M, Prucha M, Rychlikova E, Pastorkova A, Sram RJ. Differences between the spectra of respiratory illnesses in children living in urban and rural environments. Central European Journal of Public Health. 2014;**22**:3-11

[19] Ghosh R, Amirian E, Dostal M, Sram RJ, Hertz-Picciotto I. Indoor coal use and early childhood growth. Archives of Pediatrics & Adolescent Medicine. 2011;**192**:492-497

[20] Baker RJ, Hertz-Picciotto I, Dostal M, Keller JA, Nozicka J, Kotesovec F, et al. Coal home heating and environmental tobacco smoke in relation to lower respiratory illness in Czech children, from birth to three years. Environmental Health Perspectives. 2006;**114**:1126-1132

[21] Gebhart JA, Dytrych Z, Tyl J, Sram RJ. On the incidence of minimal brain dysfunction syndrome in children (In Czech). Psychiatry. 1990;**86**:1-6

[22] Sram RJ, Veleminsky M Jr, Veleminsky M, Stejskalova J. The impact of air pollution to central nervous system in children and adults. Neuro Endocrinology Letters. 2017;**38**:389-396

[23] Baker E, Letz R, Fidler A, Shalat S, Plantamura D, Lyndon M. A computer-based neurobehavioral evaluation system for occupational and environmental epidemiology: Methodology and validation studies. Neurotoxicology and Teratology. 1985;**7**:369-377

[24] Otto D, Skalik I, Kenneth Hudnell H, House D, Sram RJ. Neurobehavioral effects of exposure to environmental pollutants in Czech children. In: Sram RJ, editor. Teplice Program: Impact of Air Pollution on Human Health. Prague: Academia; 2001. pp. 217-242

[25] Czech Statistical Office. 2018. Available from: http://www.czso.cz [Accessed: April 17, 2019]

[26] CHMI. 2018. Available from: http://portal.chmi.cz/files/portal/docs/uoco/isko/tab_roc/2018_enh/pollution_my/CZTOS_BaP_CZ.html [Accessed: June 18, 2019]

[27] Dostal M, Pastorkova A, Rychlik S, Rychlikova E, Svecova V, Schallerova E, et al. Comparison of child morbidity in regions of Ostrava, Czech Republic, with different degrees of pollution: A retrospective cohort study. Environmental Health. 2013;**12**(1):74

[28] Hertz-Picciotto I, Baker RJ, Yap PS, Dostál M, Joad JP, Lipsett M, et al. Early childhood lower respiratory illness and air pollution. Environmental Health Perspectives. 2007;**115**:1510-1518

[29] Sram RJ, Binkova B, Dostal M, Merkerova-Dostalova M, Libalova H, Milcova A, et al. Health impact of air pollution to children. International Journal of Hygiene and Environmental Health. 2013;**216**:533-540

[30] Rossnerova A, Tulupova E, Tabashidze N, Schmuczerova J, Dostal M, Rossner P, et al. Factors affecting the 27K DNA methylation pattern in asthmatic and healthy children from locations with various environments. Mutation Research. 2013;**741-742**:18-26

[31] Choi H, Tabashidze N, Rossner P Jr, Dostal M, Pastorkova A, Kong SW, et al. Altered vulnerability to asthma at various levels of ambient benzo[a] pyrene by CTLA4, STAT4 and CYP2E1 polymorphisms. Environmental Pollution. 2017;**231**:1134-1144

[32] Choi H, Dostal M, Pastorkova A, Rossner P Jr, Sram RJ, Ho S-M. Greater susceptibility of girls to airborne benzo[a]pyrene for obesity-associated childhood asthma. Environment International. 2018;**121**:308-316

[33] Choi H, Song WM, Wang M, Dostal M, Pastorkova A, Libalova H, et al. Benzo[a]pyrene is associated with dysregulated myelo-lymphoid hematopoesis in asthmatic children. Environment International. 2019;**128**:218-232

[34] Topinka J, Rossner P Jr, Milcova A, Schmuczerova J, Svecova V, Sram RJ. DNA adducts and oxidative DNA damage induced by organic extracts from PM2.5 in an acellular assay. Toxicology Letters. 2011;**202**:186-192

[35] Ambroz A, Vlkova V, Rossner P Jr, Rossnerova A, Svecova V, Milcova A, et al. Impact of air pollution on oxidative DNA damage and lipid peroxidation in mothers and their newborns. International Journal of Hygiene and Environmental Health. 2016;**219**:545-556

[36] Binkova B, Chvatalova I, Lnenickova Z, Milcova A, Tulupova E, Farmer PB, et al. PAH-DNA adducts in environmentally exposed population in relation to metabolic and DNA repair gene polymorphisms. Mutation Research. 2007;**620**:49-61

[37] Sram RJ, Rossner P, Rossnerova A, Milcova A, Ambroz A, Honkova K, et al. Impact of air pollution to genome of newborns. In: ISEE Conference Abstracts, Vol. 2016, Issue 1, Abstract Number: O-076. Available from: https://ehp.niehs.nih.gov/doi/10.1289/isee.2016.4303 [Accessed: 17 August, 2016]

[38] Rossner P Jr, Mistry V, Singh R, Sram RJ, Cooke MS. Urinary 8-oxo-7,8-dihydro-2′-seoxyguanosine values determined by a modified ELISA improves agreement with HPLC-MS/MS. Biochemical and Biophysical Research Communications. 2013;**440**(4):725-730

[39] Rossner P Jr, Svecova V, Milcova A, Lnenickova Z, Solansky I, Sram RJ. Seasonal variability of oxidative stress markers in city bus drivers-part II: Oxidative damage to lipids and proteins. Mutation Research. 2008;**642**:21-27

[40] Honkova K, Rossnerova A, Pavlikova J, Svecova V, Klema J, Topinka J, et al. Gene expression profiling in healthy newborns from diverse localities of the Czech Republic. Environmental and Molecular Mutagenesis. 2018;**59**:401-415

[41] Urbancova K, Lankova D, Rossner P, Rossnerova A, Svecova V, Tomaniova M, et al. Evaluation of 11 polycyclic aromatic hydrocarbon metabolites in urine of Czech moths and newborns. Science of the Total Environment. 2017;**577**:212-219

[42] Nie J, Li J, Cheng L, Li Y, Deng Y, Yan Z, et al. Maternal urinary 2-hydroxynaphthalene and birth outcomes in Taiyuan, China. Environmental Health. 2018;**17**:91

[43] Pulkrabova J, Stupak M, Svarcova A, Rossner P, Rossnerova A, Ambroz A, et al. Relationship between atmospheric pollution in the residential area and concentration of polycyclic aromatic hydrocarbons (PAHs) in human breast milk. Science of the Total Environment. 2016;**562**:640-647

[44] Dejmek J, Solansky I, Podrazilova K, Sram RJ. The exposure of non-smoking and smoking mothers to environmental tobacco smoke during different gestational phases and fetal growth. Environmental Health Perspectives. 2002;**110**:601-606

[45] Pavlikova J, Brebera D, Sram RJ. Quality of diet in pregnant mothers in two different regions. Journal of Nursing, Social Studies, Public Health and Rehabilitation. 2018;**9**:27-33

[46] Honkova K, Rossnerova A, Pavlikova J, Gmuender H, Svecova V, Veleminsky M Jr, et al. Analysis of gene expression profile in newborns from districts with different level of air pollution. In: Poster, 47 Annual Meeting of Environmental Mutagenesis and Genomics Society; 24-28 September 2016; Kansas City, USA. 2016

[47] Sram RJ, Ambroz A, Dostal M, Honkova K, Hajslova J, Pulkrabova J, et al. The Ostrava region, Czech Republic: Impact of air pollution on children's health. Public Health Panorama. 2017;**3**(2):156-164

Chapter 3

Placenta Abruption and Delivery Method

Miljana Z. Jovandaric and Svetlana J. Milenkovic

Abstract

Placental abruption is a significant contributor to maternal mortality worldwide. Early and skilled medical intervention is needed to ensure a good outcome, and this is not available in many parts of the world. Abruptio placentae are defined as the premature separation of the placenta from the uterus. Placental abruption must be considered whenever bleeding is encountered in the second half of pregnancy, since it is a significant cause of third-trimester bleeding associated with fetal and maternal morbidity and mortality. If the bleeding persists, fetal and maternal distress may develop. Fetal and maternal death may occur if appropriate interventions are not undertaken. The severity of fetal distress correlates with the degree of placental separation. In near-complete or complete abruption, fetal death is inevitable unless an immediate cesarean delivery is undertaken.

Keywords: pregnancy, abruptio placentae, etiology, delivery, newborn

1. Introduction

Abruption of the placenta is the most common cause of late pregnancy bleeding. In humans, it refers to the abnormal separation after 20 weeks of gestation and prior to birth. It occurs on average in 0.5%, or 1 in 200, deliveries. Placental abruption is significant contributor to maternal and newborns mortality worldwide. Skilled medical intervention is needed to ensure a good outcome, and this is not available in many parts of the world [1].

The primary cause of placental abruption is usually unknown, but multiple risk factors have been identified. However, only a few events have been closely linked to this condition, including hypertension disorders. The risk of recurrence of abruption placentae is reportedly 4–12%. If the abruption placentae occur in 2 consecutive pregnancies, the risk of recurrence rises to 25%. If the abruption is severe and results in the death of the fetus, the risk of a recurrent abruption and fetal demise is 7% [2].

1.1 Pathophysiology

Abruption of the placenta occurs due to the burst of the spiral arteries located in the basal decidua. This bleeding is often called "high blood pressure bleeding". The amount and volume of bleeding may be different, resulting in different clinical pictures and different consequences for the fetus. The removal of the entire placenta or more than half of the placenta leads to the death of the fetus due to the interruption of oxygenation of the fetus. In partial placental abruption, the consequences for the

fetus correlate with the size of the placenta that is ejected from the function. After abruption of more than half of the placenta area, fetal asphyxia occurs [3].

In rare cases, bleeding can originate from the fetal blood vessels of the placenta. The blood that accumulates between the placenta and the wall of the uterus creates a retroplacental hematoma that can be located centrally or peripherally. Because of the location of the peripheral retroplacental hematoma, even a small amount of blood can be manifested as an external bleeding. With central retroplacental hematoma, it is possible that larger amounts of blood remain behind the placenta, with the absence of visible external bleeding. Only when the hematoma touches the walls of the placenta, the blood flows out between the mesometrium and the wall of the uterus in the vagina and out. Amniotic fluid may be more or less colored due to the penetration of retroplacental hematoma into the amniotic cavity. The release of thromboplastin from decidual cells causes the formation of thrombin, which, in addition to the effect on coagulation, can cause hypertension of the uterus and its contractions, the bursting of fetal mesometrium and the onset of birth [4].

1.2 Classification of placental abruption

Classification of placenta abstraction is based on the degree of separation (partial or complete) and the separation site (marginal or central) [5].

Class 0—asymptomatic abruption of the placenta.

In such cases, the abruption may go unnoticed, and the diagnosis is made retrospectively after delivery. The criterion for diagnosis is the existence of an old, organized hematoma.

Class 1—mild abruption of the placenta (represents approximately 48% of all cases).

First degree abruption is a mild form of abruption, which can occur without external bleeding or with mild bleeding and a slightly painful sensitive uterus.

Class 2—moderate abruption of the placenta (represents approximately 27% of all cases). Second-degree abruption is a medium-severity abruption that can occur without external bleeding, but can also be moderately profuse.

Class 3—severe abruption of the placenta (represents approximately 24% of all cases). Third degree abruption or massive abruption is characterized by painful, toned uterus and most often severe vaginal bleeding.

1.3 Frequency

The frequency of placental abruption significantly varies across parts of the world. The lowest frequency is reported in Finland, amounting to 0.33%. In the United States, the rate of abruption in 2007 was 1.2%. In addition, in all European countries there has been a decline in the frequency in recent years, while an increase is reported in North America. In rural areas of Pakistan, the frequency of abruption is 2.2–7%, with high perinatal mortality from 50.63 to 62.5% [6].

1.4 Etiology

Risk factors in abruption placentae include the following: maternal hypertension - most common cause of abruption, occurring in approximately 44% of all cases, maternal trauma (e.g. motor vehicle collision (MVC), assaults, falls)-Causes 1.5–9.4% of all cases, cigarette smoking, alcohol consumption, cocaine use, short umbilical cord, sudden decompression of the uterus, premature rupture of membranes, delivery of first twin, idiopathic (probable abnormalities of uterine blood

vessels and decidua), previous placental abruption, chorioamnionitis, prolonged rupture of membranes (24 h or longer), maternal age 35 years or older, maternal age younger than 20 years, male fetal sex, low socioeconomic status, elevated second trimester maternal serum alphafetoprotein (associated with up to a 10-fold increased risk of abruption), subchorionic hematoma [7–9].

1.5 Clinical picture

The clinical picture of abruption depends on the degree of bleeding. The mildest form is the abruption of zero degree that has a subclinical form. In such cases the abruption can remain undetected, and it is only diagnosed retrospectively, upon delivery. The criterion for diagnosis is the existence of an old, organized hematoma. Abruption of the first degree is a milder form of abruption, which can also pass without external bleeding or with slight bleeding and a slightly sensitive uterus. Abruption of the second degree is a moderate abruption that can also pass without external bleeding, but the bleeding can also be moderately abundant. The uterus is painful, the mother suffers from hypotension, tachycardia and hypo-fibrinogenemia and the fetus suffers from distress. Abruption of the third degree or massive abruption is characterized by painful, toned uterus, and most commonly, by severe vaginal bleeding. The mother has severe hypo-fibrinogenemia and coagulopathy, hemorrhagic shock and other complications are also common, often followed by fetal death. Massive abruption can cause blood flow through the myometrium to the uterine serosa and oviduct, and blood can also be found in the peritoneal cavity. The uterus is enlarged and dark purple to black in color. The described condition is called apoplexy of the uterus, or by the author who described it, it is also called Couvelaire syndrome. Rapid onset and rapid development of clinical picture is typical for severe abruption. The blood in the vagina can be liquid or clotted. A pregnant woman often does not feel fetal movements due to severe fetal distress or fetal death. Kayani and associates compared the intervention interval of 20 and 30 minutes. The authors report that the rate of neonatal morbidity and mortality is considerably lower in cases of previous interventions. A particular form of placental abruption is a chronic abruption in which the pregnant woman has relatively scarce, chronic, intermittent bleeding and indications of placental insufficiency with oligohydramnion and intrauterine stagnation of fetal growth [10–12].

1.6 Diagnosis

The diagnosis of placenta abruption is based on clinical and ultrasound imaging, laboratory findings and placental examination after delivery. Diagnosis is primarily clinical, and the other findings contribute to the diagnosis. An ultrasound finding that supports abruption is a retroplacental hematoma. It can be of different sizes and appearance, hyper-, hypo- or iso-hemogenic compared to the placenta. Ultrasound findings may be falsely negative especially in fresh, acute abruptions where the retroplacental hematoma has not fully developed [9].

The sensitivity of ultrasound for the diagnosis of abruption is only 25–50%. The positive predictive value is high (88%), especially in cases where typical symptoms of abruption are present [13].

Laboratory findings do not only help to establish the diagnosis of abruption, but they are also important for assessing hemorrhage and coagulation preservation. Fibrinogen shows the best correlation with the severity of mother's bleeding. Concentration of fibrinogen in pregnancy increases as pregnancy advances, and normal fibrinogen levels in the third trimester are from 373 to 619 mg/dL [14].

Values of 200 mg/dL and less, have a 100% positive predictive value for severe postpartum bleeding. Values higher than 400 mg/dL indicate that the coagulation status is still preserved. For severe abruption, a rapid development of disseminated intravascular coagulation (DIC) is typical [15]. Diagnosis of DIC is based on elevated values of thrombin, decreased values of fibrinogen and platelets, and elevated values of degradation products of fibrin and D-dimers. A frequent laboratory finding of placenta abruption is anemia. According to the World Health Organization (WHO), anemia in pregnancy is defined as a hemoglobin value below 110 g/L and a hematocrit value below 0.33. Also, according to hemoglobin values, the anemia is divided into mild (100–109 g/L), medium severe (70–99 g/L) and severe (less than 70 g/L), (WHO 1989). Hematoma of different sizes and locations can be noticed by the examination of placenta. If hematoma exists for a long time, a defect on the fetal surface of the placenta can be noticed after separation from the placenta. A histopathological examination often discovers placenta infarcts along with the presence of retroplacental hematoma. If a clinical diagnosis is unclear, histopathological finding can help to confirm chronic abruptions and atypical abruptions [16].

1.7 Treatment

In the treatment of abruption, consideration should be given to gestational age, clinical picture, maternal and fetal condition. Continuous fetal monitoring is needed, and in the pregnant woman the assessment of hemodynamic status by measuring heart rate, arterial pressure, diuresis, and blood loss. It is necessary to have a wide vein for taking blood samples and an adequate compensation of circulating volume. Following parameters are monitored from laboratory findings: complete blood count, coagulation parameters, acid–base status, creatinine and hepatogram, but if necessary, other parameters are monitored as well. If the blood loss ranges from 500 to 1000 mL, the lost blood has to be compensated by the fresh one. In the case of fetal death, all further procedures are determined according to the condition of the patient. Cesarean section is indicated if the hemodynamic status is unstable, and vaginal delivery is not expected to be rapid. In such cases, the preservation of coagulation status is of crucial importance because the uncontrolled DIC can compromise the surgical procedure. If the mother is hemodynamically stable, vaginal delivery is proposed. In cases where the fetus is alive and with a normal cardiotocography record, an immediate vaginal delivery is indicated. Very often the clinician makes a decision on how to end the childbirth, depending on the dynamics of clinical picture development, laboratory findings, estimation of the rate of progression of labor and the assessment of fetal condition. In cases of moderate abruption and severe abruption and the fetus is viable delivery is necessary. This approach is justified by a relatively low neonatal morbidity of neonates born after 36 weeks of pregnancy thus avoiding the risk of abruption exacerbation. Vaginal delivery is preferred, but if there are indications, a cesarean section is performed [1].

The method of delivery completion depends on all of the above criteria. The use of tocolytics is debatable and it is a persistent subject of discussions in terms of reducing contractions or subsequent bleeding intensification. According to some authors, the application of tocolytics is useful since it stops the labor, which in case of abruption can cause its progression as well as excessive bleeding. It also provides the time for the application of corticosteroids. Some authors state that the application of tocolytic increases the duration of pregnancy with complicated bleeding in the third trimester [17]. This would justify the application of tocolytics, especially nifedipine as the first choice. On the other hand, the negative effect of tocolytics

on the cardiovascular system, and consequent tachycardia and hypotension can mask the clinical picture, aggravate abruption, and cause additional hemodynamic instability. According to the above, it follows that the application of tocolytics is a matter of clinician's individual assessment [18, 19]. Sheehan's syndrome is a rare complication of postpartum hemorrhage. With advancement in obstetric care, Sheehan's syndrome has become uncommon except in developing countries. A high index of suspicion is necessary in diagnosing such patients. Acute renal failure related to rhabdomyolysis in a patient with Sheehan syndrome, while other diseases that could cause rhabdomyolysis were excluded. Treatment with thyroxine and glucocorticoids resulted in complete recovery after attaining euthyroid and eucortisolemic state. Review of literature revealed the rarity of the disorder, with only four cases reported so far. Multiple anterior pituitary hormone deficiencies in Sheehan's syndrome are responsible for pancytopenia; replacement of thyroid and cortisol hormones results in complete recovery [20].

Fetal morbidity is caused by the insult of the abruption itself and by issues related to prematurity when early delivery is required to alleviate maternal or fetal distress. Delivery is required in cases of severe abruption or when significant fetal or maternal distress occurs, even in the setting of profound prematurity. In some cases, immediate delivery is the only option, even before the administration of corticosteroid therapy in these premature infants. All other problems and complications associated with a premature infant are also possible. Treatment depends on the amount of blood loss and the status of the fetus. If the fetus is less than 36 weeks and neither mother nor fetus is in any distress, then they may simply be monitored in hospital until a change in condition or fetal maturity whichever comes first [21, 22].

2. Conclusion

Fetal and maternal death may occur if appropriate interventions are not undertaken. The severity of fetal distress correlates with the degree of placental separation. In near-complete or complete abruption, fetal death is inevitable unless an immediate caesarian delivery is performed.

Conflict of interest

No potential conflict of interest was reported by the authors.

Funding

None.

Author details

Miljana Z. Jovandaric* and Svetlana J. Milenkovic
Clinic for Gynecology and Obstetrics, Department of Neonatology, Clinical Center of Serbia, Belgrade, Serbia

*Address all correspondence to: rrebecca080@gmail.com; visegradska.gak@gmail.com

IntechOpen

References

[1] Oyelese Y, Ananth CV. Placental abruption. Obstetrics and Gynecology. 2006;**108**:1005-1016

[2] Coleman J, Srofenyo EK, Ofori EK, Brakohiapa EK, Antwi WK. Maternal and fetal prognosis in abruptio placentae at Korle-Bu Teaching Hospital, Ghana. African Journal of Reproductive Health. 2014;**18**:115-122

[3] Tikkanen M. Placental abruption: Epidemiology, risk factors and consequences. Acta Obstetricia et Gynecologica Scandinavica. 2011;**90**:140-149

[4] Ananth CV, Berkowitz GS, Savitz DA, Lapinski RH. Placental abruption and adverse perinatal outcomes. JAMA. 1999;**282**:1646-1651

[5] Ananth CV, Lavery JA, Vintzileos AM, Skupski DW, Varner M, Saade G, et al. Severe placental abruption: Clinical definition and associations with maternal complications. American Journal of Obstetrics and Gynecology. 2016;**214**:272.e1-272.e9

[6] Ananth CV, Keyes KM, Hamilton A, Gissler M, Wu C, Liu S, et al. An international contrast of rates of placental abruption: An age-period-cohort analysis. PLoS One. 2015;**10**:e0125246

[7] Roy KK, Subbaiah M, Kumar S, Sharma JB, Singh N. Feto-maternal outcome in pregnancies complicated by isolated fetal congenital complete heart block. Journal of Obstetrics and Gynaecology. 2014;**34**:492-494

[8] Tikkanen M, Luukkaala T, Gissler M, Ritvanen A, Ylikorkala O, et al. Decreasing perinatal mortality in placental abruption. Acta Obstetricia et Gynecologica Scandinavica. 2013;**92**:298-305

[9] Ghaheh HS, Feizi A, Mousavi M, Sohrabi D, Mesghari L, et al. Risk factors of placental abruption. Journal of Research in Medical Sciences : The Official Journal of Isfahan University of Medical Sciences. 2013;**18**:422-426

[10] Kayani SI, Walkinshaw SA, Preston C. Pregnancy outcome in severe placental abruption. BJOG. 2003;**110**:679-683

[11] Kobayashi A, Minami S, Tanizaki Y, Shiro M, Yamamoto M, Yagi S, et al. Adverse perinatal and neonatal outcomes in patients with chronic abruption-oligohydramnios sequence. The Journal of Obstetrics and Gynaecology Research. 2014;**40**:1618-1624

[12] Rasmussen S, Ebbing C, Linde LE, Baghestan E. Placental abruption in parents who were born small: Registry-based cohort study. BJOG. 2018;**125**:667-674

[13] Shinde GR, Vaswani BP, Patange RP, Laddad MM, Bhosale RB. Diagnostic performance of ultrasonography for detection of abruption and its clinical correlation and maternal and foetal outcome. Journal of Clinical and Diagnostic Research. 2016;**10**:QC04-QC07

[14] Abbassi-Ghanavati M, Greer LG, Cunningham FG. Pregnancy and laboratory studies: A reference table for clinicians. Obstetrics and Gynecology. 2009;**114**:1326-1331

[15] Charbit B, Mandelbrot L, Samain E, Baron G, Haddaoui B, Keita H, et al. PPH Study Group. The decrease of fibrinogen is an early predictor of the severity of postpartum hemorrhage. Journal of Thrombosis and Haemostasis 2007;**5**:266-273

[16] James D, Steer P, Weiner C, Gonik B, Crowther C, Robson S, et al. Pregnancy

and laboratory studies: A reference table for clinicians. Obstetrics and Gynecology. 2010;**115**:868

[17] Saller DN Jr, Nagey DA, Pupkin MJ, Crenshaw MC Jr. Tocolysis in the management of third trimester bleeding. Journal of Perinatology. 1990;**10**:125-128

[18] Umazume T, Yamada T, Morikawa M, Ishikawa S, Kojima T, Cho K, et al. Occult fetomaternal hemorrhage in women with pathological placenta with respect to permeability. The Journal of Obstetrics and Gynaecology Research. 2016;**42**:632-639

[19] Arora R, Devi U, Majumdar K. Perinatal morbidity and mortality in antepartum haemorrhage. Journal of Obstetrics and Gynaecology of India. 2001;**51**:102

[20] Thyagaraj V, Kumar MJ. Diagnosis delayed but not denied - Sheehan's syndrome. JNMA; Journal of the Nepal Medical Association. 2015;**53**:31-33

[21] Kyrklund-Blomberg NB, Gennser G, Cnattingius S. Placental abruption and perinatal death. Paediatric and Perinatal Epidemiology. 2001;**15**:290-297

[22] Sheiner E, Shoham-Vardi I, Hallak M, Hadar A, Gortzak-Uzan L, Katz M, et al. Placental abruption in term pregnancies: Clinical significance and obstetric risk factors. The Journal of Maternal-Fetal & Neonatal Medicine. 2003;**13**:45-49

Chapter 4

Childbirth Education: Comparative Analysis

Matilde Fernández Fernández-Arroyo

Abstract

Prenatal education programs are a powerful tool to increase maternal and child health. Today, no one knows the most effective educational approach. The objective of the study is to identify differences in approaching and methodology of major schools of childbirth education. Methodology includes the review of the databases such as PubMed, Embase, Lilacs, Scielo and Cochrane since 2000; review the websites of the schools; study the documentation using the comparative method; and analysis using a database with Excel. Results analyzed and compared the five old one schools and 12 of emerging new one schools. The chapter concludes the conceptual approach and methodology of the schools, which can facilitate the choice for professionals and research design to increase the quality of programs.

Keywords: antenatal education, childbirth education, parenthood education, centering pregnancy/group care, pregnancy, prenatal care/methods

1. Introduction

The paths that can lead women to become pregnant are multiple and not always happy [1]. Depending on the circumstances of life, the decision to accept a pregnancy may not be easy. The knowledge of being pregnant produces a feeling of ambivalence of whether I want it or not, in all women and their partners [2]. This feeling raises doubts about whether it is the right time, if you have the resources necessary to raise a child and if you are going to be able to play the role of mother or father [3]. Once the decision is made to continue with a pregnancy that the woman, or the woman and her partner accepts, it is necessary to advise the future parents about the care of the gestation, delivery and the puerperium. A personal work of bonding with the child must also be initiated, which lays the foundations for the development of the affective warp that every human being needs in order to fully develop. This element is so important that it is the axis of much international research on attachment and attachment in early childhood [4].

Science has shown that child health begins in the prenatal stage, in pregnancy, and this makes prenatal education very important. Everything from the mother's diet to her emotions influences the future health of her child [5, 6]. So from the World Health Organization and from all related scientific societies education is promoted at this stage [7]. Prenatal education has ceased to be a concern of midwives and obstetricians to become a field of study that is approached from multiple disciplines, such as pediatrics, psychology and pedagogy. This makes it necessary for professionals to know the history of prenatal education and the main paradigms from which their study has been developed [8]. In this chapter, we are

going to approach the evolution of health education for women and their partners in pregnancy.

The objective of this work is to identify differences in approaching and methodology of the major schools of childbirth education.

2. Methodology

In the first quarter of 2019, a review was made of publications in the health sector in both Spanish and English, going back a maximum of 19 years. MeSH terms were selected that best reflect the objective of this work, these being: antenatal education, childbirth education, parenthood education, centering pregnancy/group care, pregnancy, prenatal care/methods and their equivalents in Spanish. The PubMed, Embase, Lilacs, Scielo, Cuiden, Cinhal and Cochrane databases were consulted. The websites of the main current antenatal education schools were reviewed and the relevant studies of the main European schools pre-2000 were located. Once the documents had been located, they were studied and analyzed using the comparative method. To conduct the analysis, a database was set up using Excel.

3. Developing

The results have been structured in four sections:

1. Prenatal education before the twentieth century.

2. The beginning of prenatal health education.

3. The first large prenatal education schools, prenatal education schools.

4. The new prenatal education schools.

3.1 Prenatal education before the twentieth century

Until the twentieth century, women gave birth in their homes attended by midwives and accompanied by the women of the family and the environment [9]. According to anthropological studies, there are few cultures in which women separated from the group and were to give birth by themselves. There are references that cite some Eskimo and Indian tribes of North America. In general, childbirth was a common phenomenon in people's lives. Women and girls, of all ages, had seen their mothers, sisters, daughters and/or neighbors give birth [10]. In this situation, birth should not have been as feared a moment as it is now. In her home, the woman in childbirth had greater prominence and control, but the mortality and morbidity rates were very high. In fact, today, in those parts of the world where women give birth without health care assistance, childbirth continues to be the first cause of death [11]. To remedy this situation, each culture has developed special care for pregnancy, childbirth and puerperium. This great variability of care is related to the eminently social nature of every human birth and the need for group survival [12]. These first cares constitute an informal prenatal education that occurred within social groups in a natural way.

3.2 The beginning of prenatal health education

At the end of the twentieth century, great changes took place in the health sector, which gave another profile to hospitals. These had arisen from the hand of religious orders dedicated to charity. Over time they were developed, technified and became the great centers of training and development of medicine. At this time, the first maternities arose to serve the most disadvantaged women. Progressively, delivery assistance moves from homes to hospitals [13]. Women no longer had the opportunity to see their relatives give birth and lost ancestral control over their physiology and their natural knowledge of childbirth. In hospitals, seeking to improve perinatal outcomes, deliveries are intervened and instrumentalized. These interventions led to pain and anxiety for women in childbirth, so the need arose to look for ways to reduce pain [14]. As early as in 1870 James Young Simpson tries to apply chloromorphic anesthesia to childbirth. At the beginning of the century, studies were developed throughout Europe to achieve analgesia in childbirth with psychological means [13, 15, 16]. Obstetricians start prenatal education programs for childbirth. These early programs are the forerunners of the current Maternity/Paternity education programs.

3.3 The first large prenatal education schools, prenatal education schools

In Europe, the first models of prenatal education emerge in the first half of the century. Their sole object is to reduce the pain of women in childbirth and consist of only a few sessions. Gradually the programs expand their objectives and their sessions, and deal with pregnancy, the couple, bonding and the newborn.

3.3.1 The school of hypnosis and autosuggestion

The schools of Charcot (Paris) and Berhein (Nancy) investigated clinical hypnosis [17–19]. In 1922 the obstetricians Schultze and Rhonhof proved that the introduction of educational sessions before childbirth reduced the time needed to achieve a hypnotic state. In 1923, Kogerer used post-hypnotic self-suggestion [20, 21]. These two techniques posed some difficulties so new methods were sought to relieve pain during labor [22].

3.3.2 The English school

In 1932, the obstetrician Grantly Dick Read published "Natural Childbirth." He viewed childbirth as a physiological phenomenon in which pain is created by fear which unleashes the defense mechanisms in the form of muscular tension. He formulated the *Fear-Tension-Pain* concept and developed a method featuring explanatory conversations, relaxation, breathing techniques and strategies that enhance trust in the healthcare team. He did not rate gymnastic exercises and warned against any muscle training. This concept has been disseminated worldwide and has undergone many changes [23, 24].

3.3.3 The Russian school

At the same time, Drs. Velvoski, Platinov and Nikolaiev, who were working with hypnotic suggestion, were looking for new approaches (Obstetric Psychoprophylaxis) [25]. In accordance with Pavlov's Classical Conditioning Theory, they concluded that pain in labor is a reaction conditioned by sociological and religious-cultural stimuli. They suggested de-conditioning the fear through aseptic language, relaxation (Schultze), positive thinking, the celebration of maternity and

obstetric information [26]. To get the woman actively involved, they introduced breathing and muscle exercises [17, 27]. They came up with a simple and accessible method which encouraged its spread throughout Russia, Eastern Europe and China.

3.3.4 The French school

Dr. Lamaze (1940) learned from the Russian school and was familiar with the English school. He created a more technical method that insisted on the need for a loving environment with the presence of a partner. His partner, Dr. Vellay, insisted on the therapeutic power of speech and the active role of the woman [28]. Later, in his book "*Birth Without Violence*" (1975), Leboyer popularized the creation of an environment of tranquility in the labor room and the submersion of newborns in a small bath of warm water; he is thus regarded as the precursor of water births [29].

3.3.5 The Spanish school

In 1955, the midwife Consuelo Ruiz presented her book "Labour Without Pain" featuring the new tendencies [30]. In 1956, Aguirre de Cárcer founded the school of "Obstetric Sophropedagogy or Maternal Education" and gave a substantial change from the focus of pain during labor for that of achieving a new sociocultural standard whereby both the woman and her partner would acquire the necessary knowledge to face labor with serenity, having diminished their fears, and experience this transcendental moment in their lives with full consciousness and satisfaction, as this experience will impact on the child by encouraging the development of the "Emotional Network" [31]. In 1959, the Compulsory Health Insurance entrusted her with a program and in 1986 Maternal Education was included in the service portfolio of the National Health System. This helped with its dissemination and facilitated significant further development [32].

3.4 The new prenatal education schools

In the middle of the twentieth century, these first methods obtained good perinatal results, with which they developed and spread throughout the world [33]. Subsequently, multiple methods have emerged and, in every country, there are professionals concerned about improving care for women in childbirth and that disseminate this concept. Next, the emerging models that have a greater presence in the review are presented.

3.4.1 International childbirth educators' association

In 1960 the International Childbirth Educators' Association (ICEA) was founded, which further evolved the Lamaze method. It is a non-profit organization that promotes freedom of choice for women and their partners based on the informed knowledge of childbirth options. Its orientation is centered on maternity care and the care of the newborn by the family. It respects the individuality of the woman and her sense of autonomy [28, 34, 35].

3.4.2 Husband-coached childbirth

In 1965, Robert Bradley, in his book "Husband-Coached Childbirth," claimed that the partner is the person who should ensure that the woman is in a safe, quiet environment and who should know her well enough to be able to help her in this process. He empowers fathers to 'coach' their partners with instructions, relaxation techniques and massages [36]. He was the pioneer of 'father training' (American Academy of Husband-Coached Childbirth).

3.4.3 Mindfulness-based childbirth and parenting

In 1970, Kabat-Zinn developed the *Mindfulness-Based Childbirth and Parenting* (MBCP) method at the University of Massachusetts Medical School, based on Mindfulness-Based Stress Reduction. This method emphasises the development of the conscience at a precise moment through meditation. The results indicate that this helps to reduce pregnancy-related depression and anxiety [37, 38]. It is also giving rise to new models such as "*Centering Pregnancy*®."

3.4.4 Birth your way

In the 1970s, Sheila Kitzinger reinstated the wisdom of a woman's body in giving birth. The author of "Birth Your Way: Choosing Birth at Home or in a Birth Centre" proposes that women tune in to their contractions in the way they feel they achieve harmony and rhythm and acquire the knowledge to make their own decisions. The presence of the husband, the instructor and the midwife create a favorable environment for childbirth. Her partner, Janet Balaskas, created the Active Birth Movement and proposed the practice of yoga adapted to pregnancy [39].

3.4.5 Haptonomy

In the Netherlands, in the 70's, a new approach to preparation for birth appeared: "Haptonomy," which passed to France in 1978 by Frans Velman and later extended to Switzerland and Spain. Dr. Etienne Herbinet explains that haptonomic work is exercised on touch, on palpation in its affective aspect, on tactile contact as a means of communication. During preparation at birth the haptonomic approach can help future parents to have a more emotional perception of the baby to be born. Through touch they develop an active affective relationship between the mother, the father and the baby. The method helps to establish and develop a sense of paternity/maternity through affective contact with the baby [40].

In 1975, in the United States, the percentage of pregnant women who used this type of practice was higher than 6–7% according to the program carried out under the name of "Prepared Childbirth" assumed by the "American Society for Psychoprophilaxis in Obstetrics" (2010) [41].

3.4.6 Primal health research center

The French obstetrician, Michel Odent (1977) popularizes birth in water and founds the "Primal Health Research Center." He guides his work to help each woman choose the way she will give birth following her own instincts and respecting at all times the physiological process of childbirth. Author of numerous books, he postulates that the emotional situation of the pregnant mother is determinant in the psychological and physical future of the individual, and also points out the temporal importance of childbirth and the subsequent moments on the development of the person. He highlights the role of birth hormones (oxytocins and endorphins) and provides numerous investigations [42].

3.4.7 Respiratory autogenic training and psychoprophylaxis in obstetrics

In Rome, in 1984, Umberto Piscicelli, professor at the Catholic University of Rome, publishes his book "Respiratory Autogenic Training and Psychoprophylaxis in Obstetrics." His method is known as "Respiratory Autogenic Training" or R.A.T. It is inspired by Schultz's autogenous breathing, the laws of conditioning,

group psychotherapy, relaxation therapy and his deep knowledge of psychosomatic medicine. Its objective is the psychological therapy of pain through its connections with uterine contractions, but also the correction of negative psychic aspects and non-adaptive behaviors. For this, the woman is given maximum autonomy to be the protagonist of her birth and is prepared to act in an environment full of stimuli [43].

3.4.8 Waterbirth

In the US, Barbara Harper, is one of the great scholars and disseminators of childbirth in water around the world. She founded Waterbirth International in 1987 after visiting Russia for the first time and sitting with Igor Charkovsky, where she was "influenced by her faith in the parturients and their babies" [44]. She has also worked extensively with Binnie Dansby in the early 1980s on cognitive learning and repressed experiences and memories of birth. She is a nurse, midwife, doula and perinatal educator. She has been Founder and Director of the World Association for Maternal and Child Health, and Founder and Director of Waterbirth International. She is recognized worldwide as an expert researcher and author of protocols for delivery in water since 1983 and responsible for the opening of and instituting policies for delivery in water in 140 hospitals in the United States.

3.4.9 HypnoBirthing

In 1990 Marie Mickey developed the Mongan Method, known as HypnoBirthing. Based on the premise that all women have within them the power to call on their natural instincts to achieve the best birth for their baby and for themselves, it works with mothers and families on birth expectations and taking a positive approach to the experience. It puts a lot of emphasis on language, breathing, relaxation, visualization and self-hypnosis and it highlights the fact that childbirth does not have to be painful [45].

3.4.10 Intrauterine harmonization

In 1992 a new method or program appears based on the affective bond with the baby: "intrauterine harmonization." Dr. Thomas Verny and Pamele Weintraub prepare parents with music, deep relaxation, visualization and massage. They strengthen the bond between parents and children through dream induction, guided work with images, drawings, lullabies and words addressed to the child. The conflicts that future motherhood can arouse in parents are solved by examining their own childhood and positive thinking techniques [46].

3.4.11 Birthing from within

In 1998, Pam England and Rob Horowitz devised a holistic approach to the preparation for childbirth and the postpartum period, known as *Birthing from Within*. As well as information on childbirth and children's upbringing, they also addressed introspection and self-discovery from the perspective of the woman's own internal experience [47].

3.4.12 Awareness of welcome

In 2004, Dr. Wendy Anne McCarty, co-founder of the Masters and Doctorate programs of "Santa Barbara Graduate Institute" in Prenatal and Perinatal Psychology, reviewed 30 years of clinical research in this field. Her book, "Awareness of Welcome," presents an integrated model of early development

that was a reflection of the clinical results found in her research of prenatal and perinatal psychology. The transcendental aspects of consciousness and human rights from the beginning of life become the central thread of this holistic model. It is an integrating model of early human experience, learning, development and care (from before conception to early childhood) that includes our sensitive nature and integrates several fields such as theories of infant development, new clinical investigations of babies that incorporate a conscious state, prenatal psychology and perinatal, paternity practices and some ideas that make up the new physics sciences. The author affirms that the most important thing is to reconstruct our sensitive spiritual nature as well as our fundamental nature of Sensitive Human Beings [48].

4. Comparison between the main models of prenatal education

Maternal and child health and the emotional attachment around birth are so important that they are the axis of multiple health guidelines worldwide [49], and the body of numerous international research [50]. However, despite the importance of prenatal education, according to the latest reviews, neither the results nor the best educational approaches are known [51–56]. This situation makes it necessary to consider studying and analyzing the most representative prenatal education schools. For this, we must look for the paradigm that lies behind each school and know the methodology they use. This work is arduous because of the difficulty of finding detailed information about some schools. In order to make the comparison work more explicit, **Tables 1–4** have been made. Schools that have not found a paradigm have not been included in them.

Education models	Main elements of teaching	Characteristics of the sessions	Paradigm
Hypnosis (1922)	• Hypnosis explanation • Relaxation, somnolence • Precise suggestions • Hypnosis practice	• Individuals • Before childbirth • 3 or 4 sessions • Coach at childbirth	"Childbirth under hypnosis = painless childbirth"
Read (1932) English school	• Natural childbirth explanation • Relaxation (Jacobson) • Steady, deep and natural breathing • Passive childbirth collaboration • Trust in the trust in the team	• Individuals or small groups • Before childbirth • 4 or 5 sessions • Childbirth team • Natural childbirth course	"Fear of childbirth = pain."
Velvoski (1939) Russian School	• Natural childbirth explanation • Pain de-conditioning • Relaxation (Schultze) • Fast thoracic breaths during contractions • Directed push • Pregnancy exercises • Active collaboration in childbirth • Simple language • Trust in the trust in the team	• Individuals or small groups • Before childbirth • 4 or 5 sessions • Childbirth team • Obstetric Psychoprophylaxis course	"Childbirth = De-conditioning pain"

Education models	Main elements of teaching	Characteristics of the sessions	Paradigm
Lamaze (1940) French school	• Natural childbirth explanation • Relaxation (Jacobson) • Fast thoracic breaths during contractions • Directed push • Pregnancy massage • Pregnancy exercises • Communication skills • Positive ideas • Health measures • Active collaboration in childbirth • Trust in the team	• Small groups • With partner • Before childbirth • 4 or 5 sessions • Childbirth team • Care of the birthing atmosphere • Obstetric • Psychoprophylaxis course/painless childbirth	"Childbirth = Preparedness"
Aguirre de Cárcer (1956) Spanish School	• Explanation Natural birth • Educate Maternidad • Relaxation (sophrological) • Thoracic breathing • Directed push • Gymnastics in sophrology • Communication skills • Welfare measures • Baby care • Breastfeeding	• Small group • With couples • Prior to delivery • 6 or 8 sessions • Environmental care • After childbirth • 2–4 sessions • Maternal Education Program	"Childbirth = emotional encounter"

The first large prenatal education schools.

Table 1.
Comparison between the main models of prenatal education.

Education models	Main elements of teaching	Characteristics of the sessions	Paradigm
International Childbirth Educators Association (ICEA) (1960)	• Centred on family care in maternity • Freedom of choice of childbirth options • Educational programs • Choice of programmes at instructors' discretion (exercises, relaxation, breathing exercises)	• Individuals or small groups • Before childbirth • From 1 to 4 or more sessions • Postpartum • Sessions (educator's choice) • Education program for childbirth	"Childbirth = Family experience/ informed choice"
Robert Bradley (1965)	• Natural childbirth explanation • Coaching of fathers for childbirth • Avoidance of medication and medical procedures • Nutrition and wellbeing • Abdominal breathing • Aerobic exercises with partner • Relaxation tailored to the partner • Pregnancy massage given by the father	• Small groups of 2–6 couples • Before childbirth • 12 sessions • Partner at childbirth • Bradley Method or "Husband-Coached Childbirth"	"Childbirth = Coaching fathers for childbirth"

Education models	Main elements of teaching	Characteristics of the sessions	Paradigm
Kabat-Zinn (1970) *Mindfulness-Based Childbirth and Parenting*	• Natural childbirth explanation • Stress reduction • Full attention • Relaxation (meditation) • Exercises (yoga) • Abdominal breathing • Discussion group • Positive emotions	• Small groups of 2–6 couples • Before childbirth • 9 × 3-h sessions + 1 day rest • Postpartum 1 session • Commitment to 30 min per day of meditation and yoga • "Centering Pregnancy®"	"Childbirth = awareness of birth and upbringing"
Kitzinger (1970) *Active Birth Mouvement*	• Natural childbirth explanation • Women's freedom during labor • Free breathing • Free relaxation • Exercises (yoga) • The woman as the protagonist of childbirth	• Individuals or small groups • With partner • Before childbirth • Variable number of sessions • Childbirth team • Active childbirth movement	"Childbirth = No pain, Active childbirth movement"
Velman (1970) Haptonomy	• Tactile contact as a means of communication • Emotional perception of the baby that will be born	• Individuals or small groups • With partner • Before childbirth • Variable number of sessions • Touch work in pregnancy	"Childbirth = develop a feeling of parenthood through touch"

The new prenatal education schools [1].

Table 2.
Comparison between the main models of prenatal education.

Education models	Main elements of teaching	Characteristics of the sessions	Paradigm
Leboyer (1975) French school	• Natural childbirth explanation • Relaxation (Jacobson) • Thoracic breaths • Pregnancy exercises • Communication skills • Wellbeing measures • Active collaboration • Trust in the team	• Small groups • With partner • Before childbirth • 4 or 5 sessions • Childbirth team • Labor room atmosphere • Baby bath • Non-violent birthing course	"Childbirth = Baby fear" (non-violent birth)
Michel Odent (1975)	• Non-interventional labor, following instincts. • Free relaxation • Music-therapy • Exercises or dance • Women's freedom during labor • Activation of endorphins and endogenous oxytocin	• Small groups • With partner • Before childbirth • 6 or 8 sessions • Childbirth team • Rooms for natural childbirth • Training in "Primal Health"	"Childbirth = Recovering natural instincts. Personal and intimate experience"

Education models	Main elements of teaching	Characteristics of the sessions	Paradigm
Piscicelli (1984) Respiratory autogenous training	• Autogenous Schultz breathing • Conditioning • Group psychotherapy	• Small groups • With couples • Prior to delivery • Before childbirth	"Childbirth = woman protagonist of her birth in an environment full of stimuli"
"National Health System, Spain (1986) Maternal Education Program Spanish School	• Explanation pregnancy/delivery/puerperium care • Educate Motherhood/ Paternity • Emotional education • Free relaxation • Abdominal and free breathing • Directed and expiratory push • Labor positions • Aerobic gymnastics or yoga • Communication skills • Wellbeing measures • Baby care (up-bringing) • Breastfeeding • Family reorganization	• Small groups • With couples • Prior to delivery • Before childbirth—three levels • Level 1: second trimester—from 1 to 4 sessions • Level 2: third trimester—from 6 to 10 sessions—Care of the birthing atmosphere • Level 3: postpartum—2 to 4 sessions • Educational program for parents	"Childbirth = emotional encounter"
Harper (1987) Waterbirth	• Cognitive learning • Repressed experiences and memories of birth • Cognitive learning • Repressed experiences and memories of birth • Waterbirth	• Small groups • With couples • Prior to delivery • Before childbirth • Cognitive learning • Repressed experiences and memories of birth—Waterbirth	"Childbirth = Waterbirth

The new prenatal education schools [2].

Table 3.
Comparison between the main models of prenatal education.

Education models	Main elements of teaching	Characteristics of the sessions	Paradigm
Mongan (1990) Hypnobirth	• Natural childbirth explanation • Working in peace and quiet • Deep breathing • Abdominal breathing • Exercises (yoga) • Denial of the fear-tension-pain cycle • Positive focus • Emotional education • Family unity • Hypnobirth	• Individuals or small groups of 2–6 couples • Before childbirth • 5 sessions • Childbirth team • Hypnobirth	"Childbirth = Hypnobirth No pain"

Education models	Main elements of teaching	Characteristics of the sessions	Paradigm
Verny (1992) "Intrauterine Harmonization"	• Work with the music • Deep relaxation • Visualization • Massage • positive thinking	• Small groups • With couples • Prior to delivery • Before childbirth • Music	"Childbirth = Intrauterine Harmonization"
Horowitz (1998) "Birthing From Within"	• Natural childbirth explanation • Holistic and spiritual focus • Creative expression (diary writing/painting) • Relaxation (meditation) • Joint creation of classes between coach and couples • Facing challenges • Education on child upbringing	• Small groups • With partner • Before childbirth • No. of sessions at the coach's discretion • Postpartum sessions at the coach's discretion • "Birthing From Within"	"Childbirth = Self-discovery (birthing from within)"
McCarty (2004) Welcome awareness	• Holistic model • Awareness • Human rights since the beginning of life • Rebuild our sensitive spiritual nature	• Small groups • With partner • Before childbirth • Rebuild our sensitive spiritual nature	"Childbirth = Welcome awareness"

The new prenatal education schools [3].

Table 4.
Comparison between the main models of prenatal education.

5. Conclusions

Given this multiplicity of methods, Walker affirms that we are at a crossroads [14]. Women and their partners have, in the developed world, more information opportunities on pregnancy and labor than ever before, but does this information really reach them in a way that they are capable of applying to their personal experience? Do we know which is the best educational method? Do we know which elements should be included in educational programs to obtain the best results? The professionals who work in antenatal education need to understand the current situation of women and be able to guide them in making informed decisions based on scientific evidence. It is also necessary to eradicate the current belief that technology and medical interventions guarantee the well-being and safety of women during childbirth. Therefore, education for women and their partners on care during pregnancy, labor and the postpartum period is still, in the twenty-first century, an issue of great concern in order to recover the experience of childbirth for women and to reinstate the birth of a human being as an integral part of the family experience from the beginning of the pregnancy [57].

6. Implications for practice

This work allows us to see how the first courses on "childbirth education," "natural birth" and "painless labor," in which the main approach was to reduce the pain for women in hospital childbirth, have evolved toward educational health programs in which. The main approach is maternal-infant health during pregnancy, labor and the postpartum period and the emotional bond with the newborn.

The work describes the characteristics of the five main schools and of the main new models of antenatal education. The comparative analysis is the basis for identifying the similarities and differences of each of them. This will help professionals to choose the educational approach that best meets the characteristics of their environment. It can also lay the foundations for the design of research questions that remain unresolved, such as finding the best educational approaches and the best learning strategies in this environment [14, 49–56]. The biggest limitation was restricting the search for works published in English and Spanish, as there may be schools in other languages that identify with different cultures. In the review, only three articles were found that analyzed the different models [8, 14, 33], so there is not a great deal of scientific literature with this approach for investigation. This means that the results offer the opportunity of thinking about the importance given to this subject, as health professionals, and the strategies we use to address and develop them. It also allows us to re-think the approach of antenatal education that underlies the care of women and their families at such a crucial point in life and health that is labor and the birth of a child. This can only be of benefit to health professionals, who will be able to provide more appropriate and efficient care, as well as to all future mothers and fathers who could receive a higher quality of medical attention.

Acknowledgements

All the mothers and fathers who during the last 35 years have given me the opportunity to bring me closer to their moment of birth.

All the academic and health institutions that have made this work possible.

Notes

This work is an update of chapter two of the doctoral thesis: Fernández M. Preparation, validation and application of an evaluation tool for maternal education programs of the primary care centers of the Community of Madrid. Madrid: Comillas Pontifical University. 2012. Available from: https://www.educacion.es/teseo/mostrarRef.do?ref=1003407 [Accessed: 01 May 2019].

Author details

Matilde Fernández Fernández-Arroyo[1,2]

1 San Juan de Dios School of Nursing and Physical Therapy, Comillas Pontifical University, Madrid, Spain

2 Research Institute of the University Hospital La Paz, IdiPAZ, Madrid, Spain

*Address all correspondence to: mfernandezarroyo@gmail.com

References

[1] Mendez-Figueroa H, Dahlke JD, Vrees RA, Rouse DJ. Trauma in pregnancy: An updated systematic review. American Journal of Obstetrics and Gynecology 2013;**209**(1):1-10. DOI: 10.1016/j.ajog.2013.01.021. Available from: https://www.ajog.org/article/S0002-9378(13)00068-9/fulltext [Accessed: 01 May 2019]

[2] Cutler A, McNamara B, Qasba N, Kennedy HP, Lundsberg L, Gariepy A. "I just don't know": An exploration of women's ambivalence about a new pregnancy. Womens Health Issues. 2018;**28**(1):75-81. DOI: 10.1016/j.whi.2017.09.009

[3] Krumm S, Kilian R, Becker T. Mentally ill women's subjective views on social context of desire for children. A qualitative approach. Psychiatrische Praxis. 2011;**38**(1):23-30. DOI: 10.1055/s-0030-1248620

[4] Mountain G, Cahill J, Thorpe H. Sensitivity and attachment interventions in early childhood: A systematic review and meta-analysis. Infant Behavior & Development. 2017;**46**:14-32. DOI: 10.1016/j.infbeh.2016.10.006

[5] Nandi A, Bhalotra S, Deolalikar AB, Laxminarayan R. Chapter 27: The human capital and productivity benefits of early childhood nutritional interventions. In: Bundy DAP, Nd S, Horton S, Jamison DT, Patton GC, editors. Child and Adolescent Health and Development. 3rd ed. Washington (DC): The International Bank for Reconstruction and Development/The World Bank; 2017. p. 20

[6] Ordóñez AE, Collins PY. Advancing research to action in global child mental health. Child and Adolescent Psychiatric Clinics of North America. 2015;**24**(4):679-697. DOI: 10.1016/j.chc.2015.06.002

[7] WHO. Mental Health Action Plan 2013-2020. Geneva, Switzerland: World Health Organization; 2013

[8] Fernandez M. Comparative analyses of main childbirth education schools. Index de Enfermería. 2013;**22**(1-2):40-44. Available from: http://dx.doi.org/10.4321/S1132-12962013000100009. [Accessed: 01 May 2019]

[9] Contreras J. The training of midwives: An approach to the study of the evolution of this profession. [thesis]. Complutense University of Madrid, Faculty of Nursing, Physiotherapy and Podiatry; 2015. Available from: https://eprints.ucm.es/40265/1/T38037.pdf [Accessed: 01 May 2019]

[10] Fernández M. Preparation, validation and application of an evaluation tool for maternal education programs of the primary care centers of the Community of Madrid. Madrid: Comillas Pontifical University; 2012. Chapter 2; Available from: https://www.educacion.es/teseo/mostrarRef.do?ref=1003407c

[11] Alkema L, Chou D, Hogan D, Zhang S, Moller AB, Gemmill A, et al. Global, regional, and national levels and trends in maternal mortality between 1990 and 2015, with scenario-based projections to 2030: A systematic analysis by the UN maternal mortality estimation inter-agency group. Lancet. 2016;**387**(10017):462-474

[12] Bujalkova M. Birth control in antiquity. Bratislavské Lekárske Listy. 2007;**108**(3):163-166

[13] Peart K. Birth planning—Is it beneficial to pregnant women? Australian Journal of Midwifery. 2004;**17**(1):27-29

[14] Walker DS, Visger JM, Rossie D. Contemporary childbirth education

models. Journal of Midwifery & Women's Health. 2009;**54**(6):469-476

[15] Becerro de Bengoa C. Maternal education and maternal plasma beta endorphins during labor. U.C. Madrid; Doctoral Thesis Collection no 168/93. Madrid; 1993

[16] Gomez Ruiz MD. Childbirth preparation. Old and new techniques. Nursing Science. 1995;**156-157**:38-40

[17] Nicolaiev A. Painless Childbirth. Buenos Aires: Artago; 1957

[18] De Piano FA, Salzberg HC. Clinical aplications of hipnosis to three psychosomatic disorders. Psychological Bulletin. 1979;**86**(6):1223-1235

[19] Stampone D. The history of obstetric anesthesia. The Journal of Perinatal & Neonatal Nursing. 1990;**4**(1):1-13

[20] Werner WEF, Schauble PG, Knudsen MS. An argument for the revival of hypnosis in obstetrics. The American Journal of Clinical Hypnosis. 1982;**24**(3):149-171. DOI: 10.1080/00029157.1982.10404046

[21] Ramón y Cajal S. Labor pains considerably attenuated by hypnotic suggestion. Trébede: Monthly Aragonese Analysis, Opinion and Culture. 2002;**63**:72-73

[22] Teleska J, Roffman A. A continuum of hypnotherapeutic interactions: From formal hypnosis to hypnotic conservation. The American Journal of Clinical Hypnosis. 2004;**47**(2):103-115

[23] Chertok L. Psychosomatic methods of preparation for childbirth. Obstetrics and Gynecology. 1967;**98**(5):698-707

[24] Dick-Read G. Childbirth Without Fear: The Principles and Practice of Natural Childbirth. London: Pinter & Martin; 2004

[25] Velvoski IZ. Psychoprophylactic. Medguiz: Leningrado; 1954

[26] Bacialli L. Modern views on the psychophysical preparation for childbirth. Revista de Ginecologia e d'Obstetrícia. 1957;**51**(1):27-35

[27] Piscicelli V. Training Autogeno respiratorio y psicoprofilaxis en Obstetricia. Podova: Piccin; 1986

[28] Lamaze E. Painles Childbirth: The Lamaze Method. New York: Poler Books; 1972. L

[29] Leboyer M. For a Birth Without Violence. Barcelona: Daimon; 1984

[30] Ruiz V-FC. Primer to Learn to Give Birth. 1ª ed. Madrid: Talasa; 1998

[31] Aguirre de Carcer A. Preparation for Motherhood. Madrid: Morata; 1989

[32] Ministry of Health. Education for Motherhood Volume I and II. Madrid: National Institute of Health. General Secretary; 1995

[33] Koehn ML. Childbirth education outcomes: An integrative review of the literature. The Journal of Perinatal Education. 2002;**11**:10-19

[34] Browne AD. Preparation for childbirth. A review. Journal of the Irish Medical Association. 1966;**58**(344):31-34

[35] International Childbirth Education Association (ICEA). Available from: http://www.icea.org/ [Accessed: 01 May 2019]

[36] Hathaway M, Hathaway J. The Bradley Method Student Workbook. Sherman Oaks, CA: American Academy of Husband-Coached Childbirth; 2002

[37] Warriner S, Crane C, Dymond M, Krusche A. An evaluation of mindfulness-based childbirth and

parenting courses for pregnant women and prospective fathers/partners within the UK NHS (MBCP-4-NHS). Midwifery. 2018;**64**:1-10. DOI: 10.1016/j.midw.2018.05.004

[38] Duncan LG, Bardacke N. Mindfulness-based childbirth and parenting education: Promoting family mindfulness during the perinatal period. Journal of Child and Family Studies. 2009;**19**:190-202

[39] Kitzinger S. The New Great Book of Pregnancy and Childbirth. Barcelona: MEDICI; 2003

[40] Decant D. Haptonomy, What Do I Know? Barcelona: Davinci; 2008

[41] Amis D, Green J. Prepared childbirth : the family way. 7th ed. Plano, TX: Family Way Publications; 2007. ISBN: 10 0976975823, ISBN: 13 9780976975823

[42] Odent M. The Birth in the Plastic Age. Barcelona: Ob Stare; 2011

[43] Piscicelli U. Respiratory autogenic training in preparation for labor (RAT method). Minerva Medica. 1975;**66**(75):3926-3939

[44] Barbara Harper RN. Gentle Birth Choices. Healing Arts Press; 2005. ISBN: 13 9781594770678. https://www.innertraditions.com/gentle-birth-choices.html

[45] Mogan MF. HypnoBirthing—A Celebration of Life. HypnoBirthing; 2011

[46] Verny T, Kelly J. The Secret Life of the Child Before Being Born. Urano; 2009

[47] England P, Horowitz R. Birthing from Within: An Extra-Ordinary Guide to Childbirth Preparation. 1st ed. USA: ParteraPress; 1998

[48] McCartney PR. Centering pregnancy: A renaissance in prenatal care? MCN: American Journal of Maternal Child Nursing. 2004;**29**(4):261

[49] World Health Organization. Adelaide Statement on Health in All Policies. WHO, Government of South Australia, Adelaide. 2010. Available from: http://www.who.int/social_determinants/spanish_adelaide_statement_for_web.pdf [Accessed: 01 May 2019]

[50] Kim L, Lauren C, Lucy T, James L, Philip W, Christopher G, et al. Measuring attachment in large populations: A systematic review. Educational and Child Psychology. 2010;**27**(3):22-32

[51] Suto M, Takehara K, Yamane Y, Ota E. Effects of prenatal childbirth education for partners of pregnant women on paternal postnatal mental health and couple relationship: A systematic review. Journal of Affective Disorders. 2017;**210**:115-121. DOI: 10.1016/j.jad.2016.12.025

[52] Bastos MH, Furuta M, Small R, McKenzie-McHarg K, Bick D. Debriefing interventions for the prevention of psychological trauma in women following childbirth. Cochrane Database of Systematic Reviews. 2015;**4**:CD007194. DOI: 10.1002/14651858.CD007194.pub2

[53] Archabald K, Lundsberg L, Triche E, Norwitz E, Illuzzi J. Women's prenatal concerns regarding breastfeeding: Are they being addressed? Journal of Midwifery & Women's Health. 2011;**56**(1):2-7

[54] Bailey JM, Crane P, Nugent CE. Childbirth education and birth plans. Journal of Midwifery & Women's Health. 2009;**54**(6):469-476

[55] Armigo C. Prenatal education regarding gestational development, viability, and survivorship: Looking

to our obstetric colleagues for change. Advances in Neonatal Care. 2008;**8**(3):185-189

[56] Gagnon AJ, Sandall J. Individual or group antenatal education for childbirth or parenthood, or both. Cochrane Database of Systematic Reviews. 2007;**18**(3):CD002869

[57] Hanson L, VandeVusse L, Roberts J, Forristal A. A critical appraisal of guidelines for antenatal care: Components of care and priorities in prenatal education. Journal of Midwifery & Women's Health. 2009;**54**(6):458-468

Chapter 5

Consanguinity Marriage Increases Risk of Newborn's Congenital Anomalies in Sulaimani City

Niaz Mustafa Kamal

Abstract

Consanguineous marriage may cause the transfer of two recessive defective mechanisms, one from the mother and the other from the father, to offspring, which may cause the appearance of congenital anomalies. This study is aimed at determining the role of consanguineous marriage with congenital anomalies and their types in Sulaimani City. This is a retrospective case-control study based on hospital records. The study was conducted in Maternity Teaching Hospital of Sulaimani City from January 1 to December 31 of 2018. A record of 522 neonates (260 newborns with CA and 262 newborns with the absence of CA) were delivered from the Maternity Teaching Hospital and all private hospitals which were collected from the statistic section of the maternal and child care unit of the Preventive Health Department. The sample of neonates without congenital anomalies was collected randomly from hospital records, and stillbirth was excluded. Categorical variables were summarized as frequencies and percentages, while for numeric variables mean and the standard deviation were used. Chi-square test was applied to compare categorical variables and odds ratios using STATA 12. A p value less than 0.05 was considered statistically significant if p smaller than 0.001 was reported as < 0.001. The mean age of the newborn children with CA was (1.79, SD 2.04) and for the mother's cases was (29.59, SD 4.97). The commonest type of CA was congenital heart disease (25%); low birth weight and gender were statistically associated with types of CA (χ^2 = 30.53 and p = 0.006 vs. χ^2 = 45.3, p = <0.000, respectively). There was a significant correlation between parental marriage with anomalies (OR, 1.83, p = 0.001) and increase mothers age 30 years and over (OR, 2.56, p = 0.03). For eliminating this problem, there is an urgent need for educating unmarried people on the deleterious effects of consanguineous marriage, especially in Sulaimani City with high overall consanguinity rates.

Keywords: consanguinity, congenital anomalies, spina bifida, Sulaimani, neonates

1. Introduction

Birth defects, congenital abnormalities, and congenital anomalies (CAs) are interchangeable terms used to describe developmental defects that are present at birth and can be defined as structural or functional anomalies, including metabolic disorders, which are present at the time of birth [1]. Birth defects are various groups of disorders of prenatal origin that can be caused by single gene defects, chromosomal disorders, multifactorial inheritance, environmental teratogens, and

micronutrient deficiencies. Maternal infections such as rubella, maternal illnesses like diabetes mellitus (DM), iodine and folic acid deficiency, exposure to medicinal and recreational drugs including alcohol and tobacco, certain environmental chemicals, and doses of radiation are all other factors that cause birth defects [2]. Birth defects are encountered frequently by pediatricians and regarded as an important cause of childhood morbidity and mortality. Birth defects can be classified according to their severity and pathogenic mechanism or whether they are involving a single system or multiple systems [3]. Structural anomalies are considered overt when they are visible on inspection; otherwise, they are considered "occult" [4].

Congenital malformation (CM) began to emerge as one of the major childhood health problems, and it refers to any abnormality, whether genetic or not, which is present at birth. Treatment and rehabilitation of children with CM are costly, and complete recovery is usually impossible [5].

The etiology of CM is genetic (30–40%) and environmental (5–10%). Among the genetic etiology, chromosomal abnormality constitutes 6%, single gene disorders 25%, and multifactorial 20–30%; however, for nearly 50% of CM, the cause is yet to be known [6]. The pattern and prevalence of congenital anomalies may vary over time or with geographical location, thereby reflecting a complex interaction of known and unknown genetic and environmental factors including sociocultural, racial, and ethnic variables [7].

Consanguineous marriage is referred to a marital union among close biological kin. In clinical genetics, it is called the relationship by marriage between first and second cousins [8, 9]. Consanguineous marriage is most common in the Middle East and among Islamic populations. The rate of consanguineous marriage in different countries is dependent on different factors like education level, religion, local tradition, and socioeconomic status [9]. Studies over several decades have shown that there is a high correlation between consanguineous marriage and inherited congenital malformation [10]. There are many risk factors increment to the prevalence of congenital malformations; however, the consanguineous marriage remains the risk factor contributing to congenital anomalies [11]. The current study was conducted to determine if there is a correlation between parental consanguinity and the appearance of congenital anomalies in Sulaimani City.

2. Methodology

This is a retrospective case-control study based on hospital records. The study was conducted in Maternity Teaching Hospital of Sulaimani City from January 1 to December 31 of 2018. A record of 522 neonates (260 newborns with congenital anomalies and 262 newborns without congenital anomalies) were delivered from the Maternity Teaching Hospital and all private hospitals which were collected from the statistic section of the maternal and child care unit of the Preventive Health Department. The Ph.D. is the main body responsible for preventive health services and collection of public health-related data from all hospital and health-care centers of the city. The sample of neonates without congenital anomalies was collected randomly from hospital records. The study excluded stillbirth. The recorded data included demographic data and neonatal and maternal data. The parental consanguinity data were obtained from the hospital records which were recorded as first and second relatives. The study was approved by the ethics committee of the Technical College of Health, and permission was also taken from the Preventive Health Department.

The type of birth defects was classified by the diagnostic standardization of CM from the ICD-10 system [12]. Records of neonates with multiple congenital

anomalies were grouped depending on whether those anomalies qualified as a specific syndrome or not. The diagnosis was made by a pediatrician examining the neonate immediately or within a few days of delivery. If they qualified as a specific syndrome, they were then categorized into that syndrome. If no syndrome could be classified, then the anomaly is referred to the system affected and by the specific anomaly. When more than two systems were involved, it was recorded as multiple congenital anomalies. Birth weights ≥2.5 kg was considered to be normal weight, while birth weight <2.5 kg as low birth weight. Categorical variables were summarized as frequencies and percentages, while for numeric variables mean and the standard deviation were used if normally distributed variables. The chi-square test is used for determining the association between categorical variables. Odds ratio and adjusted odds ratio were calculated to determine risk factors, and p value equal and less than 0.05 was considered statistically significant. Smaller p values were reported as <0.001 if they were smaller than 0.00.

3. Results

The study included 522 neonates (260 neonates with CA and 262 neonates without CA). 51.5% of the neonates with CA was male and 48.5% was female. Of the 54.6% of CA neonates from inside the city and 62.2 of non-CA neonates from

Characters	**Congenital anomalies n=(260)**	**None congenital anomalies n=(262)**	χ^2	p **value**
Sex			0.007	0.9
Male	134 (51.5%)	136 (51.9%)		
female	126 (48.5%)	126 (48.1%)		
Residence			3.1	0.08
Inside Sulaimani	142 (54.6%)	163 (62.2%)		
Outside Sulaimani	118 (45.9%)	99 (37.8%)		
Mothers occupation			1.3	0.3
Employed	222 (85.4%)	214 (81.7%)		
None employed	38 (14.6%)	48 (18.3%)		
Mother's age				
<25	10 (3.9%)	13 (5.1%)	40.43	<0.0001
26-29	100 (39.4%)	167 (66%)		
≥30	144 (56.7%)	73 (28.9%)		
Parental consanguinity			6.7	0.01
Yes	58 (22.1%)	35 (13.5)		
No	204 (77.9%)	225 (86.5%)		
Birth weight			0.38	0.5
Low birth weight g < 2500	161 (62.2%)	169 (64.8%)		
Normal birth weight g> 2500	98 (37.8%)	92 (35.2%)		

Table 1.
Comparison of Socio-demographic characteristic of congenital and none congenital anomalies.

Category	Mean case	Mean controls	*p* value
Child age/days	1.79 (2.04)	2.58 (5.86)	0.04
Mothers age/years	29.59 (4.97)	32.13 (5.32)	<0.0001

Table 2.
Mean age distribution of the mothers and neonates.

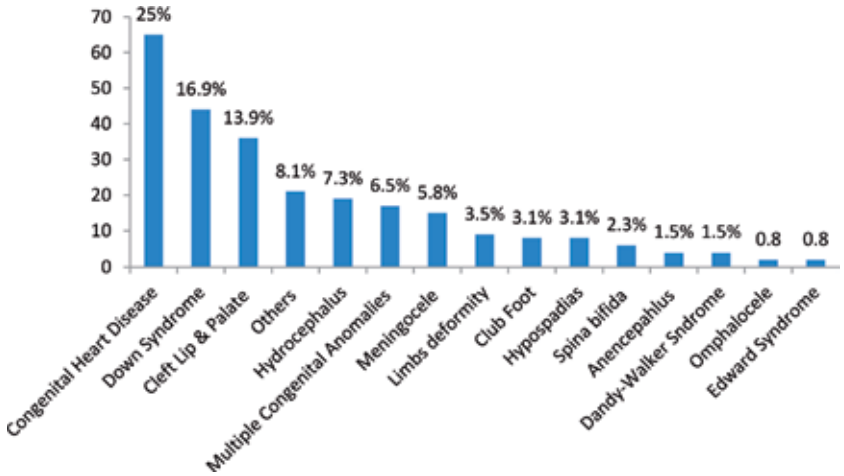

Figure 1.
Distribution types of congenital anomalies.

outside the city, 85.4 and 81.7% of mothers for two groups are employed, while the rest (14.6 and 18.3%) were not employed. Mothers have children with CA aged below 25 was (3.9%), 26–29 years was (39.4%) and those aged 30 and over was (56.7%), while mothers have children without CA aged 25 and below was (5.1%), 26–29 years was (66%) and those aged 30 and over (28.9%). This difference was statistically significant in the p = <0.0001. The consanguineous marriage of mother's neonates with CA and with the absence of CA was (22.1 vs. 13.5%), respectively, this difference was sadistically significant p = 0.01. There was a slight difference between the birth weight of CA and none a neonate which was presented in the **Table 1**.

The mean age of the newborn children with CA was 1.79, SD 2.04, and for the newborn without CA was 2.58, SD 5.86, with p = 0.04. The mean age of the mother's cases was (29.59, SD 4.97) and the mother's controls were (32.13, SD 5.3) with p = <0.0001 (**Table 2**).

Figure 1 shows the distribution types of congenital anomalies; the commonest type of CA was congenital heart disease (25%), followed by Down syndrome (16.9%) and left lip and plate (13.9%), while the less common types were omphalocele and Edwards syndrome (0.8%), respectively.

The gender and birth weight (low birth weight < 2.5 kg) are compared with each type of congenital anomalies. There is a statistically significant association between gender and birth weight with the types of congenital anomalies (**Table 3**). Congenital heart disease was common in male (61.5%) than female (38.5%), left lip and palate (66.7%) in male compared to female (33.3%), and Down syndrome (52.3%) in male higher than female (47.3%), while others, MCA and club foot, were higher among female than male. This difference was statistically significant with χ^2 = 30.53 and p = 0.006. Low birth weight was statistically associated with types of

Congenital anomalies	Neonate gender		Low birth weight < 2.5 kg
	Male	Female	
Congenital heart disease	40 (61.5%)	25 (38.5%)	35 (53.9%)
Omphalocele	2 (100%)	0 (0%)	2 (100%)
Cleft lip and palate	24 (66.7%)	12 (33.3%)	31 (86.1%)
Hydrocephalus	9 (47.4%)	10 (52.6%)	13 (68.4%)
Multiple congenital anomalies	4 (23.5%)	13 (76.5%)	2 (12.5%)
Meningocele	4 (26.7%)	11 (73.3%)	8 (53.3%)
Limb deformity	4 (44.4%)	5 (55.6%)	5 (55.6%)
Club foot	2 (25%)	6 (75%)	6 (75%)
Hypospadias	8 (100%)	0 (0%)	6 (75%)
Spina bifida	2 (33.3%)	4 (66.7%)	3 (50%)
Anencephalus	2 (50%)	2 (50%)	2 (50%)
Dandy-Walker syndrome	2 (50%)	2 (50%)	0 (0%)
Down syndrome	23 (52.3%)	21 (47.3%)	28 (63.6%)
Edwards syndrome	1 (50%)	1 (50%)	1 (50%)
Others	7 (33.3%)	14 (66.7%)	19 (90.5%)
Total	**n = 260 (100%)**		**n = 161 (62.2%)**
Statistical analysis	**$\chi 2 = 30.53, p = 0.006$**		**$\chi 2 = 45.3, p = <0.0001$**

Table 3.
Different congenital anomalies by gender and child birth weight of any congenital anomalies.

Congenital anomalies	Mother's age	Parental consanguinity
	30 years and over	
Congenital heart disease	20 (31.8%)	9 (13.9%)
Omphalocele	0 (0%)	0 (0%)
Cleft lip and palate	9 (25%)	6 (16.7%)
Hydrocephalus	5 (26.3%)	4 (21.1%)
Multiple congenital anomalies	6 (35.3%)	2 (11.8%)
Meningocele	5 (35.7%)	2 (13.3%)
Limb deformity	3 (33.3%)	1 (11%)
Club foot	2 (28.6%)	1 (12.5%)
Hypospadias	1 (12.5%)	1 (12.5%)
Spina bifida	0 (0%)	0 (0%)
Anencephalus	1 (33.3%)	1 (25%)
Dandy-Walker syndrome	2 (50%)	1 (25%)
Down syndrome	13 (30.9%)	5 (11.4%)
Edward syndrome	0 (0%)	0 (0%)

Congenital anomalies	Mother's age	Parental consanguinity
	30 years and over	
Others	6 (28.6%)	2 (9.5%)
Total	**n = 135 (28.8%)**	**n = 35 (13.5%)**
Statistical analysis	**$\chi 2 = 30.1, p = 0.3$**	**$\chi 2 = 4.3, p = 0.1$**

Table 4.
Different congenital anomalies by mother's age and parental consanguinity of any congenital anomalies.

Risk factors	Occurrence of congenital anomalies					
	OR (95% CI)	**Chi square**	***p*-value**	**AOR (95% CI)**	**Chi square**	***p*-value**
Consanguineous marriage						
No	Reference			Reference		
Yes	1.83 (1.1–2.9)	6.7	0.001	1.42 (0.9–2.3)	2.04	0.2
Mother's age						
<25	Reference			Reference		
26–29	0.78 (0.3–1.8)	0.33	0.6	0.8 (0.3–2.0)	0.2	0.7
≥30	2.56 (1.7–6.2)	4.7	0.03	2.6 (1.1–6.5)	4.9	0.03

Table 5.
Factors associated with the occurrence of congenital anomalies.

CA with $\chi^2 = 45.3$ and $p = <0.000$. CHD was 53.9%, cleft lip and palate 86.1%, Down syndrome 63.6%, and others and hydrocephalus 90.5 vs. 68.4%, respectively.

We analyzed the type of congenital anomalies with the mother's age (30 years over) and parental consanguinity. Overall, 28.8% of the anomalies were to mothers aged 30 years and over, 13.5% of the anomalies from consanguineous marriage. It's found there was no association between two factors and type of congenital anomalies (**Table 4**).

To found the parental consanguinity was confounder risk factors for increased the risk of congenital anomalies the odds and adjusted odds ratio was calculated **Table 5**. Consanguineous marriage will have a greater risk of having children with CA, (odds 1.83, CI 1.1–2.9, χ^2, 6.7, and $P = 0.001$). Increasing age of the mothers 30 years and over also increases the risk of congenital anomalies (odds 2.56, CI 1.7–6.2, χ^2, 4.7, $\boldsymbol{p} = 0.03$). When we adjusted consanguinity with the mother's age, it remains a risk factor for those mothers aged 30 and over for increasing the chance of CA (AOR 2.6, CI, 1.1–6.5, χ^2, 4.9, $p = 0.03$).

4. Discussion

The current study aimed to identify the association between parental consanguinity and congenital malformations and their types in the Maternity Teaching Hospital in Sulaimani City. The most common birth defects were congenital heart diseases, Down syndrome, and cleft lip and palate. They were presented in 25, 16.9, and 13.9% out of 260 congenital anomalies, respectively. Is similar to the studies done in Sulaimani [13, 14] and also is contrary to the study was done in Saudi Arabia [15]. The study demonstrated a highly significant difference between

the birth weight of newborn (low birth weight < 2500 kg) with different types of congenital anomalies with $p = 0.006$. Is corresponding with the population study was performed in Centers for Disease Control, Atlanta and the case–control study done in Sulaimani, Iraq [13, 16] and also gender showed that there is a significant difference with types of congenital anomalies which is in accordance with the study done in Neliti and the United State [11, 17], while is in contrary with the studies done in Sulaimani and Iran [13, 18]. When we analyzed parental consanguinity with the patterns of anomalies, we found there is no correlation between these factors with types of CA. These findings are consistent with the study on the prevalence of congenital malformations in consanguineous and non-consanguineous marriages [19], and also the study was done in India [20]. In addition, when we analyzed the rise of maternal age > 30 years with types of congenital malformations, we found no difference in this factor with the occurrence of congenital anomalies. Our finding is in contrary to a retrospective study in Latvia [21]. Our study represented consanguineous marriages that play a major role in the occurrence of congenital malformations compared with non-consanguineous marriage (odds 1.83), and when we adjusted consanguinity with maternal age, it remains a significant risk factor. The results are in agreement with the study [19] and the study done in Saudi Arabia [22]. Our finding shows no increased risk of advanced maternal age with congenital anomalies which is not in agreement with the study of the United States [23]. The current study has some limitations which should be considered before making extrapolation. The major limitation of this study was a retrospective case–control study based on data derived from passive sources of the hospital records. It is therefore likely that the study missed some data and congenital anomalies that do not present early in life, such as heart defects, pyloric stenosis, and anomalies of the urinary system, which could also explain the low level of defects found compared with other studies.

5. Conclusion

In conclusion, congenital anomalies were mostly observed among consanguineous marriage compared with non-consanguineous marriage. It is highly recommended that consanguineous marriages be prevented especially if the previous consanguinity is present in the family. Premarital counseling, especially on the subject of parental consanguinity, is advised.

Acknowledgements

We would like to express our gratitude to the staffs of the statistic section of the maternal and child care unit at Sulaimani Maternity Teaching Hospital and the child care unit of the Preventive Health Department for their help during the data collection process.

Author details

Niaz Mustafa Kamal
Anesthesia Department, Technical College of Health, Sulaimani Polytechnic University, Sulaimani, Iraq

*Address all correspondence to: niaz.kamal@spu.edu.iq

References

[1] Tanteles GA, Suri M. Classification and etiology of birth defects. Paediatrics and Child Health. 2007;**17**:233-243

[2] Mashuda F, Zuechner A, Chalya PL, Kidenya BR, Manyama M. Pattern and factors associated with congenital anomalies among young infants admitted at Bugando medical center, Mwanza, Tanzania. BMC Research Notes. 2014;**7**:195

[3] El Koumi MA, Al Banna EA, Lebda I. Pattern of congenital anomalies in newborn: A hospital-based study. Pediatric Reports. 2013;**5**

[4] Khoshkalam M, Eslamlou HF. The prevalence at birth of overt congenital anomalies in Urmia, northwestern Iran. Archives of Iranian Medicine. 2008;**11**:148-151

[5] Tayebi N, Yazdani K, Naghshin N. The prevalence of congenital malformations and its correlation with consanguineous marriages. Oman Medical Journal. 2010;**25**:37

[6] Rajangam S, Devi R. Consanguinity and chromosomal abnormality in mental retardation and or multiple congenital anomalies. Journal of the Anatomical Society of India. 2007;**56**:30-33

[7] Ali A, Zahad S, Masoumeh A, Azar A. Congenital malformations among live births at Arvand hospital, Ahwaz, Iran-a prospective study. Pakistan Journal of Medical Sciences. 2008;**24**:33

[8] Hamamy H. Consanguineous marriages. Journal of Community Genetics. 2012;**3**:185-192

[9] Bittles AH. Consanguinity and its relevance to clinical genetics. Clinical Genetics. 2001;**60**:89-98

[10] Taboo ZA-A. Prevalence and risk factors for congenital anomalies in Mosul city. Iraqi Academic Scientific Journal. 2012;**11**:458-470

[11] Rittler M, Liascovich R, López-Camelo J, Castilla EE. Parental consanguinity in specific types of congenital anomalies. American Journal of Medical Genetics. 2001;**102**:36-43

[12] World Health Organization. ICD-10: International Statistical Classification of Diseases and Related Health Problems. Geneva: World Health Organization; 1992

[13] Kamal NM, Othman N. Incidence and types of congenital anomalies in newborns in Sulaimaniyah City in Iraq. Acta Medica Iranica. 2018:769-776

[14] Kamal NM, Othman N. A case-control study for assessing risk factors for congenital anomalies among children in Sulaimani City. Kurdistan Journal of Applied Research. 2018:90-95

[15] Fida NM, Al-Aama J, Nichols W, Nichols W, Alqahtani M. A prospective study of congenital malformations among liveborn neonates at a university hospital in western Saudi Arabia. Saudi Medical Journal. 2007;**28**:1367-1373

[16] Mili F, Edmonds LD, Khoury MJ, McClearn AB. Prevalence of birth defects among low-birth-weight infants: A population study. The American Journal of Diseases of Children. 1991;**145**:1313-1318

[17] Elghanmi A, Razine R, Berrada R. Gender difference in specific congenital anomalies. World Journal of Research and Review;**5**

[18] Karbasi SA, Golestan M, Fallah R, Mirnaseri F, Barkhordari K, Bafghee MS. Prevalence of congenital

malformations. Acta Medica Iranica. 2009:149-153

[19] Movahedian A, Mosayebi Z, Yosofian S. The prevalence of congenital malformations in consanguineous and nonconsanguineous marriages. Feyz Journal. 2005;**81**:84-88

[20] Nath A, Patil C, Naik V. Prevalence of consanguineous marriages in a rural community and its effect on pregnancy outcome. Indian Journal of Community Medicine. 2004;**29**:3

[21] Zile I, Villerusa A. Maternal age-associated congenital anomalies among newborns: A retrospective study in Latvia. Medicina (Kaunas, Lithuania). 2013;**49**:29-35

[22] Murshid WR. Spina bifida in Saudi Arabia: Is consanguinity among the parents a risk factor? Pediatric Neurosurgery. 2000;**32**:10-12

[23] Goetzinger KR, Shanks AL, Odibo AO, Macones GA, Cahill AG. Advanced maternal age and the risk of major congenital anomalies. American Journal of Perinatology. 2017;**34**:217-222

Chapter 6

Low Birth Weight and Adverse Perinatal Outcomes

Melaku Desta

Abstract

Globally, annually an estimated 15–20% of all births are low birth weight (LBW). Low birth weights are at a greater risk of neonatal and postneonatal mortality and morbidities. Therefore, this chapter is aimed to highlight the prevalence of low birth weight, predictors and adverse perinatal outcomes, and the respective possible prevention modalities. Sociodemographic, obstetric (previous abortion, hypertensive disorder, antenatal visits, and prematurity), and nutritional factors increased the risk of low birth weight. Low birth weight neonates were associated with adverse perinatal and childhood outcomes: low Apgar score, neonatal death, malnutrition, academic, and mental disorders. Improving the care of women who have previous or recent morbidities, hypertensive disorders of pregnancy, and prematurity should be priorities aimed at reducing low birth weight and its adverse perinatal outcomes. Incorporating mental health in the prenatal visit, improving the care for a high-risk pregnant woman, and community-based kangaroo mother care practice were also recommended.

Keywords: low birth weight, prematurity, adverse perinatal outcome

1. Introduction

Low birth weight (LBW) is defined as a weight of <2500 g (5.5 lb) at birth. Low birth weight includes both appropriately grown preterm neonates (<37 completed weeks of gestation) and term and preterm growth-restricted neonates (less than the 10th centile of weight for gestational age). It is an important marker of maternal and fetal health, predicting mortality, stunting, and adult-onset chronic conditions [1]. Globally an estimated 15–20% of all births are low birth weight, representing more than 20 million births a year [1, 2]. In 2015, an estimated 20.5 million live births were LBW, 91% from low-and-middle-income countries, 48% in Southern Asia, and 24% at sub-Saharan Africa [3].

Low birth weight is associated with short- and long-term complications such as prematurity and its associated morbidities; 1.1 million babies die from complications of prematurity accompanied with LBW. Neonates with LBW have a higher risk of mortality than neonates with normal birth weight [4, 5]. Those who survive tend to remain that predispose newborns to many health disorders: hypoglycemia [6–8], hypothermia [9, 10], neurodevelopmental problems (mental retardation) [11], malnutrition, and have impaired immune function. Low birth weight neonates are not only at high risk of death but also are at increased risk of long-term neurologic disability, impaired language development, reduced cognitive abilities,

and greater risk of medical disorders including cardiovascular disease and diabetes [1, 12, 13]. Moreover, immaturity of multiple organs resulted in respiratory distress, interventricular hemorrhage, sepsis, blindness, and gastrointestinal disorders [14]. Medical conditions, medications prescribed, and mortality rate were significantly higher among preterm and underweight neonates admitted to NICU [15].

Maternal dietary diversity practice was associated with the risk of LBW. Low birth weight was also associated with multiple gestations, previous abortion, socioeconomic status, infections, maternal lifestyle, and complications during pregnancy: hypertensive disorders, fetal infection, and placental pathologic conditions [2, 16, 17]. Different stakeholders are working against reducing low birth weight by 30% by the year 2025 [18]. Despite those activities, low birth weight is increasing in Ethiopia based on 11% in 2011 to 13% in 2016 [10–12] and developing countries. Concerning perinatal outcomes, there is a paucity of study across the globe. Therefore, this chapter aimed to highlight the prevalence, predictors, and adverse perinatal outcomes of low birth weight newborns as well as the possible preventive modalities.

2. Epidemiology of low birth weight

Globally an estimated 15–20% of all births are low birth weight, representing more than 20 million births a year [1]. LBW was lowered in developed countries [19]. The prevalence of LBW varies in in the world, which was higher in African countries [20, 21] and which was 15.9% in 10 developing countries based on the demographic and health surveillance data [20]: 13.45 in Burkina Faso, 10.2% Ghana, 12.15 in Malawi, 15.7% in Senegal, and 10% in Uganda, respectively [22]. The incidence of LBW in Ethiopia hospital was 16.6% in Hawassa and 17% in Ethiopia based on the recent meta-analysis [23]. The findings of Zambia [24] and Tanzania [25] showed 10.6% of prevalence of LBW. The highest prevalence that occurred in developing countries might be due to the high prevalence of home delivery, preterm delivery, and hypertension during pregnancy, antepartum hemorrhage, and study area difference, which increased the referral of complicated cases and increased risk of LBW. Studies revealed that the prevalence of LBW varies across the countries: 7.3% in Nigeria [26], 40.0% in India, and 5–12% in Iran [27].

3. Predictors of low birth weight

The most common diagnoses associated with indicated low birth weight and preterm birth are hypertensive disorders, hemorrhage, and acute or chronic fetal compromise (fetal distress or intrauterine growth restriction). A recent study in Hawassa University Comprehensive Specialized Hospital, Southern Ethiopia, showed that previous abortion, hypertensive disorder of pregnancy, frequency of ANC visit, and gestational age at birth were the commonest predictors of LBW [28]. Sociodemographic (**Figure 1**),

3.1 Sociodemographic factors

Maternal age was a significant predictor of LBW. A study in developing countries [20], maternal age of 35–49 years old increased the odds of LBW. In addition, maternal age <20 years [23, 26, 29], absence of social support [27, 30] and rural

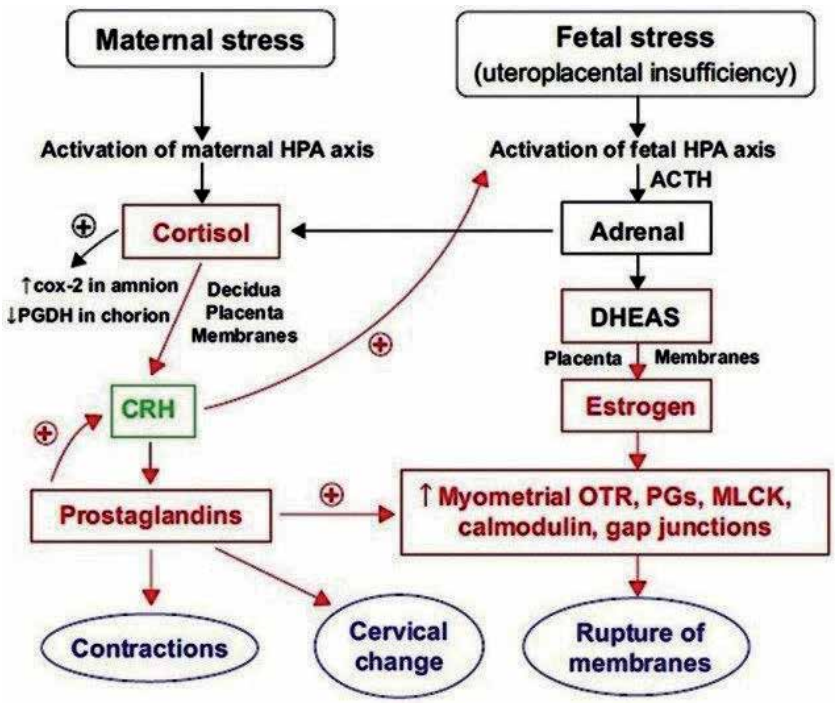

Figure 1.
Pathophysiology of preterm birth and low birth weight due to stress.

residence [31, 32], and absence of formal education [20, 27, 33, 34] were another factor associated with LBW.

3.2 Obstetrical factors

Prematurity was the single most predictive of LBW in the world. It is evidenced by different studies [26, 29, 34–37], and gestational age below 37 weeks significantly increased the risk of LWB. Those women who deliver before 37 completed weeks are more at risk to give low-weight births. This is in accordance with different studies [36], and a systematic review and meta-analysis done in Ethiopia [23] reported that preterm birth was significantly associated with the increased odds of LBW. When the neonates were delivered before reaching the recommended due date of delivery or 37–42 weeks, they are likely to be small and to have decreased skeletal muscle mass and subcutaneous fat tissue. Moreover, hypertension, preeclampsia and eclampsia [29, 35], lack of antenatal care follow-up [20, 27, 30, 36, 38–41], pregnancy interval <24 months [23, 39], depression during pregnancy [42], and maternal near miss [37, 43–45] were also other common predictors of LBW. A recent study done in Ethiopia also found that mothers who have a previous abortion, frequency of ANC visit, gestational age at birth, and hypertensive disorders of pregnancy were significant predictors of low weight at birth.

Moreover, hypertensive disorder of pregnancy, a leading cause of maternal near miss and perinatal mortality, has a significant effect on the increasing trend of LBW in Africa. There was a higher risk of delivering a low-weight infant among mothers with hypertension during pregnancy as compared with their counterparts [28]. The association is increased if the delivery occurs before reaching

37 weeks of gestation [46]. Other studies have similar findings [36]. This can be due the reason that hypertension results in uteroplacental insufficiency. Similarly, the studies also reported that mothers who had fewer ANV visit than the WHO recommendations (<4 ANC visit) were more likely to give a low-weight newborn than those who adhered to the recommended ANC visits, who have more than four times [28]. This is also supported by other evidences [36, 40, 47]. This is similar with studies done by Gizaw et al. [27], Mahmud et al. [20], Outlay et al. [40], and Kamala et al. [48].

In addition, findings also showed that those women who have at least one previous abortion were at greatest risk of giving LBW neonates as evidenced by a study done in Ethiopia [28], Denmark, and the USA [49, 50] and a meta-analysis in Canada [17]. The report also in-line with the study by Bossley [51] showed that women who had an abortion in the first or second trimester had a 35% increased risk of a LBW baby and a 36% raised risk of a preterm baby in later pregnancies and Ethiopia [52] found that previous adverse pregnancy outcomes were associated with recent outcome. This can be explained by physical damage to the cervix caused by types of abortion, reduced tensile strength of the cervical plug, preterm birth subsequently causing LBW, and stress/depression for the previous occurrence of the event. Thus, stress-depression is significantly associated with previous abortion [53, 54] and lowers dietary diversity of women, reduces fetal nutrients vital for development, and leads to an increased risk of LBW. In addition, untreated antenatal depression was also another significant predictor of; a meta-analysis revealed that women who have antenatal depression [55] and maternal anemia [56, 57] were more likely to have LBW.

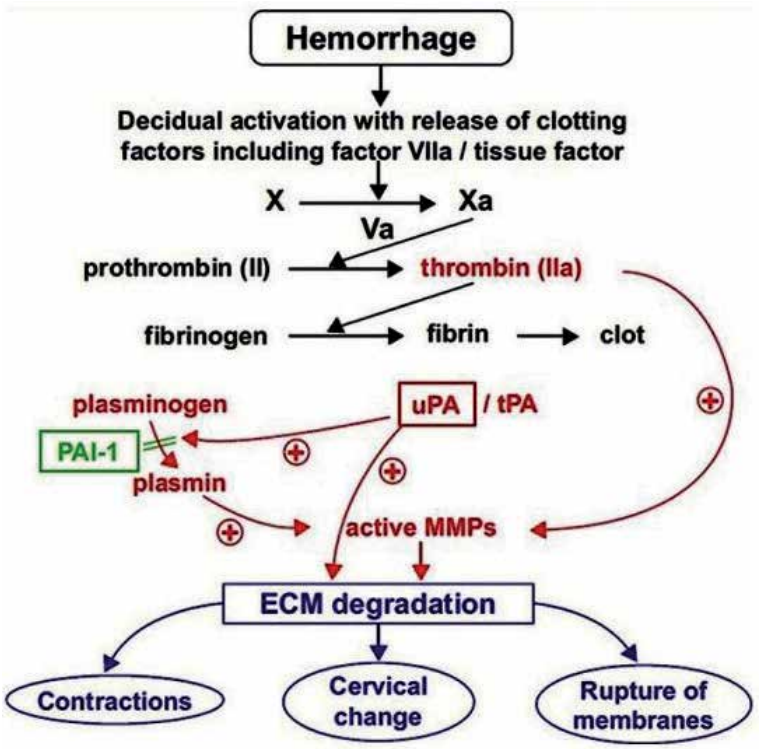

Figure 2.
Association of hemorrhage and preterm labor/LBW.

3.3 Nutritional factors

A study in Tanzania showed that pregnant women with malnutrition were another factor that increased the risk of LBW [35]. Studies done in developing countries [20, 39], meta-analysis done in Ethiopia [22, 23], and another study [29, 31] showed that BMI <18.5 kg/m increased the odd of LBW. Another study done in Ethiopia also showed that lacking nutrition counseling during pregnancy, lacking iron/folic acid supplementation during pregnancy [34, 36, 58–60], not taking snacks during pregnancy, maternal undernutrition, maternal anemia, and inadequate minimum dietary diversity score of women were independently associated with LBW.

An evidence-based medicine showed that the benefits of iron supplements in improving birth weight illustrate the need for increased efforts to improving coverage of antenatal programs and promoting food fortification. Underlying social factors, such as poverty and women's status, are also important, especially in South Asia [61]. Strategies that combine nutrition-based interventions, such as improving food intakes and micronutrient status, especially iron status, with approaches that improve women's status and reproductive health are needed to reduce LBW (**Figure 2**).

4. Adverse perinatal outcomes of low birth weight

Important birth outcomes related to LBW include both fetal and neonatal death, postneonatal death, short-term morbidities such as respiratory distress syndrome and necrotizing enter colitis, and long-term morbidities such as blindness, deafness, hydrocephaly, mental retardation, and cerebral palsy.

A recent study revealed that 68% of the LBW neonates and 48% of the NBW neonates had adverse perinatal outcomes [28]. LBW newborns significantly increased the greater risk of low Apgar score (42%), early neonatal death (19.3%) and NICU admission (22.6%) [28], and increased chronic kidney disease (CKD) [62]. Similarly, LBW newborns are associated with an increased risk of a low Apgar score and early neonatal death as evidenced with a study in Brazil [63] and Tanzania [25]; Bangladesh [63] showed that the probability of early neonatal mortality was increased among LBW newborns. The possible reason for this can be explained due to that low weight increases the risk of intrauterine growth restriction and early neonatal death. It is also explained due to the high burden of preterm birth and its complications. Hence, several organ systems of the human fetus usually immature before the end of 37 weeks of gestational age lead to difficult to maintain extrauterine environment.

Accordingly, LBW infants experienced a higher fold of mortality rate and hospitalization than appropriate birth weight infants in the postneonatal period. LBW infants also experienced 33% more days with diarrhea and 32% more days with vomiting [64]. Moreover, studies revealed that LBW affects adulthood social relationships and lower educational qualifications, decreased rate of employment, and increased rate of receipt of social benefits in adulthood [65, 66], disability [67], and common chronic health conditions [68]. A systematic review and meta-analysis supported that adults born with LBW were less likely to have ever experienced a romantic partnership, to have had sexual intercourse to have become parents (OR) [66]. This might be due to the lack of sexual or partner relationships that might increase the risk of decreased well-being and poorer physical and mental health and subsequent psychiatric disorders. Thus, children born with LBW had an increased risk of neurocognitive impairment [69].

5. Prevention of low birth weight and associated adverse outcomes

5.1 Prevention of preterm birth or prematurity

Prematurity is the single leading cause of neonatal mortality, resulting from 35% of the world's deaths annually (3.1 million) and risk of lifelong impairment among survivor [70, 71], and cause of child death in all high- and middle-income countries [71] when accompanied with LBW. For this, prevention of preterm birth is the major area of intervention. As a result, the March of Dimes plans to reduce prematurity to 8.1% in 2020 and 5.5% in 2030 in the USA [72]. To achieve this goal, the following roadmap interventions in the area and in the globe should be followed in appropriate manner:

- Elimination of nonmedically indicated early elective deliveries
- Access to progesterone shots for women with a previous preterm birth
- Smoking cessation
- Birth spacing and expanding group prenatal care
- Low-dose aspirin to prevent preeclampsia
- Vaginal progesterone and cerclage for short cervix
- Reduce multiple births conceived through assisted reproductive technology

5.1.1 Elimination of nonmedically indicated elective deliveries

Inductions and cesarean sections (CS) scheduled before 39 weeks gestation without medical reason increase the risk of early-term and late-preterm birth and their health consequences [72]. The rate of cesarean section is increasing globally.

5.1.2 Use of progesterone to prevent recurrent preterm birth

The weekly progesterone injections for at-risk women starting at 16–21 weeks gestation is a proven recommendation to reduce very early as well as later preterm birth effectively in women with a prior preterm birth [72]. Different clinical trials supported that early initiation of intramuscular 17-alpha hydroxyprogesterone caproate is recommended to prevent preterm birth [73]. Women starting with early initiation (at a mean $17^{6/7}$ ± 2.5 weeks) of 17-alpha hydroxyprogesterone caproate trended toward lower rates of preterm birth <37 weeks than those with late-start 17-alpha hydroxyprogesterone caproate (17P), which reduce a woman's risk of recurrent preterm birth by 33% [74]. Later initiation of 17-alpha hydroxyprogesterone caproate was significantly associated with increased odds of preterm birth <37 weeks. In addition to this, women with early 17-alpha hydroxyprogesterone caproate initiation also had lower rates of major neonatal morbidity than those with later 17-alpha hydroxyprogesterone caproate initiation [73]. The effectiveness of 17-hydroxyprogesterone caproate is reduced as the gestational age increased; nonresponders increased as evidenced by a study done by Manuck and his collaborator's [75]. Consideration of the factors that increased nonresponse for the hormone should be considered during initiation, mainly placental abruption or significant

vaginal bleeding, gonorrhea and/or chlamydia in the current pregnancy carriage of a male fetus. For thus, a clinical prediction score is needed before prescribing the hormone [75].

A meta-analysis of clinical trial showed that regarding the safety or efficacy of vaginal progesterone versus injections, daily vaginal progesterone (either 100–200 mg suppository daily or 90 mg gel daily) started at about 16 weeks' gestation is reasonable, if not weekly 17-OHPC injection for prevention of SPTB in women with singleton gestations and prior SPTB despite low level of quality [76]. The rate of women who reported recurrence of preterm birth adverse drug reactions and rate of neonatal intensive care unit admission was significantly lower in the vaginal progesterone group than the 17-OHPC neonatal outcomes. In addition, cervical Pessary is another prevention of spontaneous preterm birth in women with singleton pregnancies and short cervical length based on a recent clinical trial [77].

5.1.3 Low-dose aspirin and birth spacing

Preeclampsia can only be cured by delivering the infant, regardless of the gestational age in case of severe preeclampsia and eclampsia. The US Preventive Services Task Force and Prematurity Campaign recommends that all at-risk women should take a daily low-dose aspirin [72]. The initiation of daily low-dose (60–80 mg) aspirin beginning in the late first trimester for women with a medical history of early-onset preeclampsia and preterm delivery at <34.0/7 weeks of gestation or preeclampsia in more than one prior pregnancy was recommended by the American College of Obstetrics and Gynecology. In addition, appropriate inter-birth interval according to the WHO recommendations at least 24 months is better to reduce preterm birth. A meta-analysis [78] supported that short birth interval was associated with preterm birth.

5.2 Improving kangaroo mother care (KMC) utilization

Kangaroo mother care (KMC) is the placement of the newborn baby into skin-to-skin contact with the mother's chest and abdomen coupled with frequent and preferably exclusive breastfeeding. Thus, the premature baby or LBW newborn is kept warm in the maternal pouch and close to the breasts for unlimited feeding. KMC has emerged as a nonconventional low-cost method for newborn care that provides warmth and touch and confers significant survival benefit. An updated Cochrane review has reported that KMC benefits breastfeeding outcomes and cardiorespiratory stability in infants without negative effects [79]. Thus, findings of the clinical trial done in India support that wider implementation of KMC has a significant improvement in vital physiological parameters of LBW newborn; individual abnormalities (hypothermia, bradycardia, tachycardia, and low SpO_2) were corrected during the KMC sessions [80] and 51% reduction of early neonatal mortality and series morbidities associated with preterm birth based on the meta-analysis findings [81]. The utilization of KMC service is lower in LMICs among preterm newborn; only 14% of LBW newborn and <25% of preterm babies receive KMC in Ethiopia. For this, to improve the service provision of training of health-care facilities, community-based education on KMC should be focused, and community-based KMC should be improved [82]. Hence, provision of training of hospital-provided KMC services increases to 36% of preterm babies in Ethiopia [83]. In addition, a KMC indicator has been included in the HMIS. It is expected that there will be a national-level data about the preterm babies who are initiated in KMC [84].

Kangaroo mother care adapted from a meta-analysis done in LMICs (put on cover page) [81].

6. Conclusions

Sociodemographic, obstetrical factors (previous abortion, hypertensive disorder, antenatal visits and prematurity), and nutritional factors increased the risk of low birth weight. Low birth weight neonates were associated with adverse perinatal and childhood outcome: low Apgar score, neonatal death, malnutrition, academic, and mental disorders. Improving the care of women who have previous or recent morbidities, hypertensive disorders of pregnancy, and prematurity should be priorities aimed at reducing low birth weight and its adverse perinatal outcomes. Incorporating mental health in the prenatal visit, improving the care for a high-risk pregnant woman, and community-based kangaroo mother care practice were also recommended.

Acknowledgements

The authors are thankful for IntechOpen publisher for the invitation and consideration. The content is solely the responsibility of the author and does not necessarily represent the official views of ethical committee of an institution.

Conflict of interests

The authors declare no competing interests.

Authors' contributions

MD conceived and designed and revised and wrote up the book chapter.

Funding

No funding sources.

Abbreviations

ANC	ante natal care
ARR	adjusted relative risk
LBW	low birth weight
NBW	normal birth weight
WHO	World Health Organization

Author details

Melaku Desta
Department of Midwifery, College of Medicine and Heath Science, Debre Markos University, Debre Markos, Ethiopia

*Address all correspondence to: melakd2018@gmail.com

References

[1] WHO. Global Nutrition Targets 2025: Low Birth Weight Policy Brief. Geneva: World Health Organisation; 2014

[2] Wardlaw TM et al. Low Birthweight: Country, Regional and Global Estimates. New York: UNICEF; 2004

[3] Blencowe H, Krasevec J, de Onis M, Black RE, An X, Stevens GA, et al. National, regional, and worldwide estimates of low birthweight in 2015, with trends from 2000: A systematic analysis. The Lancet Global Health. 2019;**7**(7):e849-ee60

[4] Kramer MS et al. Determinants of low birth weight: Methodological assessment and meta-analysis. Bulletin of the World Health Organization. 1987;**65**(5):663

[5] Badshah SML, McKelvie K, Payne R, Lisboa PJ. Risk factors for low birthweight in the public-hospitals at Peshawar, NWFP-Pakistan. BMC Public Health. 2008;**8**(1):197

[6] Azoumah K, Djadou K, Aboubakari A, Bothon A, Agbodjan-Djossou O, Agbèrè A. Evaluation of the glycemia of low-weight newborns within the 24th hour of life at Lomé University Hospital (Togo). Archives de Pediatrie: Organe Officiel de la Societe Francaise de Pediatrie. 2011;**18**(10):1037-1043

[7] Zhou W, Yu J, Wu Y, Zhang H. Hypoglycemia incidence and risk factors assessment in hospitalized neonates. The Journal of Maternal-Fetal & Neonatal Medicine. 2015;**28**(4):422-425

[8] Lubchenco LO, Bard H. Incidence of hypoglycemia in newborn infants classified by birth weight and gestational age. Pediatrics. 1971;**47**(5):831-838

[9] Tasew H, Gebrekristos K, Kidanu K, Mariye T, Teklay G. Determinants of hypothermia on neonates admitted to the intensive care unit of public hospitals of central zone, Tigray, Ethiopia 2017: Unmatched case-control study. BMC Research Notes. 2018;**11**(1):576

[10] Seyum T, Ebrahim E. Proportion of neonatal hypothermia and associated factors among new-borns at Gondar University teaching and Referral hospital, Northwest Ethiopia: A hospital based cross sectional study. General Medicine: Open Access. 2015;**2015**

[11] Gutbrod T, Wolke D, Soehne B, Ohrt B, Riegel K. Effects of gestation and birth weight on the growth and development of very low birth weight small for gestational age infants: A matched group comparison. Archives of Disease in Childhood. Fetal and Neonatal Edition. 2000;**82**(3):F208-F214

[12] Zerbeto AB, Cortelo FM, Élio Filho B. Association between gestational age and birth weight on the language development of Brazilian children: A systematic review. Jornal de Pediatria (Versão em Português). 2015;**91**(4):326-332

[13] UNICEF. Undernourishment in the Womb Can Lead to Diminished Potential and Predispose Infants to Early Death. New York: UNICEF; 2016

[14] You DHL, Ejdemyr S, Idele P, Hogan D, Mathers C, et al. Global, regional, and national levels and trends in under-5 mortality between 1990 and 2015, with scenario-based projections to 2030: A systematic analysis by the UN inter-agency group for child mortality estimation. Lancet. 2015;**386**(10010):2275-2286

[15] Undela K, Mohammed BTS, Gurumurthy P, Doreswamy SM. Impact of preterm birth and low birth weight

on medical conditions, medication use and mortality among neonates: A prospective observational cohort study. World Journal of Pediatrics. 2019:1-8

[16] Villar JPA, Knight HE, Gravett MG, Iams J, Waller SA, et al. The preterm birth syndrome: A prototype phenotypic classification. American Journal of Obstetrics and Gynecology. 2012;**206**(2):119-123

[17] Shah PS, Zao J, Births KSGoDoPL. Induced termination of pregnancy and low birthweight and preterm birth: A systematic review and meta-analyses. BJOG: An International Journal of Obstetrics & Gynaecology. 2009;**116**(11):1425-1442

[18] WHO. WHA Global Nutrition Targets 2025: Low Birth Weight Policy Brief. Geneva: WHO; 2014. [Accessed on: 1 June 2017]

[19] Goldenberg RL, Culhane JF. Low birth weight in the United States. The American Journal of Clinical Nutrition. 2007;**85**(2):584S-590S

[20] Mahumud RA, Sultana M, Sarker AR. Distribution and determinants of low birth weight in developing countries. Journal of Preventive Medicine and Public Health. 2017;**50**(1):18

[21] Qadir M, Bhutta ZA. Low birth weight in developing countries. In: Small for Gestational Age. Vol. 13. Karger Publishers; 2009. pp. 148-162

[22] He Z, Bishwajit G, Yaya S, Cheng Z, Zou D, Zhou Y. Prevalence of low birth weight and its association with maternal body weight status in selected countries in Africa: A cross-sectional study. BMJ Open. 2018;**8**(8):e020410-e

[23] Endalamaw A, Engeda EH, Ekubagewargies DT, Belay GM, Tefera MA. Low birth weight and its associated factors in Ethiopia: A systematic review and meta-analysis. Italian Journal of Pediatrics. 2018;**44**(1):141

[24] Chibwesha CJ, Zanolini A, Smid M, Vwalika B, Kasaro MP, Mwanahamuntu M, et al. Predictors and outcomes of low birth weight in Lusaka, Zambia. International Journal of Gynecology & Obstetrics. 2016;**134**(3):309-314

[25] Mitao M, Philemon R, Obure J, Mmbaga BT, Msuya S, Mahande MJ. Risk factors and adverse perinatal outcome associated with low birth weight in Northern Tanzania: A registry-based retrospective cohort study. Asian Pacific Journal of Reproduction. 2016;**5**(1):75-79

[26] Dahlui M, Azahar N, Oche OM, Aziz NA. Risk factors for low birth weight in Nigeria: Evidence from the 2013 Nigeria demographic and health survey. Global Health Action. 2016;**9**(1):28822

[27] Karimlou M, Sajjadi H, Dejman M, Vameghi M. Low birth weight and its association factors in Iran: According world health organization model. Archives of Rehabilitation. 2012;**13**(3):75-87

[28] Desta M, Tadese M, Kassie B, Gedefaw M. Determinants and adverse perinatal outcomes of low birth weight newborns delivered in Hawassa University Comprehensive Specialized Hospital, Ethiopia: A cohort study. BMC Research Notes. 2019;**12**(1):118

[29] Sutan R, Mohtar M, Mahat AN, Tamil AM. Determinant of low birth weight infants: A matched case control study. Open Journal of Preventive Medicine. 2014;**4**(03):91

[30] Wado YD, Afework MF, Hindin MJ. Effects of maternal pregnancy intention, depressive symptoms and social support on risk of low birth weight:

A prospective study from southwestern Ethiopia. PLoS One. 2014;**9**(5):e96304

[31] Valadbeigi T, Tabatabaee HR, Etemad K, Keyghobadi N, Mahdavi S, Enayatrad M, et al. The association between low birth weight and mothers diseases in Iran: A case-control study. Journal of Neonatal-Perinatal Medicine. 2019

[32] Mekie M, Taklual W. Magnitude of low birth weight and maternal risk factors among women who delivered in Debre Tabor Hospital, Amhara Region, Ethiopia: A facility based cross-sectional study. Italian Journal of Pediatrics. 2019;**45**(1):86

[33] Apte A, Patil R, Lele P, Choudhari B, Bhattacharjee T, Bavdekar A, et al. Demographic surveillance over 12 years helps elicit determinants of low birth weights in India. PLoS One. 2019;**14**(7):e0218587

[34] Adam Z, Ameme DK, Nortey P, Afari EA, Kenu E. Determinants of low birth weight in neonates born in three hospitals in Brong Ahafo region, Ghana, 2016—An unmatched case-control study. BMC Pregnancy and Childbirth. 2019;**19**(1):174

[35] Siza J. Risk factors associated with low birth weight of neonates among pregnant women attending a referral hospital in northern Tanzania. Tanzania Journal of Health Research. 2008;**10**(1):1-8

[36] Asmare G, Berhan N, Berhanu M, Alebel A. Determinants of low birth weight among neonates born in Amhara regional state referral hospitals of Ethiopia: Unmatched case control study. BMC Research Notes. 2018;**11**(1):447

[37] Hailu LD, Kebede DL. Determinants of low birth weight among deliveries at a referral Hospital in Northern Ethiopia. BioMed Research International. 2018;**2018**

[38] Zeleke BM, Zelalem M, Mohammed N. Incidence and correlates of low birth weight at a referral hospital in Northwest Ethiopia. The Pan African Medical Journal. 2012;**12**(1)

[39] Demelash H, Motbainor A, Nigatu D, Gashaw K, Melese A. Risk factors for low birth weight in Bale zone hospitals, South-East Ethiopia: A case–control study. BMC Pregnancy and Childbirth. 2015;**15**(1):264

[40] Oulay L, Laohasiriwong W, Phajan T, Assana S, Suwannaphant K. Effect of antenatal care on low birth weight prevention in Lao PDR: A case control study. F1000 Research. 2018;**7**

[41] Aboye W, Berhe T, Birhane T, Gerensea H. Prevalence and associated factors of low birth weight in Axum town, Tigray, North Ethiopia. BMC Research Notes. 2018;**11**(1):684

[42] Grote NK, Bridge JA, Gavin AR, Melville JL, Iyengar S, Katon WJ. A meta-analysis of depression during pregnancy and the risk of preterm birth, low birth weight, and intrauterine growth restriction risk of PTB, LBW, and IUGR with antenatal depression. JAMA Psychiatry. 2010;**67**(10):1012-1024

[43] Liyew EF, Yalew AW, Afework MF, Essén B. Maternal near-miss and the risk of adverse perinatal outcomes: A prospective cohort study in selected public hospitals of Addis Ababa, Ethiopia. BMC Pregnancy and Childbirth. 2018;**18**(1):345

[44] Adeoye IA, Onayade AA, Fatusi AO. Incidence, determinants and perinatal outcomes of near miss maternal morbidity in Ile-Ife Nigeria: A prospective case control study. BMC Pregnancy and Childbirth. 2013;**13**(1):93

[45] Oliveira LC, Costa AA. Fetal and neonatal deaths among cases of maternal near miss. Revista

da Associação Médica Brasileira. 2013;**59**(5):487-494

[46] Xiong X, Demianczuk NN, Saunders LD, Wang F-L, Fraser WD. Impact of preeclampsia and gestational hypertension on birth weight by gestational age. American Journal of Epidemiology. 2002;**155**(3):203-209

[47] Nobile CG, Raffaele G, Altomare C, Pavia M. Influence of maternal and social factors as predictors of low birth weight in Italy. BMC Public Health. 2007;**7**(1):192

[48] Kamala BA, Mgaya AH, Ngarina MM, Kidanto HL. Predictors of low birth weight and 24-hour perinatal outcomes at Muhimbili National Hospital in Dar es Salaam, Tanzania: A five-year retrospective analysis of obstetric records. The Pan African Medical Journal. 2018;**29**(1):1-13

[49] Zhou W, Sørensen HT, Olsen J. Induced abortion and low birthweight in the following pregnancy. International Journal of Epidemiology. 2000;**29**(1):100-106

[50] Brown J, Adera T, Masho S. Previous abortion and the risk of low birth weight and preterm births. Journal of Epidemiology and Community Health. 2008;**62**(1):16-22

[51] Boseley S. Abortions may pose risk to future babies, according to study. The Guardian. 2009

[52] Tsegaye B, Kassa A. Prevalence of adverse birth outcome and associated factors among women who delivered in Hawassa town governmental health institutions, South Ethiopia, in 2017. Reproductive Health. 2018;**15**(1):193

[53] Bisetegn TA, Mihretie G, Muche T. Prevalence and predictors of depression among pregnant women in Debre Tabor town, Northwest Ethiopia. PLoS One. 2016;**11**(9):e0161108

[54] Abajobir AA, Alati R, Kisely S, Najman JM. Are past adverse pregnancy outcomes associated with maternal anxiety and depressive symptoms in a sample of currently pregnant women? Ethiopian Journal of Health Sciences. 2017;**27**(4):351-362

[55] Jarde A, Morais M, Kingston D, Giallo R, MacQueen GM, Giglia L, et al. Neonatal outcomes in women with untreated antenatal depression compared with women without depression: A systematic review and meta-analysis. JAMA Psychiatry. 2016;**73**(8):826-837

[56] Rahman MM, Abe SK, Rahman MS, Kanda M, Narita S, Bilano V, et al. Maternal anemia and risk of adverse birth and health outcomes in low- and middle-income countries: Systematic review and meta-analysis. The American Journal of Clinical Nutrition. 2016;**103**(2):495-504

[57] Bodeau-Livinec F, Briand V, Berger J, Xiong X, Massougbodji A, Day KP, et al. Maternal anemia in Benin: Prevalence, risk factors, and association with low birth weight. The American Journal of Tropical Medicine and Hygiene. 2011;**85**(3):414-420

[58] Ismail IM, Venugopalan P. Case-control study on risk factors of low birth weight in a tertiary care hospital, Kerala. Annals of Community Health. 2016;**4**(3):5-12

[59] Girma S, Fikadu T, Agdew E, Haftu D, Gedamu G, Dewana Z, et al. Factors associated with low birthweight among newborns delivered at public health facilities of Nekemte town, West Ethiopia: A case control study. BMC Pregnancy and Childbirth. 2019;**19**(1):220

[60] Mosha D, Liu E, Hertzmark E, Chan G, Sudfeld C, Masanja H, et al. Dietary iron and calcium intakes during pregnancy are associated with

lower risk of prematurity, stillbirth and neonatal mortality among women in Tanzania. Public Health Nutrition. 2017;**20**(4):678-686

[61] Ramakrishnan U. Nutrition and low birth weight: From research to practice. The American Journal of Clinical Nutrition. 2004;**79**(1):17-21

[62] White SL, Perkovic V, Cass A, Chang CL, Poulter NR, Spector T, et al. Is low birth weight an antecedent of CKD in later life? A systematic review of observational studies. American Journal of Kidney Diseases. 2009;**54**(2):248-261

[63] Gebremedhin M, Ambaw F, Admassu E, Berhane H. Maternal associated factors of low birth weight: A hospital based cross-sectional mixed study in Tigray, Northern Ethiopia. BMC Pregnancy and Childbirth. 2015;**15**(1):222

[64] PIC Lira AA, Morris SS. Low birth weight and morbidity from diarrhea and respiratory infection in Northeast Brazil. The Journal of Pediatrics. 1996

[65] Bilgin A, Mendonca M, Wolke D. Preterm birth/low birth weight and markers reflective of wealth in adulthood: A meta-analysis. Pediatrics. 2018;**142**(1)

[66] Mendonça M, Bilgin A, Wolke D. Association of preterm birth and low birth weight with romantic partnership, sexual intercourse, and parenthood in adulthood: A systematic review and meta-analysis. JAMA Network Open. 2019;**2**(7):e196961-e

[67] Doyle LW, Anderson PJ. Adult outcome of extremely preterm infants. Pediatrics. 2010;**126**(2):342-351

[68] Saigal S, Day KL, Van Lieshout RJ, Schmidt LA, Morrison KM, Boyle MH. Health, wealth, social integration, and sexuality of extremely low-birth-weight prematurely born adults in the fourth decade of life lifestyle, social integration, and sexuality of ELBW adults lifestyle, social integration, and sexuality of ELBW adults. JAMA Pediatrics. 2016;**170**(7):678-686

[69] Aarnoudse-Moens CSH, Weisglas-Kuperus N, van Goudoever JB, Oosterlaan J. Meta-analysis of neurobehavioral outcomes in very preterm and/or very low birth weight children. Pediatrics. 2009;**124**(2):717-728

[70] Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: A systematic analysis for the global burden of disease study 2010. Lancet. 2012;**380**:2197-2223

[71] Liu L, Johnson HL, Cousens S, Perin J, Scott S, Lawn J, et al. Global, regional and national causes of child mortality: An updated systematic analysis for 2010 with time trends since 2000. The Lancet. 2012;**379**:2151-2161

[72] Edward RBM, Carrino GE, Russell RB, Howse JL. Fighting for the next generation: US prematurity in 2030. American Academy of Pediatrics. 2014

[73] Ning A, Vladutiu CJ, Dotters-Katz SK, Goodnight WH, Manuck TA. Gestational age at initiation of 17-alpha hydroxyprogesterone caproate and recurrent preterm birth. American Journal of Obstetrics and Gynecology. 2017;**217**(3):371.e1-371.e7

[74] ACOG Committee Opinion. Prediction & prevention of preterm birth. 2012

[75] Manuck TA, Stoddard GJ, Fry RC, Esplin MS, Varner MW. Nonresponse to 17-alpha hydroxyprogesterone caproate for recurrent spontaneous preterm birth prevention: Clinical prediction

and generation of a risk scoring system. American Journal of Obstetrics and Gynecology. 2016;**215**(5):622.e1-622.e8

[76] Saccone G, Khalifeh A, Elimian A, Bahrami E, Chaman-Ara K, Bahrami MA, et al. Vaginal progesterone vs intramuscular 17-alpha-hydroxyprogesterone caproate for prevention of recurrent spontaneous preterm birth in singleton gestations: Systematic review and meta-analysis of randomized controlled trials. Ultrasound in Obstetrics & Gynecology: The Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2017;**49**(3):315-321

[77] Saccone G, Maruotti GM, Giudicepietro A, Martinelli P. Effect of cervical pessary on spontaneous preterm birth in women with singleton pregnancies and short cervical length: A randomized clinical trial. Journal of the American Medical Association. 2017;**318**(23):2317-2324

[78] Conde-Agudelo. Birth spacing and adverse perinatal outcomes: A meta-analysis. JAMA. 2006;**295**(15):1809-1823

[79] Moore ER, Anderson G, Bergman N, Dowswell T. Early skin-to-skin contact for mothers and their healthy newborn infants. Cochrane Database of Systematic Reviews. 2012;**5**

[80] Bera A et al. Effect of KMC on physiology of newborn. Indian Journal of Community Medicine. 2014;**39**(4)

[81] Lawn JE, Mwansa-Kambafwile J, Horta BL, Barros FC, Cousens S. 'Kangaroo mother care' to prevent neonatal deaths due to preterm birth complications. International Journal of Epidemiology. 2010;**39**(suppl_1):i144-ii54

[82] Sloan NL, Ahmed S, Mitra SN, Choudhury N, Chowdhury M, Rob U, et al. Community-based kangaroo mother care to prevent neonatal and infant mortality: A randomized, controlled cluster trial. Pediatrics. 2008;**121**(5):e1047-e1e59

[83] Mathewos B, Sitrin D, Valsankar B, Musena Y, Tadesse L, Chan G, et al. Delivery of kangaroo mother care in ethiopian facilities: Results from a rapid assessment in three zones. 2015

[84] Central Statistical Agency (CSA) [Ethiopia] and ICF. Ethiopia Demographic and Health Survey 2016 [Online]. Available from: www.dhsprogram.com/data/dataset/Ethiopia_StandardDHS_2016.cfm?flag=1 2016

Chapter 7

Towards Salutogenetic Birth Space

Zalka Drglin

Abstract

How can we improve the birth space to protect the normal physiological birth; how do we enable, preserve and promote it? The place where childbirth takes place, including the persons in this space, affects a woman's well-being (she feels safe, connected, relaxed or scared, strained or endangered) and the way she responds as an incarnate being and also influences the course of childbirth. According to the effects of the place of giving birth, we distinguish between pathogenetic—experienced by the woman giving birth as dangerous, even hostile—and salutogenetic effects with "birthing shelter" characteristics. Modern findings of different disciplines (physiology, architecture, neuroscience, social and evolutional anthropology and culturology) contribute to our understanding of the complexity of childbirth, the needs of the woman and her baby and lead to maternity hospitals being designed as places of support for the holistic health of both; they also present basic recommendations for transforming maternity hospitals into salutogenetic birth places. We present changes that are taking place in the design of birth spaces and research results that are encouraging, supporting birth physiology at its best.

Keywords: salutogenetic childbirth environment, physiological birth, needs of birthing woman and newborn, maternity hospital design

1. Introduction: maternity hospital between pathogenesis and salutogenesis

This text regards the "birth environment" as every space where a woman gives birth, regardless of being a dedicated space such as a maternity hospital or a birth centre or a space temporarily adapted for birth (e.g., home birth), or an environment that was not deliberately chosen for birth (if the birth process surprises a woman and has such a rapid course that she has to give birth in an environment such as in a car). A birth environment consists of a birth space and the people in it. Before the intensive institutionalisation of birth, which peaked in the second half of the twentieth century, women normally gave birth in their home towns, most frequently at home or where contractions caught them. In the (post)modern globalised world, hospitals are perceived as a "normal" birth environment. As they are a predominant and socially desirable choice, they are often also compulsorily chosen as the only possible place for childbirth.

However, several different birth environments are appearing: midwifery units in hospitals and birth centres led by midwives. Home birth has never completely disappeared. This text relates to birth environments in healthcare institutions: both maternity departments in a hospital or autonomous maternity hospitals. We are focusing on a single aspect of the birth environment, the issue of "birth space". Another aspect is otherwise crucial for the birth process—people—the woman

giving birth, her relatives, the newborn, midwife, obstetrician and other medical experts and doulas—since we know that birth space significantly defines their well-being, actions and behaviour. Verbal and non-verbal messages are ideally mutually supporting (congruent) and relate to the messages of the birth space.

Buildings or different environments built and designed by humans—from micro- to macro-level, that is, from an individual residential space to a metropolis—influence health significantly. In the last quarter of the twentieth century, the number of studies of relations between built environments and health increased. The American architect Roslyn Lindheim is among key authors today regarded as one of the founders of interdisciplinary studies of health-related spaces and healthy places, including the hospital environment. In her article "Environments, People, and Health", published in 1983 and co-authored with S.L. Symen in the Annual Review of Public Health, she emphasised that our health is integrally dependent on two crucial types of bonds: bonds with other people and bonds with our biological and cultural heritage; if these are broken, our health is endangered [1]. With such insights, a new approach to hospital planning began: planning of spaces where ill and injured persons are treated. Contrary to self-evidently perceiving the hospital environment as non-harmful per se, research has shown that this environment either promotes health or influences it adversely and supports treatment, healing, recovery or not. Cooperation between architects, urbanists, psychologists, sociologists, theoreticians, who look at a space in terms of philosophy and cultural studies, and various medical experts has evolved gradually to co-create hospitals that would support health and transform existing buildings from potentially or actually "pathogenic" to more neutral or ideally to "salutogenetic environments". This transdisciplinary collaboration is essential, because it makes it possible to surpass the (overly) narrow traditional views of key phenomena, birth and space.

If we speak of a directly man-made environment and health, we think of the physical building and the environment it creates, of its psycho-social influence and of meanings of the space, man-made environment and equipment, as perceived/understood by an individual. The space enables certain activities but limits and prevents others and also (to a certain extent) defines how particular activities and a certain physical activity will be performed. The environment influences our well-being and our attitude towards a particular action. To sum up, individual messages of the space span from pathogenetic on the one hand to salutogenetic on the other, but their final effect is more than just a sum of these factors.

2. When a man is ill or injured, he/she needs a healing place, a "shelter"; we need a supportive environment in transformative processes: the old and the modern world

Since the beginnings of humanity, an ill or injured man sought shelter for healing; as healing tools and effective medication were scarce, a safe and supportive environment with natural forces that supported healing and recovery processes was especially significant [2]. Every approach to treatment is related to a specific culture and understanding of health, disease, life and transitions such as birth and death. According to historical sources, healing places were planned and designed, for example, in ancient Egypt—we should not forget that the architect Imhotep was also the first known doctor in the world—some temples were renowned healing places. The Egyptologist François Daumas discovered a sanatorium [3] in a temple, dedicated to the goddess Hator in Dendera in Egypt, while the temple complex in Deir el-Bahari was a place where pilgrims sought health during the Ptolemaic era. In ancient Greece, healing temples or asclepeions were dedicated to Asclepius, the god

of medicine, for example, the temple in Epidaurus in the Peloponnese, which is one of the best-known healing places in the ancient world. Their location and architecture supported the healing of the patient.

Whatever is considered a desired property of the healing environment to maintain or restore health and heal injuries also applies to the birth process to a certain extent. The needs of a woman giving birth and the newborn for a safe shelter during birth and immediately after it conform to the needs of a person who requires a safe, calm and beneficial place to overcome a disease. As far as can be ascertained, the women of ancient Egypt, Greece and Rome mostly gave birth in the spaces where they lived their ordinary life and birth only rarely took place in a dedicated space far from home. Some assume that in ancient Egypt, women gave birth on rooftops or perhaps in garden sheds, but it is also possible that they used a special space in their local settlement, which was formed like a pavilion and made from papyrus, decorated with vine leaves [4]. Individual, usually smaller temples were located within temple complexes, dedicated to goddesses of motherhood, fertility, birth and rebirth, where births of deities were worshipped and fertility rituals were performed. The French Egyptologist and linguist Jean-François Champollion coined a name for them using the Coptic words "mammisi", which is supposed to mean a birth place; a birth house as referred to in modern literature does not match the meaning of a modern "birth house" or birth centre. The people of ancient Rome also knew them. These are smaller chapels, free-standing or a part of a bigger temple, for example, the one in Dendera or in Edfu in Egypt, built according to Imhotep's plans; "mammisi" is also a part of the temple in the Egyptian city of Kom Ombo. There are no authentic sources with regards to women actually giving birth there. What is more, women in the late stages of pregnancy and after birth were generally forbidden from entering temples, intended for healing. We barely know any more about the birth environments of common women than that they gave birth in a standing position with other women present, using dedicated accessories such as "birth bricks" [4].

Nowadays, we can relate the findings of studies of the healing environments of the old world, understanding their integration in the culture and spiritual tradition, with scientific insights into ways of designing, building and measuring and transforming "healing environments". We are establishing the key elements of "healing environments" that very likely contribute to optimising physical, mental, emotional and spiritual healing according to individual patient needs—considering the patient's different circumstances, cultures and wide spectre of beliefs and approaches to illness and health [2].

We presume that individual environmental elements can be ranged from harmful to those that are physically and mentally safe. The atmosphere of the space influences those who are using it. Environmental elements of spaces for the ill should be inherently salubrious or promote health [2]. Environments should be actively "salutogenetic" or ensure a "positive context" to actions. Due to the complexity of factors that co-create a common message of the space and due to the lack of research in this field, the preparation of common guidelines to design salutogenetic spaces remains unfinished. By reviewing modern findings, we already contribute to considering, analysing and actually (re)designing health-related spaces. Based on the increasing number of findings, we can conclude that the appearance of buildings, our experience of them and their functioning influence our well-being, for example, experiencing stress, because people respond to the environment and are sensitive to it [5]. Studies confirmed the connection between stress and our physical environment, and minimising stress is also one of the key elements that support health. Architects are increasingly including aesthetic aspects to improve hospital spaces and minimise stress and anxiety, increase patient satisfaction and promote health and treatment [2].

3. Birth is the culmination of a key life transition of an adult woman

Our starting point is the fact that the birth experiences of women are always shaped and characterised by the space where they give birth. Birthing includes complex physiological processes that (only) in certain situations become pathological and require medical interventions; at the same time, birth includes biological, cultural and psychological factors that influence its course and are closely intertwined. The more we understand them and are capable of considering them in forming birth environments, the more they will meet the needs of a woman giving birth. In a transformative process, an individual requires an environment that is as supportive as possible. According to anthropological studies, birth is the culmination of a key life transition of an (usually) adult woman. Due to the liminal status in this process, they are especially sensitive and susceptible for messages from the environment; one level of the process contains information on the birth process and the second contains key messages of the dominant culture about the woman and her role (for more about authoritative knowledge, and the position of mothers and midwives, see [6]). By reviewing the messages of the particular birth space, we can clearly recognise if the woman giving birth has enough freedom and room in the birth room or is she just a passive patient who lies obediently on the bed most of the time?

In the second part of the twentieth century, births are finally moved to a hospital environment, the medicalisation of birth is in full swing and care for the woman giving birth starts to follow the "production line" idea. Examples of routine care were established for uncomplicated births, equal for all—consisting of vaginal examinations at admission and throughout labour, shaving and enema, showering, often inducing or accelerating labour using medications, lying on the delivery bed on the back in the first and second stage of labour, often or even continuous monitoring of the status of the newborn and contractions using a CTG, frequent use of episiotomy and fundal pressure, cutting the umbilical cord right after childbirth and taking care of the newborn away from the mother. Much has been written on such technocratic obstetric care already. The majority of critics of medicalised births criticised the routinely and too frequently used processes and procedures and overconfidence in technology, alerted to the underestimations of women's labouring abilities, the inferiority of the woman giving birth and the objectivisation of the female body [7, 8]. An analysis of the spatial aspect of perinatal care in such a paradigm indicates a distribution of the birth process between various spaces in the hospital, from the admission room with a dressing room, enema room with toilets and shower, room for the first stage of labour, delivery room for the birth of the child to the post-natal department for mothers and nurseries for newborns. As a result, the woman was treated similarly to an object on a production line, which travels through functionally specialised hospital areas where she was often treated by different experts. The above has resulted in separation of the mother and the newborn immediately after birth in the delivery room and later while staying in the hospital, when the newborn spent time with the mother only at predefined time periods for breastfeeding. The newborn could not make bonds with the father until partners were allowed (sic!) to be present at birth and to make visits at the post-natal department. The described manner of obstetric maternity care and inability to choose a different birth environment from a hospital one in countries with no established birth assistance at home or in birth centres resulted in a forced temporary separation of the female from her partner, her relatives and home. This was maybe of benefit for females who had been experiencing intimate partner violence or other abusive domestic relationships. All others were deprived of the presence, assistance, support and encouragement from their relatives, which is much needed for women

giving birth and a great majority of mothers with babies. In short, according to experience, a medicalised birth space negatively affects the behaviour of the woman giving birth and the course of labour; it has iatrogenic effects on the woman giving birth and on the baby.

In the last decades of the twentieth and the beginning of the twenty-first century, this concept is slowly changing and with it birth assistance practices. By merging modern findings of medicine, midwifery, physiology, neuroscience, cultural science and other sciences, the theory and practice of birth assistance are being shaped to focus on the needs of the woman giving birth and the baby. The already established co-habitation of the mother and the newborn is among the more prominent changes in Slovenia—Slovene architect Kristl [9] already researched it in 1981 to transform post-natal hospital spaces—their separation became an anachronism; the importance of skin-to-skin contact right after birth is increasingly recognised and applied in practice together with a sensitive attitude towards the newborn. To achieve this, rooms for newborns required a different status and rooms for women after birth required enough space for a baby bed and appropriate surfaces for baby care. The possibility of the partner's presence at birth (and with it some open questions on its influence on the labour process, discussed by, e.g., M. Odent) and spatial aspects related to his (presumed) activities also had to be reconsidered. Space for the future father needed to be created literally. Every change in the birth assistance concept also changes the role of medical experts. In this way, the co-habitation of the mother and the baby has changed the activity of the nurse: She took care of the baby in front of the mother, taught her and helped her change nappies. She was also there to help mothers with lactation and breastfeeding issues and questions related to their own health and well-being and that of their baby. These activities were only possible in changed spatial circumstances. This also changed the nature of relationships between the mother and the medical experts.

Considerations on paradigmatic shifts from a technocratic paradigm to a humanistic one and then to a holistic paradigm of birth assistance, conceived by the well-established American cultural anthropologist Davis-Floyd [7], were mainly focused on otherwise important questions related to the choice of an institutional or home environment as the place of birth. Nevertheless, a theoretic approach to the issue of birth environment did not get much attention for a long time despite numerous experiences and insights. To develop a theory of birth space, a profound understanding of the birth process is required, which is summarised below.

4. Physiological birth: a combination of well-functioning biological patterns and positive cultural messages

An individual experiences the messages of a space in a subjective way; they are always "filtered" by human perception, processing of information and judgement of their meaning [10, 11]. Our subconscious responds to numerous stimuli from the environment most of the time; even if we do not observe it actively, we sense it and respond to it. Our conscious and unconscious abilities to perceive, experience and synthesise numerous messages from the environment and from our interior (ourselves) are crucial for the survival of humanity and man as an individual. We are constantly responding to these messages to survive as organisms, to remain alive as individuals and to continue our species. Both aspects are being condensed during labour for the survival of the woman giving birth and the newborn and to continue the functioning of the biological pattern, which is directed to continue the species.

The experience of the space by the woman giving birth and the personnel in the building and designing modern birth spaces in hospitals has mostly been overlooked until recently or at least not regarded as a priority. This applies to health-related spaces in general and is partly due to the fact that these processes are mostly subconscious.

Examinations of childbirth in humans, the physiology of birth and the biology of a newborn show that these have not changed very much, unlike the circumstances surrounding them that have changed very much in a relatively short period of time (considering the timescale of evolution) [12, 13]. The current prevailing medicalised birth environments in maternity hospitals present a deviation from recognising and considering these rather long-lasting patterns that could be classified into pathogenic birth environments according to their effects on the woman giving birth.

Scientific studies help us find answers to questions concerning the ideal birth environment if we look through the prism of evolution. Studies of births in primates and indigenous people [14] and research into motherhood [15, 16] help us greatly. According to numerous findings, we conclude that female primates (including women) need a natural and well-known "domestic", non-intimidating and pleasant environment without disturbing elements, for example, related to cultural forms that co-design the everyday life of a certain group and those that are typical for behaviour at birth. For a smooth birth, the female or woman giving birth needs to define the limits of the specified "birth area" to control the "birth territory", allowing no intrusions. Consequently, she can give birth with all her powers and abilities without any situations that could evoke fear and with it a defensive response, withdrawal or a passive response or "freezing" (fight, flight or freeze response). A spontaneous physiological birth enables a female free movement and actions stimulated by her body; her group is nearby but respects the limits of the birth territory by maintaining an appropriate distance. In contrast to other primates, the thinking brain "silences" the instinctive behaviour of a woman at birth. Some researchers propose that for a smooth course of childbirth, women should give birth in an environment that enables them to activate the neocortex to a lesser degree and act more spontaneously, that is, according to the "primitive mammal brain" [15, 17–19]. The findings of research on specific behaviours described as "nesting" indirectly confirm its advantages. Nesting was monitored in women in less institutionalised environments such as birth centres [20] but can also be seen in modern planned home births. Research into traditional birth cultures and the practices of indigenous people unveiled some common features: birth usually occurs when accompanied by a known person. Women rarely choose to give birth accompanied by strangers and they usually give birth at home or in their current place of residence; a non-domestic environment is uncommon. If chosen, this is usually an environment that belongs to a close relative or is a special space for female activities in a certain community. A woman usually gives birth in a separate space that is usually protected, for example, divided by a blanket. A woman rarely gives birth outdoors, and companions usually motivate her and support the birth process. A woman is free to move and crouches, kneels or sits while giving birth, often supported by a person who stands or sits behind her. A (normally female) birth expert is mostly present. Females usually form the complete birth support circle [21, 22]. Studies of various birth cultures—of indigenous people as well as a modern medicalised birth—indicated different specific features of individual birth assistance in generic birthing patterns. These features reflect the prevailing beliefs of the woman's body and its abilities and are based on a specific view of a woman and her social position.

Expert literature on midwifery in popular culture also includes statements on ancient birth practices that idealise pre-medicinal forms of birth assistance and the figure of a lay midwife. These statements should be replaced by critical reflection based on facts. Due to the rapid development of information technology, data acquisition on past and current forms of birth assistance and its circumstances including spatial factors is significantly easier. We can include them in our set of knowledge and skills as part of humanity's immaterial heritage (or midwifery heritage). These forms of birth assistance need to be studied in terms of wholesomeness and the risks for the mother and child and include them in practical use if they are deemed suitable and effective.

We can summarise that only both factors—well-functioning biological patterns and chosen positive cultural practices and messages—ensure the right circumstances for an optimal physiological birth.

The findings of neuroscience and neurobiology on the complex "game of hormones" including oxytocin, endorphins and catecholamines in a woman giving birth and to a certain extent also in the present midwife explain the significant influence of the environment on the course of childbirth. Simply said: a space has an important role in enabling or inhibiting a physiological birth because of its inhibiting or stimulating effects on the excretion of antagonistic hormones: oxytocin and adrenaline. Homelike and friendly spaces adapted to the woman giving birth trigger "positive" feelings or moods via the parasympathetic nervous system and enable a pulsatory release of oxytocin in the mother's body. Birth contractions are effective and the body opens. We can mitigate or prevent negative influence on the woman giving birth by understanding which aspects of space trigger or increase stress and cause anxiety, fear and unease, related to adrenaline, and by taking suitable spatial measures according to these findings. The welfare of the woman giving birth is always of prime importance, but other people who use these spaces should also be considered because of their influence on the well-being of the woman giving birth and themselves. A midwife and the partner who feel unwell in a birth space, for example, due to the lack of a comfortable seat or being exposed to strong lights without the possibility to relax, will negatively affect the woman giving birth and the course of childbirth by building up tension and uneasiness.

5. Birth environment enables, supports or inhibits, prevents or disables a normal childbirth

The quality of the birth environment should be studied in terms of salutogenesis, which means researching it according to the following basic question: does an individual birth environment enable and support a physiological course of childbirth and post-natal period for a woman and a newborn or not or to what extent? Research findings and theoretical considerations on the influence of the birth environment on the woman giving birth and the baby are presented below. Based on them and the presentations of some already proven solutions, we give some proposals on how to create a salutogenetic birth environment that supports the health of the mother and the baby.

The messages of a pathogenetic birth space are as follows: As the woman giving birth you are in a demanding process. It is doubtful whether you can manage it which is why you should lie on the bed and hence the visible appliances to check your condition and that of your baby and to solve complications. There is not enough space beside the bed, centred in a small room that you see for the first time and feel a bit confused, to move at ease and change positions. The floor is uncomfortable for bare feet, the room's surfaces are metallic and shiny and the walls are

white or in intense colours. The space is cold, sterile and clinical. There is no toilet, shower or birthing pool in the delivery room. We need to hurry; the clock is clearly visible. Doors do not protect your private space; the personnel do not knock or wait to enter and slam the door or even keep it open. You can hear loud conversations and debates because there is no special room where the staff could discuss in private. The room has no sound insulation and noise breaks into the room from the hallway; you can hear the voices of other women giving birth, which scares you. You do not dare be loud for fear of affecting other women. When you are on the bed with your legs spread apart, you can be seen directly from the door; there is no privacy. You are not connected to your partner because he is also scared while standing/sitting by your head. You cannot relax because the room is too bright, too cold or too hot and you cannot influence these factors. You are not connected to the midwife because she also takes care of other women giving birth and comes and leaves the room constantly to check on you and your baby and the course of birth. You feel exposed to controlling looks and criticised for your behaviour. The room has no windows or a nice view of nature; it is generally not pleasant. All of this causes frustration, feeds fear, increases stress, prevents the excretion of oxytocin and endorphins and stimulates the excretion of catecholamines. Such factors inhibit physiological birth. The female body can only respond to such an environment as presenting a danger for her, the birth process and her newborn and prepares for defence or withdrawal or becomes unresponsive. The organism chooses the best possible survival response in a given situation. Since a woman cannot escape the delivery room and fight the danger, her defensive mechanisms lower the intensity and frequency of contractions or stop them completely and that disturbs the normal birth process. If the mother's nervous system interprets the detected messages of the birth environment as dangerous, spontaneous childbirth is significantly more difficult due to these hormonal activities [23].

To summarise, a smooth childbirth is not possible in certain spaces. A medicalised birth space negatively affects the behaviour of the woman giving birth and the course of labour; it has iatrogenic effects on the woman giving birth and on the baby.

6. Has anyone asked us anything? Promising approaches to designing maternity hospital and birth centre spaces: from qualitative to quantitative methods to the birth space theory

Two health-relevant complementary approaches to research health-related environments: (a) quantitative and (b) qualitative. When "health-related places" were conceptualised, quantitative studies prevailed at the beginning, based on studying spatial factors that influence health, such as size, illumination, temperature, noise and the well thought-out distribution of spaces for the efficient movement of medical staff. This means research into physical, quantitatively measurable determinants of spaces and their rational, efficient use, for example, to improve control over infections, to separate clean and unclean paths without crossing etc. Architects use these determinants to design the so-called healthcare evidence-based architecture of hospitals and other healthcare institutions.

To understand the experiencing of hospital spaces, we require qualitative research that highlights how patients experience the building, spaces and interior design according to their need for peace, privacy, positive stimuli and connection with people and nature. Quantitative data turned out to be useful and beneficial for designing birth environments, but if we limit ourselves to such criteria, this is especially inadequate if we wish to establish good birth environments. In contrast

to treating a disease or injury, birth is about a woman's physiological activity that includes extraordinary physical processes, concentrated in a fairly short time period. A woman requires an environment with specific features that will enable birth. A leap to a new quality is only possible by researching how women giving birth experience a space and to what extent it meets their needs and by studying the embodied experiences of women. Using qualitative methods, different ways of how the women giving birth, midwives and companions use an individual birth space and create certain patterns with their movements should be considered in designing new spaces or re-designing the existing ones. Experiences of a space are being explored based on the birth stories of individuals. The experiences of women giving birth with the building and interior design of spaces intended for perinatal care and individual birth rooms are being analysed.

When focusing on the development of qualitative methodological approaches, we need to highlight contributions from female architects who were sensitive to the specific needs of women during birth. Lindheim already recognised the iatrogenic issue, related to the medicalisation of the birth environment. According to the comparable needs of a carefully designed space that protects one's privacy and also enables close contact with relatives, she paralleled two key life transitions, birth and death. She studied the spatial contexts of birth and explored the attributes of births in hospitals and birth centres and at home [24], significantly influencing "birth design" and also co-operating in changing the circumstances of birth, similar to the Italian architect Bianca Lepori at a later time [25, 26].

More systematic considerations about the influences of the space on birth and initiatives to implement changes to hospitals and similar institutions have only recently received more attention in academic circles. At the turn of the twenty-first century, the birth environment is already becoming the central topic of certain scientific articles and publications with fresh perspectives on the issue of "birth territory" and interesting insights into relationships between the woman giving birth and the designed space [27–30].

To enhance our understanding of existing birth spaces and clarify the image of those we wish to design in the future, we present a couple of steps from initial studies of birth space to thorough and specifically targeted qualitative research.

Phenomenological studies present an important approach to studying birth space. They highlight the individual experiences of women, midwives and partners from different angles to clarify meanings, attributed by them.

Studying birth experiences is of great help and (also) understood by researchers as characterised by space. Women share their experience and story in questionnaires, detailed, most often semi-structured interviews or testimonies. The English organisation The National Childbirth Trust was among the first that published the significant findings of women's experiences of hospital birth spaces in 2003 [31]. The analysis of respondents to closed and open questions indicated that women giving birth found it very important: (a) to have control over the illumination and temperature of the space; (b) to have a pleasant and clean, domestic, "non-clinical" space; (c) to have room for movement, walking and enough pillows, bean bags and floor mats; (d) to have the assurance that others cannot hear them; (e) to have an accessible corner with snacks and drinks; (f) to have a birthing pool ready; (g) to have a comfortable chair for their companion and (h) bathroom with shower and bath, which would be a part of the birth space or have simple access to them [31]. The women giving birth also found it important not to be observed, to be able to control who enters the delivery room, not to change spaces during birth—they desired the freedom to do what they feel while giving birth. This report, based on the experiences of women, proved that the physical environment influences the birth experience. It demonstrated how women experienced birth environments and

exposed their needs but especially emphasised that one half of respondent women giving birth did not have access to what they desired [31].

The experience of birth and birth space is an embodied experience, which is why researchers based their studies on philosophers, architects and artists who surpassed the Cartesian separation of the body and the mind such as Maurice Merleau-Ponty with the phenomenology of perception [32] and James J. Gibson by studying visual perception. Important "perspective openers" include "poetics of space" by the French philosopher Bachelard [33], "poetics of light" by the artist James Turrell, the concept of the multi-sensory architectural experience by the Finnish architect Pallasmaa [34] and "attunement" by the architect Alberto Pérez-Gómez [35] and the theory of "transcending architecture" by Bermudez [36], among others.

For a broader embrace of these considerations and experiences, the inclusion of interpretative methodology was logical. It includes visual qualitative methods by analysing photographs of delivery rooms, using videos and reflective interviews [37] or using a semiotic analysis of architectural plans and documentation to build and operate maternity departments or maternity hospitals. If such methodology is used in researching birth spaces, for example, exploring light has a substantially different meaning. It is not merely about the suitable illumination of the midwife's work space and the baby-changing place etc. but about the role of light in the birth process, the understanding that it has an important role in the birth experience. It is about the creative use of "light-colours-darkness, the inseparable trio", the key factor in forming a birth experience according to the researcher of birth environments Doreen Balabanoff [38].

As it was important to "give voice" to women and their stories in historiography, it is essential to enable women to "occupy" the room and use it. Here, concepts of the "birth territory" have a central role [39]. By observing the activities of the woman giving birth and the midwife in various modern medicalised, institutionalised birth environments and by analysing influences on birth, it was emphasised that the birth space directs certain activities of the woman giving birth and medical staff while hindering, disabling or preventing others [40, 41]. Even if something is not explicitly forbidden, it is practically infeasible. For example, a woman can hardly move in a relaxed manner and take different positions in a very small delivery room where the bed occupies most of the space, its walls have no handles and the metal horizontal surfaces of the furniture are not meant to offer support. The mere message that welcomes a woman who enters the room is clear, even if the staff are silent: "just lay on the bed", as there is no other space for her anyway.

Research has compared different birth environments and established that women need a relaxed and domestic atmosphere, their own room and freedom of movement [37, 42]. Such spaces are more often designed in birth centres than hospitals. When women described giving birth in birth centres, they said they experienced them "as home", "an oasis of peace", "motivating environment", "a nurturing environment", where you can "build a nest" [20].

Specific research established, for example, the sub-threshold, subliminal effects of messages of hospital birth environments, which medicalise the understanding of childbirth in women giving birth and render them more passive than otherwise [43]. Research focused primarily on the negative influences of the delivery bed, especially if this is a typical childbirth bed, if it is in the centre of the delivery room and visible directly from the door. The bed became a synonym for hospital births. In their conclusions, researchers proposed a different space organisation to ensure the woman had the best possibilities for movement and changing positions while giving birth [12, 40, 44]. Some researches formed concrete proposals for different ground plans including equipment, for example, moving the bed away from the centre of the room or having a folding bed that can be folded into a closet. Promising

proposals also included transferring the bed from the delivery room to another auxiliary space where it is quickly and easily available if the woman giving birth desired to lie down or if needed due to complications [44–46].

Research into the spontaneous use of the space by the women giving birth in an individual stage of labour, especially where influences of the technocratic paradigm are minimal (e.g., home birth), is very useful. Studies can answer the question if we can define certain typical sequences of movement and physical activities and patterns of positions that should be considered in the planning of birth spaces in institutions.

As we defined at the beginning, the birth environment consists of the physical environment (birth space) and the people who are present at birth. It is characterised by a unique specific understanding of the meaning of private and public space for a woman, her socially desired roles—should she take care of the home and the family and/or be employed, to what extent and how control should be exerted over her as a mother, her behaviour and body. Research into social interactions and the balance of power relations indicates that both home and the delivery room in a maternity hospital are places where a woman could be under control and her decisions would not be autonomous. However, the opposite can also be the case; in both these environments, the woman can have control over the environmental factors and birth assistance too and decide freely. The French philosopher Michel Foucault already alerted to the importance of recognising an institutionalised space as the space that defines specific human relationships and as being shaped by relationships at the same time. A typical example is the structure of a panopticon and its function in economy of controlling people. In the buildings and spaces of medical institutions such as hospitals, traces of power relations that define the place of a patient can be read. We should reconsider the prevailing patterns of social interactions in the spaces of maternity hospitals, birth centres or homes—by changing the environment, equipment and sequence of spaces and locations of various elements and their relations, unsuitable hierarchical relationships can be transformed into more collaborative ones, ensuring a central role for the woman.

Some research has focused on the issue of the production line model applied to modern birth, primarily due to the lack of privacy and feeling of safety, and wishes to bring changes [47]. This can be done by rearranging "typical" delivery rooms in such a way that (a) one room is intended only for one woman giving birth from admission to the end of childbirth or until the departure of the mother with the baby; (b) the personnel knocks and waits for permission to enter; (c) the woman giving birth is not visible from the door: the doors are covered by curtains; the space intended for active birth is not in the field of view, including the bed and the birthing pool and (d) each delivery room has its own bathroom with shower.

As we deviate from the data within a medical-mechanic definition of birth to studying personal birth experiences, besides narrower medical and health-related aspects, categories/terms such as connection with the whole and others as movement, flow, privacy, intimacy, sensuality, interconnection, interlacing of a female and the direct environment, altered states of consciousness, resonance, phenomenological perception and undisturbed excretion of oxytocin that enables the course of birth are also included [48]. These aspects are important for all included in the process of childbirth, and a high-quality birth space should consider them.

Connection with elements of nature is especially significant for a woman giving birth. The findings of studies of natural and built environments in terms of evolution have already brought an understanding of the complex influences of built environments and the designing of healthy spaces [14]. Our emotional and cognitive brain has been shaped by the natural environment as have the brain's responses to it, which is why we are able to identify natural dangers quickly and reliably, respond

appropriately and spontaneously look for environments that are as safe as possible. But we have not yet developed a "system" to identify dangers, "built in" man-made objects and our related defensive mechanisms. A soothing environment for a man still includes contact with nature and natural elements [49], for we are oriented towards life and give priority to impulses from the environment, connected to vivacity, which are therefore also aesthetically pleasing. This is a common human attribute. Intercultural research has shown that our well-being increases when we are in contact with the natural elements—we speak of human "biophilia", love for nature [50, 51]. What is more, we may claim that a human does not only feel well when in contact with nature, but also nature actually enables and stimulates regeneration. This meaning of the embrace of nature for human existence was summed up by the Slovene architect and urbanist Janko Rožič in an insightful thought: For modern human, it is extremely beneficent to "... descend to nature's level and blend in with the whole which heals. [52]", which reminds us that etymologically speaking the word "whole" comes from an Old English "hāl" meaning "healthy, safe".

For a woman who gives birth physiologically, the sensual experiences of a birth space, enriched with natural elements, for example, the pleasant scents of fresh flowers, natural sounds, the feeling of pleasure as the body immerses into a sufficiently sized bath or birthing pool, a floor mat, pleasant for bare feet, wooden furniture and photographs of nature, will trigger responses that lead to (increased) trust and help her relax.

7. How do we define the quality of a modern birth space? Guidelines towards a salutogenetic space

The woman's need to create a personal, comfortable, pleasing and safe environment to relax and abandon herself to the birth process is rooted in the biological birth-giving of primates. To give birth, a woman needs to be able to create her own "personal territory", a limited environment that she can "control" and make decisions about, whether it is in a maternity hospital or birth centre or at home. We cannot take this for granted for all of the above environments. Nevertheless, we might reasonably claim that due to their relative unadaptability, more needs to be done in public hospital-like institutions to transform birth spaces than in birth centres or at home. According to modern findings, the planning of a new maternity hospital or its upgrade must consider and apply designs of the building and its interior with foreseeable and indirectly measurable conscious and subconscious effects, which will ensure positive physiological responses while strengthening their synergy. This also applies to the planning and building of new smaller birth environments, like an autonomous midwifery centre or a midwife maternity ward, which is still waiting for its realisation in the future in some European countries including Slovenia. To respond to the current issue of prevailing hospital births, we need to form smaller birth places. Every birth environment, regardless of whether it is an institution or a home, should become a place of health and emotional security [53].

The majority of women do not require a very structured clinical environment to give birth. If today's delivery rooms in hospitals were conceived, built and designed within the technocratic paradigm that treated birth as a potentially pathologic event, we need to adapt hospitals to the needs of most women and babies without overlooking the needs of women who experience complications at birth. We need to create such spaces that will enable relaxed movement, not hinder the spontaneous behaviour of women and set minimal limitations for them to connect with their biological and cultural heritage. If we follow the thesis of R. Lindheim, the architect mentioned in the beginning of this chapter, consistently, we may claim

that a salutogenetic birth environment enables both connections: expressions of still well-functioning biological birth patterns, supported by thoughtfully chosen positive cultural messages.

According to the nowadays recognised role of hormones required for a smooth course of childbirth, a birth environment needs to be formed, which enables, "allows", strengthens and stimulates the optimal secretion of natural oxytocin, endorphins as well as adrenaline (but only when a woman really needs it to birth the baby), because they reduce the need of procedures and interventions, carried out by medical staff on female bodies. In every birth environment, the circumstances that hinder a spontaneous course of birth must be identified. The environmental elements that evoke fear, anxiety and prevent relaxation must be changed and transformed for the well-being of the woman. This is why the renovation of birth spaces is definitely not about applying some makeup. An inner transformation is required, which will respond to the needs of women and result in a quality birth environment.

It seems that birth spaces should resemble "spas" or "wellnesses" in being comfortable, pleasant and beautiful, that is, spaces intended for well-being. According to the determined properties of a quality birth space, considerations on hotel-type delivery rooms with a bathroom, birthing pool or bath, atrium, small kitchen and bed where the woman's partner can also spend the night are in the foreground. In such a space, childbirth takes place from admission of the mother to leaving the hospital with the baby. Continuous care of "one midwife for one woman" (one-to-one midwifery) is easier to implement, at least during her stay in the institution. According to the latest findings, this type of care has several advantages over the usual shared care.

Access to maternity wards within hospitals should be separate from the entrance of patients and visitors of other hospital units and services. In this way, women or couples that come to give birth do not meet the sick or their visitors. By placing a maternity ward next to the hospital building or constructing a completely separate unit (birth centre), we avoid these challenges in a simple but effective manner. All types of birth environments require a carefully and thoughtfully designed access to the building, that is, the transfer from a public area to a half/institutionalised environment.

8. A quality birth space is a salutogenetic one

An ideal birth space should ensure that the course of birth maintains its potential energy intact as much as possible and enable its free flow, so the woman giving birth "adopts" it and actually becomes a driving force of her own birth through her activities and the use of the birth space.

While observing health safety criteria, the appropriate hygienic standards, a suitable logistical connection of multi-purpose spaces etc., a quality birth space also reflects the findings on the experience of the birth space. It makes it possible for the women to experience it as pleasant, domestic, comfortable and beautiful. Atmosphere is important and consists of carefully chosen colours, textures, materials, visual messages, interior design and furniture elements including doors and windows. An informally designed space with a thoughtful ground plan and pleasant corners for activities and rest and for relaxation and refreshment with food and beverages, with ergonomic furnishing, artistic objects, beautiful views, natural materials (stone, clay, wood, cotton, linen, wool etc.), harmonised colours in shades of the earth, sky, water, greenery, using few or no intense saturated colours, with textures that offer visual and haptic pleasures, with soft lights and a pleasant

temperature foster a sense of acceptance, familiarity and warmth and create options for a woman giving birth to relax and indulge in the course of birth, accept it in its nature of "ordered chaos".

Women need a birth environment that expresses compassion, warmth, love and care; such an environment supports her in various emotional states during birth, and it tells her that her needs are accepted and assures her that she will be listened to.

Salutogenetic birth environments enable the dynamic integration of people according to the needs of the woman giving birth: they enable a woman to connect with herself, her feelings and experiences, the baby, her partner, other relatives and the medical staff. Therefore, the possibilities of establishing emotional and physical presence between the (future) parents, the newborn and the mother, father, between the woman giving birth and the midwife need to be ensured. If she needs support, a touch, massage or a hug from her partner or other companion or doula, a salutogenetic space makes this easily possible because it is conceived multi-dimensionally, enabling various possible "uses" and activities. The space sends all involved a message that her loved ones are welcome and that people and their presence and support and assistance have priority over technological solutions and medication whenever possible, which is why medical equipment is "hidden from sight".

A salutogenetic space is simple and sufficiently spacious; contraptions for an active birth are readily available, deliberately chosen and unobtrusive when not in use and equipment is functional and defines the use of the room as little as possible; the bed is not in the centre of the room or is located in the neighbouring room. The space is not too strictly defined, the bed is hidden and emptiness lets the woman giving birth know that she can move as her body tells her and that she can be active and take a rest and breathe. It should enable various activities and ensure varied uses of spatial elements according to the changing needs of an individual. An individual place in a chosen birth environment allows different uses of equipment and space.

In-depth research findings otherwise indicate common patterns of needs of women giving birth and the newborn, which should serve as a foundation for designing a birth space that should also be simply adaptable to the dynamics of birth. Its openness to adaptations to the specialities of an individual woman (and the newborn) and relationships that are being formed between her and the environment from one moment to the next is essential, and influence birth physiology, experience and results.

Therefore, such birth spaces are required that are designed thoughtfully and in a somewhat restrained fashion. In this way, women can co-shape them according to their current need. Based on these findings, it is not recommended to paint the walls with intense, saturated colours or to install stationary equipment and predefine the location where a woman should give birth. Women can be fully involved in care, which is not routine but individually adaptable. Each woman decides what is most suitable for her [54].

A salutogenetic space by using various sensory channels ensure that the woman giving birth has contact with natural elements such as water, stone, wood, fresh air and natural light and can see plants, animals, for example, birds in the park, the landscape, the sky and weather phenomena such as rain and snow, and allows connection with nature.

A salutogenetic birth space ensures privacy with different options to establish a personal and intimate area; it allows women to temporarily "adopt" it, "control" who enters and what is going on with the space in general. In it, women giving birth regulate heat and light in simple ways; the space has sound insulation. In a salutogenetic birth space, women are not exposed to a controlling look and cannot

be observed from the hallway or through openings in doors or the wall. As opposed to a medicalised environment, nothing/no one "regulates" their behaviour or personal expression. A good-quality birth space guarantees that the woman giving birth can maintain her intimate and personal area as much as she needs it. If she or her companions need some extra personal space, they can be present in the space without crossing personal borders.

Due to the extended alienation from basic birth patterns and the related normalisation of medicalised birth assistance, some women require intensified messages to be able to safely let go; a birth environment for a physiological birth should also have a stimulating effect. Usually, it is however already enough that a birth environment enables birth to "happen" and supports processes in the baby, mother and father right after birth; in such cases, stimulation is redundant and disturbs spontaneous processes.

In the attempt to pass into a humanistic paradigm, this space, intended for a special, embodied experience, needs to be specifically designed for a woman to "settle in" and to temporarily adopt it and to think that this is actually doable. We are giving the woman back her voice, body and space. When creative and sensitive architects design a birth space, they bear in mind that a woman giving birth is going through dynamic processes including mental activities and rational decision-making, altered states of consciousness, states of contemplation and mindfulness and various physical activities that are beyond an everyday experience and at times extremely difficult. Using thoughtful spatial design solutions, they create opportunities for the space to resonate emotionally and spiritually with the life-giving process. They are striving to achieve harmony between the space and the woman giving birth. In this way, "woman-centred perinatal care", one of the key features of the humanistic birth paradigm, embodies itself in the space. A quality birth environment surpasses the existing paradigm of designing hospital spaces, which still includes maternity wards. It is exceptionally important in increasing the chances that women will (more often, frequently) give a normal, physiological birth. In birth spaces meant for high-risk births, additional medical-technical requirements must be observed.

Although it may seem that space is something that is most unalterable, research confirms that the goal of providing a birth space, which enables and supports care that is tailored to an individual woman, is realisable.

The architect Juhani Pallasmaa emphasises that a building guides, measures and frames actions, mutual relationships, sensations and thoughts and that in this sense, basic architectural experiences play the role of verbs [55]. The experiences of modern birth spaces as such should create suitable contexts for childbirth and the processes of the woman connecting with her inner self, with herself and her baby, and outwards with her relatives, medical staff, nature, and beauty; everything should align itself for a smooth childbirth.

The theory of birth space with the emergent architectural language of designing salutogenetic birth spaces is important for raising awareness and informing future designers and planners of birth environments. It should serve as a tool to face architectural challenges. New findings change the perspective of decision makers, medical staff and users. The people who decide on the planning of new birth spaces or renovate existing ones must be acquainted with it.

9. Conclusions

There is a gap between the possibilities of modern-day birth environments and assured best conditions for a physiological birth and the earliest post-natal period.

A salutogenetically designed birth environment supports the holistic health of the woman giving birth, the mother, the baby and the family. When a physiological birth is possible according to the medical condition of the mother and the baby and when a woman desires it and it takes place in salutogenetic birth environments, that is, environments that co-create health, we can look forward to seeing positive short- and long-term medical results of births for women, newborns and families.

Author details

Zalka Drglin
National Institute of Public Health, Ljubljana, Slovenia

*Address all correspondence to: zalka.drglin@nijz.si

References

[1] Lindheim R, Syme LS. Environments, people and health. Annual Review of Public Health. 1983;**4**:335-359

[2] Schweitzer M, Gilpin L, Frampton S. Healing spaces: Elements of environmental design that make an impact on health. The Journal of Alternative and Complementary Medicine. 2004;**10**(Suppl 1):S71-S83. DOI: 10.1089/1075553042245953

[3] David R. The art of medicine. The art of healing in ancient Egypt: A scientific reappraisal. Lancet. 2008;**372**(9652):1082-1083. DOI: 10.1016/s0140-6736(08)61749-3

[4] Parsons M. Childbirth and children in ancient Egypt. Tour Egypt. 2011. Available from: http://www.touregypt.net/featurestories/mothers.htm [Accessed: 2019-07-28]

[5] Shur BG. A better place to heal. Health Forum Journal. 2002;**45**(4):10-15

[6] Davis-Floyd R, Sargent CF, editors. Childbirth and Authoritative Knowledge: Cross-Cultural Perspective. Berkeley, Los Angeles, London: University of California Press; 1997. 510 p

[7] Davis-Floyd R. The technocratic, humanistic, and holistic paradigms of childbirth. International Journal of Gynecology & Obstetrics. 2001;**75**(Suppl 1):S5-S23. DOI: 10.1016/S0020-7292(01)00510-0

[8] Wagner M. Evolucija k žensko osredišče ni obporodni skrbi. In: Drglin Z, editor. Rojstna mašinerija: Sodobne obporodne vednosti in prakse na Slovenskem. Koper: Univerza na Primorskem, Znanstveno-raziskovalno središče Založba Annales, Zgodovinsko društvo za južno Primorsko; 2007. pp. 17-30

[9] Kristl S. Primerjalna raziskava arhitekturne zasnove bolnišnične porodniške oskrbovalne enote in obravnava izdelanega modela [thesis]. Ljubljana: Univerza Edvarda Kardelja v Ljubljani, Fakulteta za arhitekturo, gradbeništvo in geodezijo; 1981

[10] Pallasmaa J, Robinson S, editors. Mind in Architecture: Neuroscience, Embodiment, and the Future of Design. Cambridge: The MIT Press; 2015. 259 p

[11] Eberhard JP. Architecture and neuroscience: A double helix. In: Pallasmaa J, Robinson S, editors. Mind in Architecture: Neuroscience, Embodiment, and the Future of Design. Cambridge: The MIT Press; 2015. pp. 123-136

[12] Trevathan WR. Human Birth: An Evolutionary Perspective. 2nd ed. London: Aldine Transaction; 2011. 268 p

[13] Trevathan WR. Ancient Bodies, Modern Lives: How Evolution Has Shaped Women's Health. Oxford, New York: Oxford University Press; 2010. 272 p

[14] Trevathan W, McKenna J. Evolutionary environments of human birth and infancy: Insights to apply to contemporary life. Children's Environments. 1994;**11**(2):88-104

[15] Hrdy S. Mother Nature: Maternal Instincts and How They Shape the Human Species. New York: Ballantine Books; 2000. 752 p

[16] Hrdy S. Mothers and Others: The Evolutionary Origins of Mutual Understanding. Cambridge: Harvard University Press; 2011. 432 p

[17] Odent M. Primal Health: Understanding the Critical Period between Conception and the First Birthday. 2nd ed. East Sussex: Clairview Books; 2007. 240 p

[18] Odent M. The instincts of motherhood: Bringing joy back into newborn care. Early Human Development. 2009;**85**(11):697-700. DOI: 10.1016/j.earlhumdev.2009.08.053

[19] Odent M. The rights of the human newborn baby. In: Hayes-Klein, editor. Human Rights in Childbirth. International Conference of Jurists, Midwives and Obstetricians. Haag: Bynkershoek Publishing; 2012. pp. 85-91

[20] Walsh D. 'Nesting' and 'matrescence': Distinctive features of a free-standing birth centre in the UK. Midwifery. 2006;**22**(3):228-239. DOI: 10.1016/j.midw.2005.09.005

[21] Jordan B. Birth in Four Cultures: A Cross-Cultural Investigation of Childbirth in Yucatan, Holland, Sweden, and United States. 4th ed. London: Waveland Press; 1993. 235 p

[22] Gélis J. History of Childbirth. Fertility, Pregnancy and Birth in Early Modern Europe. Cambridge: Polity Press; 1996. 344 p

[23] Odent M. The Scientification of Love. 2nd ed. London, New York: Free Association Books; 2001. 135 p

[24] Lindheim R. Birthing centers and hopices: Reclaiming birth and death. Annual Review Public Health. 1981;**2**:1-29. DOI: 10.1146/annurev.pu.02.050181.000245

[25] Lepori RB. Freedom of movement in birth places. Children's Environments. 1994;**11**(2):81-87

[26] Lepori RB, Franck KA. Architecture from Inside Out. 2nd ed. Chichester: Willey Academy Press; 2007. 200 p

[27] Davis D, Walker K. The corporeal, the social and space/place: Exploring intersections from a midwifery perspective in New Zealand. Gender, Place and Culture: A Journal of Feminist Geography. 2010;**17**(3):377-391. DOI: 10.1080/09663691003737645

[28] Fahy K, Foureur M, Hastie C, editors. Birth Territory and Midwifery Guardianship: Theory for Practice, Education and Research. Oxford: Elsevier; 2008. 198 p

[29] Hammond AD, Homer CSE, Foureur M. Messages from space: An exploration of the relationship between hospital birth environments and midwifery practice. Health Environments Research & Design Journal. 2014;**7**(4):81-95. DOI: 10.1177/193758671400700407

[30] Forbes I, Foureur M, Leap N, Homer C. Birthing Unit Design: Researching New Principles [Internet]. 2011. Available from: http://www.worldhealthdesign.com/birthing-unit-design-researching-new-principles.aspx [Accessed: 2018-03-23]

[31] Newburn M, Singh D. Creating a better birth environment. In: Women's Views about the Design and Facilities in Maternity Units: A National Survey. London: The National Childbirth Trust; 2003. 44 p

[32] Merleau-Ponty M. Phenomenology of Perception. New York: Routledge; 2013. 696 p

[33] Bachelard G. The Poetics of Space. Boston: Beacon Press; 1994. 279 p

[34] Pallasmaa J. The Eyes of the Skin. Architecture and the Senses. New York: John Wiley; 2005. 80 p

[35] Pérez-Gómez A. Attunement. Architectural Meaning after the Crisis of Modern Science. Cambridge: The MIT Press; 2016. 304 p

[36] Bermudez J. Transcending Architecture: Contemporary Views on Sacred Space. Washington: The Catholic University of America Press. 368 p

[37] Mondy T, Fenwick J, Leap N, Foureur M. How domesticity dictates behaviour in the birth space: Lessons for designing birth environments in institutions wanting to promote a positive experience of birth. Midwifery. 2016;**43**(10):37-47. DOI: 10.1016/j.midw.2016.10.00

[38] Balabanoff D. Birthspace, Light and Embodied Experience: Insight from the Writings of Maurice Merleau-Ponty and James J. Gibson. Ontario: OCAD University; 2016. Available from: https://ulir.ul.ie/bitstream/handle/10344/5985/Balabalof_2016_birthplace.pdf?sequence=2 [Accessed: 2019-07-28]

[39] Fahy K, Foureur M, Hastie C, editors. Birth Territory and Midwifery Guardianship: Theory for Practice, Education and Research. Oxford: Elsevier; 2008. 192 p

[40] Lepori B, Foureur M, Hastie C. Mindbodyspirit architecture: Creating birth space. In: Fahy K, Foureur M, Hastie C, editors. Birth Territory and Midwifery Guardianship: Theory for Practice, Education and Research. Oxford: Elsevier; 2008. pp. 95-112

[41] Stenglin M, Foureur M. Designing out the fear cascade to increase the likelihood of normal birth. Midwifery. 2013;**29**(8):819-825. DOI: 10.1016/j.midw.2013.04.005

[42] Boulton M, Chapple J, Saunders D. Evaluating a new service: Clinical outcomes and women's assessments of the Edgware birth centre. In: Kirkham M, editor. Birth Centres. A Social Model of Maternity Care. London: Books for Midwives. Elsevier Science; 2003. pp. 115-139

[43] Gould D. Subliminal medicalization. British Journal of Midwifery. 2002;**10**(7):418. DOI: 10.12968/bjom.2002.10.7.10583

[44] Priddis H, Dahlen H, Schmied V. What are the facilitators, inhibitors, and implications of birth positioning? A review of the literature. Women and Birth. 2012;**25**(3):100-106. DOI: 10.1016/j.wombi.2011.05.001

[45] Townsend B, Fenwick J, Foureur M. The birth bed: A qualitative study on the views of midwives regarding the use of the bed in the birth space. Women and Birth. 2016;**29**(1):80-84. DOI: 10.1016/j.wombi.2015.08.009

[46] Walsh D. Improving Maternity Services. Small Is Beautiful: Lessons from a Birth Centre. Oxford: Radcliffe Publishing; 2006. 135 p

[47] Walsh D. Subverting assembly-line birth: Childbirth in a free-standing birth centre. Social Science and Medicine. 2006;**62**(6):1330-1340. DOI: 10.1016/j.socscimed.2005.08.013

[48] Joyce S. Towards a new architectural understanding of birth spaces grounded in women's experiences of giving birth [thesis]. Sheffield: The University of Sheffield; 2018

[49] Wilson EO. Biophilia. Cambridge: Harvard University Press; 1984. 157 p

[50] Gullone E. The biophilia hypothesis and life in the 21st century: Increasing mental health or increasing pathology? Journal of Happiness Studies. 2000;**1**(3):293-321

[51] Kellert SR, Heerwagen JH, Mador ML. Biophilic Design: The Theory, Science and Practice of Bringing Buildings to Life. Wiley Blackwell; 2013. 432 p

[52] Rožič J. Sestopiti na raven narave in se stopiti s celoto, ki celi. Gea. 2004;**9**:8-10

[53] Lock L, Gibb H. The power of place. Midwifery. 2003;**19**(2):132-139. DOI: 10.1016/S0266-6138(02)00109-2

[54] Frampton SB, Charmel PA, editors. Putting Patients First. 2nd ed. San Francisco: Jossey-Bass; 2009. 368 p

[55] Pallasmaa J. The Embodied Image. Chichester: Wiley & Sons Publishers; 2011. 152 p

Chapter 8

Induction of Labor: Review of Pros, Cons, and Controversies

Donald Morrish and Iffath Abbasi Hoskins

Abstract

Although induction of labor (IOL) has increased over the years, corresponding improvements in perinatal outcomes have not occurred. IOL may result in increased risks for mother and baby, due to factors like gestational age (GA), Bishop score of cervix, and the methods used. Failed IOL resulting in increased cesarean sections may be due to unripe cervix, inadequate Pitocin use, and incorrect patient choice. Medically indicated IOL does not require awaiting 39 weeks GA. Nonmedically indicated IOL prior to 39 weeks GA may result in neonatal morbidity. Patients at 39 weeks GA can be induced electively and need not await labor. Cervical ripening methods include vaginal, oral, or IV medications and can be administered as outpatients rather than in hospitals, in order to decrease financial and time constraints. Ethical issues regarding indications, GA, choice of agent, location of cervical ripening, and failed IOL can have an impact on healthcare resources.

Keywords: induction of labor, evidence-based management

1. Introduction

Induction of labor (IOL) is defined as the initiation of uterine contractions to achieve a vaginal birth before the onset of spontaneous labor. Although IOL rates, including those of elective inductions, have almost doubled, the perinatal outcomes have not improved proportionately [1].

While IOL can occur at any GA after 20 weeks, in general this intervention is reserved for those occurring at early term or late term. The definitions for the different gestational ages are shown in **Table 1** [2].

Definition	GAs
Preterm	<37 weeks GA
Term	40 weeks
Early term	37 weeks 0 day–38 weeks 6 days
Full term	39 weeks 0 day–40 weeks 6 days
Late term	41 weeks 0 day–41 weeks 6 days
Post term	≥42 weeks

Table 1.
Definitions and gestational ages (GAs).

If women are in spontaneous labor, in general, 96% will enter active phase of labor by 15 hours from the onset of contractions. If the duration of latent phase is prolonged, the rate of cesarean section (C/S) increases, as does the complication rate (e.g., postpartum hemorrhage, chorioamnionitis). However, >40% of patients with latent phase ≥18 hours will deliver vaginally [3].

If labor is induced, the vast majority of women will deliver vaginally. The failed IOL rate is 12–15% especially if the cervix is unripe at the onset of the intervention [4].

IOL should be considered as an appropriate option if it is based upon evidence-based medicine, optimizes maternal and fetal outcomes, and is cost-effective.

2. Timing of IOL

There are no clear recommendations regarding the timing of eIOL in early- and late-term pregnancies.

Awaiting 39 weeks GA is not required if there is a medical indication for IOL. Nonmedically indicated early-term IOL should not occur prior to 39 weeks GA. Because non-respiratory morbidity is also increased, simply documenting fetal lung maturity is inadequate to justify this intervention, even in suboptimally dated pregnancies [5].

Timing the IOL at 39 weeks GA vs. expectantly managing the pregnancy till onset of labor but before 42 weeks GA is a desirable option.

Bailit [6] studied 31,000 expectantly managed primiparas and found that there was a 5% rate of developing maternal hypertension after 39 weeks GA. Increased rates of fetal macrosomia and placental insufficiency also occurred. The risks for fetal death were also increased (**Table 2**).

Keulen et al. [7] described results of a study wherein IOL at 41 weeks GA was compared to expectant management until 42 weeks GA. Although there were no significant differences in the C/S rates between the two groups (10.8% in both), there were fewer adverse perinatal outcomes (5-minute Apgar score <7, meconium aspiration) in IOL group vs. in the expectant management group (1.7 vs. 3.1%).

Gulmezoglu et al. [8] reported on 9383 patients from 22 trials and found that expectant management, until onset of labor up to 42 weeks GA, resulted in a higher C/S rate (180/1000 women) vs. 160/1000 women with IOL and an increase in all-cause perinatal deaths [9] vs. 1 in the IOL group. The number needed to treat to benefit (NNTB) with IOL in order to prevent 1 perinatal death was 410 (95% CI 322–1492).

Sinkey et al. [10] reported on a Monte Carlo microsimulation model regarding eIOL at 39 weeks or expectant management (EM) with IOL for standard medical or obstetrical indications or at 41 weeks if undelivered. eIOL at 39 weeks resulted in fewer maternal and neonatal risks vs. EM with IOL at 41 weeks among undelivered

	All pregnancies/10,000	Low-risk pregnancies/10,000
GA		
39 weeks	3–4	1
40 weeks	4–5	2
41 weeks	4–7	3
42 weeks	7–12	4

Table 2.
Risk of fetal death at ≥39 weeks GA.

patients. C/S rates were statistically significantly higher in the EM arm (35.9 vs. 13.9%). When patients had an unfavorable cervix, eIOL at 39 weeks resulted in fewer C/S vs. EM (8.0 vs. 26.1%; $p < 0.01$). While there were no differences in maternal mortality between the two groups (0% eIOL vs. EM 0.01%, $p = 0.32$), the maternal morbidity in EM was 21.2 vs. 16.5% $p < 0.01$. The still birth rate in eIOL was 0 vs. 0.13% in EM ($p < 0.0003$). The neonatal deaths were 0.12% in eIOL vs. 0.25% in EM ($p < 0.03$), and neonatal morbidity was 9.4% in eIOL vs. 12.1% in EM ($p < 0.01$). Thus, preference modeling calculations revealed that 39-week eIOL was the preferred option over EM.

Grobman et al. [4] studied the perinatal consequences of IOL at 39 weeks GA among 6106 low-risk nulliparous women from 412 hospitals in an RCT parallel group, unmasked trial. Neonatal death or severe neonatal complications occurred in 4.3% in IOL group vs. 5.4% in the EM group (RR 0.80; 95% CI 0.64–1.00). The IOL group had an 18.6% C/S rate vs. 22.2% in EM group (RR 0.84; 95% CI 0.76–0.93). The rate of hypertension/preeclampsia was 9.1% in the IOL group vs. 14.1% in the EM group. They concluded that 1 C/S may be avoided for every 28 deliveries among low-risk nulliparas who undergo elective IOL at 39 weeks GA. They recommended that if eIOL option is not used, the patients should be informed of the higher likelihoods of developing hypertension/preeclampsia and of requiring a C/S when EM option is pursued.

3. Bishop score

The Bishop score is the most commonly used method for evaluating the ripeness of the cervix, which in turn helps predict the likelihood of a successful IOL, i.e., vaginal birth. This calculation was originally intended to help predict the likelihood of going into labor for multiparous women who were at term. Currently, the Bishop score is used to assess the likelihood of a successful vaginal delivery in both nulliparas and multiparas who are at term. The score includes assessment of cervical dilation, effacement, consistency, position, and station of the presenting part. A low score ≤5 suggested that spontaneous labor would not ensue within the next 2–3 weeks. A higher score (≥6–7) indicated a likelihood of labor occurring within the next 7–10 days. In the setting of a low Bishop score, the likelihood of a failed induction (i.e., need for C/S) is 25%. Thus, when an IOL is planned, every attempt should be made to first "ripen" the cervix, i.e., increase the Bishop score to a value ≥7.

4. Techniques

Misoprostol, Cervidil, Foley balloon (with or without oxytocin), amniotomy, and stripping membranes are all accepted techniques for IOL. Each of those options has inherent risks and complications.

Misoprostol is cheap, is stable at room temperature, and can be used both orally and rectally even in resource poor settings. Although it is not FDA approved for this indication, it is a commonly chosen option. Wallstrom et al. [11] studied 4002 pts who received liquid misoprostol every 2 hours vs. receiving a rectal or oral tablet. The C/S rate was 17 vs. 26% with tablets, and there were no adverse perinatal outcomes (low Apgar scores, pH values, PPH). This option can be used when more rapid and reliable absorption of the agent is desired.

Cervidil (dinoprostone) is the only FDA-approved intervention for cervical ripening but is more costly than misoprostol. Tsikouris et al. [12] compared 50 μg misoprostol vs. 3 mg dinoprostone in two vaginal doses 6 hours apart, followed as needed,

with oxytocin for labor induction in low-risk post term (>40 weeks GA) with unfavorable cervix (Bishop score ≤6). They found that women in the dinoprostone group were more likely to need a second vaginal dose in order to proceed to labor (43.4 vs. 21.5% in miso group, $p = 0.01$). Both groups had equivalent rates of successful IOL (91.6% with miso vs. 85.8% with dinoprostone). Although, there was a shorter time to delivery with misoprostol vs. with dinoprostone (11 vs. 14.1 hours, $p < 0.001$), this group demonstrated a higher rate of tachysystole miso (16.8 vs. 4.0%, $p = 0.007$).

Bauer et al. [9] reported that in an RCT in 180 multiparas randomized to simultaneous use of Foley balloon with oxytocin vs. sequential use of oxytocin given after the Foley balloon was removed, there was a statistically increased likelihood of delivery within 24 hours with simultaneous use (87.8% in simultaneous group vs. 73.3% in sequential group; $p = 0.02$). This group also had a significantly shorter induction to delivery interval and greater cervical dilation at balloon expulsion. The mode of delivery and intra-amniotic infection rates were similar. Thus, the simultaneous option is preferable.

Fruhman et al. [13] conducted an RCT on 140 women with Bishop score ≤6, receiving either tension in 30 minutes increments on the Foley balloon catheter or no tension. The outcomes (vaginal delivery within 24 hours and C/S rates) were similar in the two groups, thus concluding that this intervention was not needed.

Smyth et al. [14] reported the results of a Cochrane review regarding the effectiveness and safety of amniotomy. Although amniotomy resulted in a 20-minute decrease in the first stage of labor and a lower rate of C/S, these were not statistically significant. Thus, amniotomy should not be a routine part of labor management but should only be considered if clinical indications exist, such as the need for internal fetal scalp electrode in order to obtain reliable fetal heart tracings.

Amniotic membrane stripping results in release of prostaglandins and is a safe, effective and inexpensive method to induce labor [15]. When performed at 38–40 weeks GA, it increases the likelihood of spontaneous labor, reduces the need for additional induction methods, and decreases the likelihood of pregnancies going post term. GBS prophylaxis is not indicated for this intervention. However, there is no date regarding hepatitis B or HIV transmission to fetus with this option, and patients should be informed accordingly.

5. Requirements for IOL

All patients should have accurate dating, ideally performed by reliance on last menstrual period (LMP) which has >90% accuracy if regular periods or by an early first trimester ultrasound, which has >99% accuracy. If there is a discrepancy between the two options, the best GA estimate should be utilized (**Table 3**).

6. Complications

The use of Foley balloon is associated with increased likelihood of infections and injury to the cervix and vagina. Additionally, malpresentations have occurred after vertex presentation at insertion of the Foley balloon. Injury to fetus (bruising/necrosis of ear, face, arm) have also been reported.

Oxytocin can be administered by low-dose, intermediate-dose, or high-dose protocols. Low dose is 3 mu/min, intermediate dose is 4–6 mu/min, and high dose is >6 mu/min. The low-dose option results in longer duration of IOL. High dose results in increased rates of tachysystole with or without FHR abnormalities. Intermediate-dose protocol is preferred because it results in lower C/S rates vs. the

GA	Discrepancy	Action
First trimester (using CRL)		
<8 weeks 6 days	>5 days	Use u/s calculated dates
9 weeks 0 day–13 weeks 6 days	>7 days	Use u/s calculated dates
Second trimester (using BPD, HC, AC, FL)		
14 weeks 0 day–15 weeks 6 days	>7 days	Use u/s calculated dates
16 weeks 0 day–21 weeks 6 days	>10 days	Use u/s calculated dates
22 weeks 0 day–27 weeks 6 days	>14 days	Use u/s calculated dates
Third trimester (using BPD, HC, AC, FL)		
≥28 weeks 0 day	>21 days	Use u/s calculated dates*

**Least accurate for redating, considering IUGR.*

Table 3.
Dating of pregnancy using LMP and ultrasound.

		Autism/ASD+	Autism/ASD−
		49	104
No exposure	12%	28%	NS
Yes exposure	88%	72%	NS

Table 4.
Exposure to L&D drugs (oxytocics, epidural).

other two protocols and there is no associated increase in the induction to delivery time. Complications are hyperstimulation/tachysystole and can result in fetal compromise or uterine rupture. Water intoxication (low urine output and fluid retention) has also been reported. AF embolism although rare can occur in the third stage of labor, after placental separation.

Concerns about autism in neonates after maternal oxytocin use have not been proven. Current evidence does not identify a causal relationship between oxytocin for IOL and autism. The ACOG recommends against any changes in current practices regarding the use of this agent [16].

A research group from the SW Autism Research & Resource Center (SARRC) surveyed mothers with affected children and found that the rates were no different in groups that used medications (oxytocin + epidural) in labor vs. those who did not. Thus, the authors concluded that exposure to L&D drugs was not an independent risk factor for autism/autism spectrum disorders (**Table 4**).

7. Setting of IOL

At present, the vast majority of IOL occur within hospital settings. These interventions require the use of significant resources (lab studies, labor rooms, fetal heart rate and contraction monitoring, RN involvement, analgesia). In general, the cervical ripening process (prior to the onset of labor) requires approximately 8–12 hours. This intervention increases the overall duration of the patient's admission in the hospital. In a Cochrane review of outpatient cervical ripening, 5003 term, low-risk women were pooled from 34 RCTs. IOL, either totally in an outpatient setting or sending the patient home shortly after initial treatment had been initiated in

hospital setting, was deemed safe and satisfactory [17]. The most preferred method for this intervention was nonpharmacologic, i.e., cervical Foley balloon. Patient acceptance and satisfaction were not markedly different with this option.

8. Labor management

Spong et al. [3] recommend that for all obstetrical care, the focus should be to minimize perinatal morbidity and decrease the chance of a C/S. If maternal and fetal condition remains reassuring, nonintervention in the latent phase of labor is paramount. A latent phase up to 24 hours and the use of oxytocin for at least 12–18 hours after rupture of membranes and with adequate contractions should be obtained before declaring that IOL has failed (**Table 5**).

Failed IOL	Failure to obtain cervical dilation after 24 hours of strong/regular contractions with oxytocin use and rupture of membranes
First-stage arrest	≥6 cm dilation with rupture of membranes
	≥4 hours adequate uterine contractions
Second-stage arrest	No descent/rotation after
	≥4 hours in nullips with epidural
	≥3 hours in nullips without epidural
	≥3 hours in multips with epidural
	≥2 hours in multips without epidural

Table 5.
Definition/duration of failed inductions and arrest disorders.

9. Cost implications

At present, approximately 25% of the 4 million annual US births undergo IOL. These currently occur at varying GAs and are due to clinically accepted indications. Elective IOL in all low-risk pregnant women would result in a strain on current resources and would take away from the availability of these resources from clinically indicated scenarios (spontaneous labor). Therefore, if this option is chosen, there should be maximum communication and coordination between healthcare providers and hospital personnel along with the patient and her support personnel. Grobman [18] reported that existing opinions regarding increased costs related to IOL may be due to the belief that there is increased resource utilization and possible adverse outcomes such as C/S. When IOL is compared to spontaneous labor, observational studies lean toward increased costs. However, when IOL costs are compared to expectant management, the costs appear to be similar, but there are improved perinatal outcomes. Additionally, there is minimal to no information regarding outpatient costs due to expectant management.

10. Ethics

In a statement about ethical decision-making, the ACOG recommends that the major principles guiding IOL should involve respect for patient's autonomy,

beneficence, nonmaleficence, and justice [19]. As has been shown in the discussions within this document, at every step of the process of IOL, the clinician must make every effort to respect the patient's autonomy (i.e., self-rule, whereby she can apply her own moral principles) while acknowledging the limitations of her ability to fully understand and therefore participate in such medically complex decision-making for herself and her baby. This concept, along with the other ethical principles stated herein, creates the moral foundation of informed consent, which must be integrated into the fabric of direct patient care.

11. Conclusions

Given the option, over 50% of women with uncomplicated pregnancies would elect to be induced [20]. However, IOL is associated with increased utilization of labor and delivery resources. One way to help address these issues is to preferentially choose outpatient settings for some interventions (e.g., membrane sweeping or cervical ripening agents), in order to decrease clogging up scant inpatient resources. Creating a model similar to a VBAC calculator could be beneficial in identifying the likelihood of success with eIOL and of neonatal morbidity.

Author details

Donald Morrish[1] and Iffath Abbasi Hoskins[2*]

1 St. John's Episcopal Hospital, Queens, NY, USA

2 NYU School of Medicine, New York, NY, USA

*Address all correspondence to: iffath.hoskins@nyulangone.org

References

[1] Bonsack C, Lathrop A, Blackburn M. Induction of labor. Update and review. SMWH. Vol 59#6; November/December 2016

[2] ACOG Committee Opinion # 579. Definition of term pregnancy; Reaffirmed 2017

[3] Spong C, Berghella V, Saade GR, et al. Preventing the first cesarean delivery. Obstetrics and Gynecology. 2012;**120**(5):1181-1193

[4] Grobman WA, Bailit Y, et al. Defining failed IOL. American Journal of Obstetrics and Gynecology. 2018;**218**:122.e1-122.e8

[5] ACOG Committee Opinion #561 Nonmedically indicated early-term deliveries; May 2018

[6] Bailit JL. Ohio perinatal quality collaborative. American Journal of Obstetrics and Gynecology. 2010;**203**:e1-e3

[7] Keulen JKJ, Bruinsma A, Kortekaas JC, et al. BMJ. 2019;**364**:1344

[8] Gulmezoglu AM, Crowther CA, Middleton P, Heatley E. IOL for improving birth outcomes at or beyond term. Cochrane Database of Systematic Reviews. 2012;(6):CD004945

[9] Bauer AM, Lappen JR, Gecsi KS, et al. Cervical ripening balloon with and without oxytocin in multiparas: An RCT. American Journal of Obstetrics and Gynecology. 2018;**219**(3):294, e6

[10] Sinkey RG, Lacevic J, Reljic T, et al. Elective induction of labor at 39 weeks among nulliparous women: The impact on maternal and neonatal risk. PLoS ONE. 2018;**13**(4):e0193169

[11] Wallstrom T, Jambert Pettersson H, Stenson D, et al. Labor induction with orally administered misoprostol: A retrospective cohort study. BioMed Research International. 2017:6840592. ePub September 18

[12] Tsikouris P, Koukouli Z, Manav B, et al. Induction of labor in post term nulliparas and parous women-potential advantages of misoprostol over dinoprostone. Geburtshilfe und Frauenheilkunde. 2016;**76**(7):785-792

[13] Fruhman G, Gavard JA, Amon E, et al. Tension compared to no tension on a Foley transcervical catheter for cervical ripening: RCT. American Journal of Obstetrics and Gynecology. 2017;**216**(1):67

[14] Smyth RM, Markham C, Dowswell T. Amniotomy for shortening spontaneous labor. Cochrane Database of Systematic Reviews. 2013;**6**:CD006167

[15] Hellman E, Sushereba E. Amniotic membrane sweeping. Seminars in Perinatology. 2015;**39**(6):466-470

[16] ACOG. Committee opinion # 597: Labor induction or augmentation and autism. Obstetrics and Gynecology. 2014;**123**(5):1140-1142

[17] Vogel JP, Osoti AO, Kelly AJ, et al. Pharmacological and mechanical interventions for labour induction in outpatient settings. Cochrane Database of Systematic Reviews. Sep 2017;(9):CD007701

[18] Grobman WA. Costs of elective IOL. Clinical Obstetrics and Gynecology. 2014;**57**(2):363-368

[19] ACOG Committee Opinion # 390. 2007. Ethical Decision Making in Obstetrics and Gynecology; Reaffirmed 2019

[20] Out JJ, Vierhout ME, Verhage F, et al. Characteristics and motives of women choosing eIOL. Journal of Psychosomatic Research. 1986;**30**:375-380

Chapter 9

Preventing Maternal Mortality during Childbirth: The Scourge of Delivery with Unskilled Birth Attendants

Omosivie Maduka and Rosemary Ogu

Abstract

The death of a woman during childbirth is devastating. The Sustainable Development Goals aim to reduce the global maternal mortality ratio to less than 70 per 100,000 births. No country is expected to have a maternal mortality ratio of more than twice the global average. In settings with weak health systems and suboptimal service delivery, more and more women continue to utilize traditional birth attendants during childbirth. Traditional birth attendants are unskilled and unable to prevent or treat the complications during pregnancy or childbirth that leads to maternal deaths. Every effort must be made to prevent maternal mortality. This chapter utilizes qualitative research methodology and discusses the challenges of preventing maternal deaths in a setting where women routinely utilize traditional birth attendants. The reasons for the persistence of the traditional birth attendants are examined. A solution out of the predicament is fundamental.

Keywords: childbirth, maternal mortality, traditional birth attendant, skilled birth attendant, Nigeria

1. Introduction

Maternal health refers to the health of women during pregnancy, childbirth and the postpartum period. While motherhood is often a positive and fulfilling experience, for too many women, it is associated with suffering, ill-health and even death. Maternal mortality is the death of a woman during pregnancy and within 42 days of delivery irrespective of the gestational age and site of the pregnancy. Maternal mortality ratio is the number of maternal deaths per 100,000 live births while maternal mortality rate is the number of maternal deaths per 100,000 women of reproductive age. The maternal mortality ratio is a key performance indicator for efforts to improve the health and safety of mothers before, during, and after childbirth per country worldwide. 94% of all maternal deaths occur in developing countries [1].

With almost 200 million inhabitants, Nigeria is Africa's most populous country. Nigeria is also the country where nearly 20% of all global maternal deaths happen. Between 2005 and 2015, it is estimated that over 600,000 maternal deaths occurred in Nigeria [2]. To enable reduction of maternal mortality worldwide, maternal mortality reduction in Nigeria must be tackled.

The Sustainable Development Goals (SDGs), aimed at transforming our world through the 2030 Agenda for Sustainable Development," are an intergovernmental set of 17 aspiration Goals with 169 targets [3]. The United Nations in 2015 committed to accelerating the progress made in reducing newborn, child and maternal mortality by ending all such preventable deaths before 2030. This commitment aimed at ensuring universal access to sexual and reproductive health-care services, including for family planning, information and education. By 2030, the UN SDG target is to reduce the global maternal mortality ratio to less than 70 per 100,000 live births. This is largely impossible in the face of the weak health systems operational in developing countries. Urgent strides must be made if the goals are to be attained in countries with weak health systems.

Health systems. A health system, sometimes referred to as healthcare system, is the organization of people, institutions, and resources that deliver health care services to meet the health needs of target populations. A good health system delivers quality services to all people, when and where they need them. The exact configuration of services usually varies from country to country, but in all cases requires a robust financing mechanism; a well-trained and adequately paid workforce; reliable information on which to base decisions and policies; well-maintained facilities and logistics to deliver quality medicines and technologies. A well-functioning health system responds in a balanced way to a population's needs and expectations by: improving the health status of individuals, families and communities, defending the population against what threatens its health, protecting people against the financial consequences of ill-health, providing equitable access to people-centred care [4].

Human resources for health. The health workforce is central to achieving health. A well performing workforce is a skilled workforce that is responsive to the needs and expectations of people, is fair and efficient to achieve the best outcomes possible given available resources and circumstances. Countries are at different stages of development of their health workforce but common concerns include improving recruitment, education, training and distribution; enhancing productivity and performance; and improving retention. This requires: arrangements for achieving sufficient numbers of the right mix (numbers, diversity and competencies), payment systems that produce the right kind of incentives, regulatory mechanisms to ensure system wide deployment and distribution in accordance with needs, establishment of job related norms, deployment of support systems and enabling work environments, mechanisms to ensure cooperation of all stakeholders (such as health worker advisory groups, donor coordination groups, private sector, professional associations, communities, client/consumer groups).

With relation to childbirth, the skilled birth attendant is the focal human resource to prevent maternal deaths. A skilled birth attendant is a midwife, physician, obstetrician, nurse or other health care professional who provides essential and emergency health care services to women and their newborns during pregnancy, childbirth and the postpartum period. The World Health Organization (WHO) recommends as an indispensable intervention for improving maternal and perinatal outcomes in low-income countries, women's ready access to evidence-based maternal and perinatal care delivered by a skilled birth attendant [5]. Consultation on improving measurement of the quality of maternal, newborn and child care in health facilities [6]. Standards for improving quality of maternal and newborn care in health facilities.

The best markers of maternal and perinatal health and wellbeing are seen in countries with the highest rates of skilled maternal health attendance even after controlling for other extra parameters of development [7]. Nigeria presently has the second highest number of maternal and perinatal deaths in the world [8].

Poor access to maternal and perinatal health services is the major factor that puts women at increased risk of adverse maternal and perinatal outcomes. Women die during pregnancy and delivery when skilled maternal care is lacking. Evidence shows that unskilled delivery dramatically increases the risk of maternal and perinatal death [9–11]. The most common direct causes of maternal mortality are obstetric hemorrhage, pregnancy-induced hypertension, obstructed labour, unsafe abortion and puerperal infection [6]. Known interventions for preventing these direct causes of maternal mortality include the following interventions: family planning to prevent unwanted and unintended pregnancies, prenatal care to promote early screening and identification of pregnancy complications and thus manage accordingly to prevent morbidity and mortality, emergency obstetric care using effective medications and treatment regimens to reduce fatalities from obstetric complications such as eclampsia, ruptured uterus, obstructed labour, retained placenta, abruptio placenta, antepartum hemorrhage, postpartum hemorrhage, abnormal lie in labour, fetal distress in labour, skilled birth attendant (SBA) at childbirth (to effectively manage potential complications of childbirth), and postnatal care (to promote maternal recovery, infant feeding practices and the health of the newborn baby). Despite these known interventions for preventing maternal deaths, it is worrisome that women continue to use traditional birth attendants who are unable to provide these interventions. Accordingly, this lack of intrapartum care by the SBA with the basic knowledge about aseptic technique, manual and pharmacological uterotonics, basic antibiotics, and magnesium sulfate, results in preventable maternal mortality.

Care during childbirth. Nigeria currently has the second highest absolute number of maternal and perinatal deaths in the world. More often than not, women who die during pregnancy, or have perinatal deaths, are women who did not receive antenatal care, women who during childbirth had their deliveries with an unskilled birth attendant or women who delivered at home alone. The evidence is out that unskilled delivery dramatically increases the risk of maternal deaths. National data from the Demographic Health Survey indicate that only about 65% of Nigerian women receive antenatal care during pregnancy, while less than 33% are attended to by skilled birth attendants (SBA) at the time of delivery. The World Health Organization defines a traditional birth attendant (TBA) as: "a person (usually a woman) who assists a pregnant woman at childbirth, and who initially acquired her skills delivering babies by herself or working with other TBAs". Estimates indicate that between 60 and 90% of births in some parts of sub-Saharan Africa are assisted by TBAs, with countries such as Chad, Niger and Nigeria reaching extremely high proportion of TBA-attended deliveries [12]. In sittings where the number of skilled birth attendants are inadequate to meet the needs of the community, calls have been made for empowering the TBAs with health information and skills to enable them improve their practice and prevent maternal deaths. Prevention of maternal deaths is through the provision of essential and emergency health care services during pregnancy, childbirth and the postpartum period.

This chapter utilizes qualitative research methodology and discusses the challenges of preventing maternal deaths in a setting where women routinely utilize traditional birth attendants. The reasons for the persistence of the traditional birth attendants are examined.

2. Methodology

2.1 Study population and methods

Investigators from the Medical Women's Association of Nigeria Rivers State Branch, as part of efforts to improve outcomes of gestational diabetes mellitus, implemented

a research that screened 20,000 pregnant women for hyperglycaemia in Pregnancy. The study was conducted in 42 communities in five local government areas (LGAs) in Rivers State. Rivers State is one of the 36 states of Nigeria, situated in the oil-rich region of the country known as the Niger Delta. The LGAs included in the study were Ahoada East LGA, Khana LGA, Obio-Akpor LGA, Okrika LGA, and Port Harcourt City LGA. Social mobilization officers of the various LGAs, Local Government Agency for the control of HIV AND AIDs (LACA) officers, Women Leaders, and Medical Officers of Health assisted in getting the TBAs. The discussions with the pregnant women centred on why the women choose to attend the TBA home, while the discussions with the TBAs centred on their level of education, where the TBAs conduct the childbirth, what they do to retain the patronage of parturient amongst other questions.

2.2 Ethical approval

The ethical approval for this study was obtained from the Research Ethics Committee of the University of Port Harcourt. Consent was obtained from the Ministry of Health, Primary health care board, chairmen of the selected Local Government areas, advisory counselors on health of the concerned LGAs and medical officers of health of the various LGAs. Informed consent was obtained from the women before beginning the interactions.

3. Results

In-depth interviews and 10 group discussions were carried out in the five LGAs; one each per pregnant women and one each per TBAs. The pregnant women ranged in age from 25 to 42 years (median = 31 years) while the TBAs ranged in age from 34 to 67 years (median = 44 years). A large proportion of the pregnant women had secondary level of education while the TBAs had no formal education. The pregnant women patronized the TBAs because they were close by, they were cheaper and they were allowed to pay in installments.

About a third of the TBAs claimed God showed them in the dream that they should conduct childbirth. A quarter said they had longed to be nurses but could not afford formal training as nurses, so they opted to be TBAs and learnt from already practicing TBAs. Another quarter said they were trained as auxiliary nurses but decided to set up TBA practice. The rest were cleaners in maternity units, retired health workers or family members to thriving TBAs practice.

Majority of the TBAs conducted the childbirth in their personal bedrooms. They did not have a separate facility while some TBAs had a separate room for conducting childbirth and a few had facilities such as a two-bedroom apartment. To maximize patronage by parturient, the TBAs responded that they sang and danced, cooked pepper soup and collected fees in installments. The TBA wished that government would employ them as health care providers.

4. Discussion

Childbirth-related complications constitute major drivers to the increasing burden of death and disability. The direct causes of deaths during childbirth (maternal deaths) are eclampsia, obstetric hemorrhage, obstructed labour, sepsis, abruptio, and ruptured uterus. To avert these medical conditions during childbirth requires skilled care. Yet our women continue to patronize these unskilled birth attendants because of poverty, ignorance and cultural acceptance. Our interaction

with the pregnant women revealed they go to TBAs because they are closer to them, they are allowed to pay their bills in installments and because they pet them—singing and dancing for them. Pregnant women want easy access to care. Stakeholders must take this into cognizance and strategize to save lives. Our interaction with the TBAs reveal they are uneducated and unable to provide the requisite care needed to prevent maternal mortality and morbidity. A large proportion of the TBAs had no formal education and had no idea of the treatment or management of childbirth related complications. This is similar to the findings by Ofili and Okojie as far back as in 2005 [13]. The scourge of TBAs has been a long-standing challenge for maternal health improvement in Nigeria and countries of Africa and Asia. In an editorial in 2014, Okonofua and Ogu [14] posited that interventions based on provision of social safety nets in terms of cost reduction, transport provision and conditional cash transfers for women who seek hospital delivery would likely be effective in increasing the proportion of women delivered by skilled birth attendants in the population of women who patronize TBAs because of lack of transportation. Poverty underlies the patronage of TBAs—Women's inability to pay for services at government or private facilities offering quality care. During the index discussions, women reiterated that they utilized the TBAs because it was cheaper for them. Poverty is real and cannot be waved off. Economic empowerment is part of the solution to reducing maternal mortality.

Some have made calls for the integration of TBAs into the provision of quality care during childbirth, yet despite these calls, the practitioners are mostly uneducated. They are largely women who desire to look after pregnant women but were either unable to afford orthodox education fees or were unable to gain admission into training schools. The lax nature of health services in developing countries like Nigeria has enabled the TBA to exist as an unskilled provider of health service—service here being the care of pregnant women and care of parturients during childbirth. There is an obvious need for more skilled attendants at childbirth. The estimated 2 per 1000 persons currently available in Africa is a far cry from the approved expected. Thus, the unmet need for skilled birth attendants is filled by the TBAs. However, the TBAs is ill-equipped and cannot prevent morbidity and mortality during childbirth. Some have equally called for a ban of TBAs. Will government banning TBAs be the solution to the scourge of TBAs? A 2012 study in the western part of Nigeria found more than 77% of users of TBA opposed the banning of TBA services [15]. A recent study from Malawi found that a ban on TBA patronage markedly aggravated the barriers pregnant women faced in attempting to access healthcare during childbirth [16].

The "care" rendered by the TBA in the face of ruptured uterus, obstetric hemorrhage, malpresentation, eclampsia, and obstructed labour will not prevent or treat the complications of childbirth which results in morbidity or mortality. Accordingly, a TBA without the knowledge and skills to utilize and implement aseptic techniques, uterotonics, antibiotics, anticonvulsants, blood transfusion will basically cause preventable maternal and perinatal mortality. We reiterate that only long-term action, backed up by political commitment and adequate investments, will lead to the transformative changes required to attain sustainable results in developing the health workforce [17]. For a truth; there can be no health without a workforce. A clear lesson learned so far is the need to move away from piecemeal approaches and short-term solutions; retraining TBAs to be aware of danger signs in pregnancy and childbirth will not improve outcomes if they continue to try to provide care that they are incapable of providing. A TBA cannot transform into a skilled birth attendant. The basic foundation gained during the training in medical and nursing school is missing. The implementation of an effective intrapartum-care strategy is an overwhelming priority in the quest to prevent maternal deaths.

Therefore, concerted efforts to support and strengthen existing healthcare systems to provide skilled emergency obstetric care is imperative. A health facility intrapartum-care strategy is the best scenario to reduce the high rates of maternal mortality. Delivery in a health facility with a skilled birth attendant who can ensure clean environment and delivery technique to prevent puerperal infections and optimize childbirth outcomes. The Partograph is essential for labour surveillance to detect early complications and avoid prolonged and obstructed labour. Active management of third stage of labour with oxytocics is imperative to prevent postpartum hemorrhage. The ability to use magnesium sulfate in the management of eclampsia, antibiotics to prevent puerperal sepsis, delivery of operative interventions such as cesarean sections and hysterectomy where applicable saves lives. Here, skilled assistance to a woman during labour and childbirth, including supportive companion where feasible, detects complications early. This detection of maternal complications early and referral of all parturient with maternal complications early prevents all-causes of maternal mortality. In the same vein, early detection of newborn complications and prompt referral of all newborns with complications prevents neonatal morbidity and mortality. Simple procedures such as resuscitation of the newborn with at least an ambu-bag, adequate newborn warmth, hygienic cord care, early breastfeeding through advice promoting early and exclusive breastfeeding ensures survival of the newborn. Pre-arranged organized transport to referral facilities is crucial to prevent all-causes of mortality. These intrapartum interventions are crucial for the reduction of mortality and morbidity during childbirth. Despite the skilled birth attendance challenge by personnel shortages and persistent financial, transport, and geographic barriers, TBAs are not trained, equipped or able to manage obstetric emergencies.

In our interaction with the TBAs, their prayer was that government employs them. They craved our intervention to government to incorporate and integrate TBAs into the health Workforce by employing them as health assistants who will be paid salaries/remuneration. This may well be the solution to the scourge of women delivering with an unskilled attendant. The TBAs can be employed by government and paid for ensuring that all pregnant women are guided to the health facilities to deliver with skilled attendants. There may be a workable strategy—a situation where government employs the TBAs to act as health promotion officers—they could undergo a one-month training to learn about the danger signs of pregnancy and childbirth and how to effectively enable referrals. The education about the danger signs of pregnancy and childbirth is to enable them see the impracticability of them attempting to provide skilled care. Their employment as health promotion officers will be to assist the pregnant women to a health facility with available skilled attendants. Bryne and Morgan [18] in their systematic review showed that building the interpersonal and communication skills of formal health workers to improve their interactions with TBAs is a mechanism for integration and raises TBA referrals and skilled birth attendance.

Thus, training health workers to collaborate effectively with TBAs and women as applied in Peru [19] and by Mullany and Colleagues [20] increased skilled birth attendance substantially from 37 to 95% and from 5 to 48.7%, respectively. In the same vein, integrating TBAs into the formal health sector without first engendering community participation may be ultimately detrimental to the continuum of care as seen in Malawi [16]. Thus the Primary Health Care Development Agency as the arm of government charged with ensuring primary health care should as a matter of urgency do more and decimate the way forward. Too many women have died in their inability to afford skilled birth care during childbirth. As the TBAs home is the first port of call by numerous pregnant women, the healthcare management board should take charge and ensure that appropriate care is delivered at the relevant

health facilities with skilled attendants. Emergency ambulances and transportation of the pregnant woman/TBA Pair should be deployed to quickly bring them to the appropriate health facilities.

Furthermore, efforts should be put in place to enable and sustain the training of skilled birth attendants such as midwives and doctors. Medical Schools and Universities such as the Ondo State University of Medical sciences should be encouraged, supported and funded to produce health personnel. Only long-term action, backed by political commitment and adequate investments, will lead to the workforce required to improve maternal health and prevent morbidity and mortality during childbirth.

5. Conclusion

Poverty, ignorance and cultural acceptance continue to fuel pregnant women's use of traditional birth attendants. The traditional birth attendants are ill-equipped to prevent maternal mortality or manage obstetric complications. We advocate that the traditional birth attendants are employed by government and remunerated for ensuring that all pregnant women are guided to the health facilities to deliver with skilled attendants. Medical Schools and Universities should be funded to produce the requisite skilled health workforce/manpower. Women's economic empowerment, health workers improved welfare, government increased commitments for functioning health facilities are some interventions needed to prevent maternal death. Only long-term action, backed by political commitment and adequate investments, will lead to the workforce required to improve maternal health and prevent morbidity and mortality during childbirth.

Acknowledgements

The authors are grateful to the Medical Women's Association of Nigeria, Rivers State Branch; the World Diabetes Foundation for WDF16-1347 Gestational Diabetes Mellitus Program in the Niger Delta; and the Medical Officers of Health in the respective Local Government Areas, Rivers State, Nigeria: Ahoada East LGA, Khana LGA, Obio-Akpor LGA, Okrika LGA, and Port Harcourt City LGA.

Author details

Omosivie Maduka and Rosemary Ogu*
University of Port Harcourt, Port Harcourt, Nigeria

*Address all correspondence to: rosemary.ogu@uniport.edu.ng

References

[1] WHO. 2019. Reproductive Health. Available from: https://www.who.int/reproductivehealth/maternal-health-nigeria/en/ [Accessed: 14th October 2019]

[2] World Health Organisation. 2019. Available from: https://www.who.int/maternal-health/en/

[3] United Nations. Transforming our world: The 2030 Agenda for Sustainable Development. 2015. Available from: https://sustainabledevelopment.un.org/post2015/transformingourworld [Accessed: 14 October 2019]

[4] WHO. Health Systems. 2010. Available from: https://www.who.int/healthsystems/publications/hss_key/en/ [Accessed: August 20, 2019]

[5] World Health Organization. Consultation on Improving Measurement of the Quality of Maternal, Newborn and Child Care in Health Facilities. Geneva: World Health Organization; 2014. Available from: http://apps.who.int/iris/bitstream/10665/128206/1/9789241507417_eng.pdf [Accessed: August 10, 2019]

[6] World Health Organisation. WHO | Standards for Improving Quality of Maternal and Newborn Care in Health Facilities [Internet]. WHO; 2016. Available from: http://www.who.int/maternal_child_adolescent/documents/improving-maternal-newborn-care-quality/en/ [Accessed: August 4, 2019]

[7] Moyer CA, Dako-Gyeke P, Adanu RM. Facility-based delivery and maternal and early neonatal mortality in sub-Saharan Africa: A regional review of the literature. African Journal of Reproductive Health. 2013;**17**(3):30-43

[8] Trends in Maternal Mortality: 1990 to 2015: Estimates by WHO, UNICEF, UNFPA, World Bank Group and the United Nations Population Division. Geneva: World Health Organization; 2015. Available from: http://www.who.int/reproductivehealth/publications/monitoring/maternal-mortality-2015/en/ [Accessed: August 5, 2019]

[9] Harrison KA. The struggle to reduce high maternal mortality in Nigeria. African Journal of Reproductive Health. 2009;**13**(3):9-20

[10] Harrison KA. Are traditional birth attendants good for improving maternal and perinatal health? No. BMJ. 2011;**342**:d3304

[11] Montoya A, Calvert C, Filippi V. Explaining differences in maternal mortality levels in sub-Saharan African hospitals: A systematic review and meta-analysis. International Health. 2014;**6**(1):12-22

[12] World Health Organization. Pregnancy, Childbirth, Postpartum and Newborn Care: A Guide for Essential Practice. 3rd ed. Geneva: WHO; 2015

[13] Ofili AN, Okojie OH. Assessment of the role of traditional birth attendants in maternal health care in Oredo Local Government Area, Edo State, Nigeria. Journal of Community Medicine and Primary Health Care. 2005;**17**(1):55-60

[14] Okonofua FE, Ogu R. Traditional versus birth attendants in provision of maternity care: Call for paradigm shift. African Journal of Reproductive Health. 2014;**18**(1):11-12

[15] Ebuehi OM, Akintujoye I. Perception, and utilization of traditional birth attendants by pregnant women attending primary health care clinics in a rural Local Government Area in Ogun State, Nigeria. International Journal of Women's Health. 2012;**4**:25-34

[16] Uny I, de Kok B, Fustukian S. Weighing the options for delivery care in rural Malawi: Community perceptions of a policy promoting exclusive skilled birth attendance and banning traditional birth attendants. Health Policy and Planning. 2019;**34**(3):161-169. DOI: 10.1093/heapol/czz020

[17] Campbell J, Dussault G, Buchan J, Pozo-Martin F, Guerra Arias M, Leone C, et al. A Universal Truth: No Health without a Workforce. Forum Report, Third Global Forum on Human Resources for Health, Recife, Brazil. Geneva: Global Health Workforce Alliance and World Health Organization; 2013

[18] Bryne A, Morgan A. How the integration of traditional birth attendants with formal health systems can increase skilled birth attendance. International Journal of Gynecology & Obstetrics. 2011;**115**(2):127-134

[19] Gabrysch S, Lema C, Bedriñana E, Bautista MA, Malca R, Campbell OM, et al. Cultural adaptation of birthing services in rural Ayacucho, Peru. Bulletin of the World Health Organization. 2009;**87**(9):724-729

[20] Mullany LC, Lee TJ, Yone L, Lee CI, Teela KC, Paw P, et al. Impact of community-based maternal health workers on coverage of essential maternal health interventions among internally displaced communities in eastern Burma: The MOM project. PLoS Medicine. 2010;**7**(8):e1000317

Edited by Miljana Z. Jovandaric and Svetlana J. Milenkovic

In 2015, there were about 135 million births globally. Each year, complications from pregnancy and childbirth result in about 500,000 maternal deaths, 7 million women have serious long-term problems, and 50 million women have negative health outcomes following delivery. Most of these occur in the developing world. This book discusses many aspects of childbirth and provides recommendations for improving maternal and fetal health. Chapters covers such topics as placental abruption, induced labor, low birth weight, prenatal education programs, and improving the birth space. Authors examine effects of air pollution, consanguineous marriage, and the use of traditional birth attendants on maternal morbidity and mortality.

Published in London, UK

IntechOpen

ISBN 978-1-83962-779-8