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Review

Early Prediction of Placenta Accreta Spectrum by Different Modalities: An Evidenced-based Analysis

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Abstract

Objective: Early prediction of placenta accreta is crucial for proper decision making, proper preoperative preparation and proper planning for the best management. To review published data and extract strong evidence about early prediction of placenta accreta spectrum (PAS). **Mechanism**: Published data were extracted from trusted search engines and literature databases, such as Google Scholar, Cochrane library, Clinical Key, PubMed, Researchgate, and Medline, in the period from 1 January 2000 to 31 August 2023. Revision of collected data was conducted by the 3 authors and final results were gathered. **Findings in Brief**: Many articles were found addressing prediction of PAS but the vast majority of these articles were in the late second and third trimesters. Prediction of PAS in early pregnancy was addressed by few articles which were analyzed in this research. In this study, evidence-based analysis found that PAS could be predicted by many modalities. **Conclusions**: Early prediction of PAS allows good preparation of both patient and obstetrician to conduct the best management with minimal complications. PAS could be predicted early by either clinical risk factor, imaging in early pregnancy or by biomarkers.

Keywords: PAS; placenta accreta; prediction; biomarkers; ultrasound markers

1. Introduction

Placenta accreta spectrum (PAS) was first described by Irving *et al*. [1] in 1937, following vaginal delivery as unsuspected failure of placental separation from the uterine wall. The pathognomonic feature of PAS is the pathological adhesion of trophoblastic tissue to the uterine wall [2]. The main pathology in these disorders is the damage into the endo-myometrial interface. The incidence of PAS is increasing, and parallel to increased cesarean delivery rates worldwide [3]. Indeed, Wu *et al*. [4] found that the incidence raised 4 folds (0.08–0.3%) in a 20-year period. Other risk factors for PAS included endometrial curettage, endometrial resection, hysteroscopic myomectomy, and hysteroscopic adhesiolysis [5].

PAS disorders are associated with severe complications, either intraoperatively or postoperatively. These complications are the cause of major maternal morbidity and mortality, thus require multiple resources and multidisciplinary team for its best management. Meticulous assessment of PAS cases by different modalities is a crucial step in minimizing complications linked to PAS disorders [6].

Prediction of PAS has a lot of benefits, including reduction of peripartum complication [7], help decision-making and peripartum management [6], predict degree of severity, predict operative blood loss [8], and predict maternal morbidity and mortality [9].

Chantraine *et al*. [7] compared the incidence of emergency hysterectomy and massive transfusion rates. They allocated 40 women in the antenatal diagnosis group and 26 women within intrapartum diagnosis group. They found that emergency hysterectomy rates were (12% *vs.* 69%, p = 0.0004) and massive transfusion rates were (20% *vs.* 46%, p = 0.025) in the antenatal diagnosis versus the intrapartum diagnosis groups, respectively [7]. Similarly, Tikkanen *et al*. [10] also observed a significant decrease in blood loss (4500 mL *vs.* 7800 mL, p = 0.012) and blood transfusion units (7 *vs.* 13.5, p = 0.026) in women diagnosed antenatally.

In this review, we addressed the role of different modalities in the prediction of PAS. Many modalities do exist. We also addressed advantages and disadvantages of each modality.

2. Methods

A literature search was conducted on the literature databases and search engines, such as Google Scholar, Cochrane library, Clinical Key, PubMed, Researchgate, and Medline to identify studies investigating the role of biomarkers in prediction of PAS. The search included studies in the period from 1 January 2000 to 31 August 2023. The search words were “placenta accreta spectrum”, “low implantation”, “biomarkers in PAS”, “prediction of PAS”, “Early detection of PAS”, “clinical risk factors for PAS”, “ultrasound in prediction of PAS”, and “first-trimester detection of PAS”. Articles addressing diagnosis of PAS were excluded. Also, articles addressing prediction of PAS in the third-trimester were excluded. Similarly, we excluded articles addressing the role of magnetic resonance imaging (MRI) in the prediction of PAS, as most are in the late second- and third-trimester of pregnancy.

3. Pathogenesis of PAS

3.1 Early Placental Development

Upon implantation, fetal trophoblast cells start invasion and migration into the maternal decidua and these trophoblasts form masses of cytotrophoblasts (CTBs) and primitive syncytiotrophoblasts (STBs). The distal CTBs located at the tips of anchoring villi form columns that merge together, creating shells that encapsulate the developing gestational sac (GS). The CTBs located on the outer surface of the shell change their proliferative to invasive potential. This invasive potential helps these cells to migrate beyond the decidual stroma. These trophoblasts are called "extravillous trophoblasts" (EVTs). EVTs share some key similarities with carcinomas in their ability to invade healthy tissues, form new vessels, and promote immunotolerant environment [11–13].

EVTs differentiates into 3 subpopulations: (1) endovascular subpopulation, that replaces endothelial cells of uterine vessels; (2) endoglandular subpopulation, which invades endometrial glands and opens their lumen towards the intervillous space; and/or (3) interstitial subpopulation, that invades into the decidual interstitium, thereby anchoring the placenta to the uterus [14], as shown in Fig. 1.

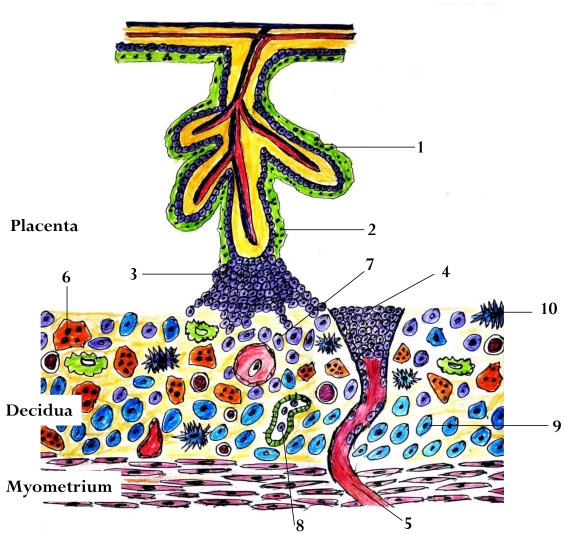

Fig. 1. Feto-maternal unit. (1) Floating villous, (2) anchoring villous, (3) extravillous trophoblasts (EVTs), (4) endovascular EVTs making trophoblastic plugs, (5) spiral artery, (6) giant cells, (7) interstitial EVTs, (8) endoglandular EVTs, (9) decidual cells, (10) decidual natural killer cells.

Invasion of EVTs to the endometrium presents a lot of benefits. This invasion helps in placental fixation, remodeling of spiral arteries to maintain good blood supply, and contributes to immunological defenses (tolerogenic responses). The interstitial EVTs migrate into the endometrial stroma until they reach the inner third of the myometrium, and at this level they fuse together forming multinucleated trophoblast giant cells [14], as shown in Fig. 1.

Spiral arteries remodeling passes into 2 waves. The first wave (6–12 weeks) involves trophoblastic invasion into spiral arteries to form EVTs plugs (Fig. 1). These plugs prevent the maternal blood flow into the intervillous space at this early gestation. These plugs make a low oxygen environment with O_2 levels of 1–5%. During the second wave (16–18 weeks), the EVTs plugs gradually dissolve and endovascular EVTs start to migrate proximally along the spiral arteries, leading to spiral artery dilation. These changes result in the development of a well-established maternal–placental circulation. Furthermore, the O_2 levels rapidly increase to 8–10% to support fetal growth [15].

There are some factors that promote trophoblastic invasion, while other factors limit this invasion. Factors promoting invasion include factors facilitating degradation of extracellular matrix (serine proteases, proteinases, and collagenases), immune system suppression, angiogenic factors and hypoxic states. Plasminogen activators convert plasminogen into plasmin that enhances extracellular matrix degradation. Trophoblastic invasion is limited by the inhibiting factors. These inhibitory factors are produced by decidual cells and include plasminogen activator inhibitor-1 (PAI-1) that inhibits the activity of urokinase-type of plasminogen activator (uPA). Another inhibitory factor is the tissue inhibitor of metalloproteinases (TIMPs) which regulate the activities of metalloproteinases (MMPs). Decidual transforming growth factor-β (TGF-β) has a major role in limiting trophoblastic invasion. TGF-β acts by upregulation of both PAI-1 and TIMPs [16].

3.2 Pathological Features of PAS

In the current study we started by identifying the pathological features that occur in the great majority of PAS disorders. The pathological findings in PAS disorders were myometrial scarification and thinning (100%), myofiber disarray (100%), tissue edema (100%), deeply implanted villi with no villi crossing the entire thickness of the uterine wall (88.1%), dense fibrinoid deposits with a varying thickness from 0.5 to 2 mm at the utero-placental interface (74.4%), and basal plate myofibers [17,18].

The clinical situations met during management of PAS disorders arise from understanding pathological issues. Serosal invasion was attributed to myometrial defects, extensive scarring, and failure of normal decidualization, which bring the anchoring villi close to the surface of the uterus. The damaged endometrium at the site of implantation allows the EVTs to reach the radial and/or arcuate arteries, and remodeling of these large vessels results in major hemorrhage at attempt of placental separation. The extensive adhesion between placenta and uterine wall was attributed to the presence of excessive fibrinoid deposition at the uteroplacental interface [18].

4. Modalities of PAS Prediction

4.1 Clinical Risk Factors

The clinical risk factors evaluated include maternal characteristics, such as maternal age, body mass index (BMI), parity, previous uterine surgery, previous cesarean delivery, number of cesarean sections, pregnancy after *in vitro* fertilization (IVF), and history of medical disorders, such as diabetes mellitus and hypertension [19,20].

Kyozuka *et al.* [21] conducted a nationwide cohort study in Japan on 90,554 participants, treated in 15 regional centers, during the period of 2011 to 2014. They found that the most risk factors for occurrence of PAS were placenta previa, conception by assisted reproductive technologies (ART), and smoking during pregnancy [21].

Imafuku *et al.* [22] conducted a prospective cohort study on 4146 pregnant women whom experienced PAS. They found that history of prior cesarean delivery, dilatation and curettage, hysteroscopic surgery, uterine artery embolization, current pregnancy via ART, and the presence of placenta previa in the current pregnancy are high risk for PAS [22].

Ogawa *et al.* [23] conducted a multicenter cross-sectional study on 472,301 women with singleton deliveries, in the period from 2013 and 2015. They reported that the most powerful predictor for PAS was the number of previous cesarean sections. On the other hand, in absence placenta previa or previous cesarean delivery, conception through ART was a strong predictor of PAS [23].

Smoking is another major risk factor studied for the pathogenesis of PAS. However, the relation between maternal smoking and PAS was not proven [24]. Furthermore, other study attributed this association to placental inflammation from smoke pollutants [25].

4.2 Ultrasound in Early Pregnancy

D'Antonio *et al.* [26] conducted a meta-analysis to predict PAS disorders in the first-trimester of pregnancy. They used three signs suggestive of PAS in the first-trimester. The signs were implantation of the GS in lower uterine segment, reduced myometrial thickness, and lacunae. They found that when at least one sign of PAS was found, the presence of PAS was confirmed in 91.4% of patients [26].

Calì *et al.* [27] investigated the role of early first-trimester ultrasound (5–7 weeks) in prediction of PAS in third-trimester. They evaluated three signs: cross-over sign (COS-1) [27] and site of implantation of GS, either on the scar or in the scar niche [28], and position of the GS below or above the midline of the uterus [29]. They found that early ultrasound could predict the stage of PAS later on, where implantation of the GS in the niche and below the uterine midline occurs, with high predictive accuracy for PAS-3. Moreover, adverse surgical outcomes were linked to implantation in the niche and below the midline of the uterus, with 95.5% and 90.9% reliability, respectively. They concluded that early first-trimester ultrasound in women with previous cesarean delivery can predict reliably PAS disorders [30].

Accordingly, Doulaveris *et al.* [31] assessed and graded the suspicion of PAS disorders in the first-trimester (11 to 14 weeks) in patients with one or more cesarean delivery. They found that low implantation inside scar niche had a positive predictive value of 100%, and a negative predictive value of 99.4%. They concluded that early transvaginal (TV) ultrasound (11–14 weeks) in patients delivered by cesarean section can predict PAS disorders [31].

Another predictor of PAS and its surgical outcomes was intracervical lakes (ICL), which is a new ultrasound sign presented by di Pasquo *et al.* [32]. They examined risky patients with placenta previa or low-lying placenta at $\geq$26 weeks, in 332 patients. They found that ICL could predict major postpartum hemorrhage, cesarean hysterectomy, and placenta percreta. They concluded that ICL could be used as a marker of deep villus invasion. It was linked to poor maternal outcomes and severe morbidity [32].

Yule *et al.* [33] conducted a retrospective study to evaluate the role of TV ultrasound color cines obtained in the first-trimester in prediction of PAS and its related morbidity. They found that increased color pixel area in the interface of bladder and uterus was noticed in women requiring peripartum hysterectomy [33].

4.3 Scoring Systems

The scoring systems identified combine different characters and then calculate a score that could predict PAS disorders. The characters included were demographic information, clinical characteristics, and sonographic findings. One of the suggested scores included 67 cases and found that their scoring model could predict severe postpartum hemorrhage, and hysterectomy [34].

Another risk model was introduced by Sargent *et al.* [35], where only four ultrasound markers (loss of clear zone, placental bulge, abnormal placental lacunae, and bladder wall interruption) were used at 17–36 weeks to predict PAS. They reported that their new model has a high accuracy [35].

Placenta Accreta Index (PAI)

PAI was useful in the prenatal prediction of not only PAS disorders, but also women that will require cesarean hysterectomy [36]. PAI is displayed in Table 1.

Another index called placenta previa with adherent placenta (PPAP) score was introduced by Tanimura *et al.* [37], including past history and imaging findings. PPAP score $\geq$8 was considered a high risk for PAS disorders. The PPAP score had sensitivity (91.3%), specificity (98.0%), positive predictive value (PPV) of (87.5%) and negative predictive value (NPV) of (98.7%) for predicting abnormal adhesions of placenta in women with placenta previa [37].

Finally, Quiner *et al.* [38] examined the accuracy of nine systems for prediction of PAS in first-trimester. They

Table 1. Placenta Accrete Index (PAI).

Parameter	Value	Total score	Probability of PAS
Number of CS $\geq$2	3	>0	5%
Lacunae		>1	10%
Grade 2 (4–6 lacunae)	1	>2	19%
Grade 3 (>6 lacunae)	3.5	>3	33%
Smallest sagittal myometrial thickness		>4	51%
$\leq$1 mm	1	>5	69%
1 mm – $\leq$3 mm	0.5	>6	83%
>3 mm – $\leq$5 mm	0.25	>7	91%
Anterior placenta previa	1	>8	96%
Bridging vessels	0.5	Placenta accreta index	

PAS, placenta accreta spectrum; CS, cesarean sections.

found that all proposed scoring systems have poor diagnostic accuracy, and none of them had any improved diagnostic accuracy over the others [38].

4.4 Biomarkers' Role in Prediction of PAS

The basis of biomarkers detection is the understanding of promoting and limiting factors in placental invasion. It was noted that a normal pregnancy is the balance between promoting and limiting factors of placental invasion. In cases of excessive invasion (which occurs in PAS), factors promoting invasion are increased while decrease in the limiting factors. On the other hand, decreased placental invasion (which occurs in preeclampsia), factors limiting invasion are more predominant [39,40].

4.4.1 Hormones of Aneuploidy

These include pregnancy-associated plasma protein A (PAPP-A), alpha fetoprotein (AFP), and beta-human chorionic gonadotropin (β-hCG) [41].

Studies conducted on AFP biomarker are shown in Table 2 (Ref. [42–45]). AFP is mainly used as a predictor for PAS disorders in the second-trimester, and also predicts cases that will require peripartum hysterectomy. AFP has many limitations, such as (a) insufficient evidence to support its reliability and accuracy, (b) first-trimester predictive potential of AFP for PAS and their associated complications remains unknown, (c) AFP is affected by other placental abnormalities and congenital fetal abnormalities, and we must consider these conditions to reduce bias, (d) in addition, there is no definite cut-off value for AFP as a predictor for PAS disorders [41].

Regarding β-hCG, studies are shown in Table 3 (Ref. [42,46–48]). All the included studies reported an association between β-hCG and PAS disorders. Limitations in β-hCG predictive power were: (a) the wide fluctuation of β-hCG levels during the first-trimester; (b) β-HCG levels are affected by fetal abnormalities and other pregnancy abnormalities, such as abortion and ectopic pregnancy; and (c) it is difficult to differentiate between abnormal β-hCG levels in PAS and other conditions. Therefore, β-hCG could be a feasible biomarker for PAS if these difficulties could be managed [41].

PAPP-A is produced by STBs and is considered a member of zinc MMPs family. Its concentrations levels increase in maternal circulation until delivery. The functions of PAPP-A are not well known, but it could play a role in trophoblastic growth and invasion. Literature reviews found that low PAPP-A levels were associated with limited placental invasion, resulting in placental insufficiency and its related adverse obstetric disorders. The studies on PAPP-A are presented in Table 4 (Ref. [42,43,46–49]). PAPP-A levels in the first-trimester not only predicts PAS, but also predicts the amount of blood loss at the time of delivery. PAPP-A could be used as biomarker for the prediction of PAS disorders, being easy for researchers to test in maternal serum [39].

Zhang *et al*. [41] conducted a literature review to summarize the evidence of suggested biomarkers in prediction of PAS. They found that a combination of biomarkers and ultrasound will provide an attractive theme for diagnosis of this challenging condition [41].

4.4.2 Factors Controlling EVT Invasion

As previously mentioned, factors affecting invasion of EVTs play an important role in the pathogenesis of PAS disorders. These factors are displayed in Table 5. In PAS disorders, there were reduced levels of factors limiting invasion and increased factors promoting invasion. Moreover, PAS cases were associated with decreased immune function at the damaged endometrium. This was detected by decreased decidual natural killer (dNK) cells population in specimens of cesarean hysterectomy. Interleukin-35 (IL-35) was also involved in the pathogenesis of PAS disorders and could be considered a potential biomarker for the prediction of PAS [40,50,51].

4.4.3 Angiogenic Factors

It is well known that PAS disorders are associated with excessive neovascularization on the surface of lower uterine segment and at bladder-uterine interface. These new vessels are upregulated by angiogenic factors like vascular endothelial growth factor (VEGF), antithrombin III (ATIII), and other angiogenic factors. Moreover, it is downregu-

Table 2. AFP levels in cases of PAS and controls.

Study	Trimester	Description of study findings
Dreux *et al.* [42]	Second-trimester	They included 69 cases. The levels of AFP were higher in PAS cases than in controls. The cutoff levels of AFP were not mentioned. There was positive histopathological confirmation.
Lyell *et al.* [43]		They included 736 cases. Cutoff level was 1.79 MoM. No histopathological confirmation was done.
Oztas *et al.* [44]		They included 316 cases. The levels of AFP were higher in PAS cases than in controls. There was positive histopathological confirmation.
Berezowsky *et al.* [45]		They included 301 cases. The levels of AFP were higher in PAS cases than in controls. There was positive histopathological confirmation.

AFP, alpha fetoprotein; PAS, placenta accreta spectrum; MoM, multiple of the median.

Table 3. β-hCG in PAS and controls.

Study	Trimester	Description of study findings
Dreux *et al.* [42]	Second-trimester	They included 69 cases. Levels of β-hCG were higher in PAS than in controls. Neither clear cutoff level was determined, nor histopathological confirmation.
Desai *et al.* [46]		They included 82 cases. Levels of β-hCG were slightly lowered in PAS than in controls. Neither clear cutoff level was determined, nor histopathological confirmation.
Thompson *et al.* [47]	First-trimester	They included 516 cases. They found that β-hCG levels were lowered in PAS than in controls. The cutoff level 0.81 MoMs. There was positive histopathological confirmation.
Büke *et al.* [48]		They included 88 cases. Levels of β-hCG were higher in PAS than in controls. The cutoff level was 1.42 MoMs. There was positive histopathological confirmation.

β-hCG, β- human chorionic gonadotropin; PAS, placenta accreta spectrum; MoM, multiple of the median.

lated by soluble Fms-like tyrosine kinase 1 (sFlt-1), TGF-β, and tumour necrosis factor-α (TNF-α) [52]. These factors are shown in Fig. 2.

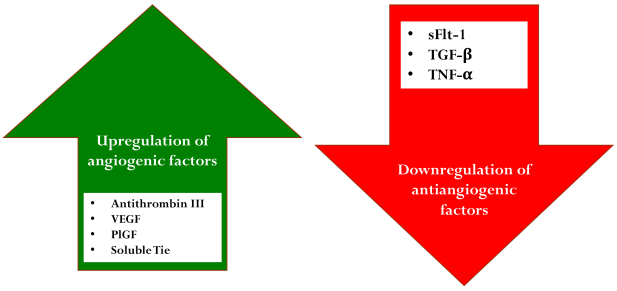

Fig. 2. Upregulation and downregulation of angiogenic factors. VEGF, vascular endothelial growth factor; PlGF, placental growth factor; sFlt-1, soluble Fms-like tyrosine kinase 1; TGF-β, transformation growth factor–β; TNF-α, tumour necrosis factor-α.

Biberoglu *et al.* [52] studied angiogenic factors in their case–control study. They reported no statistical difference in the levels of sFlt-1, placental growth factor (PlGF), sFlt-1/PlGF ratio, and VEGF in PAS, compared to controls [52]. On the other hand, Zhang *et al.* [53] found that sFlt-1 levels and the sFlt-1/PlGF ratio were lower in PAS group than in the controls, while PlGF levels in the PAS were higher than in the controls. They concluded that sFlt-1, PlGF, and sFlt-1/PLGF ratio could differentiate between patients with PAS from those with placenta previa [53].

4.4.4 Structures Released by Human Placenta

Normally, placenta releases hormones, genetic materials (microRNA (miRNA), mRNA, cell-free fetal DNA (cffDNA)), trophoblasts, and extracellular vesicles (EV). These are used extensively in future research. EVs or exosomes are nonnucleated structures bound by a lipid bilayer and are released by the placenta. They play a crucial role in the synergy between the immune system and trophoblasts, resulting in immune tolerance, appropriate placentation, vascular endothelial cell migration, and remodeling of spiral arteries. In PAS these EVs are increased [54–56].

4.4.4.1 Circulating Trophoblasts (cTBs). cTBs are also used in early prediction of PAS disorders. These can be detected by NanoVelcro microchips, and are detected either single or in clusters. Afshar *et al.* [57], conducted a study on 168 pregnant women and 15 non-pregnant women to detect these cTBs. They found that clustered trophoblasts were more predominant than single cells, and that cTBs were more detected in PAS than in controls. Moreover, cTBS can differentiate placenta previa from placenta accreta [57].

4.4.4.2 cffDNA. cffDNA is another marker used in the prediction of PAS. cffDNA is secreted during pregnancy and disappears rapidly within 2 hours postpartum. Clinical applications of cffDNA included the detection of chromosomal aneuploidies and adverse pregnancy disorders, such as preeclampsia, fetal growth restriction and preterm la-

Table 4. PAPP-A and its predictive levels in PAS and controls.

Study	Trimester	Description of study findings
Dreux *et al*. [42]	1st trimester	They included 69 cases. Levels of PAPP-A were higher in PAS than in controls. No definite cutoff level was determined. Positive histopathological confirmation was done.
Desai *et al*. [46]		They included 82 cases. Levels of PAPP-A were higher in PAS than in controls. No definite cutoff level was determined. Positive histopathological confirmation was done.
Thompson *et al*. [47]		They included 516 cases. Levels of PAPP-A were higher in PAS than in controls. Cutoff level was 1.40 MoMs. Positive histopathological confirmation was done.
Lyell *et al*. [43]		They included 736 cases. Cutoff level was 2.63 MoMs. No histopathological confirmation was done.
Büke *et al*. [48]		They included 88 cases. Levels of PAPP-A were higher in PAS than in controls. No definite cutoff level was determined. Positive histopathological confirmation was done.
Penzhoyan *et al*. [49]		They included 48 cases. Levels of PAPP-A were higher in PAS than in controls. Cutoff level was 1.30 MoMs. Positive histopathological confirmation was done.

PAPP-A, pregnancy-associated plasma protein A; PAS, placenta accreta spectrum; MoM, multiple of the median.

Table 5. Factors affecting EVTs invasion.

Limiting factors	Promoting factors
uNK (uterine natural killer cells)	ATIII (antithrombin-III)
PAI-1 (plasminogen activator inhibitor-1)	uPA-1 (urokinase-type of plasminogen activator-1)
TNF-α (tumour necrosis factor-α)	VEGF (vascular endothelial growth factor)
TIMP (tissue inhibitor of matrix metalloproteinases)	PlGF (placental growth factor)
TGF-β (transformation growth factor–β)	MMPs (matrix metalloproteinases)
sFlt-1 (soluble Fms-like tyrosine kinase 1)	sTie2 (soluble Tie2)
	HSPA4 (heat shock protein 4)

EVTs, extravillous trophoblasts.

bor. Wertaschnigg *et al*. [58] reported that PAS cases had elevated cffDNA levels (35.3%) at the end of the first-trimester, which was higher than the normal levels for this gestational age. cffDNA has a lot of disadvantages as its levels are affected by technique of isolation, gestational age and length range of cffDNA [58].

4.4.4.3 Cell-free miRNA. Cell-free miRNA is a non-coding RNA that consists of 22 nucleotides. The miRNAs play important roles in cell differentiation, embryonic growth, cell migration, adhesions, and angiogenesis. The miRNAs circulate in maternal blood, can thus be collected easily and be utilized in fetal genetic assessment to detect many fetal disorders. In PAS, miRNAs are considered the potential biomarker for the prediction of PAS disorders [59]. In a study by Chen *et al.* [60], the important miRNAs investigated in pathogenesis of PAS were miR-139-3p, miR-196a-5p, miR-518a-3p, and miR-671-3p.

4.4.4.4 Placenta-specific mRNA. The placenta also secretes cell-free mRNA. These placental mRNAs could be detected easily in the maternal circulation, and thus be easily isolated and quantified. Therefore, placental mRNA could be used to assess placental function and placental-related disorders. The most commonly investigated mRNAs are β-hCG and human placental lactogen (hPL) mRNAs. Li *et al*. [61] measured maternal plasma hPL mRNA in women with PAS, placenta previa and normal controls. They found that multiple of the median (MoMs) for hPL mRNA was significantly elevated in the PAS group. They concluded that hPL mRNA may predict PAS, but cannot predict peripartum hysterectomy [61].

4.5 Machine Learning Models

Machine learning models are electronic models designed to reduce the workload and mental stress of obstetricians managing PAS disorders. These electronic models could detect the amount of bleeding during PAS surgery, improve decision-making, and help in choosing the best lines of management. Pictures of ultrasound or MRI and plasma biomarkers are translated accurately by these electronic models and could yield accurate results [62].

Liu *et al*. [62] designed models to predict the amount of blood loss during cesarean delivery, using MRI images translated by DeepLab-V3 network and Visual Geometry Group Network-16. They reported an accuracy of 75.61% [62]. Accordingly, Akazawa *et al*. [63] designed two machine learning models using MRI images to predict the amount of blood loss in PAS surgery.

Andreasen *et al*. [64] developed a model using ultrasound images translated by convolutional neural networks (CNN), with an accuracy of 81%. Yaşar *et al*. [65], used XGBoost electronic algorism and Adaboost models with 10 folds accuracy. Shazly *et al*. [66] used two machine learning models in the prediction of peripartum outcomes related to PAS disorders. Lastly, combined models using ultrasound and MRI images were used by An *et al*. [67].

5. Conclusions

From this evidence-based analysis, we conclude that PAS disorders could be predicted by different modalities. Ultrasound markers are more accurate, easy to trace, and had positive correlation to PAS surgical outcomes, such as blood loss and peripartum hysterectomy.

We put a caution note on the use of scoring systems, as more than ten scores are herein discussed, and none of them was superior to the others. Furthermore, none of the scores showed absolute accuracy in prediction of PAS disorders.

Biomarkers measurements vary according to technique of estimation and gestational age. Sometimes, there were no differences and sometimes there was some overlap between cases and controls, and most studies were retrospective. Biomarkers are still investigational, and further assessment of these biomarkers in predicting PAS disorders should be kept for research purposes only.

Author Contributions

ASD: contributed in study idea, manuscript design, revision and submission. HRE: contributed in study design, scientific writing, manuscript edition, and final revision. MAR: contributed in study design, manuscript writing, and figures design. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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