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Placental Abnormalities

Alexander L. Juusela

Abstract

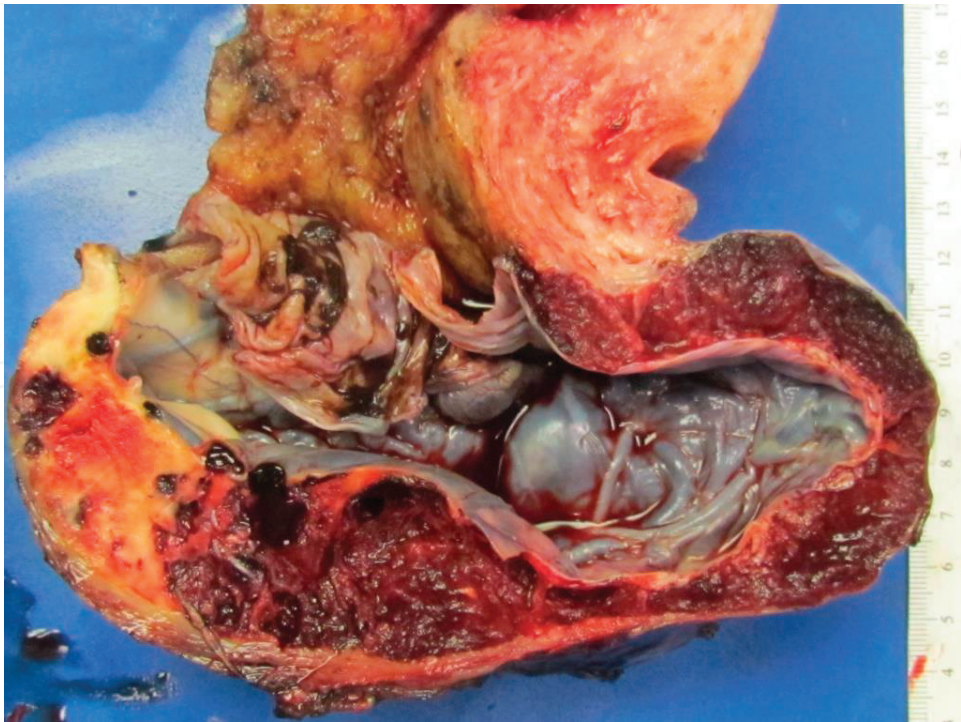
A detailed discussion of normal placental development and physiology is beyond the scope of this chapter and is discussed in other chapters. Instead, this chapter will focus on an overview of congenital placental abnormalities and the obstetrical complications that can arise. The goal of this chapter is to delineate the real-world implications of placental abnormalities and provide the reader with a basis for understanding the other chapters that will delve into microbiology, genomics, immunohistochemistry, and biochemistry of the placenta. The focus of this chapter will be on the developmental anomalies and this chapter will not discuss acquired anomalies (e.g., chorioamnionitis, amnion nodosum, metastatic tumors, and umbilical cord true knots). As the intention of this chapter is to focus on the etiopathogenesis of abnormal placentation, it is not intended to instruct the medical management of the described conditions, and therefore the discussions of management will be brief. The information provided is intended for general knowledge only and is not intended for use in diagnosing or treating a health problem or disease without consultation with a qualified healthcare provider. This chapter is not a substitute for professional medical advice, or treatment for specific medical conditions.

Keywords: abnormal placentation, intrinsic placental abnormalities, implantation abnormalities, placental perfusion, placenta accreta, placenta previa, ectopic pregnancy, abruption, hematoma, vasa previa, circumvallate placenta, chorioangioma, amniotic band sequence, placenta membranacea, battledore placenta, single umbilical artery, velamentous umbilical cord, preterm labor, intrauterine growth retardation, intrauterine fetal demise, pregnancy complications, high-risk pregnancy, maternal-fetal medicine, embryology, fetal development, fetal intervention, obstetrical emergency, fetal surgery

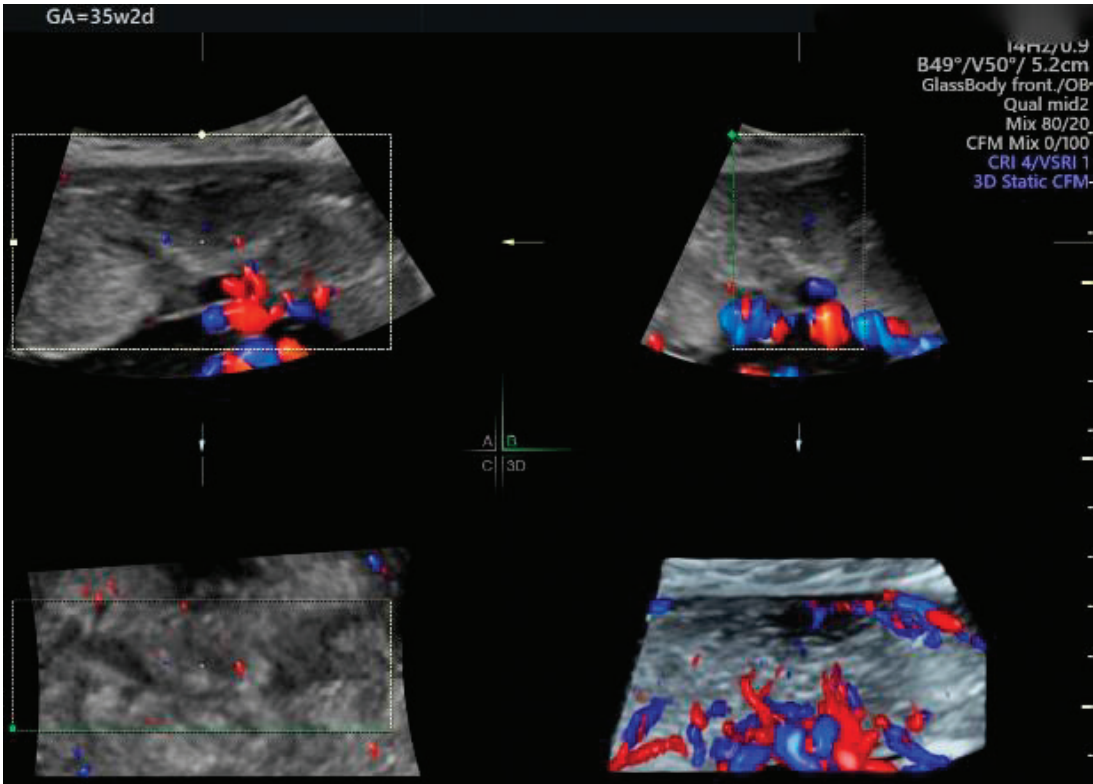
1. Introduction

The placenta is a fascinating organ, unique in that it is critical for human development, yet becomes dispensable once extra-uterine life has begun. During embryogenesis, the placenta functions as the maternal-fetal interface and performs the roles of the lungs, liver, and kidneys for the growing gestation, as well as providing nutrition. Placental development is intriguing in the balancing act performed when invading the maternal endometrium to permit growth of the blastocyst, however, unlike neoplasms, its invasion and growth has set end points, beyond which pathologic states can develop **Pictures 1–6**.

The term *placentation* is defined as the formation or arrangement of the placenta in the body of a woman or female animal. As discussed later in this chapter under the ectopic implantation discussion, the definition of placentation will be extended beyond implantation only in the uterus to “the body”.



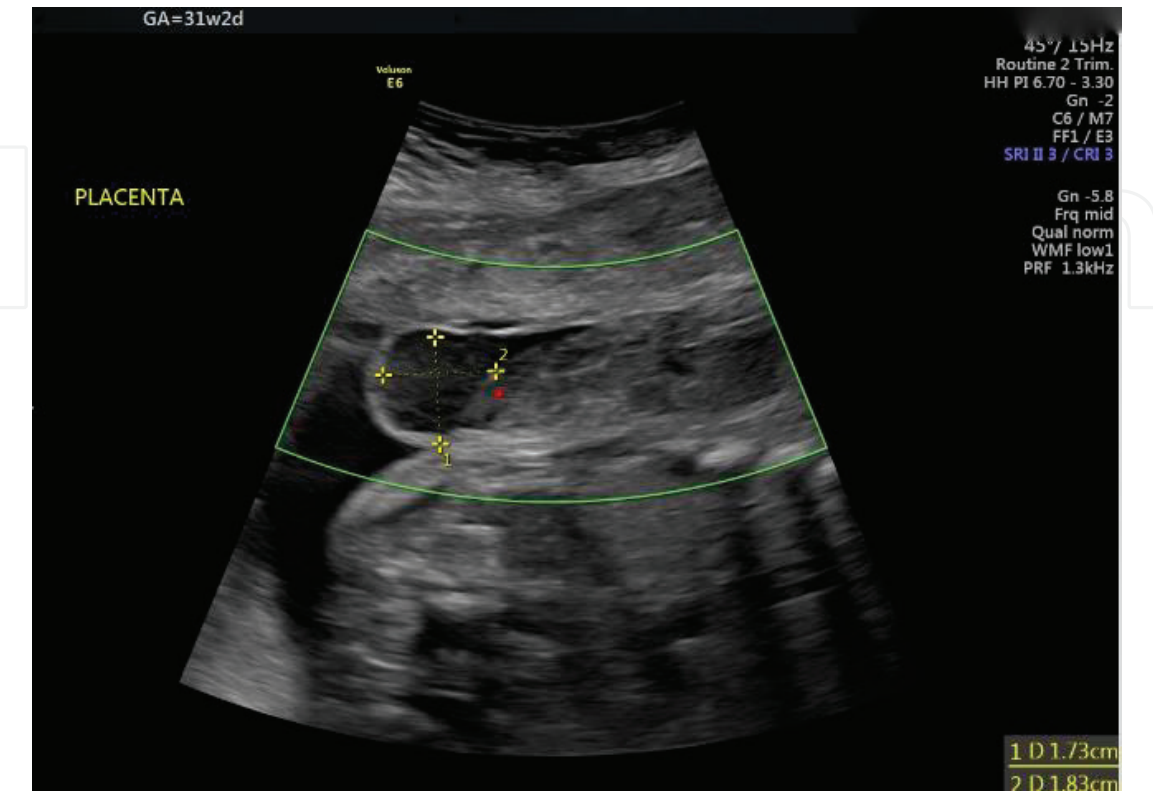
Picture 1.
Placenta previa with placenta accreta.



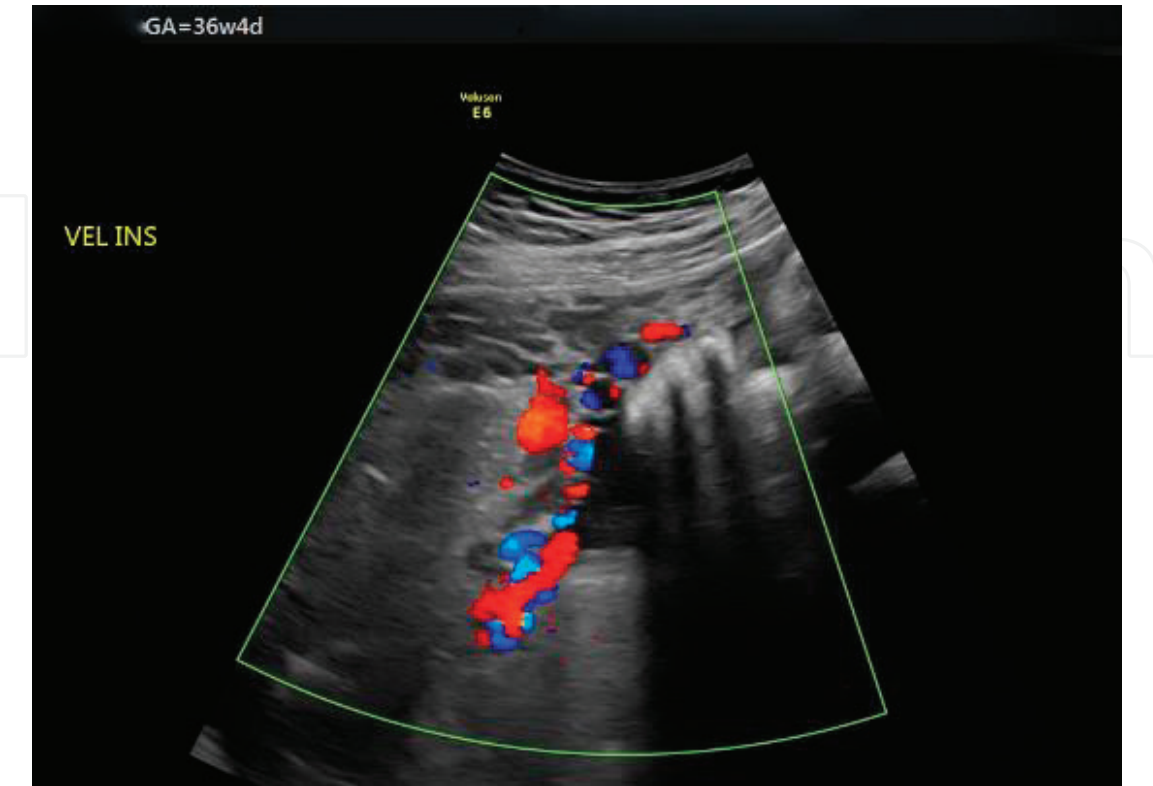
Picture 2.
Increased endometrial invasion by placental vasculature suspicious for placenta accreta.

Over the last couple centuries, scientific investigation has allowed us to understand the embryology, anatomy, and physiology of normal and abnormal placentation on both an organ system and a molecular level. We have established and continue expanding our understanding of how placental abnormalities and malfunctions contribute to the development of maternal, fetal, and neonatal disease, with

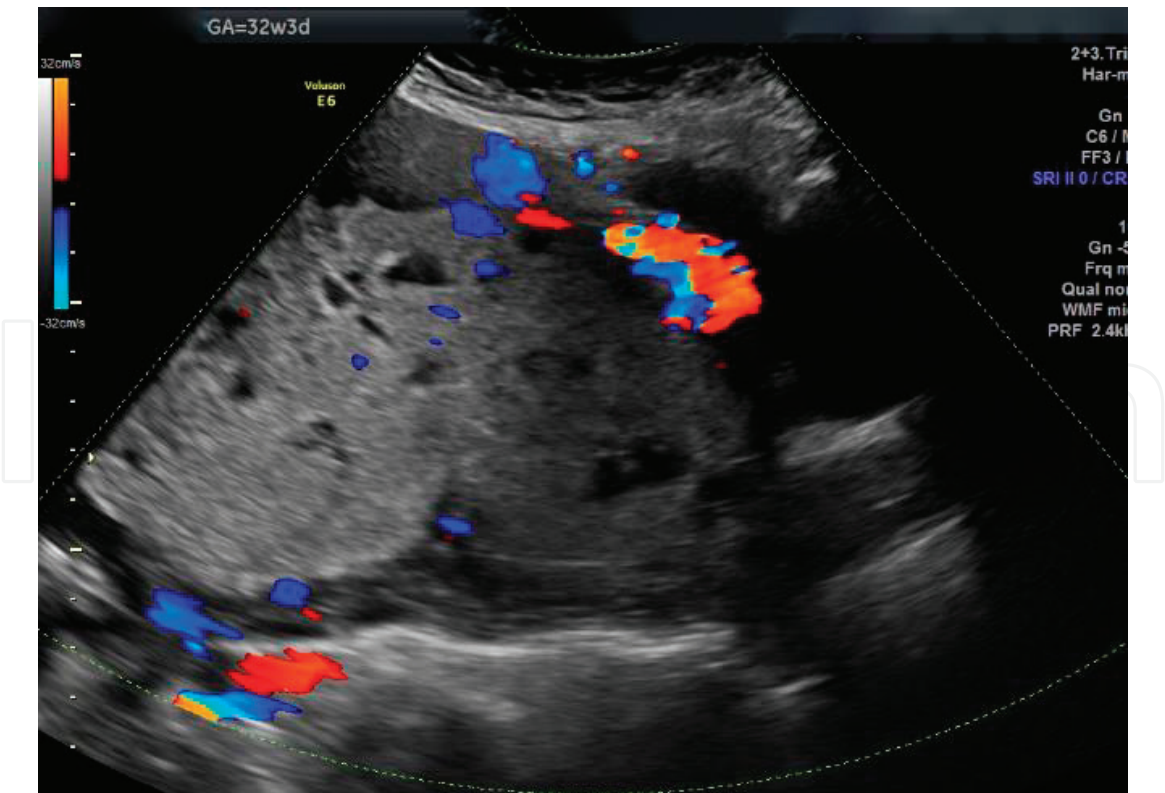
current investigations examining the correlations between in utero conditions on future disease development during childhood and adulthood. Placental organogenesis, development, function, and malfunction remain fields of vast potential research



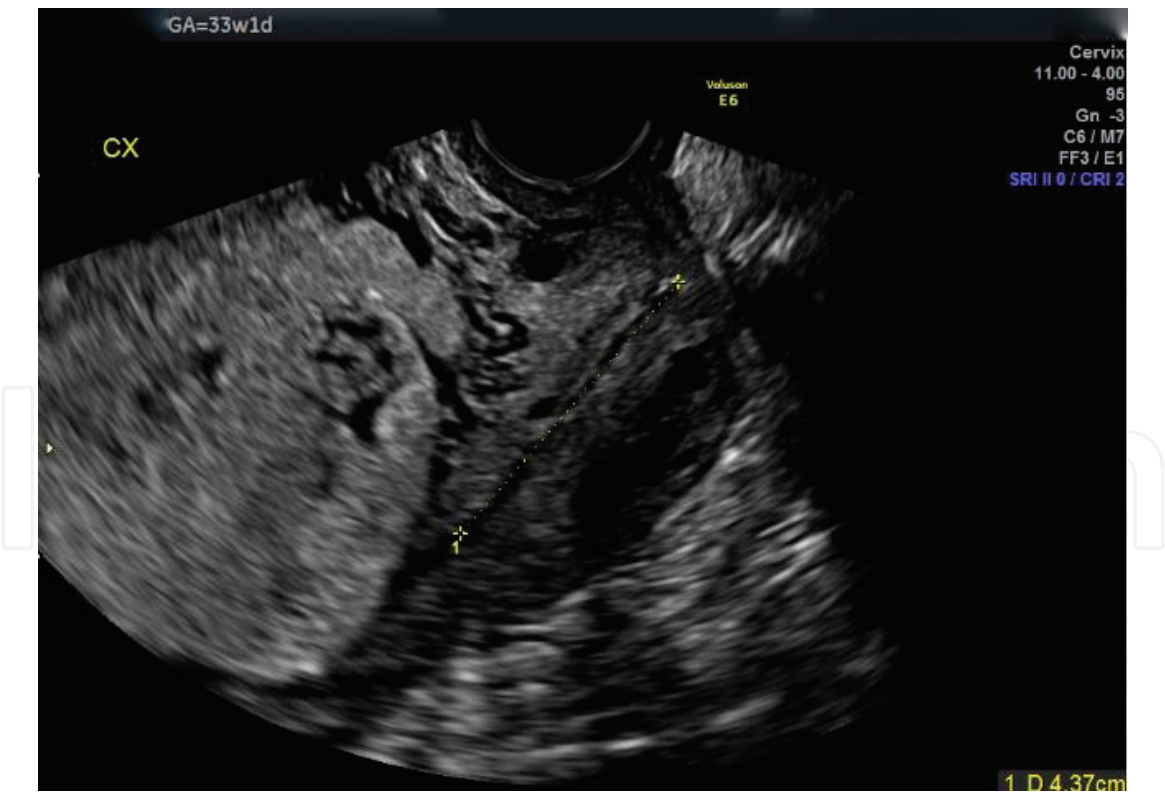
Picture 3.
Placental separation.



Picture 4.
Velamentous cord insertion.



Picture 5.
Placenta previa with placenta percreta invading the bladder.



Picture 6.
Placenta previa with measured Cervical Canal.

that are covered in depth in other chapters in this book. The goal of this chapter is to delineate the real-world implications of placental abnormalities and provide the reader with a basis for understanding the other chapters that delve into microbiology, genomics, immunohistochemistry, and biochemistry of the placenta **Table 1**.

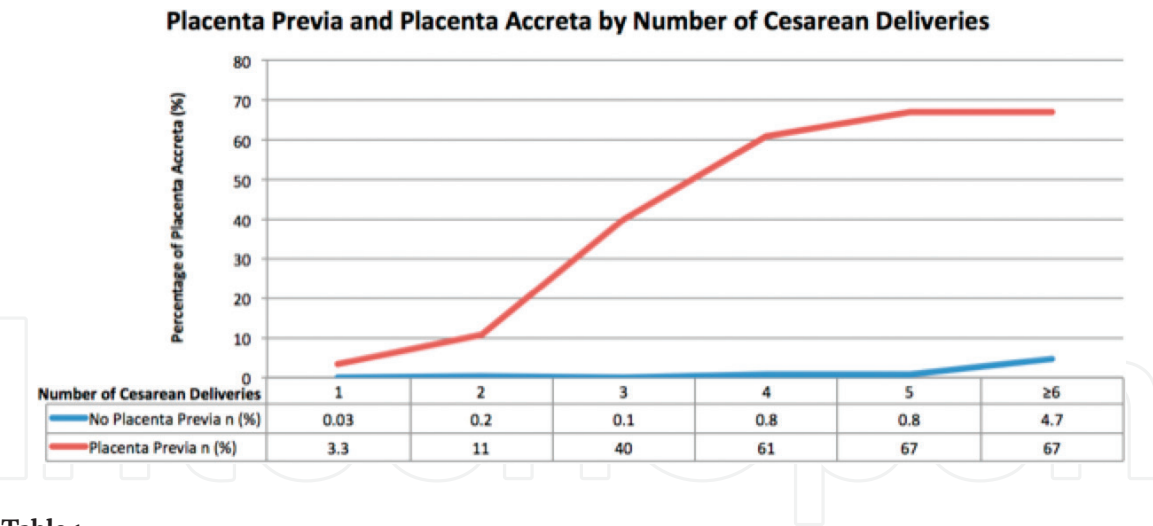


Table 1.
Placenta previa and placenta accreta by number of cesarean deliveries.

2. Part 1: intrinsic placental abnormalities

A. *Amniotic band syndrome (sequence)*—This congenital structural defect can lead to both minor and major malformations via entanglement of fetal structures in constricting rings. The malformations formed depend on the structure(s) entrapped in the band(s), and can range from minor constriction mediated limb abnormalities, amputation of extremities, complex body wall defects, craniofacial defects, and even gross defects non-compatible with life [1, 2]. The presumed etiopathogenesis leading to the clinical presentation of ABS is that mesodermal bands from the chorionic side of the amnion separate during early gestation and become attached to or entrap the embryo or germ disc [2–5]. Then, as the fetus grows, either via tethering bands or mechanical constriction, malformations develop. There is variance in the definition and debate regarding the associated sequences, complexes, and syndromes. When an abnormal band is noted on prenatal ultrasound, the differential diagnosis must include uterine synechiae, a residual gestational sac, and uterine septa. Once these differential diagnoses are ruled out, further investigation must be taken to identify other fetal or placental abnormalities. To date, there are no known biochemical markers or genes to definitively diagnose the syndrome, however, there is an association with chromosomal abnormalities, and therefore the work-up often includes amniocentesis for karyotype as well as single nucleotide polymorphism (SNP) microarray [6–12]. As the presentation and complications are diverse, management depends on individual cases and ranges from expectant management with intervention in the neonatal/pediatric period, to fetoscopic band transection (fetal surgery), and even termination of pregnancy. The wide range of potential malformations has led to the varied terminology frequently found in the literature, which includes but is not limited to: amniotic band syndrome, amniotic band sequence, amniotic deformity, adhesion mutilation (ADAM) sequence, amniotic band disruption complex, limb body wall complex, body wall complex with limb defects [3–5, 11, 13–18]. The confusion upon review of literature regarding the subject is immediately evident when reviewing the nomenclature. Further investigation is needed to determine if the ABS is a spectrum of one pathologic process or rather a collection of differing pathologic processes which result in similar outcomes.

- B. *Bipartite placenta (placenta duplex)*—condition in which the placenta develops into two nearly symmetrical lobes with the umbilical cord insertion inserting between the two lobes. The insertion can either connect with a chorionic bridge or into the membranes (see *velamentous insertion*). A rare condition, placentas with more than two equivalently sized lobes are termed *multilobate*. When a placenta is comprised of two or more unequally sized lobes, the smaller lobe(s) (or *succinturiate lobe*) can develop in the membranes, distal to the primary larger lobe, with connecting vessels running through the membranes in a similar fashion to *velamentous insertion*. The second lobe can sometimes be located quite distant from the main lobe. Placentas with succinturiate lobes are not correlated with adverse fetal effects; it is at the time of labor and delivery that they are subject to the complications. If the succinturiate lobe or connecting vessels are covering the internal cervical os, the risk of vessel avulsion, marginal placental separation, and hemorrhage exist—equivalent to vasa previa and placenta previa. As the succinturiate lobe is often implanted in the membranes, it remains at risk for avulsion and becoming retained at the time of placental removal. This can lead to uterine atony, postpartum hemorrhage, and endometritis.
- C. *Chorioangioma*—a benign tumor of the placenta, found in approximately 1% of all pregnancies, which develops from abnormal proliferation of primitive chorionic vessels [19]. *Chorioangiomas* are typically small masses without clinical consequences, however, large *chorioangiomas*, typically lesions larger than 4 cm, can cause hydramnios, arteriovenous (AV) shunting, and fetal red blood cell (RBC) sequestration. AV shunting and RBC sequestration can lead to fetal anemia, non-immune hydrops fetalis, fetal cardiomyopathy, intrauterine fetal growth restriction (IUGR), and even fetal demise [19–22]. *Chorioangiomas* are diagnosed via ultrasonography as well circumscribed solid or complex masses located on the fetal side of the placenta with turbulent hypervascular flow on Doppler-flow imaging. Management depends on the size of the mass, evidence of hydramnios, and evidence of fetal compromise, with management ranging from amnioreduction, percutaneous intrauterine transfusion, and embolization or laser coagulation of feeding vessels [20–22].
- D. *Circummarginate placenta*—a rare embryologic abnormality in which hemorrhage and fibrin deposition separate the placenta and amniochorion. This condition is more common in multigravidas and has no known clinical significance. In comparison to circumvallate placenta, there is no firm ridge at the edge of the placenta and the margin is thin and flat. It typically is an incidental finding during prenatal ultrasound.
- E. *Circumvallate placentation*—a rare embryologic abnormality in which the chorionic plate is unusually smaller than the basal plate, causing the amniotic membranes to insert medial to the placental edge. On examination, there is a characteristic white ring around the surface of the placental disk that is comprised of a double layer of amnion and chorion with fibrin and necrotic villi. It is predisposed to abnormal separation and commonly presents with 2nd trimester vaginal bleeding, being diagnosed via ultrasound or after delivery [23]. Pregnancy complications are common and include oligohydramnios, small for gestational age (SGA) neonates, abruption, and intrauterine fetal demise (IUFD) [24–26]. Management depends on the individual cases and subsequent maternal and/or fetal complications.
- F. *Four-vessel umbilical cord*—During embryogenesis the umbilicus develops initially with two arteries and two veins. During the 1st trimester one umbilical

vein atrophies and the normal human placenta develops with one large umbilical vein and two smaller umbilical arteries. Four-vessel umbilical cords are rare phenomena in which both umbilical veins and both arteries remain. This condition is associated with congenital anomalies, and when found should prompt further investigation; however, when it is an isolated finding the clinical prognosis is improved [27–29].

- G. *Marginal (battledore) umbilical cord insertion*—This condition is called battledore placenta secondary to the shape of the placenta and cord. In this condition, the cord inserts at the edge of the placenta and gives it the appearance of the racquet used in the precursor game to badminton. Marginal umbilical cord insertions are present in approximately 6.3% of singleton gestations and 10.9% in twin gestations, especially in monochorionic twin gestations [30]. This condition rarely causes complications in singleton gestations prior to the 3rd stage of labor, during which, the marginal cord insertion can be avulsed during placental delivery [31]. In monochorionic twin gestations, a marginal cord insertion may lead to unequal sharing of the placental mass and therefore lead to discordant fetal weight [32].
- H. *Placenta membranacea*—in this rare condition, the chorionic sac is nearly or completely covered by placental villi. The placenta is thin, yet deeply implanted in the endometrium, which places it at risk for forming placenta accreta and previa, with the subsequent sequelae of the aforementioned conditions. Aside from the risks associated with placenta previa and accreta, placenta membranacea is also at risk for recurrent antepartum bleeding, intra-uterine growth retardation (IUGR), miscarriage, preterm labor, intrauterine fetal demise (IUFD), retained placenta after delivery, and postpartum hemorrhage [33–35].
- I. *Single umbilical artery (SUA)*—SUA is an umbilical cord anomaly in which only one umbilical artery develops, and is the most common congenital umbilical cord anomaly. There are currently three proposed mechanisms of action leading to SUA. The first is primary agenesis of one of the umbilical arteries. The second is secondary atresia or atrophy of one artery in a normal three-vessel umbilical cord. The third is persistence of the embryologic single allantoic artery of the body stalk. When a SUA is identified on fetal ultrasonography, further work-up (detailed fetal ultrasonography, fetal echocardiography, and amniocentesis for karyotype) are warranted, as there is an associated high incidence of major chromosomal and congenital anomalies, as well as abnormalities of the renal and cardiac structures [36–41]. SUA is associated with intrauterine growth retardation (IUGR), preterm labor (PTL), small-for-gestational-dates (SGA) neonates, and the aforementioned structural anomalies. Twin gestations are affected in approximately 4–11%, without a difference in incidence between monochorionic and dichorionic twins [42]. When isolated SUA (iSUA) is identified, the fetus usually has normal chromosomes, and routine neonatal examination and care is indicated [43].
- J. *Succinturiate placental lobe(s)*—see *Bipartite placenta* for discussion.
- K. *Vasa previa*—an uncommon condition occurring in an estimated 0.60 per 1000 pregnancies, in which, like to *velamentous umbilical cord*, the vessels pass within the membranes and cross over the internal cervical os [44]. In fact, *vasa previa* is often identified in conjunction with *placenta previa*, a *velamentous cord*, *succinturiate lobes*, and in the setting of in vitro fertilization (IVF). These vessels are also at risk of compression when fetal parts become engaged with the cervix. Equivalent to velamentous insertion, vasa previa is at risk of vessel avulsion

during membrane rupture and cervical dilation. Upon vessel avulsion, the fetus can precipitously exsanguinate, therefore, prenatal diagnosis is paramount in preventing potentially catastrophic peripartum complications [45]. The diagnostic modality of choice is transvaginal ultrasound with Doppler flow [46–48]. When diagnosed in the antepartum period, the preferred method of birth is planned cesarean delivery prior to the onset of labor or rupture of membranes.

- L. *Velamentous insertion of the umbilical cord*—a potentially catastrophic umbilical cord anomaly in which the umbilical vessels separate in the membranes before the cord reaches the chorionic plate. The vessels are not covered by Wharton’s jelly and can therefore be easily compressed, lacerate, and rupture, leading to fetal hemorrhage [46]. The vessels are at greatest risk with rupturing of membranes as the vessels can tear. A common presenting sign is increased vaginal bleeding at the time of spontaneous rupture of membranes (SROM) or artificial rupture of membranes (AROM) [49]. Pregnancies complicated by velamentous insertion of the umbilical cord are associated with increased risk of PPROM, preterm labor, abruption, peripartum non-reassuring fetal heart tracing (NRFHT), cord avulsion requiring manual removal of the placenta, cesarean delivery, and fetal/neonatal death [31, 46, 49, 50]. When diagnosed in the antepartum period, management depends on whether or not the velamentous cord insertion is associated with vasa previa. When it is associated with vasa previa, the preferred method of birth is planned cesarean delivery prior to the onset of labor or rupture of membranes. In the absence of vasa previa, there is currently no evidence that cesarean delivery or induction of labor improve outcomes. As the vessels lack the Wharton’s Jelly found in normal umbilical cords, the vessels are prone to compression and avulsion, therefore laboring patients should have continuous fetal heart rate monitoring to allow prompt diagnosis of fetal distress. Additionally, there is an increased risk of cord avulsion when traction is applied to the umbilical cord in the third stage of labor.

3. Part 2: implantation abnormalities

A. Abnormal implantation

- a. *Ectopic implantation* (ectopic pregnancy) occurs when the blastocyst implants in a site other than the uterine endometrium and is estimated at between 0.5 and 1.5% of all 1st trimester pregnancies in the United States [51, 52]. Ectopic implantation is most common in the fallopian tube (approximately 96% of ectopic pregnancies) [53], but it can occur in the uterine cornua, ovary, cervix, and even parasitically implanting into the intraabdominal organs and vessels [54–58]. Unlike the uterus, structures like the fallopian tube, cervix, cesarean scar, and ovary cannot accommodate a growing fetus, are prone to acute rupture, and the resulting hemorrhage can be life threatening. The current era in medicine, with diagnostic modalities such as ultrasound and Beta-HCG hormone blood and urine level testing, diagnosing ectopic pregnancy rapidly has led to decreased morbidity and mortality. In the United States, the mortality rate from ectopic pregnancy has decreased since the 1980s, with ectopic pregnancy comprising 3% of all cause pregnancy-related deaths in a 2017 study [59, 60]. Risk factors for ectopic pregnancy include history of sexually transmitted or other pelvic infection (such as chlamydia, gonorrhea, pelvic inflammatory disease and tubo-ovarian abscess), prior ectopic pregnancy, tubal surgery, tobacco smoking, pelvic adhesions (e.g., secondary to endometriosis, salpingitis, pelvic abscess, appendicitis), assisted reproductive technology, congenital fallopian tube abnormalities, diethylstilbestrol exposure, and Salpingitis isthmica

nodosa [61–63]. Patient presentation and outcomes depend on the pregnancy location and range from pregnancy failure with reabsorption, to spontaneous abortion, to continued growth leading to surrounding structure rupture and hemorrhage. Management depends on a multitude of factors including the site of implantation, size of the gestational sac or fetus, beta-human chorionic gonadotropin (Beta-HCG) hormone level, and the patient's presenting signs and symptoms and range from expectant management, to intrauterine or systemic methotrexate (MTX), to surgical intervention.

- b. *Placenta previa* is the term when placental implantation is either adjacent to or covering the internal cervical os. The prevalence varies per region, however, has been estimated between approximately 4 and 5.2 per 1000 pregnancies, with the incidence of marginal placenta previas decreasing as gestational age increases (see discussion below for further details) [64, 65]. Further distinction is made between complete coverage of the internal cervical os or *complete placenta previa* versus when the leading edge of the placenta is implanted within less than 2 cm from the internal cervical os or *marginal placenta previa*. The severity of complications varies widely based on the location of the placenta in relation to the cervical os, as well as the degree of placental separation. The location of the placenta over or at the margin of the internal cervical os leads to a predisposition for hemorrhage if cervical dilation occurs as any cervical dilation will expose placental blood vessels, leading to a range from concealed bleeding (i.e., no observed vaginal bleeding) to frank exsanguination. Complications during labor arise from both the placental separation and the structural blockage of fetal expulsion from the uterus by a complete previa. Depending on the placental implantation site, as the uterus grows throughout the gestation, marginal placenta previas, when followed by serial ultrasound examination have a documented tendency to become progressively distanced away from the internal cervical os. However, placenta previa remains at risk of interface separation and subsequent hemorrhage when contractions and/or cervical dilation occur at any time during the pregnancy. The etiopathogenesis of placenta previa remains elucidated, and the two current hypotheses are: 1. Lack of a suitable implantation site in the uterine fundus or corpus. Secondary to uterine trauma from previous surgery (e.g., cesarean deliveries, myomectomies, dilation & curettage) and/or multiple pregnancies, the sites of normal implantation develop areas of suboptimally vascularized uterine decidua, which predispose to implantation of the trophoblast in the lower uterine segments [64]. 2. Large placental surface area, secondary to conditions such as multiple gestations and *placenta membranacea*, increases the probability of the placenta implanting or extending over the internal cervical os. Known major risk factors include: 1. Previous placenta previa, which has a recurrence in 4–8% of future pregnancies [64, 66, 67]. 2. Previous Cesarean deliveries, with a dose–response pattern in the risk of placenta previa, the risk increasing with the number of cesarean deliveries previously performed [68, 69]. 3. Multiple gestations—in a retrospective cohort study that included 67,895 pregnancies, 2.1% of singleton and 2.5% of twin gestations had previa diagnosed. A subgroup analysis demonstrated that dichorionic twin gestations were at an increased risk for ultrasonography-diagnosed previa when compared with monochorionic or single gestations [70]. Minor risk factors include: 1. Increasing maternal age. 2. Increasing parity. 3. Previous non-cesarean delivery surgeries (uterine evacuation, myomectomy, infertility procedures). 4. Drug usage (tobacco smoking and cocaine usage). 5. Non-white race. 6. Male fetus. Management of placenta previa depends on if it is a complete or marginal previa, if there is a suspected concomitant placenta accreta, and then individualized

based on multiple factors: the estimated gestational age (EGA), the distance of the placental edge from the internal cervical os, any evidence of abruption, maternal vaginal bleeding, hemodynamic instability, or evidence of fetal distress. Therefore obstetricians must base management on their assessment of individual cases. An actively bleeding placenta previa is a potential obstetrical emergency, and should be handled as if having the potential for rapid hemorrhage and requirement for massive transfusion of blood products and crystalloid. Upon the onset of labor, if both the mother and fetus are stable, and the placenta is at least 2 cm from the internal cervical os, the patient can safely undergo labor.

- c. *Placenta accreta spectrum (PAS)*—a collection of conditions of abnormal placentation caused by trophoblastic invasion into the myometrial tissue beyond the normal boundary established by the Nitabuch fibrinoid layer. The PAS includes the diagnoses of *placenta accreta*, *inacreta* and *percreta*, with the definitions differing solely based on the depth of invasion of the placenta into the uterus and even beyond the uterus into adjacent structures and organs. Whereas, in normal placentation, placental villi attach to the decidual basalis, microscopic analysis of PAS has demonstrated partial or complete absence of the decidual layer such that the placental villi attach and/or interdigitate with myometrial fibers [71–75]. Mechanical disruption of the endometrial tissue from cesarean deliveries, myomectomies, uterine ablation, dilation and curettage, or endometritis is the current leading hypothesized etiopathogenesis of PAS [71–79]. Investigation is currently underway to identify other factors such as increased growth expression and angiogenesis that may contribute this pathologic process [75, 76, 80]. Physiologically, separation between placental cotyledons and the uterus occurs at the decidual layer, which functions as a cleavage line. In the absence of a decidual layer, separation between the placental cotyledons and the uterine spiral arteries does not occur, and the uterus continues to perfuse the cotyledons, which, in turn, leads to hemorrhage [77]. The current estimated incidence of PAS is 3.0 per 1000 pregnancies [81]. Secondary to the rise in frequency of operative procedures (specifically cesarean deliveries, with an estimated incidence increasing from 12.5% in 1982 to 32.2% in 2014 [78, 81]), there was a concomitant estimated increase in PAS of 0.8 per 1000 deliveries during the 1980s to the current estimate of 3.0 per 1000 pregnancies [78, 81–86]. Undiagnosed PAS can lead to massive intrapartum and postpartum hemorrhage, consumptive coagulopathy, disseminated intravascular coagulopathy, hypovolemic shock, and maternal mortality [71, 79, 87, 88]. The importance of antepartum placental analysis has been well established, and the individual practitioner must have a high index of suspicion at the time of delivery [89]. US and magnetic resonance imaging (MRI) are the diagnostic modalities most frequently used [90–93]. Identification of placental invasion of the myometrium can be made with US, with a positive predictive value (PPV) of 68%, a negative predictive value (NPV) of 98%, and a sensitivity of 89.5% [90]; with MRI, the sensitivity is 88%, specificity is 100%, PPV is 100%, and NPV is 82% [91]. Establishing a suspected diagnosis of PAS before delivery allows for a scheduled delivery and pre-operative planning with a multidisciplinary team based on the severity of the PAS. This can include consultation with a Maternal-Fetal Medicine specialists, gynecologic-oncologists, general surgeons, urologists, vascular surgeons, anesthesiologists, neonatologists, intensive care specialists, interventional radiologists, blood bank personnel, and nursing staff. There currently is inconclusive evidence for improved outcomes with pre-delivery placement of ureteral stents or internal iliac artery occlusive devices. Management of PAS varies as widely as the degree of abnormal placentation. Case by case

management depends on whether or not it was identified before delivery, estimated gestational age (EGA), maternal factors (co-morbidities, previous surgery, status of labor), the size of the morbidly adherent placenta, the hemorrhage encountered, structures invaded by the placenta, adhesions, parity, presence of placenta previa, and other individualized factors. No randomized controlled trials (RCT) exist to guide management; therefore management varies between institutions and practitioners. The definitive treatment for PAS is cesarean-hysterectomy; however, experimental modalities aimed at uterine conservation have included leaving the placenta en situ followed by hypogastric artery ligation, uterine artery embolization, compression sutures, intrauterine balloon tamponade, and adjuvant methotrexate [94]. It should be noted that these experimental methods remain at risk for hemorrhage and delayed hysterectomy. It is the opinion of both the American College of Obstetricians and Gynecologists (Committee Opinion No. 529) as well as this author, that cases should be individualized, but “the recommended management of suspected placenta accreta is planned preterm cesarean hysterectomy with the placenta left in situ.” [95] If the practitioner believes that adequate care cannot be administered, then transfer of care to a tertiary care center, specifically a center of excellence for PAS, is recommended.

- d. *Cervical ectopic pregnancy* is a rare phenomenon, estimated at <1% of all ectopic pregnancies [57], while *cervical placenta accreta* is an even rarer condition. In contrast to the endometrium, the cervix does not contain a decidual layer; therefore, it is hypothesized that pathogenesis of cervical accretas is attributable to direct damage from cervical instrumentation during in vitro fertilization, intrauterine device placement, dilation and curettage, cesarean delivery, and previous cervical and/or uterine surgery [96, 97]. While diagnosis of a cervical ectopic pregnancy is made via ultrasound, cervical placenta accreta is a pathologic diagnosis made after surgical procedures such as trachelectomy and hysterectomy. Therefore, management is that of a cervical ectopic pregnancy. Ultrasound has allowed for early diagnosis and attempts at preservation of reproductive capacity via intragestational potassium chloride or methotrexate (MTX), local or systemic MTX, and/or uterine and hypogastric artery embolization [57, 96, 97]. However, when conservative measures fail in the acute scenario, the conventional gold standard remains total abdominal hysterectomy (TAH) [98].

B. Abnormal cytotrophoblastic invasion

- a. Implantation of the blastocyst into the endometrium occurs between days 6 and 7 after fertilization and is a highly regulated process that occurs in three phases: 1. Apposition, or initial contact of the blastocyst with the endometrium; 2. Adhesion, or adhesion between the blastocyst and decidua, and; 3. Invasion, or continued penetration into and invasion of the decidua by the syncytiotrophoblast and cytotrophoblasts, down to the inner third of the myometrium, followed by union with the uterine vasculature. Studies are currently underway to identify the exact pathways and mechanisms by which the blastocyst, like a neoplasm, invades the decidua, inner third of the myometrium, and stimulates local angiogenesis to promote its own growth [99, 100]. Unlocking this complex process has enormous potential for the fields of oncology and reproductive endocrinology [101]. Investigation into the three phases of implantation have identified numerous growth factors [e.g., vascular endothelial growth factor (VEGF), placental growth factor (PlGF), transforming growth factor-B1 (TGF-B1)], angiogenic factors, adhesion molecules, cytokines, interleukins, receptors, transcription factors,

and associated pathways [102–105]. For example, adhesion of the blastocyst to the endometrium depends on hormonally mediated Integrins, one of the four classes of cell receptors termed cellular adhesion molecules (CAMs) [106–108]. The mechanisms of impaired trophoblast migration are also currently being elucidated, and are associated with local placental hypoxia and abnormal placental growth factors, including placental growth factor (PlGF), hypoxia inducible factor (HIF), tyrosine kinase 1 (sFlt1), and reactive oxygen species [109–111]. Defective implantation and placentation clinically leads to recurrent spontaneous abortion, PPROM, IUGR, and preterm labor [112]. Inadequate or absence of secondary invasion of the endovascular trophoblast into the maternal spiral arteries of the myometrial layers during weeks 15 to 22 of gestation is associated with maternal chronic hypertension (CHTN), preeclampsia, and diabetes [112, 113].

4. Part 3: processes affecting placental perfusion

A. Abnormal placental separation

- a. The author acknowledges that there are various medical conditions and mechanisms of action (such as trauma and hypertension) that can lead to abnormal placental separation, however, this topic is included in this chapter as current investigation is underway correlating genetics and characteristics of certain placentas to a predisposition for abnormal placental separation. The pathways and cascades that interact to prevent or promote separation and rupture of membranes include cytokines, transcription factors, thrombin, matrix metalloproteinases (MMP), prostaglandins, hormones, collagen, proteoglycans, and fetal fibronectin (FFN) [114–116].
- b. *Chorionic hematoma*—a hematoma (collection of blood) between the chorion and the uterine wall. It occurs in an estimated 3.1% of all pregnancies and typically presents with first trimester vaginal bleeding, and is associated with spontaneous abortion when occurring in the first trimester [117]. Sonographically, hematomas appear as hypoechoic crescents with location depending on the type. Chorionic hematomas may mimic a thickened placenta because the hematoma is often isoechoic to the placenta; however, on color Doppler ultrasound there is the absence of internal blood flow. Three types exist:
 - i. *Subchorionic hematoma*—the partial detachment of the chorionic membranes from the endometrium due to mass effect by a hematoma. It is the most common form.
 - ii. *Subamniotic (preplacental) hematoma*—a rare form of hematoma that is contained within the amnion and chorion.
 - iii. *Retroplacental hematomas*—complete or partial detachment of the placenta from the uterine wall with a hematoma confined behind the placenta. When the Large hematomas can decrease trans-placental perfusion and lead to intrauterine growth retardation (IUGR) and oligohydramnios [118].
- c. *Placental abruption*—Abnormal placental separation, termed abruption placentae or placental abruption, is defined as the complete or partial separation of a normally implanted placenta from the uterine wall after 20 weeks of gestation,

but before delivery of the fetus. This condition affects an estimated 1 in every 100–120 pregnancies and typically presents after 20 week of gestation; however, the gestational age-specific incidences depend on the underlying etiopathogenesis of individual cases [44, 119–121]. Placental abruption is a clinical diagnosis, and even with prompt diagnosis, the maternal and fetal morbidity and mortality can be devastating. The presentation varies from the classic scenario of post-mechanical event (such as trauma) acute-onset painful life-threatening obstetrical hemorrhage with associated fetal distress noted on external fetal monitoring to incidentally identify painless concealed focal retroplacental hematomas with intraplacental anechoic areas to chronic painless vaginal bleeding [122–124]. It should be noted that ultrasound has a low sensitivity for diagnosing abruption, and therefore diagnosis should be based on clinical suspicion. Known risk factors include trauma, hypertensive disorders, preterm premature rupture of membranes (PPROM), subchorionic hematomas, and cocaine [123, 125, 126]. Management is individualized to the degree and severity of individual cases, ranging from emergent cesarean delivery for acute complete abruptions to serial surveillance and expectant management for contained retroplacental hematomas. While management of acute abruptions is part of the standard training for obstetricians, the individualized management of chronic and/or partial abruptions without evidence of fetal compromise or maternal instability is a less defined arena which must take account maternal factors (such as medical co-morbidities, hemoglobin and hematocrit level, blood type, evidence of coagulopathy, Bishop score, and patient reliability for close surveillance) as well as fetal considerations (such as gestational age, viability, fetal presentation, complications, estimated fetal weight, chorionicity, practitioners experience). It is a scenario that often leads to consultation with Maternal-Fetal Medicine specialists for assistance and guidance. The mechanical separation at the maternal-fetal interface can decrease the placental perfusion in a fashion similar to placental infarcts and acute atherosclerosis of the spiral arteries (please see the relevant sections of this chapter) and can lead to fetal acidemia, intrauterine fetal growth restriction (IUGR), small for gestational age (SGA) neonates, chronic abruption-oligohydramnios sequence, and preeclampsia [127–129]. Abruptions with large volume hemorrhage can lead to cardiovascular compromise, disseminated intravascular coagulation (DIC), and both fetal and maternal mortality. Patients with a history of one previous placental abruption are at 3–15% risk of future abruption, and women with a history of two previous abruptions are between 20 and 25% risk of repeat abruption [44, 130–133]. Research focused on preventing placental and maternal interface infarcts is currently active with small randomized controlled trials (RCTs) demonstrating a protective effect with anticoagulants administered in a subcuticular manner [134].

5. Conclusions

The placenta is an indispensable, yet temporary, organ of the developing human that we are rapidly improving our knowledge of via scientific investigation. Clinical correlates of placental abnormalities and malfunction are a common occurrence at prenatal testing centers and on the labor and delivery wards throughout the world. Placental abnormalities can lead to adverse fetal outcomes such as SGA/IUGR, discordant growth in twins, preterm birth, IUFD as well as maternal adverse outcomes such as hemorrhage requiring blood transfusion, surgery for retained products of conception, hysterectomy, and even mortality. When diagnosed in the antepartum or peripartum period, practitioners must take into account minimizing adverse consequences to both the fetus/neonate as well as the mother. Neonatal outcomes

vary as widely as the placental pathology outlined in this chapter and depend both on the EGA at diagnosis, severity of the pathology, duration, fetal attributes, as well as peripartum events.

Through the course of this chapter intrinsic and extrinsic placental abnormalities and their clinical correlates have been described. Hopefully, this chapter provided you with an overview of the complex processes of abnormal placentation in relation to real-world outcomes, and will allow you to better understand the following chapters in this book.

Acknowledgements

The author would like to thank the contributions of Rosa Montoya, RN, as well as the indispensable tutelage and mentorship of Martin Gimovsky, MD and Munir Nazir, MD. Writing this book chapter would not have been possible without their prior and continued support, guidance, and love of medicine.

Conflict of interest

The author denies any conflicts of interest associated with this publication.

Future investigation

As medical practitioners, our current prenatal toolkit for treating placental malfunctions is limited, with the main tool being increased fetal surveillance, and when things go awry, the definitive intervention is delivery of the fetus. Until more is known regarding placental pathology and we develop methods for preventing, modifying, treating, or possibly even reversing the pathology, then expedited, and often preterm, delivery with its associated sequelae remains our principal method of therapy. Scientific investigation carries on at a fevered pace, with new findings piecing together the complex biological nature of this fascinating organ. It is this author's hope that during his lifetime, new insights into the placenta on molecular, genetic, physiologic, anatomic, and clinical levels will lead to fetal interventions which thereby decrease the iatrogenic preterm birth rate, and will permit affected pregnancies to progress closer to term in their natural environment.

Appendices and nomenclature

ADAM	amniotic deformity adhesion mutilation sequence
AROM	artificial rupture of membranes
CAM	cellular adhesion molecule
CHTN	chronic hypertension
DIC	disseminated intravascular coagulation
EFW	estimated fetal weight
EGA	estimated gestational age
FFN	fetal fibronectin
HIF	hypoxia inducible factor
IUFD	intrauterine fetal demise
IUGR	intrauterine growth retardation
IVF	in vitro fertilization

MMP	matrix metalloproteinase
MTX	methotrexate
NPV	negative predictive value
NRFHT	non-reassuring fetal heart tracing
PAS	placenta accreta sequence
PIGF	placental growth factor
PPROM	preterm premature rupture of membranes
PPV	positive predictive value
PTL	preterm labor
RCT	randomized controlled trial
sFlt1	soluble FMS-like tyrosine kinase 1
SGA	small for gestational age
SUA	single umbilical artery
iSUA	isolated single uterine artery
SNP	single nucleotide polymorphism
SROM	spontaneous rupture of membranes
TAH	total abdominal hysterectomy
TGF-B1	transforming growth factor-B1
VEGF	vascular endothelial growth factor

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