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Review article

The prenatal diagnostic indicators of placenta accreta spectrum disorders

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ABSTRACT

Placenta accreta spectrum (PAS) disorders refers to a heterogeneous group of anomalies distinguished by abnormal adhesion or invasion of chorionic villi through the myometrium and uterine serosa. PAS frequently results in life-threatening complications, including postpartum hemorrhage and hysterotomy. The incidence of PAS has increased recently as a result of rising cesarean section rates. Consequently, prenatal screening for PAS is essential. Despite the need to increase specificity, ultrasound is still considered a primary adjunct. Given the dangers and adverse effects of PAS, it is necessary to identify pertinent markers and validate indicators to improve prenatal diagnosis. This article summarizes the predictors regarding biomarkers, ultrasound indicators, and magnetic resonance imaging (MRI) features. In addition, we discuss the effectiveness of joint diagnosis and the most recent research on PAS. In particular, we focus on (a) posterior placental implantation and (b) accreta after in vitro fertilization-embryo transfer, both of which have low diagnostic rates. At last, we graphically display the prenatal diagnostic indicators and each diagnostic performance.

1. Introduction

Placenta accreta spectrum (PAS) disorders is divided into placenta accreta (the placental villi attach directly to the surface of the myometrium without invading), placenta increta (invade into the myometrium), and placenta percreta (invade into the serosa or surrounding structures) based on the degree of placenta villi invasion. The most popular explanation for the cause of PAS is that defects in the endometrial-myometrial interface prevent normal decidualization in the cicatricial area of the uterus, thereby permitting abnormally deep placental anchoring and trophoblast infiltration [1]. The incidence of PAS is rising sharply from 0.01% to 1.1% due to the increasing rates of cesarean delivery [2,3]. PAS is frequently associated with serious obstetric complications, such as uterine inertia at the site of implantation and placenta retention after delivery, and the complications could lead to postpartum hemorrhage and subsequent adverse outcomes including disseminated intravascular coagulation (DIC), local organ damage, and even maternal death

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Table 1
Summary of PAS prenatal diagnostic indicators and predictive performance.[a]

	Indicator	Explanation	Diagnostic performance	
Risk Factor			**Odds ratio (95% CI)**	
	Previous cesarean section (CS)	Caused by cesarean scar stimulation of implantation of the blastocyst in the area of the cicatrice and the abnormal adherence or invasion of villi within the scar tissue.	Any previous CS 8.8 (6.1−12.6) [9] 1 prior CS 6.6 (4.4−9.8) 2 prior CS 17.4 (9.0−31.4) ≥3 prior CS 55.9 (25.0−110.3) Prior CS not previa 3.7 (2.3−5.8)	
	Placenta previa (PP)	CS-related uterine scarring most frequently occurs in the thin bottom part of the uterus.	292 (196–400) [9]	
	Placental sites	Lateral and posterior PAS easily be ignored in prenatal diagnosis.	/	
	IVF-ET	Cause uterine contraction, possibly due to the release of prostaglandins following mechanical stimulation of the internal cervical os.	8.7 (3.8–20.3) [25]	
	Maternal age ≥35 years	Linked to confounding factors, rather than isolated maternal age.	4.6 (3.2–6.7) [9]	
	Twin pregnancies	Caused by confounding factors like IVF-ET, PP, and prior uterine surgery.	3.41 (2.57–4.52) [35]	
Biomarker			**Cut-off value**	**AUC (95% CI)**
	Alpha-fetoprotein (AFP)	AFP has certain predictive efficacy, but it cannot be an early indicator.	1.25 MoM [49]	0.573 (0.515–0.630)
	Human chorionic gonadotropin (hCG)	Diagnosis has certain limitations. Diagnosis should be made under the premise of excluding fetal malformations, even with PP.	1.25 MoM [46]	0.662 (0.605–0.715)
	Pregnancy-associated plasma protein-a (PAPP-A)	May help predict massive blood loss at delivery in the first trimester. Early diagnosis of pregnancies at high risk of PAS.	1.22 MoM [51]	/
	Cell-free fetal DNA (cffDNA) Cell-free placenta mRNA	cffDNA: still controversial and lacks related reports. Cell-free placenta mRNA: can reflect abnormal placental formation.	/	
	Angiogenic factor	The imbalance of VEGF[b], PIGF[c], and sFlt1[d] may cause placenta implantation.	/	
Ultrasound sign			**%Sensitivity (95%CI)**	**%Specificity (95%CI)**
	Cross-over sign (COS-1)	Can predicted the ultrasound staging and surgical outcome of PAS.	79.6 (66.5–89.4) [63]	91.0 (84.8–95.3)
	Placental lacunae	Irregular, hypoechoic spaces within the placenta containing vascular flow (which can be seen on grayscale and/or color Doppler imaging).	77.4 (70.1–83.1) [70]	95.02 (94.1–95.8)
	The abnormal uteroplacental interface	Include loss of the retroplacental hypoechoic zone, myometrial thinning, and sub-placental hypervascularity loss of clear zone was considered the most general ultrasound sign.	66.2 (58.3–73.6) [70]	95.8 (94.9–96.5)
	Abnormalities of uterus–bladder interface	Include uterine bladder wall interruption and bridging vessels.	49.7 (41.4–58.0) [70]	99.8 (99.5–99.8)
	Color Doppler abnormalities	Abnormalities on color Doppler and presence of abnormal vessels performed best as predictors of disorders of invasive placentation in high-risk women.	90.8 (85.2–94.7) [70]	87.7 (84.6–90.4)
MRI Sign			**%Sensitivity (95%CI)**	**%Specificity (95%CI)**
	Placental/uterine bulge	Deviation of the uterine serosa from the expected plane caused by abnormal bulge of placental tissue toward adjacent organs, typically toward the bladder and parametrium.	79.1 (60.3–90.4) [104]	90.2 (76.2–96.4)
	Intraplacental dark T2 bands	One or more areas of hypo-intensity on T2-weighted images, which are usually linear in configuration and often contact the maternal surface of the placenta	87.9 (70.9–95.6) [104]	71.9 (55.6–84.0)
	Myometrial thinning/ disruption	Thinning of the myometrium over the placenta to less than 1 mm or even invisible.	92.0 (79.2–97.2) [104]	75.6 (50.4–90.4)
	Loss of low T2 retroplacental line	Loss of a thin dark line behind the placental bed, as seen on T2-weighted image.	81 (57–93) [105]	81 (57–93)
	Bladder wall interruption	Irregularity or disruption of the normal hypointense bladder wall, which can be accompanied by blood products in the bladder lumen.	80.0 (28.0–99.5) [104]	98.6 (92.2–100)
	Focal exophytic placental mass	Placental tissue seen protruding through the uterine wall and extending beyond it. Associated with placenta percreta.	69.2 (41.8–87.5) [106]	98.9 (57.8–100)
	Abnormal vasculature of the placental bed	This can be seen as flow voids on MRI or color Doppler positive vascularity that extends from the placenta onto the serosa or urinary bladder wall, also referred to as “bridging vascularity”.	81.6 [104]	100

[a] Adapted from Hobson SR et al. [5] and Jauniaux E et al. [107].
[b] VEGF, Vascular endothelial growth factor.
[c] PIGF, Placental growth factor.

[d] SFlt1, Soluble fms-like tyrosine kinase 1.

[4]. PAS is typically asymptomatic but frequently causes serious complications during surgery, making effective preoperative screening and prediction crucial [5]. Ultrasound (US) and magnetic resonance imaging (MRI) are the most common prenatal screening modalities. However, existing studies are compromised by inconsistencies in diagnostic criteria, terminology, and reported outcomes, undermining the validity of their conclusions. Consequently, a summary of the current prenatal indicators would be of great interest. This article focuses on an overview of all commonly used prenatal indicators and recent research advancements and concludes with a discussion of the implications of combining multiple screening tools to improve diagnostic accuracy.

2. Clinical factors

2.1. Previous cesarean delivery

Recent epidemiological research has established a direct link between an increasing rate of cesarean section (CS) and the incidence of PAS in subsequent pregnancies [6–9]. The exact pathogenesis is still unknown, but the possible mechanism is that scar tissue stimulation to the blastocyst affects the normal implantation of villi, which leads to abnormal adhesion or invasion of the placenta in the scar of cicatrice [10]. There was a dose-response relationship between the number of prior cesarean deliveries and PAS when stratified by that metric [9]. Interestingly, the timing of the initial cesarean delivery also affects the occurrence of PAS in subsequent pregnancies, and it was found that elective CS was associated with a high risk of subsequent pregnancies with placenta previa combined with PAS (OR 3.0, 95% CI 1.47–6.12) [11–13]. A plausible explanation could be that changes in the structure of the uterus during labor make the tissue more adaptable to injury, and the activation of immune function also facilitates the repair of the myometrium [14–17]. Interestingly, prior vertical uterine incision also increases the incidence of PAS in the second pregnancy, especially placenta percreta and uterine rupture [18]. More research is required to better understand the etiology of the association between vertical hysterotomy and placenta implantation.

2.2. Placental location

The risk of placenta previa (PP), which frequently occurs in conjunction with a prior cesarean section, increases with the number of prior CS, and it is an independent risk factor for PAS [9]. A systematic review and meta-analysis found that the prevalence of PP increased from 10/1000 deliveries with 1 prior cesarean delivery to 28/1000 with 3 cesarean deliveries. PP combined with a scarred uterus has a significantly increased risk of PAS [19,20]. Patients with PAS and PP benefit from effective treatment as a result of clinician attention. However, 30% of patients who had a hysterotomy for a histologically confirmed PAS did not have a PP at delivery, and their rates of severe morbidity were comparable to those of patients with PP [21]. For that reason, other medical histories should be considered in PAS patients without PP, and a large cohort study should be conducted to retrospectively analyze images of these patients to identify sensitive and stable screening indicators.

We found fewer reports about the effect of placental sites on diagnosis, risk factors, and resultant outcomes in cases of PAS. Limited studies indicate that PAS with lateral and posterior placental locations is not less likely to have severe maternal morbidity than anterior PAS. Still, the rate of prenatal diagnosis is significantly lower than theirs [22,23]. These studies base on placental location should alert us the presence of PAS even if it is not detected by prenatal ultrasound.

2.3. Assisted reproductive technology

In vitro fertilization-embryo transfer (IVF-ET) has recently been demonstrated to be a significant independent risk factor for PAS, with an adjusted OR (aOR) of 8.7 (95% CI 3.8–20.3) [24–26]. Embryos were inserted into the uterine cavity via a catheter through the cervix during IVF-ET. This process may cause uterine contractions, possibly due to the release of prostaglandins by mechanical stimulation of the internal cervix os. It is possible that these mechanically generated irregular uterine contractions could result in an increase in the frequency of implantation in the lower uterine segment, hence increasing the risk of placenta previa [27,28]. In addition, it has been suggested that PAS can arise following IVF-ET regardless of placental position; however, the pathophysiology underpinning this association has yet to be determined [24].

Different types of blastocyst transfer and endometrial preparation also impacted the risk of PAS, with frozen-thawed embryo transfer (FET) and hormone replacement cycles (HRC) increasing the risk of PAS. The risk of PAS in FET was reported to be higher than that in fresh embryo transfer (OR 4.60, 95% CI 3.42–6.18) [24]. Notably, women with FET on hormone replacement cycles had a significantly higher prevalence of PAS than women with FET on natural ovulatory cycles (aOR 6.91, 95% CI 2.87–16.66) [29]. Women on hormone replacement cycles had less mean endometrial thickness than those on regular ovulatory cycles or fresh ET [30,31]. Therefore, PAS may be caused by thin endometrium, and more research is needed to find out if the endometrial thickness and PAS are linked.

2.4. Other etiologies

Impairment of endometrial integrity is not only the result of CS, but other procedures such as dilatation and curettage,

myomectomy, and endometrial resection are associated with PAS in subsequent pregnancies (Table 1) [32]. In recent years, factors like advanced maternal age and twin pregnancies have been considered risk factors for PAS. However, rather than being directly caused by those factors, this association is most likely the result of confounding variables like IVF-ET, PP, and risk of prior uterine surgery [33–36].

The above discussion of clinical factors has deepened our understanding of PAS. As stated by the American College of Obstetricians and Gynecologists (ACOG), the absence of ultrasound findings does not preclude the diagnosis of PAS [37]. Consequently, clinical risk factors remain equally important as ultrasound finding predictors, especially in economically backward areas or areas with limited prenatal ultrasound expertise.

3. Biomarkers

3.1. Alpha-fetoprotein

Maternal serum alpha-fetoprotein (MSAFP) is produced in the yolk sac and fetal liver after 6 weeks of gestation in the first trimester and is transported to maternal serum through the placenta or diffusion across the fetal membranes, reaching a robust stage in the second trimester and returning to the average within 2 weeks postpartum [38–40]. Over the past 30 years, MSAFP has been used as a serum marker for first-trimester aneuploidy screening and has been effective in identifying pregnant women at high risk for additional adverse perinatal outcomes such as pre-eclampsia, fetal loss, and preterm delivery, leading many researchers to gradually focus on the association of MSAFP with pathological placentation [41–45]. More reports have shown that elevated MSAFP levels are associated with a higher risk of PAS, possibly due to disruption of the maternal-fetal interface for placental implantation [46,47]. Above the diagnostic threshold of AFP concentration (1.64 MoM), women with uterine scarring have a 2.5-fold elevated risk of placental implantation (RR 2.5, 95% CI 1.17–5.36, P = 0.0185) [47]. Recently, it has been suggested that increased MSAFP is associated with hysterotomy in patients with PAS and is considered a complementary factor to more complex procedures, but this conclusion is controversial [48,49].

3.2. Human chorionic gonadotropin

Human chorionic gonadotropin (hCG), a glycoprotein hormone with alpha (α) and beta (β) subunits, is primarily produced by the syncytiotrophoblast and maintains pregnancy by stimulating the corpus luteum to produce progesterone [38]. Free β-hCG also increases angiogenesis, cytotrophoblast differentiation, immunosuppression, and prevents the phagocytosis from invading trophoblast cells, indicating that it can reflect the activity of trophoblast cells [50]. The levels of free β-hCG in maternal serum varied between the PP, PAS, and control groups. The median free β-hCG MoM was 1.04 in the control group, 1.08 in the PP group (P = 0.859), and 0.81 in the PAS group (P = 0.06) [51]. However, Berezowsky et al. reported that patients with PAS had higher statistically β-hCG MoM than normal pregnancy (1.42 vs. 0.93, P = 0.042). Additionally, in the second trimester, β-hCG also predicted PAS with an area under the ROC (AUC) of 0.662 (95% CI 0.605–0.715) and a cut-off value of 1.25 MoM demonstrated a sensitivity and specificity of 58% and 68%, respectively [46]. It can be seen that there is a correlation between hCG and PAS, but its correlation may be affected by factors such as race, gestational age, and sampling time.

The function of hyperglycosylated hCG (hCG-H) in gestational trophoblastic disease has been described as preventing apoptosis and thereby promoting placental invasion [52]. In assessing the function of hCG-H in predicting PAS, Einason et al. discovered that patients with PAS had lower hCG-H values than controls and that the threshold was 7.6 μg/L, which had the optimal predictive value [53]. However, these findings are limited to single-center studies, and the conclusions are controversial and cannot be widely generalized.

3.3. Pregnancy-associated plasma protein-A

Pregnancy-associated plasma protein-a (PAPP-A) is produced by syncytiotrophoblasts and deciduas and secreted into the maternal blood [38,54]. PAPP-A may play a significant role in regulating trophoblast invasion via the thrombin protease-activated receptor (TPAR) signal, and its levels should increase as trophoblast invasion increases [51]. PAPP-A was positively associated with PAS and showed promise for PAS risk stratification in high-risk pregnancies, with a median PAPP-A MoM of 1.01 in the control group and 1.05 in the PP group (P = 0.83) compared with 1.22 (P = 0.16) in PAS cases [51]. Additionally, PAPP-A levels demonstrated a trend toward higher distribution in the group that underwent hysterotomy [54,55], but this index is influenced by gestational characteristics like gestational age, race, and mode of conception in early pregnancy, and there are insufficient studies to evaluate it scientifically [55].

3.4. Others

Using cell-free fetal DNA (cffDNA) and cell-free placental mRNA to screen for PAS is a new topic. Maternal serum cffDNA originates from the apoptosis of cytotrophoblast and syncytiotrophoblast cells. Maternal immune responses to myometrial invasion during placental implantation can lead to the destruction of the cellular trophectoderm and an increase in maternal cffDNA [56]. Circulating cell-free placental mRNA has emerged as a possible marker due to its ability to be extracted and quantified from maternal plasma, and its results potentially indicate aberrant placental formation [57]. The association between the two metrics and PAS has only been reported in small sample studies, and larger clinical cohort trials are expected in the future.

Researchers have also identified other biomarkers associated with PAS (Table 1). In early pregnancy, an imbalance of angiogenic

factors is thought to be associated with placenta accreta [58]. MicroRNAs have been shown to be closely associated with the occurrence and development of placental implantation [59–61]. As the pathogenesis of PAS is investigated, more biochemical factors are expected to provide a basis for clinical diagnosis when confirmed by large-scale studies.

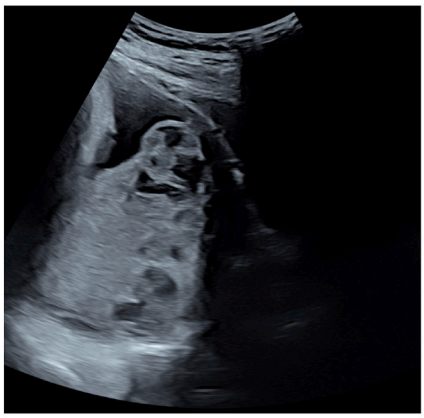
4. Ultrasound

4.1. First trimester

Transvaginal ultrasound detection of implantation of a gestational sac in the lower uterine segment is one of the most common indicators of PAS in early pregnancy. Cali et al. predicted the ultrasound staging and surgical outcome of PAS based on assessing of the relationship between the gestational sac and the endometrial line in cesarean scar pregnancy (called the cross-over sign; COS) [62,63]. Bhatia et al. discovered that the presence of placental implantation on an exposed lower uterine scar appeared to be a significant predictor of PAS risk in women with a history of CS, with an excellent negative predictive value [64]. Early pregnancy ultrasound relies on the position of the gestational sac about the uterine scar, a strategy that allows the assignment of high-risk women to the appropriate management pathway to optimize pregnancy outcomes. However, this screening protocol only identifies women at high risk of developing anterior or central placenta accreta, as posterior and lateral PAS cases are more difficult to predict and diagnose prenatally.

Loss of the clear zone, placental lacunae, bladder wall interruption, and myometrial thinning, typically described in the second and third trimesters, have been identified in the first trimester and are associated with PAS with PP to varying degrees. When at least one of these ultrasound images was used for prenatal diagnosis during early pregnancy, the sensitivity was 84.3% (95% CI, 74.7–91.4%) and the specificity was 61.9% (95% CI, 51.9–71.2%). The sensitivity is best for loss of the clear zone, and the specificity is highest for bladder wall interruption. Moreover, when combining the two ultrasound signs above, both sensitivity and specificity were optimal [65,66].

a.



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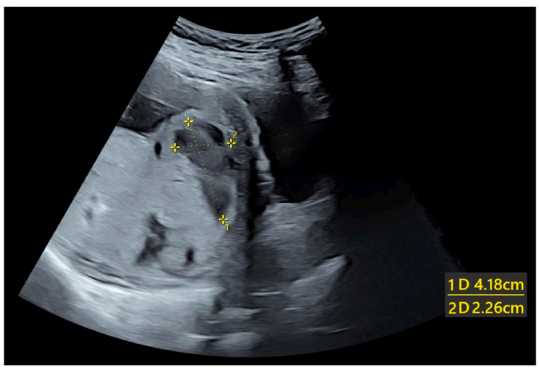


Fig. 1. Abnormal placental lacunae (a,b) and bladder wall interruption (b) on grayscale ultrasound.

4.2. Second and third trimesters

Transabdominal ultrasound is usually performed during pregnancy to determine placenta position and to assess those at high risk for PAS. However, the current standard mid-pregnancy obstetric ultrasound screening reveals a low PP and PAS detection rate [67]. This is a result of pregnancy-related placental migration, growth toward better blood flow, and development of the lower uterine segment. In a recent study, Jansen et al. reported lowering the internal cervical os threshold from 20 mm to 5 mm for monitoring the anterior low-lying placenta. This recommendation may reduce the number of unnecessary follow-ups without excluding any women at high risk [68].

According to the proposal of the European Working Group on Abnormally Invasive Placenta (EW-AIP), late pregnancy obstetric ultrasound compiled a list of 11 PAS ultrasound markers based on ultrasound modalities (Figs. 1–3) [69]. Generally, diagnosing of PAS relies on typical ultrasound findings, such as placental lacunae and loss of the retroplacental clear zone (Table 1) [70], and color Doppler is considered a promising tool for good visualization of uteroplacental vascularization. Several recent retrospective studies have also verified these classical signs in recent years. Placental lacunae are defined as irregular, hypoechoic spaces within the placenta containing vascular flow. With negative predictive values for PAS ranging from 88% to 100%, the absence of lacunae in pregnancies with placenta previa and previous cesarean delivery is a reassuring sign [71,72]. A review evaluated the value of various ultrasound signs and found that in placenta accreta and increta, loss of clear zone was considered the most general ultrasound sign, with an odds of 71.4% and 84.6%, respectively [73].

According to a multicenter prospective study, Fratelli et al. found that grayscale ultrasound findings in the third trimester have good negative predictive values for clinically relevant PAS [74]. However, in a systematic evaluation and meta-analysis involving 3707 patients at risk for PAS, color Doppler had the best combination of sensitivity and specificity among the various ultrasound signs [70]. The differences are attributed to the heterogeneity of the same markers across studies, and operator subjectivity that can influence the conclusions.

4.3. Updated markers

Recently, several new flags have been used to improve forecasting efficiency. A “rail sign” was described as two parallel neovascularizations across the bladder mucosa and uterovesical junction that were shown on color Doppler sonography and had bridging arteries linking them that were perpendicular to both. Patients with rail sign had a significantly increased risk of PAS (83.3% vs. 27.9%) and a higher risk of adverse clinical outcomes, according to research [75,76]. The “intracervical lakes” is defined as the anechoic space of the endocervical tortuosity that appears to be a hypervascular space on color Doppler, using a pulse rate frequency $<$1.3 kHz. In women with suspected PAS on antenatal sonography, it may serve as a marker of deep villus invasion and signal impending serious maternal morbidity [77]. “Jellyfish” is defined as lacking the usual linear demarcation between placenta previa and cervix, which helps predict increased maternal morbidity (Table 2) [78]. However, the above findings should be verified in larger prospective studies.

Prenatal ultrasound is a promising screening and diagnostic tool for PAS in current obstetric practice, but it is still limited by subjectivity. It is hoped that future studies will come up with uniform definitions and standardized ultrasonography methods to make it easier to compare data and improve the outcomes for PAS patients.

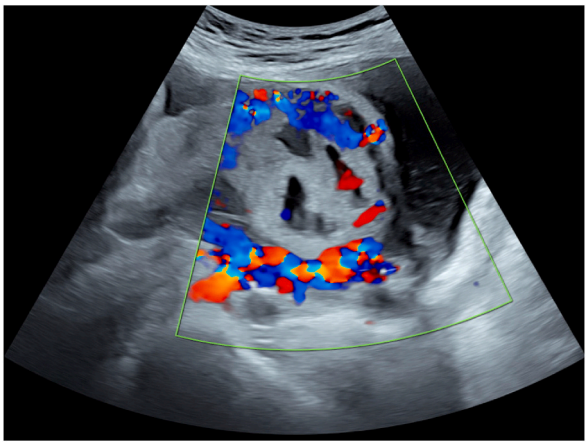


Fig. 2. Subplacentals hypervascularity and bridging vessels on color Doppler imaging.

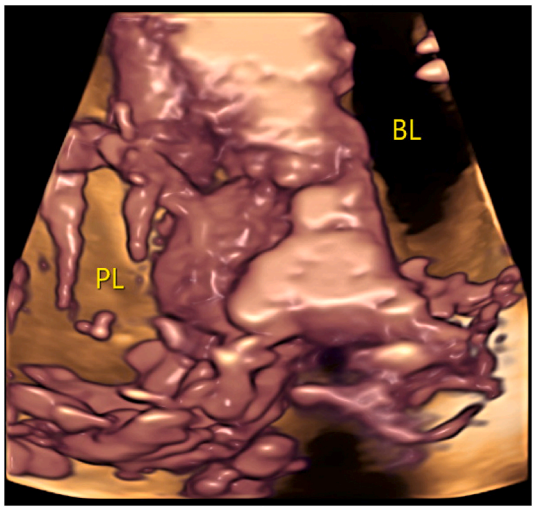


Fig. 3. Intraplacental hypervascularity on three-dimensional power Doppler.

Table 2
Recent ultrasound and MRI update signs in PAS.

Sign/Approach	Definition
● US	
Rail sign	2 parallel neovascularization depicted by color Doppler over the uterovesical junction and bladder mucosa, with interconnecting bridging vessels perpendicular to both.
Intracervical lakes	The anechoic space of the endocervical tortuosity that appears to be a hyper-vascular space on color Doppler.
Jellyfish	Lacking the usual linear demarcation between placenta previa and cervix.
Separation sign [108]	Detects different rates of rebound after an ultrasound probe is used to apply pressure over the uteroplacental interface
● MRI	
Intraplacental fetal vessel diameter [109]	Enlarged subchorionic and dry vascular trunks that origin from the umbilical cord and penetrate the placental parenchyma, often reaching its maternal surface.
Gadolinium	Producing better contrast between the placenta and the myometrium, but it is not recommended.
Functional MRI	Includes arterial spin labeling (ASL), blood oxygen level dependent (BOLD), diffusion weighted imaging (DWI), intravoxel incoherent motion (IVIM), MR spectroscopy (MRS), and dynamic contrast enhanced (DCE) MRI.
Radiomics	Overcame the problem of low agreement between observers.
Textural analyses	Identify an algorithm to predict PAS and intraoperative complications in placental MRI.
Three-dimensional (3D) models [110]	An accurate 3D models of MRI images can help understand the depth and pattern of placental invasion, the location of defects, and bladder involvement.

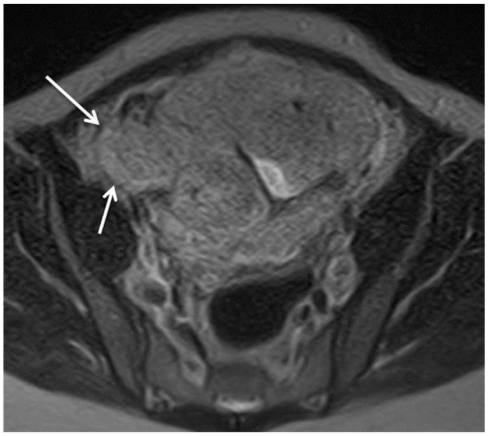
5. Magnetic resonance imaging

5.1. Routine MRI signs

The Society of Abdominal Radiology (SAR) and European Society of Urogenital Radiology (ESUR) joint consensus statement recommends 7 MRI features, namely uterine/placental bulge, intraplacental dark T2 bands, myometrial thinning/disruption, loss of low T2 retroplacental line, bladder wall interruption, focal exophytic placental mass, and abnormal vasculature of the placental bed (Figs. 4–6) [79]. The first three are widely used in prenatal PAS diagnosis (Table 1). An abnormal uterine bulge appears to have the strongest performance in diagnosing severe PAS on both ultrasound and MRI. Thiravit et al. evaluated the performance of ultrasound and MRI features for predicting PAS, with an emphasis on placental bulge signs, and found that on ultrasound, the finding with the highest accuracy for severe PAS was placental bulge (85.5%), which was associated with sensitivity of 91.7% and specificity of 76.9%; on MRI, the finding with the highest accuracy was also placental bulge (90.3%), which was associated with sensitivity of 94.4% and specificity of 84.6% [80]. These findings suggest the efficacy of placental bulge has potentially relatively more robust performance on MRI. Intraplacental dark T2 bands are thought to represent areas of fibrin deposition due to repetitive intraplacental hemorrhage or infarcts. A retrospective study showed that the most relevant MRI features of PAS were the placental bulge, followed by the dark intraplacental bands on T2W (sensitivity 0.83/specificity 0.80) [81]. Myometrial thinning/disruption has been described as an early sign suggesting placenta accreta. When the myometrium is well demonstrated, focal wall interruptions are seen at invasion sites with placental tissue extending through the breach in case of percreta. In the study by Romeo et al. only the intraplacental dark T2 bands and myometrium focal interruption were independently associated with PAS after multivariate analysis [82].

MRI was formerly thought to have the advantage of multiplanar imaging and excellent soft tissue resolution, and has demonstrated

a.



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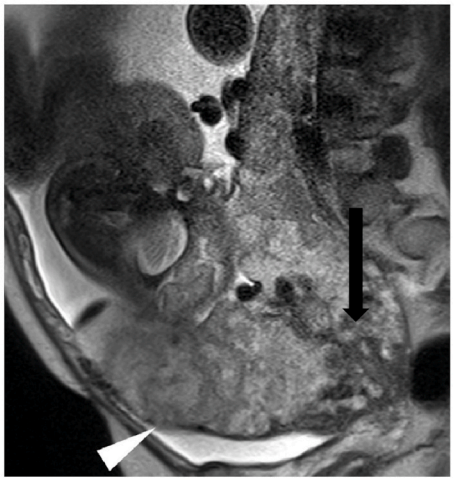

Fig. 4. The uterine/placental bulge sign on MRI.

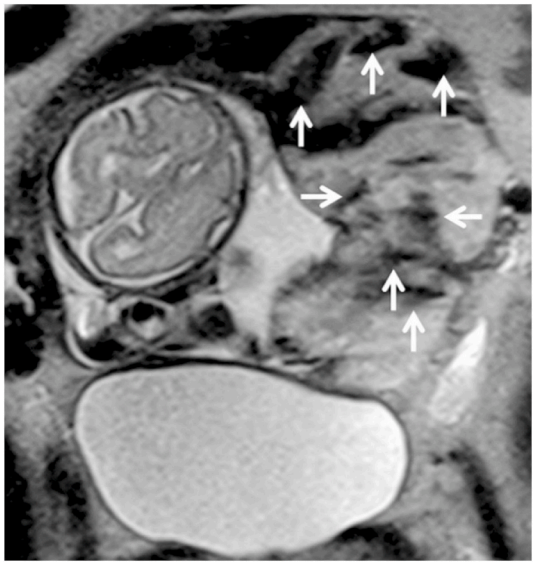

Fig. 5. The intraplacental dark T2 bands sign on MRI.

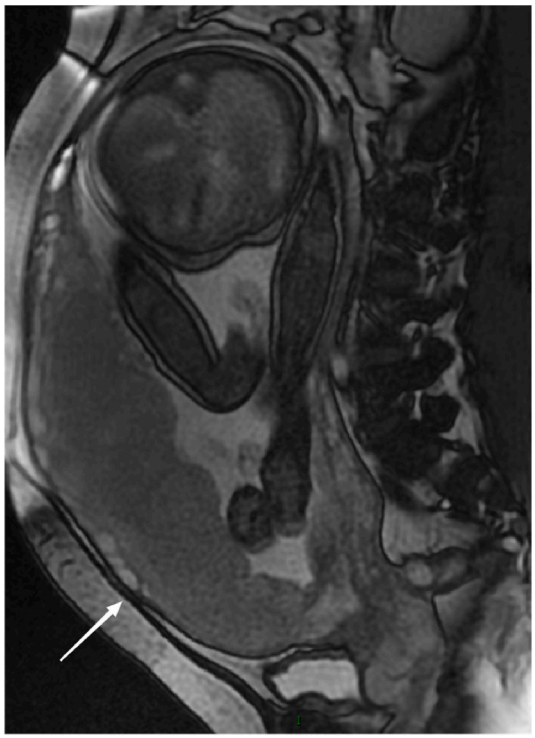

Fig. 6. The myometrial thinning/disruption sign on MRI.

outstanding performance in defining the topography and depth of abnormal placentae [83]. Consequently, MRI is frequently used as a complementary diagnostic tool to ultrasound in the diagnostic system, and expert opinion recommends its use when ultrasound evaluation is uncertain [84]. Nonetheless, several recent studies have demonstrated that the diagnostic efficacy of ultrasound and MRI is comparable [85,86]. MRI does not provide identifiable benefit either in cases of severe PAS suspected by ultrasound or in the application of posterior and lateral placenta locations [87,88]. The reason for this discrepancy is not only the lack of independent studies of MRI, which is only used as an adjunct to ultrasound for highly suspected PAS. What's more, there is a lack of consensus on standardized reporting of US and MRI for PAS, and the predictive performance of both imaging modalities still heavily depends on the experience and expertise of the physician.

5.2. Advances in MRI imaging techniques

Admittedly, the use of contrast agents such as gadolinium can improve the conspicuity of MRI and has been shown to compensate for the lack of experience of radiologists [89]. Gadolinium can enter fetal circulation through the placenta and is discharged into the amniotic fluid by the fetal kidneys, restricting its use during pregnancy [90]. Thanks to the development of functional MRI techniques, the prenatal diagnosis accuracy of PAS is significantly improved, and it will not cause adverse effects on fetal development. For example, diffusion weighted imaging (DWI) intravoxel incoherent motion (IVIM), MR spectroscopy (MRS), blood oxygen level dependent (BOLD) and others can distinguish heterogeneous placental signals from abnormal vascular signals, making them more useful for observing the uteroplacental interface and clinical classification (Table 2) [91]. The emergence of radiomics and its application in medical imaging have overcome the problem of low operator consistency. Peng et al. developed an MRI-radiomics-clinical-feature-based nomogram for prenatal prediction of PAS, yielding a robust performance both in the training cohort and external validation cohort [92]. In addition, using machine learning algorithms to analyze the texture features of MRI images to forecast the incidence of PAS and surgical outcomes is another hot topic in current research [93,94]. Both radiomics and machine learning algorithms have problems of poor data stability and openness, and there is still a long way to go for their application in clinical transformation.

6. Combined markers

Assessment of PAS by ultrasound alone has limited sensitivity and may be missed in patients with atypical ultrasound signs. To improve the accuracy of PAS prediction, researchers developed the placental accreta index (PAI), a predictive equation based on ultrasound parameters and clinical features in a cohort of women at increased risk of placental invasion. PAI score was generated based on placental position, number of CS, and a few ultrasonography signals, resulting in an AUC of 0.87 (95% CI 0.80–0.95) [95]. This

model is often used in pregnancies with a history of CS and PP or low-lying placenta in the third trimester. In addition, PAI holds promise as a predictor of high-risk pregnant women requiring hysterotomy (Table 3) [96].

Furthermore, Tovbin et al. established a scoring system based on placental position, number of previous CS, and ultrasound signs. The scoring system is capable of performing risk stratification for pathologically adherent placenta, with 0.9%, 29.4%, and 84.2% in the low, medium, and high probability groups, respectively ($P < 0.0001$) (Table 3) [97]. These scoring systems incorporate placental lacunae and uteroplacental demarcation into the ultrasound criteria. Previous studies have described the relationship between placental lacunae, obliteration of the uteroplacental interface, and placenta implantation, and the PAI is a more detailed stratification of postplacental myometrial thickness.

As with the ultrasound PAI, scholars have also proposed a scoring model using six MRI features (intraplacental T2 dark bands, intraplacental abnormal vascularity, placental bulge, heterogeneous placenta, myometrial thinning, and placental protrusion sign) to improve diagnostic performance (Table 3) [98]. In addition, Zou et al. constructed an MRI scoring system based on 10 MRI signs and 2 clinical features (number of previous CS, placenta location) that not only assessed the type of pernicious placenta previa, but also predicted the risk of bleeding [99]. Although these scoring models are somewhat helpful for clinical diagnosis, their acceptance and validation in clinical practice have yet to be realized.

7. Special types of PAS

The posterior PAS and PAS after IVF-ET (IVF-PAS) are gradually gaining attention because of their low prenatal diagnosis rate and severe postpartum hemorrhage during surgery. Given this, we specifically overview the current research progress of these two types of PAS.

A recent meta-analysis of 2619 PAS pregnancies revealed that PP, past uterine surgery (mostly CS or curettage), and multiparity were related to posterior PAS, and only 52.4% of them could be identified preoperatively on ultrasound [100]. Similarly, Morgan et al. found that posterior PAS was often associated with assisted reproductive technologies [23]. When exploring the outcomes of posterior PAS, placenta percreta was present 19%, lower than anterior PAS (47%, $P = 0.055$), and the ureteral injury was the common surgical complication ($P = 0.037$) [23]. Regarding prenatal diagnosis, the US image of placental lacunae, loss of the clear zone, and bladder wall interruption were observed in the posterior PAS, but the sensitivity was poor. The performance of MRI is better than in the US, with 73.5% confirmed cases could be detected. However, the distribution of the different signs was less reported [100].

As mentioned above, IVF has been identified as an essential risk factor for PAS. However, the risk factors, pregnancy outcome and prenatal diagnosis of IVF-PAS have been less explored. A recent study by Yu et al. noted that those with PAS and IVF conception were less likely to develop PP, previous CS, and the antenatal diagnosis of PAS, with only one-quarter of cases being detected [101,102]. The incidence of serious maternal complications in the IVF-PAS group did not differ from that of PAS with spontaneous conception [101]. Meanwhile, prenatal ultrasound has a low diagnostic rate for IVF-PAS(<12.9% vs. 46.9%) [102]. Similarly, the prenatal MRI diagnostic rate was lower than that of PAS with spontaneous conception, with a sensitivity of 22.2%, specificity of 93.3%, and AUC of 0.578 [103].

Due to the low incidence, these studies were limited by the small sample size. However, considering the severe impact of PAS on the maternal and fetus, these two particular types of PAS also deserve our vigilance.

8. Conclusion

Due to the high degree of prenatal diagnosis variability, PAS remains one of the most challenging obstetrical disorders. Therefore, it is crucial to standardize the management of patients with PAS. Risk factors are useful in identifying and categorizing high-risk groups of people; biomarkers are anticipated to be early screening indicators, and ultrasound is still a first-line aid. In particular, improvements in ultrasound technology and new symptoms have facilitated the classification of PAS and the stratified management of patients. MRI is still used as an additional diagnostic tool for patients with suspected PAS and to assess the degree of preoperative implantation, but its true performance needs to be confirmed by independent studies. The prenatal detection rate can be significantly increased by combining several indications.

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Author's contribution

Xiafei Wu drafted the manuscript, which was then edited by Huan Yang, Xinyang Yu, and Jing Zeng. Juan Qiao contributed to the creation of the images. Hongbo Qi and Hongbing Xu revised the final version of this manuscript. Xinyang Yu provided financial support for this project and also served as a guarantor for this paper together with Hongbing Xu.

Ethical review statement

Informed consent was obtained from patients for the ultrasound images cited in this article. The Institutional Review Board of the

Table 3
Summary of studies on a scoring system for predicting PAS based on ultrasound and MRI parameters.

Author	Combined markers	Imaging signs	Population characteristics	Value
Ultrasound signs				
Rac et al. (2015) [95]	Placental location; number of CS[a]	(1) loss of retroplacental clear zone; (2) irregularity and width of uterine-bladder interface; (3) smallest myometrial thickness; (4) presence of lacunar spaces; (5) bridging vessels	≥1 prior CS and PP[b] or low-lying placenta;	AUC[c]: 0.87
Tovbin et al. (2016) [97]	Placental location; number of CS	(1) placental lacunae; (2) obliteration of the demarcation between the uterus and placenta; (3) color Doppler signals within placental lacunae; (4) hypervascularity of the placenta-bladder and/or uteroplacental interface zone;	Suspected PAS; ≥1 previous CS;	High or moderate probability score: SEN[d]: 91.3% SPE[e]: 93.6%
Tanimura et al. (2018) [111]	Surgical abortion and/or uterine surgery; number of CS; MRI: adherent placenta suspected	(1) lacunae; (2) Loss of clear zone; (3) Turbulent blood flow; (4) Irregular signs;	PP;	Sen: 91.3% SPE: 98%
Luo et al. (2019) [112]	Number of CS;	(1) placental lacunas; (2) vascularity at the uterus–bladder interface; (3) myometrial thickness and loss of hypoechoic retroplacental zone; (4) bladder line;	PP;	Predicting PAS severity; PPV[f]: 96.68% NPV[g]: 95.44%
Boroomand Fard et al. (2020) [113]	/	(1) utero-vesical; hypervascularity; (2) bladder interruption; (3) new lacunae;	≥1 previous CS;	ACC[h]: 100%
Romeo et al. (2021) [82]	Smoking; number of CS;	(1) loss of the retroplacental clear space; (2) myometrial thinning <1 mm; (3) placental lacunae; (4) intraplacental dark bands (IDB); (5) focal interruption of myometrial border (FIMB); (6) abnormal vascularity;	PP;	AUC: 0.97
MRI signs				
Ueno et al. (2016) [98]	/	(1) dark band on T2-weighted images; (2) intraplacental abnormal vascularity; (3) placental bulge; (4) heterogeneous placenta; (5) myometrial thinning; (6) placental protrusion sign;	Pathologic-proved PAS;	AUC: 0.92 ACC: 91.4%
Chu et al. (2019) [114]	number of CS; abortion; placenta previa;	placenta-myometrial interface interruption	Pathologic-proved PAS;	Combined one risk factor with MRI sign: ACC: 83.5% SEN: 92.9%
Delli Pizzi et al. (2019) [115]	/	(1) abnormal vascularity; (2) percretism signs;	PP;	AUC: 0.833 SEN: 67% SPE: 100%
Yan G et al. (2022) [116]	dMRI-based feature of myometrial fiber discontinuity	(1) presence of dark band; (2) discontinuous myometrium; (3) bladder wall interruption	Suspected PAS;	
Zou L et al. (2022) [99]	CS; Placental location;	(1) placental/uterine bulges; (2) placental heterogeneity; (3) T2-dark bands in placenta; (4) abnormal intraplacental vascularity; (5) abnormal vascularization of the placental bed; (6) loss of T2 hypointense interface; (7) bladder wall interruption; (8) penetrating implantation; (9) myometrial thinning and interruption;	Pernicious placenta previa;	AUC: 0.885 SEN: 80.21% SPE: 86.94%
Peng L et al. (2022) [92]	PP; history of uterine surgery;	(1) uterine/placental bulge; (2) abnormal vasculature of the placental bed;	Pathologic-proved PAS;	AUC: 0.91 SEN: 68.8% SPE: 96%

[a] CS, Cesarean section.
[b] PP, Placenta previa.
[c] AUC, Area under the ROC curve.
[d] SEN, Sensitivity.

[e] SPE, Specificity.
[f] PPV, Positive predictive value.
[g] NPV, Negative predictive value.
[h] ACC, Accuracy.

First Affiliated Hospital of Chongqing Medical University approved this study in September 2022. (review approval number: 2022-K416).

Data availability statement

No data was used for the research described in the article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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Abbreviations

PAS	Placenta accreta spectrum
US	Ultrasound
MRI	Magnetic resonance imaging
CS	Cesarean section
PP	Placenta previa
IVF-ET	In vitro fertilization-embryo transfer
MSAFP	Maternal serum alpha-fetoprotein
hCG	Human chorionic gonadotropin
AUC	Area under the ROC curve
hCG-H	Hyperglycosylated hCG
PAPP-A	Pregnancy-associated plasma protein-a
cffDNA	Cell-free fetal DNA
PAI	Placental accreta index

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