ISSN: 2641-6247
DOI: 10.33552/WJGWH.2021.05.000608
World Journal of Gynecology & Women's Health
Iris Publishers

Review Article

Common Placental Abnormalities Review

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Received Date: July 26, 2021

Published Date: September 03, 2021

Introduction

The placenta is comprised of specialized epithelial cell types, collectively referred to as trophoblast cells, situated among mesenchymal cells and vasculature, at the maternal-fetal interface. Trophoblast stem and progenitor cell populations give rise to specialized trophoblast cell lineages these cells differentiate into trophoblast giant cells, spongiotrophoblast cells, glycogen trophoblast cells, invasive trophoblast cells, and syncytiotrophoblast.

Trophoblast cells are specialized cell types capable of accessing and modifying maternal structures and controlling the bidirectional flow of nutrients and wastes. In humans a hemochorial placenta is formed. This form of placenta is characterized by a limited cellular barrier for maternal-fetal delivery of nutrients and extensive intrauterine trophoblast cell invasion and uterine arterial remodeling.

Although gross inspection and histopathology as well as various chromosome and molecular studies are needed for ultimate diagnosis, ultrasonography is the definitive prenatal modality for evaluating the majority of these conditions.

This manuscript provides an overview of common abnormalities of the human hemochorial placenta with its determination of maternal and fetal health as well as postnatal health and susceptibility to disease.

Placental Structural Variants

Structural placental variants are relatively common and can be diagnosed using ultrasound. Not all forms are known to result in risk for maternal or fetal complications.

Bilobed placenta is a placenta composed of two roughly equal-sized lobes separated by a membrane. It occurs in 2% to 8% of placentas. The umbilical cord may insert in either lobe, in velamentous fashion, or in between the lobes. While there is no increased risk of fetal anomalies with this abnormality, bilobed placentas can be associated with retained placental tissue.

Succenturiate placenta is a condition in which one or more accessory lobes develop in the membranes apart from the main placental body to which vessels of fetal origin usually connect them. The vessels are supported only by communicating membranes. If the communicating membranes do not have vessels, it is called placenta supuria. Advanced maternal age and in vitro fertilization are known risk factors for the succenturiate placenta.

Circumvallate placenta is an extrachorial, annularly-shaped placenta with raised edges composed of a double fold of chorion, amnion, degenerated decidua, and fibrin deposits. In this condition, the chorionic plate is smaller than the basal plate, resulting in hematoma retention in the placental margin. It is associated with increased risk of vaginal bleeding beginning in the first trimester, premature rupture of the membranes (PROM), preterm delivery, and placental abruption.

Circummarginate placenta is an extrachorial placenta similar to a circumvallate placenta except that the transition from membranous to villous chorion is flat. This form is clinically insignificant.

Placenta membranacea is a rare placental abnormality where chorionic villi cover fetal membranes either completely (diffuse placenta membranacea) or partially (partial placenta membranacea), and the placenta develops as a thin structure occupying the entire periphery of the chorion.

Battledore Placenta is a term describing a placenta where the umbilical cord is attached at the margin. It occurs in 7- 8% in singleton pregnancies and 24-28% in twin pregnancies and may affect placental function/fetal growth.

Abnormal Placental or Cord Location

Placental location can be confidently established by abdominal and transvaginal ultrasound studies. Low-lying placentation, present in up to 60% of early second trimester studies, persists as placenta previa in only 1% to 2% of patients at term. Fetal vessels near the cervix can be visualized using color Doppler, facilitating the diagnosis of funic (umbilical cord) presentation and vasa previa (fetal vessels overlying the os). Normally inserted centrally in the placenta, the umbilical cord may later, as a result of asymmetric placental growth, be located marginally or even on adjacent membranes; in the latter position, traumatic lacerations, hemorrhage and compression-linked heart rate changes are potential consequences.

Morbidly Adherent Placenta (MAP)

Morbidly adherent placenta (MAP) or placenta accreta spectrum (PAS) encompasses the histopathological diagnoses of placenta accreta (a small focus or more generalized muscular invasion), placenta increta (deeper myometrial invasion up to the uterine serosal layer) and placenta percreta (through the serosa to adjacent visceral or vascular structures) [1-3]. It is potentially life threatening, as forced removal of an abnormally invasive placenta can lead to catastrophic maternal hemorrhage; management of all but the most circumscribed lesions usually require hysterectomy.

PAS was previously diagnosed only when failed attempts to remove the placenta were followed by massive bleeding. Improvements in antenatal diagnosis enabled reductions in maternal mortality and morbidity by allowing planned cesarean delivery at 34-35 weeks by experienced multidisciplinary teams [1]. Placental accretion is significantly more likely in women with the combination of placenta previa and a history of one or more cesarean sections, after myomectomy or curettage, and with high parity [1]. The frequency of accretion, now complicating 1/2,500 deliveries, has increased more than 10-fold in the past 20 years, echoing rising cesarean rates [1].

Sonographic criteria for placenta accreta were developed using conventional gray-scale, 2D and 3D color and power Doppler transabdominal and transvaginal ultrasonography in high-risk women. In the early first trimester between 6- 9 weeks, ultrasound markers of PAS include low implantation of the gestational sac and cesarean scar pregnancy [4]. Studies show that most PAS cases have a low implantation in the early first trimester scans; however, low implantation is noted in only 28 percent in the late first trimester [4]. In addition, elevated maternal serum levels of PAPP-A in the first trimester has been linked to risk for placental accretion [3]. A cesarean scar pregnancy (CSP) is diagnosed if the chorionic sac is adjacent to or embedded in the scar of a previous cesarean delivery, in close proximity to the bladder, wedged in a niche, and demonstrates extensive vascularization or an arteriovenous malformation. CSP is considered as a precursor of PAS, as histopathology of both appear indistinguishable [5]. The implantation in the niche rather than the scar, and a thin remaining myometrium may be helpful to define cases that will evolve into the most severe types of PAS [6].

In the late first, second, and third trimester, the sonographic characteristics of PAS are lacunae (multiple large sonolucent spaces in the placenta), abnormal uteroplacental interface (described as loss/irregularity of the echo-free "clear space" between the uterus and the placental basal plate, myometrial thinning, or increased vascularity on Doppler), abnormal uterovesical interface (bridging vessels extending from the placenta across the myometrium and/or beyond the serosa, increased vascularity between the uterus and bladder, and interruption of the bladder wall), placental bulge and exophytic mass (diagnostic for placenta percreta)7. Among these markers, loss of the clear zone performs best with a sensitivity of 84 % and a specificity of 82 % with a diagnostic odds ratio of 24 in the late first trimester, i.e., at 11-14 weeks [7]. Coexisting markers such as lacunae or bladder wall interruption increases the diagnostic performance7. In the second and third trimester, the presence of large multiple lacunae (>3) with irregular borders and high turbulent flow is the most sensitive marker with a negative predictive value of 88% to 100%. The presence of an exophytic mass or placental bulge increases the risk for deep invasion, i.e., increata or percreta [4]. In a recent study the European Working Group on Abnormally Invasive Placenta, the researchers have suggested a total of 10 sonographic finding detected by 2D grayscale and color Doppler study to be very helpful in diagnosing abnormally invasive placenta45.Combined sonographic markers perform the best with 81% sensitivity and 98.9% specificity with a PPV of 91% and NPV of 98% [8].

Antepartum diagnosis of abnormal placental attachment permits multidisciplinary planning for prematurity management, anesthesia, transfusion, hemostatic and uterotonic medications, balloon tamponade, arterial embolization, or scheduled preterm (around 34-35 weeks) cesarean-hysterectomy prior to onset of labor1. MRI mapping is most helpful when there is posterior placentation, suspected lateral extension, after myomectomies, for evaluation of adjacent viscera with percreta or when ultrasound findings are ambiguous [9].

Placental Abruption

Placental abruption is defined as complete or partial separation of the placenta from the myometrium that presents with hemorrhage in the retroplacental, subchorionic or placental chorionic space on ultrasound. Most patients have pain and bleeding except for rare cases of concealed abruption. The diagnosis of placental abruption remains a clinical one due to low diagnostic sensitivity of ultrasound. The role of imaging in this disorder is to exclude placenta previa and other sources of bleeding. One series reported 24% sensitivity and 53% negative predictive value for ultrasound diagnosis of abruption [10]. However, positive ultrasound findings indicated severe abruption and were associated with need for aggressive management and increased risk of adverse outcome [10]. Subchorionic hematomas are often noted on transvaginal scans early in gestation; symptomaticity, size, and persistence have been traditionally linked to poorer outcomes such as abortion, stillbirth, preterm delivery and preterm membrane rupture [11]. On the contrary, two recent studies reported that subchorionic hematomas were not independent risk factors for adverse outcome when controlled for maternal risk factors, vaginal bleeding, and gestational age [12,13]. Later placental abruptions are more difficult to visualize; acute bleeding is isoechoic with placenta and can be

mistaken for placentomegaly. Hypoechoic fluid collections and hyperechoic infarcted areas appear in more chronic presentations. Abruption can accompany fetal growth restriction and can present with Breus' mole characterized as a massive subchorionic collection on the chorionic side of the placenta [14].

Abnormal Placental Location

Placenta previa is defined as placenta overlying the internal os. In the second trimester, placenta previa or a low-lying placenta with the inferior edge 2cm from the internal os is seen frequently, approximately in 5-20% of the ultrasound studies [15]. The prevalence decreases to 0.3-0.5% at term [15]. A posterior low-positioned placenta is more likely to persist into the third trimester [15]. Transvaginal ultrasound is superior to transabdominal approach and is safe for evaluation of placenta previa. A persistent low-lying placenta or placenta previa is an indication for cesarean delivery and follow up scans are recommended at 32 weeks and 36 weeks for delivery planning [16].

Vasa Previa

Vasa previa is characterized by the presence of unprotected fetal blood vessels by the umbilical cord or placenta over the cervical os or within 2cm from the cervical os. It complicates 1 in 2500 deliveries. Membrane rupture prior to or labor can lead to fetal hemorrhage, exsanguination, and death and sequela in survivors [17]. Prenatal identification prior to onset of labor or rupture of membranes improves survival to 98.6% from 72% and intact survival to 96.7% from 28.1% [17]. Ultrasound study typically shows fetal vessels over the cervical os that appears like bubbles or lines on gray scale. Fetal arterial waveforms can be confirmed by Doppler. Vessels with venous flow should be followed to their origin if possible to differentiate maternal vessels. Low-lying placenta, resolved placenta previa, velamentous cord insertion, accessory lobes, bilobed placenta, multiple pregnancies, and artificial reproductive therapy increase the risk of vasa previa. In these cases, consideration should be given to rule out vasa previa, preferably by transvaginal imaging [18].

Placental Cystic Structures

Placental lakes are hypoechoic spaces with slow venous flow and are benign findings; however, they need to be differentiated from retroplacental or subchorionic hemorrhage. Despite their ominous appearance they are not associated with maternal of fetal morbidity.

Partial or complete mole in the first trimester, placenta accreta spectrum, mesenchymal dysplasia, chorioangioma and confined placental mosaicism can present with cystic spaces in the placenta [19].

Chorangioma usually presents as a solitary nodule or, less frequently, as multiple nodules. Its frequency is about 1%, even though literature reports vary [20]. It is a benign, biologically indolent neoplasm, frequently referred to as placental hemangioma or haemangioblastoma. It is found on the fetal surface of the placenta or in placental parenchyma. Most chorangiomas are small and possess no clinical significance. On the contrary, clinically significant chorangiomas, greater than 5cm or multiple chorangiomas, may be associated with pregnancy complications.

Chorangioma is a nontrophoblastic tumor characterized by abnormal vascular development within the placental parenchyma, which is most frequently observed in the third, and less frequently in the second trimester of pregnancy [20]. It is usually an incidental microscopic finding. Even though it has no fibrous capsule, it is sharply demarcated from the surrounding placental parenchyma by a single or, less frequently, double layer of chorionic epithelium. It is most frequently found on the fetal surface of the placenta, often in the vicinity of the umbilical cord insertion, with larger tumors being usually attached to the chorion. On gross examination, it is well-circumscribed, with fleshy, congested, red to tan cut surface. It is microscopically composed of numerous proliferative blood vessels in various stages of differentiation, from capillary to cavernous [20].

Clinically significant chorangiomas, greater than 5cm or multiple, may be associated with fetal hydramnios, hemorrhage, premature delivery, premature placental separation and placenta previa [20]. These manifestations may result in severe fetal distress and intrauterine death. They may also lead to nonimmune hydrops fetalis. Anemia, thrombocytopenia or congestive cardiac failure may be seen in a neonate.

Differential diagnosis of chorangioma includes chorangiosis and chorangiomatosis, that presents as diffuse or more often a focal proliferation of villous angioblastema with villi that are not present in chorangioma21. Chorangiosis is a proliferation of capillaries in terminal chorionic villi and is considered to be a marker for hypoxia and poor clinical outcome. Focal chorangiosis is associated with a decrease in Apgar scores, increased placental weight, fetal vascular thrombosis (fetal vascular malperfusion), umbilical cord abnormalities, increased fetal nucleated red blood cells, and villous dysmaturity [21].

The hallmark of diffuse chorangiomatosis is capillary dysvasculogenesis, diffusely involving the placenta causing massive placental enlargement. It has been associated with fetal cardiomegaly, microangiopathic hemolytic anemia and thrombocytopenia [22].

Placental Viral and Parasitic Villitis

Chronic inflammatory lesions of the placenta are characterized by the infiltration of the organ by lymphocytes, plasma cells, and/or macrophages and may result from infections (viral, bacterial, parasitic) or be of immune origin (maternal anti-fetal rejection) [23]. The 3 major lesions are villitis (when the inflammatory process affects the villous tree), chronic chorioamnionitis (which affects the chorioamniotic membranes), and chronic deciduitis (which involves the decidua basalis). Maternal cellular infiltration is a common feature of the lesions. Villitis of unknown etiology (VUE) is a destructive villous inflammatory lesion that is characterized by the infiltration of maternal T cells (CD8+ cytotoxic T cells) into chorionic villi [23].

Chronic placental inflammatory lesions can be due to maternal anti-fetal rejection, a process associated with the development of a novel form of fetal systemic inflammatory response. The syndrome

is characterized by an elevation of the fetal plasma T-cell chemokine [23].

Recently Shanes, et al. have reported on placental pathology from 16 patients with COVID-19 infection [24]. No pathognomonic features were identified; however, there were increased rates of maternal vascular malperfusion features and intervillous thrombi, suggesting a common theme of abnormal maternal circulation, as well as an increased incidence of chorangiosis. These findings provide mechanistic insight into the observed epidemiologic associations between COVID-19 in pregnancy and adverse perinatal outcomes. Collectively, these findings suggest that increased antenatal surveillance for women diagnosed with SARS-CoV-2 may be warranted [24].

Placental Vascular Malperfusion

Fetal vascular malperfusion is the most recent term applied to a group of placental lesions indicating reduced or absent perfusion of the villous parenchyma by the fetus. The most common etiology of malperfusion is umbilical cord obstruction leading to stasis, ischemia, and in some cases thrombosis [25]. Other contributing factors may include maternal diabetes, fetal cardiac insufficiency or hyper viscosity, and inherited or acquired thrombophilia. Severe or high grade fetal vascular malperfusion is an important risk factor for adverse pregnancy outcomes including fetal growth restriction, fetal CNS injury, and stillbirth. Overall recurrence risk for subsequent pregnancies is low [25].

Placental Mesenchymal Dysplasia

Placental mesenchymal dysplasia (PMD) is a rare placental abnormality/condition of as yet undetermined etiology with an incidence of about 0.02 per 1000 deliveries [26].

PMD can be associated with fetal Beckwith-Wiedemann syndrome (BWS), fetal tumors of various organs, fetal growth restriction as well as intrauterine and neonatal death [27].

Although placental PMD related cystic changes may be seen as early as 8 weeks PMD cases are typically detected in the early second trimester once the placental cysts progressively enlarge, becoming more numerous and complex as gestation proceeds.

PMD is characterized by multiple hypoechoic vesicles which are similar to molar changes in the placenta. A characteristic feature of PMD is varicose dilation of chorionic vessels. Gradual reduction in size of PMD's placental vesicular lesions by serial study of placental images has been reported. In contrast, dilated placental vessels on the fetal side became apparent at 38 weeks [28].

Based on similar sonographic findings of enlarged, and thickened placenta with cystic spaces, PMD is most often mistaken for molar pregnancy, chorioangioma, complete mole with coexisting normal fetus, subchorionic hematoma, spontaneous abortion with hydropic changes and partial hydatidiform mole [29].

It is of utmost importance to realize that sonographic findings indicative of PMD warrant careful evaluation of the fetus and placenta to rule out the presence of polyhydramnios, placentomegaly, macrosomia, macroglossia, omphalocele, visceromegaly, hemi hypertrophy, as well as fetal hepatic and lung mesenchymal tumor [30,31].

Maternal serum analysis might be somewhat helpful in differentiating PMD from other forms of cystic placentas. PMD is more likely to be associated with elevated maternal serum AFP levels [32].

Androgenetic-biparental mosaicism (ABM), in which a subset of cells in the placenta are diploid but harbor only paternal chromosomes, has been the most consistent molecular alteration observed in PMD. The androgenetic cells in ABM have pan-genomic paternal uniparental disomy (paternal alleles and imprinting at all loci), and detection of allelic imbalances consistent with ABM is considered confirmatory evidence for the diagnosis of PMD [33]. In addition to ABM, some cases of PMD may result from a mosaic distribution of placental cells with segmental forms of uniparental disomy, possibly restricted to the BWS locus on chromosome 11p15.5 [34].

Hydatidiform Moles

Hydatidiform moles are divided into complete and partial hydatidiform moles. These are genetically different lesions, with complete moles usually comprised of a diploid complement, both paternally derived, while partial moles are diandric triploids in most cases. Digynic triploids are not moles. Rarely, complete moles may be biparental, in familial complete moles, associated with mutations of the NLRP7 gene. Genetic variations from the usual chromosomal complements seen in molar disease have been reported. Recognizing moles and distinguishing complete from partial moles is important due to differing risk of persistent trophoblastic disease, which is considerably greater after a complete mole (15–20%) than a partial mole (<5%). Recurrence rates of moles in future pregnancies are the same (1-2%) [35].

The risk of developing choriocarcinoma following complete moles is approximately 2% to 3%. There is a rather low but finite risk (0.1%–0.5%) of developing choriocarcinoma after partial moles [36]. Uterine bleeding is the most common symptom, but extra uterine hemorrhagic events may be the first presentation in a patient with extra uterine spread: lung, liver, central nervous system, and gastrointestinal tract [37]. High levels of serum human chorionic gonadotropin (hCG) are invariably present in all patients. The diagnosis of post molar choriocarcinoma is made in an average of 13 months (range, 1–48 months) after the evacuation of hydatidiform mole. In most patients with choriocarcinoma following term delivery, the pathologic diagnosis is made 1 to 3 months after delivery [38].

Confined Placental Mosaicism

Confined placental mosaicism (CPM) is defined as the presence of chromosomal abnormalities in the extra-embryonic tissue which are absent from the fetal tissue. These chromosomal abnormalities are observed in about 1 to 2% of chorionic villus samplings (CVS) carried out for prenatal diagnosis between the 9th and 12th weeks of amenorrhea [39]. Once identified, CPM can be classified into three subtypes (types 1, 2 and 3 CPM) according to the placental localization of the chromosomal abnormality [40]. In type 1 CPM (CPM1), the chromosomal abnormality is found exclusively in the

cytotrophoblast (i.e. the chromosomal abnormality is observed only after examination of short-term culture villi (STC-villi)). For type 2 CPM (CPM2), the chromosomal abnormality is limited to the mesenchymal core of the chorionic villi (i.e. the chromosomal abnormality is observed only after examination of long-term culture villi (LTC-villi)). Type 3 CPM (CPM3) is defined as the presence of a chromosomal abnormality in both the cytotrophoblast and the mesenchymal core of the chorionic villi (i.e. the chromosomal abnormality is present after both STC-villi and LTC-villi analysis).

In a study by Toutain et al, CPM of meiotic origin, CPM3 were clearly associated with preterm births, low birth weights and adverse pregnancy outcomes, while CPM2 had no effect on fetal development [41]. CPM of meiotic origin (mainly CPM3) has also been reported by others associated with an increased risk of intrauterine growth restriction and SGA newborns [42,43].

Placental polyp is an intrauterine polypoid or pedunculated mass of placental tissue retained for an indefinite period after delivery or abortion. Placental polyps should be suspected when an abundant blood supply is visualized by power Doppler imaging in an intrauterine polypoid mass in a patient with elevated serum hCG and a normal level of the free β-subunit [44].

Acknowledgement

None.

Conflict of Interest

Author declares no conflict of interest.

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