Formation of the placental membranes and pathophysiological origin of associated great obstetrical syndromes

Graham J. Burton, MD, DSc, FMedSci, FRS; Eric Jauniaux, MD, PhD, FRCOG; Ashley Moffett, MD, FRCOG, FMedSci

Formation of the smooth membranes is an essential phase of human placentation to allow safe rupture of the chorionic sac and birth of the fetus without damaging the placenta. The membranes form through regression of two-thirds of the villi that cover the early gestational sac shortly after implantation. Regression is associated with locally high levels of oxidative stress secondary to partial onset of the maternal arterial circulation to the placenta. Onset starts preferentially in the peripheral zone from ~6 to 8 weeks of gestation, reflecting the lesser extent of plugging of maternal spiral arteries by endovascular trophoblast in this region. Plugging is part of the arterial remodeling essential to control adequate and even perfusion of the placenta. As the chorionic sac expands, extensive necrosis occurs in the overlying decidua capsularis, which consequently makes no contribution to the mature membranes. Once the sac fuses with the decidua parietalis lining the opposite wall of the uterus, at around 16 weeks of gestation, the cytotrophoblast cells of the chorionic epithelium proliferate and form a stratified epithelium with features reminiscent of the skin barrier. A sharp demarcation exists between this epithelium and the cells of the decidua parietalis in the mature membranes, with no evidence of trophoblast migration. Preterm premature rupture of the membranes and preterm labor are associated with deficient remodeling of the spiral arteries that is mediated by extravillous trophoblasts derived from the cytotrophoblastic shell. The resultant placental malperfusion causes maternal and placental oxidative stress, as in the other great obstetrical syndromes, causing release of proinflammatory cytokines and stimulating uterine contractility. Deficient remodeling is also likely a proxy marker for poor development of the cytotrophoblastic shell. The shell anchors the gestational sac at the maternal—placental interface postimplantation, and weakness of this interface predisposes to subchorionic hemorrhage. Hemorrhages that abut the membranes may induce local inflammation, senescence, and weakening. Ensuring normal development of the cytotrophoblastic shell is therefore essential to prevent the great obstetrical syndromes. At this stage of pregnancy, placental development is supported by histotrophic nutrition from the decidua. Hence, optimizing endometrial function prior to conception should become a healthcare priority.

Key words: amnion, chorion laeve, decidualization, placental development, premature delivery, prematurity, preterm labor, preterm premature rupture membranes, smooth membranes, threatened miscarriage

Introduction

The great obstetrical syndromes (GOS) comprise common complications of pregnancy that share epidemiological, genetic, and histological links to defective placentation.[1–4] They display a spectrum of clinical presentations, ranging in severity from miscarriage through abruption to early onset preeclampsia, fetal growth restriction, unexplained stillbirth, late-onset preeclampsia, preterm premature rupture of the membranes (PPROM), and preterm labor (PTL). This spectrum reflects a corresponding range of developmental defects within the placental bed, the area of the decidua abutting the placenta. A histopathologic feature common to all the GOS is deficient remodeling of the maternal spiral arteries that supply the placenta.[3,5] Remodeling is mediated by extravillous trophoblast cells that migrate from the tips of the placental anchoring villi into the decidua during the first and early second trimesters[6,7] and is an essential process that ensures adequate and even perfusion of the placenta.[8]

While mechanistic links can be drawn among deficient spiral artery remodeling, fetal growth restriction, and preeclampsia based on placental malperfusion and oxidative stress,[5,9–11] it is less easy to see causal connections with conditions such as PPROM and PTL that have no direct vascular basis. The fact that adverse events at the maternal—placental interface during early pregnancy, such as threatened miscarriage and subchorionic hematoma, are risk factors for these later complications suggests their pathophysiology also

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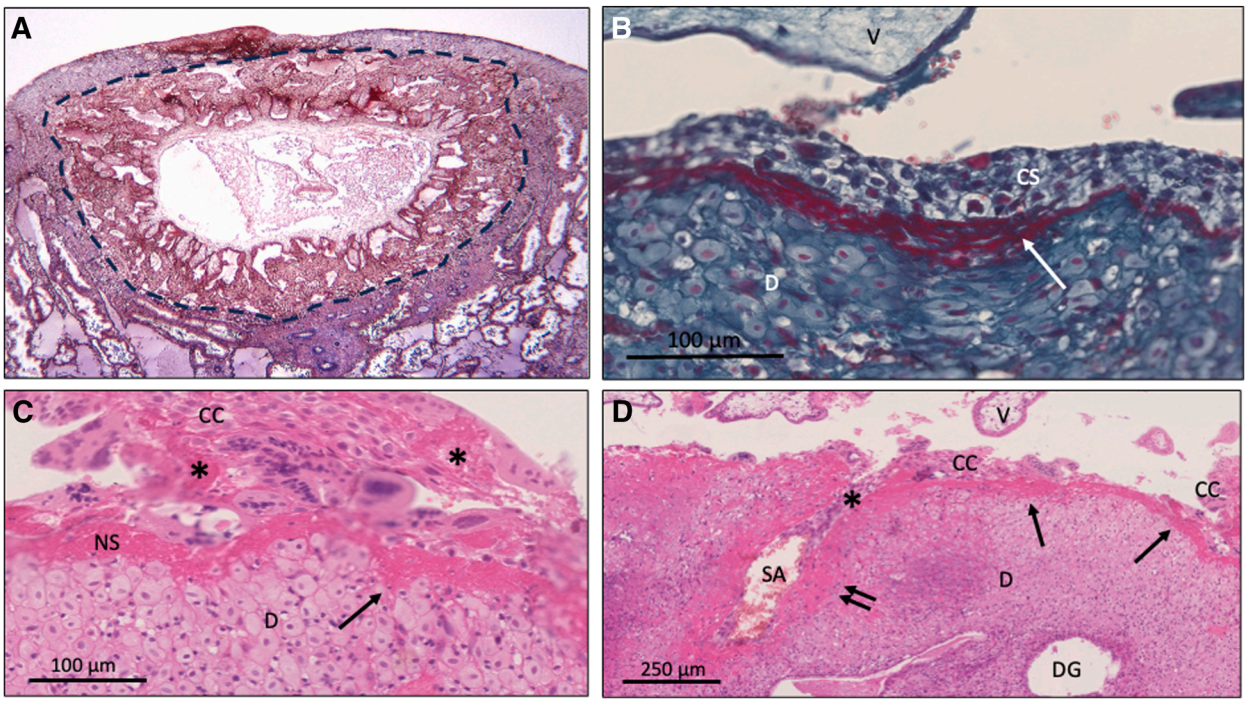
originates during the first trimester.[12] Indeed, in our view, insufficient development of the cytotrophoblastic shell that forms the utero-placental interface shortly after implantation provides a more complete unifying hypothesis for the origin of the GOS than deficient arterial remodeling alone.[13] The latter may act as a proxy marker for formation of the shell, which is a transient structure and inaccessible for study.

Although the histology of the mature smooth membranes is well documented,[14–17] few accounts describe their development in detail. This is largely due to the limited availability of suitable tissue samples. Here, we illustrate their formation with examples from an archival collection of placenta-in-situ hysterectomy specimens and isolated placentas from 6 weeks of pregnancy through to 32.5 weeks. We consider how aberrations in early placentation may contribute to the pathophysiology of PPROM and PTL, and link these conditions with the other GOS.

Formation of the smooth membranes

By day 11 postfertilization, the conceptus is fully implanted in the uterine wall and enclosed by the maternal decidua. The original outer wall of the blastocyst, the trophoblast, becomes lined on its inner surface by extraembryonic mesoderm to form the chorionic sac. Initially, the sac is surrounded by the rapidly expanding primary syncytium but villi soon bud through this layer and develop over its entire surface, forming the chorion frondosum (Figure 1A). These villi consist of a stromal core and a 2-layered covering of trophoblast, the outer multinucleated syncytiotrophoblast and an underlying layer of uninucleate progenitor cytotrophoblast cells. Anchoring villi

FIGURE 1
Formation of the cytotrophoblastic shell



(**A**) Photomicrograph of a human implantation site at stage 7 (approximately 15–17 days postfertilization), showing early villi developing over the entire surface of the gestational sac. At the distal ends of the villi cytotrophoblast cells merge with neighbors to create the shell, indicated by the dashed line, that forms the utero-placental interface. Specimen from the Carnegie Collection and image by courtesy of the late Allen Enders. (**B**) Placenta-in-situ specimen at 8 weeks postfertilization showing the cytotrophoblastic shell (CS) apposed to the decidua (**D**). At the interface, matrix-type fibrinoid is laid down by the trophoblast cells, forming Nitabuch's stria (arrowed and staining red). Fibrillar material from the stria intermingles with the decidual cells, aiding adherence of the conceptus. V, placental villus. Stain, Masson's trichrome. (**C**) Photomicrograph from the same specimen showing a cytotrophoblast cell column (CC) attached to the decidua (D). Extracellular matrix secreted by the cells in the column (asterisks) merges with that of Nitabuch's stria (NS), which in turn intermingles with that of the decidua (arrowed). This blending of the matrices aids anchorage of the placenta to the decidua. Stain, hematoxylin and eosin. (**D**) Photomicrograph from the same specimen showing a spiral artery (SA) undergoing remodeling mediated by extravillous trophoblast migrating down the lumen (asterisk). Fibrinoid deposited in the vessel wall (double arrow) as part of remodeling can be seen to be continuous with that of Nitabuch's stria (single arrows). This continuity 'welds' the artery to the developing basal plate of the placenta and ensures a blood-tight union. Stain, hematoxylin and eosin

CC, cytotrophoblast cell column; *DG*, decidual gland; *V*, placental villus.

contact the decidua and at these points cytotrophoblast cells break through the syncytiotrophoblast and form a column of cells, the cytotrophoblastic cell columns. At their distal ends, the columns merge laterally with neighbors, creating the cytotrophoblastic shell that encapsulates the gestational sac at the maternal—placental interface.

The cytotrophoblastic shell is of critical importance and serves several functions. It anchors the sac into the superficial decidua by means of an extracellular matrix. As cytotrophoblast cells progress along the cell columns, they differentiate into extravillous trophoblasts, a subpopulation of trophoblasts that migrates beyond the confines of the placental disc and has both a secretory and migratory phenotype. Extravillous trophoblasts secrete several products, including collagen IV, laminin, heparin sulfate, and onco-fetal fibronectins,[15,18,19] that appear as amorphous red material on hematoxylin and eosin staining. This is referred to as matrix-type fibrinoid to distinguish it from fibrin deposits in the placenta that originate from serum fibrinogen.[20] Secretion starts toward the distal end of a column but is most extensive in the outer layers of the shell.[19] There, fibrillar strands of this matrix intermingle with decidual cells and their extracellular matrix (Figure 1B and C), contributing to a band of fibrinoid referred to eponymously as Nitabuch's stria.[21] Ghosts of dead extravillous trophoblasts and polymorphonuclear neutrophils are also seen within the stria. The matrix proteins secreted by extravillous trophoblasts have been referred to as 'trophoblastic glue',[22] and undoubtedly play an important role in adherence of the conceptus to the decidua and in strengthening the utero-placental interface.

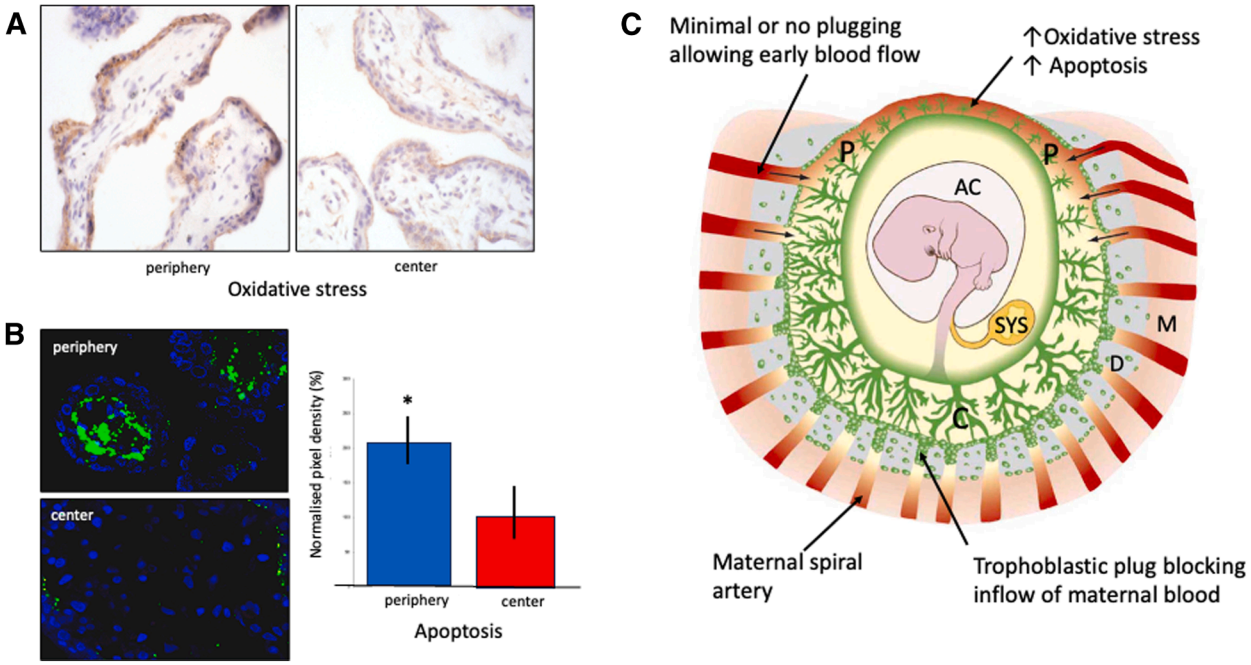
The cytotrophoblastic shell also plays a key role in supplying the extravillous trophoblast that will mediate spiral artery remodeling. Establishing an arterial supply to the human placenta poses unique hemodynamic challenges. First, the high pressure and velocity inherent in the maternal circulation must be reduced to avoid damage to the delicate villous trees.[8] Second, a firm seal must be formed between the spiral arteries and the developing basal plate of the placenta to prevent hemorrhage and subchorionic hematomas at the utero-placental interface. Third, the smooth muscle medial cells in the hypercontactile segment in the junctional zone that limits blood loss during menstruation must be removed to ensure constancy of blood flow to the placenta.[8] Remodeling of the spiral arteries meets all these requirements. The process is mediated by extravillous trophoblast cells that migrate toward the arteries and surround them externally, and then by endovascular trophoblasts that subsequently migrate down the arterial lumens.[6,7,23] The smooth muscle cells within the walls of the arteries are replaced by vaso-inert matrix-type fibrinoids secreted by the extravillous trophoblast.[23] This fibrinoid merges with Nitabuch's layer in the basal plate, ensuring that the mouths of the arteries are effectively 'welded' watertight to the deep surface of the developing placenta (Figure 1D). Consequently, the distal parts of the arteries break away with the placenta during delivery and can be observed attached to the maternal surface of the basal plate.[24] Loss of the contractile smooth muscle media causes the terminal portions of the arteries to dilate,[25] reducing the pressure and velocity of the inflowing maternal blood.[8]

During much of the first trimester, the endovascular extravillous trophoblast that migrates from the shell down the arterial lumens forms loose aggregates that effectively 'plug' the vessels.[25—27] These plugs severely restrict maternal blood perfusing the placenta so that the intervillous space is filled with a clear fluid comprising maternal plasma and secretions from the decidual glands.[27,28] Consequently, the oxygen concentration within the developing placenta is low during this stage of gestation, at approximately 20 mmHg.[29,30] This level equates approximately to that in adult resting muscle and should therefore not be considered hypoxic. By limiting aerobic respiration, it does, however, probably minimize the risk of free-radical teratogenesis[31,32] and maintains stem cells in a pluripotent state.[33—35]

Once organogenesis is complete, a higher concentration of oxygen to support fetal growth can be tolerated. Onset of the maternal arterial circulation to the placenta starts in the periphery of the implantation site toward the end of the first trimester at 8 to 10 weeks of gestation and extends into the central regions over the next few weeks.[36] This pattern mirrors inversely the extent of extravillous trophoblast migration into the decidua, and hence of arterial plugging, across the implantation site.[37] The associated 3-fold rise in oxygen concentration poses an oxidative challenge for the early placental tissues that have low levels of antioxidant defenses.[38] Villi sampled from the peripheral regions toward the end of the first trimester display increased markers of oxidative stress (Figure 2A), activation of the apoptotic cascade within endothelial and stromal cells (Figure 2B), and degeneration of the syncytiotrophoblast compared to those taken from the central region.[39,41]

Consequently, villi in the periphery and over the superficial pole of the chorionic sac undergo regression and the intervillous space narrows (Figures 2C and 3). Clumps of shrunken, darkly staining syncytiotrophoblastic nuclei are shed from the villi (Figure 3B), whereas the cytotrophoblast appears healthy (Figure 3D). Cytotrophoblast cells that morphologically resemble extravillous trophoblasts appear to migrate into the fibrinous mass that enmeshes the villi (Figure 3C). At the ultrastructural level, degeneration of the syncytiotrophoblast and of stromal and endothelial cells is apparent (Figure 3D). As a result, all that remains of the villi are the avascular collagenous cores, referred to as 'villous ghosts'. This regression transforms the chorion frondosum into the smooth chorion, or chorion laeve, and the developing discoid placenta. There is no clear boundary between the regressing villi and the decidua capsularis, and no remnants of the cytotrophoblastic shell. The decidua capsularis appears largely degenerate with a massive infiltration of

FIGURE 2
Oxidative stress and apoptosis in peripheral villi during villous regression



(**A**) Immunohistochemical staining for hydroxynonenal, a marker of oxidative stress, is more inetense in villi sampled from the periphery of a 10-week gestational age placenta compared to those from the central region. (**B**) Immunofluorescence for active caspase 3, the mediator of apoptosis, is more intense in peripheral villi, in particular within the stromal core, than in central villi. (**C**) Diagram of the gestational sac at 8 to 9 weeks showing how inflow of maternal arterial blood (arrows) starts in the peripheral (P) regions of the placenta where plugging of the spiral arteries is least extensive. Localized oxidative stress induces apoptosis and degeneration that are thought to contribute to villous regression and formation of the placental membranes. A and B modified from Burton G.J. et al[39] and C modified from Jauniaux E. et al.[40]

AC, amniotic cavity; *C*, central region under the cord insertion; *D*, decidua; *M*, myometrium; *SYS*, secondary yolk sac.

maternal polymorphonuclear neutrophils, characteristic of necrosis (Figure 3B).

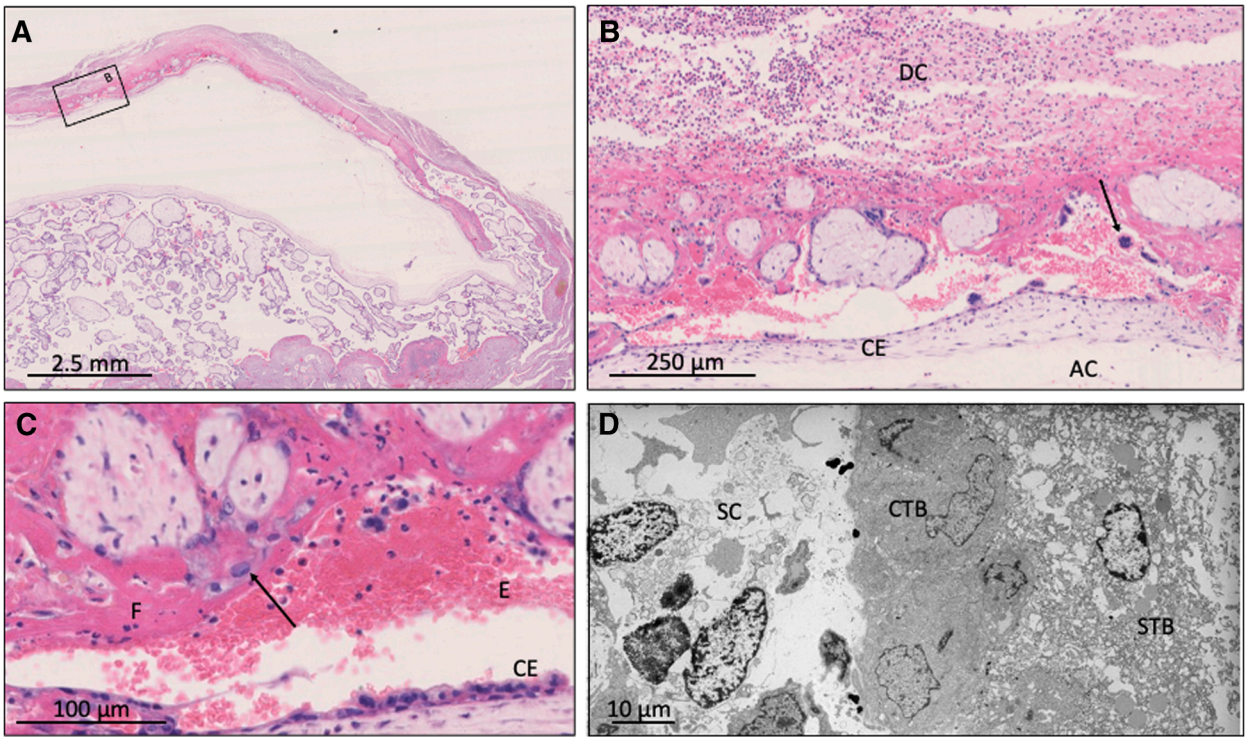
Early in the second trimester, the uterine cavity is obliterated when what remains of the decidua capsularis comes into extensive contact with the decidua parietalis lining the opposite wall of the uterus (Figure 4A). The membranes are extremely attenuated where they are not yet apposed to the decidua parietalis (Figure 4B and C), consisting of a thin layer of extraembryonic mesoderm, a single layer of chorionic epithelial cells, scanty villous ghosts embedded in fibrinoid, and a thin layer of residual degenerating decidual cells on the outer surface (Figure 4C). The uterine epithelium cannot be identified. By comparison, where the membranes are in contact with the decidua parietalis, the chorionic epithelium appears healthier, is several cell layers thicker, and is separated from the decidual cells by a thin band of fibrinoid (Figure 4D). The margins of the placental disc are clearly defined by this stage through fusion of the chorionic and basal plates (Figures 4A and B).

By 20 weeks of gestation, the membranes have taken on their mature form (Figure 5A and B). The chorionic epithelium consists of a compact layer of cytotrophoblast cells 5 to 10 cells thick supported by a basement membrane, under which is a layer of extraembryonic mesoderm. The cytotrophoblast cells show no evidence of migration into the decidua parietalis. Villous ghosts are embedded in the epithelium especially near the margin of the placental disc. The amnion is closely approximated to the inner layer of the chorionic epithelium, but has not yet fused.

Unresolved questions

The periphery-center pattern of onset of the maternal arterial circulation to the placenta and subsequent locally high levels of oxidative stress, apoptosis, and necrosis provides a mechanistic explanation for villous regression (Figure 2C).[39,41] Identical features to those of villous regression are observed in villous tissue from cases of missed miscarriage that have been retained in utero for several days after fetal demise, reinforcing this observation.[42] Onset of the maternal circulation is both precocious and spatially disorganized in these cases,[41] due to deficient development of both the cytotrophoblastic shell and plugging of the spiral arteries.[43] The

FIGURE 3
Villous regression toward the end of the first trimester



(**A**) Low-power photomicrograph at 8 weeks gestational age (CRL 15 mm). The intervillous space still extends up the lateral aspect of the chorionic sac but is virtually obliterated over the superficial pole. (**B**) Higher-power view of villi over the superficial pole. Regressing villi are enmeshed in maternal erythrocytes and a mass of fibrin-type fibrinoid. The syncytiotrophoblast layer is degenerate, with clumps of pyknotic nuclei being shed (arrow). The cytotrophoblast shell is no longer present and the fibrinoid is in direct contact with the decidua capsularis (DC) which shows extensive necrotic changes and polymorphonuclear neutrophil infiltration. The chorionic epithelium (CE) is a single layer of trophoblast cells supported by a layer of extraembryonic mesoderm. (**C**) Villous remnants enmeshed in the fibrinoid (F) are devoid of a syncytiotrophoblastic covering and only the collagenous stromal cores remain. Cells resembling extravillous trophoblast (arrow) appear to be migrating away from the cores. The chorionic epithelium (CE) is 1 to 2 cells thick. (**D**) Transmission electron micrograph showing degeneration of the syncytiotrophoblast (STB) and cells of the stromal core (SC). By contrast, the cytotrophoblast cells (CTB) appear healthy. Stain **A**–**C**, hematoxylin and eosin.

AC, amniotic cavity; *CRL*, crown rump length; *E*, maternal erythrocytes.

villous regression that occurs during the formation of the membranes and in early pregnancy failure are therefore 2 aspects of the same oxidative-induced phenomenon, the former physiological and the latter pathological.

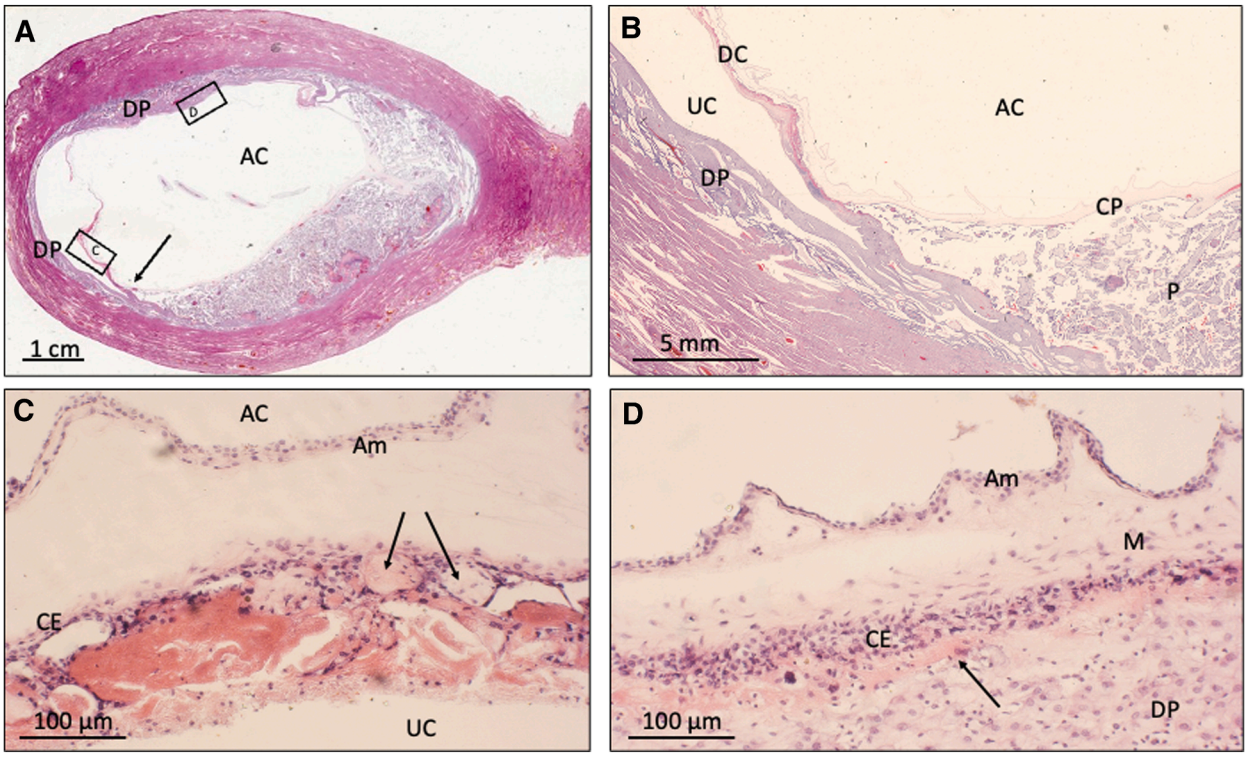
An intermediate state exists in cases of fetal growth restriction associated with deficient spiral artery remodeling. The placenta often takes on a globular shape, characterized by only a small attachment to the uterine wall and an increased thickness.[44–46] The normal tapering margins of the placental disc are lost, which is thought to reflect excessive villous regression secondary to precocious onset of maternal blood flow in the periphery of the early placenta.[9,39,47] This concept is difficult to test, and further prospective imaging studies at the time of onset of the maternal circulation are required. Circumstantial support comes, however, from the finding of twice the number of villous ghosts at a standardized distance from the placental margin in early-onset preeclampsia associated with fetal growth restriction compared to age-matched samples from normotensive preterm deliveries.[48] We interpret this finding as reflecting excessive regression rather than increased proliferation, as suggested by the authors.

Despite this advancement in our understanding of the mechanism of villous regression, several aspects of the formation of the membranes remain unresolved:

What is the cause of the necrotic changes in the decidua capsularis toward the end of the first trimester?

Previous classical studies have described how the decidua capsularis becomes stretched and thinned during the second trimester.[49,50] The maternal blood

FIGURE 4
The membranes during the early second trimester



(**A**) Low-power photomicrograph at 13.5 weeks of gestational age (CRL 73 mm). The intervillous space is sealed at the margin of the placental disc through fusion of the chorionic and basal plates (arrowed). The membranes are extensively, but not completely, apposed to the decidua parietalis (DP). (**B**) Higher power view of the margin of the placental disc, illustrating the union of the decidua parietalis (DP) and decidua capsularis (DC). At their union, both are covered by an epithelium, confirming the space between the 2 is the uterine cavity (UC) and not a processing artefact. (**C**) Higher-power view of the area denoted by the box labeled C in A. The decidua capsularis is extremely thin and necrotic, and there is no uterine epithelium. The chorionic epithelium is a single layer of cells and the collagenous cores of regressing villi (arrows) are enmeshed in fibrinoid. The amnion (Am) has not fused with the chorion. (**D**) Higher-power view of the area denoted by the box labeled D in A where the decidua capsularis has fused with the decidua parietalis (DP). The chorionic epithelium (CE) is here several cell layers thick, and separated from the decidua parietalis by remaining fibrinoid (arrow). The decidua parietalis shows no sign of neutrophil infiltration. The amnion (Am) is closely apposed to the chorionic epithelium, separated by a layer of extraembryonic mesoderm (M). Stain **A**—**D**, hematoxylin and eosin.

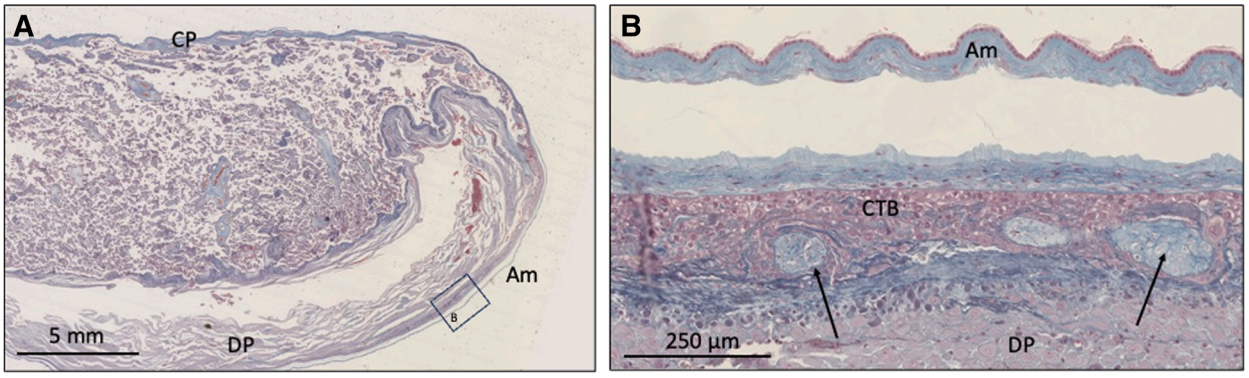
AC, amniotic cavity.

supply to the decidua capsularis is thought to be compromised as the vessels become compressed as they pass over the enlarging gestational sac.[50] The capsularis has been described as taking on a mottled appearance with variable degrees of congestion, hemorrhage, and tissue necrosis.[51] Our observation of an extensive infiltration of polymorphonuclear neutrophils is also consistent with ischemic necrosis,[52] but further studies are needed for confirmation. The uterine epithelium appears to be invariably lost and at some points the focal necrosis may be so extensive that the outer surface of the smooth chorion is exposed to the uterine cavity.[17,53] The necrotic changes mean that the decidua capsularis does not contribute significantly to the formation of the definitive membranes, nor can it provide support to retain the gestational sac in situ, which is largely dependent on the tensile strength of the amnion.[17]

What is the source of the cytotrophoblast layer in the definitive membranes?

The mature membranes consist of a layer of cytotrophoblast cells 5 or more cells thick, yet these cells cannot arise from the cytotrophoblastic shell as this disappears during the first trimester (Figure 3).[26] Instead, they must originate from the chorionic epithelium along with cytotrophoblast cells that have migrated from the regressing villi. This is supported by recent single-cell RNA sequencing comparing cytotrophoblast cells isolated from villi and the smooth chorion during the second trimester. A progenitor common to both locations was identified, although their respective locations are not yet known.[54] In the smooth chorion, there is no differentiation toward syncytialization but upregulation of transcription

FIGURE 5
The membranes mid-pregnancy



(**A**) Low-power view of a separated placenta at around 20 weeks of gestational age (CRL 140 mm). The membranes have become folded under the basal plate, and consequently the normal order of the amnion (Am) and decidua parietalis (DP) is reversed. (**B**) Higher-power view of the area denoted by the box labeled **B** in **A**. The cytotrophoblast (CTB) of the chorionic epithelium is now multilayered and surrounds the collagenous remnants of former villi (arrowed). The fibrinoid present earlier has organized into bundles of collagen fibers lying against the decidua parietalis (DP).

Am, amnion; *CP*, chorionic plate.

factors (KLF4 and YAP1) consistent with a stratified epithelial fate with features reminiscent of the skin barrier.[54] Cytotrophoblast cells of the smooth chorion contain higher levels of HIFl-a response genes and are more resistant to oxidative stress and hypoxia than other placental cell types.[38] This may account for their resistance to the necrosis that affects other cell types in the decidua capsularis. However, it appears that contact with the decidua parietalis is necessary to stimulate proliferation of the cells within the chorionic epithelium; the signals are likely to be the better supply of oxygen, nutrients, and growth factors, including insulin-like growth factor 1[48] and epidermal growth factor,[55] that apposition provides. This means that the development of the chorionic epithelium may be responsive to levels of pregnancy-associated plasma protein A, which regulates availability of insulin-like growth factor 1. Levels of pregnancy-associated plasma protein A are lower in all the GOS,[56] including PPROM.[57]

What mechanisms underlie the heterogeneity of cytotrophoblast cells within the smooth chorion?

Increasing evidence, including single-cell RNA sequencing, indicates that the cytotrophoblast cells within the membranes are transcriptionally and functionally different from those within the placental villi.[58] Some display an extravillous phenotype because they express its characteristic marker human leukocyte antigen-G, yet all merely abut the decidua parietalis and show minimal or no migratory tendency.[53] Approximately, 20% of the cytotrophoblast cells in the smooth chorion are cycling, confirming earlier reports based on incorporation of ^{3}H-thymidine.[59] These are located principally in the basal layer, close to the amnion, but exit from the cell cycle with differentiation equivalent to villous cytotrophoblast and extravillous trophoblast is not seen. Increased expression of interferon-induced transmembrane proteins important for defense against pathogens, and in addition reported to inhibit syncytialization, is also seen.[54] There is a further distinct resident population more prominent in the upper layers near the decidua parietalis that uniquely express the keratin KRT6, not found in villi. In addition, the cytotrophoblast cells in the smooth chorion express genes that encode extracellular matrix proteins, *COL5A1* and *LAMA3*, that might provide structural integrity and help prevent rupture. Intriguingly, spatial transcriptomics have revealed that in PPROM and PTL, the cytotrophoblast and amniotic epithelial cells show increased expression of genes associated with cellular reorganization-associated signals, characteristic of cells attempting to maintain membrane homeostasis under strain.[60]

Whether these differences warrant classification of chorionic cytotrophoblast cells as a separate subpopulation of trophoblasts distinct from villous cytotrophoblast cells remains to be decided. To date, only one single-cell RNA sequencing study comparing the 2 has been performed early in gestation when the membranes are forming. Further studies are required, along with spatial transcriptomic analyses to shed light on the regional heterogeneity in the physical properties that exist over the surface of the membranes.[61]

Rupture of membranes

Biomechanical studies reveal that the strength of the membranes is principally derived from the amnion and associated collagen fibers, primarily collagens I and III. By comparison, the choriodecidual layer is weak and the first to rupture in either term deliveries or cases of PPROM. A process of collagenolytic remodeling of the extracellular matrix mediated by matrix metalloproteinase enzymes is therefore a key antecedent to normal rupture, and may be stimulated by increases in uterine pressure and

stretching of the membranes as gestation advances.[61,62] The proinflammatory cytokines tumor necrosis factor alpha and interleukin (IL) 1ß cause equivalent activation of matrix metalloproteinase-9 and suppression of its tissue inhibitors.[61] These cytokines may mediate the remodeling in cases of PPROM, as they are induced by oxidative stress, infection, and many of the other conditions implicated in the causation of PPROM.[63,64]

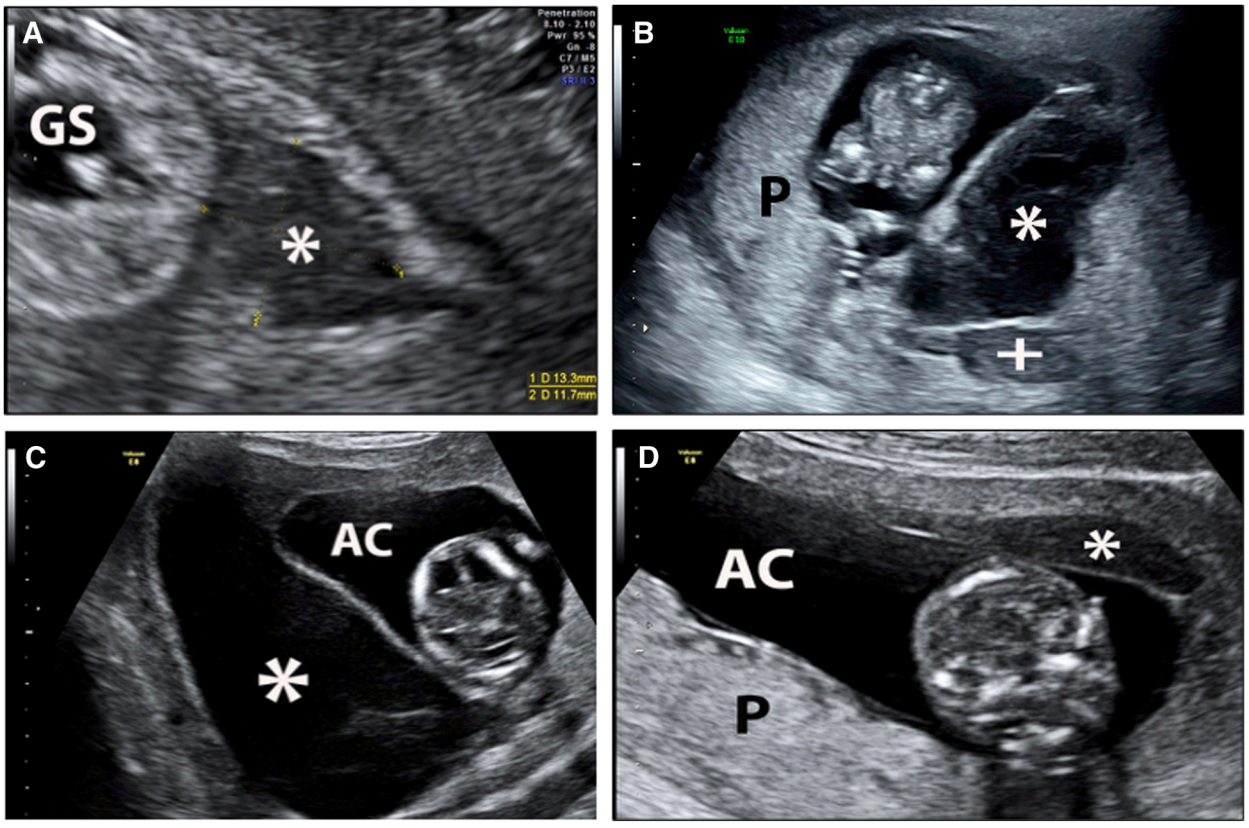
Relationship of preterm premature rupture of the membranes to spiral artery remodeling

Deficient spiral artery remodeling has been associated with both PPROM and PTL,[65,66] and although the causality is harder to determine than for other GOS, such as fetal growth restriction, we propose there are at least 2 possible mechanisms.

First, deficient spiral arterial remodeling could be a proxy for poor development of the cytotrophoblastic shell, and hence weakening of the uteroplacental interface during early pregnancy. Incomplete remodeling will lead to less fibrinoid being deposited in the arterial walls and hence a weaker seal with Nitabuch's stria and the developing basal plate, increasing the risk of hemorrhage. Around 15% of pregnant patients present with a 'threatened miscarriage' in early pregnancy, which may include vaginal bleeding, a closed cervix, and a live fetus.[67] The outcome depends on the gestational age of bleeding; if less than 7 weeks, the risk of further complications is small,[68] whereas after 7 weeks, threatened miscarriage is associated with poor obstetric outcomes and ~10% risk of complete pregnancy loss.[67,69,70] The most common ultrasound finding is a subchorionic hematoma detaching the membranes from the uterine wall close to the edge of the placenta (Figure 6). The echogenicity of the hematoma varies according to the timing of the bleeding; a recent lesion shows increased echogenicity that decreases with time to become sonolucent after 10 days (Figure 6B and C).

There is no direct link between the size of a subchorionic hematoma and

FIGURE 6
Ultrasound views of subchorionic hematomas at different gestational ages and different stages of evolution



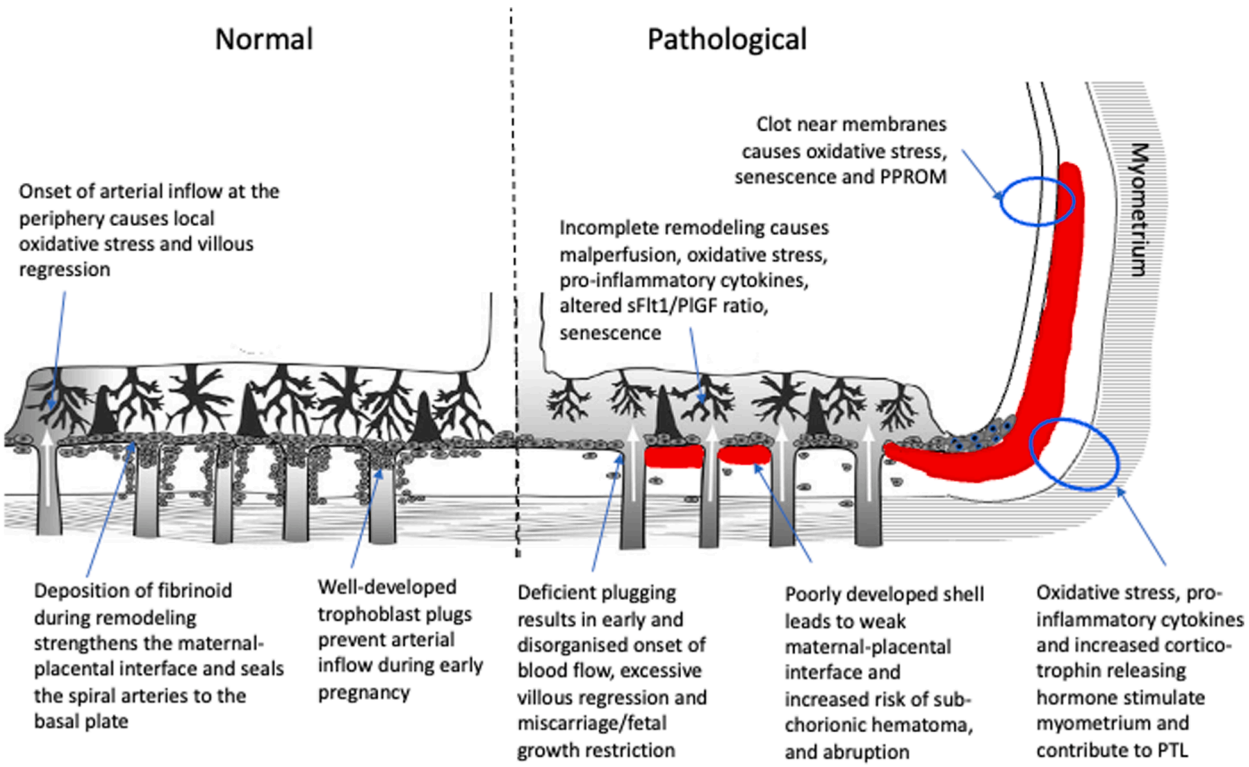
(**A**) Transvaginal ultrasound at 6 weeks of gestation showing a recent subchorionic hematoma (*). (**B**) Transabdominal scan showing large old subchorionic hematoma (*) and small recent one (+) at 12 weeks of gestation. (**C**) Transabdominal scan at 12 weeks of gestation showing a large old hematoma (*) 3 weeks after the bleeding episode. (**D**) Transabdominal scan at 14 weeks of gestation showing a small recent hematoma (*) 48 hours after the bleeding episode.

AC, amniotic cavity; *GS*, gestational sac; *P*, placenta.

pregnancy outcomes, but if the hematoma extends to the utero-placental interface at 7 to 9 weeks of gestation and ruptures the anchoring villi securing the gestational sac to the decidua, a complete miscarriage results.[67] Overall, patients with a first-trimester threatened miscarriage have ~2x increased risk of further complications including PPROM.[12,71,72] Conversely, 43% of placentas delivered prematurely display hemosiderin deposits characteristic of previous hemorrhage in the decidua basalis or membranes, compared to <1% of term deliveries.[73] The presence of a subchorionic hematoma between the uterine wall and the membranes will induce local oxidative stress with secondary tissue damage (Figure 7). High levels of oxidative stress could induce cell death through apoptosis, and disruption of iron metabolism also stimulates ferroptosis.[74] There are many risk factors associated with preterm birth,[75] all possibly operating through a final common pathway by inducing chronic oxidative stress, weakening the membranes, and releasing inflammatory factors.[16,63,76,77]

Second, failure to fully remodel the arteries may contribute to an overall increase in placental oxidative stress by increasing placental malperfusion.[8,78] As in cases of PTL with intact membranes, the placental villi display histologic evidence of maternal vascular malperfusion.[79] Circulating markers of oxidative stress are elevated,[80] and immunohistochemical and biochemical markers of senescence are often increased in the membranes and amniotic fluid.[81] Oxidative stress activates a number of signaling pathways within the villous syncytiotrophoblast, culminating in the secretion of proinflammatory factors, such as tumor necrosis factor alpha, IL-1α, IL-1ß, IL-6, IL-8, and cell-free fetal DNA.[82,83] Additional proinflammatory cytokines may be released through the induction of cell senescence, including IL-1ß, IL-6, and IL-8.[81] These factors may trigger sterile inflammation within the myometrium, stimulating contractions and PTL (Figure 6). Stress also promotes secretion of corticotrophin-releasing hormone by the syncytiotrophoblast into the maternal circulation, and levels are increased in various of the GOS.[84,85] Corticotrophin-releasing hormone has been implicated in the timing of parturition[86] and provides another pathway by which placental malperfusion could lead to PTL.[64]

FIGURE 7
Diagrammatic representation of how failure of impoverished formation of the cytotrophoblastic shell during early pregnancy may lead to the GOS



Adapted from Burton G.J. et al[13] with permission.

GOS, great obstetrical syndromes.

In both scenarios, differences in antioxidant defenses due to genetic variations, dietary insufficiencies, cigarette smoking, obesity, and environmental pollutants may exacerbate the situation and render individuals at a greater risk of PPROM and PTL.[16] These concepts are difficult to test, however. As imaging techniques continue to improve, it may become possible to visualize aspects of onset of the maternal circulation, villous regression, and formation of the membranes in greater detail. If so, prospective studies of the importance of subchorionic hematomas and other aberrations of the utero-placental interface for obstetric outcome might be informative.

Contribution of endometrium to preterm premature rupture of the membranes

Formation of the cytotrophoblastic shell occurs early in the first trimester, when placental development is stimulated by histotrophic nutrition derived from the decidua prior to onset of the maternal placental circulation.[87] This realization has emphasized the importance of the dialog between the placenta and the endometrium/decidua during the periconceptional period, yet little is known about what constitutes a healthy functional endometrium or the composition of histotroph during early pregnancy. In domestic species, there is strong evidence that the placenta stimulates its own development through a signaling loop with the endometrium and uterine glands, upregulating the expression of growth factors and nutrients.[88–90] Data from endometrial organoids suggest that the same is likely to be true in humans.[91] Prolactin appears to play a particularly important role, and in humans is secreted by the decidua rather than the trophoblast.[92]

Increasing evidence associates poor decidualization with the development of preeclampsia and other adverse outcomes.[93–96] This association is highlighted by comparison of endometrial preparation during in vitro fertilization procedures; replacement of frozen embryos in natural cycles is associated with better outcomes, including less preterm birth, than in hormone replacement cycles.[97,98] The effect may operate through various pathways including the absence of the corpus luteum and its additional secreted products apart from progesterone. Failure of normal decidualization could also result in deficient histotrophic stimulation of early trophoblast proliferation, and aberrant recruitment and differentiation of the decidual immune cells, particularly the distinctive uterine Natural Killer cells that recognize extravillous trophoblasts and alter their functions.[99,100] The ability to derive endometrial organoids responsive to early pregnancy hormones and endometrial stromal cells noninvasively from menstrual fluid presents opportunities to assess endometrial function preconceptionally.[101] The capacity for decidualization, the responsiveness of the glands to hormonal cues from the decidua and trophoblast, the composition and bioactivity of the histotroph, and the uterine Natural Killer profile could all be tested. Data could be correlated prospectively with pregnancy outcome, aiding the development of new therapeutic interventions. Ensuring endometrial function is optimal prior to conception through lifestyle or therapeutic interventions may thus improve obstetric outcomes.

Clinical implications

The importance of both the cytotrophoblastic shell and the smooth membranes for successful pregnancy is greatly underestimated. However, the shell is a transient structure that exists only for the first few weeks after implantation and is inaccessible for study. An incomplete and discontinuous shell is observed in 70% of spontaneous miscarriages, independent of the fetal karyotype, and is associated with precocious and spatially disorganized onset of the maternal placental circulation.[36,43] We suggest that less severe deficiencies might weaken the utero-placental interface, increasing the risk of subchorionic hematoma, and also lead to incomplete plugging and remodeling of the spiral arteries. Consequently, onset of the maternal circulation and villous regression is likely to be abnormal, and associated with placental malperfusion and PPROM later in pregnancy.

Monitoring villous regression in vivo and testing this concept is currently not possible. Apart from subchorionic hematomas, events taking place during formation of the membranes occur at too fine a scale to be resolved by current imaging techniques. Even if it becomes possible to visualize temporo-spatial variations in onset of the maternal circulation in the future, repeated scans would be needed to test associations with villous regression, which would require ethical permission and resource implications in a clinical setting. Circulating biomarkers offer a potentially attractive alternative, but a recent systematic review that evaluated more than 50 biomarkers arising from 14 studies that sampled maternal blood between 6 and 14 weeks of gestation showed only weak and inconsistent associations with PPROM.[102] Further studies of C-reactive protein, placental growth factor, and soluble fms-like tyrosine kinase 1 are recommended.[102] Placental-specific microRNAs may be another potential marker given the volume of trophoblast degeneration associated with villous regression.

Biomarkers are likely to be more successful later in pregnancy once the pathophysiology in the membranes becomes established. The soluble fms-like tyrosine kinase 1/placental growth factor ratio is well established as an indicator of trophoblastic stress induced by maternal vascular malperfusion. Classifiying the GOS depending on the presence or absence of placental histological changes at delivery indicative of malperfusion may enable the ratio to be more informative of the pathophysiology earlier in gestation.[103] In addition, placental exosomes hold much promise as a liquid biopsy for diagnosis of placental pathologies.[104,105] More specifically, exosomes released from amniotic epithelial cells display a unique protein signature in cases of PPROM compared to PTL and term deliveries.[106] The exosomes are capable of crossing to

GLOSSARY

Chorionic cytotrophoblast cells: the subpopulation of cytotrophoblast cells that form the amniochorion
Cytotrophoblast cells: a progenitor population of trophoblast cells that can differentiate along different lines
Cytotrophoblastic shell: a transient multilayered aggregation of cytotrophoblast cells that forms the maternal—fetal interface in the first weeks after implantation and gives rise to the extravillous trophoblasts and the trophoblastic plugs that occlude the spiral arteries during the first trimester
Extravillous trophoblast: a subpopulation of cytotrophoblast cells that migrate beyond the confines of the placenta into the decidua where they are involved in remodeling of the maternal spiral arteries
Human Leukocyte Antigen-G: a nonclassical class I histocompatibility antigen that is expressed by, and a marker of, extravillous trophoblasts
Maternal vascular malperfusion: abnormal maternal arterial bloodflow to the placenta resulting from deficient remodeling of the uterine spiral arteries during early pregnancy and causative of placental oxidative stress
Oxidative stress: an imbalance between the production of pro-oxidant species and the antioxidant defenses that can lead to indiscriminate damage to biomolecules and induce apoptosis and cell death
Subchorionic hematoma: a collection of blood between the chorion (free placental membranes) and the uterine wall
Syncytiotrophoblast: the outer epithelial covering of the placental villi formed by fusion of villous cytotrophoblast cells

the maternal side where their inflammatory cargo may contribute to the onset of parturition,[107] but potentially could also be isolated for diagnostic purposes. Equally, exosomes derived from the chorionic trophoblast may be informative of stress and senescence if unique markers can be identified, and further studies are required. ■

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000 Formation of the placental membranes and pathophysiological origin of associated great obstetrical syndromes

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