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# ABNORMALLY INVASIVE PLACENTA: A LITERATURE REVIEW ON RISK FACTORS, DIAGNOSTIC CHALLENGES, PATHOPHYSIOLOGY, AND CLINICAL MANAGEMENT

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## **ABSTRACT**

Placenta accreta spectrum (PAS) is a term used to describe a pathological condition characterised by abnormal placental adherence or invasion of the myometrium or extrauterine structures (1). The condition is characterised by adhesion to the myometrium in the presence of placenta accreta, invasion of the myometrium by placenta increta, and extension of the placenta through the serosa into adjacent organs, a condition known as placenta percreta(1–4) Placenta accreta spectrum disorders (PASDs) are a group of conditions characterised by the excessive adherence of the placenta, which results in the failure of the placenta to separate during birth.

It is widely acknowledged that PASD represents one of the most dangerous conditions associated with pregnancy. In a considerable number of cases, the condition remains undiagnosed prior to delivery. Achieving correct prenatal diagnosis is imperative in order to reduce the burden of maternal and fetal morbidity. Despite the fact that ultrasound remains the imaging modality of choice, magnetic resonance imaging (MRI) is necessary for the evaluation of areas which are difficult to visualise using ultrasound, as well as for the assessment of the extent of placenta accreta (1,2,5,6).

The implementation of effective management strategies is paramount in achieving optimal outcomes. A multidisciplinary approach is required, in addition to the establishment of adequate infrastructure (1). This article defines the characteristics, risk factors, diagnosis, management and outcomes of placenta accreta spectrum, highlighting a multidisciplinary approach.

#### KEYWORDS

Placenta Accreta, Prenatal Diagnosis, Risk Factors, Pathophysiology, Ultrasonography, Prenatal, Postpartum Hemorrhage

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# Introduction.

The term 'placenta accreta spectrum' (PAS) is used to denote a pathological condition characterised by abnormal adhesion of the placenta to the myometrium of the uterus. The condition is also referred to as 'morbidly adherent placenta' or 'abnormally invasive placenta', and includes a range of serious complications(6,7).

It is important to note that there is a possibility of life-threatening pregnancy complications arising from abnormal placentation(7,8).

The spectrum encompasses the conditions known as placenta accreta (where the placenta becomes attached to the myometrium without the presence of the decidua) and placenta increta (where the placenta penetrates the myometrium)(1,9).

The most severe form of this condition is known as placenta percreta, which is characterised by the invasion of the serosa surrounding the uterus. In some cases, this condition may extend to adjacent organs, such as the bladder, intestines, and parametrial ligaments. The frequency distributions of PAS disorders are: 75% placenta accreta, 18% placenta increta and 7% placenta percreta(10).

## **Epidemiology**

Since the 1960s, the rate of PAS has increased. It has increased by 60 times. It went from 1 in 30,000 pregnancies to 1 in 533 pregnancies (5). Research shows that the prevalence of PAS ranges from 0.01 to 0.1% of deliveries(11). A major factor contributing to this increase is the increasing number of caesarean sections worldwide(12).

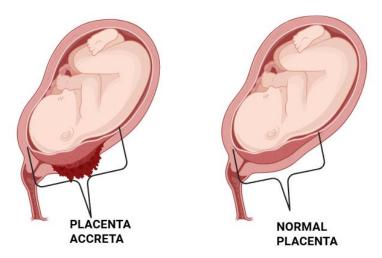


Fig. 1. The placenta accreta spectrum and normal placenta. (Created with BioRender.com.)

## Risk Factors

The exact cause of the disease is still unclear. Potential underlying factors are of a mechanical nature, including primary decidua. The issue is due to reduced blood flow resulting from injury to the uterine wall in a specific area. Some of the factors that can be taken into consideration include abnormal maternal responses to trophoblast (11). The two most significant risk factors for placenta accreta spectrum are placenta previa and previous caesarean delivery. The risk stratification of patients with PAS is of critical importance. This is intended for the purpose of planning delivery. The prevalence of risk factors associated with the development of PAS has been well documented, and their significance is widely acknowledged. The following are examples of surgical procedures or manipulations of the endometrium, including CS, myomectomy, curettage, hysteroscopy or endometrial ablation, with cumulative risk per procedure. It is important to note that additional risk factors for placental disorders include advanced maternal age, in vitro fertilisation (IVF), Asherman's syndrome, multiparity, BMI ≥30, and smoking cigarettes (8,11,13−15). The findings indicated that a short interpregnancy interval does not appear to be a risk factor for the development of PAS during pregnancy(16).

## **Pathophysiology**

The invasion of the extravillous trophoblast (EVT) into the uterine wall is a pivotal process in the normal course of pregnancy. Although the differentiation of the cytotrophoblast (CTB) into extravillous trophoblast (EVT) is a well-documented part of this process, the mechanisms that regulate the initiation and termination of this invasion, and the precise mechanisms by which the differentiation itself takes place, are not yet fully understood(17).

It has been demonstrated that, in the initial trimester, CTB to EVT differentiation occurs through the epithelial-mesenchymal transition (EMT), with EVTs adopting a partially mesenchymal, "unstable" phenotype(17).

In the third trimester, normal EVTs lose their invasive capacity, although they still show traces of EMT. In contrast, EVTs from pregnancies with AIP do not demonstrate this attenuation; they exhibit a more mesenchymal character, suggesting a permanently increased invasiveness(17).

The precise pathogenesis of PAS remains to be elucidated; however, the risk factors offer some insight into the potential mechanisms involved. The predominant theory concerning this matter posits that antecedent uterine surgical procedures that encompass the endometrial-myometrial interface result in defective decidualization within a uterine scar. This, in turn, facilitates the abnormal adhesion of the anchoring villi of the placenta to the myometrium. This, in turn, facilitates further trophoblast invasion(18).

The identification of mechanisms of trophoblast differentiation has the potential to facilitate a more profound comprehension of pathologies associated with impaired trophoblast invasion, and to inform future therapeutic interventions(17).

# Diagnosis

Early recognition of placental abnormalities using ultrasound allows appropriate prophylactic measures to be implemented and serious complications, including haemorrhage, to be avoided. The following are examples of irregularities that may be observed:

- The image of the uterine-bladder border is abnormal, exhibiting an interrupted border.
- Large lacunae within the placenta with turbulent flow in the absence of a fossa.
- It is evident that there is a hyperechoic zone between the uterine serosa and the bladder wall, which is referred to as the "bright bladder line".
- The phenomenon of loss of hypoechoic presumptive zone, otherwise referred to as the "clear zone", has been observed.
  - Exophytic masses that extend into the bladder (percreta type);
- The presence of thin uterine muscle (i.e. muscle measuring less than 1 mm) and uterine serosal protrusion was also observed.
- Hyperunion at the junction of the uterus and bladder was characterised by a significant increase in colour Doppler signal intensity between the uterine myometrium and the posterior bladder wall.
- The presence of multiple, branching vessels with multidirectional flow is observed, along with the presence of aliasing artefacts(1,18).

Early and accurate diagnosis of PAS is imperative, as incorrect diagnosis can result in substantial haemorrhage and surgical complications. Ultrasonography remains the primary imaging modality; however, magnetic resonance imaging (MRI) is essential in cases that are difficult to assess with ultrasound and to accurately determine the extent of perilymphatic sac (PAS) effusion(2). Magnetic resonance imaging is an additional diagnostic modality that may be employed, specifically for the evaluation of posterior placentas and extension into adjacent organs. A number of studies have been conducted that make comparisons between ultrasound and MRI. The following is a list of the diagnostic criteria for PAS: Notwithstanding the considerable heterogeneity amongst the studies and the results obtained, MRI is defined as a method that is not considered essential for the diagnosis of PAS(1). A systematic approach to the interpretation of MRI images is imperative in order to diagnose PAS, and this approach should include the following:

- Assessment of placental location. The determination of the location of the placenta in relation to scars from previous caesarean sections or other uterine surgery is a crucial step in the medical process.
- The identification of specific MRI features, including the presence of dark intraplacental bands has been observed.
  - The placental bulge is a term used to describe the protuberance of the placenta from the uterus.
  - The phenomenon of placental signal heterogeneity.
- Assessment of the depth of invasion: the determination of the degree of penetration of the placenta into the uterine muscle or beyond is of crucial importance for the planning of surgical treatment (1,2,19).

The published literature revealed potential biomarkers in maternal serum that could be used to predict PAS in the future, which is an exciting development. While some of these biomarkers show promise in diagnosing PAS, they are not currently specific or sensitive enough to replace existing imaging methods. However, when used alongside imaging studies, these biomarkers could improve diagnostic accuracy. They could also enable earlier detection of PAS(21). Elevated levels of  $\beta$ -hCG (chorionic gonadotropin) may indicate abnormal trophoblast invasion. AFP (alpha-fetoprotein) levels may be increased in PAS, but this is not specific. A lower value of PAPP-A (pregnancy-associated plasma protein A) may be indicative of an elevated risk of PAS. cffDNA (cell-free fetal DNA) levels in maternal serum may be higher in cases of PAS, but interpreting the results is complex. Further study is needed on specific microRNAs and placental mRNA, which show promise as biomarkers due to their stability and specificity(21).

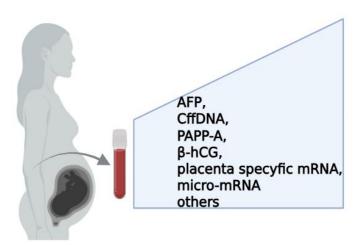


Fig. 2. Biomarkers related to PAS. (Created with BioRender.com.)

The identification of PAS constitutes a pivotal component of the diagnostic process, yet it represents merely the initial stage of a multifaceted evaluation. Furthermore, it is imperative to ascertain the precise location and extent of the lesions, a task which is instrumental in the planning of surgical intervention. Surgical teams require improved models to predict the risk of complications and more effective PAS grading systems(19). The ideal classification of PAS should therefore combine clinical data and imaging findings to accurately predict surgical risk, rather than simply confirming the presence of the condition. It is evident that, even in specialised centres, the diagnosis of PAS can be challenging and not always accurate. Consequently, physicians should exercise a high level of clinical vigilance and be willing to refer patients to reference centres with experience in treating PAS(19).

## **Treatment**

In the United States, immediate hysterectomy is currently considered to be the optimal surgical intervention for placenta accreta spectrum(22).

Thi Pham and colleagues have described a novel surgical method for the treatment of PAS. This method involves the preservation of the uterus, and is a significant development in the field. The surgical technique combines partial uterine resection, arterial ligation, tourniquet application and compression sutures. The success of the procedure is contingent upon the expertise of the surgical team, who operate within a centre with extensive experience in treating PAS. The collective expertise of the surgical team is the primary factor contributing to successful surgical outcomes, rather than the specific technique employed. The issue arises when surgeons with less experience encounter a case of PAS during a caesarean section, particularly as it is impossible to completely eliminate cases undiagnosed before delivery. In such cases, it is imperative that the patient is transferred expeditiously to a centre with a proven track record in such cases, in order to forestall the onset of irreversible complications(23).

It is evident that most national and international obstetric societies have published guidelines for the management of placental abnormal adhesion spectrum. It is recommended that a team approach be adopted, based on established protocols, carried out by a group of specialists with experience in multiple areas of medicine, working within Regional "Centres of Excellence" for the diagnosis and treatment of PAS(24).

The composition of the surgical team should be as follows:

- The obstetrician in question is likely to be an experienced professional, typically in the field of maternal-fetal medicine.
- A specialist in the field of anaesthesia with a proven track record in the management of complex obstetric cases.
  - A surgeon with expertise in complex pelvic surgery, frequently specialising in gynaecological oncology.
  - The position is for a urologist with expertise in open surgery and ureteral transplantation.
  - The medical practitioner in question is an interventional radiologist.
- The medical practitioner specialising in surgery of the gastrointestinal system, specifically the colon and rectum, is referred to as a colorectal surgeon.

• The medical practitioner specialising in vascular surgery is known as a vascular surgeon.

The presence of a seasoned surgeon at the delivery stage, when PAS is suspected, has been demonstrated to significantly mitigate the risk of haemorrhage and the necessity for transfusions when compared with a policy of reactive referral (24).

The findings of this analysis imply the potential efficacy of fertility-preserving techniques, such as Bakri balloon tamponade or segmental uterine resection, as effective alternatives to hysterectomy in the management of PAS, with the advantage of achieving comparable clinical outcomes to hysterectomy while maintaining patients' fertility. The selection of an appropriate treatment modality is to be made on the basis of individual patient requirements and the expertise of the surgical team(25).

In underdeveloped regions, patients exhibiting symptoms consistent with PAS, coupled with an anterior placenta devoid of active bleeding, should undergo childbirth between the 34th and 36th weeks of gestation. The surgical intervention should be adapted to the characteristics of the individual patient and the resources available, with the option of hysterectomy if significant bleeding persists(26).

The occurrence of unexpected PAS in hospitals with limited resources has been demonstrated to increase the risk of maternal mortality. The surgical approach most commonly employed for this procedure is to perform open-close abdominal surgery and to leave the placenta in situ(27).

# **Hemostatic Considerations**

Postpartum haemorrhage is a significant cause of obstetric haemorrhage. It is evident that PPH continues to be a significant cause of maternal mortality on a global scale, with cases occurring with alarming frequency on a daily basis(28).

Haemostatic disorders and peri- and post-partum haemorrhage are two distinct medical conditions. PAS is frequently linked to substantial haemorrhage, a factor that poses considerable challenges for medical teams. Patients diagnosed with PAS are predisposed to significant blood loss, often exceeding two litres, the necessity for transfusion, and prolonged hospitalisation.

• The management of blood transfusions and the prevention of thrombosis

Anaesthetists must be prepared for the possibility of massive blood loss, which requires the rapid administration of appropriate blood products and strategies to prevent coagulopathy. Moreover, the implementation of thromboprophylaxis postpartum is imperative to mitigate the risk of venous thromboembolism.

• The role of multidisciplinary teams

The effective management of PAS necessitates the collaboration of specialists from various disciplines, including obstetricians, anaesthesiologists, surgeons and interventional radiologists. Such collaboration facilitates superior preparation for surgery and a more expeditious response to potential complications (29).

In the absence of concomitant placenta previa, patients with PAS experience reduced blood loss during childbirth; the mean difference was 1.19 litres. Furthermore, the probability of requiring hysterectomies is diminished(30).

## **Conclusions**

Placenta accreta spectrum (PAS) is a grave pregnancy complication characterised by abnormal trophoblast invasion into the uterine muscle, frequently resulting in substantial haemorrhage and necessitating surgical intervention. As demonstrated in the extant literature, the early identification of risk factors – including, but not limited to, a history of caesarean sections, placenta praevia, and previous uterine surgery – is of crucial importance in order to reduce maternal mortality and morbidity.

Notwithstanding considerable advances in prenatal imaging, particularly in the domains of ultrasound and MRI, the diagnosis of PAS remains a considerable diagnostic challenge. The absence of consistent criteria, the manifestation of symptoms that overlap with other pathologies, and the technical limitations of imaging studies have a detrimental effect on the variable sensitivity and specificity of the environment. These factors may contribute to the development of new biomarkers and prevention strategies.

The analysis of the available data leads to several conclusions, which emphasise the necessity of a multispecialty approach to the management of patients with PAS, as well as the necessity of further clinical and molecular research aimed at improving the quality of diagnostic and therapeutic care. The importance of integrated management, based on early diagnosis, appropriate birth planning and surgical intervention, in optimising maternal-fetal outcomes remains paramount. Simultaneously, it is imperative to comprehend the pathophysiology of PAS, encompassing implantation abnormalities and temporal microanatomical variations.

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Methodology: Barbara Wołoszyn, Patrycja Rzeźnik, Aleksandra Chajnowska Formal Analysis: Małgorzata Zach, Aleksandra Chajnowska, Julia Guzowska Investigation: Małgorzata Zach, Wiktoria Suchcicka, Aleksandra Borowy Writing – Original Draft: Weronika Stachera, Maciej Sobczyk, Julia Stępień

Writing – Review & Editing: Barbara Wołoszyn, Patrycja Rzeźnik Supervision: Julia Guzowska Aleksandra Borowy, Wiktoria Suchcicka

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## Declaration on the Use of AI

In preparing this manuscript, the authors used ChatGPT for language improvement and enhancing readability. Following the use of this tool, all content was reviewed and edited by the authors, who take full responsibility for the accuracy and integrity of the final version.

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