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Debunking 20th century myths and legends about the diagnosis of placenta accreta spectrum

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Introduction

Placenta accreta is a spectrum disorder, which was originally defined by Irving and Hertig in 1937[1] clinically as having difficulties in delivery of the placenta and histologically by the absence of decidua with direct attachment of placental villi to the superficial myometrium[1]. It is a congenital disorder meaning that the process leading to the abnormal attachment of the placenta to the uterine wall develops *in-utero*[2,3]. Although, both the clinical and histological features of accreta placentation appear on a spectrum, meaning that patients are affected in different ways and to different degrees, Irving and Hertig definition has prevailed for over 80 years. In particular, histopathologic studies have used the absence of the decidua with direct attachment of the villous tissue to the superficial myometrium as the gold-standard for the diagnosis of placenta accreta spectrum (PAS) including when reporting on more severe PAS grades, i.e. placenta increta and percreta[4-7]. The ~~pathological~~ concept of an intact fibrin layer serving as a barrier to abnormal placental invasion extends even further back to 1887, the year of Raissa ~~–~~Nitabuch's dissertation on the topic of normal placental circulation[6]. Most authors of clinical studies have and continue to describe cases of PAS as "confirmed by histopathology" without any detailed description of the methodology used. This has led to considerable heterogeneity in epidemiology data with wide variations in the prevalence of PAS and incidence of its different grades in general population studies[8,9].

Following the worldwide exponential increase in caesarean delivery (CD) rates, women with a prior history of CD, presenting with an anterior low-lying/placenta previa, now have the highest risk of PAS disorders[2,10,11]. This risk increases directly with the number of prior CDs[12]. The combination of placenta

previa and accreta placentation leads to high maternal morbidity and sometimes mortality due to massive obstetric hemorrhage at delivery, in particular if the surgeon is unaware of the presence of PAS[11]. This group of patients should be the primary target of national screening programs[13]. However, the use of terminology and clinical description referring to neoplastic disorders[14,15] such as “placental invasion” or “retro-placental neovascularization” combined with the use of Irving and Hertig basic criteria to confirm the diagnosis of all grades of accreta placentation has becoming increasingly confusing and is potentially delaying progress in the diagnosis and management of PAS. In this commentary, we discuss these issues, their impact on our understanding of the pathophysiology of accreta placentation, and the need to develop new non-evidence-based protocols for the diagnosis of accreta placentation.

Clinical and histopathologic confirmation of the diagnosis at birth

Several clinical grading systems for PAS have been proposed to define the degree of abnormal placental attachment at vaginal birth and/or cesarean including intraoperative findings[16-18]. However, for the so-called cases of placenta percreta they mainly describe uterine dehiscence and adhesions between the uterine serosa and the posterior wall of the bladder. To standardize the definition of PAS categories, the International Federation of Gynecology and Obstetrics (FIGO) has recently proposed a classification for the diagnosis and grading of PAS which includes anatomical clinical criteria at delivery confirmed by histopathologic findings[20] and has been used as the background for the histopathologic reporting guidelines [21].

The clinical symptoms of the superficially adherent placenta, also called placenta “creta” or “adherenta”, include difficult manual placental delivery as described by Irving and Hertig.[1] More recent descriptions have also included

"piecemeal removal of the placenta," absence of spontaneous placental separation 20-30 min after birth despite active management, retained placental fragment requiring curettage after vaginal birth, and heavy bleeding from the placentation site after removal of the placenta during cesarean delivery[8]. These descriptions are similar to those of placental retention which is merely a non-accreta placenta entrapped in the uterus owing to constriction of the cervix after childbirth[21]. If the retained placental tissue is delivered in full, in one piece or in several pieces, within 30 min to 24h after birth these cases should not be reported as PAS.

The concept of the "invasive placenta" was introduced by Lukes et al[4] in 1966, although most of their cases were described using Irving and Hertig histologic criteria for superficial abnormal placental adherence and they showed no image of placenta percreta in their manuscript. They proposed a histological classification for PAS based on the depth of the villous penetration of the myometrium which has been used ever since. A major limitation with relying on histo-pathologic evaluation as the gold standard of PAS is the reality that the specimen sent from the surgical team often does not represent the disorder as it existed in the body. M~~They also reported that as m~~ost hysterectomy specimens arrive at the laboratory distorted by attempts to remove the placenta during delivery, so macroscopic examination and accurate sampling of the accreta areas are considerably limited. When u~~U~~sing a method of fresh sampling of the accreta area[22], we found no evidence of transmural villous tissue[23]. Similarly, our systematic literature review of case reports of placenta percreta with histopathologic images found no histologic evidence supporting the existence of a condition where the villous tissue invades the entire uterine wall including the serosa and/or beyond[23]. Our data support the concept that even in severe cases of PAS, where the placenta is visible through the serosa of a dehiscent

lower segment, the villous tissue is almost always contained within the thin scar shell[24] and it is the surgical manipulation and dissection that leads to false diagnosis of placenta percreta (**Figure 1**). If the placenta can be fully delivered in these cases, without having to perform a partial myometrial resection to remove accreta villous tissue, they should not be reported as PAS. The concept of a scar shell is reinforced by other researchers who have provided evidence that placental extension to the serosa without evidence of serosal invasion is a finding common to cesarean scar pregnancies (CSPs)[2,25] ~~(reference)~~ which are histologically similar to, and thought to be a precursor for, PAS.

We recently showed that > 70% of samples from accreta areas at delivery present with a layer of thick fibrinoid deposition at the level of the utero-placental interface on microscopic examination[26,5]. These ~~changes~~ fibrinoid deposition ~~are~~ is associated with distortion of the "Nitabuch's membrane" and practically glues the anchoring villi to the scarred myometrium. This can explain the loss of parts of the physiological site of detachment of the accreta placenta. ~~By contrast, in controls, the Nitabuch's stria and basal plate became discontinuous with advancing gestation bring the villous tissue in close contact with the superficial myometrium[25].~~ The depth of abnormal villous attachment may vary depending on the residual thickness of the scar and different depths of abnormal villous attachment often co-exist in the same specimen (**Figure 2**) but in no cases did we find villous tissue inside or beyond the uterine serosa. These findings challenge for the first time, the 1937 concept of Irving and Hertig that the absence of decidua with villous tissue ~~directly~~ simply attached to the superficial myometrium is the main mechanism for accreta placentation[1].

Prenatal imaging diagnosis

Tabsh et al[2]~~[7]~~[6] were the first in 1982 to ~~report~~ describe a case of prenatal ultrasound diagnosis of PAS which presented at 24 weeks as an anterior placenta previa with absence of the subplacental sonolucent zone (clear zone) under a thin lower segment uterine wall. T~~t~~hey described their case as placenta "increta" but ~~.~~ ~~Interestingly,~~ the histologic image included in their report showed placental villi simply abutting to an apparently normal uterine wall as described by Irving and Hertig for superficial placenta accreta[1]. The main ultrasound features of PAS were essentially described by Finberg and Williams[2]~~[8]~~[7] and by Chou et al[2]~~[9]~~[8] for grey-scale and colour Doppler imaging (CDI), respectively. In 2016, the European Working Group on abnormally invasive placenta (EW-AIP) published a proposal to standardize these ultrasound signs by Delphi consensus[30]~~[29]~~. The signs were described according to ultrasound findings on grey scale, 2D CDI, or 3D power Doppler. The most commonly used ultrasound signs for grey-scale imaging are the loss of clear zone (98%) and placental lacunae (96.1%) and for CDI, subplacental hypervascularity (85.7%) and bridging vessels (61.9%)[15]. The 2018 American College of Obstetrician Gynecologists (ACOG) and Society for Maternal-Fetal Medicine (SMFM) guidelines states that although ultrasound evaluation is important, the absence of ultrasound findings does not preclude a diagnosis of PAS and that clinical risk factors remain equally important as predictors of PAS by ultrasound findings[3]~~[1]~~[0].

A recent report of the SMFM[3]~~[2]~~[1] has highlighted that most studies on the prenatal ultrasound screening of PAS are retrospective in design, lack control "low-risk" comparison groups, and do not provide clear definitions of the PAS markers being studied. There has also been considerable variability in the ultrasound criteria

used for the diagnosis of low-lying/placenta previa and the gestational age at which the diagnosis is confirmed[9]. Furthermore, most studies lack detailed information on the criteria used to confirm the diagnosis of PAS at birth or they simply refer to Irving and Hertig clinical and histologic criteria for abnormally adherent placenta[8,9]. These issues limits considerably the ability to make comparisons among studies and evaluate the reported diagnostic performance statistics. This could explain why ultrasound imaging has a lower diagnostic rate for posterior PAS than magnetic resonance imaging (MRI) in some studies[32] but this should not be an issue for specialized diagnostic teams with experience in transvaginal sonography (TVS).

We have previously reviewed the pathophysiology of the different ultrasound signs[43]. The main ultrasound features used for the diagnosis of PAS can be separated into anomalies of uterine contour or uteroplacental interface i.e loss of clear zone, myometrial thinning and placental bulge; and abnormalities of the utero-placental circulation including subplacental hypervascularity and lacunae. Anomalies of the uterine contour are secondary to uterine remodelling following scarification (Table 1). These changes are more pronounced in the third trimester when the lower uterine segment is stretched by the combined action of the fetal presentation and Braxton-Hicks uterine contractions and in women with multiple prior CDs[43]. We recently showed that in women with a prior history of multiple CDs presenting with a low-lying/placenta previa, contour anomalies are found with a similar incidence in non-PAS and PAS cases[54]. These data support the concept that these anomalies are secondary to scarification and remodelling of the lower uterine segment rather than to accreta placentation.

By contrast, anomalies of the utero-placental circulation are a common finding in the majority of cases of PAS confirmed at delivery near term[22,36]. However, changes in the subplacental vasculature in the early second trimester are similar in ~~cesarean scar pregnancies (~~CSPs~~)~~ and non-PAS low-lying/placenta previa (**Figure 3**) indicating that the increase in subplacental vascularity of the definitive placenta is essentially physiological and secondary to its lateral growth[37]. In addition, the definition of what constitutes sub-placental or utero-vesical "hypervacularity" in the second half of pregnancy remains elusive and there is currently no vascularity score to assess relative degrees of abnormality. Placental lacunae have been reported from 11-14 weeks in pregnancies with confirmed PAS at birth[36-37,39]. However, differences between lacunae and placental lakes are not always clear (**Figure 4**) and not all cases of PAS present with lacunae. Finberg and Williams[28] proposed a score for placental lacunae (0= none; 1+= 1-3; 2+= 4-6; 3+=>6) and high scores are strongly associated with PAS[34-36]. More recently, Cali et al have proposed an ultrasound staging which mixes contour and uteroplacental vascular anomalies[17]. However, their classification does not differentiate between lakes and lacunae and refers to both the degree of trophoblastic and villous invasion. Due to the small number of CSPs that continue into the second half of pregnancy, data on changes of utero-placental vascular features with advancing gestational age in histologically confirmed cases of PAS at birth are currently limited and would benefit from the development of an international database.

The main MRI features of accreta placentation include abnormal uterine bulging, dark intra-placental bands on T2-weighted imaging, heterogeneous signal intensity within the placenta and disruption of the uteroplacental zone[40-48]. Recent data suggest that the finding of a placental budge on MRI had the highest sensitivity

for the diagnosis of severe PAS[43,1]. However, as a placental bulge is a hernia of placental tissue through a dehiscence of the uterine wall and is independent of accreta placentation (Table 1), this sign is unlikely to add much to the prenatal diagnosis of PAS. A recent study found that interobserver agreement is almost perfect for the diagnosis of placenta previa; substantial for myometrial interruptions and placental bulging; and moderate to slight for other signs of PAS but the accuracy and predictive value are modest and lower than previously reported[46,5]. Furthermore, MRI results in a change in diagnosis that could alter clinical management of PAS in more than one third of cases, but when changed, the diagnosis is often incorrect[47,6].

Studies comparing the diagnostic accuracy of ultrasound imaging and MRI in diagnosing placenta accreta are inevitably biased towards MRI, as only suspected cases of PAS on ultrasound scan are subjected to MRI examination[44,3,45,4]. Gadolinium-based MRI contrast improves visualisation of the utero-placental vasculature, but the agents cross the placental-fetal barrier and its use is therefore not recommended during pregnancy[40,39,41,0,48,7]. Overall, national and international guidelines have concluded that given its high cost and limited clinical value, MRI should not be used routinely as an adjunct to ultrasound in the routine diagnosis of PAS[3,10,40,39,48,7]. Clinicians faced with a difficult PAS diagnosis need clearer evidence-based guidance on when MRI may be appropriate or helpful. In its absence, our anecdotal experience is that clinicians turn MRI as a tie-breaker or confirmatory test when ultrasound impression is unclear. This approach is, in our opinion, usually unhelpful (particularly outside of highly experienced radiology units) and until

research demonstrates a clearly-defined benefit of MRI, we believe it should be used only sparingly as a diagnostic test for PAS outside of research protocols.

Moving forward in the diagnosis of PAS

Current clinical classification systems are prone to confirmation bias, with the surgeon more likely to confirm what has been reported on prenatal imaging and pathologists basing their diagnosis on what the surgeon has reported. The main impact is at both ends of the spectrum of accreta placentation with placenta retention and remodelling of the lower segment after CD being misdiagnosed as PAS. Thus, there is need to develop new standardized clinical description and classification using intra-operative features that reflects evidence-based histopathologic findings beyond Irving and Hertig's simplistic description. These new classifications and descriptions should abandon the concept of 'invasive' villous tissue which, in our opinion, is not part of the progression or pathophysiology of PAS beyond the physiological phenomenon of extra-villous trophoblastic migration into the uterine wall[2,3,3443,3665].

There is also a need to use new standardised ultrasound protocols that include a description of gestation age at diagnosis, changes in appearance with advancing gestational age and TVS evaluation of cervical length, the precise placental location, the lower segment vasculature including vasculature of the cervix and remodelling of the lower uterine segment immediately above and around the cervix. It is these factors, not quantification of depth of placental 'invasion', that may better meaningfully predict outcomes. More data are also needed on the ultrasound

signs that can identify CSPs at risk of uterine rupture in early second trimester and/or of developing into PAS in the second half of pregnancy.

Conclusions

Recent findings have challenged the 20th century myth that the severity of PAS is due to the abnormal invasiveness of the villous tissue and the existence of the legendary placenta percreta defined by transmural villous invasion into the uterine serosa and beyond. Accurate estimation of the prevalence and outcome of PAS is currently problematic because of the varying use of imaging and clinical criteria to define it before and at birth and the lack of detailed histopathologic pathologic confirmation of the diagnosis in most series. Current histopathologic criteria do not accurately reflect pathophysiology and only modestly correlate with clinical outcomes. Standardization and modernization of sonographic, clinical, and pathologic criteria for PAS diagnosis and grade is pivotal to improvements in diagnosis and treatment of PAS. Health provision for the development of centres of excellence with specialist surgeons, equipment, drugs, blood bank and intensive care infrastructure to safely manage women presenting with PAS requires an accurate evaluation of its prevalence and outcomes.

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FIGURE LEGENDS

Figure 1. A: Preoperative longitudinal transabdominal ultrasound view of the lower uterine segment showing and anterior placenta (P) previa covering the cervix (Cx) with increased vascularity of the utero-bladder (B) interface and large lacunae (*) with a large feeder vessel; **B**: Intra-operative view showing a dehiscent lower segment through which the placenta can be seen (*). Note a tangled bed of dilated vessels running cranio-caudally next to the dehiscent area; **C**: Hysterectomy specimen showing the placenta protruding through the serosa of lower segment following dissection of the bladder below the dehiscent area at 37 weeks in a patient with 4 prior CDs.

Figure 2. Diagram showing superficial attachment (SA) and deep attachment (DA) of placental (P) villous tissue in the scar area of the myometrium (M) and adhesions (dark brown) between the uterine serosa ~~(orange)~~ covering the lower segment of the uterus and the serosa of the bladder (B). In the accreta areas, the villous tissue is covered by a thick layer of fibrinoid deposition (red) and remains contained within the serosa. AC= Amniotic cavity; ~~M= Myometrium;~~ Cx= Cervix.

Figure 3. A: Longitudinal transabdominal ultrasound view of the lower uterine segment and CDI mapping of the utero-placental vasculature at 14 weeks in a patient with 2 prior CDs presenting with a low-lying anterior placenta. **B**: Longitudinal transabdominal ultrasound view of the upper uterine segment and CDI mapping of the utero-placental vasculature at 13 weeks in a patient with 2 prior vaginal births and no history of uterine surgery. Note the increase utero-placental vascularity in both cases and the irregular placental basal plate in B (*). Both had a normal placental delivery at term. P: Placenta; AC: Amniotic cavity; B: Bladder.

Figure 4. A&B: Longitudinal transabdominal and transvaginal ultrasound views of the lower uterine segment at 20 weeks showing a placenta previa (P) with increase vascularity and large lacunae with feeder vessels (*) in a patient with 3 prior CDs and a focal area of placenta increta at birth; **C&D**: Longitudinal transabdominal ultrasound views of a posterior high and anterior high placenta (P) at 20 weeks showing large lakes with a lacunae appearance (*). Note the absence of large feeder vessels. Both patients had a normal placental delivery. AC: Amniotic cavity; Cx: cervix.

Table 1: Ultrasound description and pathophysiology of the main ultrasound associated with PAS.

Ultrasound signs	Ultrasound description[30,29,32,35]	Pathophysiology[34,36]
Loss of the 'clear zone'	**GSI**: Loss or irregularity of the normal hypoechoic plane in the uterine wall underneath the placental bed.	The thickness of this layer, which probably corresponds to the decidua decreases with advancing gestation and is altered by remodelling of the uterine wall during the scarification process.
Myometrial thinning	**GSI**: Myometrial thickness <1mm or undetectable.	Area of the myometrium lost during the scarification process of the lower uterine segment. The myometrial thickness decreases with advancing gestation and number of prior CDs.
Bladder wall interruption	**GSI**: Partial or complete interruption, loss or irregularity of the bladder wall or of the hyperechoic line between uterine serosa and bladder lumen.	Anatomical artifact associated with the remodelling of the uterine wall during the scarification process and the increase in subplacental vascularity.
Placental bulge	**GSI**: 'Ballooning' of the uterus containing the placenta into the surrounding pelvic structure.	Large placental tissue hernia through a dehiscent uterine wall following myometrial thinning during the scarification process.
Exophytic mass	**GSI**: Focal area of the myometrium where the placenta appears to protrude outside the uterine wall.	Focal placental tissue hernia through a small defect of the uterine wall following scarification.
Subplacental hypervascularity	**CDI**: Striking amount of colour Doppler signal seen in placental bed demonstrating multidirectional flow and aliasing artefact.	Excessive dilatation of the deep uterine circulation (radial and arcuate) resulting from development of part of the definitive placenta in a scar defect.
Placental lacunae	**GSI & CDI**: Large, irregular hypoechoic intra-placental spaces located above large feeder vessels, giving the placenta a "moth-eaten" appearance.	Distortion of a placental cotyledon due to chronically high velocity maternal blood flow entering the intervillous space directly from a radial or arcuate artery.
Bridging vessels	**CDI**: Vessels appearing to extend from placenta bed, across uterine wall into bladder or other pelvic organs.	Dilated radial or arcuate arteries between the accreta area and the uterine serosa.

GSI: Grey-scale imaging; CDI: Colour-Doppler imaging; CD: caesarean delivery