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The Placenta Accreta Spectrum: Pathophysiology and Evidence-based Anatomy for Prenatal Ultrasound Imaging

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Condensation: The pathophysiological basis of ultrasound signs in placenta accreta is secondary to permanent damage of the uterine wall and invasion of the deep uterine circulation.

Abstract

The placenta accreta spectrum (PAS) is a complex obstetric complication associated with a high maternal morbidity. It is a relatively new disorder of placentation, and is the consequence of damage to the endometrium-myometrial interface of the uterine wall. When first described 80 years ago, it mainly occurred after manual removal of the placenta, uterine curettage or endometritis. Superficial damage leads primarily to an abnormally adherent placenta, and is diagnosed as the complete or partial absence of the decidua on histology. Today, the main cause of PAS is uterine surgery and, in particular, the uterine scar secondary to a caesarean delivery. In the absence of endometrial re-epithelialization of the scar area the trophoblast and villous tissue can invade deeply within the myometrium, including its circulation, and reach the surrounding pelvic organs. The cellular changes in the trophoblast observed in PAS are probably secondary to the unusual myometrial environment in which it develops, and not to a primary defect of trophoblast biology leading to excessive invasion of the myometrium. PAS was separated by pathologists into three categories: placenta creta (PC) when the villi simply adhere to the myometrium, placenta increta (PI) when the villi invade the myometrium, and placenta percreta (PP) where the villi invade the full thickness of the myometrium. Several prenatal ultrasound signs of PAS have been reported over the last 35 years, principally the disappearance of the normal utero-placental interface (clear zone), extreme thinning of the underlying myometrium and vascular changes within the placenta (lacunae) and placental bed (hypervascularity). The pathophysiological basis of these signs is due to permanent damage of the uterine wall as far as the serosa, with placental tissue reaching the deep uterine circulation.

Adherent and invasive placentation may co-exist in the same placental bed and evolve with advancing gestation. This may explain why no single, or set combination of, ultrasound sign(s) has been found to be specific for the depth of abnormal placentation, and accurate for the differential diagnosis between adherent and invasive placentation. Correlation of pathological and clinical findings with the prenatal imaging is essential to improve screening, diagnosis and management of PAS, and standardised protocols need to be developed.

Key Words: Placenta accreta; increta; percreta; ultrasound imaging; caesarean delivery; prenatal diagnosis.

INTRODUCTION

The first case series of placenta accreta (PA) was published in 1937 by Irving and Hertig.[1] They reviewed 18 cases, which they described clinically as “the abnormal adherence of the afterbirth in whole or in parts to the underlying uterine wall” and histologically as “the complete or partial absence of the decidua basalis”, signs that are still used today. They described all their cases as “vera” or “adherenta” where the villi were attached to the surface of the myometrium without invading it.

The grading classification of PA according to the depth of villous invasiveness inside the myometrium was introduced by modern pathologists in the 1960s.[2-4] They separated PA into three categories: placenta creta (PC) when the villi simply adhere to the myometrium, placenta increta (PI) when the villi invade the myometrium and placenta percreta (PP) where the villi invade the full thickness of the myometrium (Figure 1). This terminology is still used by most pathologists. It is, however, often impossible to clinically differentiate between these categories, especially as they may co-exist in the same placental bed (Figure 2), and confusion frequently occurs amongst clinicians regarding the difference between the terms ‘accreta’ and ‘creta’. Given the lack of international consensus on nomenclature, for the purposes of this paper, we have chosen to refer to it as the placenta accreta spectrum (PAS), which includes both abnormal adherence and abnormal invasion. We will then use placenta creta (PC), increta (PI) and percreta (PP) for specific examples where the histology is known.

In PAS, the lack of a plane of cleavage between the placental basal plate and the uterine wall leads to major hemorrhage if an attempt is made to forcibly remove villous tissue embedded within the myometrium.[5-8] The severity of the complications varies

according to the depth of villous invasion. In PP, not only is there potential villous invasion of surrounding pelvic organs, but excessive neovascularity is often present making any surgical procedure technically difficult. Multi-disciplinary team working and operator experience has been shown to reduce collateral damage, with several studies demonstrating that maternal morbidity is significantly reduced by delivery in a specialist centre.[9-12] Thus, the prenatal diagnosis of PAS has become essential to its management and outcome. The first prenatal diagnosis of PAS was reported in 1967 by Sadovsky et al using radioisotope placentography[13], and the first prenatal ultrasound description was made by Tabsh et al[14] in 1982.

Ultrasound imaging and magnetic resonance imaging (MRI) are now commonly used for the prenatal diagnosis of PAS.[15-18] However, recent population studies have indicated that it remains undiagnosed before delivery in between half[19,20] and two-thirds of cases.[21] The cost and limited access of MRI make it impractical as a screening tool, and ultrasound has therefore become essential in identifying women at high risks of PAS and tailoring their management. Although many ultrasound diagnostic signs have been described, wide heterogeneity in both study design and terminology used by different authors has made it difficult to define the ultrasound markers that enable the different grades of villous adhesion or invasion to be distinguished.[18] In this review, we have evaluated the pathophysiology of the different ultrasound signs associated with the PAS to better understand their relevance to the prenatal screening and diagnosis of accreta placentation.

PATHOPHYSIOLOGY OF THE PLACENTA ACCRETA SPECTRUM

Several concepts have been proposed to explain why and how PAS occurs. The oldest concept is based on a theoretical primary defect of trophoblast biology leading to excessive invasion of the myometrium. The current prevailing hypothesis is that a secondary defect of the endometrium-myometrial interface leads to a failure of normal decidualisation in the area of a uterine scar, allowing abnormally deep placental anchoring villi and trophoblast infiltration.[5] There is no doubt that the decidua normally regulates trophoblast invasion, as evidenced by the aggressive invasion of the muscular and serosal layers seen at sites of ectopic implantation in the Fallopian tube[22] or in the abdomen.[23]

Scar implantation

During the secretory phase of the menstrual cycle, the endometrium transforms into a well-vascularised receptive tissue, which is characterised by the proliferation and differentiation of the stromal cells into decidual cells, the infiltration of maternal immune cells and vascular remodelling of the endometrial vessels.[24,25] Decidualisation of the endometrium stroma precedes blastocyst attachment and trophoblast infiltration. The process is complex and involves many local uterine components and external maternal cells and hormones. It is essential for implantation and normal placental development.

The development of PAS has been mainly linked to surgical damage, which disrupts the integrity of the uterine endometrium and smooth muscle layers of the myometrium. The increased use of caesarean delivery (CD) has had a direct effect on the incidence of all grades of accreta placentation, but cases have been described following smaller and more superficial damage to the uterine wall such as that

associated with uterine curettage, manual removal of the placenta or post-partum endometritis.[1,3-5] Cases of PAS have even been described in primigravida women with no surgical history, but presenting with a uterine pathology such as bicornuate uterus, adenomyosis, submucous fibroids or myotonic dystrophy.[3-5] These latter cases suggest that microscopic defects of the endometrium or interferences with its normal biological functions may lead to abnormal villous tissue adhesion or even invasion.

A uterine scar may range from a small defect of the decidua and superficial myometrium to a wide and deep defect of the myometrium with clear loss of substance from the endometrial cavity down to the uterine serosa.[26] In women with a history of prior CD, scar defects have been found to range between 20% and 65% of the myometrium after delivery on transvaginal ultrasound. Women with a residual myometrial thickness of <50% of the adjacent myometrium are more likely to develop chronic complications such as inter-menstrual spotting.[27] The myometrial fibres around a scar often show hyalinisation or degenerative changes, with a local increase in fibrous tissue and infiltration by inflammatory cells.[3] The comparison of ultrasound features of uterine caesarean scar with histological findings has shown that large and deep myometrial defects are often associated with absence of re-epithelialisation of the scar area.[28] Leucocyte recruitment to the endometrium during the secretory phase may also be affected by the presence of a CD scar. A recent study of the uterine circulation in women with a previous CD has shown that the uterine vascular resistance is increased, whilst the volume blood flow is decreased, compared to women with a previous vaginal birth.[29] These data suggest that the blood circulation around the scar is impaired. Poor

vascularization of the scar area may lead or contribute to permanent focal myometrial degeneration, as well as reduced or absent re-epithelialisation of the scar area.

Prior CD, and in particular prior pre-labor CD, are associated with a two-fold increase in the risk of placenta previa in subsequent pregnancies.[30] Only 4.1% of women with one prior CD presenting with a placenta previa will also have a PAS[31], demonstrating that normal implantation can occur over scar tissue. A caesarean scar pregnancy is the implantation of a sonographically detectable gestational sac into a uterine scar. It has been suggested that a scar pregnancy is not a separate entity from PAS, but rather a continuum of the same condition.[32,33] However, not all scar pregnancies require major surgery or life-saving hysterectomy at the time of delivery,[34] suggesting that in some cases the scar defect can be large enough to host an entire gestational sac without the villi of the definitive placenta implanting deep into the remaining myometrium or into the uterine serosa. This also suggest that if the gestational sac implants by the side of a CD scar this may lead to focal accreta placentation with no clinical symptoms in early pregnancy allowing the pregnancy to continue in the second trimester without being diagnosed as PAS.

Overall, these data support the concept that macroscopic and/or microscopic disruptions to the uterine cavity inflict permanent damage to the endometrio-myometrial interface. This damage has a primary impact on the biology of the scar area creating conditions for preferential attachment of the blastocyst to the scar tissue as well as a secondary impact on decidualization of the endometrium around the scar. The absence of decidua in first-trimester cases of PAS[35] refutes previous suggestions that the

decidual layer is normal at the beginning of gestation and atrophies as pregnancy progresses.

Scar placentation

Human placentation is almost unique amongst mammals in that it is physiologically highly invasive. Soon after implantation, mononuclear cytotrophoblast cells proliferate at the tips of anchoring villi, and form columns of cells that merge together to form the cytotrophoblastic shell that encapsulates the conceptus.[36,37] Those cells on the outer surface that make contact with the decidua undergo a partial epithelial-mesenchymal transition, lose their proliferative potential, and invade the decidual stroma. These cells are collectively called extravillous trophoblast (EVT). They differentiate primarily into interstitial and endovascular sub-populations that migrate through the decidual stroma and down into the lumens of the spiral arteries respectively. Interstitial EVT invade the uterine wall as far as the inner third of the uterine myometrium, where they fuse to form multinucleated trophoblast giant cells (MNGCs).[38] This area is known as the junctional zone (JZ).[37] Migration of the EVT is facilitated by their secretion of a variety of matrix metalloproteinases (MMPs) comprising collagenases, gelatinases and stromelysins.[4] During normal migration these enzymes break down the extracellular matrix between the decidual cells, but can equally well digest scar tissue if implantation overlies a myometrial lesion.

In accreta placentation, EVT cells invade the uterine wall to a greater depth, are hypertrophic, and their numbers are increased whereas the number of MNGCs is

reduced.[39-41] It is not clear from these observations whether the EVTs are genuinely hyperplastic since cell densities rather than total numbers have been reported. In PAS, the proliferative index and apoptotic rate are similar to normally implanted placentas and so it may be that the normal number of EVTs is packed into a smaller volume of decidua. Deeper trophoblast invasion of the myometrium and infiltration of chorionic villi into myometrial vascular spaces has been recently documented in both PI and PP.[42] These events lead to an absence of the normal plane of cleavage above the decidua basalis, thus, preventing placental separation after delivery in cases of PAS (Figure 5). Deeper placental tissue invasion may not be due to a further invasion of EVT in the uterine wall. This may arise secondary to dehiscence of a scar, possibly under the actions of MMPs, leading to the presence of chorionic villi deep within the uterine wall, and thus giving EVTs greater access to the deep myometrium (Figure 4). Overall, superficial damage, such as after a curettage, or distortion of the deciduo-myometrial layer, such as with a sub-mucous fibroid, will probably lead to mainly superficial abnormally adherent placentation. This possibly explains the very rare cases of PAS which have been reported in primiparous women.[3-5]

Stronger labelling of the villous syncytiotrophoblast for epidermal growth factor receptor (EGFR) has been observed in PAS compared to normal pregnancies[43-45], suggesting that abnormal villous adherence develops as a result of aberrant expression of growth-, angiogenesis- and invasion-related factors in trophoblast populations. However, there was no change in staining intensity for the EVT, and the functional significance of differences in receptor expression between the syncytiotrophoblast, which has no invasive capacity, and the invasive EVT in PAS is difficult to interpret.

Increased vascular endothelial growth factor (VEGF) and phosphotyrosine immunostaining has also been observed in EVT cells from placenta previa accreta.[46] These cells also co-expressed vimentin and cytokeratin-7, an epithelial-to-mesenchymal transition feature and tumor-like cell phenotype.[46] One of the mechanisms proposed by which EVTs lose their invasive phenotype is through syncytial-type fusion into MNGCs.[35] More recently, lower immunostaining for soluble fms-like tyrosine kinase (sFLT-1), which is a potent antiangiogenic growth factor, has been found in the EVT cells in cases of of PAS[47]. These findings suggest that VEGF and sFLT-1 play a pivotal role in the pathological programming of EVTs toward increased motility and invasiveness in PAS. The cellular changes in the trophoblast observed in PAS are probably also secondary to the unusual myometrial environment in which it develops. In particular, to the loss of the physiological utero-placental oxygen gradient can have a direct impact on the cytotrophoblastic differentiation patterns.[48,49] There may also be differences in the local populations of maternal immune cells that interact with the EVT, notably the uterine Natural Killer (uNK) cells that release cytokines regulating invasion.[50]

Overall, these findings emphasise the role of the decidua in modulating placentation. Its replacement by scar tissue results in secondary dysfunctional decidualization and trophoblastic over-invasiveness in PAS. There is no firm evidence of a primary trophoblastic biological defect in any of the different grades of PAS, unlike those observed in placental insufficiency and hydatidiform moles.

Vascular remodelling

The uterine arteries provide the main blood supply to the uterus.[51] They give rise to the arcuate arteries which in turn give rise to the radial arteries that are directed towards the lumen of the uterus. As they reach the JZ, each radial artery gives off lateral branches, the basal arteries, that supply the myometrium and the deeper basalis part of the endometrium. The vessel then continues as a spiral artery. Each spiral artery gives off small branches supplying the capillary plexus surrounding the uterine glands. In the non-pregnant state, the walls of the spiral and radial arteries contain large quantities of smooth muscle equipped with a rich autonomic innervation which makes them highly responsive to both exogenous and endogenous adrenergic stimuli.[49]

In normal placentation, EVT cells penetrate the JZ via the action of their proteases on the intercellular ground substance, affecting its mechanical and electrophysiological properties. The structure and properties of the walls of the spiral arteries are also changed.[37] The remodelling of the arteries is characterized by the progressive loss of myocytes from their media and their internal elastic lamina, which are replaced by fibrinoid material. Consequently, these vessels lose their responsiveness to circulating vasoactive compounds and become a low-resistance vascular network through dilatation.[49] This transformation, termed "physiological changes", results in the metamorphosis of small calibre spiral vessels into flaccid distended arteries with a 5-10-fold dilation at the vessel mouth (Figure 3). This dilatation is generalised, but non-uniform with considerable variation in size between arteries within the same specimen, and even at different points along individual arteries.[49] The terminal coils of the spiral arteries are extremely dilated, often reaching 2-3 mm in diameter which represents an approximately 4-fold increase in the diameter of the

vessel at the myometrial-endometrial boundary and within the distal myometrium.[49] Around 30-50 spiral arteries are transformed during the first and early second trimesters. In normal pregnancies transformation of these utero-placental arteries is completed around mid-gestation.[51] By contrast, the segment just below the JZ represents the limit of physiological trophoblast invasion and the radial and arcuate arteries remain highly vaso-reactive throughout pregnancy.[49]

If the numbers of interstitial EVTs are increased in PAS, spiral artery remodeling has been described as reduced, more so in cases of PAS without local decidua.[41,52] Decidua is sometimes completely absent in the accreta area,[52] probably due to atrophy of the uterine circulation within the scar area in non-pregnant women with prior CD.[29] There is no clinical evidence of utero-placental insufficiency and impairment of fetal growth associated with any of the different grades of PAS. This is in contrast with the reduction in trophoblast invasion and failure of conversion of the spiral arteries which is observed in complications of pregnancy, such as preeclampsia and fetal growth restriction. This suggests that in both abnormally adherent and invasive placentation the incomplete remodelling of the spiral arteries is limited to the accreta area without impacting entire placental function. Another possible hypothesis is that in the absence of a decidua, the normal release of proteases and cytokines from activated maternal immune cells is missing, impairing arterial remodelling focally.

In cases of invasive placentation, an unusual uteroplacental vasculature has been observed in which physiological changes were present in large arteries deep in the myometrium.[52] Invasion of larger vessels beyond the level of the JZ is probably determined by access rather than a pre-existing defect in trophoblastic differentiation

that would produce uncontrolled invasion of EVT through the entire depth of the myometrium.[35] Prenatal imaging and macroscopic observation at delivery of the hypervascularity of the placental bed in most cases of invasive placentation suggest a phenomenon of neovascularisation around the scar area in addition to the vasodilatation of the radial and/or arcuate uterine vasculature in the accreta area.

ULTRASOUND CHANGES SEEN IN PAS

A wide variety of different medical and non-medical terms have been used to describe placental lesions on ultrasound since the first description of a complete hydatidiform mole by MacVicar and Donald in 1963.[53] The ultrasound features of PAS were essentially described by Finberg and Williams[54] for grey-scale and by Chou et al[55,56] for color Doppler imaging (CDI), and both have been used by many authors of subsequent cases reports and cohort series.[18] Very few authors have reported on the use of transvaginal sonography (TVS) in PAS outside the location and follow-up of placenta praevia accreta.[57] Thus, most case reports and cohort studies have described ultrasound images obtained transabdominally from PAS diagnosed in the late second and early third trimesters. This, and the fact that the resolution of ultrasound imaging has improved over the last three decades, may explain the wide variation in terminology used to describe the prenatal ultrasound features associated with PAS.

In 2016, The European Working Group on Abnormally Invasive Placenta (EW-AIP) proposed standardized descriptions of ultrasound signs used for the prenatal diagnosis of PAS[58], the pathophysiology of which we have analyzed below:

Loss of the 'clear zone': is used when the normal hypoechoic retroplacental zone in the myometrium under the placental bed is not visible on ultrasound. It was one of the first signs identified by grey-scale ultrasound imaging in cases of PAS.[59,60] This sign is supposed to represent an abnormal extension of the placental villi through the decidua basalis into the myometrium and has been used by many authors as a marker of PAS on grey-scale ultrasound.[18]

The anatomy of the placental bed changes with advancing gestation. At the end of the first trimester, when the definitive placenta is fully formed it is made of 2 layers i.e. a thick decidua containing numerous glands and the terminal coils of spiral arteries and the superficial myometrium containing the basal arteries. As pregnancy advances, the decidual layer becomes thinner and discontinuous (Figure 5) and the myometrium will also become thinner and more heterogeneous due to the progressive dilatation of the utero-placental circulation. These layers generate an echolucent ultrasound signal under the placenta (Figure 6).

Loss of the clear zone has been reported in around 70% of cases in those series that have included data on the depth of villous myometrial invasion.[18] Some authors have found that this sign is not accurate for the diagnosis of PAS as its appearance will vary with advancing gestation.[61,62] In addition, it will also change with the location of the placenta inside the uterine cavity, direct pressure of the ultrasound probes and/or the filling of the bladder (Figures 6 and 7) and may be obscured by the amount of scar tissue present.

Myometrial thinning: to <1mm or to where the myometrium becomes undetectable on ultrasound, has been used a prenatal diagnostic sign for PAS[63-66] but it is only reported in 50% of the cohort studies.[18] This can be seen when the placenta develops underneath a major scar defect, where the myometrium is thinner than normal or completely replaced by scar tissue. In this case, the myometrium will become thinner with advancing gestation independently of any abnormal villous invasion. This thinning effect is more pronounced in the third trimester, in particular after 32-34 weeks when the lower uterine segment is further stretched by the combined action of the fetal presentation and Braxton-Hicks uterine contractions. This may contribute to false positive diagnoses where extreme myometrial thinning is incorrectly diagnosed as abnormal invasion. Occasionally, the myometrium may partly dehisce or become so thin that the placenta can be seen through it at delivery; this phenomenon should be described as a 'uterine window' (Figure 8) as it represents deficient myometrium rather than abnormal placentation.

In true PAS, especially PP, the myometrium appears excessively thin or undetectable due to villous invasion. This not only results in the loss of the clear zone but also changes the echogenicity of the myometrium itself, resulting in a loss of visual contrast between placental tissue and myometrium. In invasive placentation, as the villi breach the serosa, the myometrial echogenicity becomes indistinguishable from that of the placental tissue (Figure 9). The sonographer must take care with this sign as like the clear zone, myometrial thickness will also be influenced by direct pressure of the ultrasound probes, and the fullness of the maternal bladder.

Placental lacunae: are numerous, large, irregular sonolucent intra-placental spaces often described on ultrasound[5,54,60,61] giving the placenta a “moth-eaten” appearance in PAS in both transabdominal (Figure 10) and transvaginal (Figure 11) ultrasound. It is the most common ultrasound sign described in PAS with around 80% of the authors reporting them antenatally, independently of the depth of invasion.[18] Other terms have been used to describe these spaces including “placental lakes” [6,55,67] and “Swiss cheese”.[67,68]

Placental lakes are seen as echolucent areas often in the centre of a lobule or cotyledon (Figure 12), under the chorionic plate or in the marginal zone. These lakes are a common finding in normal pregnancies from the end of the first trimester but changes in their peripheral echogenicity (resulting in the term echogenic cystic lesions) has been associated the development of intervillous thrombosis[69] and utero-placental insufficiency.[70,71] The shape and number of lakes will vary with gestational age, with the location of the placenta inside the uterine cavity and with direct pressure of the ultrasound probes (Figure 12).

The difference between the lacunae associated with abnormal invasion and placental lakes is not clear cut, but relates to number, shape, location and velocity of the blood flow inside the space. Finberg attempted to classify these features, with grade 3 representing the lacunae seen with invasive placentation.[54] The lacunae are often numerous in one part of the placenta, large and irregular in size. They develop secondary to the distortion of the anatomy of one or more cotyledons including an inter-lobular septa[3] due to the arrival of high velocity (peak systolic velocity often >10 cm/sec) maternal blood from a radial or arcuate artery (Figure 13).[72] Placental lakes may also

arise secondary to the presence of a larger than average feeder vessel supplying an increased blood flow volume to the lobule (Figure 13), thus focally distorting its anatomy, but the impact on the cotyledon is less pronounced as the vessel involved is a spiral artery (Figure 3). However, in normal placentation, it is unlikely that there will be many such vessels resulting in fewer lakes and the underlying myometrium is of normal thickness. Both lacunae and lakes become more prominent from the end of the first trimester when the intervillous circulation is established[48,49] and will change in size and shape as pregnancy advances.

By contrast, the “Swiss cheese” transformation of the placenta describes the cystic hydropic changes of the villi found in a partial hydatidiform mole.[73] These lesions are smaller and distributed at random within the placental structure. They never contain a fetal circulation and thus the “Swiss cheese” terminology should not be used to describe the vascular lacunae found in PAS.

Bladder wall interruption: often described on grey-scale ultrasound as an interruption, loss or irregularity of the bladder wall or of the hyperechoic line between uterine serosa and bladder lumen.[54,74] This sign may arise as a direct result of villous invasion into the muscle of the posterior wall of the bladder, thereby changing its echogenicity, but is most likely an ultrasound artefact arising from the massive neovascularity found within the peritoneal fold between the anterior wall of the uterus and the posterior wall of the bladder (Figure 14). Insonation of the walls of the numerous tangled vessels disrupts the flat surface required to provide the bright straight line usually seen resulting in the apparent interruptions.

Care must be taken by the sonographer to ensure that the break seen in the bright line representing the posterior bladder wall is a genuine area of echolucency and not artefact as a result of ultrasound dropout from the angle of insonation.

Placental bulge: describes the 'ballooning' of the uterus containing the placenta away from its expected plane into the surrounding tissue, usually the bladder. This sign is seen on ultrasound (Figure 14) and MRI imaging. It most likely represents villous invasion deep into and/or through the myometrium resulting in loss of structural integrity of the surrounding uterine muscle. The placenta will then 'bulge' outwards into surrounding structures. This phenomenon is seen at laparotomy and has been described as the 'snowman sign'.[75]

Exophytic mass: describes the invasion of the villous tissue through the myometrium and the serosa into adjacent extrauterine organs, usually the bladder. This focal exophytic mass of placental tissue, extending beyond the uterine serosa should only occur in cases of PP. In case reports and cohort studies that provide detailed data on the depth of invasion, bladder wall interruption, bladder bulge and exophytic mass are collectively reported in 33% of the cases of invasive placentation.[18]

Sub-placental and/or utero-vesical hypervascularity: resulting from excessive dilatation of the utero-placental circulation beyond the spiral arteries i.e. including the radial and arcuate arteries, is a prominent feature of PAS on prenatal ultrasound.[18,55,56,74,76-79] This is often accompanied by extensive neovascularization

within the peritoneum, especially between the anterior wall of the uterus and the posterior wall of the bladder.

The use of CDI (Figures 10 and11) has enabled visualization of the utero-placental circulation in greater detail; up to 81% of the cases of PI and 75% of the cases of PP present with hypervascularisation patterns within or under the placental bed (the subplacental zone).[18] In addition, vessel distributions are more heterogeneous in PI with the size and spatial organization of the PI vascular architecture at the utero-placental interface differing from normal placentation.[79] A combination of sonography, vascular casting and oxygen measurements has shown that an extensive network of arterio-venous shunts normally exist within the myometrium in the placental bed.[80] Villous invasion into these deep shunts may partly explain the persistence of significant blood flow after delivery in PAS[81] as well as differences seen in vessel distribution, size and spatial organisation in the placental bed area. Invasion into these shunts is the proposed cause of the large areas of abnormal vascular confluence seen with 3D power Doppler imaging in cases of PP.[76] In addition, the vasculature characteristics of the placental bed may vary in PAS depending on the position of the placenta inside the uterine cavity, whether near to or far from the main uterine arteries, and on the remodelling of the myometrial circulation around the scar area. Thus, like the placental bed, myometrial thickness and lacunae, the vascular features under and around the accreta area will change with advancing gestation.

Placental lacunae feeder vessels: seen as vessels with high velocity blood flow arising from the deep arterial vasculature of the myometrium i.e. radial or arcuate

arteries and feeding the lacunae (Figure 13). An ultrasound study has found that the total area occupied by vessels in normal and PI placental beds is similar, but that vessels are significantly sparser and larger in invasive placentation.[79] This could explain the abnormal haemodynamics underlying the development of the lacunae in invasive placentation.

Bridging vessels: are seen as CD signals arising in the myometrium and appearing to travel beyond the uterine serosa and into the bladder before disappearing (Figure 14). This 'bridging' is an ultrasound artefact as these vessels do not traverse between the myometrium and the bladder but are actually the contorted vessels of the neovascularity within the peritoneum caught in cross-section in a 2D image (Figure 14). They have been referred to as "bladder varicosities" in cases of placenta previa accreta.[77, 78]

Collectively, these CDI features have been reported in 66% of the cases of AIP diagnosed prenatally[18], and are due to the dilatation of large and deeper myometrial vessels below the JZ of normal implantation.

PATHOLOGICAL CORRELATIONS

Many imaging cohort studies on PAS do not include a histopathological confirmation, or when they do it is limited to a brief description of the number of cases that were examined without a precise description of the extension of the abnormal placental attachment, degree of invasion and/or spatial relationship of the accreta villous tissue with the previous CD scar, cervix, main uterine circulation etc. In a recent systematic review, we found that detailed correlations between ultrasound findings and accreta

grading of a delivery were only reported in 34 out of 1078 cases[18], although more than 90% of the cases had a caesarean hysterectomy or a secondary hysterectomy after a failed attempt at conservative management. This limits the correlation between prenatal ultrasound features and clinical evidence at the time of delivery. This will also lead inevitably to false positive diagnosis of PAS in many cases, in particular when the surgeon is able to remove the placenta manually and the bleeding is secondary to uterine atonia and not to damage of the myometrial circulation, or when the placenta is praevia and there is a scar dehiscence with placental tissue visible through the uterine serosa.

The first histopathological series of PA by Irving and Hertig included only cases of abnormal adherence.[1] All of their 18 cases presented clinically as “failure of the placenta to separate” and 14 required a secondary hysterectomy to control the bleeding. In seven cases, the obstetrician was able to remove the placenta manually and in three cases the retained villous tissue was removed by curettage. None of their cases of hysterectomy with placenta “in situ” presented with macroscopic evidence of an excessive dilatation of the radial and arcuate circulation, and in all cases the diagnosis was made exclusively on the histological finding of “complete or partial absence of the decidua with villi directly embedded in the myometrium”. Only one of their patients (case 12) had a prior CD, and the only different pathological finding in that case was that the scar area where the placenta was attached was thinner than the rest of the uterine wall. All their remaining patients had a history of manual removal, curettage and/or endometritis, suggesting that minor traumas and/or chronic inflammation can lead an abnormally adherent placenta in the next pregnancy. On one

occasion, they found on microscopic examination “an increased number of dilated veins in the superficial layers of the myometrium”. Similarly, out the 86 cases of PAS included in their literature review up to 1935, there were 19 cases of previous manual removal of the placenta, 10 cases of previous curettage, three cases of endometritis and only one case of prior CD.[1]

Until the 1970s, the diagnosis of PAS was almost exclusively histological[2,3,82,83] and only very rare cases of placenta increta and percreta were reported in the literature before that period, and without evidence of obvious macroscopic uterine vascular changes.[84-86] Lukes et al[2], were the first to highlight the need to differentiate between abnormally adherent and abnormally invasive placentas, and suggested to use the “adherent or invasive placenta” to describe the over-all group of PAS. Modern pathological studies have also shown that the lateral extension of a PAS can vary and be focal, partial or total according to the number of accreta lobules involved.[2-5] They have also shown that the degree of villous adhesion or invasion is rarely uniform across the placental bed and that many cases of PAS have creta and increta areas (Figure 2). The fact that accreta placentation can be heterogeneous may explain why no ultrasound sign, or combination of ultrasound signs, has so far been found to be specific of the depth of accreta placentation and accurate for the differential diagnosis between adherent and invasive placentation.

Attempts at manual removal of the placenta can distort the spatial relationship between the accreta villous tissue and the uterine wall.[2] This may limit in some cases the accuracy of the microscopic diagnosis, in particular, if the histological examination of the utero-placental interface is incomplete.[2-5] Macroscopic changes in the radial/arcuate

circulation may not always be obvious to the pathologist as the vasculature will collapse during the hysterectomy procedure. The decidual layer becomes thinner and discontinuous with advancing gestation (Figure 5), and this can also make the microscopic diagnosis of adherent placenta difficult in particular if the accreta area of the myometrium is not extensively sampled.[2] Dannheim et al[87] have recently proposed methods of gross dissection, microscopic examination and reporting of hysterectomy specimens containing PAS. Their protocol facilitates retrospective correlation with surgical and imaging findings as well as standardized tissue sampling for potential research. It is essential that similar protocols are used to improve not only the diagnosis but also the management of the PAS.

Conclusions

Placenta accreta spectrum is a histopathologic term that defines abnormally adherent and invasive placentation. Both are the consequence of a deciduo-myometrial disorder, and the trophoblastic changes of accreta placentation are probably secondary to their migration beyond the JZ and their exposure to a different biological environment. This loss of control by the decidua of trophoblast invasion and spiral artery remodelling gives the extravillous trophoblast greater access to the deep myometrium and its circulation. The depth of penetration of the villous tissue is likely to be related to the extent of the deciduo-myometrial damage. Microscopic damage secondary to manual removal, uterine curettage and endometritis are more likely to lead to superficial adherent placentation. By contrast, a surgical scar defect is associated with both the absence of

endometrial re-epithelialization of the scar area and vascular remodeling around the scar area and favors the development of invasive placentation.

In the adherent placenta, the chorionic villi are in direct contact with the myometrium with no obvious plane of cleavage. The clinical differential diagnosis between an abnormally adherent placenta and a retained placenta can be difficult if the placenta is only partially adherent. In invasive placentation, the placental villi penetrate deeply within the uterine wall, including in the myometrial circulation, and cannot be removed manually and/or by curettage. With the exponential increase of CD around the world and also with increasing maternal age and the need for artificial reproductive techniques and minor uterine surgical procedures, the number of PAS cases, and in particular invasive placentation, will continue to increase.

Ultrasound signs of adherent and invasive placentation vary with gestational age, and depend on the thickness and composition of the placental bed, prior scar defects, depth of invasion and the lateral extension of the villous tissue. Abnormal adherence and invasion may co-exist in the same placental bed, and thus accurate correlation of pathological and clinical findings with the imaging is essential. It is therefore necessary that these protocols are standardised and used by both clinicians and pathologists to improve the diagnostic accuracy of ultrasound imaging and to define ultrasound signs that may be useful in the screening of women at high risk of PAS.

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Figure legends

Fig 1: Diagram showing an anterior placenta previa on a caesarean scar and the different grades of placenta previa accreta: Creta (PC) where placental (P) villi adhere to the myometrium (M), Increta (PI) where the villi invade the myometrium and Percreta (PP) where the villi invade the entire myometrium and cross the uterine serosa (S).

Fig 2: Diagram showing an anterior placenta previa accreta combining areas of abnormal adherence and invasion: Creta (PC), Increta (PI) and Percreta (PP). D= Decidua; M= myometrium; S= Serosa.

Fig 3: Diagram showing a placental cotyledon in normal placentation (A) and increta placentation (B) reaching the deep myometrial circulation. Note that distortion of the normal cotyledon anatomy in the increta placentation with the loss of the inter-cotyledon septa and formation of a lacuna (L).

Fig 4: Microscopic view of the placental bed from a hysterectomy specimen at 34 weeks in a pregnancy complicated by placenta previa increta (H&E x 4) showing the disruption of the decidua (D) by placental villi (PV) and the very thin myometrium (M).

Fig 5: Microscopic views of the placental bed from hysterectomy specimens with placenta in-situ (Boyd collection, The Centre for Trophoblast Research, University of Cambridge): A: Specimen H1094 CRL 73 mm showing a thick decidua (D) between the placental villi (PV) and the myometrium (M) (H&E x 2.5); B and C: Specimen H751 CRL 260 mm. The decidua is much thinner (H&E x 2.5) and absent in some areas (Reticulin x 10). Scale bar (A and B) = 0.5 mm, C = 0.1 mm.

Fig 6: Transabdominal ultrasound longitudinal views of the same part of a placental bed of a low-lying placenta (P) at 32 weeks using exactly the same machine settings. A: Full bladder (B) and minimal probe pressure; B: Full bladder with increased probe pressure; C: Empty bladder and minimal probe pressure. Note the changes in the clear zone (arrows)

Fig 7: Transabdominal ultrasound longitudinal views of the placental bed at 34 weeks in a pregnancy after 3 prior caesarean sections showing the changes on the clear zone (arrows) with probe pressure (right).

Fig 8: Myometrial thinning secondary to uterine thinning at a scar defect. A: Transabdominal ultrasound longitudinal view of a placenta (P) previa at 36 weeks showing a myometrium defect (arrow) under the bladder (B). Note the absence of the clear zone and myometrium in the area. B: Findings at surgery later the same day of a ‘uterine window’ (arrow).

Fig 9: Myometrial thinning secondary to abnormally invasive placenta accreta. A: Transabdominal ultrasound longitudinal view of a placenta previa at 36 weeks showing no clear zone or myometrium detectable (arrow) between the placenta (P) and the

bladder (B). B: Findings at surgery later the same day showing the neovascularization and myometrial distension over the accreta area.

Fig 10: Transabdominal ultrasound longitudinal views of a placenta (P) previa accreta at 36 weeks showing: A. “moth eaten” area with numerous lacunae of different size and shape secondary and B. high velocity, turbulent blood flow within the lacunae on CDI next to the bladder (B).

Fig 11: Transvaginal ultrasound views of a placenta previa increta at 20 weeks showing: A. “moth eaten” appearance of the placenta with numerous lacunae of different size and shape secondary (arrow) and B. high velocity, turbulent blood flow within the lacunae on CDI.

Fig 12: Transabdominal ultrasound longitudinal views of placenta (P) at 33 weeks of gestation in pregnancies with no surgical history and no placenta accreta at birth showing. A. Centro-cotyledon lake (arrow) with minimal probe pressure (left) and increased probe pressure (right). B. Multiple irregular lakes mimicking a “moth eaten” appearance similar to that seen in invasive placentation.

Fig 13: Transabdominal ultrasound longitudinal views of placenta (P) showing: A. Placenta previa accreta at 20 weeks with a feeding artery from the arcuate circulation between the placenta and the bladder (B) entering a lacuna and B. Centro-cotyledon lake at 28 weeks of gestation in an uncomplicated pregnancy. Note the presence of the uterine myometrium (M); C. Velocity flow entering the lake from the corresponding feeder spiral artery.

Fig 14: Placenta (P) previa accreta. Transabdominal ultrasound longitudinal views at 28 weeks showing: A. bladder bulge demonstrating bladder (B) wall interruption (arrow) and B. bridging vessels on CDI; C. Findings at surgery at 34 weeks showing the extensive neovascularity and myometrial distension over the increta area.