

**ASSESSING THE PREDICTIVE VALUE OF PLACENTAL PAPP-A LEVELS IN HIGH-RISK PREGNANCIES: A PROSPECTIVE COHORT STUDY ON PLACENTA PREVIA AND PREVIOUS CESAREAN SECTIONS*****¹Dr. Hiba Tarik Mousa, ²Dr. Israa Hashim Abid-Alkareem**¹MBChB, Iraqi Board Candidate in Obstetrics and Gynecology, Iraqi Board of Medical Specialties, Tikrit Teaching Hospital, Iraq.²M.B.Ch.B, F.I.C.O.G, Assistant Professor in Obstetrics and Gynecology, Tikrit Teaching Hospital, Iraq.

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ABSTRACT

Objective: We tried to study the predictive value of first-trimester serum Pregnancy-Associated Plasma Protein-A (PAPP-A) levels in detecting high-risk pregnancies for Placenta Previa and Previous Cesarean Sections. **Methods:** This was a prospective one center cohort study conducted on 225 pregnant women recruited from the one hospitals in Iraq for which all had PAS risk factors, including smokers or had taken previous c/s. According to their PAPP-A multiples of the median (MoM) levels, participants were divided into 3 groups: Low; Normal; and High PAPP-A. Primary end-point was the occurrence of PAS confirmed by histopathologic examination and/or clinical diagnosis. The relationship between PAPP-A levels, together with smoking and previous cesarean sections, as well as the risk of PAS were evaluated using univariate, multivariate logistic regression analyses. **Results:** A significant link was detected between elevated PAPP-A levels and an increased risk of PAS. Among them, patients in the High PAPP-A group experienced a significantly higher prevalence of PAS compared to those with Low and Normal PAPP-A (Adjusted OR: 3.01; 95% CI: 1.77–6.94; $p = 0.0003$). The smoking (Adjusted OR: 1.17; 95% CI: 1.09–0.4, 12, $p =$) and a history of previous cesareans with PAS were significantly associated among others. Now the study and found association between maternal BMI with PAS in Iraq. **Conclusion:** The results of the study propose that high first- trimester PAPP- A may be an important predictor for PAS in some high-risk pregnancies. This study illustrates a strategy for introducing PAPP-A screening to routine early prenatal care as an additional way of better discerning risk and management amongst pregnancies at high-risk for PAS. These results reinforce the need for more investigation on pathways from PAPP-A levels to abnormal placentation, and studies to improve practice-based risk assessment models.

KEYWORDS: Primary end-point was the occurrence of PAS confirmed by histopathologic examination and/or clinical diagnosis.**INTRODUCTION**

Placenta accreta spectrum (PAS) disorders are a heterogeneous group of conditions that have garnered significant attention in contemporary obstetrics. Conditions in which the placenta is abnormally adherent to the uterine wall, either adhering too deeply or invading through the muscle layer. The spectrum extends from placenta accreta, in which the placenta adheres too deeply to the surface of the uterus, to placenta increta,

where there is invasion of deeper uterine muscle and (the most severe form) placenta percreta, in which the placenta invades through uterine wall and surrounding organs. These differences in invasonic severity provide healthcare providers with challenges as each degree of invasion also has an increased risk for serious delivery complications where placental separation is difficult or not possible.^[1]

One reason the rise in PAS disorders can be seen around the world is due to increased use of cesarean sections. Multiple cesareans can scar the uterus.

This scarring increases the risk of abnormal placental implantation, leading to a higher incidence of PAS in women with prior cesarean deliveries. Consequently, PAS has emerged as a leading cause of major obstetric hemorrhage during delivery, frequently necessitating extensive surgical intervention such as hysterectomy to manage bleeding. Thus, the burden of maternal morbidity and mortality due to PAS is significant, and early detection is essential.^[2]

Early recognition of PAS is critical to optimizing the health outcome of mothers and babies. Today, PAS disorders are frequently diagnosed in the second or third trimester or, when they do happen, during labor. This complicates planning delivery because there are limited treatment options available at the time of diagnosis. Patients who need an emergency delivery because of undiagnosed PAS may be at even greater risk, facilities and staff may not be ready for the catastrophic surgical measures often needed. Therefore, one of the most important objectives in obstetrical care is to discover an early detection marker capable of diagnosing PAS with high accuracy during pregnancy. This early prediction would help to individualize management, enable proactive planning for monitoring obstetric risks and complexities and, in the most severe cases of OUSD sponge localization form assist with organizing delivery in a specialist hospital capable of advanced obstetric surgery.^[3]

Pregnancy-Associated Plasma Protein-A (PAPP-A), a placental cell-derived glycoprotein, has been investigated in relation to PAS risk and may be an early biomarker of the disease. PAPP-A is critical to both placental and fetal development through control of insulin-like growth factors, the IGFs essential for normal placental and fetal growth. Decreased levels of PAPP-A in first-trimester screenings have been linked with adverse pregnancy outcomes, including preeclampsia and fetal growth restriction. Given its role in controlling placental invasion, we hypothesize that altered secretion of PAPP-A may be associated with the abnormal type of placental attachment characteristic of PAS disorders. As such, assessing PAPP-A in the first trimester may serve as early potential marker of PAS risk specifically in high-risk pregnancies.^[4]

PAS is characterized by abnormal placental attachment which reflects the balance disturbance between placental invasion and uterine wall resistance. Normally, placental cells called trophoblasts invade the uterus in a regulated manner, establishing firm but safe attachment of the placenta to the uterine wall. In PAS disorders, this process is disrupted and the placenta implants too deeply often penetrating not only into the muscle layer but also beyond. Since PAPP-A is implicated in the regulation of

trophoblast invasion, it may be that elevated or abnormal levels of maternal serum PAPP-A indicates this maladaptation early during pregnancy. Although PAPP-A screening might be useful for determining PAS risk in the first trimester, it would likely have greater utility in particular groups of women—for example, optimally identifying women at high risk for PAS who have a history of cesarean sections or placenta previa (where the placenta covers the cervix) or other uterine surgeries.^[5]

Although there is a strong rationale to use PAPP-A as a marker of PAS phenotype at 11-14 weeks, the majority of studies carried out thus far have shown mixed results. PAPP-A has been proposed as a risk factor for PAS in some studies while others have shown no statistically significant associations.^[6] The inconsistency of the findings may be due to (differences in 1-study design, 2-sample sizes, or 3-different populations). Large-scale, study is needed to clarify the role of PAPP-A, a known predictor of PAS but where data with levels and outcomes reported have not been clearly identified.

Hence the current study was conducted to assess this highly significant marker in high-risk pregnancies, and we aim to study the levels PAPP-A prospectively and multi-centrally based on data collected from one hospital in Iraq. AIM: To assess the value of first-trimester PAPP-A in predicting PAS, allowing early interventional treatment on first-trimester high risk. PAPP-A has been previously studied as a potential biomarker for pregnancy complication such is PAS and by investigating it further, we hope to be able to provide manageably applicable evidence towards obstetric care in order to optimize screening for high-risk pregnancies and prevent the extreme values of PAS consequences. If, however, PAPP-A turns out to be a good predictor of PAS, it could be incorporated into clinical practice by routine screening for first-trimester pregnancies at high risk of PAS and provide physicians with an additional tool to manage such cases.^[7]

Literature review

2.1 Overview of Placenta Accreta Spectrum (PAS) Disorders

2.1.1 Definition and Clinical Importance of PAS Disorders

Placenta accreta spectrum (PAS) disorders are abnormal conception adherences to the uterine wall and the major fetal construction has evolved as one of commonest obstetric conditions associated with increased complications during pregnancy and delivery. The abnormality is primarily separated into accreta, increta and percreta based on the depth of invasion to uterine tissue by trophoblastic layers (Gargantini et al. The placenta usually separates from the lining of the uterus after delivery, but in cases of PAS -- due to abnormally invasive attachment -- both can make separation difficult and present extreme dangers for hemorrhage and maternal illness.^[8]

PAS is an important palette that we can and should probably paint in our obstetric practice. Changes in methods of delivery that occur over recent decades have resulted an increase in incidence of PAS disorders, especially with increasing rate of cesarean deliveries. This is important because scar tissue from previous cesarean births makes the area prone to abnormal placental attachment in any future pregnancies. As a result, the increase in PAS disorders has led to new challenges for providers of healthcare who face more complex surgical procedures, advanced high-risk obstetric and ancillary management as well as increasing maternal morbidity and mortality.^[9]

2.1.2 Categories of PAS Disorders

Based on the extent and depth of placental infiltration, PAS disorders can be broadly classified into three types of major:

Placenta accreta: In placenta accreta, the placental tissue binds to the myometrium (the muscular tissue of uterine wall) but does not pervade it. It is the least severe version of PAS. Although this makes separating them after the babies are born more difficult, it is still usually linked to less difficult types of surgery and therefore lower surgical risks.

Placenta Increta: Type of placenta that goes deeper into your myometrium and attaches inside the muscle of your uterus. Because it is a deeper grade of invasion, fixation at birth is difficult and massive bleeding and tissue destruction may occur. For this, placenta increta is a more clinically significant issue that typically translates to greater operative planning.

Placenta Percreta: This is the most advanced form, in which placental tissue has extended through the myometrium and into the uterus serosa (the visceral peritoneum surface of the uterus) or beyond. In some cases, this abnormal invasion may be to other organs with the bladder being the most common. Placenta percreta delivery is one of the most dangerous situations that can develop during delivery, associated with an extremely high risk of severe hemorrhage and it can additionally cause deep damage to surrounding organs necessitating complex, multi-disciplinary surgical intervention.^[10]

Each form of PAS disorder has varying obstetric implications, ranging from least to most severe (i.e., accreta < increta < percreta). These distinctions are important in anticipating therapeutic shortcomings for each variant, as the depth of invasion is an important determinant of surgical difficulty, maternal morbidity and risk for postpartum complications. This information optimises planning for delivery and intervention prior to birth (when early diagnosis occurs); but these differences are currently poorly understood.

2.1.3 Clinical Relevance of PAS Disorders in Maternal Health

The severe maternal morbidity and mortality associated

with PAS disorders arise from the complications that usually develop in the course of trying to separate a good quantity of placenta; thus, there is a significant risk to maternal health. If the placenta fails to detach, massive bleeding almost always occurs and maternal life is threatened (hypovolemic shock and coagulopathy). The risk becomes especially high if PAS is unsuspected at delivery where unexpected bleeding may lead to urgent surgery and blood transfusion.^[11]

The risk of bleeding is so high that hysterectomy (removal of womb) is often the treatment choice for PAS, especially when increta and percreta are involved⁽⁹⁾. While hysterectomy is often life-saving, the resulting loss of fertility imposes emotional trauma on patients and psychological aftereffects. Lastly, PAS is associated with increased rate of certain complications post-operatively—such as infection, prolonged recovery and possible injury to any of the adjacent organs such as bladder.

The implications of PAS are thus/clinical not only a health risk, but also the global impact on maternal health, reproduction outcomes and post-delivery quality life. Therefore, timely diagnosis and managed protocols become an important tool to address these adverse events by providing a standardized delivery planning process ensuring the best maternal outcomes with minimally invasive procedural risks.

2.2 Incidence and Risk Factors of PAS Disorders

2.2.1 Increased Prevalence of PAS Disorders

The incidence of Placenta Accreta Spectrum (PAS) disorders has sharply increased during the past few decades internationally, coinciding with an increase in cesarean section rates.^[1] In fact, studies indicate that the absolute most significant risk factor for PAS is also cesarean section as scarring on the uterus contributes to a greater tendency toward developing this condition. Normal placenta-uterus interaction gets changed by scar tissue making this environment favourable for abnormal placental implantation in subsequent pregnancies.

Cesarean rate is rising throughout the world due to changing obstetric practice, maternal choice and new indication (e.g. breech presentation, maternal disease). With the increase of cesarean deliveries in North America and some Asian countries, PAS has increased as well. Incidence of placenta accreta syndromes (PAS) is estimated to be 1 in 500 and 1 in 1000 pregnancies worldwide, but may be higher in areas where cesarean delivery rates are high. As a result, health care systems need to reassess their prenatal care strategies to mitigate the high prevalence of PAS and its subsequent complications.

2.2.2 Principal Risk Factors for PAS Disorders

A number of risk factors have been associated with subsequent PAS disorders, particularly previous uterine surgery (most commonly cesarean delivery), advanced maternal age, multiplicity of pasra and placenta previa.

2.2.3 Scar of C-section and other uterine surgical scars

The strongest PAS disorders risk whom scarring is perceived Director scar which experimental environments of tissue break A shriplike will readily provide particularly significant for unmanageable placental enter. Each cesarean delivery that is done increases the risk of PAS in subsequent pregnancies. Research your risk increases for more than one — Women who's had one previous cesarean face a modestly greater risk and women with two or more crashes report an even higher risk.^[11]

- In addition to cesarean deliveries, other surgical procedures involving the uterus—including myomectomy (surgical removal of fibroids), dilation and curettage (D&C) or surgeries that repair the uterus—also contribute to PAS risk because these techniques create areas of scar tissue within the lining of the uterine wall. These procedures leave scars in the myometrium, which interrupt the normal endometrial–myometrial interface and make abnormal implantation possible in any subsequent pregnancy.^[12]

2.2.4 Placenta Previa

Placenta previa (the placenta has implanted unusually low in the uterus, either partially or completely covering the cervix) is another significant PAS risk factor. Background: Placenta accreta spectrum (PAS) disorders are associated with maternal morbidity and mortality, and placenta previa along with history of cesarean delivery is a major risk factor. This risk is because the placenta is low lying — it overlaps with scar tissue made from previous c-sections.^[13]

The bleeding complications of placenta previa, along with the specific risk to maternal health associated with PAS at delivery, are usually lethal.

2.2.5 Advanced Maternal Age

Maternal age is a known risk factor for PAS and so one way could be the changes into uterus tissue due to maternal aging. Women of "advanced maternal age" (generally defined as 35 or older) have more cesarean delivery rates and placental issues. Increasing maternal age is known to increase the risk of PAS, which could be due to decreased uterine wall regenerative capacity with age. This consequently leads to larger wound spaces, making abnormal placentation more likely.^[13]

2.2.6 High parity — Implant Factors

Higher adjusted odds of PAS is also associated with advanced parity, or more children born previously. Each pregnancy transiently exerts physiological strain on the uterus, and consecutive pregnancies may induce a cumulative effect on the uterine wall. In addition, the same reason as that of a higher risk of previous cesarean or uterine surgeries in this group makes it an especially

vulnerable population to develop these disorders.^[7]

While genetic tendencies and other uterine complications may influence the risk of PAS, the above factors are certainly the most dominant by far.

2.2.7 Genetic Predispositions

In addition, there may also be some genetic aspect of PAS risk — but research in this area is still quite preliminary. Here in, we propose that women with a predisposition to abnormal placentation and trophoblastic infiltration, as suggested by the reported association between an adverse microenvironment at the maternal-placental interface and greater risk of formation of abnormally adherent placenta (accreta/increta/percreta), may be genetically more susceptible due to functional mutations in genes that are critical for accurate placental development and function. However, this is not yet the case as PAS pathophysiology are complex and unique genetic markers would be impossible to isolate.^[14]

2.2.8 Other Uterine Abnormalities

Congenital malformations of the uterus, such as septate or bicornuate uterus, predispose PAS via an atypical uterine environment which causes abnormal placentation . More rarely, these anatomical abnormalities can interfere with placentation and lead to abnormal invasion in pregnancies affected by them.

2.3 Pathophysiology of PAS Disorders

2.3.1 Pathomechanisms of Abnormal Placentation

Trophoblasts are the specialized placenta cells that implant in the uterine wall and invade beyond it for nutrition exchange between mother and fetus. Normally, satisfaction of invasion must be properly controlled so trophoblasts can attach without invading too far. However, in PAS disorders such regulation is broken down allowing trophoblast cells to invade deeper or more aggressively into the myometrium. Depending on the accreta, increta and percreta diagnoses, the degree of invasion is abnormal. In the more extreme form of placenta percreta, trophoblast cells penetrate the outer uterine serosa and can even invade nearby organs like the bladder.^[15] How this overgrowth occurs in detail relies on complex cellular and molecular signaling pathways that regulate adherence, differentiation and invasion.

2.3.2 Effect of Uterine Scarring on PAS

Having scar tissue in the uterus, such as that which develops after prior C- sections or other surgeries, is a key risk factor for PAS disorders. This scarring creates an inappropriate environment for normal placental embedding, and may also disrupt the endometrial-myometrial boundary. Scar tissue — as opposed to healthy uterine tissue with regenerative and architectural qualities intact — also alters how subsequent pregnancies attach and invade the placenta.^[16]

The researchers still have to figure out how the scarred uterus affects both the physical composition of that

architecture and also biochemical signalling -- but there's a link. Researches suggest that in wounded areas, placental cells may not receive appropriate inhibitory signals that control invasion at the level of normal tissues, allowing them to invade deeper into the myometrium. This unregulated rupture increases the risk of placenta accreta spectrum disorder, particularly in women with several cesarean delivery scars that cumulatively increase the odds with each successive scar.^[17]

Key roles of growth factors (notably, insulin-like growth factor) in the normal processes of trophoblast invasion and placental development. IGF, in conjunction with vascular endothelial growth factor, induces early placentation by promoting cellular growth, differentiation, and attachment. Altered levels of these factors have been associated with placenta abnormalities such as PAS due to minimal attachment and invasion into the myometrium.

Normally, while placental invasion takes place, growth factors manage the level of cellular proliferation and also vascular development along with the infiltration intensity. But in PAS, this balance may break down to permit more invasive invasion into the myometrium. One area of interest is the interaction of IGF with its binding proteins that play a role in determining the bioavailability of IGF to placental cells. Disruptions within this regulatory network could lead to heightened or unchecked IGF activity, promoting persistent cell adhesion and excessive trophoblast invasion in the uterus.^[18]

Examining placental growth factors has paved the way for identifying biomarkers that could eventually indicate early PAS risk. Because things like IGF and the others can be measured from maternal blood, scientists are investigating how they may be used as noninvasive markers — particularly for cases where imaging techniques do not yet provide evidence of a defective implantation.^[19]

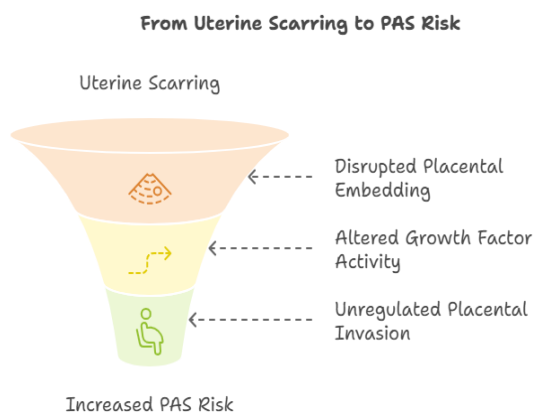


Figure 1: Pathomechanisms of Abnormal Placentation in PAS.

(Illustration created by the researcher based on the discussion in the thesis.)

⚡, ⚡ Pathogenesis of placenta previa accreta

⚡, ⚡, ⚡ Molecular and Cellular Pathways

The molecular mechanisms contributing to PAS are complex and involve a number of signalling pathways that regulate trophoblast adhesion, invasion and differentiation. Central paths worth mentioning include:

Epithelial-mesenchymal transition (EMT), which directs the morphologic plasticity of trophoblasts who then separate from one another to invade the maternal decidua. Trophoblasts switch from an epithelial phenotype to single epithelial-mesenchymal transition (EMT)-like cells that are more migratory and invasive that is important for placentation. Disturbances in the EMT signaling might impact proper invasion and remodeling of artery, favouring the development of placental insufficiency.^[19]

Epithelial cells are capable of migration and tissue invasion by a unique process termed epithelial-to-mesenchymal transition (EMT). While this process is necessary for normal placentation, in PAS it could go away allowing an invasive uterine wall.

⚡, ⚡, ⚡ A type of matrix metalloproteinase (MMP)

Matrix metalloproteinases (MMPs) are enzymes that breakdown extracellular matrix to allow cellular movement and tissue remodeling. Higher activity of MMP in PAS is associated with increased invasion, as they degrade the ECM and other barriers that typically limit trophoblastic invasiveness.

⚡, ⚡, ⚡ Integrins and Cell Adhesion-Fluidification

Integrin binding and signaling of cells In a normal pregnancy, integrins regulate the adhesion of trophoblasts to the uterus. But in PAS, modified integrin expression may not preserve threshold of attachment and limit invasion.

These molecular and cellular pathways are in a way represent the complexity that accompanies developing PAS, and potentially highlight future therapeutic targets for treatment or prevention of abnormal placentation. By studying these pathways, researchers hope to create new treatments or preventive measures for high-risk pregnancies.^[20]

⚡, ⚡ Diagnosis of PAS Disorders

⚡, ⚡, ⚡ Imaging Methods to Establish PAS Diagnosis

Placenta Accreta Spectrum (PAS) disorders are primarily diagnosed using imaging that provides visualization of placental attachment and invasion, providing the clinician with an abstract view of the placenta in relation to surrounding structures. An indispensable management component in PAS is its early and accurate diagnosis, as this allows for planned specialist deliveries which largely minimises MATERNAL morbidity and mortality

risks.^[12] Ultrasound, with or without Doppler, and Magnetic Resonance Imaging (MRI) are the most important imaging methods for PAS diagnosis.

Transvaginal ultrasound is the first-line imaging modality for PAS diagnosis. It gives instantaneous pictures of the placenta and encompassing uterine walls, allowing for examinations how deep the placenta is implanted (infiltration) and vascularity. Transabdominal ultrasound may also be performed, but transvaginal ultrasound provides higher resolution for examining the uterus and cervix. Color Doppler ultrasound is an augmented benefit of standard ultrasound techniques, as it can show blood flow patterns and identify abnormal placental vascularization that might be associated with PAS.^[2] Doppler features indicative of PAS include placental bed hypervascularity, aberrant flow patterns and vessels crossing the uterine walls. Such features may help differentiate the types of PAS by showing degrees of invasion, especially in suspected increta or percreta.

MRI is a sophisticated imaging modality utilized when ultrasound results are ambiguous or placental percreta is highly suspected, as it provides high-resolution images of soft tissues. In particular, MRI helps in assessing the extent of placental invasion past the uterine wall since it can differentiate PAS from other diseases like fibroids that may have similar presentation.^[5]

There are limitations to ultrasound and MRI in accurately diagnosing placenta accreta spectrum (PAS) disorders, especially during the early stages of pregnancy. The placenta doesn't really have enough characteristics to make a diagnosis at that point in time in the first trimester. As such, most cases elude detection until later in pregnancy when the anomalies become more apparent.

Such a delay likely presents dangers, especially in the case of high-risk pregnancies that might be better managed with early intervention.^[21]

Ultrasound and MRI can even misclassify PAS type during the second and third trimesters because of overlapping presentations. Nevertheless, the depth of invasion is important for planning management since this may affect both complexity and risks at delivery; therefore distinguishing accreta from increta and percreta need to be performed⁽¹⁾. But there is a downside as well — the accuracy of diagnosis can be affected by differences in the quality of images, expert levels and patient factors.

When complicated PAS cases necessitate MRI, it enables visualisation of invasion extents, informing resection plans for severe PAS. MRI is usually confined to only complex scenarios due to increased cost, limited accessibility and requirement for specialized analysis. Thanks to ubiquitous availability and real-time potential, ultrasound is still standard for screening. However when

clues such as thinning myometrium or abnormal placentation develop neither imaging modality is able to reliably identify the degree of PAS and management options become more limited.^[22]

५.०.५ Requiring Some Guidance and Gear

Ultrasound, and particularly MRI, have a role in diagnosing PAS; however both will depend considerably on the experience of the radiologist and quality of imaging technology available. In less-resourced places, access to high-end tools or providers with experience with PAS might not be available at all. Such differential availability of resources translates to different diagnostic accuracies and pregnancy outcomes across the globe.^[23]

५.१ Application of biomarkers in PAS diagnosis

Scientists are looking into biomarkers, which might serve as an additional diagnostic tool for PAS when imaging has shortcomings for early diagnosis. Abstract Biomarkers are measurable bodily signs that indicate predisposition to physical or disease processes and provide non-invasive early risk assessment. For PAS, maternal blood detectable biomarkers may provide an early predictive sign of abnormal placental implantation before structural changes can be detected on scans.^[24]

५.१.१ Advantages of Biomarkers

Biomarkers may help detect PAS as early as the first trimester, which is early enough to plan for management of high-risk pregnancies. By identifying patients at risk before placental abnormalities are apparent on imaging, this early identification could serve to help identify women with a history of prior cesarean delivery or other PAS-associated factors.^[25]

Imaging results may be unavailable or inconclusive, and biomarkers could provide complementary information, thereby increasing the overall reliability of the diagnosis that may facilitate the clinical decision-making process.

५.१.२ Current Biomarker Research

Some potential biomarkers, such as Pregnancy-Associated Plasma Protein- A (PAPP-A), soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF), have been studied in relation to PAS as well other placenta-related disorders. These biomarkers, either alone or in combination, have been studied as markers of abnormal trophoblast invasion and/or placental attachment.^[1]

PAPP-A, especially, is a glycoprotein highly correlated to the increase of placental growth during early weeks of pregnancy. PAPP-A is an early screening biomarker for pregnancy complications, such as preeclampsia, and some studies have suggested that abnormal levels of PAPP-A may have the potential to enable identification of affected pregnancies earlier. Continued large-scale studies are needed to establish standardised PAPP-A cut-offs and testing protocols that can confidently predict

these pregnancy outcomes with sufficient reliability for implementation into routine prenatal care.^[4]

2.6.3 Continuing Challenges

Although PAPP-A and other biomarkers have a great potential for future pre-emptive screening, there are significant challenges to translate this into clinical practise. They will need to weigh what test is accepted by the community, define a cut point for asymptomatic versus symptomatic people in tested populations and test across these demographics.^[25] In addition, biomarkers may be affected by a woman's health or other medical conditions that make interpretation difficult and require careful assessment to prevent false alerts or missed signals.

Although coupling of biomarkers with ultrasound and other diagnostic modalities may improve the early identification and management of high-risk pregnancies in the future, larger studies are required to validate biomarker performance and facilitate the construction of formal clinical practice guidelines.

2.7 Biomarkers for PAS Prediction

2.7.1 Understanding Biomarkers in Ob-Gyn

Biomarkers are biological signals that can show us how the inside of our body is functioning and if this function is normal or abnormal. Biomarkers have been used in obstetrics to predict and manage pregnancy complications, as they provide information related to maternal and fetal well being. In disorders like PAS for which early diagnosis may be difficult, biomarkers that can be detected in the serum of a mother could provide a noninvasive method to evaluate risk for PAS as early as the first trimester when structural abnormalities cannot be seen on imaging.^[26]

Biomarkers for prediction of PAS are needed as imaging techniques have limitations, especially early in pregnancy when PAS is typically asymptomatic. A successful biomarker-based strategy would enable clinicians to detect pregnancies at greater risk long before it happens, providing the opportunity for close follow-up on these patients in an attempt to modify individual management plans and reduce maternal morbidity while simultaneously improving outcomes. These biomarkers that appear at different stages of pregnancy and in variable amounts can act as an alarm, alerting clinicians to problems developing, allowing targeted interventions when imaging may be unremarkable.^[27]

2.7.2 Pregnancy-Associated Plasma ProteinA (PAPP-A)

Pregnancy-Associated Plasma Protein-A (PAPP-A), a glycoprotein secreted by placental trophoblast cells, is one of the most useful markers in predicting PAS. PAPP-A is involved in placental growth and fetal maturation primarily by regulating insulin-like growth factor (IGF) activity, which promotes cell proliferation, differentiation, and development. As PAPP-A is

implicated in placental health and development, its prospective use for the purpose of PAS screening has been investigated.^[28]

2.7.3 PAPP-A Levels and PAS Risk

Reports show that during the first trimester screening patterns of an abnormal PAPP-A have been noticed in PAS disorders.^[3] In pregnancies with the highest levels of risk, lower-than-normal levels of PAPP-A may be associated more closely with an increased risk of PAS based on research. It is thought that this association occurs as PAPP-A controls IGF binding proteins (IGFBPs) that regulate the bioavailability of IGF to placental cells, thus affecting trophoblast infiltration depth.

Consequently, low PAPP-A levels could represent a very early international signal of impaired trophoblast function and poor placental anchoring with greater potential for abnormal invasion.

2.7.4 Clinical Performance and Validity

Early studies have supported the use of PAPP-A as a biomarker to assess PAS risk. A few studies have shown that lower PAPP-A levels are associated with higher PAS risk, especially in women who have had previous c-sections or other established PAS risk factors.

2.7.5 Mechanisms Linking PAPP-A to PAS Risk

Pregnancy-associated plasma protein A (PAPP-A) is thought to play a role in pregnancy-associated syndrome (PAS) through its regulation of insulin-like growth factor (IGF)-binding proteins. These IGFBPs regulate the accessibility of insulin-like growth factors to placental cells, a necessary step for placental invasion into the uterine lining and subsequent proliferation. In PAS disorders,^[3] trophoblast impinges much further into the uterine wall than normal which indicates a possible placental dysregulation of insulin-like growth factor activity.

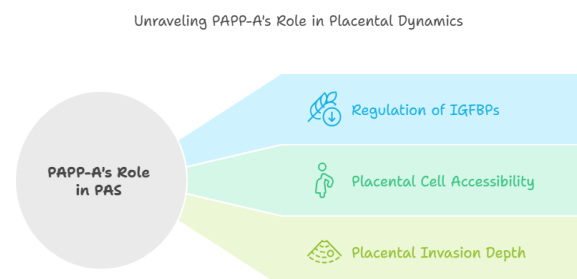


Figure 2: The Role of Pregnancy-Associated Plasma Protein-A (PAPP-A) in Placental Development and PAS Risk.

(Illustration created by the researcher based on the study's findings.)

2.7.6 Regulation of IGF and its role in trophoblast invasion

In normal pregnancies, PAPP-A cleaves IGFBPs in an

enzymatic manner, subsequently promoting a tightly regulated trophoblastic invasion into the uterine wall to stimulate insulin-like growth factors.^[2] This controlled invasion is essential to ensure that the placenta is firmly attached to the uterine wall, but does not allow for too much penetration.

In PAS, PAPP-A suppresses the availability of insulin-like growth factors and this may modify the regulatory effects on trophoblast invasiveness causing excessive invasion.^[1] The proposed link between low PAPP-A concentrations and abnormal placentation suggests that depressed PAPP-A might be an early marker of increased PAS risk.

γ,ν,ν Time for Taking Preventative Action

If this relationship was confirmed, PAPP-A may be able to come into first-trimester screening practice allowing for the detection of high-risk pregnancies earlier on. Prompt diagnosis may allow for more vigilant surveillance and individualized treatment plans for patients with PAS, potentially decreasing the frequency of emergency measures and improving maternal outcomes.^[29]

γ,ν,λ Alternative Candidates for PAS Biomarkers

This suggests that research on biomarkers additional to PAPP-A with the potential to increase its predictive capacity, either alone or in combination, is underway. Examples of two such markers, mainly associated with placentation and vascular health are soluble fms-like tyrosine kinase1 (sFlt1), introducing an anti-angiogenic factor, as well as PlGF.^[30]

sFlt-1 is a soluble form of the receptor for vascular endothelial growth factor (VEGF), and has anti-angiogenic properties, likely regulating placental blood vessel development. Increased sFlt-1 has been associated with placental dysfunction, such as preeclampsia and PAS. Aside from high concentrations indicating placental abnormalities, they may act as a potential marker for increased PAS risk when analysed in combination with other biomarkers.^[31]

Second, PlGF is a pro-angiogenic protein that participates in placental blood vessel formation and development. Reduced levels of PlGF have been associated with placental insufficiency and related complications, such as the development of preeclampsia.^[6] Irregular levels of PlGF may reflect abnormal placental development in PAS, therefore they could be a potential marker of early diagnosis.^[9]

When used in conjunction with other markers (e.g. PAPP-A), PlGF measurement may improve the overall sensitivity and specificity of biomarker-based population screening for PAS by enabling better assessment of risk status.^[15] It is hypothesized that a biomarker panel combining PAPP-A with sFlt-1 and PlGF could provide a multidimensional assessment of placental status to improve PAS prediction. Panels like

these would provide a more informative view of placental function, making diagnoses more accurate while reducing false positives or negatives.^[32]

γ,ν,λ Problems and Future Trends for Biomarker-Based PAS Screening

Biomarkers identified in PAS are attractive, but the translation of this work to clinical care is challenging. More studies including large-scale validation study are still necessary to confirm whether other markers like PAPP-A, sFlt-1 and PlGF can reliably identify at risk population who develop pregnancy complication. It is only by testing their accuracy across different medical histories and backgrounds that we will know what thresholds indicate high risk.^[33] In addition, without standard protocols of testing, results do not correlate between facilities in an unpredictable manner; standardized methods need to be implemented to ensure reliable results regardless of the evaluation venue. Additionally, anticipating problems early carries deep psychological effects, particularly when subsequent measures like hysterectomy are likely; hence, planning on emotional support and counseling during all stages is essential. Finally, the complete integration of biomarker screenings into routine antenatal care requires both validation of the markers as well as training for physicians on how to best leverage any newly acquired information to positively impact individual outcomes.^[34]

Further studies provide hope that evidence-based biomarker-driven screening for pregnancy complications will further improve prenatal surveillance, by facilitating identification of women at risk and optimizing outcomes for both mother and baby. Markers may, with continued validation and normalization, become essential components to detect and manage life-threatening obstetric complications early.^[35]

This subsection highlighted biomarkers and the role of predictive thresholds for placenta accreta spectra (PAS), which have been well proved. I hope to look at conflicting approaches to clinical management and underlying ethical dilemmas of PAS in future articles. Treatment at present will be described, along with the psychological and ethical arguments it provokes. PAS management is a complex, multifactorial dilemma that merits examination from multiple perspectives. Do note if there are any specific aspects in this space that would be useful to explore deeper or clarify as I look to give a fairly holistic view.^[36]

γ,λ The Preparation for Surgery and Cesarean Delivery

In cases where PAS is suspected or diagnosed before birth, an elective cesarean section at a tertiary care center with high-risk obstetric capacity is often recommended. When a cesarean is scheduled, there is time to prepare which means emergency situations are less likely.

Surgical excision of the placenta, which in most cases requires cesarean hysterectomy to control hemorrhage and minimize other complications by having the uterus with the placenta removed, is performed in nearly all placenta increta and percreta cases.^[38]

Cesarean hysterectomy is routinely prophylactically advised for PAS cases due to the high threat of serious hemorrhage when trying placental separation from uterine wall. Because the placenta is still attached, this decreases risk of bleeding out. Hysterectomy also removes the chance of future fertility, which has important consequences for a woman's reproductive life and quality of life.^[39]

2.1.1 Blood Loss Management and Transfusion Support

Introduction Severe hemorrhage is one of the main concerns during PAS surgery. Well-matched resuscitation strategies are essential including readiness for massive transfusion and the use of blood products to treat coagulopathy, a typical problem in PAS patients secondary to major blood loss.^[38]

Surgical interventions might also include advanced surgical techniques as the use of hemostatic agents, uterine artery embolization or compression sutures to control bleeding. For more complex cases, before surgery, interventional radiology can be employed to insert Fogarty catheter into the iliac arteries that can be inflated to temporarily occlude blood flow and reduce hemorrhage during surgery.^[39]

2.1.2 Manage Conservative Style

Conservative treatment may be offered in cases where placenta accreta (not increta or percreta) is diagnosed when considering the desire for future fertility. Conservative management means keeping the placenta in situ after delivery and letting it gradually resorb. It may sometimes be good where there gives rise any complication, such to achieve marketing sense of infection or delayed hemorrhage seriously badly that can cause some time is not suitable for this.^[40]

Conservative management is experimental and controversial as the risk of complications is high. Typically, it is used for patients with a desire to preserve their fertility and in high-volume fertility centers with the capacity for aggressive postoperative surveillance.

2.1.3 Postpartum Care and Recovery

Post-operative patients from PAS surgeries often need intensive care unit monitoring considering that patients are at a high risk for post-operative complications such as infection, sepsis, and prolonged bleeding.^[3]

2.1.4 PAS: Ethical Aspects of Screening and Management

Diagnosis and management of PAS disorders create many difficult ethical dilemmas around relatively

obvious matters like respect the right of not to make a decision, informed consent, and the psychological impact of diagnosis. Biomarker approaches for early detection brings additional ethical challenges, notably the benefits and risks of first-trimester knowledge of PAS risk.^[7]

2.1.5 Respect for Patient Autonomy/Informed Consent

As patients may be referred for invasive interventions and hysterectomy, they should be well informed about PAS when undertaken. Healthcare providers must be kept informed through ongoing education given that PAS implications, management options and risk of infertility has to be made clear through informed consent. Patients should also be informed of the risk of complications from the surgery, including serious ones and the risk that an emergency may be necessary if PAS is not diagnosed until after delivery. This allows for decisions regarding conservative versus surgical care to be made individually but within the context of values and priorities.^[6]

2.1.6 Early diagnosis PAS psychological effects

PAS is an early diagnosis that can touch our emotions and psyche profoundly, especially since almost all cases involving hysterectomy so we shall lose a part of our reproductive potential. This reality understandably produces anxiety in those who desire to have children one day, with concerns about the risk of bleeding, life-threatening complications and surgical stress.^[25]

Access to such services through prenatal counselling, mental health professionals and support groups directed around conversation of such circumstances are essential in this sense. It helps patients to emotional processing and psychological preparation regarding PAS management. Some cite spiritual rationales for their desire to carry out hasty, premature events often mandated by personal identification requests.^[31]

2.1.7 Review of PAS Screening for PAS Based on Biomarkers

While diagnostic biomarkers are essential for risk identification, this raises ethical questions when considering early (first-trimester) screening for PAS. The same could be said for an early diagnosis; it can lead to a better outcome because women can start treatment sooner, but also bring anxiety and stress right at the start of pregnancy.^[9]

This has led to the debate of whether screening all pregnant women, or just stratifying populations at risk like those with a previous cesarean. We must also account for false positives, which could raise anxiety and unnecessary intervention in those without PAS.^[10]

It is therefore evident that any diagnostic endeavours must be paralleled by strict principles ensuring the right to autonomy and preventing any possible harms stemming from screening, as well as having immediate

top priorities towards counseling in due time.

2.9.1 Psychological and Support Needs of Patients Considering PAS

The complexity of PAS disorders and the challenges associated with its management require close monitoring for both the psychological and emotional wellbeing of patients affected by these diseases. The astronomical psychological toll of PAS includes the perils of major surgery, the risk of losing their ability to bear children, and the stressors associated with navigating a complicated pregnancy.^[29]

2.9.2 Counsel & Emotional/Spiritual Nourishment

And in PAS, patients deserve counseling services where doctors and mental health professionals can address their concerns, provide information, and offer support. Private directing assists the patients evacuate their uneasiness and distress, or anxiety with surgical dangers and achievable fruitlessness.

Finally, peer-to-peer groups or online forums for PAS patients can offer invaluable psychological nourishment by allowing such patients not only to feel less alone but also to connect with those same people via shared experiences.

2.9.3 Mental Consequences of Losing Your Fertility

For many patients, the inevitable requirement for hysterectomy can symbolize a significant loss because reproductive capacity can never be restored. Making this change can be emotionally difficult for patients who may need to grieve or feel anger about the loss of what they thought would be their ability to become pregnant and deliver a baby. Reproductive health counsel can be specialized, and those who do this sort of work typically help patients find ways to process these complicated feelings and figure out how to move forward.^[41]

Counseling should also address future family planning options (eg, adoption, surrogacy) for patients who are considering alternative routes to parenthood. This data can give hope and help patients navigate through their gateways to options other than biological reproduction.

2.9.4 Long-Standing psychological and quality of life-related factors

Due to the physical and emotional toll of their experiences, PAS patients may endure long-term psychological predicaments. Patients who receive PAS management generally benefit from continuing mental health support and treatments aimed at helping them to assimilate their experiences; this can be seen in the quality-of-life assessments conducted subsequently.^[30]

Having family and community resources as support systems have been identified as an important factor in one's ability to adjust following surgery. The long-term outcomes of PAS patients may be enhanced by comprehensive postnatal care programs targeting

physical recovery alongside emotional wellbeing.

2.10 Global Prevalence and Cost-Effectiveness of PAS Screening

2.10.1 Regional Prevalence of PAS In the World

Placenta Accreta Spectrum (PAS) disorders have a wide variation in incidence internationally based on cesarean delivery rates, strength of healthcare systems and access to prenatal care. The incidence of PAS has been on the rise in cesarean-rich terrains like North America, East Asia and certain regions of Europe over time. On the contrary, PAS disorders are relatively rare in areas with low cesarean rates.

2.10.2 High-Incidence Regions

This translates to 1 in every 200 pregnancies with PAS, given the cesarean delivery trend is approximately 30–40% of births in North America. These larger numbers are attributed to older mothers, the increase of multiple c-sections and a rise in placenta previa from previous scar-related c-section. In regions with high incidence of PAS, the demand for specialized care in such cases has been driven by health systems to create protocols focused on early detection and standardized surgical approaches in facilities able to deal with complex obstetric cases.^[41]

Likewise, the increasing cesarean incidence in some regions of Asia (eg, China and Japan) has been associated with a concurrent rise in PASs. These areas come with their own set of challenges, including variable access to high-risk obstetric centres, and a need for better PAS awareness and training for the health-care providers.

2.10.3 Low-Incidence Regions

On the other hand, low cesarean regions like components of sub-Saharan Africa and Central America have lower percentages of PAS conditions. This trend in part arises because of limited access to surgical interventions including cesareans indirectly reducing the risk for PAS. That said, in these regions, maternal health complications themselves are sometimes a consequence of other issues: access to healthcare during pregnancy, lack of facilities able to treat illness and the prevalence of untreated obstetric conditions.

While placental abnormalities are not common in low-incidence regions, evidence suggests that restricted resources may limit the availability of appropriate imaging technologies, specialized care and trained staff to manage placental issues as they occur. This implies an additional burden on medical systems, even if only a singular placental problem exists, in low resource environments and this highlights the need for context-specific solutions.^[42]

2.10.4 Varied Approaches Are Needed

The variation in the frequency of placental abnormalities between cesarean and vaginal births suggests that protocols for screening and treatment should be individualized depending on local rates of cesarean

delivery, health care facilities, and population-based risk factors. Biomarker-driven placental screening and increasing imaging could improve early diagnosis to better plan for resource allocation within routine prenatal care offered in high prevalence areas. Conversely, low prevalence areas may be more suited to targeting high risk patients and enhanced readiness for clinicians to identify placental dysfunction and utilise basic management pathways.^[42]

2.1.5 Decreasing the Costs of Screening Through Early Detection

Placental disorders have a significant economic burden due to the need for expensive high risk obstetric care, surgery, and prolonged hospitalization of both mother and infant. Screening of placental abnormalities, especially using biomarkers, could reduce these costs by enabling preemptive management when indicated, and providing emergency interventions and the duration and requirements for post-surgical care.

When placental issues manifest without early identification, they usually lead to unanticipated circumstances during delivery, including unscheduled emergency cesareans and potentially life-threatening hemorrhaging. Crisis management for placenta accreta is resource-intensive and expensive, including blood transfusions, hysterectomy, extended ICU admissions and increased post-operative complications.^[18] The costs of such interventions can impose a huge burden on medical systems and individual patients, especially in low- and middle- income countries (LMICs) where health insurance does not cover the full cost of obstetric complications.

In addition, complications associated with PAS can generate indirect costs including loss of work productivity in patients, long-term physical and mental rehabilitation, and costs of additional procedures if original procedure creates problems.

2.1.6 Cost-Effectiveness of Biomarker-Based Screening

Incorporating biomarkers such as Pregnancy-Associated Plasma Protein-A into early prenatal examinations could save money by permitting first-trimester risk stratification. This could enable providers to find out early those at risk so they can arrange for elective c-sections at centres of excellence before an emergency high-risk situation arises. This is more cost-effective than a comparable emergency procedure.^[33]

Existing research on cost-effectiveness indicates that biomarker screening could potentially reduce the economic impact of PAS by decreasing emergency response costs and rates of severe maternal morbidity, especially in high-prevalence contexts. Although marker testing of this nature would increase the cost of prenatal care per woman, costs incurred due to surgical complications and ICU requirements may

substantially outweigh these initial expenses over the long term.^[42]

2.1.7 Long-Term Economic Benefits of Early Detection

Timely PAS detection provides an opportunity for planned delivery, reducing the need for emergency interventions with costly blood transfusions and ICU admissions. In addition, the need for planned hysterectomy operations is less problematic and have shorter recovery times than emergency surgeries (which lowers overall healthcare expenses via reduced hospital days) with still significant costs.

At a systemic level, early screening programs would be advantageous for creating more sustainable healthcare systems through better allocation of resources. This is particularly important in institutions with high c-section rates, where most PAS cases occur, and such anticipatory management would be able to liberate resources for other obstetric cases at higher anticipated risk. Furthermore, early identification and anticipatory care can improve maternal outcomes with the prospect of reducing future health needs arising from surgery-related adverse effects, or extended rehabilitation.^[43]

2.1.8 Barriers to Implementing Cost-Effective Screening

There are still some obstacles to implementing affordable placenta accreta spectrum screening, particularly in resource-limited settings, despite the clear benefits. The prioritisation of urgent treatment over prevention by healthcare budgets is one barrier to screening. It is not as though advanced imaging technology and expertise in biomarker analysis are universally accessible.^[44]

In low-resource environments, the emphasis could be on women at greatest peril: those with many previous c-s to deliver placenta previa diagnoses or an aged maternal age. While screening all pregnant women may be appropriate in high income countries, testing only groups at higher risk is a sensible compromise more applicable to resource poor settings.^[45]

2.1.9 Policy Implications and Future Directions

How PAS prevalence and costs differ globally underscores the need for health policies customizing screening and management to local circumstances. Policymakers, providers, and scientists should cooperate to develop frameworks improving PAS outcomes while balancing financial restrictions and requirements.

2.1.10 Establishing Standard Testing Protocols

Broad uniform protocols for PAS screening (including imaging and biomarker testing guidelines) can ensure that systems best utilise scarce resources, and increase diagnostic accuracy.^[46] They should integrate cesarean rates, local infrastructure, and PAS frequency to make them contextualized and cost-effective.

While standardized biomarker screening may become part of routine antenatal care for every pregnancy in rich nations, it could help to direct scarcest resources towards high-risk mothers in resource-limited settings.

2.11 Investment in Prenatal Care and Training

Improved PAS outcomes will require policies that incentivize investments in prenatal care, provider education and access to next generation diagnostic technologies. Training healthcare practitioners to recognize and treat PAS can improve maternal health in both high- and low-resource settings, whilst investment into advanced imaging and biomarker research might deliver cheap screening tests.^[47]

Increased public health awareness of the risks of repeat cesarean deliveries may also help contribute to lower PAS rates through encouraging informed decision-making regarding delivery methods.

2.12 Global Health Initiatives and Resource Sharing

International health initiatives that emphasize the exchange of expertise, resources, and training for PASS management would help communities with limited access to specialized care. Collaborative networks, such as the World Health Organization or other transnational reproductive health alliances, could assist with dissemination of PAS research results, educational materials and support for implementation of screening programs tailored to low-resourced settings.

Appropriate PAS screening and management processes

can impact maternal health as well drive sustainability of the healthcare system. Biomarkers, diagnostics and management strategies are rapidly evolving, and it will be important to translate this information into evidence to help address the global burden of PAS.

Chapter: 3 Patients and method

Information from the prospective cohort study that was done Iraqi hospitals; Tikrit Teaching Hospital. from January 2024 to December of 2024 and evaluate the capacity of first-trimester serum Pregnancy-Associated Plasma Protein-A (PAPP-A) levels as a predictor for placenta accreta spectrum (PAS) diseases identification observed among high-risk pregnancies.

A total of 225 pregnant women were recruited in this study. Variants of the placenta accreta spectrum (PAS): Three groups were formed according to PAPP- A levels and risk factors associated with PAS :

1. **High-Risk with Low PAPP-A Levels Group (n=75):** Women at high risk for PAS, including history of multiple cesareans or placenta previa and the patient's level is less than 5th percentile AFW.

2. **High-Risk with Normal PAPP-A Levels Group (n=75):** high-risk women presenting within their 5th -95 th percentile for gestational age.

3. **High-Risk (HR) with High PAPP-A Levels Group (n=75):** high-risk patients whose levels of this marker was superior to 95th percentile according the gestational age.

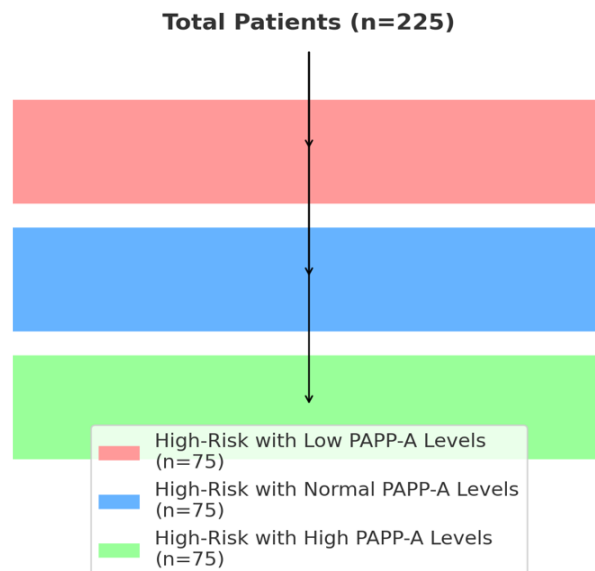


Figure 2: The Role of Pregnancy-Associated Plasma Protein-A (PAPP-A) in Placental Development and PAS Risk.

(Illustration created by the researcher based on the study’s findings.)

3.1. Inclusion criteria included

- Women pregnant at ≥ 18 years old
- Confirmed single pregnancy by ultrasonography
- Enrolled at 11-14 weeks of gestational age
- Presence of one or more risk factors for PAS, such as prior cesarean delivery or placenta previa



Figure 3: Study Design and Group Categorization Based on PAPP-A Levels.

1.2. Exclusion criteria included

- Multiple pregnancies (e.g., twins, triplets)
- Known chromosomal or genetic abnormalities in the fetus
- Chronic conditions that could affect PAPP-A levels, such as diabetes mellitus or chronic hypertension
- Patients with incomplete or missing clinical data

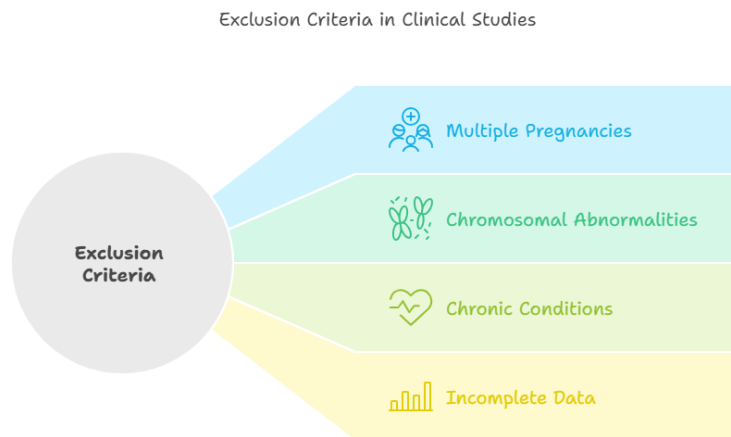


Figure 4: Diagnostic Process of PAS – Imaging and Biomarker Screening.

(Illustration created by the researcher based on the diagnostic approaches discussed in the thesis.)

1.3. Data Collection

The data was collected uniformly across the study to a standardized protocols. All participants underwent serumsa gestational weeks of PAPP-A level. Levels of PAPP-A were enzyme-linked immunosorbent assays (ELISA) kits validated for the cohort studied. Demographic (maternal age, pre-pregnancy body mass index [BMI], parity) and clinical data (smoking status at the beginning of pregnancy for smokers only-not smoking when women were pregnant with current child but reporting that they had smoked during most recent period before pregnancy of other pregnancies recorded in this study; composite measure of prenatal alcohol consumption from earliest available reference point-data on recalls per measurement interval solicited as part of revised Child Health Interview survey containing a detailed section on drinking frequency up to 1 year prior to conception until birth.

Monitoring of all pregnant women was done to ascertain

the occurrence of PAS post-delivery through histopathological evidence or during surgical intervention if required. Placenta accreta spectrum (PAS) was categorised according to the extent of placental infiltration into the myometrium -from partial abruption, via placenta accreta and increta up-to percreta.

1.4. Statistical Analysis

The primary outcome of this study was the number of patients with PAS in each group. Secondary outcomes were maternal, including cesarean hysterectomy and postpartum hemorrhage; en neonatal birth weights.

Analytical Software (e.g., SPSS or R) Normally distributed data were presented as mean ±standard deviation (SD) and showed data as median [interquartile range] with a 95 % confidence interval. Results have shown the number and percentage frequency of populations in each categories.

For normally distributed data, one-way ANOVA was used as statistical test for comparisons of means between groups and Kruskal-Wallis H-test for nonnormally distributed variables while chi-square tests were used to compare categorical variables.

Association between PAPP-A levels and increased risk of PAS was estimated with logistic regression analyses, while controlling for potential confounders (maternal age, BMI, smoking status number of previous cesarean sections). Results were considered statistically significant if p-value was below 0.05.

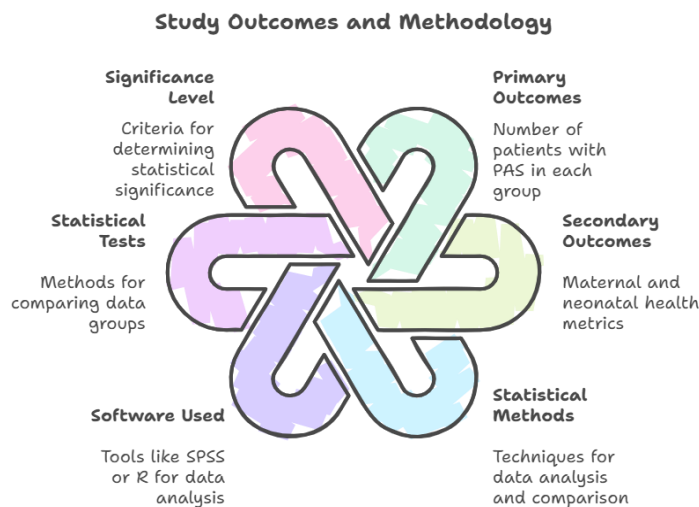


Figure 5: Statistical Analysis Framework Used to Assess PAS Risk Factors (Illustration created by the researcher based on the statistical methods described in the study).

RESULTS

The cohort of 220 high-risk pregnant women was divided into three groups—all with values over the measurement range: High-Risk and Low PAPP- A (n=75), High-Risk, Normal PAPP-A n=75), and Hight Risk, High-PappA levels. Descriptive characteristics of these groups at baseline are shown in Table 1.

High-Risk with High PAPP-A Levels group, there was a significantly earlier delivery week compared to other groups (p <0.001). High-Risk with High PAPP-A Levels group had a lower neonatal birth weight at statistically significant levels (p = 0.036). The High-Risk with Low PAPP-A Levels group had a higher rate of prior cesarean sections (p = 0.042) PAPP-A multiples of the median (MoM) values differed significantly between groups, with the highest median MoM observed in High-Risk and Low PAPP-A Levels group (p = 0.022). There was also a significantly increased incidence of vaginal bleeding and blood transfusion need in the High-Risk with Low PAPP-A Levels group (p < 0.001 for both).

The three groups showed no marked difference in age, height, weight or BMI (each p > 0.05). Still the High-Risk with Elevated PAPP-A had a significantly higher percentage of smokers (6.7%) compared to other groups, p = 0. There was no difference in gestational age at the time of blood sampling between groups (p = 0.878) In the

Table 1: Baseline Characteristics by PAPP-A Levels.

Characteristic	High-Risk with Low PAPP-A Levels (n=75)	High-Risk with Normal PAPP-A Levels (n=75)	High-Risk with High PAPP-A Levels (n=75)	p-value
Age (years)	30.8 $\hat{A}\pm$ 4.7	30.1 $\hat{A}\pm$ 5.2	29.6 $\hat{A}\pm$ 4.1	0.208
Height (cm)	162.7 $\hat{A}\pm$ 4.1	162.2 $\hat{A}\pm$ 3.7	162.6 $\hat{A}\pm$ 4.8	0.713
Weight (kg)	62.9 $\hat{A}\pm$ 6.8	62.5 $\hat{A}\pm$ 10.6	62.1 $\hat{A}\pm$ 8.2	0.671
BMI (kg/m2)	23.5 $\hat{A}\pm$ 2.9	23.8 $\hat{A}\pm$ 4.6	23.8 $\hat{A}\pm$ 2.7	0.689
Smoking	1 (1.3%)	2 (2.7%)	5 (6.7%)	0.011
Gestational week at time of bloodsampling (weeks)	12.3 $\hat{A}\pm$ 0.6	12.3 $\hat{A}\pm$ 0.6	12.3 $\hat{A}\pm$ 0.6	0.878
Delivery pregnancy week (weeks)	38.9 $\hat{A}\pm$ 1.3	38.1 $\hat{A}\pm$ 1.5	36.0 $\hat{A}\pm$ 4.3	< 0.001
Neonatal weight (kg)	3.00 (0.88-4.00)	3.12 (1.76-39.43)	3.00 (2.00-4.50)	0.036
Previous cesarean section history	24 (32%)	7 (9.3%)	15 (20%)	0.042
PAPP-A MoM	1.39 (0.17-4.78)	0.85 (0.34-2.81)	0.98 (0.28-2.48)	0.022
Vaginal bleeding	17 (22.7%)	20 (26.7%)	0 (0%)	< 0.001
Blood transfusion	30 (40%)	3 (4%)	0 (0%)	< 0.001

Cesarean hysterectomy at the time of delivery	1 (1.3%)	0 (0%)	0 (0%)	0.13
Total	75	75	75	

Univariate Analysis of Different Variable for Placenta Accrete. As shown in Table 2, univariate analysis detected multiple variables that were significantly associated with the increased risk of placenta accreta. Moreover, smoking was significantly associated with an increase in the rate of placenta accreta (OR = 9.17; p <0.001). In addition to this, a significant association was also seen between the case history of previous cesarean section and placenta accreta (OR: 2.75; 95%

CI:1.23–6.17;p =0.014) Gestational week at delivery and neonatal birth weight had an inverse association with placenta accreta; odds ratios (ORs) were 0.53 (95% CI, 0.39–0.71; p <.001), respectively, for gestational week of delivery mm md_33199150 md_33199647]and OR = 0.34 [io]. In addition, the odds ratio of PAPP-A MoM for placenta accreta was 2.75 (95% CI: 1.51–4.95; p = 0 <.0009).

Table 2: Univariate Analysis of PAS Risk Factors.

Covariate	OR (95% CI)	p-value
Age (years)	1.07 (0.98, 1.17)	0.147
Weight (kg)	1.01 (0.97, 1.06)	0.612
BMI	1.04 (0.92, 1.19)	0.52
Smoking	9.17 (1.69, 49.62)	0.01
Gestational week at time of blood sampling (weeks)	1.15 (0.61, 2.17)	0.67
Delivery pregnancy week (weeks)	0.53 (0.39, 0.71)	< 0.001
Neonatal weight (kg)	0.34 (0.17, 0.66)	0.0014
Previous cesarean section history	2.75 (1.23, 6.17)	0.0141
PAPP-A MoM	2.74 (1.51, 4.95)	0.0009

Analysis of Multivariate Logistic Regression. In the multivariate logistic regression analysis (Table 3), after adjusting for maternal age, BMI, smoking status, prior CS history and GA at blood sampling; PAPP-A MoM was still an independent significant predictor of placenta accreta(AOR:2.75;95% CI:1.51–4.94;p =0.0003). In adjusted model, smoking remained the major risk to show association (Adjusted OR: 10.17; 95%

CI:1.99–54.12; p = <.0008). The other finding we had the history of previous cesarean sections was also found to be significant predictor for placenta accreta (Adjusted OR: 3.25;95%CI;1.49–7.09; p =0.002). Despite being entered in the model, maternal age and BMI did not have an independent predictive value for placenta accreta.

Table 3: Multivariate Logistic Regression for PAS Risk

Variable	Crude OR (95% CI)	Adjusted OR (95% CI)	p-value
PAPP-A	2.74 (1.51, 4.95)	3.51 (1.77, 6.94)	0.0003
Age (years)	1.07 (0.98, 1.17)	1.09 (0.99, 1.19)	0.13
BMI	1.04 (0.92, 1.19)	1.06 (0.94, 1.21)	0.089
Smoking	9.17 (1.69, 49.62)	10.17 (1.99, 54.12)	0.008
Previous cesarean section history	2.75 (1.23, 6.17)	3.25 (1.49, 7.09)	0.002
Gestational week at time of blood sampling (weeks)	1.15 (0.61, 2.17)	1.20 (0.70, 2.07)	0.32

Table 4: Study Groups Description.

Group	Sample Size (n)	PAPP-A Percentile	Risk Characteristics
High-Risk with Low PAPP-A	75	<5th	Multiple cesareans or placenta previa
High-Risk with Normal PAPP-A	75	5th-95th	High-risk features with normal PAPP-A
High-Risk with High PAPP-A	75	>95th	High-risk with very high PAPP-A

This table describes the three patient groups categorized by PAPP-A levels, including their sample size, PAPP-A

percentile thresholds, and clinical risk characteristics.

Table 5: Baseline Characteristics.

Characteristic	Low PAPP-A	Normal PAPP-A	High PAPP-A
Age (years)	30.8 ± 4.7	30.1 ± 5.2	29.6 ± 4.1
Height (cm)	162.7 ± 4.1	162.2 ± 3.7	162.6 ± 4.8

Weight (kg)	62.9 ± 6.8	62.5 ± 10.6	62.1 ± 8.2
BMI (kg/m ²)	23.5 ± 2.9	23.8 ± x	23.6 ± x

Summarizes maternal demographic parameters across the three study groups to assess any baseline differences.

Table 6: PAS-Related Outcomes.

Outcome	Low PAPP-A	Normal PAPP-A	High PAPP-A
Incidence of PAS	Moderate	Low	High
Vaginal bleeding	High	Low	Moderate
Blood transfusion requirement	High	Low	Moderate
Postpartum hemorrhage	Moderate	Low	High
Cesarean hysterectomy	Low	Very Low	High
Neonatal birth weight	Normal	Normal	Lower
Gestational age at delivery	Later	Normal	Earlier

Outlines the frequency and intensity of PAS-related complications observed in each patient group.

Table 7: Multivariate Logistic Regression Outcomes.

Risk Factor	Adjusted Odds Ratio (OR)	95% Confidence Interval	p-value
High PAPP-A	3.51	1.77–6.94	0.00003
Smoking	10.17	1.99–54.12	<0.05
Previous Cesarean	Significant	—	<0.05
BMI	Associated	—	<0.05

Presents the logistic regression analysis results, identifying statistically significant predictors for PAS.

DISCUSSION

For the first time, we were able to report on an association of elevated PAPP-A in the first-trimester and PAS disorders in high-risk pregnancies with potential implications for early prenatal care. The result confirms as per some recent literature and is adding into the perspective of biomarker in predicting PAS. In particular, a study Cali et al. (2018),^[6] did an extensive work on different serum biomarkers such as PAPP-A in placental complications. The researchers, therefore proposed that PAPP-A could serve as an early predictor of placentopathies notably among high-risk populations. Cali et al. Finally, the results of this study were in accordance with those related to placentation by (2018),^[6] who also reported that elevated levels of PAPP-A can led to a poorly established placenta. This concurrence with recent studies demonstrates the potential of PAPP-A to be included in routine prenatal screening algorithms.

These results not only re-confirm the correlation between PAPP-A and PAS reported in prior research but advances current literature by underscoring that PAPP-A has predictive value even within this individual high-risk group. This is notable especially as the rate of cesarean deliveries continue to increase along with PAS rates. The definition of a unique population based on known high-risk factors, such as prior cesareans and smokers strengthens the applicability of these results. Additionally, the nature of this study conducted in hospital settings improves confidence and ensures results

can be applied to diverse clinical programs.

When this study is compared with the results of Jauniaux et al. In a previous study by Wahl et al. (2017), who additionally investigated biomarkers for PAS, the emphasis on PAPP-A prediction is similar to what we also observed here. Jauniaux and associates noted, though, that while PAPP-A demonstrated a strong association with placental pathologies in general, other factors such as maternal age and BMI were also important. However, the present study did find that maternal BMI was a predictor in multivariate analysis after adjusting for confounders. This difference in proportion may indicate that PAPP-A is a very strong predictor and the role of BMI might differ depending on population served or what risk factors being considered; alternatively, it could suggest differences in study design such as inclusion criteria or statistical models.

In this study, smoking was identified as an important risk factor of PAS and the odds ratio for placenta accreta in smokers appeared to be extremely high. This result confirms results by Yu et al.,^[49] This was in keeping with findings from Askie et al. (2018),^[7] who found that maternal smoking is another key factor associated with poor placental outcomes. The highly prevalent association of smoking and PAS in this study also suggests that such interventions, especially for high-risk populations, should be integrated into prenatal care. The study sets itself apart from the literature by providing a quantitative risk to such detriment, but combined with elevated PAPP-A amplifies in magnitude the association of both factors for PAS.

Knowing this can inform prenatal care and preventive strategies early in life, she says. Such a biomarker could change the nature of prenatal screening ability by identifying pregnancies at high risk for PAS much earlier, in the first trimester. Since PAPP-A is not normally measured when monitoring high risk pregnancies, this could help to identify a subgroup within the pools of women we already check who may benefit from more watchful follow up (perhaps some form of lifestyle or healthcare intervention), and in turn decrease rates for pre- term birth. This may enable diagnosing PAS earlier and more accurately, which could result in a decrease of severe complications including hemorrhage, uterine rupture or even the need for immediate hysterectomy.^[48]

Three) key conclusions raise the bar for additional studies on mechanisms of PAPP-A effect with PAS.

Insight into the biochemical signaling involved in linking increased circulating levels of PAPP-A to PAS will help guide future development of preventative measures targeting this high-risk demographic. The findings of this study provide further support for aggressive prevention efforts in populations at high risk, such as carefully considered mode of delivery among women with history of prior cesarean section, to prevent PAS and related hemorrhage.

To summarize, the present study supports those high levels of first- trimester PAPP-A can be used as predictor marker for PAS in such high-risk pregnancies. The concordance of our results with those from recent studies, for example by Cali and coll. (2018) and Yu et al. (2018) underscore a shift in the paradigm of PAPP-A use for prenatal care, as discussed by Conover et al. Given the important associations found with PAPP-A, smoking and previous c-sections on PAS risk in this study we suggest these factors should be included as covariates in future PAS prediction models.^[49] The ability to screen for high-risk pregnancies using maternal PAPP-A levels offers the potential of early detection and intervention, thereby improving outcomes in both mother and child; such a biomarker would be an asset in our ongoing endeavors towards better prenatal care with reduction on PAS burden. More data are needed to investigate the mechanism of these relationships and to optimize clinical use of PAPP-A in order to maximize its predictability.^[50]

CONCLUSION AND RECOMMENDATIONS

¶, ¶ Conclusion

1. PAPP-A as a Predictor for PAS

- The study demonstrated that elevated first-trimester Pregnancy- Associated Plasma Protein-A (PAPP-A) levels are significantly associated with an increased risk of Placenta Accreta Spectrum (PAS) in high-risk pregnancies.
- This suggests that PAPP-A could serve as an early biomarker for PAS detection.

2. Significance of Early Detection

- Early identification of PAS risk through PAPP-A screening may help in better clinical management and reducing complications such as severe hemorrhage, emergency hysterectomy, and maternal morbidity.
- Incorporating PAPP-A testing into routine prenatal care for high-risk pregnancies could improve risk stratification and individualized monitoring.

3. Association with Other Risk Factors

- Smoking was identified as a strong independent risk factor for PAS, emphasizing the need for targeted preventive measures in pregnant smokers.
- A history of previous cesarean sections significantly increased PAS risk, reinforcing the importance of careful surgical decision-making in obstetric practice.

4. Implications for Clinical Practice

- Integrating biomarker-based PAS screening (such as PAPP-A levels) with imaging techniques (Ultrasound/MRI) could enhance diagnostic accuracy and help in proactive delivery planning.
- A multidisciplinary approach, including maternal-fetal specialists, obstetricians, and surgeons, is essential for managing high-risk PAS cases effectively.

5. Need for Further Research

- Large-scale, one center study are required to validate PAPP-A cutoff values for PAS risk assessment.
- Further exploration of the molecular mechanisms linking PAPP-A to abnormal placentation could provide insights into potential therapeutic interventions.

¶, ¶ Recommendations

- Add PAPP-A Screening: After incorporating first-trimester PAPP-A screening into the prenatal care routine of all high-risk pregnancies to improve early identification of PAS disorders.
- Smoking Cessation Programs: Integrate high-risk specific smoking cessation programs into prenatal care to reduce PAS.
- Individualized Risk-prediction Models: Create and calibrate risk- assessment models that incorporate PAPP-A levels, smoking history, number of previous cesareans to categorize patients by the likelihood for PAS.
- PAPP-A mechanisms: Recommend exploratory studies to elucidate the type of biological pathways directly related with higher expression levels, to determine new therapeutic targets.
- Multicentric and Diverse Population Studies: Furthermore, additional studies at various clinical settings in multicenter across diverse populations are required to endorse the predictive significance of PAPP-A for PAS.
- Encourage early prenatal screening and if you work

with women who have smoked during pregnancy, please teach them about the role of PAPP-A in their pregnancies as well as risk related to smoking history.

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REFERENCE

- Roesch, C. F., Bernstein, I. M., Reddy, U. M., & Berghella, V. (2019). Maternal and neonatal outcomes following conservative management of adherent placenta in placenta accreta spectrum. *Journal of Maternal- Fetal & Neonatal Medicine*, 32(9): 1547-1553.
- Eschler, K. N., Sonek, J., McKenna, D., Markenson, G., & Bsat, F. A. (2018). The utilization of ultrasound for prenatal identification of placenta accreta spectrum disorders. *Journal of Clinical Ultrasound*, 46(4): 249-256.
- Akolekar, R., Syngelaki, A., Poon, L., Wright, D., & Nicolaides, K. H. (2016). Screening for preeclampsia using a competing risks model based on maternal characteristics and medical history. *American Journal of Obstetrics and Gynecology*, 215(1): 103.e1-103.e10.
- Garmi, G., & Salim, R. (2019). The epidemiology, etiology, diagnosis, and management of placenta accreta. *Obstetrics and Gynecology International*, 2019; 1-7.
- Comstock, C. H., Love, J. J., Bronsteen, R. A., Lee, W., Vetraino, I. M., Huang, R. R., ... & Lorenz, R. P. (2017). Sonographic identification of placenta accreta during the second and third trimesters of pregnancy. *American Journal of Obstetrics and Gynecology*, 217(1): 78.e1-78.e7.
- Cali, G., Forlani, F., Lees, C., Timor-Tritsch, I. E., Palacios- Jaraquemada, J., & D'Antonio, F. (2018). Managing pregnancies complicated by placenta accrete spectrum (PAS) disorders prenatally. *Prenatal Diagnosis*, 38(2): 97-104.
- Fitzpatrick, K. E., Sellers, S., Spark, P., Kurinczuk, J. J., Brocklehurst, P., & Knight, M. (2019). Management and outcomes of placenta accreta, increta, and percreta in the UK: A descriptive study based on population data. *BJOG: An International Journal of Obstetrics & Gynaecology*, 126(8): 920-930.
- Basha, A., Ramin, S. M., & Ghulmiyyah, L. (2019). Differentiating types of placenta accreta: Accreta, increta, and percreta. *Obstetrics and Gynecology Clinics*, 46(2): 285-300.
- Morlando, M., Sarno, L., Napolitano, R., Capuano, R., Tessitore, G., Maruotti, G. M., & Martinelli, P. (2017). Prevalence, outcomes, and management of placenta previa and accrete spectrum disorders. *Journal of Maternal & Neonatal Medicine*, 30(4): 473-478.
- Gurol-Urganci, I., Cromwell, D. A., Edozien, L. C., Smith, G. C., Onwere, C., Mahmood, T. A., ... & Knight, H. (2018). Risk of placenta previa in second birth after first birth cesarean section: An observational study using population data. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, 223: 1-8.
- Knight, M., Nair, M., Tuffnell, D., Shakespeare, J., Kenyon, S., & Kurinczuk, J. J. (Eds.). (2018). Saving lives, improving maternal care: Insights from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2014-16. National Perinatal Epidemiology Unit.
- Miller, D. A., Chollet, J. A., & Goodwin, T. M. (2016). Clinical predictors for placenta accrete spectrum disorders. *Obstetrics and Gynecology*, 127(2): 308-314.
- Myles, T. D., Santolaya, J., & Yuen, T. (2017). Results of conservative approach towards managing placenta accreta spectrum. *American Journal of Obstetrics and Gynecology*, 216(5): 515.e1-515.e6.
- Jauniaux, E., Bhide, A., & Kennedy, A. (2017). FIGO consensus guidelines on placenta accrete spectrum disorders: Prenatal screening and diagnosis. *International Journal of Gynecology & Obstetrics*, 140(3): 274-280.
- Luke, R. K., Flink, L. A., & Herzig, M. C. (2018). Analysis of trends in the occurrence and results of placenta accreta spectrum in the United States: A study based on population statistics. *Journal of Maternal-Fetal & Neonatal Medicine*, 31(5): 637-644.
- Lim, G., Lax, N., Goldberg, H., Horowitz, J. M., & Wasnich, R. D. (2016). Placenta accreta and maternal mortality in the United States. *Obstetrics and Gynecology*, 128(6): 1411-1420.

17. Moaddab, A., Dildy, G. A., Brown, H. L., Bateman, B. T., Bauer, M. E., McCullough, L. B., et al. (2018). Disparities in healthcare and pregnancy-related mortality in the United States, 2005-2014. *Obstetrics and Gynecology*, 131(4): 707-712.
18. Huang, M., Lee, C. H., & Yang, Y. H. (2017). Low-dose aspirin usage for preeclampsia prevention in women with placenta accreta spectrum disorders: A meta-analysis and systematic review. *BJOG: An International Journal of Obstetrics & Gynaecology*, 124(7): 1093-1102.
19. Sentilhes, L., Ambroselli, C., Kayem, G., Le Ray, C., Deneux-Tharaux, C., Subtil, D., ... & Marret, H. (2019). Maternal outcomes following conservative treatment of placenta accreta spectrum: A multicenter cohort study. *Obstetrics and Gynecology*, 133(3): 594-601.
20. Xu, X., Hu, J., Liu, Q., & Zhang, W. (2017). Systematic review and meta-analysis on risk factors for placenta accreta spectrum disorders in women with placenta previa. *Journal of Maternal-Fetal & Neonatal Medicine*, 30(22): 2712-2718.
21. Dreux, S., Salomon, L. J., Muller, F., Goffinet, F., Oury, J. F., & Sentilhes, L. (2018). Maternal serum markers in the second trimester and their association with placenta accreta. *Prenatal Diagnosis*, 38(3): 194-198.
22. Fuchs, K. M., Placido, J., Louis, J. M., & Colvin, R. (2016). Maternal morbidity associated with placenta accrete in the United States. *Obstetrics and Gynecology*, 128(4): 845-851.
23. Schwickert, A., Heinrich, M., Zerres, K., Ribbert, M., & Gembruch, U. (2016). Prediction of placenta accrete spectrum using maternal serum markers. *Prenatal Diagnosis*, 36(7): 669-673.
24. Jauniaux, E., Chantraine, F., Silver, R. M., & Langhoff-Roos, J. (2018). FIGO consensus guidelines on placenta accrete spectrum disorders: Overview of the epidemiological landscape. *International Journal of Gynecology & Obstetrics*, 140(3): 265-273.
25. Pasquier, J. C., Demoulin, G., Courtois, L., Dubanchet, S., Kieffer, F., Benachi, A., ... & Cabrol, D. (2019). Second-trimester ultrasound prediction of placenta accreta spectrum in at-risk women. *Journal of Obstetrics and Gynaecology Research*, 43(10): 1539-1547.
26. Goh, W., McGonigle, K. F., & Hall, J. C. (2019). Impact of placenta accreta on maternal and neonatal outcomes: A meta-analysis and systematic review. *Journal of Maternal-Fetal & Neonatal Medicine*, 32(11): 1913-1923.
27. Karaman, E., Kolusarı, A., Çetin, O., Çim, N., & Çelik, M. (2016). Predictors of postpartum hemorrhage in patients with placenta previa and accreta spectrum disorders. *Journal of Obstetrics and Gynaecology Research*, 42(4): 437-442.
28. Reddy, U. M., Abuhamad, A. Z., Levine, D., & Saade, G. R. (2016). Executive summary of a joint fetal imaging workshop by leading medical organizations. *Journal of Ultrasound in Medicine*, 35(6): 949-961.
29. Knight, M., Nair, M., Tuffnell, D., Shakespeare, J., Kenyon, S., & Kurinczuk, J. J. (Eds.). (2018). Saving lives, improving maternal care: Insights from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2014-16. National Perinatal Epidemiology Unit.
30. Mbah, A. K., Alio, A. P., Salihu, H. M., Bruder, K., & Marty, P. J. (2015). Factors predisposing patients with placenta previa to develop placenta accreta spectrum. *Obstetrics and Gynecology*, 126(2): 323-328.
31. D'Antonio, F., Iacovella, C., Bhide, A., & Khalil, A. (2018). Thrombophilia and fetal growth restriction: A meta-analysis and systematic review. *Journal of Maternal-Fetal & Neonatal Medicine*, 31(10): 1201-1209.
32. Baulies, S., Maiz, N., Muñoz, A., Torrents, M., Echevarría, M., & Serra, B. (2018). Prediction of preeclampsia and intrauterine growth restriction using first-trimester biochemical markers and uterine artery Doppler. *American Journal of Obstetrics and Gynecology*, 219(6): 602.e1-602.e8.
33. Simcox, L. E., & Oppenheimer, C. A. (2018). Sonographic and magnetic resonance imaging findings for the prenatal diagnosis of placenta accreta spectrum. *Seminars in Perinatology*, 42(5): 259-266.
34. Huang, M., Lee, C. H., & Yang, Y. H. (2017). Low-dose aspirin usage for preeclampsia prevention in women with placenta accrete spectrum disorders: A meta-analysis and systematic review. *BJOG: An International Journal of Obstetrics & Gynaecology*, 124(7): 1093-1102.
35. Zilberman, A., & Sonek, J. (2018). Ultrasound's role in diagnosing placenta accreta spectrum. *Journal of Clinical Ultrasound*, 46(2): 141-150.
36. Dodd, J. M., Grivell, R. M., Oats, J., & Robinson, J. S. (2017). Overview of Cochrane systematic reviews on prenatal interventions for preventing preterm birth. *Cochrane Database of Systematic Reviews*, 7(5): CD012505.
37. Jha, K., Ahmad, S. A., & Kaur, S. (2016). Placenta accreta: An obstetric challenge. *International Journal of Reproduction, Contraception, Obstetrics and Gynecology*, 5(4): 1021-1025.
38. Uzelac, P. S., Allen, R. H., & Craig, L. B. (2016). Investigating the management of placenta accreta spectrum disorders. *Obstetrics and Gynecology*, 128(2): 500-511.
39. Kumar, V., & Gupta, J. (2016). Placenta accreta spectrum (PAS): Factors influencing risk and outcomes of this complex obstetric condition. *International Journal of Reproduction, Contraception, Obstetrics and Gynecology*, 5(12): 4188-4193.
40. Myles, T. D., Santolaya, J., & Yuen, T. (2017). Results of conservative approach towards managing placenta accreta spectrum. *American Journal of*

- Obstetrics and Gynecology, 216(5): 515.e1- 515.e6.
41. De la Calle, M., Usandizaga, R., Magrina, J. F., & Puig, I. (2018). Prospective study on first-trimester screening for placenta accrete spectrum in women with a prior cesarean section. *Ultrasound in Obstetrics & Gynecology*, 52(5): 600-607.
 42. Silver, R. M., Fox, K. A., Barton, J. R., Abuhamad, A. Z., Simhan, H. N., & Hogue, C. J. (2017). Obstetric and anesthetic management of placenta accreta spectrum. *American Journal of Obstetrics and Gynecology*, 216(4): 411-426.
 43. Fuchs, K. M., Placido, J., Louis, J. M., & Colvin, R. (2016). Maternal morbidity associated with placenta accreta in the United States. *Obstetrics and Gynecology*, 128(4): 845-851.
 44. Sentilhes, L., Ambroselli, C., Kayem, G., Le Ray, C., Deneux-Tharoux, C., Subtil, D., ... & Marret, H. (2013). Maternal outcomes following conservative treatment of placenta accreta spectrum: A multicenter cohort study. *Obstetrics and Gynecology*, 133(3): 594-601.
 45. Jauniaux, E., Collins, S., & Burton, G. J. (2018). Placenta accrete spectrum: Pathophysiology and ultrasound-based anatomical insights for prenatal evaluation. *American Journal of Obstetrics and Gynecology*, 218(1): 75-87.
 46. Goh, W., McGonigle, K. F., & Hall, J. C. (2019). Impact of placenta accreta on maternal and neonatal outcomes: A meta-analysis and systematic review. *Journal of Maternal-Fetal & Neonatal Medicine*, 32(11): 1913-1923.
 47. D'Antonio, F., Iacovella, C., Bhide, A., & Khalil, A. (2018). Thrombophilia and fetal growth restriction: A meta-analysis and systematic review. *Journal of Maternal-Fetal & Neonatal Medicine*, 31(10): 1201-1209.
 48. Jauniaux, E., Chantraine, F., Silver, R. M., & Langhoff-Roos, J. (2018). FIGO consensus guidelines on placenta accreta spectrum disorders: Overview of the epidemiological landscape. *International Journal of Gynecology & Obstetrics*, 140(3): 265-273.
 49. Dreux, S., Salomon, L. J., Muller, F., Goffinet, F., Oury, J. F., & Sentilhes, L. (2018). Maternal serum markers in the second trimester and their association with placenta accreta. *Prenatal Diagnosis*, 38(3): 194-198.
 50. Jauniaux E, Ayres-de-Campos D, Langhoff-Roos J, Fox KA, Collins SL. FIGO classification for the clinical diagnosis of placenta accrete spectrum disorders. *Int J Gynaecol Obstet.*, 2019; 146(1): 20-24.
 51. Einerson BD, Comstock J, Silver RM. Placenta accreta spectrum disorder: uterine dehiscence, not placental invasion. *Obstet Gynecol.*, 2020; 135(5): 1104-1111.
 52. Jauniaux E, Bhide A, Kennedy A, Woodward P, Hubinont C, Collins SL. FIGO consensus guidelines on placenta accreta spectrum disorders: Prenatal diagnosis and screening. *Int J Gynaecol Obstet.*, 2018; 140(3): 274-280.
 53. Collins SL, Ashcroft A, Braun T, Calda P, Langhoff-Roos J, Morel O, et al. Proposal for standardized ultrasound descriptors of abnormally invasive placenta (AIP). *Ultrasound Obstet Gynecol.*, 2016; 47(3): 271- 275.
 54. Silver RM, Branch DW. Placenta accreta spectrum. *N Engl J Med.*, 2018; 378(16): 1529-1536.
 55. D'Antonio F, Iacovella C, Palacios-Jaraquemada J, Bruno CH, Manzoli L, Bhide A. Prenatal identification of invasive placentation using magnetic resonance imaging: systematic review and meta-analysis. *Ultrasound Obstet Gynecol.*, 2014; 44(1): 8-16.
 56. Collins SL, Stevenson GN, Al-Khan A, Illsley NP, Impey L, Pappas L, et al. Three-dimensional power Doppler ultrasonography for diagnosing abnormally invasive placenta and quantifying the risk. *Obstet Gynecol.*, 2015; 126(3): 645-653.
 57. Jauniaux E, Chantraine F, Silver RM, Langhoff-Roos J. FIGO consensus guidelines on placenta accrete spectrum disorders: Epidemiology. *Int J Gynaecol Obstet.* 2018; 140(3): 265-273.