Placenta–From Basic Facts to Highly Sophisticated Placenta Accreta Story

ABSTRACT

The study of the placenta is a fundamental aspect of pregnancy management from the first to the third trimester. In the last years, the increased ultrasound technology has given us new possibilities of diagnosis, often with great importance in the clinical practice. This paper discusses the most know placental diseases but highlights the importance of some emerging pathological entities, whose early diagnosis or suspect may significantly improve maternofetal outcomes.

Keywords: Early diagnosis of pathological entities, Placenta, Placental diseases


Source of support: Nil

Conflict of interest: None

ANATOMOPATHOLOGICAL ASPECTS OF PLACENTA

A normal pregnancy depends on the harmonious balance of three biologic systems: mother, fetus, and placenta. The last one permits the transfer from woman to the fetus of the elements it needs to grow up. O₂, active metabolites, hormones, growth factors reach the fetus through the umbilical vein.

Gaseous and metabolic exchange between mother and fetus take place in a vascular microenvironment, which is composed of intervillous space (where maternal blood flows, oxygenated and full of nutrients), villus venous capillary (where fetal blood lows, deoxygenated and full of metabolic waste) and vasculo-syncytial membrane consisting of basal membrane, trophoblast and villus capillary endothelium.

The anatomical elementary unit of the placenta is the lobule, whose function (fetal oxygenation and nutrition) depends on the presence and integrity of vasculo-syncytial membrane. The lobule includes the villus tree (the vascular ramification of the trophoblast) and the intervillous space. Five/ten placental lobules together form the placental cotyledon.

At the end of its morphological development (33 weeks of gestation), the villus tree of placental lobule consists of: stem villi, immature intermediate villi, mature intermediate villi, and terminal villi, developing between 13 and 41 weeks of gestation (GW), 8 and 24, 25 and 32, after 33 GW respectively.

The progressive ramification of villi ensures both greater ease in gaseous and metabolic maternal-fetal exchanges and greater extension of exchange surface. The reduction of villi thickness implicates the approach of villus capillary to the intervillous space, with the formation of the vasculo-syncytial membrane.

Placental lobule inlet is constituted by uterine-placental arteries which derive from the remodeling of spiral arteries of decidua basalis. Blood returns to maternal circulation via drain-like uterine veins.

Placental oxygenation depends on an adequate perfusion of the intervillous vascular space by oxygenated maternal blood flowing through uterine-placental arteries.

After 3 to 4 weeks of implantation, the invasive intermediate trophoblast commences to invade maternal spiral arteries progressively.¹ This invasion results in disruption of extracellular matrix and replacement of maternal endothelium by cells of trophoblastic origin leading to the development of low impedance and large capacitance vascular bed that will cater to the increased requirement of blood flow in pregnancy.²

There is the progressive passage from a "low flow and high resistance circle" (spiral arteries) to "high flow and low resistance circle" (uterine-placental arteries).

The physiologic remodeling of spiral arteries can be hindered by a broad range of anomalies such as atherosclerosis, a persistence of tunica media, fibrinoid necrosis, lymphoctic vasculitis, etc. The lack of remodeling leads to the reduction of uterine-placental arteries and the consequent inadequate supply of oxygen and active metabolites to intervillous space.

The complete cessation of maternal vascular perfusion of the intervillous space induces placental infarct, acute and chronic. Small infarcts in a terminal placenta can have not clinical significance, while big or multiple small
Infarcts involving a significant part of the placenta (>10% of its surface) are functionally devastating and important markers of maternal vascular disease, in particular, hypertension. Decidual vasculopathy, fast maturation of villi and placental infarct have been observed in pregnancies complicated by preeclampsia and gestational hypertension, systemic lupus erythematosus, lupus anticoagulant, and antiphospholipid antibody syndrome.\(^3\)\(^4\)

**SHAPE AND DIMENSION**

Sonographically placenta can be identified since 8 GW. It appears evenly isoechoic till 20 GW, and its thickness is no more than 3 cm. After this age, we can observe the appearance of calcifications and hyperechoic areas and placental thickness reaches about 4 to 5 cm. At the term of pregnancy placental diameter usually is 15 to 20 mm. However, during the course of ultrasound examination, assessment of the size of the placenta is often subjective.\(^5\)

According to many authors, placental shape and dimension are a mirror of fetal well-being.\(^6\)

A thin placenta can be an index of intrauterine growth restriction (IUGR).

The excessive increase of placental thickness in the second/third trimester can be associated with negative perinatal outcome. A homogeneous thickening can be related to diabetes mellitus, anemia, hydrops, infections (Table 1). A previous intraplacental hemorrhage can cause a heterogeneous thickening.

Placental calcifications are usually present during pregnancy. They generally are considered signs of maturation/aging of the placenta. According to their frequency and distribution, Grannum et al.\(^7\) created a system of ultrasound evaluation (placental grading) (Fig. 1):

- **Grade 0**: Homogeneous placenta;
- **Grade 1**: Lobulations of the surface are evident. Chorionic indentations do not extend to the basilar plate. Cotyledons are not delineated, and no hyper-echogenicity or calcification is evident;
- **Grade 2**: Chorionic indentations are extending to the basilar plate and echogenic marginal delineation of placental cotyledons. No calcification is evident;
- **Grade 3**: Extensive calcification is evident.

Widespread calcification may be favored by various factors (hypertension, diabetes, IUGR, smoking).

Aging signs can be seen very well with a microscopic examination of the placenta. An eventual vascular injury causes thrombosis and consequent infarct areas. In case of arterial occlusion, these areas are generally C, while they are prevalently cyanotic in case of venous obliteration. However, infarcts are not evident on ultrasound examination.

| Table 1: Diseases associated with the increase of placental thickness or placentomegaly |
|-----------------------------------|---------------------------------|
| Uteroplacental insufficiency       | Diabetes mellitus               |
| Maternal anemia                   | Fetal anemia                    |
| Fetal hydrops                     | Placental hemorrhage            |
| Intrauterine infection            | Lupus anticoagulant             |
| Congenital neoplasia              | Beckwith–Wiedemann syndrome     |
| Chromosomal abnormalities         | Placental mosaicism             |

**Table 1: Diseases associated with the increase of placental thickness or placentomegaly**

- Uteroplacental insufficiency
- Diabetes mellitus
- Maternal anemia
- Fetal anemia
- Fetal hydrops
- Placental hemorrhage
- Intrauterine infection
- Lupus anticoagulant
- Beckwith–Wiedemann syndrome
- Chromosomal abnormalities
- Placental mosaicism
Succenturiate Placenta

This is a morphologic anomaly characterized by a smaller accessory placental lobe that is not part of the main disc of the placenta, but is linked to it by blood vessels. There can be more than one succenturiate lobe. It can work normally but can be associated to complications like placenta previa or vasa previa.

Succenturiate placenta is similar to bilobate placenta and the difference between these two entities is not clear. Some Authors use the term “bilobate” when the placental segments have almost the same dimension, while “succenturiate” when there is a greater difference between them.8

The incidence is of 3 to 6%. At the basis of its development there is the tendency of trophoblast to grow where decidua is richly vascularized (concept of placental trophotropism). Instead, in the areas of insufficient vascularization, placenta is atrophic.9,10

On ultrasound, we can see two separated portions of placenta: the main one (which presents the insertion of umbilical cord) and the succenturiate lobe (Fig. 2). It is important not to confuse this image with the normal placental extension across the uterus: in this case there is a flap of placental tissue which links the two parts. When succenturiate placenta is diagnosed, we have to evaluate the insertion of umbilical cord and the communicating vessels, in order to identify eventual vasa previa.

The succenturiate lobe must be distinguished from subchorionic hematoma, myoma or myometrial contracture. In this last condition, there is not any connection between the two parts and the image disappears within 30 minutes or less.

The retention of the succenturiate lobe can cause postpartum hemorrhage or infections which can manifest days or weeks after the delivery. Rarely there is the rupture of communicating vessels, with fetal hemorrhage.

Placenta Membranacea

It is a rare anomaly. All or the main part of fetal membranes remains covered by chorial villi. This anomaly is caused by non-differentiation of chorion leave and chorion frondosus.11 The frequency is 0.25 to 0.5/10000.12

Ultrasound exam shows placenta covering the main part or the whole uterine wall.

Placenta is very thin and deeply adherent, often it presents areas of acretism requiring manual removal. The risk of metrorrhagia must be taken into consideration.

Circumvallate/Circummarginate Placenta

Circumvallate placenta is a variant with the evidence of a relieved ring of membranous tissue on the fetal surface of the placenta, variably distant from umbilical cord insertion. It is determined by a double crease of chorion and amnios, with decidual degeneration and fibrin in the middle. Circummarginate placenta is a similar variant, but the ring of membranous tissue is thinner. It can be found in 20% of placentas, while circumvallate placenta has a minor incidence (1 to 2%). Both do not have clinical significance.

They are the result of the discrepancy between the dimensions of the chorial plate, which is smaller, and the basal plate. This causes the growth of extrachorial placental tissue. The ring can involve the whole placental circumference or just a part of it. The portion of placenta which is not covered by chorion is called extrachorial.

Ultrasound image is characterized by the fold of fetal membranes, associated to hyperechoic tissue in correspondence of the placental edge (Fig. 3). Ultrasound accuracy is small. Differential diagnosis is done with intrauterine synechiae and subchorionic hemorrhage.

Circumvallate placenta increases the risks of metrorrhagia for placental abruption and IUGR. However, to find it does not change the management.13,14
Abruptio Placentae

It is a complex clinic syndrome, determined by the detachment of placenta before fetal birth. It is a particularly dangerous condition, with high maternal and fetal morbidity and mortality.

Placental abruption is frequently associated with preterm delivery and high perinatal mortality (15 to 25%) for anoxia, prematurity and exsanguination foetalis.

Detachment extension can widely vary from minor forms having very little effect on outcomes, to major forms which are associated to fetal death and unfavorable maternal outcomes.

Placental abruption can be total or partial and it occurs in the 0.4 to 1% of pregnancies.15

Etiology and pathogenesis are not clear yet. They appear complex and multifactorial, with interaction between genetic and environmental factors. The most important risk factors are smoking, preclampsia, previous placental abruption. Other risk factors are: old maternal age, hypertension, IUGR, anomalous fetal presentation, polyhydramnios, oligohydramnios, multiparity, low body mass index, intrauterine infections, premature rupture of membranes, chorioamnionitis, twin pregnancies, thrombophilia (in association with hyperhomocysteinemia), diabetes mellitus, anemia, ureter anomalies, abdominal traumas, use of alcohol or drugs. An abdominal trauma can cause the detachment since 6 to 48 hours to a maximum of 5 days after. A previous cesarean section increases the risk of about 40% more than spontaneous delivery.16

About pathogenesis, abruptio placenta is the result of a bleeding between decidua and placenta, determining their separation and the consequent functional exclusion of the involved placental area. The detachment can also derive from contrasting forces in the decidua-placental interface after abdominal traumas or after the sudden decompression of a overextended uterus (for example after rupture of membranes in case of polyhydramnios or twin pregnancy).

The diagnosis is mainly clinic and based on vaginal bleeding, abdominal pain, eventual cardiotocographic anomalies. It is confirmed by the inspection of placenta after delivery.

Clinical presentation can be extremely variable, with a range from asymptomatic forms to forms with vaginal hemorrhage.

In the most severe forms, the uterus appears tense and hypertonic at palpation, there are signs of fetal distress and the possibility of maternal shock with the insurgence of consumptive coagulopathy. The quantity of vaginal bleeding is not indicative of the amount of abruption. In 10% of cases the hemorrhage is hidden and there is not any vaginal bleeding.

Ultrasound can be an auxiliary instrument even if not always decisive for diagnosis. In the evaluation of placenta, scrupulous attention should be given to its localization, dimension, anatomy, morphology and implantation, excluding the presence of placenta previa.

The placenta usually appears like a homogeneous hyperechoic mass, when compared to the myometrium. In the 3rd trimester it is more heterogeneous for the presence of calcification and vascular lacunae (anechoic region in the intervillous spaces).

The echogenicity of hemorrhage depends on the time interval between the onset of symptoms to the ultrasound examination. Acute hemorrhaging appears hyperechoic/isoechoic when its echogenicity is greater than placenta or equal. So it can be distinguished hardly. Not always it is possible to evaluate the hemorrhage extension in the first scans.

In a week, with resolution, the hemorrhage area becomes hypoechoic, so less echoic than placenta and similar to myometrium. In two weeks, this area becomes anechoic, so similar to amniotic fluid.

The volume of hemorrhage is estimated by the measurement of the three perpendicular diameters (D), on the basis of the formula: 0.52 x (D1, D2, D3).

The localization of hemorrhage is defined on the basis of the mainly involved region and is classified as:

- Subchorial (between myometrium and placental membranes);
- Retropalcental (between myometrium and placenta);
- Preplacental (between placenta and amniotic cavity).

In subchorial forms the hemorrhage can be limited and hidden. The hematoma can remain confined under membranes or the blood can make its way between membranes and reach the cervix appearing outside. Subchorial hemorrhage is the most common location (67% of cases) of placental hemorrhage observed by ultrasound after 20 GW. Generally it starts from marginal disconnection between membranes and myometrium and not always it is associated to placental abruption.

In retropalcental forms the hematoma under the placenta increases and can penetrate the myometrium, determining hemorrhage (uterine-placental apoplexy), retropalcental hemorrhage (29% of cases) on ultrasound is characterized by placental thickening and sometimes by the view of retropalcental clots (Fig. 4).

Preplacental forms can be characterized by rupture of membranes near the placental detachment and the blood reaches the amniotic cavity. Subamniotic hematoma (4% of cases) appears like a hemorrhage along the amniotic surface of placenta.17,18

Ultrasound sensibility in the diagnosis of placental abruption is low. Since the blood not always forms a hematoma, a negative ultrasound exam cannot exclude...
the diagnosis of abruption placentae. Ultrasound does not recognize three fourth of cases.

Nuclear magnetic resonance (NMR) acquired an important role in the diagnosis of abruption placentae. It has a greater sensibility than ultrasound (100% vs 53%). It is not conditioned by placenta localization and can distinguish blood from other fluid collections. Between disadvantages of NMR there are costs, time and the lack of experts in the evaluation of the exam.

**Gestational Trophoblastic Disease**

Gestational trophoblastic diseases are a heterogeneous group of pathologies, all originating from the abnormal proliferation of gestational trophoblast. On the basis of anatomical and pathological characteristics and clinical evolution, they are classified as follows in Table 2.19

The most frequent gestational trophoblastic disease is the hydatiform mole. It derives from a wrong process of fertilization, with consequent abnormal proliferation and degeneration of the gestational trophoblast.

Partial moles are because of a fertilization error in which a normal ovum is fertilized by two spermatozoa or by one spermatozoon which duplicates. The result is a triploid karyotype (69, XXY) or, rarely, tetraploid (92, XXXY).

90% of complete moles derive from the fecundation of an ovum without nucleus (so without maternal chromosomes), by an haploid spermatozoon 23, X, which duplicates its chromosomes giving origin to a homozygous 46, XX androgen diploid entity (entirely parternally derived).20

The invasive mole often is the degeneration of a hydatiform mole. It locally invades the myometrium but does not metastasize.

The choriocarcinoma is a highly malignant epithelial tumor. It metastasizes above all to lung and pelvic organs.

The placental site tumor is the most rare trophoblastic disease. It origins from the placenta implantation site after pregnancy at term or abortion, rarely after molar pregnancy.

The diagnosis of gestational trophoblastic disease is mainly based on symptomatology, ultrasound image and plasmatic beta hCG values. The clinical aspect of all the forms of trophoblastic disease is the presence of abnormal vaginal bleeding, from minimal to severe hemorrhage.

Beta hCG concentration is higher than normal.

Ultrasound is the gold standard in the evaluation of a suspected molar pregnancy. It generally appears like an echoic endometrial complex mass containing many small cysts with diameter of 2 to 3 mm. This is the classical snowstorm appearance which uniformly involves the whole mass (Fig. 5).21

In case of partial mole, ultrasound shows a bigger placenta than normal, with multiple hypo-anechoic cystic areas. It is often associated to an embryo without heart activity or to a malformed fetus and/or with severe growth restriction.

---

**Table 2: Classification of the gestational trophoblastic diseases**

<table>
<thead>
<tr>
<th>Hydatiform mole</th>
<th>Trophoblastic tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>Invasive mole</td>
</tr>
<tr>
<td>Partial</td>
<td>Choriocarcinoma</td>
</tr>
<tr>
<td></td>
<td>Placental site trophoblastic tumor</td>
</tr>
<tr>
<td></td>
<td>Epithelioid trophoblastic tumor</td>
</tr>
</tbody>
</table>

---

**Fig. 5:** Complete molar pregnancy, with the classical “snowstorm” appearance. Note the multiple hypo-anechoic cystic areas
In more than 30% of cases of complete mole on ultrasound we can find the presence of multiple ovarian cysts, secondary to the high level of beta hCG.

Invasive mole, choriocarcinoma and placental site trophoblastic tumors have a similar aspect and it is difficult to distinguish them from not invasive molar disease by Ultrasound. The most common image is that of an irregular echoic mass invading the myometrium, which appears inhomogeneous for the presence of multiple areas of necrosis and hemorrhage (Fig. 6). Color Doppler can be useful to demonstrate an accentuated vascularization at the level of the uterine spiral arteries. In case of suspect of invasive forms, it is opportune to evaluate with ultrasound also pelvis and liver, which are frequent sites of metastasis.

There is a high percentage of false positives and false negatives on ultrasound exam. So the histological exam is fundamental, because the misdiagnosis of gestational trophoblastic disease increases the morbidity and the consequent necessity of chemotherapeutic and surgery treatments.

**Chorioangioma**

It is a not-trophoblastic benign tumor deriving from an excessive proliferation of small vessels in chorial villous stroma, with variable association of stromal solid areas. Chorioangioma can be singular or multifocal.

Small chorioangiomas are present in 1% of examined placentas, while tumors reaching clinically evident dimensions are relatively uncommon (incidence between 1/3500 and 1/9000 pregnancies). Actually, the real incidence of chorioangioma is not exactly identifiable because the study of placental structure is not included between the criteria of ultrasound screening of the second trimester. Moreover, its identification can be conditioned by the gestational age, because chorioangioma is more easily diagnosable during the third trimester of gestation.

Its pathogenesis is not well defined, yet. Histologically chorioangioma is made of a group of big and dilated villi, which are not demarked by a fibrous capsule but are surrounded by villous tissue.

The ultrasound image is that of a confined solid formation with hyperechoic or hypoechoic echostructure, sometimes complex, protruding from placental surface and presenting hypervascularity (Fig. 7). It is often localized in proximity of the umbilical cord insertion. To identify intraplacental chorioangiomas is difficult if they are small. Chorioangiomas bigger than 5 cm of diameter are defined “giant”.

---

Figs 6A to D: (A to C) Poorly marginated, heteroechoic, intensely vascular myometrial lesion, compatible with the diagnosis of choriocarcinoma; (D) The lesion is characterized by low resistance flow.
The differential diagnosis of PMD is broad and includes partial molar pregnancy, complete mole with co-existing normal fetus, chorangioma, subchorionic hematoma, confined placental mosaicism and spontaneous abortion with hydropic changes.\textsuperscript{31}

In the placental parenchyma, multiple vesicles are seen especially in the first and second trimester. These vesicular changes grossly and ultrasonographically resemble partial mole measuring 0.3 to 2.5 cm.\textsuperscript{32}

On a histologic level, however, both conditions can be clearly distinguished. A partial mole is characterized by trophoblastic proliferation, which is completely absent in PMD. The characteristic changes of the latter are essentially vascular abnormalities: enlarged stem villi with dilated vessels, a focal cisternlike formation, and possibly chorangiomatoid changes. Cytogenetically, both conditions are also distinctly different: partial moles are triploid (usually diandric), whereas aneuploidy is uncommon in PMD but it is sometimes associated with rare genetic syndromes; the best known association is with Beckwith–Wiedemann syndrome (BWS). PMD is associated with

Chorioangioma must be distinguished from hematoma, placental lacunae,\textsuperscript{24} placental teratomas, partial hydatidiform mole, maternal metastases to placenta\textsuperscript{25} and vascular aneurysms.\textsuperscript{26}

It is usually asymptomatic. However, when it is big, it can cause unfavorable fetal outcomes, such as non-immune fetal hydrops, cardiomegaly, heart failure, anemia, thrombocytopenia, coagulopathy, preterm delivery, severe IUGR, sudden fetal death and mirror syndrome.\textsuperscript{27}

**Placental Mesenchymal Dysplasia**

Placental mesenchymal dysplasia (PMD) is a rare placental vascular anomaly.\textsuperscript{28}

True incidence is not known but it has been estimated at 0.02%. The underlying cause of PMD is unclear. Some genetic anomalies are considered as etiology of PMD.\textsuperscript{29}

It is characterized on ultrasound by an enlarged, hydropic placenta, depicting multiple cysts and tangles of intestinal-like chorionic vessels on gross examination (Fig. 8).\textsuperscript{30} Placentomegaly is mostly more than 90th percentile.

The differential diagnosis of PMD is broad and includes partial molar pregnancy, complete mole with co-existing normal fetus, chorangioma, subchorionic hematoma, confined placental mosaicism and spontaneous abortion with hydropic changes.\textsuperscript{31}

In the placental parenchyma, multiple vesicles are seen especially in the first and second trimester. These vesicular changes grossly and ultrasonographically resemble partial mole measuring 0.3 to 2.5 cm.\textsuperscript{32}

On a histologic level, however, both conditions can be clearly distinguished. A partial mole is characterized by trophoblastic proliferation, which is completely absent in PMD. The characteristic changes of the latter are essentially vascular abnormalities: enlarged stem villi with dilated vessels, a focal cisternlike formation, and possibly chorangiomatoid changes. Cytogenetically, both conditions are also distinctly different: partial moles are triploid (usually diandric), whereas aneuploidy is uncommon in PMD but it is sometimes associated with rare genetic syndromes; the best known association is with Beckwith–Wiedemann syndrome (BWS). PMD is associated with
raised maternal serum alfa-fetoprotein (AFP) levels but normal or mildly elevated beta hCG levels.

Placental Mesenchymal Dysplasia (PMD) is usually associated with normal fetus; unlike hydatidiform mole, the pregnancy extends to the third trimester. The fetus usually has normal karyotype with female predominance but PMD is associated with intrauterine growth retardation (IUGR), stillbirth, prematurity and BWS. PMD is associated with intrauterine growth retardation (IUGR), stillbirth, prematurity and BWS.28,36-38

Beckwith–Wiedemann syndrome (BWS) is present in 25% of cases and is characterized by macrosomia, viseromegaly, hemihyperplasia, macroglossia, omphalocele, and increased childhood tumors.

Diagnosis should be considered with specific sonographic findings, including enlarged, cystic placenta with dilated chorionic vessels Abnormal levels of biochemical analytes, identified as part of aneuploidy screening, especially elevated msAFP, further support the diagnosis. Karyotype should be obtained to exclude partial molar pregnancy, as this is the most common misdiagnosis of PMD, and termination of pregnancy is recommended in this situation. A detailed anatomical survey should be performed to rule out fetal anomalies, especially abnormalities consistent with BWS.

The anatomical ultrasound should include a thorough evaluation of the fetal abdomen to rule out hepatic tumors. The placenta should be sent for pathological evaluation after delivery for confirmation of PMD.

Pregnancy outcomes range from healthy, uncomplicated pregnancies to adverse maternal and/or neonatal complications.

Diagnosis of Abnormally Invasive Placenta

Introduction

The study of placenta is one of the most important aspects of pregnancy management, since the 1st trimester. In this period, ultrasonography allows the diagnosis of possible subchorionic hematomas, gestational trophoblastic disease and twin chorionicity.

In the last years, because of the increase of cesarean sections (CS) and the improvement of imaging techniques, we observed a rising incidence of scar pregnancies and morbidity adherent placenta (MAP) in the I trimester. In the II and III trimester, the study of placental insertion is fundamental. Above all, it enables to select cases with risk of acrism.

The anomalies in placental insertion and invasion, such as placenta previa and the various forms of acrism (placenta accreta, increta and percreta) are today a rising obstetric pathology.

In the past placenta accreta was a catastrophic but extremely rare event, while in the last decades its incidence gradually and steady increased. According to epidemiological data, it occurs in two cases out of a thousand pregnancies. It is important to underline the existence of known risk factors, first of all a previous CS. Also placenta previa is a condition associated with MAP and its frequency is correlated to CS too.39-44

In the USA the rate of CD increased from 5 to 32.9% in 2009. Similar or even higher rates of CDs are reported elsewhere in the world with countries such as Brazil (45%), Mexico (44%), China (42%), Italy (38%).46

Figs 8A to D: (A) Placental mesenchymal dysplasia; (B) Enlarged, hydropic placenta; (C) depicting multiple cysts and dilated chorionic vessels; (D) Surgical specimen
In consideration of the epidemiologic emergency, the great maternofetal morbidity and mortality and the possible medico-legal implications, the prenatal diagnosis of acretism is extremely important above all for a correct management.\textsuperscript{47}

**Placenta Previa**

Placenta is defined previa when it is implanted on the lower segment of the uterus. We distinguish:

- **Central placenta previa**, which completely covers the internal uterine orifice (IUO);
- **Marginal placenta previa**, which is in contact with the IUO but does not cover it;
- **Lateral placenta previa** which is implanted more than 2 cm far from the IUO.

Recently placenta previa has been more easily classified in:

- **Maior**, when it completely covers the IUO (Fig. 9);
- **Minor**, when the IUO is not covered (Fig. 10).

The best imaging modality to evaluate a placenta implanting on the lower uterine segment is transvaginal ultrasound (TVU), which shows with good precision the topographic relation and the distance between placenta and IUO.\textsuperscript{48}

Furthermore TVU allows to overcome the possible limits about bladder filling, scant echogenicity and/or fat.

The incidence of placenta previa is different in relation to the gestational age, with a range from 5\% in the 2nd trimester to 0.5\% at the end of pregnancy.\textsuperscript{49} In fact, in diagnosis of placenta previa, it has to be considered the phenomenon of “placental migration”, that is to say the physiologic moving of placenta to the fundus of uterus.

This event is linked to the progressive development of the uterine lower segment\textsuperscript{50} and to the lower vascularization of cervicoisthmic region.\textsuperscript{51} The migration is more evident during the second trimester and continues, but in a smaller scale, in the third trimester.\textsuperscript{52} Oppenheimer et al.\textsuperscript{53} highlighted that, since the 26th week of gestation, if the placental edge is more than 2 cm distant from the IUO, the following migration cancel the risk of placenta previa at the end of pregnancy. On the contrary, when the placental edge covers the IUO for more than 20 mm, placenta remains previa. Royal College of Obstetricians and Gynaecologists guidelines (2011) suggests a careful ultrasound follow-up since the 20th week of gestation when placenta is implanted on the lower uterine segment involving completely or marginally the IUO. Through this follow-up we can monitor the process of

---

**Fig. 9**: Placenta previa maior. The placenta completely covers the IUO (arrows)

**Fig. 10**: Placenta previa minor. The IUO is not covered by the placenta
Placenta–from Basic Facts to Highly Sophisticated Placenta Accreta Story

**Placenta Accreta (Accreta, Increta, Percreta)**

Placenta accreta (PA) is an abnormal adherence of placenta to the uterine wall. It occurs when chorionic villi have an excessive capacity of infiltration or when the decidua reaction is inadequate in containing villi penetration. The Nitabuch fibrinoid layer is a layer of fibrin between endometrium and cytotrophoblas. When this membrane is compromised, the placenta will attach itself deeply into the uterine wall between the myometrial fibers. Placenta is defined accreta when chorionic villi attach to the myometrium, increta (PI) when villi invade the myometrium and percreta (PP) when villi invade through the myometrium.

There is not a specific clinical symptomatology of MAP and in many forms of acretism there is not bleeding during the gestation. So we have to suspect its presence if the patient has risk factors. Placenta previa, previous curettage, multiparity, maternal age over 35 years, hysterotomic scars and above all previous CS are linked to a high risk of PA. In fact, the increasing rate of these events correlates with the rising incidence of MAP in western countries.

At delivery this condition exposes to a big risk of severe haemorrhages with possible necessity of hysterectomy. So, an accurate prenatal diagnosis (or at least a suspect) is required to reduce the risk of maternal/fetal morbidity and mortality.54

Prenatal diagnosis allows to plane the availability of compatible blood, to consider the various therapeutic options and to ensure the presence of a multidisciplinary team with adequate experience. Furthermore, if the patient shows a strong desire of preserving fertility, a prompt diagnosis could permit the planning of a conservative treatment.55

In the past the diagnosis of PA was made intrapartum often with catastrophic consequences for the woman, because of the attempts of instrumental removing of placenta.

Therefore, in order to have a diagnosis of placental acretism as early as possible, in the last years many Authors have studied the validity of various ultrasound criteria.56-59

The generally used criteria are:

- loss or irregularity of hypoechoic area between placenta and myometrium (clear space);
- placental vascular lacunae;
- thinning or interruption of the hyperechoic interface between uterine serosa and bladder wall (bladder line)
- papillary extroversion of placental-like tissue on the uterine serosa and/or into the bladder;
- the reduction of myometrial thickness.

Clear space: it is the hypoechoic area between placenta and myometrium (Fig. 11A). It coincides with the vessels of the basalis decidua.60 Even if it is evident since the 12th week of gestation, sometimes the clear space is not well viewable also in cases of placenta not accreta, especially if it is implanted on the anterior wall of the uterus.61 There is a clear correlation between MAP and the absence or irregularity of clear space, related to the insufficient presence of basalis decidua (Fig. 11B).62

Other Authors studied the efficacy of clear space as single diagnostic criterion, highlighting a high rate of false positives.63,64

In 2004, Comstock suggested that an altered representation of the clear space, above all in case of anterior placenta, could depend on the pressure employed on the probe during the exam.58 However the high negative predictive value (NPV) and sensitivity legitimize the use of this criterion in the ultrasound diagnosis of acretism, in association with other criteria.65,66

**Placental vascular lacunae**

Number and small dimension of lacunae relate with the diagnosis of PA (Fig. 12).

In case of PA lacunae present a flow with high speed and low resistance (Fig. 13).24
The exact histogenetic course is not totally clear, however it seems that in case of acretism the increasing vascularization and the abnormal placental insertion could represent mechanical causes of intraplacental disruption with consequent formation of lacunae. In 1992, Findberg and Williams proposed a grading for placental lacunae: grade 0 when no lacuna is present (low risk of acretism); grade 1+ in presence of 1 to 3 lacunae; grade 2+ if there are 4 to 6 lacunae; grade 3+ in presence of many lacunae with irregular shape affecting most of placental parenchyma (high risk of acretism).

Image in Figure 14 shows placental vascular lacunae displayed by color Doppler.

In 2004, Comstock et al. observed that placental vascular lacunae showed 93% of sensitivity in women at 20 or more GW. D’Antonio et al. obtained 77.43% of sensitivity, 95.02% of specificity.

**Bladder line**

It is a hyperechoic line corresponding to the interface between bladder and myometrium, better viewable when the bladder is partly filled and the probe is positioned at 90° respect to its wall (Fig. 15). The thinning or interruption of the bladder line depend on the development of blood vessels in the space between myometrium and bladder. In case of PP they can reach the bladder wall (Figs 16 and 17). This sign can be present also in absence of acretism, above all in patients with more than one previous CS, because they develop neovascularization on the vesicouterine fold.

In an already mentioned meta-analysis of 2013, authors found that the interruption of the bladder-line presented sensitivity of 49.66% and specificity of 99.75% (66). Calì et al. proved that sensitivity of bladder line interruption was 70% with gray-scale ultrasound, but it reaches 90% with color Doppler ultrasound (Fig 18). The presence of a chaotic vascularization with confluent and tortuous vessels seems to represents the best single diagnostic criterion, with sensitivity and sensibility of 97% and 92% respectively. However, to date there is not a single diagnostic criterion which has high confidence in order to diagnose or exclude placental acretism.
3D Power Doppler

Although bidimensional ultrasound is the standard technique in diagnosis of abnormally invasive placenta (AIP), in consideration of the important maternofetal implications of this pathology it is useful to employ all the available diagnostic techniques, such as tridimensional ultrasound and 3D power Doppler.

Three-dimensional power Doppler became an instrument of frequent use in the study of placental development and vascularization, allowing a not just qualitative but also quantitative evaluation.

This instrument has the capability of obtaining multiplanar images on axial, coronal, and sagittal planes, and with rotational technique permits to visualize placenta-bladder interface more accurately. So it allows a better study of the degree of bladder invasion. This information, obviously, is very important for counselling and following management. Many studies in literature support the employment of 2D ultrasound and color Doppler in the diagnosis of placental acrretism, but until recently there was no evidence in literature about the possibility of differential diagnosis between placenta accreta, increta or percreta (Fig. 19).

According to RCOG guidelines published in 2011, 3D power Doppler diagnostic criteria are:

- Presence of vessels (linear, confluent) involving the uterine-bladder interface in basal images;
- Placental hypervascularization in lateral images;
- Inadequate distinction between intervillous and cotyledonoid circulation, tortuous vessels, chaotic ramifications in lateral images.

Calì et al., using 3D color power Doppler, demonstrated that the hypervascularization observed at the uterine-bladder interface was extended from side to side in all cases of placenta percreta they examined, with sensitivity, specificity, NPV and PPV of 90%, 100% and 97% respectively.

Combination of 2D and 3D Power Doppler Ultrasound Criteria

Diagnostic accuracy increases using more ultrasound criteria. Cali et al. used three bidimensional signs (clear
space, lacunae and bladder line interruption) and two tridimensional power Doppler signs (chaotic vascularization with confluent and tortuous vessels in the whole placental parenchyma and hypervascularization of serosa-bladder interface) and observed that all women in exam with 5 positive criteria had placenta percreta. On the contrary, no woman with normal placental insertion showed more than one ultrasound criterion.24 On the basis of ultrasound criteria evidenced in 2D ultrasound, Comstock et al. found that using two or more criteria the sensitivity was 80% and the PPV was 86%.58

An important contribute in the comparison of 3D power Doppler and Gray-scale has been given by a study by Shih et al: the results demonstrate that the use of 3D power Doppler increases the diagnostic information we can obtain with bidimensional, both in terms of PPV than NPV.65 The hypervascularization of serosa-bladder interface observed by 3D power Doppler presents PPV of 100% and, in case of percretism, is always associated to an abnormal intraparenchymal vascularization (3D power Doppler) similar to an aneurysmatic formation.24 In this study the bladder-line, evaluated with TVU 3D power Doppler and with standard bladder filling of 300 ml, can predict placental acrertism with high accuracy; furthermore the spatial reconstruction of neo-vascularization of bladder-myometrium interface with 3D ultrasound results more effective than 2D technique in the differentiation between acrertism/incretism and percretism.

An additional contribute to definition of percretism is given by the publication by Calì et al. about the utilisation of “virtual cistoscopy”;71 in the diagnostic work-up of patients with MAP, 3D-HD-flow TVU was used to analyse the vascular topography of uterine-bladder interface. Using bladder filling of 300 mL, the Authors obtained information about bladder posterior wall, which was adjacent to the abnormal placental invasion. In particular they obtained information about the amount of vascularization under the bladder mucosa (Figs 20 and 21). The technique allows to highlight the final stages of placental invasion before the perforation of bladder mucosa.

This last contribute, worthy of further confirmation on big data, could permit the identification of the cases of placenta acrata/increta which tend to evolve into percretism. This kind of diagnosis would justify an intensive monitoring and the planning of delivery trough CS also at early gestational age.

**Nuclear Magnetic Resonance**

Even if ultrasound remains the main diagnostic technique in the study of placental implantation, in the last years the interest of the utilisation of NMR increased.
Anyway, in literature there are no data collection sufficiently large for a comparison between 3D power Doppler ultrasound and NMR. The individual experience of obstetrician and radiologist is fundamental: these techniques are strictly operator-dependent in this specific situation. In a review of the literature there are almost never big differences in terms of sensitivity and specificity between Ultrasound and NMR in the diagnosis of placenta accreta. Nuclear Magnetic Resonance seems more useful to better define placental acretism degree, selecting cases of placenta increta and percreta. Anyway, few studies confirmed this result, and they are all small case series or case reports. In most cases MRI does not seem to give more information, compared to ultrasound. In 2013, Cali et al.’s study on patients with placenta previa and previous CS, ultrasound accuracy was so satisfactory that NMR was not necessary for choosing pre- and intrapartum management (Figs 22 and 23).}

Anyway, in literature there are no data collection sufficiently large for a comparison between 3D power Doppler ultrasound and NMR. The individual experience of obstetrician and radiologist is fundamental: these techniques are strictly operator-dependent in this specific situation. Actual guidelines SIEOG 2015 include between NMR indications the study of placenta, in particular in diagnosis of placenta accreta, increta and percreta. They highlight that, in the same way as TA and TV ultrasound, not always NMR allows to reach conclusive data. However, the most recent literature shows that in a selected population, the diagnostic accuracy is high.

To date we can affirm that NMR can be an useful diagnostic instrument for a second step, that is to say when the ultrasound exam is confounding or in case of posterior placenta.

In consideration of the importance of diagnosis and the possible severe consequences in case of misdiagnosis, it is appropriate that all suspected cases are subjected to a careful diagnostic study in referral centres, where it is possible to benefit from a more advanced technology and operators with higher experience.76,79

Cesarean Scar Pregnancy

Cesarean scar pregnancy (CSP) is a serious consequence of a previous CS: pregnancy with implantation of the gestational sac in the area of the scar of a previous CS. The steadily mounting rate of CS mirrors the increasing number of CSP as well as those of MAP. The true incidence of CSP is unknown. It is estimated in a the range from 1/1800-1/2500 of all CS performed.

Previous uterine surgery leads to thin or absent decidua basalis in scarred areas of the lower uterine segment. A low oxygen tension seems to be an important prerequisite for the invading trophoblast.

The scar tissue into which the placenta implants, may provide the exact environment of low oxygen tension.
stimulating the cytotrophoblast to deeply invade the scarred area.88

When a blastocyst implants on the uterine scar or in the “niche” (dehiscence) left after the healing process of the incision of the previous CD, gives rise to the CSP. The mechanism is similar to implantations after uterine surgery (myomectomy, curettage, endometrial ablation, manual removal of placenta or any intrauterine surgical manipulation).

The niche is usually larger than it appears with TVU on a sagittal section of the uterus; so, a transverse/coronal section may reveal the real size of the defect. This can be seen on a 3D ultrasound image of the uterus.

Vaginal bleeding may be the first clinical sign of a CSP, which usually is diagnosed before 12 to 13 weeks. The amount of blood may range from minimal to severe hemorrhage. Pain is usually not the first symptom and some patients may be asymptomatic.

The initial ultrasound exam is critical since many CSP are misdiagnosed as threatened abortion or simply intrauterine pregnancies.89

Such misdiagnoses may lead to a curettage for a presumed failed pregnancy resulting in profuse bleeding and emergency surgical interventions, at times ending with hysterectomy.90-92

Every woman in the 1st trimester with a history of a previous CS and a low, anterior gestational sac with or without heart activity should be considered at risk of CSP until proven otherwise.

The best imaging modality to diagnose a CSP is TVU. Sonographic criteria for CSP identification are (Fig. 24):93,94

- An empty uterine cavity and closed, empty endocervical canal;
- Detection of an early gestational sac and/or placenta in close proximity of the hysterotomy scar/niche

---

![Fig. 22A and B](image1)

**Figs 22A and B:** Comparison between NMR (A) and 3D Ultrasound; (B) in the evaluation of bladder invasion in case of placenta percreta. The arrows show the interruption of the bladder line.

![Fig. 23A and B](image2)

**Figs 23A and B:** Other images of comparison between NMR (A) and 3D Ultrasound (B) in diagnosis of placenta percreta.

![Fig. 24](image3)

**Fig. 24:** Cesarean scar pregnancy. The gestational sac is implanted in the niche.
with GW the gestational sac may assume the shape of the niche;
- An absent or thin appearing myometrial layer between the gestational sac and the bladder wall;
- Abundant blood flow around the gestational sac determined by Doppler examination.

The diagnosis of CSP can easily be made very early by its location in the uterus. The location of the center of the gestational sac relative to the midpoint axis of the uterus can be used as an easy, non-invasive “point-of-service” method for sonographic differentiation of intrauterine and cesarean scar pregnancies between 5 and 10 completed weeks of gestation. Dividing the uterus in half by an imaginary line on longitudinal sagittal scan, we can determine the location of the gestational sac:

- If the gestational sac is above the line, mostly the implantation is normal;
- If the gestational sac is below it, we can suspect a CSP or a cervical pregnancy (Fig. 25).

CSP has differential diagnosis with a cervical pregnancy and a miscarriage in progress in transition, close to the IUO or the cervical canal. Cervical pregnancies are rare and usually do not occur in patients with previous CS.

Miscarriages do not present heart activity. Pressure on the uterus with the vaginal probe at the level of the distorted gestational sac results in a sliding of the sac towards the cervical canal and back when the pressure is released. Instead, a true CSP does not move away.

If in the 2nd trimester a low, anterior placenta or previa is diagnosed in a patient with a previous CS, the examination of a 1st trimester ultrasound image is indicated for a retroactive application of the sonographic criteria of CSP.

REFERENCES

70. Placenta praevia, placenta praevia accreta and vasa praevia: diagnosis and management. RCOG Green-top Guideline No. 27 January 2011.
76. Linee guida SIEOG. Ed. 2015.