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Notice

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Meet the editor

Dr. Ahmed R.G. received his PhD in Developmental Biology (Developmental Endocrinology) from Beni-Suef University, Egypt, and research training (postdoctoral fellowship) as a visiting scholar at the Katholic University, Belgium. He also has outstanding records of scientific and academic accomplishments with multiple research funding, numerous publications (books/papers) in highly prestigious journals, and various presentations in both national and international conferences. He is a member of a number of eminent societies, organizations, and schools. In addition, he is a scientific editor and reviewer for national and international research institutions. He has a Publons Peer Review Award (one of the top 1% of peer reviewers in science and research honoring the sentinels of science and research).

Contents

Preface

Because normal placentation is vital for maintaining gestation and optimal fetal development, supplying nutrients, exchanging gases, and eliminating metabolic waste products, any disorders in placental functions can cause several pregnancy complications. *The Placenta* focuses on the natural, developmental, biochemical, immunological, and molecular basis of developing the placenta (placental hemodynamics: invasion, proliferation, and migration). The book reviews the factors that contribute to the fetoplacental axis, the placenta-derived mesenchymal stromal cells, and modulation of immunity and inflammation. *The Placenta* also explores the complications of abnormal placentation (accreta and beyond) and their management. Finally, placental therapy and the biological roles of antiinflammation and regeneration are proved. Scientists, physicians, embryologists, and lay readers engaged in placental studies or practice will find that this book offers insight into all areas of placenta research.

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Chapter 1

Chorioangioma of Placenta

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Additional information is available at the end of the chapter

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Abstract

The human placenta is a villous hemochorial structure. It is attached to the uterine wall and establishes connection between the mother and the fetus through the umbilical cord and thus plays a critical role in maternal fetal transfer. It is developed from two sources: fetal chorion frondosum and maternal decidua basalis. Various abnormal conditions have been reported with the placenta and the placental chorioangioma is one of them. Chorioangioma of placenta is the commonest benign tumor of the placenta. It consists of a benign angioma arising from the chorionic tissue. It has been found to be associated with many serious complications such as nonimmune hydrops, congenital abnormalities, hemolytic anemia, polyhydramnios, IUGR, and IUFD.

Keywords: chorioangioma, fetus, placenta, polyhydramnios, villi

1. Introduction

The human placenta is discoid in shape and is a villous hemochorial structure [1, 2]. The placenta is attached to the uterine wall and establishes connection between the mother and the fetus through the umbilical cord and thus plays a critical role in maternal fetal transfer [2]. It has a complex synthetic capacity and plays a role in the immunologic acceptance of fetal allograft [2].

2. Development

The placenta is developed from two sources. The principal component is fetal which develops from the chorion frondosum, and the maternal component consists of decidua basalis (**Figure 1**) [2].

The fertilized ovum converts into a morula and further differentiates into a blastocyst. The outer layer of the blastocyst proliferates to form the primary trophoblastic cell mass which infiltrates the endometrial lining. By the 7th post-ovulatory day, the trophoblast differentiates into two layers: an inner layer of clear mononuclear cells with well-defined limiting membranes called cytotrophoblast and the outer layer of multinucleated cells with no intercellular membrane called syncytiotrophoblasts [1]. By 10th to 13th post-ovulatory days, a series of intercommunicating spaces or lacunae develop in the rapidly enlarging and dividing trophoblastic cell mass.

The lacunae become confluent, and as the trophoblastic cell erodes the maternal vessels, they become filled with blood to form intervillous spaces. Between the lacunae spaces, there are columns having a central core of cytotrophoblasts surrounded by syncytiotrophoblasts. These form the framework for the development of villi later. From these pillars, branching sprouts appear. Those columns extent as far as the decidua and a mesenchymal core develops in them to form extraembryonic mesenchyme, which forms the villus vessels. In due course, these vessels establish continuity with those developing from the body stalk and inner chorionic mesenchyme. The distal part of the columns is not invaded by the mesenchyme but only serves to anchor it to the basal plate [1, 3]. These cells proliferate and spread laterally separating the syncytiotrophoblasts into two layers, the definitive syncytium on the fetal aspect and the peripheral syncytium on the decidual side which eventually degenerates and is replaced by a fibrinoid material and is known as Nitabuch's layer.

With deeper blastocyst invasion into the decidua, the extravillous cytotrophoblasts give rise to solid primary villi composed of a cytotrophoblast core covered by syncytium. The most deeply implanted portion of these villi forms placenta (**Figure 2**). Beginning on the 12th day

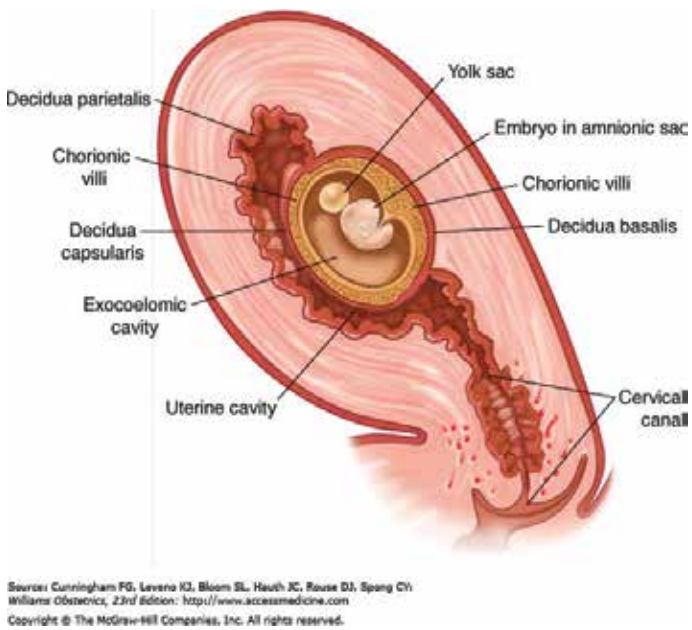

Figure 1. Decidual structure differentiating into decidua basalis, capsularis, and parietalis.

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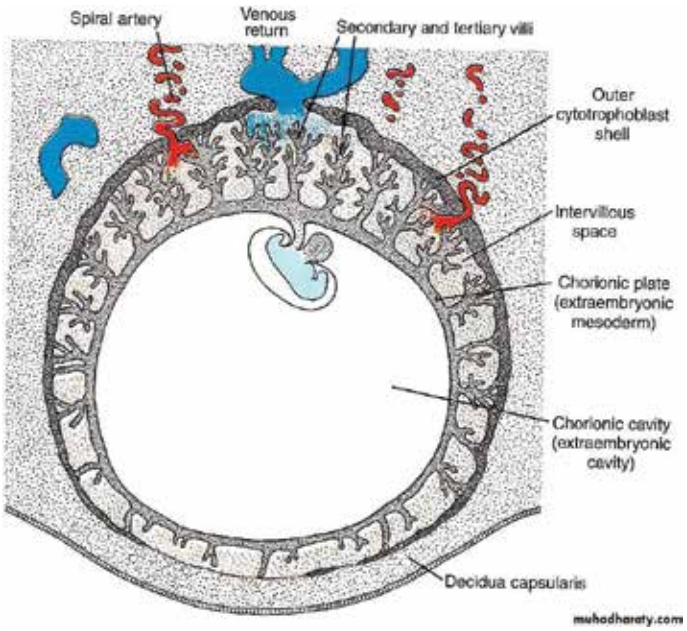

Figure 2. Development of placenta.

after fertilization, chorionic villi can first be distinguished and form secondary villi. After angiogenesis begins in the mesenchymal cores, it results into tertiary villi.

By approximately the 17th day, fetal blood vessels are functional, and a placental circulation is established. The placenta is a vascularized villus structure by the 21st day. The fetal-placental circulation is completed when embryonic blood vessels are connected with chorionic vessels. Groups of cytotrophoblasts also grow into the lumen of the spiral arteries extending as far as the decidual myometrial junction. These cells destroy the muscular and the elastic layer of the vessel wall and get replaced by a fibrinoid material which is derived from the maternal blood and proteins secreted by the trophoblastic cells. This primary invasion dilates the spiral arteriolar wall and thus augments blood flow to the placenta [1, 3]. There is a secondary invasion of trophoblast between 12 and 16 weeks extending up to radial arteries within the myometrium. Thus, spiral arteries are converted to large bore uteroplacental arteries. The net effect is funneling of the arteries that reduce the pressure of the blood to 70–80 mm Hg before it reaches the intervillous space. It thus increases the blood flow.

The placental septa appear by 12 weeks protruding into the intervillous spaces from the basal plate and divide the placenta into 15–20 lobes. Until the end of the 16th week, the placenta grows both in thickness and circumference due to growth of the chorionic villi with accompanying expansion of the intervillous space and with continuous arborization and formation of fresh villi [2].

In the first trimester, the villi are large and have a mantle of trophoblasts consisting of an inner layer of cytotrophoblasts and an outer layer of syncytiotrophoblasts with the stroma of small fetal vessels. During the second trimester, the villi are smaller, the mantle is less regular and the cytotrophoblasts less numerous, and the stroma with more collagen. The fetal vessels

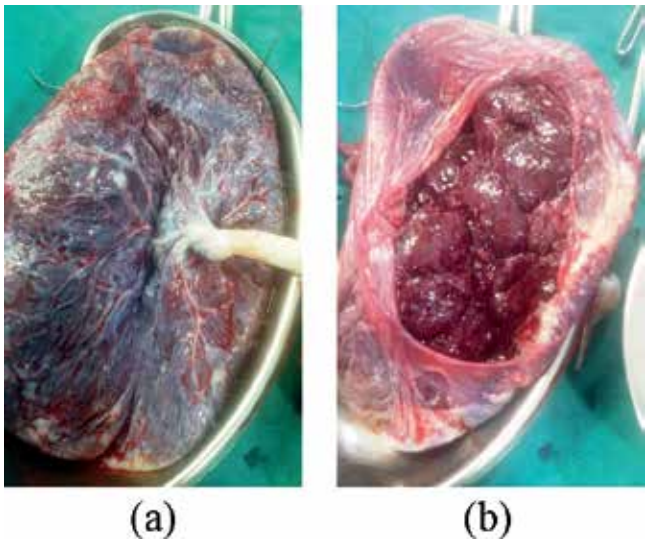

Figure 3. Placenta at term.

become larger and more toward the periphery of the villus. In the third trimester, the villi are much smaller in diameter, and the cytotrophoblasts are irregular and thinned out. The fetal vessels are dilated and lie just below the thinned out trophoblasts.

The placenta, at term, is almost a circular disc with a diameter of 15–20 cm and a thickness of about 3 cm at its center [2]. It feels spongy and weighs about 500 g, the proportion to the weight of the baby being roughly 1: 6 at term and occupies about 30% of the uterine wall. It presents two surfaces, fetal and maternal, and a peripheral margin (**Figure 3**) [2].

- The fetal surface is covered by the smooth and glistening amnion with the umbilical cord attached at or near its center [2].
- The maternal surface is rough and spongy. It consists of 15–20 lobes or cotyledons which are limited by fissures. Each fissure is occupied by the decidual septum which is derived from the basal plate [2].

The placenta consists of two plates. The chorionic plate lies internally. It is lined by the amniotic membrane. The umbilical cord is attached to this plate. The basal plate lies to the maternal aspect. Between the two plates lies the intervillous space containing the stem villi with their branches, the space being filled with maternal blood. A mature placenta has a volume of about 500 mL of blood, 350 mL being occupied in the villi system and 150 mL lying in the intervillous space [2].

3. Functions

1. Transfer of nutrients and waste products between the mother and the fetus. In this respect, it attributes to the following functions:

- Respiratory
- Excretory
- Nutritive

2. Endocrine function: placenta is an endocrine gland. It produces both steroid and peptide hormones (like progesterone, estriol, human chorionic gonadotropin, and human placental lactogen) to maintain pregnancy and support fetal growth.
3. Barrier function: placenta acts as a protective mechanism.
4. Immunological function: maternal antibodies are taken into the syncytiotrophoblasts by pinocytosis and subsequently transferred to fetal capillaries and thus fetus acquires passive immunity (**Figure 4**).

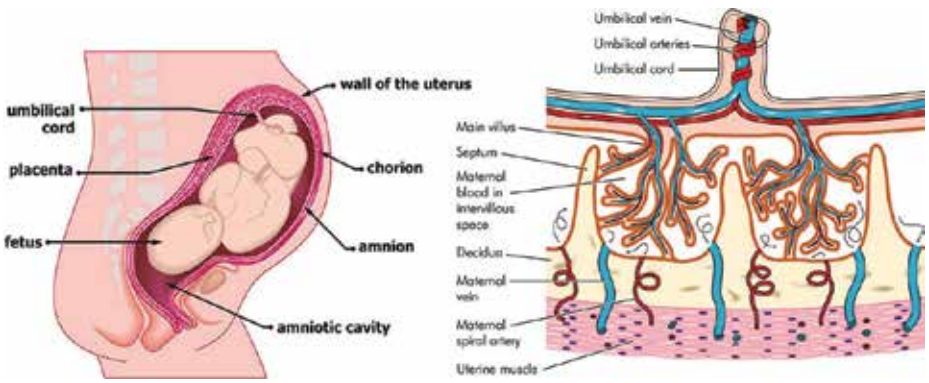

Figure 4. Blood supply of placenta.

4. Abnormalities of placenta

4.1. Placenta succenturiata

The accessory lobe is developed from the activated villi on the chorionic leave, may be placed at varying distances from the main placental margin. A leash of vessels connecting the main to the small lobe traverses through the membranes (**Figure 5**). In cases of absence of communicating blood vessels, it is called placenta spuria. The incidence of placenta succenturiata is about 3%. If the succenturiate lobe is retained, the following birth of the placenta may lead to:

a. Postpartum hemorrhage which may be primary or secondary

b. Subinvolution

c. Uterine sepsis

d. Polyp formation

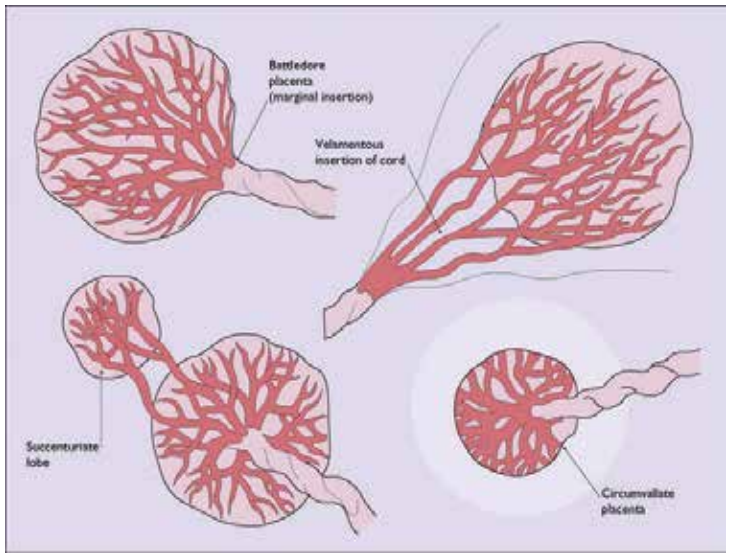

Figure 5. Placental abnormalities.

Treatment: Whenever the diagnosis of missing lobe is made, exploration of the uterus and removal of the lobe under general anesthesia is to be done.

4.2. Velamentous placenta

Normally, the umbilical cord inserts into the middle of the placenta as it develops. In velamentous cord insertion, the umbilical cord inserts into the fetal membranes (chorioamniotic membranes) and then travels within the membranes to the placenta (between the amnion and the chorion). The exposed vessels are not protected by Wharton's jelly and hence are vulnerable to rupture (**Figure 5**). Rupture is especially likely if the vessels are near the cervix, in which case they may rupture in early labor, likely resulting in a stillbirth. Once it is diagnosed, baby should be delivered by cesarean section.

4.3. Battledore placenta

Umbilical cord may be attached in the center, off center, on the edge, or in the membranes of the placenta. Battledore placenta is a placenta in which the umbilical cord is attached at the placental margin. The shortest distance between the cord insertion and the placental edge is within 2 cm. The incidence of the battledore placenta is 7–9% in singleton pregnancies and 24–33% in twin pregnancies [4, 5]. Complications associated with the battledore placenta are:

a. fetal distress

b. intrauterine growth restriction

c. preterm labor

d. decreased birth weight of baby and placenta

4.4. Placenta extrachorialis

It can be:

1. Circumvallate placenta: the fetal surface is divided into a central depressed zone surrounded by a thickened white ring which is usually complete. The ring is situated at varying distances from the margin of the placenta and is composed of a double fold of amnion and chorion with degenerated decidua (vera) and fibrin in between. Vessels radiate from the cord insertion as far as the ring and then disappear from view.

2. Placenta marginata: a thin fibrous ring is present at the margin of the chorionic plate where the fetal vessels appear to terminate.

There is increased chance of:

a. Abortion

b. Hydrorrhea gravidarum

c. Antepartum hemorrhage

d. Growth retardation of the baby

e. Preterm delivery

f. Retained placenta or membranes

4.5. Morbidly adherent placenta

Morbidly adherent placenta, which includes placenta accreta, increta, and percreta, implies an abnormal implantation of the placenta into the uterine wall (**Figure 6**). The incidence of placenta accreta has increased significantly over the past several decades, with the main risk factors including prior cesarean section and placental previa. Sonographic markers of placenta accreta can be present as early as the first trimester and include a low uterine implantation of a gestational sac, multiple vascular lacunae within the placenta, loss of the normal hypoechoic retroplacental zone, and abnormality of the uterine serosa-bladder interface, among others.

a. Placenta accreta is an extremely rare form in which the placenta is directly anchored to the myometrium partially or completely without any intervening decidua. The probable cause is due to the absence of decidua basalis and poor development of the fibrinoid layer.

b. Placenta increta: The placenta invades whole thickness of myometrium.

c. Placenta percreta: The placenta penetrates whole of the myometrium and may reach up to the peritoneum or bladder.

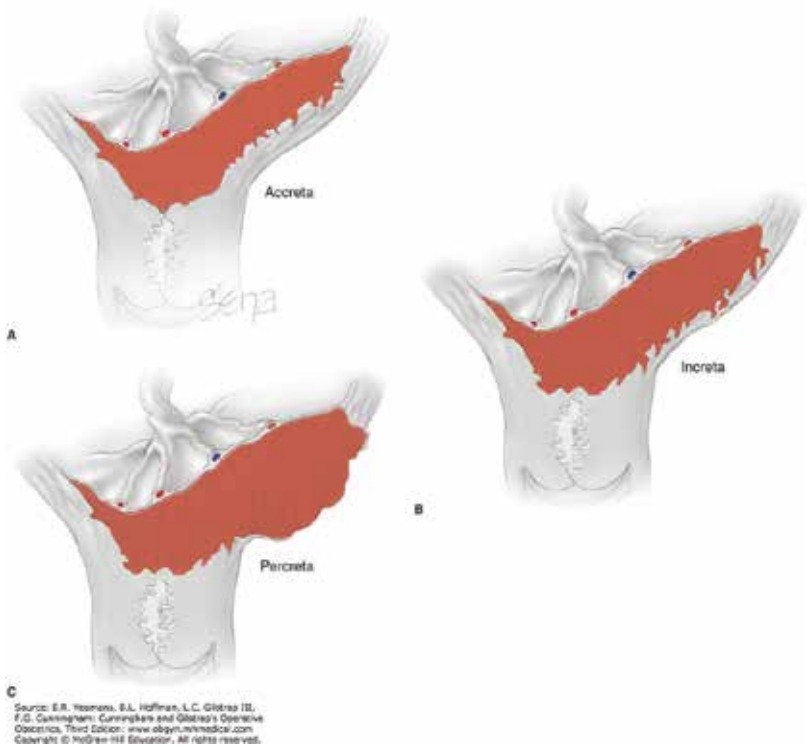

Figure 6. Morbidly adherent placenta (A: Accrete, B: Increta, C: Percreta).

4.6. Gestational trophoblastic disease/neoplasm

Gestational trophoblastic disease is divided into molar and nonmolar tumors. Nonmolar tumors are grouped as gestational trophoblastic neoplasia. It is classified as:

a. Hydatidiform mole

i. Complete

ii. Partial

b. Gestational trophoblastic neoplasia

c. Invasive mole

d. Choriocarcinoma

e. Placental site trophoblastic tumor

f. Epithelioid trophoblastic tumor

4.7. Chorioangioma of placenta

Placental chorioangioma is the commonest benign tumor of the placenta. Its incidence is around 1% when examined microscopically and is seen more frequently in multiple

pregnancies and in female babies [6]. Chorioangiomas that are clinically evident are less common with an incidence between 1:3500 and 1:9000 births [6]. It is believed to arise by 16th day of fertilization, although there is no documentation of the tumor in the first trimester [7]. In the majority of cases, it is small or microscopic and of no clinical significance. If it increases in size >5 cm, then it may be associated with serious maternal and fetal complications (**Figure 7**) [6].

The pathogenesis of these neoplasms is controversial; however, they can originate from any part of the placenta excluding the trophoblastic tissues [8]. Three histological patterns of chorioangiomas have been described: angiomatous, cellular, and degenerate [9];

- The angiomatous is the most common, with numerous small areas of endothelial tissue, capillaries, and blood vessels surrounded by placental stroma.
- The cellular pattern has abundant endothelial cells within a loose stroma.
- The degenerate pattern has calcification, necrosis, or hyalinization.

These lesions are sometimes classified as placental hamartomas rather than true neoplasia [10]. There is no malignant potential.

Large tumors probably act as arteriovenous shunts and cause complications. Maternal complications are preeclampsia, preterm labor, placental abruption, polyhydramnios, and postpartum hemorrhage [11]. The correlation of chorioangioma with hydramnios and preterm delivery is found to be significant among the various reported clinical complications. Fetal congestive heart failure may develop because of the increased blood flow through the low resistance vascular channels in the chorioangioma acting as an arteriovenous shunt. Other associated fetal complications are nonimmune hydrops, fetal demise, hemolytic anemia, congenital anomalies, fetal thrombocytopenia, cardiomegaly, intrauterine growth restriction, and neonatal death [12].

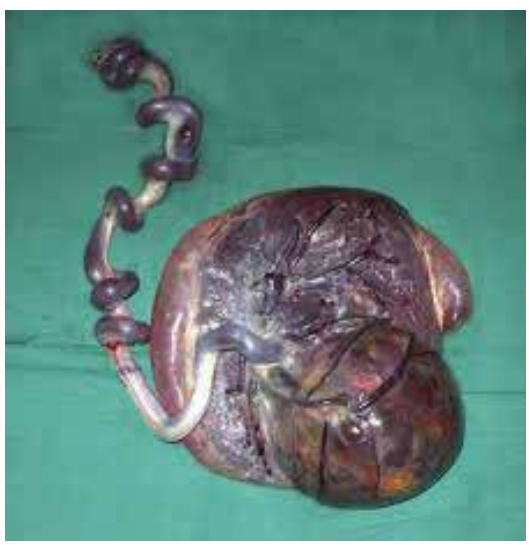

Figure 7. Chorioangioma of placenta.

Antenatal ultrasound examination has made diagnosis and follow up possible before delivery. In the present case, the placental tumor was not diagnosed in the ultrasound documentation rather polyhydramnios was reported. Doppler ultrasound examination is the gold standard in primary diagnosis of hemangioma. But unfortunately, we could not conduct Doppler USG in the present case as delivery was imminent. Magnetic resonance imaging (MRI) is used only in suspicious cases, while the computed tomography (CT) technique has a limited role in the diagnosis of the placental angioma, mainly because of the high radiation risk and poor tissue differentiation.

Chorioangioma with complications before fetal viability requires interventions. Alcohol injection, laser coagulation of feeding vessels, and microcoil embolization of the feeding vessels are described for women with fetal complications like hydrops [13, 14]. Large chorioangioma associated with polyhydramnios leads to high perinatal morbidity and mortality. Polyhydramnios is treated with therapeutic amniocentesis and maternal indomethacin therapy [12]. Steroid administration for acceleration of fetal lung maturity before 34 weeks is indicated. If complications appear late in pregnancy, delivery is the choice. A recent literature review concluded that further studies are needed to refine the appropriate selection criteria that will justify the risk of invasive in utero therapy for chorioangiomas [15].

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Chapter 2

Placenta-Derived Mesenchymal Stromal Cells: Modulation of Immunity and Inflammation

James Edinger, Kathy Karasiewicz, Shuyang He, Qian Ye and Robert J. Hariri

Additional information is available at the end of the chapter

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Abstract

As an organ generally discarded after a normal full-term birth, the placenta is one of the most studied organs from the cellular standpoint. The placenta contains large numbers of immune cells, stem cells, and stromal cells. These cell types spurred the field of regenerative medicine by catalyzing the establishment of cord blood banks and hematopoietic stem cell reconstitution in the treatment of many diseases including cancer. Previously, many scientific articles and reviews have focused on the production, phenotype, and functional characterization of bone marrow-derived mesenchymal stromal cells. In this chapter, the focus will be solely on the biology, phenotype, and functional characterization of placenta-derived stromal cells. Modulation of the immune response, including T cell proliferation, dendritic cell maturation, and monocyte differentiation by placenta-derived stromal cells, will be discussed. This chapter will span in vitro functional analyses, animal models highlighting the in vitro data culminating in a summary of current clinical activity.

Keywords: placenta, stromal cells, immune modulation, inflammation, mesenchymal, stem cells, growth factors, cytokines

1. Introduction

The placenta is an organ that has evolved to accomplish one thing, promote fetal growth during gestation. This is not a new concept, but the concept has evolved with our understanding of the molecular and cellular components required. The fetal allograft is maintained by several mechanisms including, but not limited to physical sequestration, immune modulation by hormones, cells, and metabolites. In fact, the function of T cells and dendritic cells changes

during gestation [1]. In mid gestation, there were reduced antigen-specific T cell responses, upregulation of inhibitory molecules, and reduced myeloid maturation toward dendritic cells suggesting an immune tolerance state was achieved. These changes were reversed in the third trimester toward immune activation that participated in completing pregnancy. In fact, the observation of microchimerism in mothers postpartum indicated that there was a very strong tolerance inductive mechanism produced by the placenta and its physiology. Maternal-fetal chimerism has been recently reviewed [2]. A highlight from this review discussed pregnancy-associated progenitor cells that were proposed to be tissue resident stem cells with long-term survival that led to microchimerism that was detected for decades in some individuals. We propose that these types of tissue resident stem cells can be isolated and cultured from full-term postpartum placenta. After culture, we hypothesize that the immune modulatory properties that these cells exhibit in the placenta will be translated to in vitro and in vivo experiments that form the basis of many clinical development programs.

An example of the cells that can be isolated from the human placenta is the human placenta-derived adherent cells (PDAC). PDAC are a culture expanded, plastic-adherent undifferentiated MSC-like population derived from normal full-term postpartum placental tissue. PDAC exhibit a phenotype of CD34-, CD10+, CD105+, and CD200+. PDAC constitutively express low to moderate levels of HLA Class I and undetectable level of HLA Class II, and these cells do not express the costimulatory molecules CD80 and CD86. PDAC were isolated by mechanical and enzymatic digestion of human placental tissue obtained from a normal, full-term birth as described [3]. PDAC are currently in clinical development as two separate formulations, PDA-001 (infusion product) and PDA-002 (locally injected product). This chapter will focus on developing the connection between placental immune biology (observed microchimerism) and the phenotypic and functional properties of the cells isolated from placenta tissues. These cells regardless of placental tissue source (amnion, cord, and cord blood) can mediate at least some of the immune tolerance properties of the placenta.

2. Molecular and cellular mechanisms of action

2.1. T cell proliferation and differentiation

Placenta-derived mesenchymal stromal-like cells (pMSC), including PDAC, have been isolated from various anatomical sites of the placenta, including the umbilical cord, chorion, decidua, amniotic membrane, and amniotic fluid. Like their bone marrow counterparts, these cells possess potent immune suppressive properties and exert their effects on T lymphocytes through a multitude of mechanisms that include both cell contact mediated interactions and through the modulation of secreted soluble factors. pMSC have been shown to inhibit both the proliferation and cytokine production of T lymphocytes, as well as, modulate T cell differentiation [3–5].

Many investigators have demonstrated the immune suppressive effects of pMSC in vitro via co-cultures of pMSC with CFSE-labeled, mitogen stimulated, or allogeneic T cells, known as mixed lymphocyte reactions (MLR), or with CFSE-labeled T cells stimulated by anti-CD3/

anti-CD28 monoclonal antibodies/beads, known as bead T cell reactions (BTR). In all cases, in reactions where CFSE-labeled cells were co-cultured with pMSC, significant reductions in both CD4+ and CD8+ T cell proliferation were observed. Reduced levels of proliferation were accompanied by decreased levels of Th1 cytokines (IL-2, IL-12, TNF-α, and IFN-γ) and increased levels of Th2 cytokines (IL-4 and IL-10) [3, 4, 6, 7]. Furthermore, when pMSC were co-cultured with naïve T cells under Th1 or Th17 inducing conditions, inhibition of Th1 and Th17 differentiation was observed [3].

Several factors secreted from pMSC have been implicated in the immune suppressive activities observed and will be summarized below. Indolamine 2, 3 dioxygenase (IDO) has been identified as a key mediator of pMSC anti-proliferative effects in MLRs/BTRs. IDO is a heme-containing enzyme that catabolizes the essential amino acid tryptophan into L-kynurenine. IDO-induced tryptophan degradation results in T cell cycle arrest in the G1 phase and serves as an instrumental mechanism for maintaining immune cell homeostasis and peripheral tolerance [8]. IDO gene expression and activity were induced in co-cultures of pMSC with MLRs/BTRs [6, 7, 9] and replenishment of tryptophan or treatment with IDO blocking compounds were shown to impair the antiproliferative abilities of pMSC [9, 10]. In addition, IDO was induced and subsequent suppression of T cell proliferation was intensified following stimulation of pMSC with IFN-γ [9, 11].

In addition to IDO, increased production of prostaglandin E2 (PGE2) and transforming growth factor-β (TGF-β) by pMSC, and increased secretion of IL-10 by T lymphocytes have also been implicated as key soluble factors underlying pMSC's immunosuppressive mechanism. PGE2, a bioactive lipid that is synthesized from arachidonic acid by the COX-1 and COX-2 enzymes, inhibits T cell proliferation and regulates the maturation and antigen presentation function of dendritic cells [3, 12]. TGF-β is a potent immunoregulatory protein that controls the differentiation, proliferation, and activation of various immune cells [13]. IL-10 is a well-known anti-inflammatory cytokine that controls the growth and activation of regulatory and/or anti-inflammatory cells [7]. All three secreted factors have been shown to be significantly increased in pMSC co-cultured with MLRs/BTRs [6, 7, 14]. The addition of blocking or neutralizing agents against PGE2, TGF-β, or IL-10 partially reversed and impaired the inhibitory effects of pMSC on T cell proliferation [5, 10]. Stimulation of pMSC with IFN-γ significantly upregulated the release of the tolerogenic cytokines TGF-β and IL-10 [5, 11].

Moreover, the increased levels of PGE2, TGF-β, and IL-10 can also affect T cell differentiation and lead to selective induction of Tregs [15, 16]. Tregs are CD4 + CD25 + FoxP3+ T cells that specialize in inhibiting T cell responses, allergic reactions, autoimmune disease, and graft rejection, while maintaining immune homeostasis [4]. Numerous studies have described an increase in the frequency of Tregs from co-cultures of pMSC with MLRs/BTRs [5, 6, 10, 14].

The immune modulatory effects of pMSC on T cell proliferation and differentiation have also been shown in several animal models. We reported that PDAC suppressed T cell proliferation in an OT-II T cell adoptive transfer model [3]. OT-II transgenic mice, expressing the T cell receptor specific for ovalbumin, were used to evaluate the effects of PDAC on antigen-specific CD4+ T cell proliferation. PDAC at three different doses or vehicle were administered along with the adoptive transfer of CD4+ T cells isolated from OT-II mice into

wild-type recipient mice following ovalbumin peptide immunization. PDAC treatment showed a dose-dependent decrease in the ovalbumin-specific CD4+ T cell proliferation in the spleen as compared with vehicle-treated mice. In addition, PDAC treatment resulted in an increase in the percentage of IL-10-producing splenic CD4+ T cells in a dose-dependent manner. In a rat sciatic nerve neuritis model, we showed that PDAC enhanced IL-10, but suppressed IFN-γ and IL-17 gene expression in draining lymph node, indicating that PDAC suppresses Th1 and Th17 cell differentiation [17]. We postulated that immune modulation of T cells in the draining lymph node is the mechanism underlying PDAC mediated neuropathic pain relief. To test this hypothesis, we performed two draining lymph node adoptive transfer studies in rat sciatic nerve neuritis model. Neuritis was induced by surgery and application of 1% carrageenan around sciatic nerve [17]. As shown in **Figure 1**, donor rats were treated with PDAC or vehicle 3 days after neuritis induction. One day after treatment, donor rats were sacrificed, and the draining lymph node was isolated into a single cell suspension and subsequently administered intravenously into the recipient rats with sciatic nerve neuritis.

Mechanical hyperalgesia measurement in the recipient rats showed that the draining lymph node cells from PDAC-treated animals reduced neuropathic pain in a dose-dependent manner compared with the draining lymph node cells from vehicle-treated animals (**Figure 2**).

To further identify the role of PDAC-mediated T cell modulation in the reduction of neuropathic pain, draining lymph node cells were separated into T cells and non-T cells using magnetic Pan-T microbeads, and adoptively transferred the cells to recipient rats with sciatic nerve neuritis. As shown in **Figure 3**, the whole population of draining lymph node cells as well as, the T cell fraction reduced neuropathic pain at days 4, 6 and 8. Interestingly, the non-T cell fraction also reduced neuropathic pain, with a slight time-delayed effect. These results from adoptive transfer studies demonstrated that immune modulation of the draining lymph node cells is the underlying mechanism of PDAC-mediated neuropathic pain reduction. Additional studies will be needed to sort out the differing contributions of the lymph node cells and how PDAC mediate these effects.

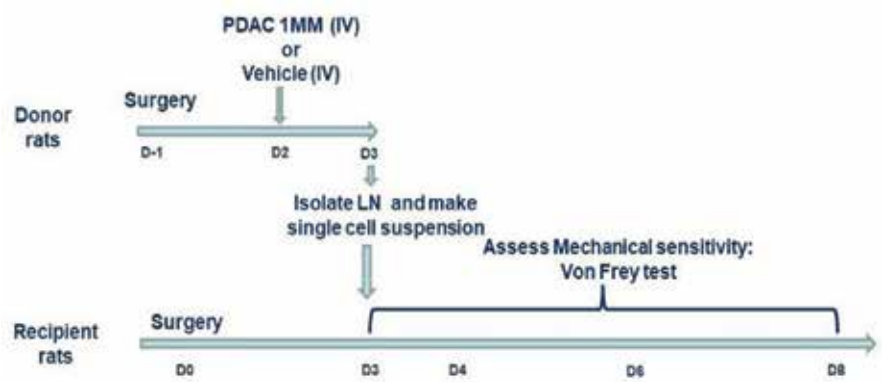

Figure 1. Schematic chart of draining lymph node cell adoptive transfer study.

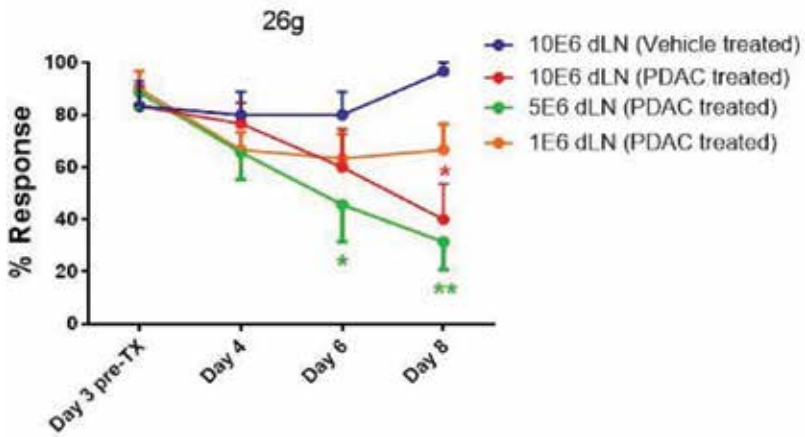

Figure 2. The effect of draining lymph node from PDAC-treated rats on mechanical hyperalgesia measured by 26 g force of von Frey fiber.

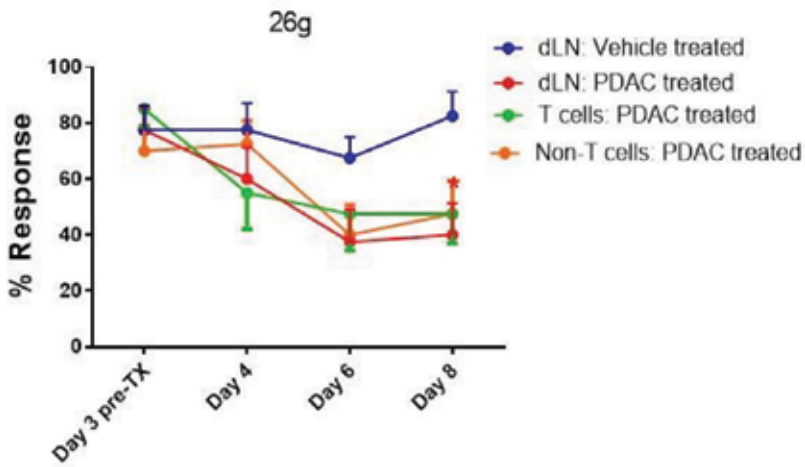

Figure 3. The effects of T cell, non-T cell subsets, and whole population of draining lymph node cells from PDAC-treated rats on mechanical hyperalgesia measured by 26 g force of von Frey fiber.

2.2. Macrophage maturation and differentiation

The migration of the monocytes to the wound site and the following maturation of monocytes to macrophages play key roles in the process of wound healing. Mesenchymal stem cells have been known to benefit the wound healing process since they have immune regulatory properties including an anti-inflammatory activity [18]. Mesenchymal stem cells derived from different placental tissues have been reported to modulate the maturation and differentiation of macrophages in both in vitro and in vivo studies. pMSC were shown to reduce the endotoxin induced activation of a mouse macrophage RAW264.7 cell line [19]. Human amnion mesenchymal cells, when co-cultured with human THP-1 macrophage cells, were shown to

inhibit the mRNA expression and secretion of TNF-α and IL-1β by THP-1 cells in vitro [20]. In addition, human placental mesenchymal stem cells shifted macrophage differentiation from inflammatory M1 to anti-inflammatory M2 macrophages presumably mediated by soluble molecules acting partially via glucocorticoid and progesterone receptors [21]. In a murine hind limb ischemia (HLI) model, a standard preclinical model of peripheral arterial disease (PAD), local administration of placenta tissue-derived mesenchymal stem cells to ischemic hind limb significantly reduced the infiltration of neutrophils and macrophages in the injured tissue compared to the sham-treated group [22].

In a separate report of studying PDAC in an HLI model, we showed that intramuscular administration of PDAC improved angiogenesis in the injured limb. Histological analysis revealed that PDAC-treated mice had an increased level of CD68+ arginase1+ M2-like macrophages in ischemic tissue. Moreover, we demonstrated that the effect of PDAC on macrophage differentiation was T cell dependent. The M2-like macrophage skewing was only observed in wild type and T cell reconstituted nude mice, but not in nude mice [23]. This observation is consistent with other reports that placental mesenchymal stem cells from amniotic membranes shifted macrophage differentiation from an inflammatory M1 to an anti-inflammatory M2 macrophage population [21, 24].

2.3. Dendritic cell maturation and differentiation

As discussed earlier, the human placenta plays a key role in maintaining immune tolerance between mother and fetus during normal pregnancy and is associated with the presence of Treg cells. It is also apparent that dendritic cells (DC) play a critical role in adaptive immunity and tolerance. While the multiple mechanisms of immune tolerance are not fully understood, it was first reported that amniotic mesenchymal tissue cells from human placenta (AMTC) can inhibit dendritic cell differentiation and maturation of monocytes from both peripheral blood and amniotic tissue [25]. When monocytes were cultured under the differentiation inducing condition, the presence of AMTC inhibited the expression of CD1a and reduced the expression of HLA-DR, CD80, and CD83. This finding suggested that placenta tissue mesenchymal stem cells could contribute to immune tolerance during pregnancy.

Another source of placenta-derived mesenchymal stem cells was reported to induce myeloid DC to a tolerogenic phenotype as demonstrated by its reduced migration in response to CCR7 and impaired ability to stimulate IFN-γ secretion from NK cells [26]. Placenta-derived mesenchymal stem cells were also shown to increase the secretion of IL-10 and reduce the secretion of IFN-γ from DC cells [27]. Placenta chorionic villous-derived mesenchymal stem cells were shown to inhibit the maturation of human dendritic cells induced by LPS in co-culture experiments. The DC cells co-cultured with placenta MSC not only expressed lower levels of costimulatory surface molecules, including CD40, CD80, CD83, and CD86 but, also reduced expressed a reduced ability to activate T cells [28].

Placental trophoblasts express a lower level of CD200 in preeclampsia and that is associated with an increase in production of Th1 cytokines, TNF-α, IL-6, IL-8, and IL-10 [29]. This result suggested that in normal placenta with higher CD200 levels on trophoblasts immune tolerance is favored [29]. Since PDAC express CD200, one can postulate that PDAC can also establish

immune tolerance. In the rat neuropathic pain model, when PDAC was administrated via tail vein, it was found that PDAC alleviates mechanical hyperalgesia [17]. This anti-neuroinflammatory activity appeared to be mediated by the suppression of dendritic cell recruitment, maturation and differentiation. Rat DC cells isolated from draining lymph nodes of the PDAC-treated animals showed reduced gene expression of CD11c, CD86, and CD80, markers of DC maturation. The relative expression of IL-12, a key pro-inflammatory cytokine secreted by differentiated DCs, was also significantly reduced in PDAC treated rats. Furthermore, the inhibition of DC infiltration and activation was observed at the ipsilateral sciatic nerve. In an in vitro co-culture experiment, PDAC inhibited differentiation of mouse DC [3], providing direct evidence of PDAC-mediated modulation of DC maturation and differentiation in vitro. In this work, mouse bone marrow cells were induced with GM-CSF and LPS to induce DC maturation with or without PDAC. The bone marrow DC exhibited a phenotype of CD86high and MHC I-A/I-E high, which was reduced in a PDAC cell dose-dependent manner. In addition, the expression of the tolerogenic DC marker, PD-L1, was enhanced. PDAC was further shown to affect the differentiation of human immature peripheral blood DC cells in vitro. When exposed to GM-CSF and IL-4, immature DC (CD1a+) differentiated to mature DC (CD86 high). The inhibition of DC differentiation and maturation by PDAC does not require cell–cell interaction since the co-culture was performed using a trans-well system separating mouse and human DC from PDAC. The conditioned medium from PDAC can also modulate DC differentiation and maturation. The DC modulation activity was in part mediated by PGE2 secreted by PDAC [3].

2.4. Clinical trial activity

In a recent review of advanced cell therapy clinical trials highlighting perinatal cells, the authors compiled data on the number of clinical trials conducted in different countries, with different cell types and in many different indications [30]. Since 2008, there was a more rapid advancement in the number of trials registered with most of the trials using cord blood or cord tissue. The use of perinatal mesenchymal stem cells has also increased to about 70% of

Figure 4. A narrow search on ClinicalTrials.gov with the search terms placenta derived cells.

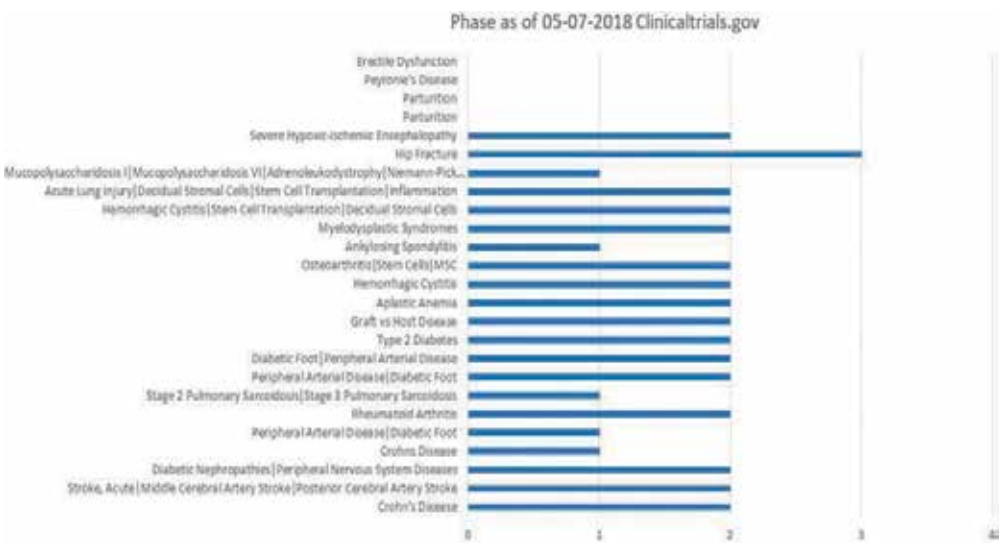

Figure 5. A narrow search on ClinicalTrials.gov with the search terms placenta derived cells illustrating the diverse diseases investigated.

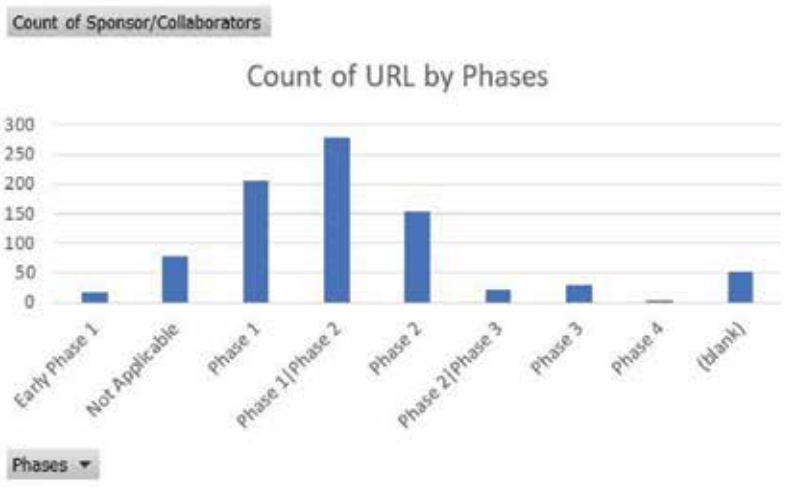

Figure 6. A search on ClinicalTrials.gov with the search terms mesenchymal stem cells illustrating the much greater numbers of clinical studies.

the annual trials registered and many of the trials were in the early phase of development (phase I or II). The cells from the amniotic membrane and placental tissue seem to be in a growth period for clinical trials. It will be important to track the progress of these trials and see which cells work in which indications.

In **Figure 4** below, the search terms on ClinicalTrials.gov included placenta-derived cells and were intentionally kept very narrow. The paucity of trials would suggest that the placenta is not an organ used to derive cells for clinical trials, however, this excluded cord tissue and cord blood as keywords in the search. As discussed above, these were the most cited trials over the last decade. The stage of development was consistent with the previous review in that the majority of studies were early phase clinical trials. The data depicted in **Figure 5** also corroborated the cited study above since there are many different diseases targeted in these trials and indicated that the search continues for the most appropriate clinical use for these cells. In **Figure 6**, the search encompassed the terms mesenchymal stem cell with no preference toward the source of cells and would include bone marrow-derived cells. As was evident, there were far more studies registered and the stage of development was slightly shifted to later stages, but still awaiting pivotal study readouts. As outlined in the sections of this review, the in vitro and in vivo data describe a broad array of immune modulation functions that suggest several pathways of clinical development and this is reflected in the number of indications pursued with these cells regardless of the biological source for the cells.

3. Conclusions

In this chapter, the observation of fetal-maternal microchimerism that can last for decades indicated that the placenta exhibited highly specific and strong immune tolerance to the host. In an attempt to explain the immune tolerance mechanisms, we highlighted several cell types from Tregs to dendritic cells and their interactions with placental derived cells using in vitro and in vivo models. There were several molecular mechanisms (examples, IDO, PGE2, T cell proliferation, and DC maturation) invoked to explain some of the interactions with T cells and dendritic cells, which included the effects of cytokine secretion on the activation and differentiation status of immune cells. The in vitro and in vivo data describe a broad array of immune modulation functions suggesting that cells of placental origin have immune modulatory and immune tolerance inducing properties that are independent of tissue source.

These immune modulatory properties highlight some of the possible ways in which the physiology of the placental graft is maintained during pregnancy and well after for microchimerism. To put these interesting results into some physiological context, a recent example of the immune system driving preterm labor described a pro-inflammatory environment at the fetal-maternal interface as a prerequisite for preterm labor [31]. In this study, the authors demonstrated that fetal T cells produced INF-γ and TNF-α which preceded myometrial cell contraction required for parturition. In addition, the authors demonstrated that fetal T cells (both CD4 and CD8) specifically proliferated in response to maternal antigen. It is interesting to speculate that the placental MSC present at the fetal-maternal interface could participate in suppressing the pro-inflammatory signals and the T cell proliferation that drive preterm labor.

This is a very active field of clinical and pre-clinical investigation and has generated huge excitement in the field of advanced cell therapy. The near future will bring us clinical results that allow the advancement of cell therapy to FDA approval and ultimately for the benefit of the patients that eagerly await these therapies.

Conflict of interest

All authors receive compensation from Celularity Incorporated.

Appendices and nomenclature

AMTC	amniotic mesenchymal tissue cells
BTR	bead T cell reactions
DC	dendritic cells
HLI	hind limb ischemia
IDO	indolamine 2, 3 dioxygenase
MLR	mixed lymphocyte reactions
PAD	peripheral arterial disease
PDAC	placenta-derived adherent cells
pMSC	placenta-derived mesenchymal stromal-like cells
PGE2	prostaglandin E2
TGF-β	transforming growth factor-β

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Chapter 3

Gene Expression Profiling of Placenta from Normal to Pathological Pregnancies

Soraya Mezouar and Jean-Louis Mege

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.80551

Abstract

The placenta is a unique temporary organ essential for growth of the fetus, which determines the success of pregnancy. Its originality relies on a combination of nutritive, endocrine and immunological functions that control maternal immune tolerance to fetus. In the present chapter, we review gene expression programs of placenta from placenta tissue to isolated cells using high throughput transcriptomic approach. Beside trophoblasts, we focused on immune cells including macrophages, dendritic cells and mast cells. From the gene expression signatures, we identify key pathways for the different trimesters of the normal pregnancy and pathological alterations including preeclampsia and gestational diabetes mellitus.

Keywords: placenta, pregnancy, preeclampsia, gestational diabetes mellitus, immune cells, gene regulation

1. Introduction

The placenta is a unique temporary organ and the central regulator of maternal-fetal environment [1]. It is a complex organ that needs to adapt constantly to maternal and fetal requirements during the progression of the pregnancy. The placenta is composed of several varieties of cells including trophoblasts, mesenchymal and endothelial cells and immune cells [2]. It is essential for materno-fetal exchange enabling the transfer of regulatory molecules to the fetus and fetal molecules to the maternal circulation [3]. The placenta is also involved in hormonal regulation [4, 5] and immunological defense of mother [6] and fetus [7]. The placenta synthetizes and secretes large number of molecules necessary for its development, metabolism

of mother and fetus growth [8]. These factors including placental hormones and growth factors lead to the regulation of gene expression critical for placenta plasticity and functions including angiogenesis, immune response, decidua invasion, endocrine regulation and fetal nutrition and growth [9].

The investigation of a complex organ such as placenta requires an approach without *a priori* that can be provided by high throughput methods such as microarray, ribonucleic acid-sequencing (RNA-Seq) and/or quantitative reverse transcription-polymerase chain reaction (qRT-PCR) technologies, which markedly changed our analysis of tissue physiology and pathophysiology. This field is expanding since the investigation of keywords including placenta, transcriptomic and gene expression on PubMed database revealed a progression of the number of publications per years from 1 in 2001 to 55 in 2017 (**Figure 1**). The transcriptomic studies have enabled identification of specific genes involved in the progression of the gestation and the outcome of complications. These gene signatures may be used as new biomarkers for maternal and fetal complications of pregnancy.

In this chapter, we will review the literature focusing on the gene expression profiling of placenta tissue and isolated cells during the progression of the gestation and pathological pregnancies.

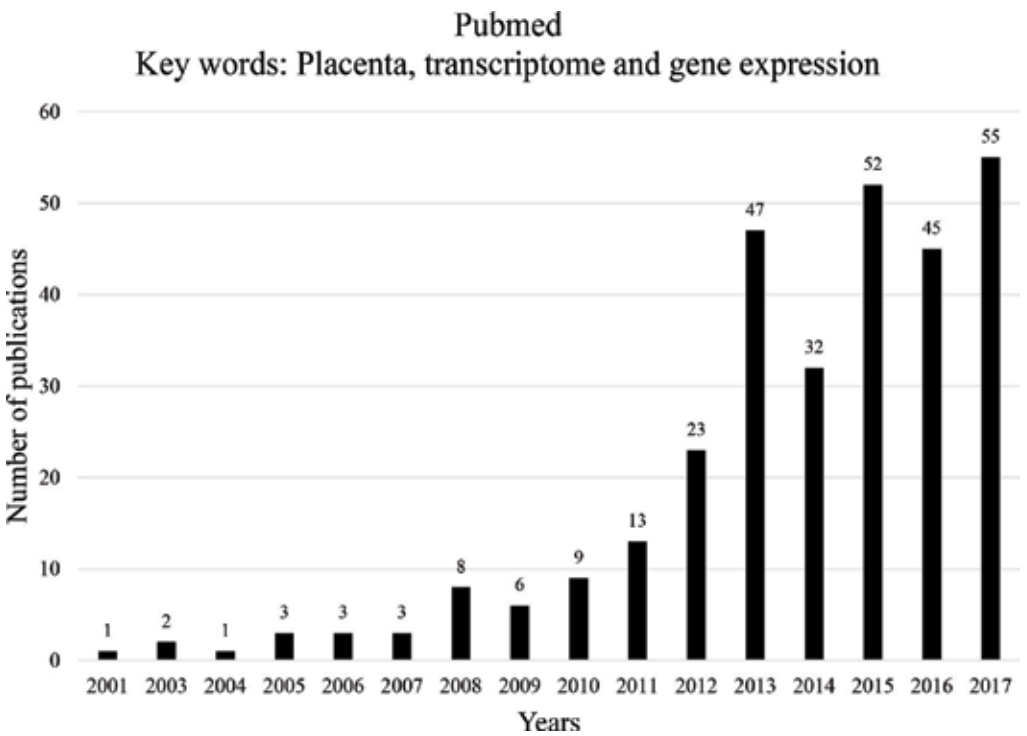

Figure 1. Number of publications associated with "placenta, transcriptome and gene expression".

2. Placenta transcriptome in normal pregnancy

2.1. Gene expression and anatomic organization of placenta

Human placenta is a feto-maternal organ composed of the fetal part (also known as chorion) and the maternal part (also known as decidua). The chorion is composed of trophoblasts, cytotrophoblasts and syncytiotrophoblasts, whereas the decidua contains enlarged endometrial stromal cells (epithelium) and leukocytes populations, thus suggesting that these two parts of placenta tissue are functionally different.

Few studies have investigated the transcriptomic profile of the different areas of the placenta tissue (**Table 1**). As shown in **Table 1**, two studies have investigated gene expression in amnion, chorion, decidua and villus parenchyma of at term placenta using microarray or RNA-sequencing. A core of gene expression patterns was observed in the different areas of the placenta; they are related to histology categories [10]. Microarray analysis revealed major differences among amnion, chorion and villus parenchyma. It showed that the gene encoding

Species	Placenta and gestational age	Technique	Results	References
Human	At term placentas (amnion, chorion, umbilical cord and section of villus parenchyma)	Microarray	• Differentially modulated genes are associated with placental trophoblast secretion, signal transduction, metabolism, immune regulation, cell adhesion and structure • Inter-individual differences are observed in gene expression between the mother and the fetal section of the placenta • The expression of a set of genes is related to the sex of the fetus	[10]
Human	At term placenta (amnion, chorion and decidua part)	RNA-sequencing	• 938, 865 and 944 genes are modulated in amnion, chorion and decidua tissues, respectively • 216 genes were commonly modulated among the three placenta tissues • Common genes were associated with placenta abnormalities including prolactin receptor, insulin-like growth factor 2 and a set of genes enriched with interleukin-1 pathway • Amnion: genes associated with cell adhesion and epidermal cell differentiation • Chorion: genes associated with angiogenesis, cell proliferation and Wnt receptor signaling • Decidua: genes associated with female pregnancy and wound healing	[11]

Table 1. Transcriptomic analysis of tissue component of the placenta.

Mucin 1 (MUC1) gene was strongly expressed in the amnion, whereas a cluster of up-modulated genes associated with signal transduction, cell differentiation and immunity categories was found in chorion. Among these genes, tissue remodeling genes, genes induced by interferon and major histocompatibility complex (MHC) genes were strongly up-modulated, suggesting a role for chorion in the plasticity and the immune tolerance of the placenta during pregnancy. Hypoxia-inducible factor (HIF)-1α, a transcription factor known to induce transcription of genes involved in glycolysis, erythropoiesis and angiogenesis [12], was expressed at low level in villus sections of placenta. In contrast, HIF-1α was up-modulated in amnion chorion and decidua [11]. It is likely that these discrepancies are related to exposition to different gradients of oxygen, which modulate HIF-1α expression.

Although these studies based on at term placentas are limited, they suggest that distinct tissue transcriptional programs exist in placenta. In addition, some inter-individual variations of the placenta structures have been observed during the second and the third trimester of the pregnancy [13]. Further investigations must include placentas at the different age of the gestation to precisely map gene expression in different areas of placenta during pregnancy.

2.2. Evolution of placenta gene expression during pregnancy

During pregnancy, the placenta gene expression is continuously modulated to adapt immune response to tolerance necessity and to modify metabolism according to pregnancy requirement. Hence, the early stages of the pregnancy are characterized by trophoblast invasion, which leads to placentation. During the mid-gestation, the placenta adapts its gene expression to maintain the fetal growth and the organ development. Finally, during the third trimester, placenta must provide enough nutriments for the growing of the fetus. Some evidence suggests that preterm birth is related to changes in gene expression during pregnancy [14].

The evolution of placenta gene expression during the different gestational stages is summarized in **Table 2**. The five studies investigated gene expression at different gestational ages in humans and mice. They identify common gene pathways involved in cell differentiation, immune response and angiogenesis (**Table 2**). In first trimester, the few genes that are found modulated are strongly involved in cell proliferation vascular development and angiogenesis. At mid-gestation several genes associated with cycle control, including cyclin family, are found up-modulated [17, 19]. There is an enrichment in gene ontology (GO) terms related to growth of the placenta, the set-up and the maturation of villous with blood vessels during first and second trimester as compared with third trimester [15, 20]. In addition, GO terms for cell differentiation and communication are also observed and are related to the organization of placenta structure and plasticity [21]. All studies observed a major change in the gene expression pattern at the end of the pregnancy. The third trimester is associated with the over-expression of genes involved in apoptosis, oxidative stress response and inflammatory process [17, 18], whereas the second and third trimesters share the up-modulation of genes associated with immune response. It has been recently shown that the gene expression program of placentas at the third trimester exhibits activation of the immune response and an increase of oxygen-rich maternal blood in placenta, which reflect labor and delivery route [22, 23].

Species	Placenta and gestational age	Technique	Results	References
Human	First trimester (45–59 days) Second trimester (109–115 days)	Microarray	• 500 genes common to the 1st and 2nd trimesters • 836 genes specific to the 1st trimester • 264 genes specific to the 2nd trimester • 1st or 2nd trimesters versus term: cell division, mitosis, DNA metabolism, pregnancy, response to chemical, immune response and regulation of cell cycle • Genes included in gestational regulation of the Wnt pathway	[15]
Human	First trimester (6–7 weeks) Third trimester (279 days)	qRT-PCR	• Cysteine dioxygenase (CDO) mRNA is up-modulated in at term placentas compared to 1st trimester placentas	[16]
Human	First (9–12 weeks) Third trimester	Microarray	• 7519 genes differentially expressed between 1st and 3rd trimesters • Biological processes up-regulated in 1st trimester: cell proliferation, cell differentiation and angiogenesis • Biological processes up-modulated in 3rd trimester: cell surface receptor-mediated signal transduction, G-protein mediated signaling, ion transport, neuronal activities and chemosensory perception • 3D separation observed for 17 imprinted genes of 1st and 3rd trimester placentas, suggesting epigenetic modifications	[17]
Human	Second (14–16 and 18–19, 21, 23–24 weeks) and third trimesters (37–40 weeks)	Microarray	• Little changes on gene expression observed during 14 to 24 weeks • 418 genes differentially modulated at the third trimester (37–40 weeks) compared to mid gestation (14–24 weeks) • These genes are involved in differentiation, motility, transcription, immunity, angiogenesis, extracellular matrix dissolution and lipid metabolism	[18]
Mice	Embryonic day 10.5, 12.5, 15.5 and 17.5	Microarray	• 599 genes differentially modulated • Up-regulation of genes associated with angiogenesis fatty acid metabolism and transport for E 10.5 compared to E 12.5 • Up-regulation of genes associated with hormonal control and ribosomal proteins for E 12.5 compared to E 10.5 • Up-regulation of genes associated with cell cycle and RNA metabolism for E 12.5 compared to E 15.5 • Up-regulation of genes associated with cellular transport for E 15.5 compared to E 12.5 • Up-regulation of genes associated with cell cycle control and RNA metabolism for E 17.5 compared to E 15.5	[19]

Table 2. Transcriptomic analysis of uncomplicated normal pregnancies at different ages of pregnancy.

2.3. Term labor and gene expression

The molecular mechanisms regulating the initiation of labor are still poorly understood. The key role of genes involved in prostaglandin synthesis and inflammatory responses in cervix, myometrium and chorio-membranes has been reported in laboring women as compared with non-laboring women [24]. **Table 3** summarized the studies evaluating placenta gene expression from preterm versus term labor with vaginal or cesarean deliveries. The commonly modulated genes are involved in immune response and apoptosis. Oros et al. showed a balance of immune modulators with an increased expression of tumor necrosis factor (TNF) and interleukin (IL)-6 and a decrease in interferon (IFN)-γ expression [26]. These results are likely related with cytokine production of at term placentas [30] and M1 polarization shift of macrophages [31]. Another study showed that gene expression associated with oxidative stress is elevated [25]. It has been previously observed that oxidative stress in placenta explants

Species	Placenta and gestational age	Technique	Results	References
Human	5–10 min before delivery (preterm labor or not)	Microarray	• Functional ontology analysis response to stress, cell surface receptor-linked signal transduction, regulation of transcription, immune system process, blood vessel development, death, cell-adhesion, cell-cell signaling, coagulation and oxygen and reactive oxygen species metabolism process	[25]
Human	Preterm (26–36 weeks) Term (>37 weeks) all with suspicion of preterm labor	qRT-PCR	• Increased expression of TNF, IL-6 and PGF • Decreased expression of IFN-γ and VEGFR1 • Term delivery after suspicion of preterm labor shows decreased VEGFA • Preterm delivery after suspicion of preterm labor shows decreased VEGFB	[26]
Human	Term (38–42 weeks) with vaginal delivery or cesarean	Microarray	• Up-regulated genes in placenta by labor are involved in angiogenic regulators, immune response, inflammatory response and apoptosis	[27]
Human	Term (34 weeks) with vaginal (laboring) delivery or cesarean (non-laboring)	Microarray	• 92 genes down- and 94 up-regulated genes in laboring placentas compared to no-laboring placentas • FOS, FOSb and GNGT1 are down-modulated in laboring placentas compared to non-laboring placentas	[28]
Human	Term and term nonlaboring cesarean deliveries	Microarray	• Labor is associated with up-modulated expression of MMP-1 gene in chorionic villus tissue • Genes involved in the extracellular matrix homeostasis are up-modulated such as fibronectin 1 and collagen XVII	[29]

Table 3. Transcriptomic analysis of uncomplicated pregnancies from preterm or term labor.

and production of inflammatory cytokines are related [25]. The TNF levels are elevated during labor, suggesting that TNF may be a biomarker of preterm labor [32, 33]. Based on gene expression in placenta, epidemiological analysis suggested a genetic predisposition to spontaneous preterm labor and preterm birth [34]. Nevertheless, additional investigation of transcriptomic analyses must be necessary to better understand the role of gene expression in term labor.

2.4. Placenta microRNAs in pregnancy

MicroRNAs are small non-coding 20–24 nucleotides that target and regulate numerous genes [35]. They are expressed by tissues and cells but can also circulate in blood. They can be used as biomarkers [36]. It has been reported that more than 500 microRNAs are produced by the human placenta and a part of them are placenta specific [37]. Their expression varies with the gestational stages; 191 microRNAs are differentially modulated in placentas from first versus third trimester [38]. During the first trimester, microRNAs are associated with angiogenesis, anti-apoptosis and oncogenesis categories, whereas microRNAs from third trimester are related to cell differentiation and tumor suppression categories. Luo et al. found that miR-378a-5p is up-modulated in first and second trimesters but not in third trimester in placenta tissue [39]. The variations of microRNAs expression during different gestational ages suggest that they may regulate specific functions during pregnancy. However, the studies investigating microRNAs in total tissue in normal pregnancy are scarce and further investigations are necessary to better characterize microRNA signature and their temporal expression pattern in the placenta at different ages of gestation.

3. Placenta transcriptome in pathological pregnancy

The alteration of gene expression pattern in placenta tissue may reflect metabolic disorders associated with pregnancy such as gestational diabetes mellitus or pathologies that compromise pregnancy success such as preeclampsia [40]. We will summarize main findings reported in preeclampsia and gestational diabetes mellitus that represent the two pathologies mainly investigated by transcriptomic analyses.

3.1. Preeclampsia

Preeclampsia is a severe placenta disease that occurs in 3–5% of pregnant women and is a source of complications for mother and fetus [41–43]. The preeclampsia is initiated at the time of trophoblast invasion and remodeling of the spiral arteries during the first and early second trimester of pregnancy [41, 44, 45]. Initial studies have shown that elevated levels of various placental proteins in maternal blood such as FLT1 (fms-related tyrosin kinase 1), sENG (soluble engolin) and PGF (placental growth factor) in early pregnancy may be predictive of preeclampsia development [46] but the presence of false negative rates limits their clinical use [47]. The use of high throughput methods such as microarray is likely useful to identify new biomarkers and potential therapeutic targets. **Table 4** summarizes transcriptional studies of

Species	Placenta and gestational age	Technique	Results	References
Human	At term preeclampsia or healthy	Microarray	• HLA-DRB1, but not HLA-A RQ and CSTM2 RQ genes, is up-regulated in placenta tissue from women with pre-eclampsia • HLA-A and HLA-DRB1 expression are related to the reduction of birthweight but not placenta weight	[48]
Human	At term preeclampsia or healthy	Microarray	• Increased glycogen phosphorylase gene in preeclampsia group compared to controls	[49]
Human	At term (>37 weeks) preeclampsia or healthy	Microarray	• Among 368 regulated genes in preeclampsia group compared to controls, 35% present an expression higher than 2.0 • Up-regulated genes are associated with cell-cycle or apoptosis functions • Up-regulation of immune-system activation-related genes • No differences of MHC complex in the two groups	[50]
Human	Term (32–40 weeks)	Microarray	• A few numbers of genes (21) are differentially expressed • Genes involved in transcriptional regulation, vaso-regulative pathways. Hypothetical protein and gene sequences with unknown functions	[51]
Human	Placenta with preeclampsia or from healthy donors (253–273 days)	Microarray	• Genes involved in cell proliferation, immune regulation, lipid biosynthesis, protein biosynthesis and transport, signal transduction are up-modulated • Genes previously involved in preeclampsia such as Flt-1, leptin, HTRA1 and SIGLEC6 are modulated	[52]
Human	Placenta with preeclampsia or from healthy donors (<32 weeks)	Microarray	• Modulation of genes involved in cell adhesion-related protein, obesity-related protein, transcription factor, immunological factor, protease inhibitor, neuro-mediator, endocrine-related protein, oncogenic factor and growth factor • Obese gene is the most up-modulated gene	[53]
Human	Placenta with preeclampsia, increased vascular resistance (notch) or from healthy donors	Microarray	• 148 genes are altered • Up-modulated genes associated with chemotaxis, NF-kappa B pathway are found in preeclampsia group compared to notch • Down-modulated genes associated with antigen processing and presentation (human leukocyte antigen B) are found in preeclampsia group compared to notch • Results suggest that progression of pre-eclampsia from notching is dependent of the development of inflammation	[54]

Species	Placenta and gestational age	Technique	Results	References
Human	Placenta with preeclampsia or from healthy donors (39 weeks)	RNA-Seq	• 53 differently expressed genes are modulated • Perturbation of pathways involved in vascular function and immunological balance in preeclampsia group • Some identified-genes have been previously reported (e.g. leptin) or not previously associated with preeclampsia	[55]
Human	Placenta with preeclampsia or from healthy donors (35–39 weeks)	Microarray	• 58 genes are modulated and associated with immune system, inflammation, oxidative stress, signaling, growth and development pathways • Some genes identified have been previously reported (leptin) or not previously associated with preeclampsia (CYP11A and CDKN1C)	[56]
Human	Placenta with preeclampsia (31–39 weeks), preterm labor (24–33 weeks) or from healthy donors (37–39 weeks)	Microarray	• 20 miRNAs and 120 mRNAs are differentially modulated in preeclampsia and preterm group compared to healthy donors • Functional analysis shows a common activity of these genes associated to cellular activities	[57]
Human	Placenta with preeclampsia (mean 34.2 weeks), with small for gestational age (mean 34.5 weeks) or both (mean 33.9 weeks)	Microarray	• No significant difference between preeclampsia and small-for gestational-age groups • Increased anti-angiogenic gene expressions are observed	[58]
Human	Placenta with preeclampsia or from healthy donors (mean 37.5 and 39.8 weeks, respectively)	Microarray	• Differentially expressed genes associated with inflammation, immune regulation and cell motivity are found	[59]
Human	Placenta with preeclampsia or from healthy donors (mean 34.6 and 38.6 weeks, respectively)	Microarray	• 896 differentially expressed genes are found • Up-regulation of HTRA4, LHB and β-hCG • Decreased of NOX4 gene	[60]
Human	Placenta with preeclampsia or from healthy donors (34–37 weeks)	Microarray	• 2109 differentially expressed genes are found • Down-modulation of CD4 • Up-regulation of LEP, FLT1, PAPPA2, INHA, SIAE and ENG	[61]

Species	Placenta and gestational age	Technique	Results	References
Human	At term placenta with preeclampsia or from healthy donors	Microarray	• 213 and 82 genes are found up- and down-modulated, respectively • Differentially expressed genes are observed between early and late onset preeclampsia • Up-regulation of FLT1, PAPPA2, CGB5, LEP and INHBA • Down-modulation of PDGFD, BHLHB3 and BMP5	[62]
Human	Variable	Meta-gene analysis on microarray experiment in published studies	• Differential expression of autophagy-associated genes is found in microarray datasets from separate published studies	[63]
Human	Term	Meta-gene analysis on microarray experiment in published studies	• The most highly affected pathways in preeclampsia placenta are Wnt, ErbB, PPAR, Hedgehog signaling pathways, mRNA surveillance pathway and ubiquitin mediated proteolysis. • Identification of specific genes for preeclampsia: LEP, HTRA4, SPAG4, LHB, TREM1, FSTL3, CGB, INHA, PROCR and LTF genes	[64]

Table 4. Transcriptomic analysis of pregnancy with preeclampsia.

placenta from women with preeclampsia. Most studies use at term placentas and report a number of modulated genes varying from 20 to more than 2000.

Among the up-modulated genes, those associated with the regulation of the immune response are most frequently reported in transcriptomic analysis of preeclampsia placentas (**Table 4**). These findings may be related to the up-regulated gene expression profile of circulating cells from pregnant women with preeclampsia [65–67] and to the observation of increased levels of inflammatory cytokines including IL-6, IL-8 and TNF [68, 69]. Indeed, using microarray approach on blood samples, we observed a specific transcriptional signature of genes up-modulated in severe preeclampsia including genes associated with ribosome and complement functions [67]. In addition, we had identified VSIG4 (V-set and immunoglobulin domain containing 4) as a biomarker of severe preeclampsia.

Among genes associated with immune response, three studies reported the modulation of human leukocyte antigen (HLA) genes [48, 54, 59]. HLA-A, HLA-B and HLA-DRB1 are up-modulated in placentas from preeclampsia as compared to control group. The molecules, HLA-A and HLA-DRB1 have been associated with preeclampsia outcome [48, 70, 71] and have been related to reduced birth weight but not to placenta weight. Clinical observations show that both birth weight [72] and placenta weight [73] are decreased in pregnant women with preeclampsia.

Gene associated with hypoxia and oxidative stress are frequently found in placenta from women with preeclampsia. The placental hypoxia associated to preeclampsia is due to shallow implantation, impaired trophoblast invasion or vascularization of placenta arteries [40, 74]. The hypoxia leads to low birth weight and newborn diseases [75]. The gene encoding leptin has emerged as a potential biomarker of preeclamptic placentas from transcriptomic analyses [52, 56, 76]. This gene is known to be up-modulated in placenta from patients who experience chronic hypoxic ischemia [77]. Other genes involved in hypoxia are down-modulated in preeclampsia: this is the case for the gene encoding a glutathione reductase, an antioxidant protein, whereas the gene encoding the thioredoxin peroxidase is up-regulated [78]. In contrast, Zhang et al. found no modulation of genes encoding enzymes involved in oxidative stress as compared to controls [79].

The transcription analysis enables the identification of several up-modulated genes including genes involved in apoptosis processes [50], activin-A, inhibin A [80], soluble sENG [61], soluble sFlt-1 [61] and placental growth factor PGF [81]. In these studies, three angiogenic genes are found differently expressed: they include sFLT1 (also known as vascular endothelial growth factor, VEGF), PGF and sENG that are up-modulated in preeclampsia and associated with severe preeclampsia [61, 62, 82, 83]. In a case-control clinical study, the level of sFLT1 increases and that of PGF decreases during normal pregnancy; this response is more pronounced in women who develop preeclampsia [46]. Thus, it has been proposed that sFLT1 could be used as biomarker for predicting the development of preeclampsia [84]. However, these genes are not found in all transcriptomic studies of preeclamptic placentas [85]. This discrepancy may be explained by the clinical heterogeneity of preeclampsia, placenta sampling sites, gestational weeks, sex of the child, labor and the method of delivery. These parameters restrict the use of these genes as biomarkers for diagnosis or prognosis of preeclampsia.

3.2. Gestational diabetes mellitus

Placenta is an endocrine organ that provides glucose to fetus. A pathological state of insulin resistance leading to glucose intolerance is called gestational diabetes mellitus (GDM) [86]. The mother may develop hemorrhage, hypertension, infection, difficulty in labor and increased risk of mortality [87]. The placentas from GDM patients exhibit histological alterations and elevation of its size and weight at third trimester. This may be due to insufficient production of placental hormones [88]. To better understand the role of placenta in the development of GDM, transcriptomic analyses of placenta from pregnant women with a GDM or mice model of diabetes have been conducted in some studies (**Table 5**). Few genes are differentially modulated and they are predominantly related to extracellular matrix remodeling, immune response and regulation of apoptosis categories.

Among the immune response category, genes such as TNF are up-modulated. TNF is known to be involved in insulin resistance, obesity and diabetes [95, 96]. Although TNF levels are increased in GDM and type 1 diabetes [97], no relation was found between placenta TNF mRNA amounts and the levels of this cytokine in maternal blood with GDM [98–100].

Species	Placenta and gestational age	Transcriptomic technique	Results	References
Mouse (Streptozotocin induced-diabetes)	E 10.5	Microarray	• 158 genes are modulated in diabetic placentas compared to controls (47% down-and 54% up-modulated genes) • Functional category: extracellular matrix, hormones, cell surface receptor, signal transduction, transcription factors, metabolism, channel, cytoskeleton and RNA binding • Diabetes-induced molecular changes and abnormal differentiation of cells, modification of growth and junctional zone and labyrinth	[89]
Human	Placenta with GDM (38 weeks)	Microarray	• Increased expression of genes involved in markers and mediators of inflammation • Increased expression of genes involved in stress-activated and inflammatory responses • Increased expression of genes encoding interleukins, leptin and TNF receptors • Gene modulation is associated with extracellular matrix component and angiogenic activators	[90]
Human	Placenta with GDM or from healthy donors (mean 37.7–38.4 weeks)	Microarray	• 66 genes are up-modulated in GDM placentas • Modulated genes are associated with cell functions (activation), immune response, organ development and regulation of cell death • Modulated genes including LEP, CEBPA and MIF have been previously described • Up-modulation of AQP3, LEP, FLT1, ADFP, CEBPA and MIF genes • AQP3 is a new gene associated with GDM outcome	[91]
Mouse (60% calories-by-fat diet induced-diabetes)	E 12.5	nCounter nanostring	• Altered gene expression in the fetal brain • GDM mice present repressed genes associated with neuro-developmental, cholinergic signaling, IFN/antiviral response, growth, cell cycle regulation and apoptosis • GDM mice present increased expression of genes associated with inflammation	[92]

Species	Placenta and gestational age	Transcriptomic technique	Results	References
Human	At term placenta with GDM or from healthy donors	Microarray	• Up-regulation of miR-508-3p and down-modulation of miR-27a, miR-9, miR-137, miR-92a, miR-33a, miR-30d, miR-362-5p and miR-502-5p • This gene signature targets EGFR, PI3K and AKT genes involved in placental development and fetal growth	[93]
Human	Placenta with GDM or from healthy donors (38 weeks)	Microarray	• 435 genes are modulated • 18.5% of modulated genes are involved in stress-activated and inflammatory responses • Up-regulation of interleukins (IL-1R), leptin, and TNF receptors	[90]
Human	Placenta with GDM (23–41 weeks)	Microarray	• 243 genes present an altered expression • TNF, IL-1β, LEP, IFN-γ and HLA-G are differentially modulated • Gene modulation is associated with cytokine-cytokine receptor interaction	[94]

Table 5. Transcriptomic analysis of pregnancy with gestational diabetes mellitus.

Transcriptional studies reveal strong association of leptin (LEP) with GDM [90, 101, 102]. LEP is up-modulated in placenta and could be a cause or a result of glucose uptake in placentas from women with GDM [102, 103]. Elevated circulating levels of LEP are found in GDM but LEP is also found in others pathological pregnancies such as preeclampsia. The changes in LEP concentration are associated with the modulation of cytokines such as TNF [102].

Finally, common modulated genes are found in transcriptome analyses of placental gene expression in term pregnancy complications, suggesting that they could be associated more to a dysfunction of the placenta than to a specific complication. As examples, FLT1 (fms-related tyrosine kinase 1) or PAPPA2 (Pappalysin-2) are commonly modulated in placenta disorders and could be used as biomarkers.

3.3. miRNAs in complicated pregnancy

Some investigations highlight dysregulation of microRNAs in preeclampsia and GDM, suggesting their role in pathological pregnancies [104]. In preeclampsia, the upregulation of miR-210, miR-20b, miR-29b, miR-16, miR-155 and miR-675 is associated with angiogenesis and trophoblast invasion [44, 105–110]. In contrast, down-modulation of miR-378a-5p, miR-376 and miR-195 is related to the promotion of trophoblast invasion and proliferation [39, 111]. However, some discrepancies are observed according to transcriptomic studies. For example, several studies showed that miR-210 represents the most up-regulated microRNAs in preeclampsia, whereas other studies found no change in placenta from preeclampsia compared to healthy donors [57].

Altered circulating levels of specific microRNAs have been reported in compromised pregnancies. For example, the low detection of miR-376c level in blood of 16–18 weeks pregnant women is related with the outcome of preeclampsia [112]. In similar conditions, three miRNAs, including miR-132, miR-29a and miR-222, are decreased in blood from women at 16–19 gestational weeks who were diagnosed a GDM at 25–28 weeks of gestation [113]. Thus, despite the promising perspectives to use microRNAs in diagnosis of complicated pregnancies, future studies are needed to provide a proof of concept.

4. Gene expression of placental immune cells

Beside the investigation of gene expression in whole placenta, several studies investigated transcriptomic profiles of isolated placental cells including immune and nonimmune cells. We focused here only on immune cells. Placental immune cells are necessary for development of the placenta bed and the semi-allogeneic tolerance of the fetal-placental unit. In addition, they are involved in the regulation of trophoblast invasion, angiogenesis and spiral artery remodeling. The distribution of immune placental cells is markedly distinct from that of circulating immune cells: NK cells and macrophages are found at high density, whereas lymphocytes, dendritic cells and mast cells are less represented. Therefore, we studied the transcriptomic response of macrophages, dendritic cells and mast cells.

4.1. Macrophages

Placental macrophages include decidual and Hofbauer cells from decidua (basalis) or villous stroma, respectively. They are the most abundant cells that persist throughout pregnancy [114, 115]. They play a central role in maintaining a homeostasis during pregnancy by controlling imbalance between anti- and pro-inflammatory features of placenta environment [116, 117]. Indeed, the pro-inflammatory (M1) polarization of macrophages or the prevention of M2 polarization (anti-inflammatory and/or immunoregulatory properties) leads to spontaneous abortion or miscarriage [118], inadequate remodeling of the uterine vessels during placentation and protection against infection [119].

4.1.1. First and second trimesters

After placentation, placental macrophages exhibit a M2 profile during the first and second trimesters. This M2 profile contributes to the anti-inflammatory environment of the first part of pregnancy and the prevention of the rejection of the fetus by maternal immune system [120]. The first study of gene expression pattern in human first trimester decidual macrophages was conducted in 2008 [121]. The authors identified 14,000 genes modulated in placental macrophages compared to blood monocytes. Genes involved in immunomodulation and remodeling categories are associated with M2 phenotype. Hence, the genes encoding CCL18, CD209, insulin-like growth factor-1 (IGF-1), mannose receptor c type (MRC)-1 and fibronectin-1 are up-modulated. Houser et al. investigated the polarization of macrophage subsets isolated from decidua from first trimester (6–12 weeks) [122]. They identified two

distinct macrophage subsets according to CD11c expression, namely $CD11c^{low}$ and $CD11c^{high}$ subsets. Both subsets expressed two M2 markers, CD209 (DC-SIGN) and CD206 (mannose receptor). Genes involved in invasion, mobility, inflammatory process and lipid metabolism are enriched in the two subsets, but genes involved in antiapoptotic pathways are found only in $CD11^{high}$ macrophages. In contrast, $CD11c^{low}$ macrophages express genes involved in growth regulation and development, and extracellular communication. These findings are in agreement with those of Svensson et al. who found two macrophage subsets, ICAM-3^{high} and ICAM-3^{low}, in macrophages from first trimester (7–12 weeks) [123]. Both macrophage populations express genes and cytokines associated with M2 profile and are related to CD11c expression.

4.1.2. Third trimester (term placentas)

The third trimester is associated to a pro-inflammatory environment. This inflammatory state is due to the synchronization of immune-endocrine cross-talk, based on especially estrogens [124], which favors M1 polarization of macrophages [125]. Indeed, a low level of estradiol is sufficient to promote macrophage M1 polarization, as measured by the secretion of inflammatory cytokines such as IL-1β, IL-6 and TNF. The investigation of DNA of at term placenta macrophages reveals the methylation of inflammatory genes including TLR9, IL-1β, IL-12RB2, CD48 and FGR and the hypomethylation of M2 genes including CCL2, CCL13, CCL14 and CD209 [126]. Using microarray analysis, we previously investigated the polarization of macrophages from at term placentas in comparison to macrophage-derived monocytes [127]. We did not find a polarization of at term placenta macrophages. Indeed, both M1 (CXCL9, EDN1, IL-15, IL-15RA and IL-2RA) and M2 (FN1, CTSC and CCL23) genes were up-modulated. Interestingly, we reported for the first time the ability of placental macrophages to formed multinuclear giant cells (MGCs). These MGCs present functional enrichment in genes associated with cytoskeleton reorganization and immune response. In addition, as observed in placental macrophages, MGCs are not polarized. Taking together, although the third trimester is associated with an inflammatory environment, the activation of placental macrophages does not reproduce the classical model of M1/M2 polarization.

4.1.3. Placenta macrophages in pathological pregnancy

Placental macrophages are likely associated with number of pregnancy complications. Here, we focused on three pathological conditions, preeclampsia, GDM and chorioamnionitis, in which the involvement of macrophages is documented [128] .

4.1.3.1. Preeclampsia

Although alterations of macrophages are suspected in preeclampsia, the studies of placenta macrophages during preeclampsia are controversial [116, 129]. Some studies reported a decreased [115, 130, 131] or an increased [132–135] number of placental macrophages. In addition, they produce inflammatory cytokines and anti-inflammatory cytokines [136, 137]. It has been also reported that the count of M2 macrophages is decreased in the decidua of

preeclamptic placentas [132]. The transcriptomic and protein expression of CD74, a HLA class II molecule, are decreased in placental macrophages of preeclampsia women. This down-regulation of CD74 interferes with trophoblast-macrophage cross-talk [138]. Prins et al. investigated macrophages in early decidua from women who later developed preeclampsia [139]. They observed an increased expression of CD68 mRNA, but decreased CD206/CD68 mRNA ratio, suggesting that the number of M2 macrophages is affected before the onset of preeclampsia. This finding may be related to the increased number of M1 macrophages in preeclamptic placenta found by other authors [140]. A better comprehension of the rupture of the M1/M2 balance may provide insight into understanding of preeclampsia pathogenesis.

4.1.3.2. Gestational diabetes mellitus

The inflammation associated with GDM leads to macrophage infiltration into placenta, suggesting a key role of these cells during this metabolic complication of pregnancy. The number of macrophages is increased in placentas from women with GDM as compared to normal pregnancy [141]. Placental macrophages, isolated from an experimental model of diabetes (rats receiving an injection of streptozotocin), change from M2 to M1 inflammatory profile under high glucose stimulation [142]. Similarly, isolated placental macrophages from diabetic women present a M1 or an atypical M2 profile [142]. Immunohistochemistry and PCR approaches show that the mRNA expression levels of TNF and IL-6 are higher in placentas from women with GDM than in controls, suggesting an inflammatory profile of placenta macrophages. Further studies are needed to define the role of inflammatory macrophages in GDM.

4.1.3.3. Chorioamnionitis

During pregnancy, placenta could be the target of infectious agents. The chorioamnionitis, mainly due to ascending polymicrobial infection, is a severe complication of the pregnancy leading to an acute inflammation of the membrane and chorion [143]. In human placenta, we observed a decreased number of macrophages expressing CD14, CD68 and CD163 in at term placentas from women with chorioamnionitis compared to placenta from normal pregnancies [127]. Our results are in agreement with other reports [144, 145]. In addition, isolated macrophages from placenta with chorioamnionitis exhibit an altered inflammatory response with decreased production of IL-10 [127]. Other reports describe a M2 profile of macrophages from chorioamnionitis placentas [146]. These findings underline the role of placenta macrophages in the control of infection in pregnant women.

4.2. Dendritic cells

Dendritic cells are found at the feto-maternal interface and in decidua basalis [147]. They represent approximately 2% of leukocytes from placenta and their number does not vary through gestation. Both mature dendritic cells (expressing CD83) and immature dendritic cells (expressing CD14 and DC-SIGN) have been identified in placenta tissue [148].

We previously isolated decidual dendritic cells from at term placentas of healthy women by combining negative selection with anti-CD14 antibodies and positive selection with anti-CD11c antibodies [149]. We found that 1525 genes are differentially modulated with a specific transcriptional profile as compared to monocyte-derived dendritic cells. It mainly consists of the up-modulation of genes involved in immunomodulatory cytokines, estrogen and progesterone gene pathway. The investigation of gene expression programs in placenta dendritic cells is emerging and will require additional investigation to associate gene expression and dendritic cells subsets in normal and pathological pregnancy.

4.3. Mast cells

Mast cells are found in human placentas [150] and it has been reported that mast cells and their products, especially histamine, could participate in the placenta development. Indeed, histamine is involved in trophoblast invasion and growth [151] and the cross-talk with trophoblasts *via* the expression of adhesion molecules by trophoblasts [152]. The alteration of these specific adhesion molecules is associated with the impairment of placenta invasion and the outcome of preeclampsia. A decreased number of mast cells have been reported in preeclampsia, GDM and intrauterine growth retardation [151, 153]. To our knowledge, no data about gene expression in placenta mast cells has been published. We isolated placenta mast cells from at term women using positive selection with CD117 and IgE antibodies. In a comparative study with a mast cell line (human mast cells, HMC-1.2), we found that a large number of genes are up-modulated in placenta mast cells. The functional analysis reveals an enrichment with three categories, FcεRI signaling, immune response and reproduction processes. In this latter category, we identified specific genes of Wnt pathway and a set of genes involved in the response to estrogen and progesterone (manuscript in preparation). These preliminary results highlight the originality of placenta mast cells among placenta innate immune cells.

4.4. Common transcriptomic signature of macrophages, dendritic cells and mast cells

To identify a common signature of these three placenta immune cells, we performed a retro-analysis of microarray data deposited in Gene Expression Omnibus at the National Center for Biotechnology Information. We evaluated the transcriptomic signatures of macrophages, dendritic cells and mast cells from at term placentas of healthy women and compared them to those of monocytes, monocyte-derived dendritic cells and the cell line HMC-1, respectively. As depicted in **Figure 2A**, the hierarchical clustering reveals two major branches that distinguish cells of placenta origin from the others (ANOVA, $p < 0.001$). Focusing on common modulated genes, we observed that 479 (**Figure 2B**) and 5671 (**Figure 2C**) genes are up- and down-regulated, respectively. Interestingly, 45% of down-modulated genes are associated with pregnancy versus 10% of up-modulated genes. Thus, these data suggest that innate immune cells express a core of genes that reflect the influence of placenta microenvironment.

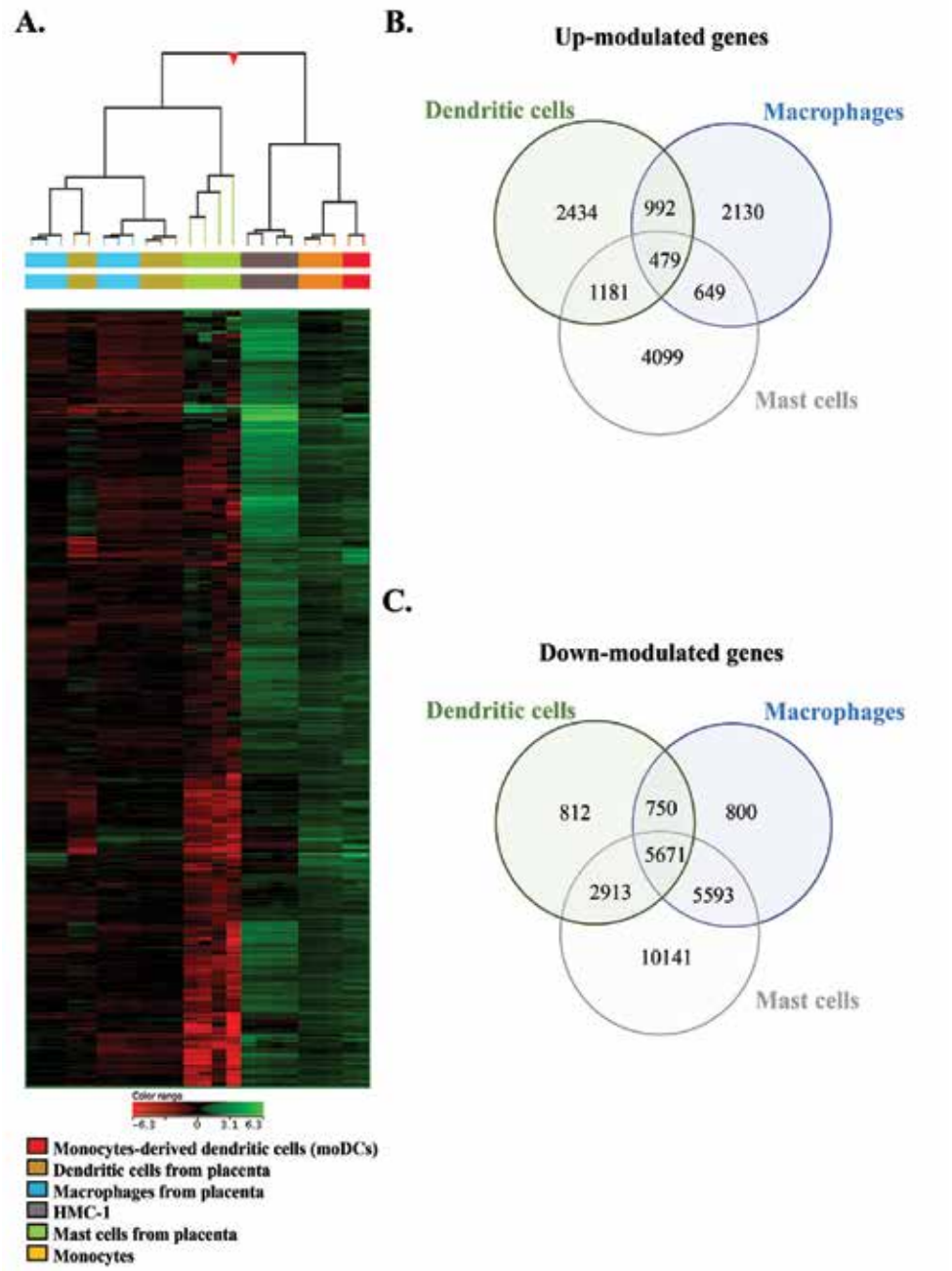

Figure 2. Transcriptomic analysis of dendritic cells, macrophages and mast cells from placenta tissue compared to controls including monocytes-derived dendritic cells, monocytes-derived macrophages and HMC-1 cell line, respectively. (A) Hierarchical clustering of placental cells showing the up- (red) and down- (green) modulated genes. Venn diagrams were realized to show the number of (B) up- and (C) down-modulated genes in common from dendritic cells (green), macrophages (blue) and mast cells (gray) from placenta.

5. Conclusion

Transcriptional analysis of placenta reveals the modulation of a very large number of genes and pathways, allowing a better understanding of tissue and cell mechanisms of normal and pathological pregnancy. The development of RNA-Seq, with a better genomic coverage and more sensitivity than microarray, and single cell technology will permit promises to detect genes with low expression level and to reveal differential new gene expression for normal and complicated pregnancies. Thus, this study reveals only the visible part of an iceberg and suggests that the immersed part must be further investigated.

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Author contributions

Soraya Mezouar and Jean-Louis Mege conceived and wrote the paper.

Declaration of interest

The authors declare no competing interests.

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Chapter 4

Complication of Abnormal Placental Implantation

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Additional information is available at the end of the chapter

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Abstract

The objective: To review all articles published from Saudi Arabia for 18 years to illustrate the complication of abnormal placentation. Materials and methods: In a retrospective study, all publications of placenta previa in our region reviewed. The survey conducted at King Abdulaziz University in J, Saudi Arabia. PubMed, which is a free database search, used to determine the number of publications of placenta previa in Saudi Arabia data collected for 18 years from January 2000 to May 2018. Only (ISI) publication is selected "All abstracts that appeared in the PubMed database collected analyzed meticulously for the year of publication, type of research, institute and the region, and the complication that illustrated in each publication." The inclusion criteria, as well as exclusion criteria, were clearly defined before the study. The studies defined according to abstract, title, year of publications, the aim, materials and methods, results, and conclusions. Statistical analysis SPSS statistical software (version 22) is used for analysis. Data are coded for numbers and percentages. Results: The number of publication retrieved when we used (placenta previa Saudi Arabia) was 40, but only 19 publications included as for inclusion criteria. Conclusion: Placenta previa is a significant cause of maternal morbidity and mortality. Every hospital must have a clear protocol and a team to manage all cases of placenta previa.

Keywords: complication, placenta previa, hemorrhage, maternal morbidity, Saudi Arabia

1. Introduction

Placenta previa (PP) defined when the placenta implanted abnormally in the lower uterine segment, it can be either a partially or totally covering the cervical Os [1, 2]. The types of placenta previa summarize as complete, partial, or marginal placenta previa [3]. This depends

on the relation of implantation of the placenta to internal Os; it is either complete placenta previa, partial or marginal [4]. Advanced maternal age, grand multiparity, abortion smoking and previous CS, or placenta previa are known risk factors to increase the risk of placenta previa [5]. Placenta accreta is a clinical condition when part or the entire placenta invades the uterine wall. Placenta increta is when the chorionic villi invade the myometrium and percreta when the invasion occurs through the myometrium and serosa, and occasionally into adjacent organs, such as the bladder [6]. The objective is to review all articles published from Saudi Arabia for 18 years to illustrate the complication of abnormal placentation.

2. Materials and methods

In a retrospective study, all publications of placenta previa in our region are reviewed. The survey conducted at King Abdulaziz University in Jeddah, Saudi Arabia, to identify the possible complication of abnormal placentation such as placenta previa. PubMed, which is a free database search, used to determine the number of publications of placenta previa in Saudi Arabia data collected for 18 years from January 2000 to May 2018. Only Institute for Scientific Information (ISI) publication is selected "All abstracts that appeared in the PubMed database collected analyzed meticulously for the year of publication, type of research, institute and the region, and the complication that illustrated in each publication." The inclusion criteria, as well as exclusion criteria, were clearly defined before the study. The inclusion criteria were studies that were ISI, carried out in and or published from (the Kingdom of Saudi all Arabia), about placenta previa in Saudi Arabia. The exclusion criteria were as follows: all studies were not ISI or were neither conducted nor published from Kingdom of Saudi Arabia. The number of publication retrieved when we used (placenta previa Saudi Arabia) was 40, but only 19 study included as for inclusion criteria. The studies defined according to their abstract, the title, year of publications, the aim, material and methods, results and conclusions. Statistical analysis SPSS statistical software (version 22) is used for analysis. Data are coded for numbers and percentages.

3. Results

A total of PubMed ISI publication full file the inclusion criteria found were 19 that published from 2000 until 2018. Number 1 (2016) is a prospective study... "Comparison between two ways of management protocols to control bleeding in cases of (PPH) during (C/S) for PP. Using Bakri Balloon versus No-balloon protocol." It is concluded that utilizing the balloon for the management of PPH after CS in cases of PP is a practical approach to reduce the complication and it should be affordable worldwide [7].

Number 2 (2016) is a retrospective study. It is concluded that 4.1 per 1000 is the prevalence of placenta previa, and it is still the vital cause of maternal morbidity and death. Every hospital must have a clear procedure and protocol designed for the management of placenta previa [8].

Number 3 (2016) is a retrospective chart review of all cases of repeat cesarean sections up to 6 CS looking at complication and outcome. It concluded that one of the complications related to multiple CS is placenta previa after the first and subsequent pregnancies [9].

Number 4 (2015) is a comparative study to identify the outcome and risk factor in grand multiparity. There are no significant associations found in placenta previa, abruption, postpartum hemorrhage, preterm labor, and neonatal intensive care unit admission. No fetal or maternal mortality reported in this study. Grand multiparity remains a major obstetric problem and has many medical and obstetrical complications [10].

Number 5 (2015) is a prospective descriptive study to identify the maternal and fetal outcomes and the prevalence of cases of major placenta previa. The frequencies of bowel injury were only a couple cases give 3.8%, and bladder injuries were 13.2% (n = 7). No maternal death is reported. The rate of placenta previa is similar to the previous publication, but the rate of complicated placenta abnormality such as accreta is higher, which gives results in more intraoperative complication and neonatal mortality [11].

Number 6 (2014) is a study to evaluate the safety of labor if the placental edge between 11 and 20 mm from the internal cervical Os diagnosed by transvaginal sonography. It is concluded that it is justified to allow a trial of labor with low risk of subsequent obstetrical hemorrhage [12].

Number 7 (2013) is a retrospective cohort study to evaluate fetal growth and maternal outcomes in patients with placenta previa (PP) and placenta accreta (PA). The babies were relatively small (level 2 evidence) [13].

Number 8 (2013) is a retrospective case-control study of multiple repeats of cesarean sections: to determine the operative difficulties, maternal complications, and fetal outcome. Patients must be informed of detailed risks of multiple CS (PP) and encouraged to have tubal ligation [14].

Number 9 (2013) is a prospective observational study. To Evaluate the use of MRI and ultrasound prenatally to diagnose placenta accreta. Ultrasound can be successfully used in the diagnosis. MRI can give additional information in doubtful cases [15].

Number 10 (2012) is a prospective study to identify the risk of complication and maternal and perinatal outcome in subjects with placenta previa with or without the previous cesarean section. One of the risk of postpartum hemorrhage is blood transfusion which more in patients with pp and previous cs [16].

Number 11 (2009) is a retrospective study to compare risks and outcome between the different class of placenta previa (PP). Marginal placenta previa or low-lying placenta carried lower risk [17].

Number 12 (2009) is a retrospective study to look at the effect of utero-vaginal packing in controlling primary postpartum hemorrhage due to placenta previa/accreta. Packing is of advantage in achieving hemostasis, in cases of postpartum hemorrhage due to low-lying placenta previa/accreta and to conserve the uterus in women with low parity [18].

Number 13 (2006) is a retrospective study to compare the complication and outcome of multiple cesarean sections with those with one previous CS. Pelvic adhesions and bladder injury and placenta previa were higher in women with a history of multiple previous CS [19].

Number 14 (2004) is a retrospective study to identify multiple cesarean section morbidity. The maternal morbidity increased with multiple CS. The risk of significant maternal morbidity was significantly higher with more than 4 CS worse at the sixth CS for placenta previa [20].

Number 15 (2004) is a retrospective study of women with multiple CS from 3 or 4 to 5–9 to determine the maternal morbidity and mortality associated with multiple repeats cesarean sections.

Repeat cesarean sections 5–9 carry no particular additional risk for the mother or the baby when compared with the lower (3 or 4) repeat cesarean sections. Repeat cesarean sections carry no particular additional risk for the mother or the baby when compared with the lower (3 or 4) repeat cesarean sections [21].

Number 16 (2003) is a retrospective study of higher order multiple repeats cesarean sections: It is concluded that the incidence of hysterectomy, uterine pelvic dehiscence, placenta previa, and accreta and bladder injury was similar in the two groups. The rate of postpartum pyrexia, wound infection, urinary tract infection, and blood transfusion was also comparable in the two groups [22].

Number 17 (2003) is a retrospective study and a review of 17 cases of emergency peripartum hysterectomy. Uterine atony is still the leading cause of primary postpartum hemorrhage and the primary indications of peripartum hysterectomy [23].

Number 18 (2001) is a case series of using Tamponed-balloon for obstetrical bleeding, caused by low-lying placenta previa, and in one woman with cervical pregnancy. Hemostasis is achieved by using a large volume, fluid-filled tamponed balloon [24].

Number 19 (2000) is a prospective observational study with an objective to determine the use of transvaginal sonography in visualizing migration and predict the mode of delivery. All the cases had confirmed the diagnosis of placenta previa before 32 weeks' gestation, and migration up to a distance of more than 3 cm from the internal cervical Os occurred in 24 patients (38%) by 36 weeks' gestation [25].

4. Discussion

In our previous study, we compare our local prevalence rate that is 4.1 per 1000 with other countries, which ranged from 3.5 to 4.6 per 1000 births [2].

Based on available limited data, the management of uncomplicated cases of placenta previa is the elective cesarean section between 36 and 37 weeks.

History of previous one or more cesarean sections, pregnancy termination, high parity, advanced maternal age, intrauterine surgery, smoking, and multiple pregnancies are known reported risk factors for placenta previa [26].

1. Comparison between two management protocols for (PPH) during (CS) in PP Balloon protocol versus non-balloon protocol. J Obstet Gynaecol Res. 2016 [7]	The objective is to compare two management protocols for(PPH) during (CS) in (PP), using Bakri balloon protocol versus non-balloon protocol	This is a prospective cohort study conducted in two hospitals in Saudi Arabia	151 cases were identified as low-lying placenta and PP. 114 developed PPH. Only two patients were unstable and required hysterectomy. 112 cases were managed by applying Bakri balloon (72 cases) or non-balloon protocols in (40). The balloon alone achieving hemostasis in 87.5% of cases.	Bakri balloon is an effective method of management for PPH after CS in cases of PP.
2. A 13-year experience in management of PP at a tertiary care centre KAUH in Saudi Arabia. Saudi Med J. 2016 [8]	The aim is to review all cases of placenta previa in the last 13 years.	This is a retrospective analysis of all cases of placenta previa managed at King Abdulaziz University Hospital (KAUH), Jeddah	The prevalence rate of placenta previa was 4.1 per 1000 births.	Placenta previa is one of the causes of maternal morbidity and death. Every hospital must have a clear procedure, and protocol designed for the management of placenta previa [8]
3. A retrospective chart review of all cases of repeat cesarean sections up to 6 J Matern Fetal Neonatal Med. 2016 [9]	The objective looking at complication and outcome.	A retrospective chart analysis at King Abdulaziz University Hospital (KAUH) in Jeddah	It concluded that one of the complications related to multiple CS is placenta previa after the first and subsequent pregnancies.	There are many long-term complications in these unique cases of higher order cesareans.

4. Grand multiparity: The risk factors and outcome of grand multiparity in a tertiary hospital: a comparative study. Med Arch. 2015 [10]	A comparative study. To determine the prevalence of grand multiparity and the associated risks factors.	Four hundred thirty grand multiparas (parity 5 or more) compared with the multiparous population (parity 2–4) concerning obstetrical problems.	The neonatal morbidity and intensive care unit admission were the same with no statistically significant difference in cases of placental complication as abruption, or previa, not only that but also in cases of postpartum hemorrhage and preterm labor, the study did report any perinatal or maternal mortality.	Grand multiparity remains a significant obstetrics problem, and it is associated with many medical and obstetrical complications.
5. The rate, maternal and fetal outcomes in cases of major placenta previa "Prospective Study" J Clin Diagn Res. 2015 [11]	To determine the prevalence of placenta previa and maternal and neonatal outcomes.	A prospective descriptive study −52 singleton pregnancies with Placenta previa in A prospective descriptive study -(January to June 2014). -Outcome prevalence of PP, maternal and neonatal outcomes.	−1.3% was the prevalence of Placenta previa. −14 patients had placenta accrete The number of previous cesarean scars was higher in patients with placenta accreta. −8 of women had a postpartum hysterectomy.	The rate of PP is equivalent to previous studies, but the rate of placenta accreta is high. Because of that, there are high rates of neonatal mortality and intraoperative complications.
6. Trail of labor in women with a placental edge 11–20 mm from the internal cervical Os. J Obstet Gynecol Can. 2014 [12]	To answer the question was could a successful vaginal delivery is safe if a trial of labor is attempted in this women.	A prospective observational study of women who had transvaginal sonography for singleton pregnancies and a placental edge between 11 and 20 mm underwent a trial of labor.	Fourteen patients with ultrasound diagnosis underwent a trial of labor during the study period.	The study concludes these patients safely justify allowing a trial of labor and carries a low risk of subsequent obstetrical hemorrhage.

7. Two consultants, 3 years of management of placenta previa and accreta Int J Women Health. 2013 [13]	This is a retrospective cohort study in patients with placenta previa (PP) and placenta accreta to evaluate maternal and neonatal outcomes	The study includes all patients who had a cesarean section for placenta previa and accreta from December 2009 to December 2012 managed by a multispecialty team, including two consultants	Two cases of fetal growth restriction, which has known to have medical diseases. Only four cases (3.3%) had small for gestational age. Fetal growth chart indicate at the 10–50th percentile	The presence of two obstetric consultants among team helped minimize massive blood transfusion. The babies were relatively small in pp. cases (level 2 evidence).
8. Multiple repeat cesarean sections: operative difficulties, maternal complications and outcome. J Reprod Med. 2013 [14]	To determine maternal/neonatal complications and outcome in patients with multiple repeat cesarean sections (CS).	144 pregnant women with > or = 4 cesarean sections were involved in the retrospective case-control study and compared with a control group of 288 women having 2–3 cesarean sections for maternal, operative and neonatal complications.	The incidence of a single major complication was higher in women with > or = 4 previous cesarean deliveries (p = 0.0011).	-Repeated CS increases the risk of uterine rupture and intraoperative complications, making these patients a high-risk group. -No absolute upper limit for the number of repeat cesarean -Patients must be informed of the risks encouraged to have a tubal ligation.
9. Is a prospective observational study. To identify the use of MRI and ultrasound prenatally to diagnose placenta accreta. Acta Obstet Gynecol Scand. 2013 [15]	Ultrasound can successfully use in the diagnosis MRI can give additional information in doubtful cases.	A prospective observational study.	All cases of placenta previa were scanned in a systematic fashion (trans abdominal and transvaginal).	The accuracy of prenatal diagnosis of placenta accreta by using MRI and ultrasound MRI can provide additional information in doubtful cases.

10. Risk of adverse maternal and perinatal outcome in subjects with placenta previa with a previous cesarean section. Kurume Med J. 2012 [16]	The objective was to compare maternal and perinatal adverse outcomes between groups of placenta previa (PP) with and without previous cesarean section (CS)	From March 2008 to August 2009 at the Department of Obstetrics and Gynecology, Hera General Hospital, Makkah, Saudi Arabia. A prospective study was carried out	The risk of postpartum hemorrhage (PPH), blood transfusion and coagulopathy was higher in-group A, p = 0.008; p = 0.03, respectively. Mean days of hospital stay (days ± SD) in group A was significantly longer than that in group (p = 0.002).	A higher risk of perinatal adverse outcome was found in-group A, but the difference was not significant. Risk of maternal morbidity was higher than that of perinatal morbidity in Group A.
11. This s a retrospective study to compare risks and outcome between the different classes of placenta previa (PP). J Obstet Gynaecol Can. 2009 [17]	The risk factors and pregnancy outcome in different types of placenta previa.	A retrospective study of 306 women diagnosed with PP over 10 years (January 1996 to December 2005)	The overall incidence of PP was 0.73%. -Major PP (complete or partial PP) occurred in 173 women (56.5%) -Minor PP (marginal PP or low-lying placenta) in 133 women (43.5%)	Marginal placenta previa or low-lying placenta carried lower risk
12. This is a retrospective study to look at the effect of utero-vaginal Saudi Med J. 2009 [18]	Packing in controlling primary postpartum hemorrhage due to placenta previa/accreta. To	This is a retrospective study covering 7 years (January 2001 to December 2007).	-In 83 patients with postpartum hemorrhage caused by placenta previa/accreta. -48 of them underwent uterovaginal packing alone For management of bleeding. -Three of them needed second surgical intervention. However, there was no maternal death among the series.	Packing is of advantage in achieving hemostasis, in cases of postpartum hemorrhage due to low-lying placenta previa/accreta and to conserve the uterus in women with low parity.

13. This is a retrospective study to compare the complication and outcome of multiple Cesarean sections with those with those with one previous CS. J Obstet Gynaecol Can. 2006 [19]	Comparison of complications and outcomes of Cesarean section (CS) in women who have had three or more with those in women with only one previous CS.	In a retrospective study of 371 patients undergoing repeat CS. Of these, –115 (31%) had previously had three or more Cesarean sections (group 1), and –256 (69%) had previously had one CS (group 2).	Statistically Significant Differences Between The Groups 1, Two About Mean Of Parity, Maternal Age, Gestation At Delivery, As Well As The Experience Of The Obstetrician ($P < 0.05$). -Emergency CS In 38 (32.9%) And 186 (72.6%) Of Patients In Groups 1 And 2, Respectively ($P < 0.05$).	Pelvic adhesions, bladder injury, and placenta previa were higher in women with a history of multiple previous CS
14. This is a retrospective study to identify multiple cesarean section morbidity. The maternal morbidity increased with multiple CS. Int J Gynecol Obstet. 2004 [19]	To quantify the maternal risk associated with multiple cesarean sections (CS)	-(January 1997–2002) -The chart of 3191 women who were delivered by CS -Indicators of maternal morbidity.	-The morbidity with successive CSs increased if less than 3 CS. -However, the risk of major morbidity was increased with the fifth, and much worse at the sixth CS for placenta previa	The risk of significant maternal morbidity was significantly higher with more than 4 CS worse at the sixth CS for placenta previa.
15. This is a retrospective study, of women with multiple CS from 3 or 4 to 5 to 9 to determine the maternal morbidity and mortality associated with multiple repeats cesarean sections. BJOG. 2004 [20]	Maternal morbidity and mortality in women with multiple repeat cesarean sections.	Retrospective study. -Security Forces Hospital -Riyadh, Kingdom of Saudi Arabia.	Operative and post-operative complications and difficulties.	Repeat cesarean sections 5–9 carry no particular additional risk for the mother or the baby when compared with the lower (3 or 4) repeat cesarean sections. Carry no particular additional risk for the mother or the baby when compared with the lower (3 or 4) repeat cesarean sections [21]

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16. This is a retrospective study of higher order multiple repeats cesarean sections. Ann Saudi Med. 2003 [21]	Multiple repeat cesarean is common in many institutions of Saudi Arabia. A retrospective study to determine the major and minor complications as well as the neonatal outcome associated with multiple repeat cesarean sections.	The relationships between the number of cesarean sections and various clinical variables in 150 patients -undergoing 4–8 cesarean sections (mean 6.0) compared with a control group of 140 patients -undergoing 2–3 cesarean sections (mean 2.5) during the period from (1996–2000) at	The incidence of cesarean hysterectomy, uterine scar dehiscence, placenta previa, placenta accreta, and bladder injury was similar in two groups.	Concluded that the incidence of hysterectomy, uterine pelvic dehiscence, placenta previa, and accreta and bladder injury was similar in the two groups. The rate of postpartum pyrexia, wound infection, urinary tract infection, and blood transfusion was also comparable in the two groups.
17. This is a retrospective study and a review of 17 cases of emergency peripartum hysterectomy, Indication of emergency peripartum hysterectomy: a review of 17 cases. Arch Gynecol Obstet. 2003 [22]	The aim to determine the incidence, indications, and complications	A retrospective analysis of 17 (January 1, 1991–December 31, 2002.)	The incidence rate was 0.5 per 1000. Uterine atony 11 (64.7%, nine without previa and 2 with previa)	Uterine atony still is the leading cause of primary postpartum hemorrhage and the primary indications of peripartum hysterectomy.
18. Tamponade-balloon for obstetrical bleeding. Int J Gynecol Obstet. 2001 [23]	The objective of this is to study the effect of a balloon (large volume, fluid-filled tamponade) in the management of post-partum hemorrhage from the implantation site of low-lying placenta/placenta previa.	For an action of tamponade function a silicone, fluid-filled balloon Five women with postpartum bleeding caused by low-lying placenta and one woman with cervical ectopic pregnancy underwent a balloon insertion as a conservative measure in the management of bleeding.	The tamponade balloon was used in five women with post-partum bleeding caused by low-lying placenta/placenta previa, and in one woman with cervical pregnancy.	Hemostasis in cases of post-partum bleeding caused by low-lying placenta/ placenta previa can be achieved by using a large volume, fluid-filled tamponade balloon.

19. Is a prospective observational study with an objective to determine the use of transvaginal sonography in visualizing migration and predict the mode of delivery? Ann Saudi Med. 2000 [24]	to diagnose placental migration using transvaginal sonography (TVS)	All cases with a diagnosis of placenta previa before 32 weeks' gestation included in a prospective observational study	Placental can migrate to a distance of more than 3 cm from the internal cervical Os occurred in 24 patients (38%) by 36 weeks' gestation.	All the cases had confirmed the diagnosis of placenta previa before 32 weeks' gestation, and migration up to a distance of more than 3 cm from the internal cervical Os occurred in 24 patients (38%) by 36 weeks' gestation.

PPH = Postpartum hemorrhage, CS = Cesarean section, PP = Placenta previa.

Table 1. 19 PubMed publication … complication of placenta previa and its management.

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Ultrasonography is the known diagnostic modality of placenta previa [4].

In spite of the significant improvement in obstetric care and management and modern transfusion service, antepartum and postpartum bleeding continues to be an essential cause of maternal morbidity and mortality [27].

A structure, a protocol, and an organized plan should be part of policy and procedure for the management of cases of massive bleeding [28].

A Canadian group has alerted the obstetrician for management of suspected placenta accrete by a multidisciplinary checklist for the preparation of these cases [29].

Placenta previa is a significant complication of pregnancy; there is no obvious case, but the risk factor is enormous, and the risk factors for placenta previa are the previous history of one or more cesarean sections, pregnancy termination including dilatation and curettage, high parity, advanced maternal age, intrauterine surgery, smoking, and multiple pregnancies.

Complication of placenta previa repeated placenta previa or major abnormal placentation like placenta accreta or percreta or increta, antepartum and post-partum hemorrhage, as well as Pelvic and uterine adhesion, urinary and bowel injury. Emergency hysterectomy, the complication of massive bleeding such as massive transfusion and effect on mother like Sheehan syndrome (**Table 1**).

The limitations of the study are: (1) a retrospective study and (2) a different obstetrician managed the cases.

5. Conclusion

Placenta previa is one of the causes of maternal morbidity and mortality. Every hospital must have a clear protocol, policy, and procedure of a team to manage all cases of placenta previa.

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Chapter 5

Placental Malformation: Accreta and Beyond

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Additional information is available at the end of the chapter

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Abstract

Abnormal placentation is a noncommon but life-threatening obstetric condition that requires a multidisciplinary approach. It is a spectrum of disorders that seems to parallel the increasing rate of cesarean sections. Imaging findings have a crucial role in detecting this abnormality early in the pregnancy and subsequently guiding and alerting the surgeon. Between accreta and percreta, the difference is huge; thus, they are managed with a different degree of radicality. The surgeon tends to treat more radically cases of placenta percreta with cesarean hysterectomy and needs to have special expertise in pelvic surgery, inter alia, and gynecologic oncology. While extrapolation does not find its way in every case of abnormally invasive placenta, a new inspired technique from gynecologic oncology surgeries and adapted to percreta cases seems to be applied safely and effectively in all circumstances of percreta. Conservative treatment is also an alternative but is limited to selected cases of placenta accreta.

Keywords: abnormally invasive placenta, cesarean hysterectomy, safety, radical, conservative, multidisciplinary

1. Introduction

Placenta accreta, placenta increta, and placenta percreta represent a spectrum of placental adhesive disorders (PAD) and occur when a defect of the decidua basalis allows the invasion of chorionic villi into the myometrium. PAD is classified on the basis of the extent of adherence to and invasion of the myometrium. Placenta accreta is the least severe of the three entities with superficial invasion of the basalis decidua by the chorionic villi (approximately 75% of cases). Placenta increta is penetration of the myometrium by the chorionic villi, while

placenta percreta is the most severe with invasion of uterine serosa or adjacent pelvic organs [1, 2]. It is worth noting that when the myometrium becomes very thin especially at the level of the cesarean section, difference between accreta and increta is obsolete.

The frequency of abnormal invasive placentation (AIP) has risen in the last 30 years parallel to the increase in cesarean delivery rate [3, 4]. Other common risk factors for abnormal placentation include placenta previa, prior myomectomy or other uterine surgery, and advanced maternal age [5].

AIP is a life-threatening condition due to massive hemorrhage and urgent need for blood transfusion, the need for peripartum hysterectomy, damage to adjacent organs due to placental invasion, and the need for admission to the intensive-care unit [4, 6, 7]. For these reasons and their consequence of decreasing the burden of maternal morbidity-mortality, it is essential to accurately diagnose the degree of placental invasion. The major predicting determinant of the outcome of women affected of AIP is the depth of placental invasion [3].

2. Imaging findings

Imaging in the antepartum should be performed with minimal risk to both the mother and developing fetus. Noninvasive techniques such as ultrasound (US) and magnetic resonance imaging (MRI) that do not use ionizing radiation are thus the preferred imaging techniques. The advantages of MRI are superior soft-tissue contrast resolution, multiplanar imaging capabilities, wider field of view, and image quality independent of the mother's size or fetus positioning. Thus, it may be superior to US in some settings [1, 2].

However, US remains the primary method of imaging the placenta. Also, its high negative predictive value for placental abnormalities assigns MRI to a supporting role reserved for equivocal US findings or incomplete evaluation as in cases of posterior placenta [5].

2.1. Ultrasound

Ultrasonography is the primary screening tool for placental invasion in women at high risk of AIP usually performed during the second and third trimesters of pregnancy [8–10]. Its sensitivity for the diagnosis of AIP ranges from 77 to 93% and specificity from 71 to 97% according to a recent review [6, 8, 11], but its sensitivity and specificity may increase to 100% when applied to a high-risk population [3].

Many US signs are described for the diagnosis of abnormal placental invasion. These signs include the following [3, 8, 9]:

1. Loss or irregularity of the hypoechoic plane in myometrium underneath placental bed ("the clear zone") or retroplacental myometrial thinning <1 mm
2. Multiple placental lacunae, often containing turbulent flow visible on grayscale or color Doppler US

3. Bladder wall loss or interruption or irregularity (loss of hyperechoic band or "line" between uterine serosa and bladder lumen)
4. Uterovesical hypervascularity, defined as striking color Doppler signal observed between myometrium and posterior wall of bladder, including vessels bridging uterine-placental margin, across myometrium and beyond serosa into the bladder or other organs; running perpendicular to the myometrium
5. Invasion of the cervix, resulting in abnormal cervical shape, cervical lacunae, and placenta previa
6. Vascular invasion of the parametria, defined as the presence of hypervascularity extending beyond the lateral uterine walls and involving the region of the parametria

In addition, we should emphasize on the US limitations especially regarding the difficult access to posterior placental locations, the evaluation of the degree of placental infiltration, or the presence of associated myometrial lesions [4, 10, 12, 13].

2.2. Magnetic resonance imaging (MRI)

MRI is a secondary diagnostic tool for AIP and indicated when US is limited and inconclusive or in cases of a posterior placenta [4, 6, 7, 10, 14]. The examination typically is made between 24 and 32 weeks of gestational age, in a supine position, but if not tolerated it can be made in left lateral decubitus or oblique position. The bladder is partially distended during the study. MRI protocol is essentially based on three-plane T2 sequences for the placental assessment (single-shot T2-weighted fast spin echo sequences or T2-weighted TSE); a T1-weighted sequence can be acquired, and recently, the utility of diffusion-weighted imaging is discussed in many studies [6]. Although contrast-enhanced imaging can improve the diagnostic accuracy of placental invasion while improving the contrast between the myometrium and the placenta, gadolinium usage during pregnancy should be avoided [6, 7]. MRI signs suggesting AIP include the following [4, 6, 10, 15]:

1. Myometrial thinning or focal interruption of the myometrium by placenta
2. Presence of dark intraplacental bands on T2-weighted imaging running perpendicular to the myometrium
3. Tenting of the bladder
4. Uterine bulging defined as a focal outward contour or a loss of the pear shape of the uterus
5. Direct visualization of focal exophytic mass breaking through uterine serosa and invading pelvic structures
6. Heterogeneous intraplacental signal intensity but can be a subjective sign depending on the gestational age of the placenta
7. Abnormal intraplacental vascularity (**Figure 1A**-**D**)

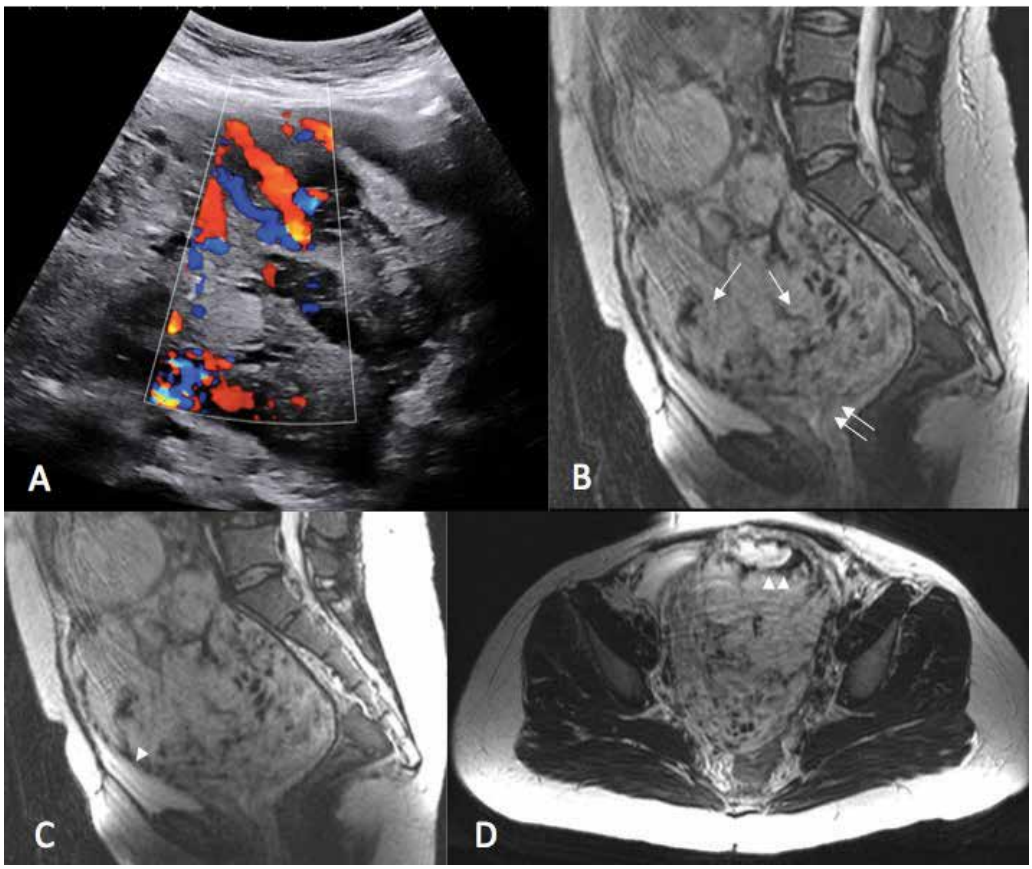

Figure 1. A 26-week-old fetus with placenta praevia showing: **A**. An increased vascularity seen in the lower uterine segment and the interface with the bladder seen on a sagittal image on US. **B**. On 1.5 MRI, sagittal sequence T2WI: a heterogeneity in the placenta (arrow) overlying the internal os (double arrows) with involvement of surrounding structures and focal myometrial interruption with extension into the bladder wall (**C**, arrowhead). **D**. On axial sequence T2WI: a heterogeneity in the placenta with dark intraplacental bands (double arrowheads). This was consistent with percreta on surgery and histopathology.

3. Surgical management

Identifying a PAD preoperatively will give the surgeon the chance to plan and modify the surgical technique in order to reduce morbidity [16]. In addition, a prenatal diagnosis or suspicion of placenta percreta can alert the obstetrician in charge to the need for an experienced pelvic surgeon in critical cases. A preoperative preparation is essential in accreta cases and requires multidisciplinary efforts. It is mandatory to involve all specialized peers in the preoperative assessment as well as in operative management: obstetrics anesthesiologist, gynecologic oncologist, urologist, vascular surgeon, and interventional radiologist [16]. This was also emphasized on in the Committee Opinion 29, where the American College of Obstetrics and Gynecologists (ACOG) has advocated the involvement of a multidisciplinary team in the

management of morbid placental adherence to minimize potential maternal or neonatal morbidity and mortality [17]. Coordination with the blood bank before beginning the procedure is essential to ensure adequate supplies of red cells, platelets, and fresh frozen plasma [16]. In their study, Brennan et al. have also specified that the early presence of a gynecologic oncologist at delivery is a key predictor of reduced blood loss and transfusion requirements when abnormally invasive placenta is suspected [18]. Furthermore, other authors have reported that outcomes are improved if delivery takes place in centers with multidisciplinary expertise and experience in PAS disorders [19].

Cesarean hysterectomy in cases of placenta percreta is often technically challenging due to the anatomic and physiologic changes of pregnancy, including a massive increase in blood flow to the uterus at term. The vessels that supply the uterus, ovaries, and bladder are substantially larger and more tortuous in pregnancy than they are in the nonpregnant state. Meticulous care in the manipulation of clamps, cutting of pedicles, and placement of sutures is required to prevent severe bleeding. Scarring from previous surgery, particularly previous cesarean sections, is a common complicating feature of cesarean hysterectomy [20]. These cesarean hysterectomies often require difficult dissection of poorly defined tissue planes, particularly of the bladder interface, and partial bladder resection is often required [21]. All these factors make this procedure associated with a higher risk of complications in comparison with abdominal hysterectomies performed for benign indications [22].

3.1. Surgical technique

In the literature, few reports of a well-standardized technique describe the steps of a cesarean hysterectomy among women with placenta percreta who need radical treatment. When performing such a procedure, the major concern is to prevent ureteral lesions in a pelvis with a distorted anatomy and to reduce blood loss. A recent study has demonstrated the effectiveness and safety of a well-standardized approach for managing all cases of placenta percreta and in all circumstances [23].

It is preferable to schedule cesarean hysterectomy in case of placenta percreta starting at 34 weeks of gestational age. However, cesarean is sometimes carried out as an emergency procedure irrespective of gestational age in cases of heavy bleeding or fetal distress.

The technique that we intend to describe was developed based on collected experience in gynecologic oncology. First of all, the placement of ureteral stents is not necessary according to this technique since it is not always possible especially during emergencies in cases with massive bleeding [24]. The surgeon starts with a vertical midline incision under general anesthesia. A peroperative US is performed to localize the placenta and to guide the surgeon while performing the hysterotomy. After delivery of the baby, the surgeon proceeds with a closure of the uterine incision with Vicryl® "0" hepatic needle sutures (Ethicon, Johnson and Johnson Companies, Somerville, NJ, USA). In a next step, the surgeon approaches the retroperitoneum just lateral to the adnexal ligaments to secure the ureters and to clip the uterine arteries at their origin after opening the paravesical space. The uteroadnexal ligaments also need to be ligated as close as possible to the uterus. After clipping the uterine arteries, these are lifted up

to expose the underlying uterine veins, which are also clipped. This is followed by a freeing of the ureters from their crossing with the uterine arteries. A crucial following step is to dissect the rectovaginal space and to perform a posterior vaginal incision aided with a flat retractor in the posterior vaginal fornix (**Figure 2**). This will aid the subsequent lifting of the uterus through this posterior incision. The bladder is filled to identify the right plane, and then it is cautiously dissected and separated. After exposing the bladder-vaginal interface, an anterior vaginal incision is done aided by placing the vaginal retractor in the anterior cul-de-sac. Subsequently, the surgeon will be able to position his index and middle fingers through both anterior and posterior incisions, to lift the uterus and to place the clamps alongside the cervix after making sure that ureters are at distance. In case of severe adherence or bladder invasion, a cystotomy or partial bladder resection might be needed [23, 24], (**Figures 3** and **4**). Of note, this procedure should not be performed by any surgeon; only a surgeon with appropriate expertise in pelvic surgery should operate on these critical cases [25]. Otherwise, the operating surgeon will be compromising the safety of the patient.

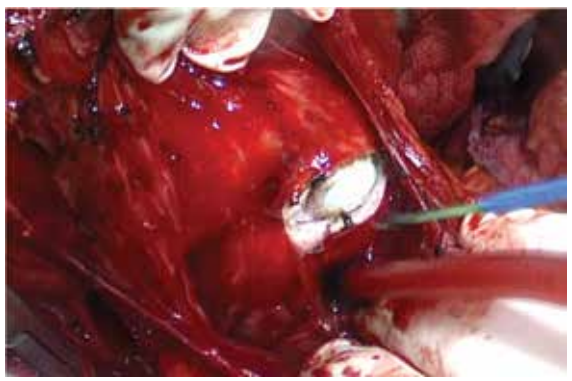

Figure 2. After filling the bladder helping its separation and dissection, incision of the anterior vagina is done right on the inserted fingers.

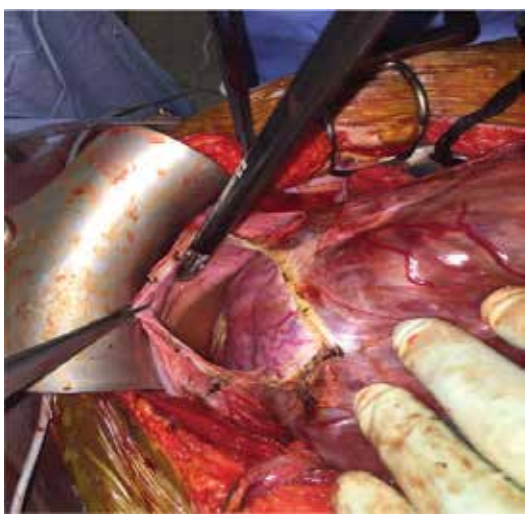

Figure 3. In this case, dissection was impossible so partial cystectomy was performed.

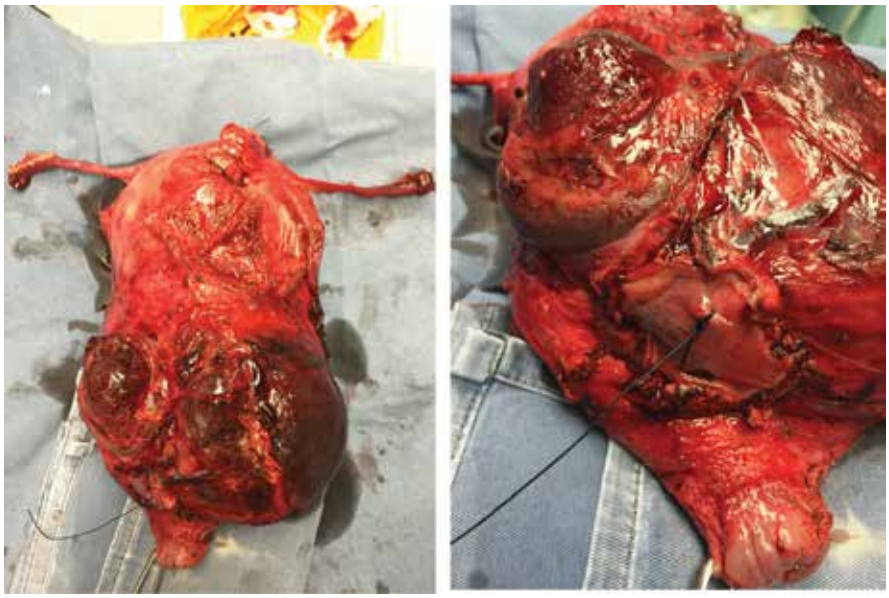

Figure 4. The specimen of hysterectomy with placenta percreta anteriorly is on the left side. A more close view on the right side allows to see the vesical patch that was resected in a case of placenta percreta invading the bladder.

On a similar note, the absence of ureteral injuries is guaranteed when performing a cesarean hysterectomy according to the aforementioned steps [23]. To prevent the development of vesicovaginal fistulas, an omentoplasty is recommended after bladder reparation [23].

Another technique was described in the literature based on a posterior approach but was criticized for the ligature of the anterior division of the internal iliac artery with the concomitant risk of bladder devascularization [23, 26]. Also, the fact of grasping a gravid cervix, as described in the latter technique, will lead to massive bleeding and is not always feasible in case of cervical effacement. However, positioning the surgeon's fingers through anterior and posterior vaginal incision will prevent hazardous bleeding as well as cervical tears.

4. Conservative management

While a radical treatment in terms of cesarean hysterectomy is often the standard of care in case of abnormally invasive placenta, conservative treatment may be applied in limited cases and when women wish to conserve fertility. This is to mention that conservative management is not an approach that fits all cases. Actually, such an alternative can be attempted in cases of placenta accreta or increta where the placenta is adhering partially or totally to the myometrium without invading the whole uterine wall.

Conservative management consist of two options: (1) to attempt prudent delivery of the placenta, applying moderate cord traction to reduce the risk of leaving a normal placenta in situ, or (2) to leave the entire placenta in situ for resorption or spontaneous delivery hoping to reduce the risk of subsequent hemorrhage by making no attempt to remove the placenta [27]. First of all, placental separation can only be attempted when obstetricians are well

experienced. They need to be able to identify whether placental separation can be attempted in an individual and to perform hysterectomy immediately after failure of placental separation to rescue the patient [28]. According to ACOG committee's opinion, placental separation by gentle external uterine massage is reasonable in selected women in whom no obvious signs of placenta accreta are seen based on the visual examination of the uterus [29]. Furthermore, placenta separation can be attempted in three situations: (1) the surgeon is unconfident with the preoperative diagnosis of abnormally invasive placenta, (2) the intraoperative US does not confirm the diagnosis, and (3) the aberrant vessels are less severe than expected [28].

Second, the entire placenta can be left in situ with or without postoperative administration of methotrexate and the placental expulsion will be expected after that. These patients might be subject to severe bleeding that may require emergent uterine embolization. This approach seems to be associated with severe long-term complications. According to a review of 119 women who had placenta left in situ, 61% (22 out of 36 cases) had complications occurring later than 24 hours postoperatively, compared with 12% of those who initially had a hysterectomy or local resection. The most frequently reported complications in these cases were secondary hysterectomy (58%, 21 out of 36 cases) and postoperative hemorrhage (44%, 16 out of 36 cases) [30].

5. Recommendations and future directions

The path to a reduced morbidity and mortality in women with AIP starts with an accurate antenatal diagnosis. However, we are not yet able to define specific US sign or set of signs when assessing the depth of placental malformation [31, 32]. Although many efforts were made to standardize the imaging description of PAD [33, 34], more prospective studies are needed to study the correlation between antenatal imaging findings and histopathology [35].

When suspecting a PAD prenatally, it is mandatory to refer the patient to a center of excellence with a dedicated multidisciplinary team and care plan [36]. Although the described techniques in the literature have shown satisfactory results in terms of safety and effectiveness, the reproducibility of the results might be improved by an analysis and an application of these techniques on larger case series in the future.

Obstetricians and gynecologists need to be counseled and advised about the indications and the situations where a conservative approach could be attempted. Case-control studies on large populations should be conducted to help the surgeon in making the decision when tending to a conservative management.

6. Conclusion

In front of such an individualized problem, a surgeon managing a case of abnormally invasive placenta should be well experienced to master this challenge but also to win it with less maternal and neonatal morbidity and mortality. While concrete standards still lack in terms of management, there are evidences that accreta and percreta are different. This difference

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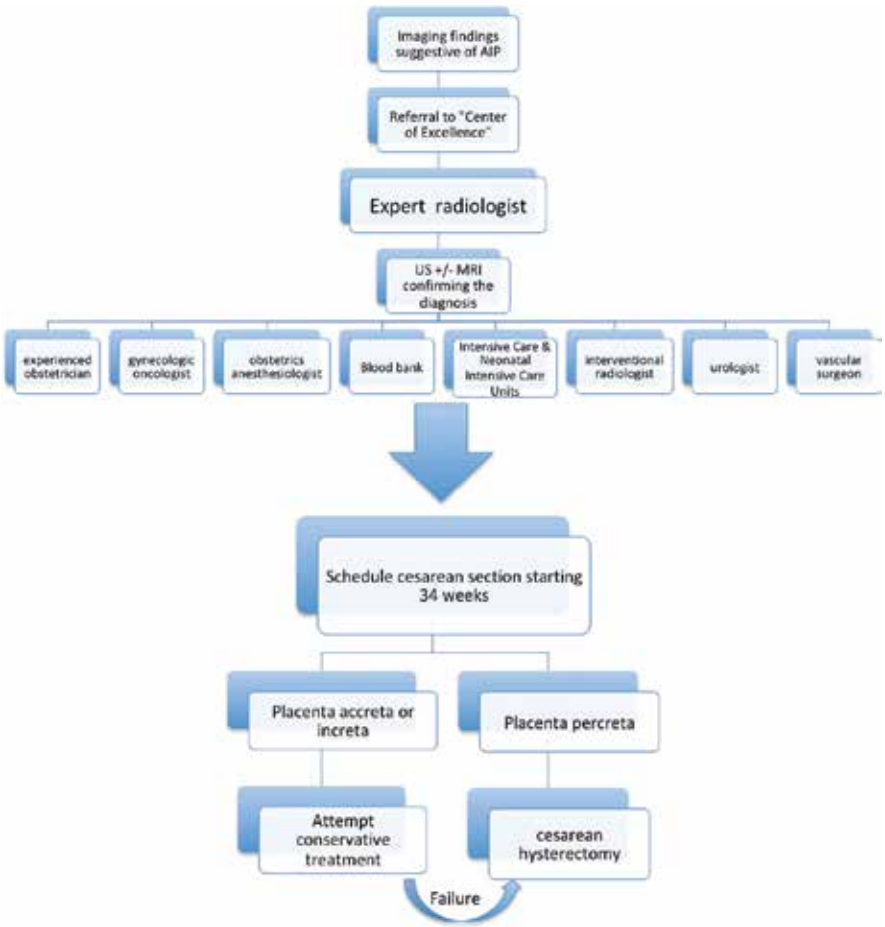

Figure 5. Schematic steps to be followed in the management of an abnormal invasive placentation (AIP).

is very important in selecting the strategy and in involving a multidisciplinary team when dealing with these critical situations. Gynecologic oncology has added a lot of value to the surgical techniques applied in cesarean hysterectomy and adapted to percreta cases. Also, we should not also underestimate the important role of the radiologist in suspecting early the diagnosis, alerting the surgeon, and subsequently inducing a cascade of preoperative preparation (**Figure 5**).

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Chapter 6

Management of Placenta Accreta in Pregnancy with Placenta Previa

Kenji Tanimura and Hideto Yamada

Additional information is available at the end of the chapter

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Abstract

Placenta accreta is a life-threatening obstetrical condition. Prenatal prediction of placenta accreta helps to minimize clinical complications. Placenta previa is one of the most important factors associated with placenta accreta. In our prospective cohort study, ultrasound finding of loss of the retroplacental hypoechoic clear zone was found to be a single predictor of placenta accreta in women with placenta previa (odds ratio, 15.6; 95% confidence interval, 2.1–114.6; $p < 0.01$). In addition, we have devised a novel scoring system for predicting placenta accreta in pregnancy with placenta previa, yielding 91.3% sensitivity, 98.0% specificity, 87.5% positive predictive value, and 98.7% negative predictive value. Planned preterm cesarean hysterectomy with the placenta left in situ is generally recommended for women with suspicion of placenta accreta. If the women have a desire for future fertility, conservative approach may be considered.

Keywords: cesarean section, placenta accreta, prenatal diagnosis, placenta previa, scoring system

1. Introduction

Placenta accreta is a life-threatening obstetrical condition. Clinical complications of placenta accreta involve massive hemorrhage, damage to adjacent organs, cesarean hysterectomy, and maternal death. Placenta previa is one of the most important risk factors for placenta accreta [1]. Prenatal prediction of placenta accreta helps to minimize clinical complications by enabling obstetricians to plan for resources that may be required during cesarean delivery,

including obstetric anesthesia, appropriate surgical expertise, available blood products, and interventional radiology for uterine artery embolization [2, 3]. Therefore, accurate prenatal prediction of placenta accreta in women with placenta previa is important.

This review will focus on the recent knowledge regarding the prenatal diagnosis and management of placenta accreta in women with placenta previa.

2. The prenatal prediction of placenta accreta in women with placenta previa

2.1. Ultrasonography

It has been reported that ultrasonography is the most useful method for diagnosing placenta accreta. Previous studies have demonstrated that ultrasound (US) findings involving the presence of placental lacunae (PL) [4], an anterior myometrial thickening [5], loss of the retroplacental hypoechoic clear zone (LCZ) [6], anomalies of the bladder-myometrium interface [7], and the presence of turbulent blood flow (TBF) in the arteries radiating from the placenta toward the uterine serosa, detected by color Doppler [8] are associated with placenta accreta. However, these previous results were based on retrospective studies for pregnant women with and without placenta previa.

In the prospective study, we aimed to determine more effective imaging for predicting placenta accreta in women with placenta previa using stepwise logistic regression analyses [9]. Univariate logistic regression analyses demonstrated that US findings of anterior placental location (odds ratio [OR], 5.1; 95% confidence interval [CI], 1.2–20.5; $p < 0.05$), grade 2 or higher PL (PL ≥ G2) (OR, 17.0; 95%CI, 4.0–71.1; $p < 0.01$), LCZ (OR, 49.4; 95% CI, 8.5–2862; $p < 0.01$), and magnetic resonance imaging (MRI) (OR, 24.6; 95% CI, 4.7–129.2; $p < 0.01$) were associated with placenta accreta. Multivariable analyses revealed that LCZ (OR, 15.6; 95%CI, 2.1–114.6; $p < 0.01$) was a single significant predictor of placenta accreta in women with placenta previa [9]. In this study, LCZ yielded 86.7% sensitivity, 88.4% specificity, 72.2% positive predictive value (PPV), and 95.0% negative predictive value (NPV) for the prediction of placenta accreta in women with placenta previa. In contrast, a previous study found that LCZ had low PPV for predicting placenta accreta, because LCZ is often observed among women with anterior placental location during normal pregnancy [10]. However, the previous study enrolled women who had anterior placental location and a history of cesarean section (CS); if the subjects were limited to women with placenta previa, diagnostic accuracy of LCZ might be improved.

Recently, we demonstrated that a novel US finding referred to as an "irregular sign" might be useful for predicting placenta accreta in women with placenta previa [11]. The irregular sign is defined as the irregularity of the border between the placenta and the myometrium around internal uterine os observed by transvaginal ultrasonography (**Figure 1**). The presence of irregular sign yielded 56.5% sensitivity, 99.3% specificity, 92.9% PPV, and 93.8% NPV for predicting placenta accreta in women with placenta previa [11].

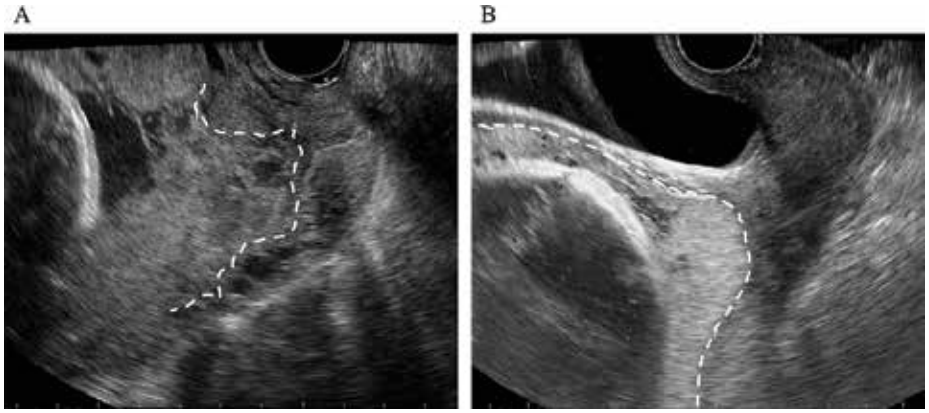

Figure 1. (A) The presence of the irregular sign in a case with placenta accreta. (B) The absence of the irregular sign in a case without placenta accreta. Dashed white marks indicate the border between the placenta and myometrium around internal uterine os [11].

2.2. Magnetic resonance imaging

Some investigators suggested that MRI was a useful tool for diagnosing placenta accreta prenatally [12, 13]. MRI findings suggestive of placenta accreta included indistinctness or the absence of myometrial wall at the placental site, loss of the thin T2 dark uteroplacental interface, a nodular interface between the placenta and the uterus, a mass effect of the placenta on the uterus causing uterine outer bulge, heterogeneous signal intensity within the placenta, dark intraplacental bands on T2-weighted images, and abnormal dilated venous lakes within the placenta [13–15]. MRI provided advantages in diagnosing placenta accreta in women who had posterior placental location [16]. We found that MRI was selected as a significant finding in predicting placenta accreta in pregnant women with placenta previa by univariate analyses in the prospective study (OR, 24.6; 95% CI, 4.7–129.2; $p < 0.01$) [9].

However, other investigators claimed that MRI was more expensive and invasive examination than US; therefore, US should be the diagnostic modality of first choice for placenta accreta, and MRI was not always necessary [17]. Dynamic contrast-enhanced MRI with gadolinium (Gd) is not recommended at any time during pregnancy, because the use of Gd increases the risk of a broad set of rheumatological, inflammatory, or infiltrative skin conditions and of stillbirth or neonatal death [18].

2.3. Diagnostic scoring systems

Diagnostic scoring systems may be more useful than a single US finding for predicting placenta accreta in women with a history of previous CS, placenta previa, or low-lying placenta [19–21]. These scoring systems include several US findings suggestive of placenta accreta, the presence of placenta previa, and the number of prior CS. Optimal cut-off values of these scores determined in the retrospective or prospective studies yielded 72.0–94.2% sensitivity, 52.5–85.0% specificity, 63.4–70.0% PPV, and 86.0–100% NPV for the prediction of placenta accreta [19–21].

We devised a novel scoring system for predicting placenta accreta in women with placenta previa, and in a prospective cohort study evaluated the diagnostic efficacy of this scoring system named the placenta previa with adherent placenta (PPAP) score [11]. The PPAP score is composed of two categories: (1) past history of CS, surgical abortion, and/or uterine surgery and (2) US and MRI findings. Each category is graded as 0, 1, 2, or 4 points, yielding a total score between 0 and 24 (**Table 1**).

Women with placenta previa who had PPAP score ≥ 8 were considered to be at a high risk for placenta accreta. The PPAP score yielded 91.3% sensitivity, 98.0% specificity, 87.5% PPV, and 98.7% NPV for predicting placenta accreta in women with placenta previa [11]. However, the

Variables		Level of variable	Score
Past history			
Number of previous CS		0	0
		1	2
		≥ 2	4
Number of previous surgical abortion		<3	0
		≥3	2
Other uterine surgery		No	0
		Present	2
		Placenta is located on the uterine scar	4
Imaging examination			
USG	Grade of placental lacunae	0	0
		1	2
		≥ 2	4
	Loss of clear zone	Absent	0
		Equivocal	2
		Present	4
	Turbulent blood flow	Absent	0
		Equivocal	1
		Present	2
	Irregular sign	Absent	0
		Present	2
MRI	Suspicious of placenta accreta	No	0
		Yes	2

PPAP, placenta previa with adherent placenta; CS, cesarean section; USG, ultrasonography; and MRI, magnetic resonance imaging.

Table 1. The variables and scores in the PPAP scoring system.

PPAP scoring failed to predict two women with placenta accreta. One woman had a history of myomectomy and PPAP score of 6 and another had a past history of myometrium resection for adenomyosis and PPAP score of 4. The presence of a history of myomectomy and myometrium resection for adenomyosis seems to increase the risk for placenta accreta in women who had PPAP score < 8. Special attention should be paid to the risk of placenta accreta regardless of US or MRI findings.

3. The management of placenta accreta in women with placenta previa

All pregnant women with placenta previa suspected to have placenta accreta should be managed at specialized tertiary centers [22]. Their deliveries should be performed by an experienced medical team consisted of obstetric surgeons, urologists, general surgeons, and gynecologic oncologists [23]. Planned cesarean hysterectomy decreases the morbidity and mortality rates in women complicated by placenta accreta [3]. The timing of delivery in such women must be individualized; however, a recent study suggested that delivery at 34 weeks of gestation (GW) in stable women with placenta accreta optimized the outcomes of both mothers and neonates [24].

The anesthesiologists should assess which anesthetic techniques are used before delivery. Both general and regional anesthetic techniques are available, and the decision of which type of technique to be used should be made on an individual basis [23]. Preoperative cystoscopy with placement of ureteral stents may help prevent accidental urinary tract injury. In addition, sufficient amount of blood products should be available in the operating room.

Planned preterm cesarean hysterectomy with the placenta left in situ is generally recommended for women with suspicion of placenta accreta, because forced removal of the placenta causes massive hemorrhage. Midline vertical incision may be considered because it provides sufficient exposure if hysterectomy is needed. CS using transverse uterine fundal incision method is often used to avoid the placenta and allow delivery of the infant.

Hysterectomy is performed in the usual fashion. In some cases with anterior placenta accreta, especially in cases with placenta percreta, partial resection of the bladder wall is necessary. On the other hand, if the women have a strong desire for future fertility, conservative approach, i.e. leaving the placenta in situ, may be considered. However, a review, which summarized the conservative management of 60 women with placenta accreta, showed that infection occurred in 11 of the 60 women (18%), bleeding in 21 (35%), and disseminated intravascular coagulation in 4 (7%) [25]. Therefore, this conservative approach should be considered only when women are willing to accept the risks involved in this approach.

There has been lack of sufficient evidence for beneficial effects of prophylactic catheter placement for balloon occlusion or artery embolization [26–28] as well as treatment with methotrexate [29–31] . Therefore, a firm recommendation on the use of these procedures cannot be made [23, 31]. It is difficult to establish evidence-based management strategies for placenta accreta in pregnancy with placenta previa. Therefore, clinicians should manage these women by suitable approaches in each medical institution.

Figure 2 shows an algorithm used in the Kobe University Hospital for the management of pregnant women with placenta previa. All pregnant women with placenta previa receive workup for placenta accreta in inpatient or outpatient care. If women have bleeding, they are hospitalized immediately and receive intravenous administration of tocolytic agents such as magnesium sulfate or β-stimulant. Even if they do not have bleeding, they are hospitalized at 32–34GW. Women have a PPAP score ≥ 8, who are suspected of having placenta accreta, receive both preoperative internal iliac artery occlusion balloon catheters placement and elective CS at 35–37GW.

Figure 3 shows a flow algorithm used in the Kobe University Hospital for the preoperative preparation and operative procedures for women with suspicion of placenta accreta. Women with placenta previa had a PPAP score ≥ 8, who were suspected of having placenta accreta, received preoperative internal iliac artery occlusion balloon catheters placement. After fetal delivery by a CS using transverse uterine fundal incision method, the internal iliac artery occlusion balloon catheters were inflated. After occlusion of the artery, local injection of oxytocin into the myometrium and uterine massage were performed to induce spontaneous placental separation. If placental separation did not occur at all and women did not have a desire for future fertility, cesarean hysterectomy was performed. When the placenta was not partially separated, partial resection of uterine wall or removal of placenta using advanced bipolar was performed.

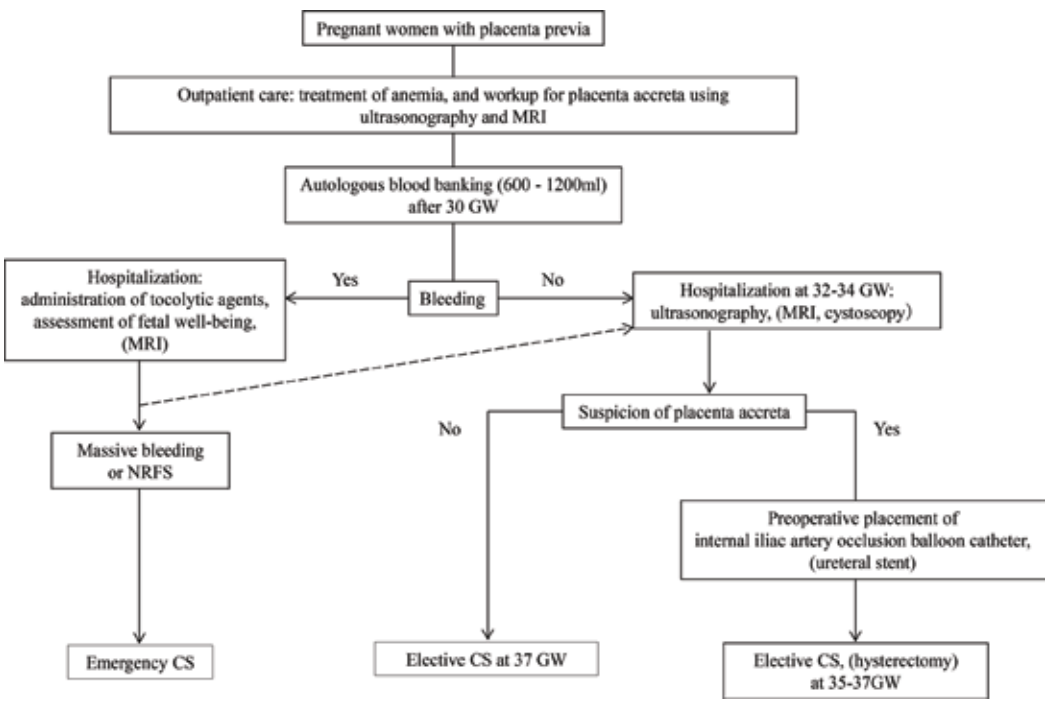

Figure 2. An algorithm for the management of pregnant women with placenta previa. MRI, magnetic resonance imaging; GW, weeks of gestation; NRFS, non-reassuring fetal status; and CS, cesarean section.

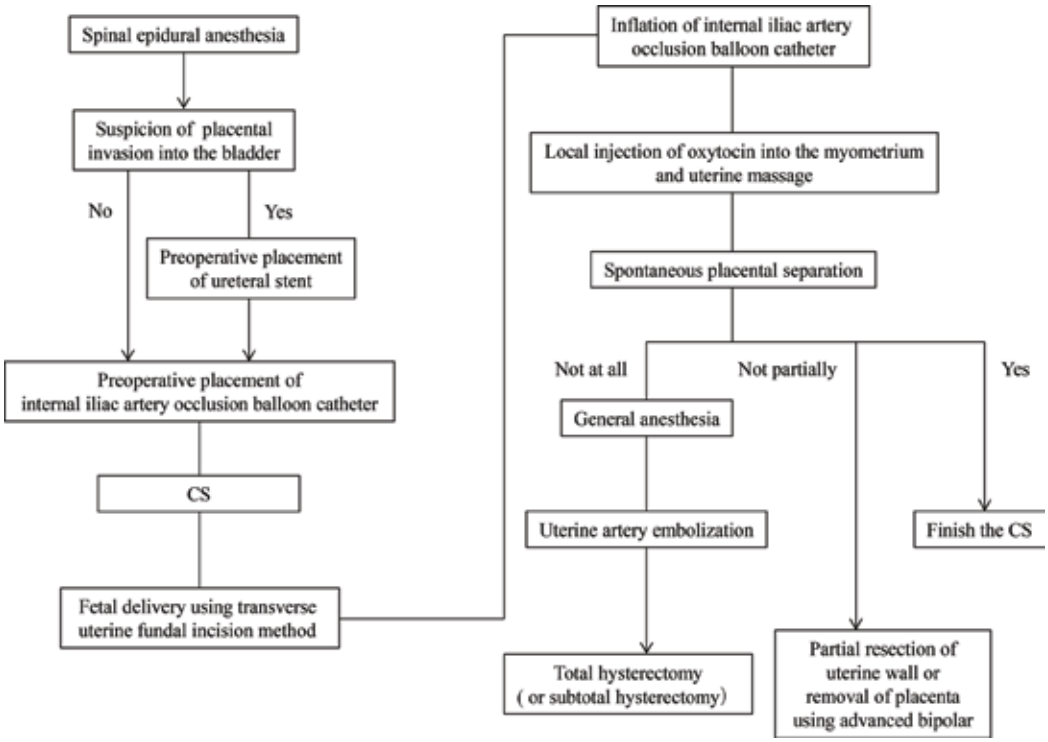

Figure 3. A flow algorithm for the preoperative preparation and operative procedures against women with suspicion of placenta accreta. CS, cesarean section.

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Chapter 7

Management of High-Risk Obstetrical Patients with Morbidly Adherent Placenta in the Age of Resuscitative Endovascular Balloon Occlusion of the Aorta

Rachel M. Russo, Eugenia Girda, Hui Chen, Nina Schloemerkemper, Misty D. Humphries and Vanessa Kennedy

Additional information is available at the end of the chapter

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Abstract

Obstetric hemorrhage is the leading cause of maternal morbidity and mortality worldwide. At highest risk of massive obstetric hemorrhage, are women with morbidly adherent placenta (MAP). The complications associated with MAP are even more devastating in very high-risk obstetrical patients, where blood transfusion is not an option, either due to lack of resources or patient refusal, such as for Jehovah's Witnesses. Resuscitative endovascular balloon occlusion of the aorta (REBOA) is a minimally-invasive technique used in trauma surgery to control non-compressible hemorrhage. REBOA is emerging as useful tool for managing high-risk obstetric surgery for MAP. This review aims to provide a framework for use of REBOA in obstetric care in challenging circumstances.

Keywords: accreta, aortic balloon, balloon occlusion, Jehovah's Witness, morbidly adherent placenta, obstetric hemorrhage, percreta, REBOA

1. Introduction

Obstetric hemorrhage is the leading cause of maternal morbidity and mortality worldwide [1]. At highest risk of massive obstetric hemorrhage are women with a morbidly adherent placenta (MAP). MAP describes the penetration of placental chorionic villi into the uterus to varying degrees classified as—placenta accreta, increta, and percreta. The incidence of MAP is increasing.

In the United States alone, the rate doubled from 5.4 in 10,000 deliveries to 11.9 in 10,000 over a period of 6 years [2]. The most severe form, placenta percreta, in which chorionic villi penetrate through the uterine wall and into adjacent organs, has increased 50-fold in the last 50 years [3].

Women with multiple prior cesarean deliveries are at greatest risk for MAP. The risk of MAP in patients after one, two, or three prior cesarean deliveries increases 2.9, 4.6 and 12.6-fold, respectively [4]. Additional risk factors include prior surgical injury to the myometrium, including dilation and curettage, and advanced maternal age.

The potential consequences of obstetric hemorrhage are most dire in women who refuse, or cannot receive, blood products. For example, the maternal mortality ratio (MMR) due to major obstetric hemorrhage in Jehovah's Witnesses was 68 per 100,000 live births in one study; 130 times that of the general population [5]. Furthermore, in low resource settings, where blood products are not readily available, the MMR can be up to 645 per 100,000 live births [6]. Obstetric hemorrhage accounts for up to 42% of maternal deaths in low resource settings [7]. With this in mind, new strategies for obstetric hemorrhage control are essential for improving transfusion-free survival.

Resuscitative endovascular balloon occlusion of the aorta (REBOA) is an emerging, minimally-invasive technique to control non-compressible hemorrhage. Although initially developed for the management of traumatic hemorrhage, REBOA has been gaining popularity for the control of non-traumatic hemorrhage. Early reports of REBOA use in obstetric hemorrhage indicate that the approach reduces blood loss, improves maternal outcomes, and decreases rates of hysterectomy compared to traditional techniques, such as uterine balloon tamponade, and hypogastric or uterine artery occlusion [8–10]. This review describes the potential applications of REBOA for control of obstetric hemorrhage in high-risk obstetric surgery for MAP.

High-quality evidence to inform management of obstetric hemorrhage when transfusion is not an option is generally lacking. Small numbers of patients, clinical heterogeneity, and ethical principles preclude against randomized studies, so most data are drawn from case series and case reports, as well as from physiological principles and expert opinions. REBOA is a growing modality with novel applications, as well as technical and technological improvements that are continually evolving. The application of REBOA to obstetric hemorrhage is in its infancy, thus comparative data and long-term follow-up are lacking. While this may limit the strength of any generalizations that can be drawn from the literature, this review aims to provide a framework for use of REBOA in obstetric care in this challenging circumstance.

2. Demographics of high-risk patients

Approximately 60% of women with MAP will experience significant morbidity, including blood transfusion, urologic injury, infection, intensive care unit admission, and readmission. A 15% of obstetric hemorrhage requiring blood transfusion are due to MAP [11]. The majority of patients with MAP will undergo invasive procedures, have extensive blood loss and require massive blood transfusion [2, 11]. A 90% of patients with placenta percreta who undergo cesarean hysterectomy will require blood transfusion due to intraoperative blood losses greater than three liters, with median transfusion of 7 units of red blood cells [12, 13].

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The morbidity and mortality associated with MAP is even more devastating when blood transfusion is not an option, either from lack of resources or patient refusal. Patients decline blood transfusions for a variety of reasons, most commonly due to religious grounds, such as for Jehovah's Witnesses. For these patients, the risk of mortality due to obstetric hemorrhage is 130 times greater than in the normal population [5].

3. Traditional hemorrhage mitigation strategies

3.1. Preoperative optimization

During the first prenatal visit, willingness to accept blood products should be addressed and alternatives to transfusion discussed. For patients who indicate that they would not accept blood transfusion, providers should investigate which, if any, blood products or alternatives may be acceptable in the case of an emergency. In addition to establishing patient capacity, a thorough discussion of the potential risks and benefits of transfusion is necessary. This discussion with patients should be performed privately and confidentially. It must be free of coercion and judgment from outside parties [14, 15]. In circumstances of a religious basis for blood refusal, patients frequently consult with religious leaders, family and friends prior to making a decision, but the final decision must rest in the hands of the patient herself. These discussions must be clearly documented in the medical record.

Preoperative optimization of hemoglobin by treating underlying anemia is ideal. Many patients who do not accept blood will accept other methods to improve hemoglobin levels. Iron, vitamin B12, folate and recombinant erythropoietin can be used preoperatively [14, 15]. Intravenous iron is preferred over oral preparations because of faster and more reliable increases in hemoglobin. Recombinant erythropoietin can optimize hemoglobin both preoperatively and postoperatively. However, there are no clear guidelines on optimal dosing. While studies suggest erythropoietin is safe to use in pregnancy, it can increase the risk of venous thromboembolism (VTE), which may exacerbate an already hypercoagulable state [16]. Consultation and coordination with a hematologist should be considered.

As the pregnancy advances, careful monitoring of the placenta is imperative to understanding the extent of MAP. A plan for delivery in an appropriately-resourced setting is crucial. Advanced directives should be established, with legal counsel as necessary. A multidisciplinary effort should be assembled to discuss the optimal approach to planned and unplanned delivery. Ideally, this team should include members of the surgical obstetric team (which may include gynecologic oncology), maternal fetal medicine, neonatology, anesthesia, and in-house emergency surgery providers (such as trauma or vascular surgery) as indicated. Working with risk management, social services, and the ethics board may be necessary to optimize outcomes in these complex, high-risk situations.

3.2. Intraoperative adjuncts

Minimization of intraoperative blood loss and optimization of anemia tolerance improves outcomes. While the surgical team focuses on hemostatic techniques to decrease blood loss,

the anesthesia team can also support this goal. Patient positioning and ventilation mode can alter venous congestion, venous preload, cardiac output and peripheral vascular resistance. Normothermia aids in hemostasis. Additionally, intentional hypotension after delivery of the fetus may help minimize blood loss. A more detailed description of the anesthetic management of patients with MAP is beyond the scope of this article and has been covered elsewhere [16].

Several other methods can improve physiologic tolerance of anemia. Intraoperative volume expansion can be achieved through acute normovolemic hemodilution (ANH). With ANH, venous blood is removed into citrated bags at the start of surgery. The blood remains in a closed circuit with the patient throughout surgery. Crystalloid is administered to increase blood volume until hemorrhage is controlled, at which point ANH blood is transfused [17, 18]. Survival after more than five liters of blood loss has been documented in Jehovah's Witness patients with placenta percreta using ANH and cell salvage [19].

There is variability in the products that Jehovah's Witnesses will and will not accept [15]. Generally, whole blood products are prohibited, but some patients will accept fractions, such as hemoglobin, albumin, cryoprecipitate, clotting factors and platelets. A study of Jehovah's Witness patients found that, although most would decline conventional blood products, 76% would accept other blood components [20]. Most will accept crystalloid, colloid, recombinant factor VIIa (rFVIIa), factor VIII (FVIII), fibrinogen, tranexamic acid (TXA), and artificial blood substitutes [14, 15], but use of individual blood components alone may have limitations. Cryoprecipitate, containing FVIII, factor XIII (FXIII), von Willebrand factor (vWF) and fibrinogen, can be used in a postpartum hemorrhage to reduce risk of coagulopathy due to hypofibrinogenemia. However, it is not a substitute for plasma due to the lack of other coagulation factors. There is limited evidence that rFVIIa is helpful in refractory postpartum hemorrhage [21]. Finally, TXA is an anti-fibrinolytic agent that can be an adjunct for hemorrhage management. A Cochrane review found that TXA decreases blood loss and hemorrhage in both vaginal and cesarean deliveries [22]. The WOMAN trial found that administering TXA for postpartum hemorrhage within 3 hours of delivery decreased the rate of death due to bleeding compared to placebo. The authors found no difference in adverse events, including VTE, organ failure, sepsis, and seizure. They also found no difference in the rates of hysterectomy in both groups [23].

Cell salvage has become an important component of operative hemorrhage management for high-risk patients. However, there are important limitations of the cell salvage to consider. Cell salvage can only utilize blood collected into the canister, must have a minimum of 500 ml of blood before the cells can be washed, and returns at most 50% of the washed blood volume back to the patient. Furthermore, this technique does not allow for easy collection of vaginal blood loss, and therefore has limited utility in many obstetric hemorrhage cases. Safe use of the cell-saver has been demonstrated in obstetric patients, particularly when no future pregnancy is planned [24].

3.3. Traditional invasive hemorrhage control techniques

Definitive management for MAP is to complete a cesarean hysterectomy. A more conservative approach is to leave the placenta and uterus in situ after cesarean delivery of the infant. Follow up plans include observation with or without methotrexate, delayed hysteroscopic resection or interval hysterectomy several weeks later [25, 26]. Although conservative management is

successful in 78.4% of cases, this treatment carries an increased risk of postoperative sepsis and hemorrhage, which could necessitate emergent hysterectomy, further increasing the risk of more serious complications [25, 27]. In patients where the placenta is left in place, a risk of bleeding and infection exists for up to 5 months [28]. The risks of this approach may be prohibitively high in patients who cannot accept blood transfusion [25].

Traditional vascular methods of hemorrhage control during cesarean hysterectomy include intraoperative hypogastric artery ligation, uterine artery balloon occlusion with or without embolization, and temporary balloon occlusion of the hypogastric arteries. These methods have come under criticism after studies failed to demonstrate a significant reduction in blood loss or transfusion volumes compared to cesarean hysterectomy without these measures [29–31].

Ligation of the hypogastric arteries theoretically reduces pulse pressure to the uterus; however, it is successful in reducing operative blood loss in fewer than 50% of cases. Furthermore, ligation is estimated to be even less useful in MAP involving the bladder [32]. The literature regarding prophylactic intravascular hypogastric balloon occlusion during cesarean hysterectomy with MAP is mixed. Some studies suggest this technique reduces intraoperative blood loss and transfusion requirements [33], but others have found no difference in blood loss even in combination with uterine artery embolization, concluding that prophylactic intravascular balloon catheters yield no significant benefit [29–31]. These disparate findings are most likely explained by the persistent proximal collateral circulation to the uterus which contributes to venous hemorrhage during surgery [34, 35].

Aortic cross-clamping can aid in hemorrhage control when hypogastric artery occlusion is insufficient [36]. Once surgical hemostasis has been maximized, damage control techniques such as packing and temporary abdominal closure may be useful in cases of disseminated intravascular coagulation.

3.4. Management of postoperative anemia

Postoperative management centers around reducing further hemorrhage and providing supportive care for profound anemia. Intensive care monitoring may be required. Hematology consultation may provide guidance regarding hemoglobin optimization with use of high dose erythropoietin, intravenous iron, and other adjuncts [16]. Using pediatric blood collection tubes and avoiding unnecessary lab draws are helpful strategies. In extreme cases, measures to reduce oxygen demand and increase oxygen delivery, including intubation, sedation, and hyperbaric oxygen, may be beneficial [16, 37]. Finally, providers must weigh the risks and benefits of anticoagulation causing increased bleeding against the risk of VTE.

4. Novel hemorrhage mitigation strategies

4.1. Resuscitative endovascular balloon occlusion of the aorta (REBOA)

REBOA is a catheter-based alternative to aortic cross clamping that can be used proactively prior to hemodynamic collapse and even prior to anticipated hemorrhage. Endoluminal aortic

• Gain common femoral arterial access
• Position the balloon in the most distal location appropriate for providing adequate hemorrhage control
• Slowly deflate the occlusion balloon when hemodynamics permit
• Remove the catheter and sheath promptly, apply pressure to access site
• Monitor the patient post-operatively for ischemia–reperfusion injury and arterial access site complications

Table 1. Principles of REBOA.

occlusion to control non-compressible torso hemorrhage was first described in 1954 [38]. The technique was popularized decades later when advances in endovascular technology made catheter-based vascular control more commonplace for repair of aortic aneurysms. Recently, the REBOA catheter has been modified to be percutaneous, wireless, and fluoroscopy-free, leading to its wider adoption for non-compressible hemorrhage control [39].

Despite advancements in technology, the general principles of performing REBOA have remained largely unchanged (**Table 1**). Most published data about REBOA come from trauma literature, but its use in obstetric emergencies and high-risk surgeries is expanding [8–10, 40]. Our institution has successfully documented the use of REBOA in a Jehovah's Witness patient with placenta percreta [41]. This section will discuss the unique considerations for performing REBOA in the high-risk obstetric patient.

4.2. Benefits

REBOA is an alternative endovascular hemorrhage control technique, which significantly reduces obstetric blood loss compared to combined hypogastric and uterine artery occlusion [8–10]. Reports of prophylactic REBOA use during MAP procedures demonstrate improved maternal outcomes and decreased hysterectomy rates [9]. Compared to uterine or hypogastric artery occlusion techniques, REBOA requires less time for placement and only unilateral arterial puncture making it useful in emergent cases (**Table 2**) [8]. REBOA use has demonstrated lower transfusion volumes than other occlusion techniques [8]. Furthermore, new modifications in REBOA allow placement without fluoroscopy which leads to little to no fetal radiation exposure [8, 42–45].

Catheter measurements based on anatomic landmarks can serve as a basis for positioning of the balloon within the aorta [39, 46]. The effect of a gravid abdomen on the accuracy of

• Single arterial access site, concurrent arterial blood pressure monitoring
• Little to no fetal radiation exposure
• Can be inserted and adjusted in the operating room
• Improved hemostasis compared to hypogastric and/or uterine artery occlusion
• Can be inserted quickly in response to emergent hemorrhage

Table 2. Benefits of REBOA.

using external landmarks for fluoroscopy-free REBOA positioning has not been established. However, alternative methods for positioning in obstetric patients include palpation of the balloon within the aorta during laparotomy or from measurements taken from a pre-operative MRI [42, 43]. Confirming catheter position with an x-ray limits radiation exposure to the fetus compared to the use of fluoroscopy. Any of these positioning methods can be performed in a standard operating room with a standard table. Additionally, the catheter can be inflated, deflated, and repositioned as needed throughout the case without the needing to move the patient or obtain additional imaging.

Previous cases of REBOA use in MAP procedures describe placement by an interventional radiologist, however fluoroscopy-free REBOAs in trauma patients are most commonly placed by surgeons or emergency medicine physicians (**Table 3**) [9, 10, 40, 42, 43, 47–50]. These providers are readily available in the hospital, allowing for expedient response times. REBOA insertion, positioning, and inflation can be completed in approximately 2–3 minutes by a

A

Author	Study design	Number of patients	Prophylactic or reactive	Device used	Image guidance
Zone 1 occlusion technique					
Russo1	CR	1	Prophylactic	7Fr (Prytime)	None
Zone 3 occlusion technique					
Bell-Thomas2	CR	1	Reactive	10Fr (BVM Medical)	None
Luo3	CS	4	Prophylactic	10Fr (Cook)	Fluoro
Masamoto4	CR	1	Prophylactic	5Fr (Sheft)	Fluoro
Paull5	CR	1	Prophylactic	8.5Fr (Cook)	Fluoro
Usman6	CR	1	Reactive	NR	None
Wei7	CS	3	Prophylactic	8Fr (Bard)	Fluoro
Duan8	CS	4	Prophylactic	8Fr (Bard)	Fluoro
Wu9	Cohort	88	Prophylactic	5Fr (Cook)	Fluoro

B

Author	Occlusion time (min)	Blood loss (L)	Blood transfused	Operative time (hours)	Length of stay (days)	Complications
Zone 1 Occlusion Technique						
Russo1	32	3	None	4.2	5	None
Zone 3 Occlusion Technique						
Bell-Thomas2	NR	Massive	>40 units	4	>60	Vesico-vaginal fistula
Luo3	NS	0.8	0.4 L	1.3	NR	Ureteral damage ×2
Masamoto4	80	3.2	1.2 L	NR	NR	None

B						
Author	**Occlusion time (min)**	**Blood loss (L)**	**Blood transfused**	**Operative time (hours)**	**Length of stay (days)**	**Complications**
Paull5	NR	1.4	None	NR	7	None
Usman6	NR	Massive	40 units	6.5	9	NR
Wei7	NS	3.33 (2–6)	3.7 (2–7)	NS	NS	NS
Duan8	22.4	0.6	0.4 L	1.1	5.5	None
Wu9	23.6	0.9	0.4 L	1.1	5.1	None

CR: case report; NR: not reported; CS: case series; NS: not specified (grouped in with other causes of hemorrhage).

Table 3. Previously reported obstetrical use of REBOA for MAP, 3A. Types of REBOA devices used, 3B. Surgical outcomes of REBOA use for MAP.

trained provider using the ER-REBOA catheter (Prytime Medical, Boerne, TX). In the future, REBOA can be used increasingly for both obstetric emergencies and complicated obstetric scenarios, such as a high-risk obstetric patient with MAP.

4.3. Risks and limitations

The risks and limitations of REBOA are still being described, and the relative incidence of each is not yet known. The majority of data published on this topic describes the application of REBOA in the trauma population that consists largely of male patients with concomitant hemorrhagic shock. Potential complications from REBOA include those related to arterial access, balloon positioning and inflation, and the physiologic changes that result from inflation and deflation of the device (**Table 4**). From the trauma literature, access site complications are similar to those encountered during other forms of arterial puncture, but may be severe, including limb ischemia requiring amputation [51, 52]. Balloon malposition into an aortic branch vessel or migration into a higher or lower position within the aorta has also been described, sometimes resulting in uncontrolled arterial rupture and death [45, 51]. In animal models, proximal hypertension resulting from aortic occlusion has led to acute heart failure, cerebral edema, and respiratory failure [53, 54]. Distal organ ischemia during occlusion can lead to renal failure, bowel ischemia, and paralysis [51, 52]. Finally, washout of toxic metabolites following balloon deflation can cause rebound hypotension with cardiac collapse [55].

The use of REBOA in obstetrics introduces a different patient population with other comorbidities and requires a different anatomic site of aortic occlusion. The ability to predict complications for this population from the available trauma literature is therefore limited. The potential for severe complications exists and providers performing the procedure should be aware of these risks to improve patient management and the informed consent process.

The optimal location and duration of aortic occlusion is controversial. The primary blood supply to the gravid uterus includes the uterine arteries and collaterals from other branches of the internal iliac artery. However, particularly in cases of abnormal placentation, robust collaterals from the external iliac, ovarian, and other systemic arteries exist [34, 35]. Most

• Access site complications, including limb ischemia requiring amputation	• Use low-profile (7Fr) sheath • Use ultrasound to obtain CFA access • Monitor ipsilateral DP/PT pulses while the sheath is in place • Consider heparin flushes • Post-procedure angiography prior to sheath removal
• Balloon malposition or migration	• Confirm balloon position with x-ray • Secure catheter while in place • Dedicated provider to maintain REBOA catheter/balloon control
• Proximal hypertension that may lead to acute heart failure, cerebral edema or ARDS	• Close communication with anesthesia • Concurrent administration of vasodilators while balloon inflated • Reposition from Zone 1 to Zone 3 when able • Minimize duration of occlusion
• Distal organ ischemia, that may cause renal failure, ischemic bowel, or paralysis	• Minimize duration of occlusion • Reposition from Zone 1 to Zone 3 when able • Institute partial or intermittent REBOA when able
• Washout of toxic metabolites, leading to rebound hypotension and cardiac instability	• Institute partial or intermittent REBOA when able • Slowly, gradually deflate balloon • Communicate with anesthesia • Time administration of fluids, calcium, and pressors ith balloon deflation

Table 4. Risks of REBOA and methods of mitigation.

reports of obstetric REBOA use describe occlusion in the infra-renal aorta (Zone 3). However, when Zone 3 occlusion is insufficient, supra-celiac (Zone 1) occlusion may further limit collateral circulation through visceral and lumbosacral vessels and reduce venous back-bleeding. Caution should be used as Zone 1 occlusion is associated with more ischemic complications than Zone 3 occlusion [41]. Extrapolating from trauma literature, Zone 1 occlusion is tolerated for minutes, not hours, and multisystem organ failure and death have been reported after long inflation times [46, 52, 56]. In a prophylactic setting, the lack of pre-existing shock may improve ischemia tolerance and reduce the anticipated risks. However, there may still be a significant risk of supra-physiologic aortic pressure leading to heart failure [55].

4.4. Risk reduction

Risks of REBOA use can be reduced with multidisciplinary expertise, proper training, and adherence to good techniques. Low-profile, 7Fr common femoral arterial sheaths placed with ultrasound guidance have fewer access site complications than larger 12Fr sheaths. Additionally, distal thrombosis is rare with 7Fr sheaths and limb ischemia requiring amputation has not been reported. REBOA requires a dedicated provider to secure against catheter migration, manage inflation and deflation, and faithfully monitor the ipsilateral lower extremity for ischemia.

During balloon inflation, the anesthesia team should work to off-set unwanted blood pressure augmentation and maintain normal physiologic pressures. The surgical teams should aim to achieve hemorrhage control rapidly to keep the duration of Zone 1 occlusion to a minimum. Other methods used to reduce ischemia include intermittent or partial balloon deflation and relocating the REBOA balloon to Zone 3 when able [55]. These techniques will allow some distal blood flow to perfuse ischemic tissues and prolong the overall duration of REBOA use. Providers should be aware that balloon deflation is associated with the rapid redistribution of circulating blood volume and the washout of ischemic metabolites, including a bolus of potassium, which can result in rebound hypotension and cardiac instability [55]. The combination of partial occlusion and relocation from Zone 1 to Zone 3, along with close communication with the anesthesia providers to time fluid and drug administration with inflation and deflation, can aid in maintaining hemodynamic stability throughout surgery.

There is a dearth of published information about management of intra-arterial balloons during high-risk obstetric procedures. Of all reported cases, there has been only one documented aortic rupture due to a smaller than expected aortic diameter [45]. Few cases describe flushing the sheath or catheters, although doing so is a well-established principle of vascular surgery. Whether the flush solution should contain heparin is additionally controversial when these catheters are used for hemorrhage control in patients that cannot receive blood. The authors' practice is to use 30 ml 2% heparin (2 units of heparin per 100 ml of crystalloid) through the sheath and another 30 ml through the central lumen of the REBOA catheter every 10 minutes, while monitoring thromboelastography to ensure the absence of systemic coagulopathy. Frequent monitoring of distal pulses in the ipsilateral extremity should be maintained throughout the case and for 24 hours after sheath removal. Continuous Doppler may be a helpful adjunct to aid in early detection of arterial access complications.

The risks and benefits of anticoagulation deserve special consideration in this patient population. Pregnancy itself confers a hypercoagulable state. These patients may be at even higher risk of clot formation due to the administration of TXA, erythropoietin, cryoprecipitate or other coagulation factors. Postoperatively, VTE risk remains high in the setting of immobility and/or symptomatic anemia. In the immediate postoperative period, the risk of death from hemorrhage may outweigh the risks from VTE. Within several days of surgery however, the probability of hemorrhage decreases, justifying prophylactic heparin administration to reduce the risk of VTE.

5. Future directions

REBOA is a novel, minimally-invasive method to control non-compressible hemorrhage. Much of the literature regarding techniques for placement and risks of use are derived male trauma patients. More research is needed to investigate the use of REBOA in a peripartum setting. Reports of prophylactic use of REBOA to minimize blood loss during high-risk obstetric operations, claim to reduce blood loss and improve rates of uterine salvage compared to other types of arterial occlusion techniques, such as hypogastric and uterine artery occlusion. Most of this evidence comes from retrospective case series out of Asia. Comparative data is needed to

examine the risks and benefits of REBOA compared to other methods of hemorrhage control utilized in the West. Although case reports and case series have shown that REBOA can successfully provide temporary control of obstetric hemorrhage, up to three liters of blood loss has been reported in these cases despite aortic occlusion. Larger studies are needed to quantify the expected hemorrhage volume during aortic occlusion to help inform perioperative plans.

Furthermore, instructions on REBOA use and placement for the obstetric patient are extrapolated from the trauma literature. Whether external landmarks on the gravid abdomen can be used reliably for positioning of REBOA has yet to be determined. More research is needed to establish whether imaging is needed to verify balloon position prior to inflation, and to assess the associated risk of radiation exposure to the fetus. The optimal zone of REBOA inflation is not known for obstetric hemorrhage. More research should focus on defining collateral pathways for circulation to the gravid uterus, especially in the case of abnormal placentation. Additionally, the effect of proximal vs. distal occlusion on blood pressure support during various stages of hemorrhagic shock should be established to aid in defining the optimal level of occlusion for initial balloon inflation in prophylactic and reactive settings.

Finally, the risks of REBOA are also generated from its reactive placement in trauma patients experiencing hemorrhagic shock. Although it can be assumed that prophylactic use of REBOA during planned obstetric procedures will have decreased risk compared to trauma situations, more research is needed to investigate this use of REBOA. As the adoption of REBOA for obstetric hemorrhage becomes more prevalent, it is expected that increasing evidence will help delineate more definitive guidelines for this population.

6. Recommendations

For high-risk patients with MAP, thorough planning throughout the prenatal period is critical to successful management. Prenatal optimization of hemoglobin and preoperative involvement of a multidisciplinary team can improve maternal outcomes. If blood products are not readily available or are declined by the patient, alternative options should be discussed. Clearly eliciting if blood fractions, clotting factors, and TXA will be accepted by the patient can assist in surgical planning. Meticulous surgical techniques and clear communication with the anesthesia team can minimize intraoperative hemorrhage. Additional adjuncts such as ANH and cell salvage may ease the effects of blood loss. Consideration of REBOA use may decrease the volume of blood lost and the need for transfusion. Planning for REBOA use in a proactive and prophylactic setting may limit the risks of the procedure and improve morbidity and mortality.

Implementing REBOA in the obstetric patient requires careful multidisciplinary management and clear communication throughout the perioperative period. General principles of vascular access should be respected. Minimizing the risk of limb ischemia requires selecting the smallest sheath possible to accommodate the selected balloon catheter, frequent vascular checks of both lower extremities, consideration of post-procedural angiography, and prompt sheath removal. The duration of balloon inflation should be minimized, and intermittent or partial balloon deflation should be used as adjuncts to reduce ischemia when necessary. Anticipating

• Assemble multidisciplinary team including all perioperative stakeholders
• Optimize preoperative blood volume and hemoglobin
• Plan risks and benefits discussion comparing available hemorrhage control adjuncts available at the institution
• Consider REBOA as an adjunct to temporary hemorrhage control
• Expeditiously achieve definitive hemorrhage control
• Provide post-operative intensive care, anticipating fluid shifts and electrolyte abnormalities associated with severe anemia and ischemia–reperfusion

Table 5. Summary recommendations.

hemodynamic and metabolic changes associated with balloon inflation and deflation is paramount and requires frequent communication between the operating and anesthesia teams to time the administration of medications and fluids.

Finally, providing supportive care for profound anemia and limiting unnecessary lab draws can improve postoperative outcomes. Careful consideration must be given to the use and timing of anticoagulation in setting where further hemorrhage could be detrimental to patients. A summary of the recommendations can be found in **Table 5**.

7. Conclusions

In conclusion, women undergoing planned operations for MAP are among those at highest risk for catastrophic obstetric hemorrhage, especially those for whom blood products are not an option. A multidisciplinary approach to management is the key to patient survival. Goals include limiting blood loss, maintaining hemodynamic stability, and reducing postoperative morbidity. In addition to the obstetric and anesthesia teams, assistance by general, acute care, trauma, or vascular surgeons may be required for hemorrhage control. REBOA is an emerging hemorrhage-control technique with benefits for obstetric applications and represents a tool that should be in the armamentarium of obstetric/gynecologic surgeons.

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Acronyms and abbreviations

ANH	acute normovolemic hemodilution
FVIII	Factor VIII
MMR	maternal mortality ratio
MAP	morbidly adherent placenta
rFVIIa	recombinant factor VIIa
REBOA	resuscitative endovascular balloon occlusion of the aorta
TXA	tranexamic acid
VTE	venous thromboembolism
vWF	Von Willebrand factor

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Chapter 8

Placenta Therapy: Its Biological Role of Anti-Inflammation and Regeneration

Kyeong Mee Park, Dong Pill Cho and Tae Hwan Cho

Additional information is available at the end of the chapter

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Abstract

Human placental extract has been used to treat fatigue, postmenopausal symptoms, wound healing, and growth retardation in Korea. Combined with acupuncture therapy, placental extract extends its therapeutic limit to pain control. Recently, we have reported acupuncture point injection (API) with placental extract modulated inflammation-involving pain symptoms in chronic pain diseases. In order to rehabilitate patients suffering from chronic pain and restricted joint mobility, placental extract was injected into acupuncture points localized on the joints, surrounding muscles acting in concert with the joints, and paravertebral muscles affecting the innervation of the joints. Here, we describe the pathology of pain syndromes including neck pain, back pain, shoulder pain, knee arthritis, fibromyalgia, and complex regional pain syndrome and propose methodology of APIs with placental extract in treating these pain diseases.

Keywords: placental extract, acupuncture point injection, regeneration, anti-inflammation, neck and back pain, shoulder pain, knee arthritis, fibromyalgia, complex regional pain syndrome

1. Introduction

The human placenta is a unique organ that connects the developing fetus to the uterine wall. The placenta provides nutrient uptake, thermo-regulation, waste elimination, and gas exchange to growing fetus via the mother's blood supply. Since the placenta is a provisional organ, it becomes a salvage material after delivery. For decades, clinicians and researchers work on the application of the placenta for therapeutic purposes. The types of placental preparation used in the studies are fragments of placental tissue, amniotic and chorionic

membranes, umbilical cord, amniotic fluid, placental extracts, and cord blood stem cells. Methods of application widely vary from subcutaneous, intramuscular, intravenous, intraoperative, biocovers, and substitutive material to oral administration [1–3].

Research on human placental extract began to thrive from the description on the method of its preparation by Russian ophthalmologist Filatov [4]. Filatov initially observed that grafting-preserved human corneas had better clinical outcomes than freshly isolated ones. He convinced that isolated tissues readjusted themselves to develop biogenic stimulators under unfavorable environmental factors. He advocated the principle of therapeutic tissues which could exhibit curative effects by adapting themselves to the tissues affected by the pathological process. Since placenta is a storehouse of potent biogenic stimulators, the application of placental extract ranges from immunology, stem cell research, genetics, and cancer research to tissue engineering. Placental extracts were demonstrated to contain wide range of peptides, proteins, minerals, amino acids, nucleotides, carbohydrates, and steroid hormones.

Experimental evidence has accumulated on the therapeutic effects of placental extracts. One of the most important roles of the placenta is to protect the embryos from oxidative stress, and therefore, placental extract has antioxidative properties [5]. Antioxidant properties of placental extract are usually associated with the protein components, especially alpha-fetoprotein [6]. Injecting placental extract to a wound margin [7] or applying placental extract topically to chronic nonhealing wounds [8] promoted healing of injured tissues. This mechanism appears to be related to an increase in transforming growth factor-beta (TGF-β) in the early phase of wound healing and vascular endothelial growth factor (VEGF) in the late phase [8]. The regeneration of sciatic axons by placental extract injection was validated by increased synthesis of regeneration-related protein factors such as GAP-43 and Cdc2 [9]. Application of placental extract in menopausal disorders allowed reducing the number of hot flushes and normalized hormone profiles [10]. Experimental animal model studies showed that placental extract decreased symptoms of fatigue and increased resistance to physical stress [11]. Placental extracts were also demonstrated to have anti-inflammatory effects in both animals and humans. In adjuvant-induced polyarthritic rats, injection of placental extract was demonstrated to alleviate arthritic symptoms including joint destruction and expression profiles of inflammatory cytokines [12]. Intra-articular injection of placental extract reduced deformity of knee joints and inhibited matrix metalloproteinase-2 and -9 activities of cartilages of osteoarthritic knee joints in rats [13].

Recently, acupuncture point injection (API), an injection at an acupuncture point of a small amount of medicinal solution, has been widely used for the treatment of various pain syndromes in China and Korea. API is derived from intramuscular injection in Western medicine and then gradually integrated into traditional Chinese medicine [14]. The medical agents administered in acupuncture points are thought to play a synergistic effect with acupuncture point stimulation, and this method is believed to have a more sustained effect than the traditional acupuncture needling or simple intramuscular injection [15]. API is reported to increase cerebral blood flow, improve adjuvant arthritis, and have analgesic and anticoagulatory effects [16–18]. In clinical studies, API improved cervical disc herniation, knee osteoarthritis, and low back pain [19–21]. Here, we intended to propose an API with placental extract in treating chronic pain syndromes. The mechanistic explanation of acupuncture points employed in the treatment of respective pain syndromes is also explored.

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2. Preparation of placental extract

Placental extracts are classified to several types depending on the methods of its preparation. Initial extraction was done by employing the Filatov's procedure [4] but an acid-hydrolyzed water extraction is prevailing in Korea due to its high recovery of functional macromolecules from placental tissues. Human placentas, collected upon full-term delivery, were tested for human immunodeficiency virus and hepatitis B and C viruses. They were cut into pieces, defatted with acetone, and extracted with water through pepsin and hydrochloric acid-catalyzed hydrolysis. Resulting placental extract was tested for germ-free, antihistamine, and endotoxin-free under the regulation of Korean Food and Drug Administration. The final placental extract product was sterilized, packaged at 2 ml/ampule, and approved for injection for human by subcutaneous and intramuscular. Insoluble macromolecules, such as polysaccharide, polynucleotide, etc., were excluded during the manufacturing processes. The trade name of the extract, "Laennec", is provided from Green Cross Ltd. (Yongin, Korea). Kong et al. [22] analyzed and reported the levels of cytokines and hormones of Laennec by using automated biochip array technology.

3. Treatment of pain based on anti-inflammation and regeneration

Musculoskeletal disorders are the most frequent cause of disability in the modern world, and the prevalence of these diseases is rising at an alarming rate. The most prominent reason for loss of joint mobility and function is chronic pain, which leads to impaired quality of life. Current therapies to alleviate pain have limited effectiveness, and some drugs produce unwanted negative side effects, thereby precluding their long-term use.

Nociceptive receptors are located throughout the joint. It has been identified in the capsule, ligaments, menisci, periosteum, and subchondral bone. If a noxious mechanical factor or inflammatory mediator is applied to the joint, the firing rate of the afferent nerve increases dramatically, and the central nervous system interprets this nociceptive activity as pain [23]. Transient pain is induced and serves as a physiological warning at brief, high-intensity stimuli, which produce little or no tissue damage. However, in chronic pain conditions, there may be spontaneous pain, as well as intermittent pain, which is induced by persistent inflammation from structural damage or functional degeneration. Chronic pain is also associated with complex changes in peripheral and central signal processing [24].

It is accepted that inflammation and the inflammatory response play pivotal roles in the occurrence, as well as progress of pain. The biochemical mediators of inflammation include cytokines, neuropeptides, growth factors, and neurotransmitters. Irrespective of the type of pain whether it is acute or chronic pain, peripheral or central pain, nociceptive or neuropathic pain, the underlying origin is inflammation and inflammatory response. Activation of pain receptors, transmission of pain signals, and modulation of neuroplasticity all belong to a continual spectrum of inflammation and inflammatory response.

Every pain syndrome has an inflammatory profile consisting of the inflammatory mediators that are present in the pain syndrome. The inflammatory profile may have variations from

one person to another and may have variations in the same person at different times. Various symptoms of pain syndromes are attributed from corresponding inflammatory profiles of discrete pain syndromes. The key to treat pain syndromes is inhibiting the production of inflammatory mediators at the same time regenerating injured or degenerative tissues. The term "regeneration" is used to describe the phenomena that allow an organism to reconstitute the structure damaged by injury and recover the functional homeostasis. A successful outcome is one that results in less inflammation, more regeneration, and thus less pain.

4. Anti-inflammatory effects of acupuncture point injection with placental extract

Acupuncture has been used in the treatment of several diseases for at least 5000 years in Asia. In the western society, acupuncture has become a central part of complementary medicine. An increasing number of patients, especially those suffering from chronic diseases, are seeking acupuncture treatment. The widespread application of acupuncture includes the treatment of infections, inflammatory diseases, autonomic dysfunction, psychological disorders, musculoskeletal diseases, and many other illnesses [25].

The neural activation by acupuncture was investigated by many researchers. With the stimulation of vision-related acupuncture points, visual cortices of the brain were found to be stimulated [26]. Liu et al. [27] and Li et al. [28] reported that the C-fiber rich afferents of the deep tibial nerve coincided with acupuncture points, implying rich distribution of nerve fibers/reflex complexes at acupuncture points. Abraham et al. [29] also proved that the acupuncture points contained a significantly higher number of transient receptor potential vallinoid type 1-positive Aδ- and C-fibers as compared with nonacupuncture points. Gao et al. [30] demonstrated that the enhancement of gastric motility induced by acupuncture point ST36 stimulation was mediated by N-methyl-D-aspartate receptors.

In acupuncture, the insertion of needle induces marked changes close to the needle in all different tissues that are penetrated. These peripheral events might improve tissue function through dilation in the skin due to axon reflexes [31]. Additional activation can be obtained through manipulation of the needle or electro-stimulation at different frequencies. Studies have shown that manual acupuncture (back-and-forth motion or up-and-down motion) or electrical stimulation in specific frequencies applied to acupuncture points can facilitate the release of specific neuropeptides in the central nervous system [32]. This activation is demonstrated to elicit profound physiological effects and even activate self-healing mechanisms [33]. Although the effect of manual acupuncture or electro-acupuncture is comparative to the effects of nonsteroidal anti-inflammatory drugs and opioid analgesics [34], maintenance of needles might be cumbersome, particularly in agitated animals. In order to overcome this disadvantage, other techniques might be used for stimulation of acupuncture points.

Acupuncture point injection (API) is a new acupuncture technique which combines acupuncture and medication. API is widely used to enhance and prolong the effect of stimulation of acupuncture points [35]. API with placental extract can be used to control pain syndromes

due to anti-inflammatory effects from each member. Numerous uncontrolled trials, as well as a limited number of controlled trials, have been published after short-term or long-term use of acupuncture in the treatment of inflammatory diseases. The direct and indirect effects of acupuncture on regulation of inflammatory mediators such as neuropeptides, cytokines, and vasoactive substances have been assessed [36]. Even though there are some pitfalls such as relatively small number of patients and incompletely described methodological procedures, the results clearly show a beneficial effect of acupuncture in the reduction of symptomatic inflammatory response. As well, anti-inflammatory effects of placental extracts were fully evaluated. Porcine placental extract was shown to protect the contact hypersensitivity of skin by modulation of immunoglobulin E production [37]. Animal model studies showed that placental extracts reduced the concentration of free radicals, inflammatory cytokines interleukin-6 (IL-6), tumor necrosis factor (TNF), and interleukin-1 (IL-1) at the same time increasing the colony formation of progenitor cells in vitro [38]. Clinical trials of API with placental extracts showed anti-inflammatory effects in pain diseases. Injection of placental extract to acupuncture points ameliorated various inflammation-associated symptoms of complex regional pain syndrome [39, 40]. In osteoarthritic patients, API with placental extract improved daily working hours, reduced knee joint swelling, and abated pain [20].

5. Regenerative effects of acupuncture point injection with placental extracts

Regenerative medicine has the potential to heal or replace tissues and organs damaged by age, disease, or trauma. The current therapy of transplantation of intact organs and tissues to treat organ and tissue failures suffers from limited donor supply and often severe immune complications. These obstacles may potentially be bypassed through the use of regenerative medicine strategies. The field of regenerative medicine encompasses numerous strategies, including use of materials and de novo generated cells, as well as various combinations. Regenerative medicine effectively replaces missing tissues both structurally and functionally, thus contributes to tissue healing. The body's innate healing response may also be leveraged to promote regeneration at the time of regenerative procedure [41].

Placental extracts are obtained by lysing human placental tissues collected from full-term delivery. The extracts do not contain cells but are rich in a wide range of proteins, minerals, amino acids, and steroid hormones. Placenta synthesizes a number of hormones, such as estradiol, progesterone, and chorionic gonadotrophin, which regulate growth and development of the fetus during pregnancy so that placental extracts have the impact on proliferation. Data indicate that placental extracts stimulate proliferation and regenerative processes in various systems. The significant increase in tensile strength and tissue DNA in the animals given human placental extract indicates the extract-induced marked collagen synthesis [42]. Human dermal fibroblasts showed an increased proliferation after treatment of human placental extract [43]. Placental extracts were also shown to enhance the proliferation of cord blood cells in vitro [44]. Animal model studies proved that the placental extract promotes fibrogenesis, neoangiogenesis, and epithelialization [8].

Acupuncture has been used to treat injured tissues and recover the degenerative functions. Experimental results have revealed the positive roles of acupuncture on injury-induced regeneration. Electro-acupuncture was shown to promote the differentiation of endogenous oligodendrocyte precursor cells into oligodendrocytes in the demyelinated spinal cord in rats [45]. In a rat tendon healing model, mechanical stimuli by acupuncture stimulation at the juxtaposition to tenotomized locus appeared to transduce mechanical stimulation to biological changes [46]. It is proposed that the mechanical stimulation by acupuncture leads to increase in small leucine-rich proteoglycan synthesis by fibroblasts close to the injury sites [47]. Clinical application of electro-acupuncture increased total cell counts, TGF-β1 and basic fibroblast growth factor (bFGF)-positive cell counts, and the mechanical strength of repaired tendon than the control groups received no treatment [48].

API with placental extract has two advantages; acupuncture stimulation *per se* and pharmacological effect of placental extract. As a needle of acupuncture arrives at the site of injured or degenerative locus with placental extract, a regenerative event begins. It is asserted that a combined therapy of acupuncture and placental extract stimulates regeneration more vigorously in injured or degenerative tissues than the separate application does.

6. Methods

Patients with pain syndrome suffer from restricted joint mobility, which leads to impaired quality of life. API with placental extract focuses therapeutic objective on pain control and joint mobilization. A joint is a connection between bones in the body, so that it links the skeletal system into a functional whole. The movable joints such as the knee, elbow, and shoulder are able to withstand compression and maintain heavy loads while still executing smooth and precise movements. According to the earlier work of Melzack [49], trigger points and acupuncture points are the same phenomena in terms of pain though they are discovered independently and labeled differently. This concept was consolidated by Dorsher and Fleckenstein [50], who used a graphic software to evaluate the anatomical relationship between the locations of classical acupuncture points and trigger points. A harmonious movement of joints can be accomplished by an interplay between properly positioned joint and its cognate muscles. The qualified acupuncture points adopted in API with placental extract are ones which are located on the joint, muscles responsible for movement of the joint, and paravertebral muscles modifying the innervation of the joint. There have been reports to support the therapeutic rule of API with placental extract in treating pain syndromes. Intra-articular injection of medication is widely applied to reduce joint pain and increase joint mobility [51]. Trigger points release with injection of pharmacological substances to dynamic motor muscles is used for the accomplishment of proper muscular kinetic chain [52]. Moreover, a higher prevalence of arthritis at other sites is validated in the patients with lumbar spine degeneration [53]. Based on the clinical effectiveness of API with placental extract, we, thus, provide a brief description on the pathology of pain diseases and methodology of API with placental extract in treating these diseases.

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6.1. Neck and back pain

Neck and back pain most commonly results from injuries to muscles, disks, nerves, ligaments, or facet joints with subsequent inflammation and spasm [54, 55]. Degeneration of disks or joints produces the same symptoms and occurs by aging, previous injury, or excessive mechanical stresses. Herniation of disk tissue produces a profound inflammatory reaction with release of inflammatory chemical mediators especially TNF-α [56]. Subsequent to the release of TNF-α, an increase in the formation of inflammatory mediators such as prostaglandin and nitric oxide as well as phospholipase A2 activation ensues [57]. In sequence, activation of motor nerves that travel from the spinal cord to the muscles results in excessive muscle tension, spasm, and pain. It is accepted that inflammation and the inflammatory response are responsible for neck and back pain both with and without herniated disk [58].

The set of acupuncture points recommended are Ex-HN15, GB21, SI14, and BL10 for neck pain. A sterile 40-mm-long 23 gauge needle is inserted into the acupuncture points at the same time as patients are seated. Ex-HN15 (**Figure 1**), a member of extra channel acupuncture points, is localized on the facet joint between the cervical vertebra 6 (C6) and 7 (C7). From the injury mechanisms during stimulated whiplash, it was revealed that capsular ligament strain reached a maximum at C6-C7 [59]. Through Ex-HN15, 1 mL of placental extract is infused to the facet joint cavity between C6 and C7.

Injection to the trigger point–related muscle areas is a good choice for eliminating shortened sarcomeres including contraction knots. Usually, 1 mL of placental extract is injected to the acupuncture points, while needles are inserted to a depth of 25 mm, which is deep enough

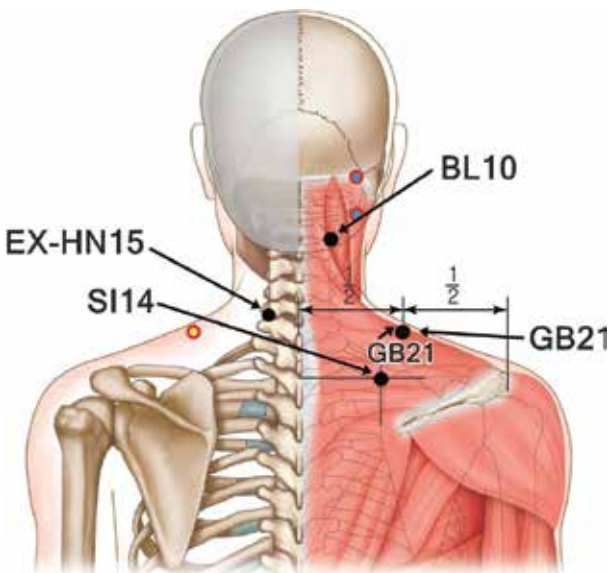

Figure 1. Acupuncture points for treating neck pain.

to penetrate the body of the muscle mass. GB21 (**Figure 1**) is the midpoint of the line on the posterior neck connecting the spinous process of C7 and the outer margin of the acromion [60] and coincides with the trigger point of the upper trapezius muscle. The upper trapezius originates at the external occipital protuberance, the medial third of the superior nuchal line, the ligamentum nuchae, and the spinous process of C7. Thus, tightness or pain in the upper trapezius is associated with range of motion limitation in neck joint. SI14 (**Figure 1**) is located 4.5 cm away from, horizontally, the lower margin of spinous process of the first thoracic vertebrae (T1) [60] and corresponds to the active trigger point of levator scapular muscle. The levator scapula is attached to the posterior tubercles of transverse processes of C1-C4, and its tightness or pain is associated with limitations in upper cervical motion [61]. BL10 (**Figure 1**) is located on the paravertebral region of the neck, at the same level as the superior border of the spinous process of C2, in the depression lateral to the trapezius muscle [60]. Stimulation of BL10 can relieve contraction knots of the semispinalis capitis and appease the muscular tension on the exporting nerve. It was demonstrated that injection to BL 10 enables the tension of the nape of the neck detangled, resulting in relief of pain such as migraine [62].

Acupuncture points BL23, BL25, BL26, and BL30 are recommended for back pain. A sterile needle with 90-mm-long 23 gauges is used for injection of placental extract to the respective acupuncture points. Acupuncture points BL23 (**Figure 2A**), BL25 (**Figure 2B**), and BL26 (**Figure 2B**) are localized on the facet joint of lumbar vertebra at the second (L2), fourth (L4), and fifth (L5) levels, respectively, and lie on the paravertebral muscles including longissimus, rotator, and multifidus. For the percutaneous treatment of low back pain, the entering point of the needle is 2.5-cm lateral from the median line, with a needle depth of 2.5–8 cm.

Meanwhile, the sacroiliac joint is regarded as a potential source of low back pain, affecting 15–30% of individuals with chronic nonradicular pain [63]. The extensive network of

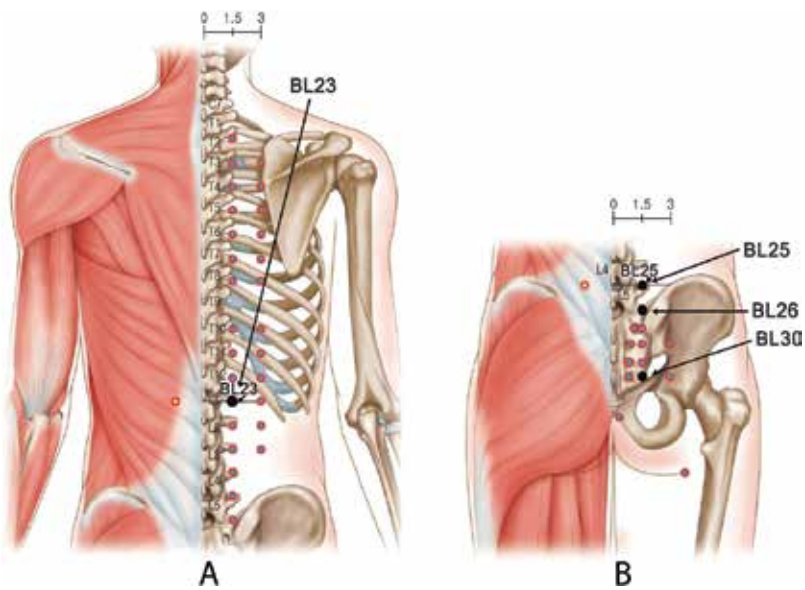

Figure 2. Acupuncture points for treating back pain.

strong ligaments maintains the integrity of the joint acting as mechanical stabilizers and is also involved with limiting the extent of sacroiliac joint motion [64]. Moreover, posterior pelvic ring ligaments, sacrospinous, and sacrotuberous ligaments significantly contribute pelvic stability. With the use of computational approaches involving finite element modeling, the increased stiffness of sacrospinous and sacrotuberous ligaments was demonstrated to decrease pelvic motion [65]. As acupuncture point BL30 (**Figure 2B**) is localized on the sacrotuberous and sacrospinous ligaments, API with placental extract to BL30 may alleviate stiffness of these ligaments and contribute pelvic stability.

6.2. Shoulder pain

A bursa is a small sac containing fluid that lies between bone and other moving structures such as muscles, skin, or tendons. The bursa allows smooth gliding between these structures by acting as an anti-friction device and shielding the structures from rubbing against bones. Tendons are the thick fibrous cords that attach muscles to bone and function to transmit the power generated by a muscle contraction to move a bone. Almost any tendon or bursa in the body can be affected, but those located around the joint are affected most often. The most frequent causes in shoulder pain are bursitis, tendonitis, rotator cuff tears, and adhesive capsulitis. In one study of 39 patients with rotator cuff diseases, the levels of the cytokine IL-1β were significantly correlated with the degree of pain [66]. In another study, immunohistological staining demonstrated the expression of IL-1β, TNF-α, TGF-β, and bFGF in subacromial bursa derived from the patients suffering from rotator cuff tear [67]. Adhesive capsulitis is characterized by pain, stiffness, and impaired function at the glenohumeral joints. Patients of adhesive capsulitis typically experience onset of shoulder pain followed by a loss of motion especially in the motion of flexion, abduction, and external rotation. As adhesive capsulitis is generally related to a shortening and fibrosis of the joint capsule surrounding the shoulder joint, the contracture of shoulder ligaments actually decreases the volume of the capsule, thus limiting the range of motion [68]. It is likely that limitations in range of motion and pains associated with adhesive capsulitis are not only related to capsular and ligamentous tightness but also fascial restrictions, muscular tightness, and trigger points within the muscles.

Acupuncture points SI10, LU1, GB21, SI11, SI12, HT1, and Ex-HN15 are recommended for the treatment of shoulder pain. Usually 1 mL of placental extract is injected to each acupuncture point, while a 40–60-mm-long 23 gauge needle is inserted to a depth of 25–40 mm. SI10 (**Figure 3A**) is localized on the posterior scapulohumeral joint, while LU1 (**Figure 3B**) is localized at the medial margin of coracoid process. In order to successfully infuse placental extract into the anterior scapulohumeral joint, the tip of needle should be entered LU1 and proceeded toward the anterior scapulohumeral joint.

SI11 (**Figure 3A**) is localized on the upper third of the line connecting the midpoint of the spine of scapula and the lower margin of scapula [60] and coincides with the trigger point of infraspinatus muscle. SI12 (**Figure 3A**) is located in the scapular region, in the supraspinatus fossa, superior to the midpoint of the spine of the scapula [60]. Clinically meaningful improvements were reported in pain and disability, while trigger points of upper trapezius, supraspinatus, and infraspinatus musculature were intervened by needling [69]. As SI11, SI12, and GB21 (**Figure 3A**) coincide with the trigger points of the infraspinatus, supraspinatus, and

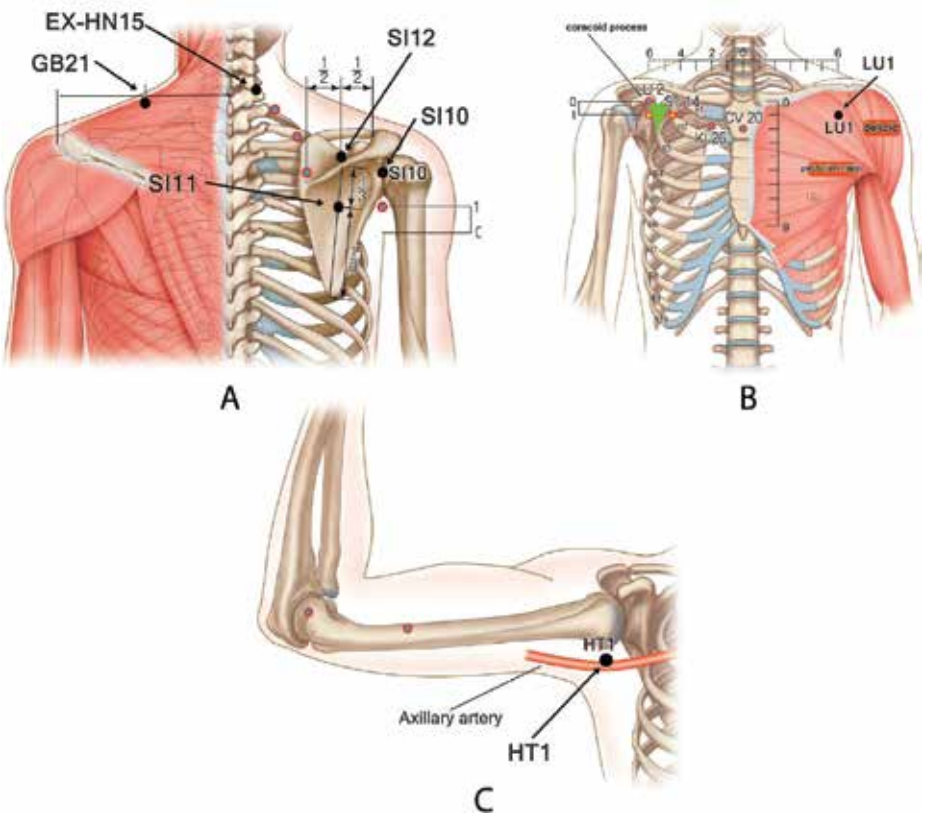

Figure 3. Acupuncture points for treating shoulder pain.

trapezius, respectively, injections of placental extract to SI11, SI12, and GB21 relieve tightness or pain in these muscles which are associated with range of motion limitation in neck and shoulder joints. Through HT1 (**Figure 3C**) on axillary fossa, the tip of needle can be finally placed on subscapularis muscle, which plays a key role in the development of adhesive capsulitis [70]. Ex-HN15 (**Figure 3A**), a member of extra channel acupuncture points, is selected for spinal modulation of shoulder joint innervation.

6.3. Knee arthritis

Arthritis means inflammation of the joints. The symptoms of knee arthritis are intermittent pain, swelling, redness, and stiffness in the joints. There are many different types of knee arthritis; some of which are rheumatoid arthritis (RA), osteoarthritis (OA), and infectious arthritis. In RA, the joints are destroyed by the immune system. OA pain is due to inflammation, which may be present in bone tissues, cartilages, joints, disks, ligaments, soft tissues, and muscles. OA affects not only the articular cartilage but also the underlying bone and adjacent joint structures. Inflammation of the synovial membrane may be absent in the earlier stages of OA. However, as the disease progresses, some degree of synovitis usually exists in OA [71].

IL-1, a cytokine produced by chondrocytes and other cells in the joint, plays an important role in cartilage degradation in OA by stimulating the synthesis of degradative enzymes that inhibit the production of proteoglycan [72]. Other cytokines that appear to act synergistically with IL-1 to promote matrix breakdown in OA are TNF-α and IL-6 [73].

Knee OA is a chronic progressive disease affecting more than 20% of people older than 45 years [74]. With the increase in life expectancy, it seems that the need for knee arthroplasty would rise, causing significant economic burdens for pain control and rehabilitation of patients. The target of knee OA treatment is pain decrement, function and mobility increment, prevention or correction of the deformity, and slowing the progression of the disease.

In regarding pain control and movement rehabilitation, acupuncture points ST35 can be chosen for API with placental extract. At the same time, APIs with placental extract to KI10, SP10, GB34, GB31, and BL25 are also helpful to ameliorate the symptoms of knee OA. ST35 (**Figure 4A**) is localized on the lateral margin of patella tendon along the knee joint line [60]. Through ST35, 6–8 mL of placental extract is reached in the synovial joint cavity by using a 10-mL syringe with 40-mm-long 23 gauge needle.

Acupuncture point SP10 (**Figure 4A**) is localized on the belly of vastus medialis muscle, GB31 (**Figure 4B**) is on vastus lateralis muscle, and GB 34 (**Figure 4C**) is on the head of fibula in the region of lower extremity. These three acupuncture points concord to the trigger points of the vastus medialis, vastus lateralis, and fibularis muscles, respectively. Acupuncture point KI10 (**Figure 4D**) is located between the tendons of semitendinous and semimembranous muscles in the region of popliteal fossa [60]. From our clinical experience, it is proposed that treating muscles around the knee joint is indispensable to improve stability of knee joint. Using a sterile syringe with 40-mm-long 25 gauge needle, each 1 mL of placental extract is injected to KI10, SP10, GB31, and GB34. BL25 (**Figure 4E**) is localized on the facet joints of L4 and lies on the paravertebral muscles including longissimus, rotator, and multifidus. For the injection to BL25, the entering point of the needle is 2.5 cm lateral from the median line, with a needle depth of 2.5–4 cm. A total of 1 mL of placental extract is injected to BL25 by a 3-mL syringe with 60-mm-long 25 gauge needle.

6.4. Fibromyalgia syndrome

Fibromyalgia syndrome (FMS) is a chronic, painful musculoskeletal disorder characterized by widespread pain, pressure hyperalgesia, morning stiffness, sleep disturbances, fatigue, and physical and psychological distress [75]. It can be divided into two forms: the primary form, with very pronounced psychogenic background, and the secondary form with rheumatic arthritis, systemic lupus erythematosus, Sjögren syndrome, or inflammatory bowel disease. Fibromyalgia has been proposed to be due to neurogenic inflammation induced by an inflammatory response to allergen, infectious agents, irritants, chemical exposures, or emotional stress [76]. Several studies have shown that there are increased levels of inflammatory neurotransmitter substance P and calcitonin gene–related peptide (CGRP) in the spinal fluid of patients with FMS [77]. Another study found increase in blood levels of cytokines IL-6 and IL-8, whose release is stimulated by substance P [78].

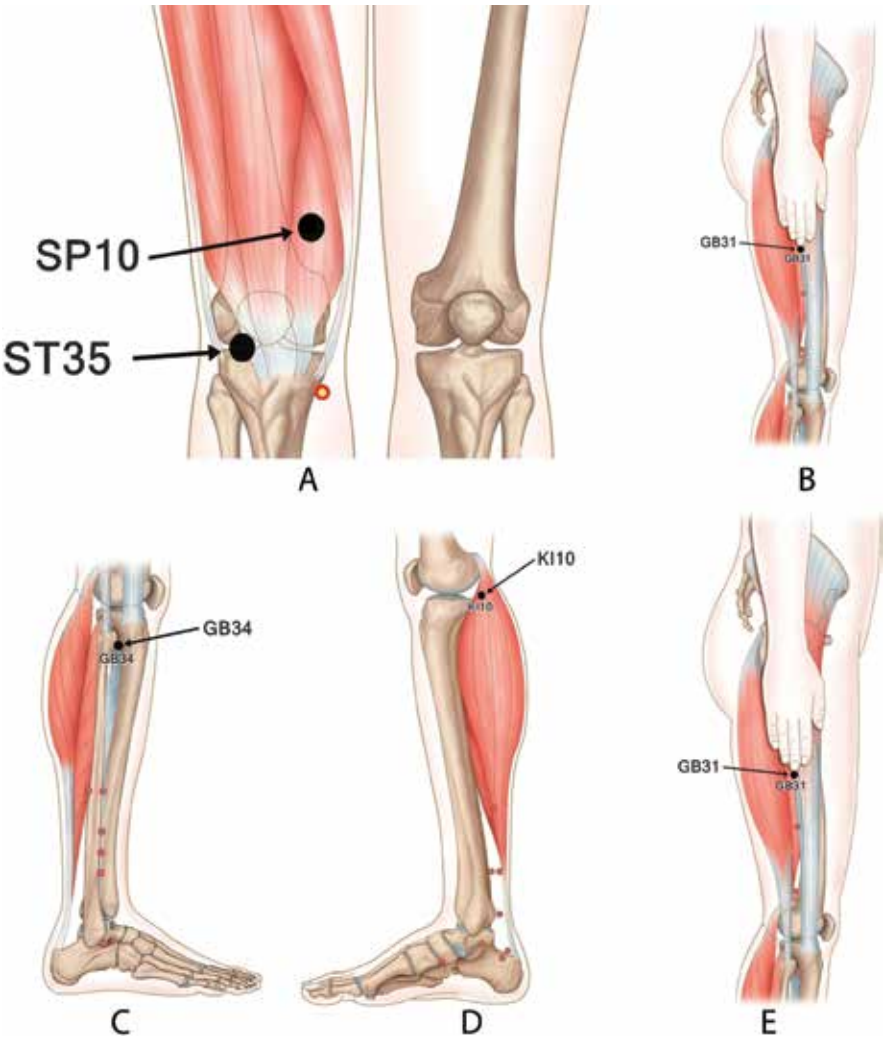

Figure 4. Acupuncture points for treating knee arthritis.

Various forms of physical trauma have been implicated as triggering events in the pathogenesis of FMS, and some patients report the initiation or exacerbation of their symptoms after a traumatic event such as a whiplash injury [79]. It was estimated that between 2.9 and 3.8% of the general population in Europe and the US are affected [80], and the majority of patients in clinical setting belongs to female. The polysymptomatic distress score (PDS) can be used to diagnose FMS. It is derived from a compilation of the number of pre-specified painful regions, which a patient has plus a rating of the severity of pain, sleep disturbance, fatigue and cognitive dysfunction, headache, abdominal pain, and depression [81]. Although there is no satisfactory treatment for FMS as yet, many patients with FMS utilize complementary and alternative medicine (CAM) therapies in addition to conventional medicine. Acupuncture is one of the most commonly employed CAM therapies.

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The recommended acupuncture points for the treatment of FMS are GB21, SI11, SI13, SI14, Ex-HN15, and BL13 (**Figure 5**). SI13 is located on the medial margin of the spine of scapula and coincides with the trigger point of supraspinatus muscle. As women with FMS show higher pain sensitivity and lower pressure pain thresholds over cervical spine and supraspinatus [82], choice of SI13 is pertinent. BL13 is located 2.5 cm lateral from the bottom of the spinous process of T3 [60] and corresponds to the trigger point of the upper rhomboid major muscle. According to the outcome of cervical pathology study, myofascial trigger points are commonly observed in the neck, parascapular region, and upper back muscles [83]. Therefore, API with placental extract to GB21, SI11, SI13, SI14, Ex-HN15, and BL13 can be used to improve the symptoms of FMS by relieving complications derived from the pathological condition of neck. A sterile 40-mm-long 23 gauge needle is inserted into the acupuncture points as patients are seated. Usually, each 1 mL of placental extract is injected to the acupuncture points, while needles are inserted to a depth of 25 mm.

6.5. Complex regional pain syndrome

Complex regional pain syndrome (CRPS) is often initiated by trauma to a nerve, neuronal plexus, or soft tissue. Diagnostic criteria are the presence of regional pain and other sensory changes following painful injury. The pain is associated with changes in skin color, skin temperature, abnormal sweating, and tissue swelling. With time, tissue atrophy may occur as well as involuntary movements, muscle spasm, or pseudoparalysis. The inflammatory mediators that are generated, especially IL-6, accelerate the rate at which bone is broken down [84].

At the start, soft tissue or nerve injury causes release of inflammatory mediators and excitation of sensory nerve fibers. Reverse firing of sensory nerves causes release of the inflammatory neuropeptides such as substance P, CGRP, and amino acids such as glutamate at the peripheral

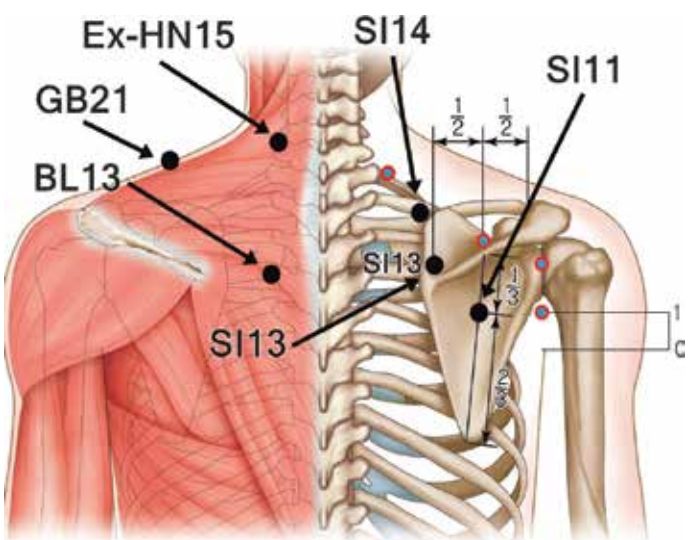

Figure 5. Acupuncture points for treating fibromyalgia.

endings of sensory fibers. These neuropeptides may induce vasodilation, increase vascular permeability, attract other immune cells, and excite surrounding nerve fibers. At the level of central nervous system, the increased input from peripheral pain receptors alters the central processing mechanisms. Perpetuation of the sympathetic response has been proposed to be related to central dysregulation of nociceptive impulses. Prolonged ischemia from sympathetic

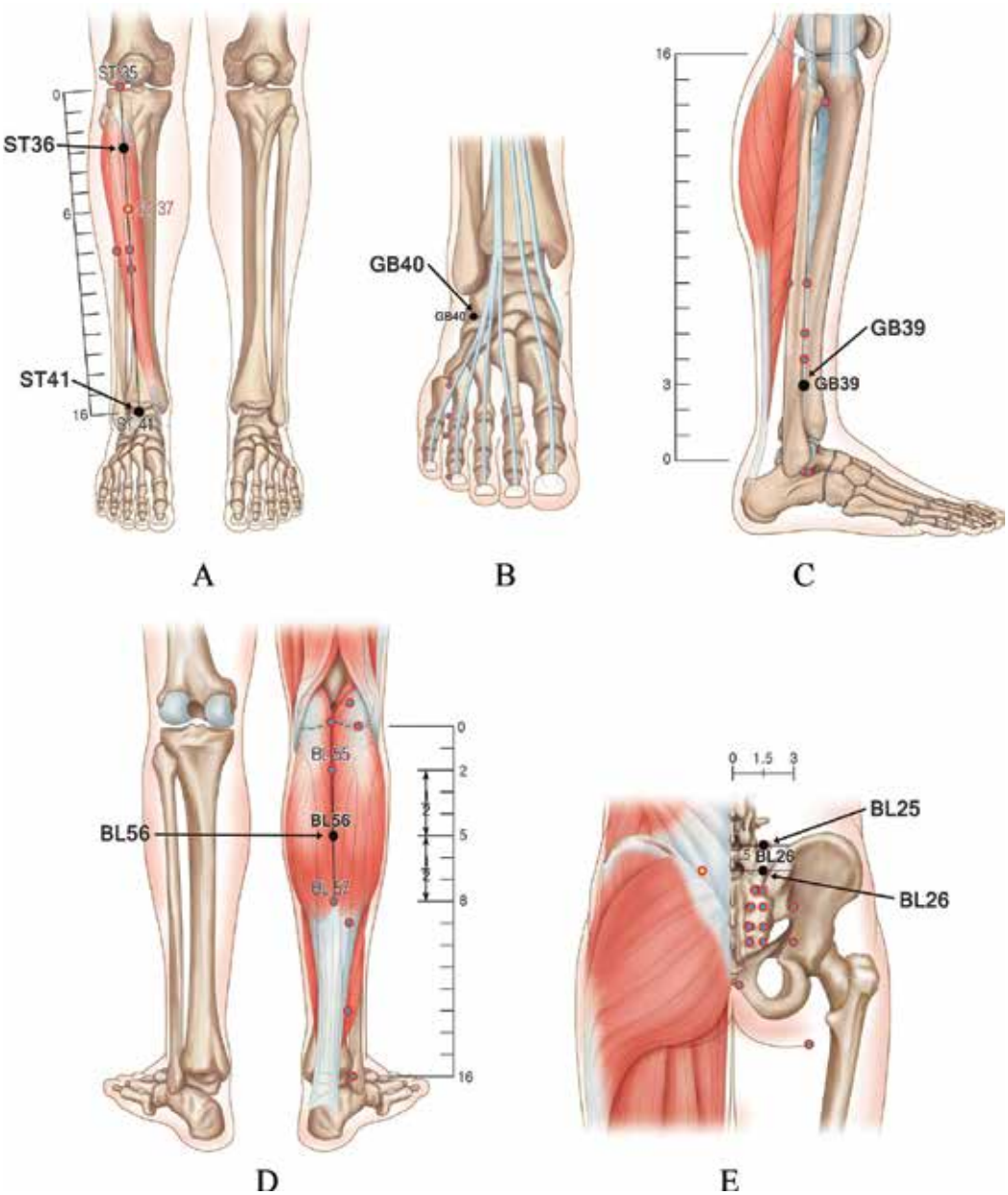

Figure 6. Acupuncture points for treating complex regional pain syndrome.

vasoconstriction produces more pain, establishing a reflex arc that promotes further sympathetic discharge and vasospasm. The results of several experimental studies suggest that sympathetic dysfunction may also consist of super sensitivity to catecholamines induced by nerve injury [85]. In the final, CRPS exhibits allodynia where otherwise innocuous stimulation will cause pain and hyperalgesia where there is exaggerated pain to a known painful stimulus. Regional osteopenia, changes of hair and nail growth, and dystrophic cutaneous changes may also occur. The magnitude of each of these features will vary between individuals, each existing on a wide spectrum. Usually, patients with CRPS affecting wrist/hand regions have neck and shoulder girdle signs on the affected side, while patients affected with ankle/foot regions suffer from back pain and lower extremity dysfunction on the affected side.

The recommended acupuncture points for the treatment of CRPS affecting ankle/foot regions are ST41, GB40, GB39, BL56, ST36, BL25, and BL26. ST41 (**Figure 6A**) is located on the anterior aspect of the ankle, in the depression at the center of the front surface of the ankle joint, between the tendons of extensor hallucis longus and extensor digitorum longus [60]. GB40 (**Figure 6B**) is located in the depression lateral to the extensor digitorum longus tendon, anterior and distal to the lateral malleolus [60]. Through ST41 and GB40, each 1 mL of placental extract is infused to the ankle joint using a 3-mL syringe with 30-mm-long 23 gauge needle.

To rehabilitate the ankle joint, GB39 (**Figure 6C**), BL56 (**Figure 6D**), and ST36 (**Figure 6A**) are suitable to be administered with placental extract. Injection to GB39, BL56, and ST36 contributes to the mediolateral stability of the ankle joint complex (i.e., talocrural and subtalar joints) by relieving the muscle tension. Each 0.5 mL of placental extract is injected to GB39, BL56, and ST36 with 40-mm-long 25 gauge needles. BL25 and BL26 (**Figure 6E**) are located at the same levels as the inferior border of the spinous process of L4 and L5, respectively. They are situated 2.5 cm lateral to the posterior median line. There is compelling evidence that lower extremity arthrosis is related with lumbar spinal disease [86]. Using 710 randomly selected cadaveric specimens, a significant association was found between lumbar disk degeneration and tibiotalar joint arthritis [87]. A cross section study comparing normal subjects and patients with lumbar disk herniation with sciatica revealed that ankle plantar flexion torque was significantly lower in the lumbar disk herniation group than the control group [88]. Moreover, in a preliminary study with collegiate football players, low back dysfunction and suboptimal endurance of the core musculature appear to be important injury risk factors for strains and sprains of foot [89]. Each 1 mL of placental extract is injected to BL25 and BL26 by 3-mL syringes with 60-mm-long 25 gauge needle.

7. Conclusion

Acupuncture point injection (API) is one of effective therapeutic interventions on inflammation-involving pain diseases, which are caused by structural injury or functional degeneration. The origin of all pain is inflammation and the inflammatory response. API with placental extract provides therapeutic effects by anti-inflammatory and regenerative effects on injured or degenerative tissues. We describe treatment methodology of API with placental extract in pain syndromes focusing on pain relief and joint mobilization. The loci of acupuncture

points adopted in API with placental extract are the joints, muscles responsible for the movement of the joints, and the paravertebral muscles regulating the innervation of the joints.

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Conflict of interests

Authors disclose no potential conflicts of interest.

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