Updates and Knowledge Gaps in Placenta Accreta Spectrum Biology

Lior Kashani-Ligumsky, MD, Olivia Scott, BS,* Guadalupe Martinez, BS,* Anhyo Jeong, BS,* Ophelia Yin, MD,† Sohum Shah, MD,* Amanda Wang,* Yazhen Zhu, MD, PhD,‡§ and Yalda Afshar, MD, PhD*‖¶*

Abstract: Placenta accreta spectrum (PAS) disorders have traditionally been characterized based on histopathologic grading, emphasizing the invasion of trophoblasts into the myometrium, and uterine serosa. Recent research has shifted the etiological understanding of PAS, moving away from the concept of aggressive trophoblast invasion to focusing on the critical role of scarred decidual-myometrial interface. This shift highlights the importance of defective scar tissue as a primary factor, reshaping prevention strategies, diagnostic accuracy, and treatment approaches for this increasingly prevalent iatrogenic and morbid pregnancy complication.

Key Words: accreta, placenta, uterine dehiscence, obstetrics, cesarean, matrix, collagen, previa, morbidly adherent placenta

(*Clin Obstet Gynecol* 2025;68:310–316)

Traditionally, placenta accreta spectrum (PAS) disorders have been clinically and radiologically described according to their histopathologic grade. This description of PAS hinges on the notion that trophoblasts not only implant into the myometrium, but also invade through or into the uterine wall.[1,2]

The incidence of PAS has increased globally, which is mainly attributed to the rising rate of cesarean births, with an incidence of 1 in 300 births in the United States.[3] It is important to note that various studies have reported a wide range of incidences, ranging from 1 in 250 to 1 in 2500, due to the utilization of different PAS case definitions and study populations.[4–8]

In recent years, there has been an etiological paradigm shift in our understanding of this increasingly prevalent disorder. We have gone from blaming the placental and trophoblasts for the rise in PAS, to learning about the central role of the scarred decidual-myometrial surface in the underlying mechanism of PAS. This is a consequence of defective scarred decidua, rather than a result of aggressive trophoblast invasion.[1,9] Embracing this perspective continues to redirect research efforts and clinical resources towards more effective prevention, precise diagnosis, and safe treatment of this increasingly prevalent and devastating disorder.

MORBIDITY AND MORTALITY

Placenta accreta spectrum is a serious complication of pregnancy associated with significant maternal morbidity and mortality.[1,10,11] The most common complication is hemorrhage; however, other potential complications include disseminated intravascular coagulation (DIC), acute respiratory distress syndrome, massive transfusion, visceral injury, infection, and thromboembolism.[12,13] Women with PAS are at a higher risk of requiring a hysterectomy at birth or during the postpartum period. Furthermore, neonates of pregnant women with PAS are at an increased risk for complications such as transient tachypnea of newborns and admission to the neonatal intensive care unit (NICU).[14] In cases where PAS goes undiagnosed and an emergent cesarean hysterectomy is required, the risk of severe morbidity and mortality is higher, with mortality rates reported to be as high as 7%.[13]

RISK FACTORS

The 2 most significant clinical risk factors for PAS are a history of cesarean birth and a placenta previa.[12,15] The risk of PAS increases with the number of previous births, with a higher risk observed in women who have had 3 or more previous cesarean births. Results of large cohort studies, including ours have shown that cesarean during labor is associated with a higher risk for PAS in subsequent pregnancies.[16] Other risk factors that can cause uterine scarring, such as a history of PAS, pelvic irradiation, uterine instrumentation, and manual removal of the placenta, have been shown to be positively correlated with PAS.[17] Several other clinical risk factors, including in vitro fertilization (IVF), embryo transfer, advanced maternal age, multiple gestation, multiparity, and smoking have also been identified as risk factors for PAS.[18,19]

PATHOPHYSIOLOGY

The exact etiology of PAS remains unknown, although several hypotheses have been proposed. The most widely accepted hypothesis is related to the presence

From the *Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology; ‖Department of Pathology, David Geffen School of Medicine; ¶Molecular Biology Institute, University of California; ‡California NanoSystems Institute, Crump Institute for Molecular Imaging; §Department of Molecular and Medical Pharmacology, University of California, Los Angeles; and †Division of Maternal Fetal Medicine and Reproductive Genetics, Department of Obstetrics, Gynecology, and Reproductive Sciences, University of California, San Francisco, California.

Y.A. is a consultant for Mirvie and Bio-Rad and has an investigator-initiated project with Natera. Y.Z. is a co-founder and shareholder in Eximius Diagnostics Corp. The remaining authors declare that they have nothing to disclose.

Correspondence: Yalda Afshar, MD, PhD, Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, David Geffen School of Medicine at UCLA, 200 Medical Plaza, Suite 430, Los Angeles, CA. E-mail: yafshar@mednet.ucla.edu

DOI: 10.1097/GRF.0000000000000929

of uterine scars, which may lead to a defect in the endometrial-myometrial interface with subsequent failure of normal decidualization.[20] PAS is associated with abnormal remodeling of the uterine arteries, leading to deeper vascular myometrial invasion, unusual uteroplacental vascularization,[21] and neovascularization in the placental bed (Table 1).[20]

PAS—MOLECULAR MECHANISM

Despite the considerable efforts to clinically characterize PAS, its molecular pathophysiology remains poorly understood. It was initially presumed to be a consequence of uncontrolled trophoblast invasion;[25] however, infiltrating trophoblasts are not remarkably proliferative.[26] Recent clinical literature has introduced a paradigm shift, challenging the prior consensus on PAS. Instead, it emphasizes the significant role played by the scarred decidua and uterine scar dehiscence, which together create an environment conducive to abnormal placentation (Table 1, Fig. 1).[1,9,20,27,28] This emerging evidence challenges the traditional perspective and highlights the

TABLE 1. Summary of molecular and cellular changes in Placenta Accreta Spectrum (PAS), categorized by vascular remodeling, epithelial-to-mesenchymal transition (EMT), extracellular matrix (ECM) modulation, immune response, and diagnostic biomarkers. Upregulation and downregulation of key factors highlight angiogenic shifts, altered trophoblast invasion, immune cell changes, and potential biomarkers for PAS detection

Vascular changes		
Protein/factor	**Regulation**	**Role/comments**
Vascular endothelial growth factor (VEGF)	Upregulated	Promotes angiogenesis
Angiopoietin-2 (Ang-2)	Upregulated	Supports neovascularization
Soluble Fms-like tyrosine kinase 1 (sFlt-1)	Downregulated	Antiangiogenic factor
VEGFR-2	Downregulated	Antiangiogenic factor
Endoglin (Eng)	Upregulated	Antiangiogenic factor, overexpressed locally
Placental relaxin (RLN) and RXFPI	Upregulated	Stimulate VEGF expression, contributing to angiogenesis and vasodilation
Von Willebrand factor (VWF)	Downregulated	Its absence leads to enhanced vascularization
Epithelial to mesenchymal transition (EMT)		
Protein/factor	Regulation	Role/comments
Epithelial cadherin (E-CAD)	Differentially expressed	Involved in cellular movement and adhesion
Beta-catenin	Differentially expressed	Forms intercellular adhesive complex with E-CAD
Actin-binding proteins (ABPs): Profilin-1, cofilin-1, VASP	Upregulated	Regulate actin polymerization and stabilization
Integrin β4	Downregulated	Enhanced migration and invasive phenotype of trophoblast cells in PAS
Collagen ECM		
Protein/factor	Regulation	Role/comments
Transforming growth factor β1 (TGFβ1)	Downregulated	Inhibits migration and invasiveness of cytotrophoblasts
Collagens 1 and 3	Upregulated	Increased in PAS, contributing to ECM modulation
MEG3 (maternally expressed gene 3)	Upregulated	Induces migration and invasion of trophoblasts by inhibiting the TGFβ1 pathway
Immune response		
Protein/factor	Regulation	Role/comments
M1 markers	Downregulated	Lower levels in PAS decidua
M2 markers	Upregulated	Higher levels in PAS decidua
CD4+ T-cells	Downregulated	Diminished in PAS specimens
FoxP3+ T regulatory (Tregs) cells	Upregulated	Elevated in PAS specimens
Decidual NK (dNK) cells	Downregulated	Reduced levels in PAS, impacting trophoblast invasion
Key proteins/factors for diagnostics		
Protein/factor	Regulation	Role/comments
Cell-free DNA (cfDNA)	Variable	Inconsistent results, potential for early PAS detection
Cell-free placental mRNA	Upregulated	Elevated in PAS, correlated with depth of invasion
Circulating trophoblasts (cTBs)	Upregulated	Increased presence in maternal circulation in PAS
Serum proteins	Upregulated	Elevated in PAS
circulating placental extracellular vesicles (EVs)[24,25]	EVs upregulated, miRNA profiling of circulating placental EVs variable	Syncytiotrophoblast-derived EVs are increased, and 40 differentially expressed miRNAs were identified
Circulating microparticle proteins[26]	Upregulated	The top-performing panel of markers distinguished PAS from controls with a mean AUC of 0.83

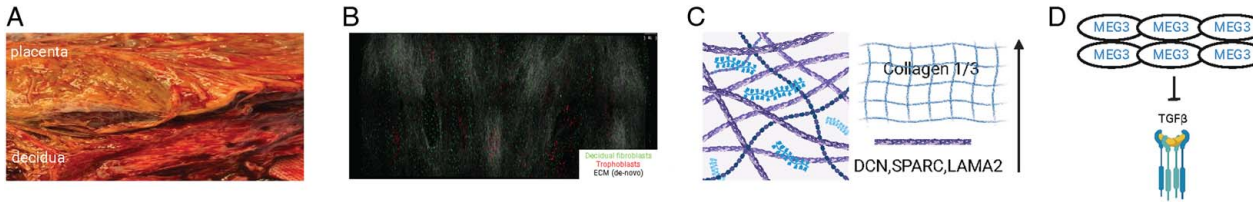

FIGURE 1. Alterations in the extracellular matrix (ECM) associated with PAS. A, Gross image of the adherent accreta area from a PAS specimen demonstrating the abnormal adherence of the placenta to the myometrium, with the disrupted boundary between placental and decidual tissues. B, Second Harmonic Generation (SHG) microscopy image of the in vitro ECM model, highlighting the disorganized collagen fibers that are characteristic of PAS. The image demonstrates the increased density and altered orientation of type collagens 1 and 3 in the scarred decidual tissue, consistent with the ECM remodeling observed in PAS. C, Schematic representation of the molecular alterations identified in PAS. An upregulation of MEG3 (maternally expressed gene 3), which promotes trophoblast migration by inhibiting the TGFβ1 pathway. Significant upregulation of collagen-related genes, including COL1A1, COL3A1, COL4A1, and COL15A1, occurs particularly within the decidua. This upregulation is accompanied by increased expression of key ECM components involved in collagen fibrillogenesis and organization, such as decorin (DCN), secreted protein acidic and cysteine-rich (SPARC), and laminin subunit alpha 2 (LAMA2). These molecular changes contribute to the pathologic ECM environment in PAS, leading to excessive placental adherence. full color online

potential importance of these factors in the development of PAS.

VASCULAR CHANGES

Abnormal placental angiogenesis is considered a key mechanism underlying the pathogenesis of PAS, supported by alterations in local angiogenic factors. Possible mechanisms contributing to excessive neovascularization in PAS include placental implantation on a uterine scar and the resulting hypoxic environment.[29,30] Compelling evidence reveals an upregulation of proangiogenic growth factors such as vascular endothelial growth factor (VEGF) and angiopoietin-2 (Ang-2), and a downregulation of antiangiogenic factors such as soluble Fms-like tyrosine kinase 1 (sFlt-1) and vascular endothelial growth factor receptor 2 (VEGFR2) within extravillous trophoblasts at the site of myometrial invasion.[31] Interestingly, hypoxia-inducible factor-1a (HIF-1a), involved in VEGF upregulation during early trophoblast invasion, is present in normal decidual cells, but not in PAS samples—this suggests that the overexpression of VEGF in accreta may not solely be correlated with hypoxia in the uterine scar.[32] Another factor implicated in abnormal angiogenesis in PAS is endoglin (Eng), an antiangiogenic factor that is overexpressed in the tissue staining of the accreta site but found at lower levels in maternal serum of women with PAS. This local overexpression of Eng may represent an adaptive response to balance placental vascular remodeling.[33] In addition, placental relaxin (RLN) and its receptor RXFPI that stimulates the expression of VEGF, are found to be upregulated in PAS specimens. This may contribute to excessive antepartum bleeding by promoting angiogenesis and vasodilation.[34,35] These findings collectively highlight the intricate interplay of environmental factors and molecular pathways involved in the abnormal angiogenesis observed in PAS.

In addition to excessive vascular formation, evidence points to irregular vascular remodeling in PAS. Epiplacental blood vessels lack VWF, Ephrin B2, and EPH receptor B4—unique markers for arterial and venous endothelial cells.[36] The absence of Von Willebrand factor (VWF) leads to enhanced vascularization.[35] Further, the suppression of VWF expression in PAS may contribute not only to excessive neoangiogenesis, but also to irregular vascular remodeling.[37] Endothelial and decidual cells in a scarred environment express factors promoting trophoblast proliferation and abnormal angiogenesis.[38] PAS specimens also show a high expression of epidermal growth factor-like domain 6 (EGFL-6), which is implicated in stimulating angiogenesis and osteogenesis.[39] EGFL-6 also leads to increased expression of CD36, a protein crucial for maintaining normal fetal capillary numbers and vascular tube formation.[40] Apolipoprotein L domain containing 1 (APOLD) and endothelin receptor type B (EDNRB) were also found to be upregulated in endothelial PAS samples. Both of these are downregulated in preeclampsia, implicated in spiral artery remodeling, and act as markers of abnormal decidua.[41,42]

EPITHELIAL TO MESENCHYMAL TRANSITION

Epithelial to mesenchymal transition (EMT) is a developmental process whereby immotile epithelial cells transform into migratory mesenchymal cells. This transition is critical for the normal invasion of extravillous trophoblast (EVT) cells and attachment of the placenta to the myometrium layer in the early weeks of gestation. During early placental development, EVT cells lose their epithelial phenotype and adopt a migratory and invasive phenotype that allows them to migrate and infiltrate into the maternal decidua and vessels.[43]

The cellular mechanisms that regulate EMT in trophoblasts are not well understood, although attempts have been made to understand EVT cells in PAS. As mentioned earlier, the understanding of trophoblastic invasion is shifting towards the idea that the pathophysiology of PAS may be explained by the environment, the absence of boundaries, and the lack of inhibition.

Epithelial cadherin (E-CAD) is responsible for controlling cellular movement, intercellular adhesion, and polarization of epithelial cells.[44] The interaction between beta-catenin and E-CAD forms an intercellular adhesive complex that activates gene expression involved in the invasion process.[45] The loss of E-CAD is a fundamental event in EMT, triggering the initiation of invasion.[46]

EMT-mediated invasion does not normally continue beyond 20 weeks of gestation.[47] However, differential expression of both E-CAD and its cytoplasmic binding partner, beta-catenin, was observed along the invasive boundary of EVT in hysterectomy specimens of PAS obtained during the third trimester.[47]

The available evidence strongly suggests that the presence of an ongoing EMT plays a significant role in facilitating sustained placental invasion within the spectrum of placenta accreta.

Actin-binding proteins (ABPs) control cellular proliferation, migration, and invasion. Profilin-1, cofilin-1, vasodilator-stimulated phosphoprotein (VASP) phosphorylated at Ser157 (pVASP-S157), and Ser239 (pVASP-S239) are ABPs that participate in the regulation of actin polymerization and stabilization, facilitating cell metastases.[48] Higher levels of ABPs were found in biopsies from the placental-myometrial junction of PAS. These changes in ABP expression may be an attempt to preserve homeostasis by neutralizing the hyperproliferative and invasive EVT phenotype in PAS.

Another factor in trophoblast cell invasion is the adhesion molecule integrin β4. Chen et al[49] showed diminished expression of integrin β4 and enhanced migration and invasive phenotype of trophoblast cells in MARVELD1 knockout mice, an animal model for PAS. MARVELD1 is a nuclear protein that is expressed in various cell types and it has been found to be epigenetically silenced through DNA methylation,[50] and thus downregulated in certain cancers.

The EMT is a crucial process in early placental development, as it allows for the migration and invasion of trophoblast cells into the maternal decidua and vessels. Abnormalities in this process, such as the deficiency of anti-invasive factors and dysregulation of matrix metalloproteinase (MMP) enzymes, have been associated with PAS. Furthermore, the downregulation of transforming growth factor β (TGFβ1) and the upregulation of essential components of the extracellular matrix (ECM), such as collagen, have been implicated in creating a permissive environment for PAS development.

COLLAGEN ECM

Uterine scars exhibit characteristic features including disorganized smooth muscle, fibrosis-containing collagen fibers, and diminished endometrial glands. The inflammatory phase plays a crucial role in the healing process, facilitating collagen organization and maturation.[51] Scarring of the myometrium and absence of the decidua layer may contribute to the hyperinvasive EVT phenotype due to a deficiency of anti-invasive factors.[52]

Transforming growth factor β (TGFβ) is a member of the TGF-β family, a group of cytokines that regulate cellular growth, movement, and tumor development. TGFβ1 inhibits the migration and invasiveness of cytotrophoblasts by up-regulating endogenous tissue inhibitors of MMP-2.[53] Overexpression and abnormal signaling of TGFβ1 initiate the EMT process in tumor invasion and cancer metastasis.[54] In correlation with these findings, several groups showed the involvement of those players in PAS. Duzyj and colleagues showed that TGFβ proteins are expressed by EVT cells at the placental invasion site, and that there is an absence of inhibitory TGFβ1 in the maternal collagen surrounding accreta EVT cells. This imbalance of TGFβ in the scarred maternal uterus may promote the continued hyperinvasive phenotype of accreta EVT cells.[33]

These findings align with a recent study conducted by Afshar et al,[9] which demonstrated an upregulation of maternally expressed gene 3 (MEG3). MEG3 has been shown to induce migration and invasion of trophoblasts by inhibiting the TGFβ1 pathway.[55] They also showed a specific increase in collagens 1 and 3 in cases of PAS. Notably, genes such as COL1A1, COL3A1, COL4A1, and COL15A1 showed significant upregulation at both RNA and protein levels, particularly within the decidua. PAS specimens exhibited modulation of the extracellular matrix, marked by increased gene expression of key components involved in collagen fibrillogenesis and extracellular matrix organization, including decorin (DCN), secreted protein acidic and cysteine-rich (SPARC), and laminin subunit alpha 2 (LAMA2),[9] supporting the hypothesis that downregulation of TGFβ1[56] may create a permissive environment for PAS development (Fig. 1).

The assessment of women with disrupted collagen expression, such as those affected by osteogenesis imperfecta or Marfan syndrome, presents an intriguing avenue for investigating tissue healing dynamics. However, these pathologies are rare, and the number of reported pregnancies is insufficient to comprehensively explore uterine healing following cesarean birth and the risk for PAS.[57]

IMMUNE RESPONSE-PAS

Achieving a successful pregnancy relies on the maternal immune system's ability to tolerate normal placentation and the invasion of EVT cells. The maternal-fetal interface is populated with diverse immune cells and cytokines, including T cells, B cells, NK cells, macrophages, dendritic cells, TNF-α, IL-8, IL-1β, IFN-γ, IL-10, and TGFβ, each playing pivotal roles.[58]

During the first trimester of pregnancy, as trophoblasts adhere to and invade the uterine stroma, there is a notable increase in the proportion of M2 subtype decidual macrophages, facilitating maternal immune tolerance to the fetus and trophoblast invasion. This shift reverses during parturition, in which decidual macrophages M1 become predominant.[59]

Decidua from patients with PAS show significantly lower levels of M1 markers, along with higher levels of the M2 markers, compared with the control. These findings suggest a greater polarization of macrophages towards the M2 subtype in the decidua obtained from PAS patients.[59]

At the cellular immune system level, immunohistochemical analysis of PAS specimens reveals diminished CD4 + T-cells, elevated in FoxP3+ T regulatory (Tregs) cells,[60,61] and a slight increase in CD25+ T-cells compared with normal pregnancies.[62] Moreover, there is a notable decrease in decidua natural killer (dNK) cell levels in PAS, potentially impacting trophoblast "invasion."

In a mouse model, increased trophoblast invasion and placental vascularization, along with extensive changes to the immune-cell profiles at the maternal-fetal interface, were observed as a result of uterine damage. Significantly diminished proportions of T and NK cells in the decidua were noted, with the greatest decline observed in decidual NK cells and M—2 macrophages. Moreover, the expression of TNF-α and IL4 was upregulated in the decidua, while the expression of IFN-γ and IL10 was significantly downregulated.[63]

ANTENATAL DIAGNOSIS

Antenatal diagnosis of PAS is crucial to improving maternal and perinatal outcomes. While ultrasound and MRI have improved antenatal diagnosis, certain factors such as placental location, elevated body mass index, or

posterior placentation can hinder the sonographic detection of PAS markers, reducing the sensitivity and specificity of these methods.[64] Therefore, there is a constant demand for the development and study of new methods to improve antenatal diagnosis, particularly in the first trimester. In the recent years, several maternal serum biomarkers that have been used to detect aneuploidy syndromes, including AFP, HCG, and PAPP-A, have been investigated for their potential role in the prenatal diagnosis of PAS. However, different studies have reported significantly different cutoff values for PAS diagnosis, and only a few have explored the relationship between these biomarkers and the prognosis of PAS.[65]

A prospective study by Farisoğullari and colleagues investigated maternal serum levels of VEGF, TNF-alpha, IL-4, and IL-10 as potential markers for PAS among patients with placenta previa. Their findings suggest elevated VEGF, TNF-alpha, and IL-4 levels, alongside decreased IL-10 levels in previa and PAS patients, underscoring their potential utility in clinical practice.[66]

There has been a notable increase in the utilization of cell-free DNA (cfDNA) for prenatal care in recent years, attracting considerable attention.[67–71] In the context of pregnancy, cfDNA, also referred to as noninvasive prenatal testing (NIPT), allows for the identification of fetal aneuploidies and sex chromosome abnormalities. NIPT has been suggested as a potential tool for early detection of PAS.

While a preliminary study showed increased cfDNA in cases of placenta previa with the highest levels seen in the 2 patients with PAS,[72] other results have been inconsistent, showing no statistically significant difference between PAS and non-PAS controls.[73]

Cell-free placental mRNA has emerged as a promising diagnostic tool for the antenatal detection of PAS.[74,75] Several studies have reported elevated levels of cell-free placental mRNA in the maternal plasma of women with PAS compared with those with normal placentation.[76] The levels of placental mRNA have been found to be directly correlated with the depth of placenta invasion.[77] However, further research is needed to establish the sensitivity and specificity of this diagnostic tool, and to validate the cutoff values for the detection of PAS.

Our group has proposed the use of circulating trophoblasts (cTBs) as a noninvasive biomarker for detecting PAS. The study demonstrated that abnormal migration led to an increased presence of cTBs in maternal circulation in PAS. The enumeration of single and clustered cTBs, as well as cTB-clusters, can be used for noninvasive detection of PAS throughout gestation, since they can be enriched from maternal circulation. The use of cTB enumeration as a noninvasive biomarker for the assessment of excessive EVT invasion may be a promising diagnostic solution to detect PAS throughout gestation.[78]

PREVENTION

To develop strategies for the prevention of PAS, it is essential to have a comprehensive understanding of the underlying biological mechanisms.

When major surgical procedures such as cesareans or myomectomies are performed, the entire uterine wall is cut, resulting in a scar that goes through all the smooth muscular layers of the myometrium. Although the epithelial layers of the endometrium and uterine peritoneum can heal by regeneration and recolonization of the scarred area, the myometrium cannot regenerate muscle fibers. Instead, it forms a scar and ECM, including collagen, during the healing process. Uterine wound healing after surgery is characterized by myofiber disarray, tissue edema, inflammation, and elastosis. The resulting scar tissue is less elastic than intact tissue and more susceptible to injury and rupture during subsequent pregnancies. Different surgical techniques such as single-layer versus double-layer closure of the myometrium, locked versus unlocked single-layer closure, and the suture material used for the closure may influence the healing process and the risks of uterine rupture. However, the evidence regarding the risk of PAS in subsequent pregnancies based on these varying techniques is limited.[79,80]

Investigating the application of collagen or other biological supplementation holds promise in promoting the healing of the uterine tissue and modulating the extracellular matrix. By enhancing the healing process and improving the integrity of the uterine wall, we may be able to decrease the likelihood of abnormal placental attachment and subsequent development of PAS.

CONCLUSION

Placenta accreta spectrum disorders represent a complex interplay of pathophysiological, molecular, and immunologic factors, centered around the scarred decidual-myometrial interface. This evolving understanding has profound implications for the prevention, diagnosis, and treatment of PAS, emphasizing the role of uterine scar healing and the modulation of extracellular matrix dynamics. Innovations in early diagnosis and the natural history of the cesarean scar pregnancy, and antenatal diagnostics, show promise in improving early detection, while prevention strategies focusing on optimizing surgical techniques and enhancing tissue regeneration offer potential avenues to reduce PAS incidence. Continued multidisciplinary research is essential to further elucidate the mechanisms underlying PAS and translate these insights into effective clinical interventions to attenuate and eradicate this increasingly prevalent disorder.

REFERENCES

1. Einerson BD, Comstock J, Silver RM, et al. Placenta accreta spectrum disorder: uterine dehiscence, not placental invasion. *Obstet Gynecol*. 2020;135:1104–1111.
2. Bartels HC, Downey P, Brennan DJ. Looking back to look forward: has the time arrived for active management of obstetricians in placenta accreta spectrum? *Int J Gynaecol Obstet*. 2025;168:48–56.
3. American College of Obstetricians and Gynecologists, Society for Maternal-Fetal Medicine. Obstetric care consensus no. 7: placenta accreta spectrum. *Obstet Gynecol*. 2018;132: e259–e275.
4. Bailit JL, Grobman WA, Rice MM, et al. Morbidly adherent placenta treatments and outcomes. *Obstet Gynecol*. 2015;125: 683–689.
5. Miller DA, Chollet JA, Goodwin TM. Clinical risk factors for placenta previa-placenta accreta. *Am J Obstet Gynecol*. 1997; 177:210–214.
6. Wu S, Kocherginsky M, Hibbard JU. Abnormal placentation: twenty-year analysis. *Am J Obstet Gynecol*. 2005;192: 1458–1461.
7. Read JA, Cotton DB, Miller FC. Placenta accreta: changing clinical aspects and outcome. *Obstet Gynecol*. 1980;56:31–34.

8. Eshkoli T, Weintraub AY, Sergienko R, et al. Placenta accreta: risk factors, perinatal outcomes, and consequences for subsequent births. *Am J Obstet Gynecol*. 2013;208:219.e1–7.
9. Afshar Y, Yin O, Jeong A, et al. Placenta accreta spectrum disorder at single-cell resolution: a loss of boundary limits in the decidua and endothelium. *Am J Obstetr Gynecol*. 2024;230:443.e1–443.e18.
10. Silver RM, Landon MB, Rouse DJ, et al. Maternal morbidity associated with multiple repeat cesarean deliveries. *Obstet Gynecol*. 2006;107:1226–1232.
11. Eller AG, Porter TF, Soisson P, et al. Optimal management strategies for placenta accreta. *BJOG*. 2009;116:648–654.
12. Silver RM, Branch DW. Placenta accreta spectrum. *N Engl J Med*. 2018;378:1529–1536.
13. Sentilhes L, Ambroselli C, Kayem G, et al. Maternal outcome after conservative treatment of placenta accreta. *Obstet Gynecol*. 2010;115:526–534.
14. Spillane NT, Zamudio S, Alvarez-Perez J, et al. Increased incidence of respiratory distress syndrome in neonates of mothers with abnormally invasive placentation. *PLoS ONE*. 2018;13:e0201266.
15. Klar M, Michels KB. Cesarean section and placental disorders in subsequent pregnancies–a meta-analysis. *J Perinat Med*. 2014;42:571–583.
16. Zeevi G, Tirosh D, Baron J, et al. The risk of placenta accreta following primary cesarean delivery. *Arch Gynecol Obstet*. 2018;297:1151–1156.
17. Bowman ZS, Eller AG, Bardsley TR, et al. Risk factors for placenta accreta: a large prospective cohort. *Am J Perinatol*. 2014;31:799–804.
18. Salmanian B, Fox KA, Arian SE, et al. In vitro fertilization as an independent risk factor for placenta accreta spectrum. *Am J Obstet Gynecol*. 2020;223:568.e1–568.e5.
19. Kaser DJ, Melamed A, Bormann CL, et al. Cryopreserved embryo transfer is an independent risk factor for placenta accreta. *Fertil Steril*. 2015;103:1176–1184.e2.
20. Jauniaux E, Collins S, Burton GJ. Placenta accreta spectrum: pathophysiology and evidence-based anatomy for prenatal ultrasound imaging. *Am J Obstet Gynecol*. 2018;218:75–87.
21. Stănculescu RV, Brătilă E, Socolov DG, et al. Update on placenta accreta spectrum disorders by considering epidemiological factors, ultrasound diagnosis and pathological exam - literature review and authors' experience. *Rom J Morphol Embryol*. 2022;63:293–305.
22. Mitchell MI, Khalil M, Ben-Dov IZ, et al. Customizing EV-CATCHER to purify placental extracellular vesicles from maternal plasma to detect placental pathologies. *Int J Mol Sci*. 2024;25:5102.
23. Tersigni C, Di Simone N, Lucchetti D, et al. Shedding of syncytiotrophoblast-derived extracellular vesicles is increased in placenta previa and accreta spectrum. *Reprod Sci*. 2024;31:2043–2048.
24. Yu HY, Gumusoglu SB, Cantonwine DE, et al. Circulating microparticle proteins predict pregnancies complicated by placenta accreta spectrum. *Sci Rep*. 2023;12:21922.
25. Fox H, Elston CW. Pathology of the placenta. *Major Probl Pathol*. 1978;7:1–491.
26. Tantbirojn P, Crum CP, Parast MM. Pathophysiology of placenta creta: the role of decidua and extravillous trophoblast. *Placenta*. 2008;29:639–645.
27. Carusi DA, Duzyj CM, Hecht JL, et al. Knowledge gaps in placenta accreta spectrum. *Am J Perinatol*. 2023;40:962–969.
28. Jauniaux E, Burton GJ. Pathophysiology of placenta accreta spectrum disorders: a review of current findings. *Clin Obstetr Gynecol*. 2018;61:743–754.
29. Roeder HA, Cramer SF, Leppert PC. A look at uterine wound healing through a histopathological study of uterine scars. *Reprod Sci*. 2012;19:463–473.
30. Schoots MH, Gordijn SJ, Scherjon SA, et al. Oxidative stress in placental pathology. *Placenta*. 2018;69:153–161.
31. Shainker SA, Dannheim K, Gerson KD, et al. Down-regulation of soluble fms-like tyrosine kinase 1 expression in invasive placentation. *Arch Gynecol Obstet*. 2017;296:257–262.
32. Duzyj C, Buhimschi I, Hardy J, et al. 105: Decreased expression of endostatin (ES) and hypoxia-inducible factor 1α (HIF-1α) is associated with excessive trophoblast invasion and aberrant angiogenesis in placenta accreta. *Am J Obstet Gynecol*. 2013;208:S58–S59.
33. Duzyj CM, Buhimschi IA, Laky CA, et al. Extravillous trophoblast invasion in placenta accreta is associated with differential local expression of angiogenic and growth factors: a cross-sectional study. *BJOG*. 2018;125:1441–1448.
34. Unemori EN, Erikson ME, Rocco SE, et al. Relaxin stimulates expression of vascular endothelial growth factor in normal human endometrial cells in vitro and is associated with menometrorrhagia in women. *Hum Reprod*. 1999;14:800–806.
35. Goh W, Yamamoto SY, Thompson KS, et al. Relaxin, its receptor (RXFP1), and insulin-like peptide 4 expression through gestation and in placenta accreta. *Reprod Sci*. 2013;20:968–980.
36. Schwickert A, Henrich W, Vogel M, et al. Placenta percreta presents with neoangiogenesis of arteries with Von Willebrand factor-negative endothelium. *Reprod Sci*. 2022;29:1136–1144.
37. Randi AM. Endothelial dysfunction in von Willebrand disease: angiogenesis and angiodysplasia. *Thromb Res*. 2016;141(suppl 2):S55–S58.
38. Uehara Y, Minowa O, Mori C, et al. Placental defect and embryonic lethality in mice lacking hepatocyte growth factor/scatter factor. *Nature*. 1995;373:702–705.
39. Shen J, Sun Y, Liu X, et al. EGFL6 regulates angiogenesis and osteogenesis in distraction osteogenesis via Wnt/β-catenin signaling. *Stem Cell Res Ther*. 2021;12:415.
40. Duan FM, Fu LJ, Wang YH, et al. THBS1 regulates trophoblast fusion through a CD36-dependent inhibition of cAMP, and its upregulation participates in preeclampsia. *Genes Dis*. 2021;8:353–363.
41. Junus K, Centlow M, Wikström AK, et al. Gene expression profiling of placentae from women with early- and late-onset pre-eclampsia: down-regulation of the angiogenesis-related genes ACVRL1 and EGFL7 in early-onset disease. *Mol Hum Reprod*. 2012;18:146–155.
42. Yu N, Wu JL, Xiao J, et al. HIF-1α regulates angiogenesis via Notch1/STAT3/ETBR pathway in trophoblastic cells. *Cell Cycle*. 2019;18:3502–3512.
43. Vićovac L, Aplin JD. Epithelial-mesenchymal transition during trophoblast differentiation. *Acta Anat (Basel)*. 1996;156:202–216.
44. Faleiro-Rodrigues C, Macedo-Pinto I, Pereira D, et al. Prognostic value of E-cadherin immunoexpression in patients with primary ovarian carcinomas. *Ann Oncol*. 2004;15:1535–1542.
45. Vignjevic D, Schoumacher M, Gavert N, et al. Fascin, a novel target of β-catenin-TCF signaling, is expressed at the invasive front of human colon cancer. *Cancer Res*. 2007;67:6844–6853.
46. Schmalhofer O, Brabletz S, Brabletz T. E-cadherin, β-catenin, and ZEB1 in malignant progression of cancer. *Cancer Metastasis Rev*. 2009;28:151–166.
47. Duzyj CM, Buhimschi IA, Motawea H, et al. The invasive phenotype of placenta accreta extravillous trophoblasts associates with loss of E-cadherin. *Placenta*. 2015;36:645–651.
48. Ali M, Rogers LK, Heyob KM, et al. Changes in vasodilator-stimulated phosphoprotein phosphorylation, profilin-1, and cofilin-1 in accreta and protection by DHA. *Reprod Sci*. 2019;26:757–765.
49. Chen Y, Zhang H, Han F, et al. The depletion of MARVELD1 leads to murine placenta accreta via integrin β4-dependent trophoblast cell invasion. *J Cell Physiol*. 2018;233:2257–2269.
50. Burton DGA, Krizhanovsky V. Physiological and pathological consequences of cellular senescence. *Cell Mol Life Sci*. 2014;71:4373–4386.

51. Debras E, Capmas P, Maudot C, et al. Uterine wound healing after caesarean section: a systematic review. *Eur J Obstetr Gynecol Reproduct Biol*. 2024;296:83–90.
52. Sharma S, Godbole G, Modi D. Decidual control of trophoblast invasion. *Am J Reprod Immunol*. 2016;75:341–350.
53. Thiery JP. Epithelial-mesenchymal transitions in tumour progression. *Nat Rev Cancer*. 2002;2:442–454.
54. Ribatti D. Epithelial-mesenchymal transition in morphogenesis, cancer progression and angiogenesis. *Exp Cell Res*. 2017; 353:1–5.
55. Yu L, Kuang LY, He F, et al. The role and molecular mechanism of long nocoding RNA-MEG3 in the pathogenesis of preeclampsia. *Reprod Sci*. 2018;25:1619–1628.
56. El-Hussieny M, Mohammed EM, Zenhom NM, et al. Possible role of TGF-β1, MMP-2, E-CAD, β-catenin and antioxidants in pathogenesis of placenta accreta. *Fetal Pediatr Pathol*. 2021;40:222–232.
57. Di Lieto A, Pollio F, De Falco M, et al. Collagen content and growth factor immunoexpression in uterine lower segment of type IA osteogenesis imperfecta: Relationship with recurrent uterine rupture in pregnancy. *Am J Obstet Gynecol*. 2003;189:594–600.
58. PrabhuDas M, Bonney E, Caron K, et al. Immune mechanisms at the maternal-fetal interface: perspectives and challenges. *Nat Immunol*. 2015;16:328–334.
59. Che J, Zheng Z, Li M, et al. Macrophage polarization in placenta accreta and macrophage-trophoblast interactions. *Am J Rep Immunol*. 2022;88:e13611.
60. Dutsch-Wicherek MM, Nowakowski B, Faryna J, et al. FOXP3-positive cell infiltration in the chorionic villi is increased in the placenta accreta and decreased in the placental abruption. *Ginekol Pol*. 2023;94:816–822.
61. Schwede S, Alfer J, Von Rango U. Differences in regulatory T-cell and dendritic cell pattern in decidual tissue of placenta accreta/increta cases. *Placenta*. 2014;35:378–385.
62. Jabrane-Ferrat N, Siewiera J. The up side of decidual natural killer cells: new developments in immunology of pregnancy. *Immunology*. 2014;141:490–497.
63. Zhou J, Chen H, Xu X, et al. Uterine damage induces placenta accreta and immune imbalance at the maternal-fetal interface in the mouse. *Placenta*. 2022;119:8–16.
64. De Oliveira Carniello M, Oliveira Brito LG, Sarian LO, et al. Diagnosis of placenta accreta spectrum in high-risk women using ultrasonography or magnetic resonance imaging: systematic review and meta-analysis. *Ultrasound Obstet Gynecol*. 2022;59:428–436.
65. Zhang T, Wang S. Potential serum biomarkers in prenatal diagnosis of placenta accreta spectrum. *Front Med*. 2022;9: 860186.
66. Farisoğullari N, Tanaçan A, Sakcak B, et al. Evaluation of maternal serum VEGF, TNF-alpha, IL-4, and IL-10 levels in differentiating placenta accreta spectrum from isolated placenta previa. *Cytokine*. 2024;176:156513.
67. Screening for fetal chromosomal abnormalities: ACOG practice bulletin summary, number 226. *Obstet Gynecol*. 2020;136: 859–867.
68. Bianchi DW, Platt LD, Goldberg JD, et al. Genome-wide fetal aneuploidy detection by maternal plasma DNA sequencing. *Obstetr Gynecol*. 2012;119:890–901.
69. Lo YMD, Corbetta N, Chamberlain PF, et al. Presence of fetal DNA in maternal plasma and serum. *Lancet*. 1997;350: 485–487.
70. Nicolaides KH, Syngelaki A, Gil M, et al. Validation of targeted sequencing of single-nucleotide polymorphisms for non-invasive prenatal detection of aneuploidy of chromosomes 13, 18, 21, X, and Y: validation study of cfDNA testing using SNPs. *Prenat Diagn*. 2013;33:575–579.
71. Norton ME, Jacobsson B, Swamy GK, et al. Cell-free DNA analysis for noninvasive examination of trisomy. *N Engl J Med*. 2015;372:1589–1597.
72. Sekizawa A, Jimbo M, Saito H, et al. Increased cell-free fetal DNA in plasma of two women with invasive placenta. *Clin Chem*. 2002;48:353–354.
73. Samuel A, Bonanno C, Oliphant A, et al. Fraction of cell-free fetal DNA in the maternal serum as a predictor of abnormal placental invasion-a pilot study. *Prenat Diagn*. 2013;33:1050–1053.
74. Ng EKO, Tsui NBY, Lau TK, et al. mRNA of placental origin is readily detectable in maternal plasma. *Proc Natl Acad Sci USA*. 2003;100:4748–4753.
75. Lo YMD, Chiu RWK. Prenatal diagnosis: progress through plasma nucleic acids. *Nat Rev Genet*. 2007;8:71–77.
76. Zhou J, Li J, Yan P, et al. Maternal plasma levels of cell-free β-HCG mRNA as a prenatal diagnostic indicator of placenta accrete. *Placenta*. 2014;35:691–695.
77. El Behery MM, Rasha LE, El Alfy Y. Cell-free placental mRNA in maternal plasma to predict placental invasion in patients with placenta accreta. *Int J Gynaecol Obstet*. 2010;109: 30–33.
78. Afshar Y, Dong J, Zhao P, et al. Circulating trophoblast cell clusters for early detection of placenta accreta spectrum disorders. *Nat Commun*. 2021;12:4408.
79. Sholapurkar SL. Increased incidence of placenta praevia and accreta with previous caesareans–a hypothesis for causation. *J Obstet Gynaecol*. 2013;33:806–809.
80. Abalos E, Addo V, Brocklehurst P, et al.; CORONIS collaborative group. Caesarean section surgical techniques: 3 year follow-up of the CORONIS fractional, factorial, unmasked, randomised controlled trial. *Lancet*. 2016;388: 62–72.