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Narrative Review

Biology and Pathophysiology of Placenta Accreta Spectrum Disorder

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Placenta accreta spectrum (PAS) disorders present a significant clinical challenge, characterized by abnormal placental adherence to the uterine wall secondary to uterine scarring. With the rising global cesarean delivery rates, the incidence of this iatrogenic disorder has increased, underscoring the critical need for an understanding of its pathophysiology to inform management and prevention strategies. Normal placentation depends on tightly regulated extravillous trophoblast invasion into the decidua, spiral artery remodeling, interactions with the extracellular matrix, and immune modulation. Uterine scarring disrupts this balance, creating an environment deficient in key regulatory signals required for coordinated implantation and decidualization. In PAS, the loss of inhibitory decidual cues and deficient boundary limits permits unrestrained trophoblast into the abnormal decidual environment. Dysregulated signaling, along with an inflammatory milieu in scarred tissues, exacerbates abnormal placental development. Current prenatal imaging focuses on the appearance of excessive fibrinoid deposition, extracellular matrix remodeling, and incomplete spiral artery transformation as surrogates of PAS risk stratification. Emerging single-cell RNA sequencing and proteomic profiling offer insights into biomarkers and pathways that enable targeted interventions. Preventive efforts should prioritize reducing cesarean delivery rates to limit uterine scarring. Advances in regenerative medicine and bioengineering, including extracellular matrix–modulating biomaterials, growth factor therapies, and antifibrotic interventions, hold promise for improving scar healing and reducing PAS risk. This review bridges foundational science and clinical application, emphasizing the importance of the underlying placental biology and pathophysiology to make a clinical difference in detecting, treating, and preventing PAS. Addressing drivers of abnormal placentation is critical for improving maternal and neonatal outcomes with this increasingly prevalent iatrogenic condition.

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Figure 1 was created with Biorender and blastocyst image courtesy of IVF unit at Wolfson Medical Center. The authors thank UCLA undergraduate Amanda Wang for help with Figure 2.

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The process of placentation is a cornerstone of human reproduction, orchestrated as an intricate interplay between maternal and fetal physiology.[1–3] Beyond its fundamental role in nurturing fetal growth and development, the placenta serves as a dynamic mediator of dialog at the maternal–fetal interface.[4–7] The placenta enables nutrient transfer, gas exchange, and waste elimination while serving as an endocrine and immunologic surrogate to maintain a pregnancy.[8–10] The development and function of this multifaceted organ are essential not only for the health of the fetus but also for maternal well-being throughout

gestation and beyond.[11–15] Immediately after birth, the temporary organ usually separates spontaneously, and a physiologic autotransfusion occurs to the mother.

In placenta accreta spectrum (PAS) disorders, the placenta does not separate at birth. The lack of separation at delivery in PAS can lead to massive hemorrhage, with significant implications for maternal morbidity.[16–18] Consequently, PAS has profound maternal physical and mental health sequalae[19–21] and is an increasingly common iatrogenic clinical and public health problem. Placenta accreta spectrum represents a spectrum of adherence of the placenta to the uterine wall that fails to detach from the underlying uterus and is often referred to as accreta placentation.[22–24] The rising incidence of PAS parallels the increasing rate of cesarean births worldwide, underscoring the urgency of understanding and addressing this condition.[25]

Accreta placentation exemplifies how disruptions in the finely tuned processes of (normal) placentation can lead to severe consequences, highlighting the interplay among uterine microenvironment, trophoblast biology, and maternal health.[26–29] This review adds a new perspective to the body of PAS literature[30–33] by synthesizing our current understanding on the mechanisms of normal placentation with the pathophysiology of PAS, offering insights into the molecular, cellular, and clinical dimensions of PAS disorders. By bridging basic science and clinical practice, we aim to provide a resource for researchers and clinicians working to reduce the significant morbidity and mortality associated with PAS.

NORMAL PLACENTATION IN THE UTERINE WALL

Trophoblast differentiation begins after the blastocyst attaches to the uterine epithelium. The trophoblast (or trophectoderm in early development) is the outer layer of the blastocyst and plays a crucial role in both implantation and placental development. The trophectoderm differentiates into two subtypes: 1) the cytotrophoblast, an inner proliferative layer; and the 2) syncytiotrophoblast, the outer layer that establishes the interaction with the endometrium at the maternal–fetal interface and produces hormones such as human chorionic gonadotropin[11] (Fig. 1). These cells form the chorionic villi, facilitating nutrient and gas exchange between maternal and fetal circulations. Extravillous trophoblasts emerge from the anchoring villi and undergo epithelial–mesenchymal transition, enabling their migration into the maternal decidua.[34] Ultimately, the trophoblast is the embryo's first connection to the maternal system, driving implantation, placental formation, and essential pregnancy adaptations. This transition is a pivotal hallmark for normal placentation that allows remodeling of spiral arteries in the decidua (Fig. 1).[34]

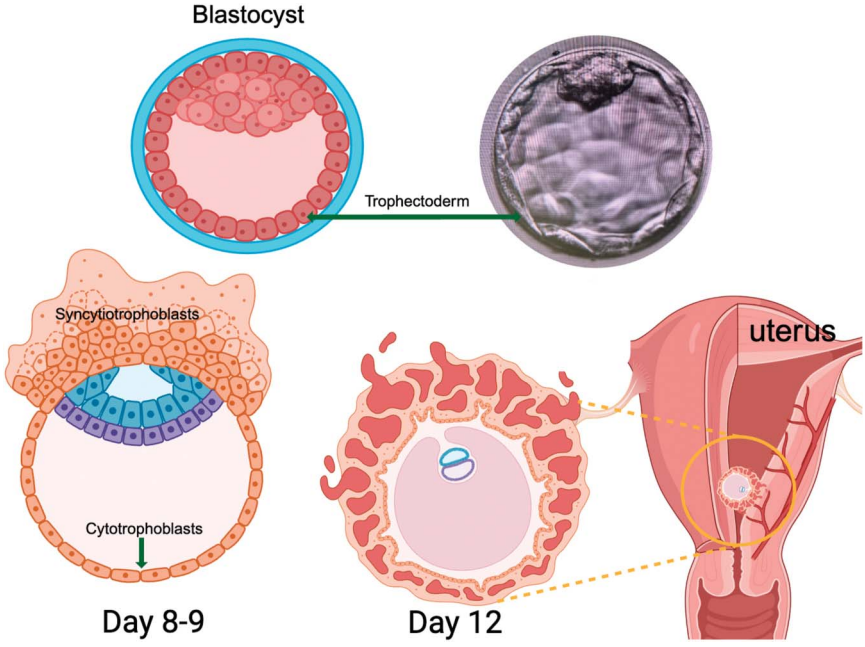

Fig. 1. Differentiation of trophectoderm into cytotrophoblasts and syncytiotrophoblasts demonstrated in a schematic and a phase-contrast image of a blastocyst. Phase-contrast image courtesy of the IVF Unit at Wolfson Medical Center. Image created with Biorender.

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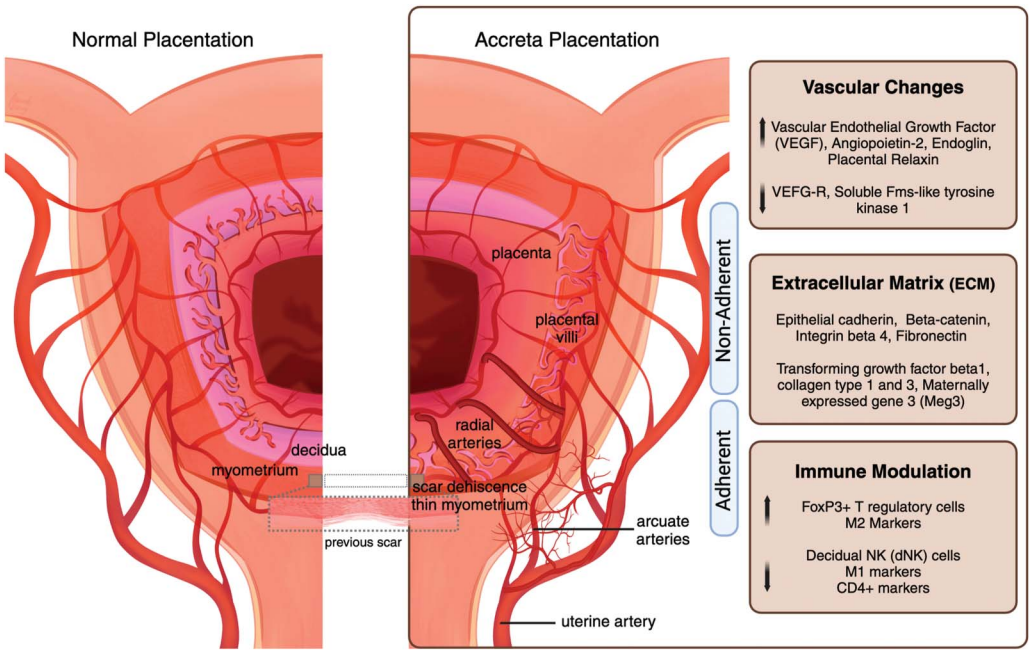

Fig. 2. Biology of accreta placentation. Normal placentation and villous formation in the setting of a previous iatrogenic uterine scar (*left*). Accreta placentation in the setting of a previous scar within a scarred irregular myometrium demonstrating adherent and nonadherent placentation modulated by a decidual defect, vascular change along the spiral and radial arteries, remodeled extracellular matrix (ECM), and immune modulation (*right*).

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The regulation of extravillous trophoblast migration is a complex interplay of mechanical and biochemical signals. Maternal cytokines, growth factors, and extracellular matrix components influence trophoblast invasion. Key players include matrix metalloproteinases, which degrade extracellular matrix barriers, and uterine natural killer cells, which secrete cytokines modulating trophoblast behavior.[12,35] As pregnancy progresses, extravillous trophoblast populations diminish, transitioning into trophoblast giant cells.[11] These cells persist in the decidua and arterial walls, maintaining structural integrity and endocrine function.[36] By the second trimester, maternal blood flow increases as extravillous trophoblast plugs in spiral arteries dissolve, ensuring uninterrupted perfusion to the intervillous space.

During the first weeks of pregnancy, placental villi develop, and these villi later branch into floating villi, essential for maternal–fetal exchange. This process transforms the arteries into low-resistance, high-capacity vessels, ensuring adequate blood flow to the growing fetus.[12,37,38] This transformation involves extracellular matrix remodeling, matrix metalloproteinases, and interaction with maternal immune cells, uterine natural killer, macrophages, and others.[35,39–41]

This tenant of normal placentation is the basis for the large body of clinical studies that suggest early pregnancy as a critical window for interventions such as low-dose aspirin to reduce the risk of preeclampsia by supporting extravillous trophoblast invasion and spiral artery remodeling.[42–47] Experimental evidence from preclinical models indicates that low-dose aspirin may mitigate abnormal placental development by modulating extravillous trophoblast migration, extracellular matrix deposition, and vascular remodeling.[48]

ABNORMAL PLACENTATION IN PLACENTA ACCRETA SPECTRUM: STOP BLAMING THE PLACENTA

The Soil: Placentation in Abnormal Uterine Walls

The majority of PAS cases result from placentation in a scarred uterine environment (Fig. 2 and Table 1).[16,49,50] The pathologic alterations in placentation are in the context of uterine scarring, most commonly from cesarean births, especially multiple cesarean births.[16,18,51] The scar disrupts the endometrial–myometrial interface, creating an environment susceptible to abnormal implantation.[23,25,52] The cesarean scar defect, or "niche," frequently harbors

Table 1. Key Mechanisms in Normal and Abnormal Placentation and Potential Interventions

Mechanism	Normal Placentation	Accreta Placentation	Potential Interventions and Timing
Trophoblast differentiation	Cytotrophoblasts form villi; syncytiotrophoblasts facilitate invasion into the maternal endometrium.	EVTs invade as a result of the loss of regulatory decidual signals.	
Cellular composition	Dynamic changes throughout pregnancy, with balanced cellular behavior in fetal stromal, maternal decidual, and immune cells	Altered gene expression in endothelial and decidual cells in scarred uterine environments; markers such as VIM, EGFL6, and SPARC drive ECM remodeling	
ECM remodeling	ECM components (eg, collagen, fibronectin) support controlled trophoblast invasion.	ECM is rigid, enriched with collagen, facilitating excessive trophoblast adhesion and invasion.	
Spiral artery remodeling	Spiral arteries are remodeled into low-resistance vessels to support fetal growth.	Incomplete or absent arterial remodeling; high-velocity blood flow into the intervillous space	Low-dose aspirin may enhance remodeling of spiral arteries, reducing vascular resistance and improving blood flow in subsequent pregnancies.
Maternal immune regulation	Uterine natural killer cells and macrophages regulate EVT behavior.	Scar tissue activates inflammatory pathways (eg, Piezo1, NF-κB), transforming fibroblasts and promoting excessive trophoblast invasion.	
Hypoxia and inflammation	Normal levels of oxygen and inflammatory cytokines support controlled placentation.	Hypoxia and inflammation in scarred tissue promote invasive trophoblast phenotypes.	
Trophoblast invasion regulation	Proper decidual signals inhibit excessive trophoblast invasion.	Scarring and loss of decidual regulation result in excessive trophoblast invasion into the myometrium.	
Fibrinoid deposition	Supports normal trophoblast attachment and detachment	Abnormal fibrinoid accumulation in PAS contributes to excessive adherence.	Biomaterials (during or after cesarean): Biomaterials such as collagen scaffolds may help modulate fibrinoid deposition, improving trophoblast function and adherence during cesarean delivery. It may also be beneficial to apply scaffolds in the previous cesarean delivery to reduce risks for PAS in future pregnancies.
Molecular signaling pathways	TGF-β and Wnt signaling regulate trophoblast differentiation and invasion.	Dysregulated TGF-β and Wnt signaling lead to abnormal trophoblast behavior.	TGF-β inhibitors (next pregnancy): Targeting TGF-β signaling can restore normal trophoblast differentiation and invasion, reducing the risk of abnormal invasion in future pregnancies.

EVT, extravillous trophoblast; ECM, extracellular matrix; NF-κB, nuclear factor-κB; PAS, placenta accreta spectrum; TGF-β, transforming growth factor-β.

trophoblasts during implantation, resulting in defective decidualization and abnormal interactions between the trophoblast and maternal tissues.[53–55]

A body of clinical literature has identified the early cesarean scar pregnancy as a precursor of some of the histopathology seen in PAS, the sequalae and natural history of placentation at the scar.[45,56–58] The cesarean scar alters the biomechanical and biochemical properties of the uterine wall. The myometrial healing is incomplete, resulting in thinner tissue,

disorganized myocyte architecture, fibrosis, and elastosis.[24,34] In a subsequent pregnancy, this scarring predisposes the uterus to defective decidualization, which is crucial for controlling trophoblast invasion.[59,60] Scarred tissues lack the regulatory signals that normally inhibit trophoblast penetration, allowing deeper invasion into the myometrium, a presumed lack of inhibitory signal or "stop signal."[26,33,61]

The Seed: Loss of a Decidual Inhibitory Signal

The decidua provides critical regulatory cues that constrain extravillous trophoblast invasion. Scarring disrupts this regulatory environment, removing both physical and biochemical barriers and a loss of decidual regulatory signals. Without these inhibitory signals, extravillous trophoblasts adhere into the myometrium and beyond.[23,39]

Several signaling pathways are implicated in PAS pathogenesis. Dysregulation of the transforming growth factor-β and Wnt signaling pathways has been observed, both of which are crucial for trophoblast differentiation and invasion.[39] Transforming growth factor-β induces type 1 collagen and tissue inhibitor of metalloproteinase and then activates myofibroblasts, which modulate mechanical stress at the scar[62] (Table 1). The decidua and myofibroblasts also secrete collagen, which leads to extracellular matrix accumulation, further modulating the scar.[61] In addition, hypoxic conditions in scarred tissues activate hypoxia-inducible factors, further promoting invasive trophoblast phenotypes.[63,64] Maternal immune cells, particularly uterine natural killer cells and macrophages, are essential for regulating extravillous trophoblast behavior. Uterine natural killer cells interact with trophoblasts through specific ligand-receptor binding, releasing cytokines that modulate invasion.[12,35] In PAS, this regulatory interplay is disrupted by the absence of normal decidual tissue, resulting in uncontrolled extravillous trophoblast proliferation and migration. The inflammatory changes of the scarred decidua increase the production of interleukin-8 and granulocyte colony-stimulating factor, which recruit trophoblasts toward a scar.[65] Furthermore, a shift toward local immune suppression in areas of uterine scarring attributable to alterations in immune cell subpopulations may further allow unregulated extravillous trophoblast invasion.[66]

Extravillous trophoblasts in PAS exhibit hyperplastic growth and form clusters or cords that invade beyond the normal placental boundary.[39] These extravillous trophoblasts infiltrate the myometrium.[67–69] Simultaneously, the population of trophoblast giant cells, which regulate local placental stability, is significantly reduced in PAS.[25] The pathogenesis involves an interplay of molecular, cellular, and structural mechanisms that result in unregulated extravillous trophoblast invasion and abnormal placental development and subsequently adherence at specific sites of the placental–myometrial interface.

Theoretically, optimizing surgical techniques at the time of cesarean delivery to minimize uterine scarring and exploring regenerative therapies to enhance scar healing are areas of potential focus.[23] A potential strategy for mitigating the invasive trophoblast behavior in PAS could draw on approaches used in skin scar healing. In both systems, scarring disrupts normal tissue regulation, leading to aberrant cell behaviors. In skin wounds, controlled extracellular matrix remodeling, modulation of inflammatory signaling, and strategic growth factor delivery (eg, transforming growth factor-β and Wnt inhibitors) have been shown to limit excessive tissue remodeling and scarring.[70] Applying similar strategies to PAS such as modulating trophoblast interactions with extracellular matrix or immune cells could potentially mitigate the hyperplastic growth of extravillous trophoblasts, restoring more controlled invasion and placental development.

The Scaffold: Fibrinoid Deposition and Extracellular Matrix Remodeling

Excessive fibrinoid deposition is a hallmark of PAS.[71] Normally, fibrinoid material at the maternal–fetal interface supports trophoblast attachment during pregnancy and detachment during delivery. In PAS, abnormal accumulation of fibrinoid material contributes to pathologic anchoring of the placenta to the uterine wall, which becomes a window into our ultrasound screening markers for PAS.[68,72] In PAS, this fibrinoid deposition is exacerbated by oxidative and mechanical stress in scarred tissues, which promote further extracellular matrix remodeling and adhesion.[23] This is supported by increased fibronectin expression at the maternal–fetal interface in PAS and decreased insulin-like peptide 4 in PAS, which results in fibrinoid disposition, inhibition of active matrix metalloproteinases, and subsequent extracellular matrix remodeling.[61,66,71,73]

As a result, scarred tissues in PAS are characterized by a rigid extracellular matrix enriched with collagen and fibronectin.[61] The local extracellular matrix environment is highly adhesive, facilitating more extensive adherence of trophoblasts locally at the scarred area. The increased expression of matrix metalloproteinases further degrades extracellular

matrix components, enhancing the invasive capacity of trophoblasts. High-velocity blood flow in PAS generates reactive oxygen species, which damage extracellular matrix structures and alter trophoblast signaling, driving further invasion.[35,74,75] High-velocity blood flow in PAS generates oxidative stress, resulting in reactive oxygen species production. Reactive oxygen species not only damage the extracellular matrix but also alter trophoblast signaling, increasing their invasive capacity. This oxidative damage further stiffens the scar tissue, creating a rigid extracellular matrix environment that facilitates deeper trophoblast invasion. In PAS, the extracellular matrix is enriched with collagen and fibronectin, providing an overly adhesive surface for invasive trophoblasts (Table 1). The increased expression of matrix metalloproteinases further degrades extracellular matrix components, enhancing the invasiveness of extravillous trophoblasts.[23,35,61,66]

The Water: Disruption of Spiral Artery Remodeling

Under normal conditions, extravillous trophoblasts remodel spiral arteries to convert them into low-resistance, high-capacity vessels that support adequate blood flow to the placenta. In PAS, the physiologic transformation of spiral arteries is incomplete or absent.[32] Under normal conditions, extravillous trophoblasts remodel spiral arteries to facilitate low-resistance, high-capacity blood flow. In PAS, this remodeling is disrupted, leading to direct, high-velocity maternal blood flow into the intervillous space.[12] These hemodynamic abnormalities contribute to oxidative stress, damage to placental villi, and lacunar formation, a key ultrasonographic finding in PAS pregnancies.[12,54]

Vascular abnormalities are a central feature of PAS. Placental tissue in PAS exhibits disorganized vascular remodeling, driven by elevated levels of vascular endothelial growth factor. These changes lead to the formation of structurally abnormal and leaky blood vessels, further contributing to placental dysfunction.[26] Histopathologic studies reveal extensive vascularization in scarred uterine tissues, with aberrant endothelial markers such as von Willebrand factor often absent, reflecting poor vascular integrity.[26]

High-velocity blood flow through unremodeled arteries generates shear stress and mechanical damage, resulting in lacunar formation and thrombosis. These hemodynamic disturbances compromise placental function, increasing the risk of adverse pregnancy outcomes. Imaging studies often reveal excessive vascularity in PAS, corresponding to the pathologic neovascularization observed histologically.[72,76–78]

Histologic studies of PAS placentas reveal extensive vascularization in scarred uterine tissues and changes in the intervillous circulation in the scar area.[68,79] These vessels often lack proper structural integrity, with aberrant endothelial cell markers such as von Willebrand factor being absent.[26] The proliferation of these abnormal vessels contributes to the excessive vascularity observed on imaging studies.

Despite the vast changes in PAS placentation, and unlike preeclampsia, in which the idea of shallow placental invasion drives clinical outcomes such as fetal growth restriction, neonates with PAS placentation do not incur heightened risk of fetal growth restriction or systematic maternal complications.[80,81] Rather, the neonatal outcomes and consequences related to preterm delivery, prematurity, and perinatal morbidity are driven by the early iatrogenic gestational age of birth.[80,82]

WHY THE BIOLOGY OF PLACENTA ACCRETA SPECTRUMMATTERS: RESEARCH GAPS AND THE FUTURE

Understanding the biological processes during labor and birth is crucial for predicting scar formation after a cesarean scar, which may influence the risk of PAS (Fig. 1 and Table 1). Single-cell RNA sequencing has revealed distinct cellular compositions in different placental and extraplacental regions, highlighting dynamic changes throughout pregnancy.[27,83–85] Notably, labor induces modulation in fetal stromal cells, maternal decidual cells, and macrophages in the chorion, suggesting their significant roles in labor. These insights into cellular behaviors and immune responses can inform how labor influences scar tissue formation and potentially affects future pregnancy outcomes, including PAS risk.[28,61]

The only true clinical prevention at our disposal for PAS is decreasing the cesarean birth rate, and, hence, attenuating the uterine scar. Beyond that, modifying the surgical technique at the time of primary caesarean delivery is a possible mechanism for reducing subsequent uterine remodeling and scarring; however, studies to date have not demonstrated clear benefits of one technique over another in reducing the risk of PAS.[86,87] Still in early stages, and far from clinical readiness, are interventions in regenerative medicine and bioengineering. Specifically, modulating hydrogels with growth factors such as vascular endothelial growth factor and transforming growth factor-β inhibitors, as well as advanced

biomaterials (scaffolds from extracellular matrix that mimic the natural tissue microenvironment), are in the pipeline to reduce scarring and improve healing at the scar.[88–91] This and cell-based therapies might have a role in improved scar formation at the surgical site. However, the truth remains that the vast majority of individuals with a cesarean birth who choose to have a subsequent pregnancy do not have accreta placentation.

Single-cell RNA sequencing, proteomic profiling, and mechanistic studies have revealed the pivotal role of the maternal–fetal interface in PAS.[61,66,92,93] Altered gene expression in endothelial and decidual cells in scarred uterine environments, particularly markers such as vimentin, EGFL6, and SPARC, drives extracellular matrix remodeling, angiogenesis, and enhanced trophoblast invasion.[61] These findings refute the "paved path" hypothesis, showing that mechanical cues from scar tissue activate inflammatory pathways such as Piezo1 and nuclear factor-κB, transforming fibroblasts and promoting excessive trophoblast invasion. Exploring these pathways may offer critical avenues for preventing PAS by targeting scar-induced cellular dynamics.[28,61,65] Predicting and subsequently personalizing the intervention for individuals who are at risk for PAS allow us to explore potential roles in genetic and molecular interventions, antifibrotic drugs (targeting transforming growth factor-β), or matrix metalloproteinase modulators, as well as laser and light therapies. The focus remains on locally modulating inflammation and reducing fibrotic responses, forming "a better scar" to reduce PAS risk (Fig. 2 and Table 1).

CONCLUSION

At its core, PAS pathophysiology is rooted in the interplay of uterine scarring, decidual dysfunction, extracellular matrix remodeling, vascular abnormalities, and dysregulated trophoblast invasion. The contributions of prior cesarean scar and uterine instrumentation underscore the role of "the scar" as the initiating substrate for abnormal placentation. This decidual "soil," disrupted by inadequate healing and fibrosis, predisposes defective decidualization, creating a permissive environment for the uncontrolled invasion of trophoblasts. The loss of decidual inhibitory signals disrupts the physical and molecular barriers of the endometrial–myometrial interface and, combined with the inflammatory milieu in scarred tissues, amplifies the invasive capacity of trophoblasts. Extracellular matrix remodeling and excessive fibrinoid deposition anchor the placenta to the uterine wall. Reducing the cesarean birth rate remains the most effective preventive measure for PAS. More so, improving clinical and ultrasound screening and recognizing early cesarean scar pregnancies can modulate outcomes. Emerging technologies such as single-cell RNA sequencing and proteomic profiling offer insights into biomarkers and pathways and may inform targeted interventions.[61,66,92,94–98] Future strategies should focus on personalizing PAS prevention and management, leveraging molecular and cellular approaches to mitigate scarring and abnormal placentation. By addressing the root causes of PAS, we can improve maternal and neonatal outcomes and reduce the overall burden of this complex condition.

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