Preeclampsia: the role of persistent endothelial cells in uteroplacental arteries

Ivo Brosens, MD, PhD; Jan J. Brosens, MD, PhD; Joanne Muter, PhD; Patrick Puttemans, MD; Giuseppe Benagiano, MD, PhD

We explore the potential role of the endothelial lining of uteroplacental arteries in the pathogenesis of preeclampsia, a severe pregnancy disorder characterized by incomplete invasion of the uterine vasculature by extravillous trophoblast and angiogenic imbalance. In normal pregnancy, the endothelium disappears progressively from the uteroplacental arteries and is replaced by trophoblast and deposition of fibrofibrinoid structure, underpinning the so-called physiological transformation of uterine spiral arteries. We hypothesize that partial persistence of the endothelium, albeit injured, initiates a chain of events leading to the emergence of preeclampsia in 3 sequential stages. The first stage results in retention of the endothelium in uteroplacental arteries secondary to incomplete physiological transformation of the vessels. Consequently, the uteroplacental vessels are reactive to pathological cues, which drives local arteriopathy. The second stage starts with progressive reduction in uteroplacental blood flow, generating oxidative stress in the whole placenta, and heightened maternal inflammation in response to circulating trophoblastic debris. In the third stage, generalized endotheliosis causes systemic angiogenic imbalance, hypertension, and other clinical manifestation of preeclampsia.

Key words: endothelium, fetal growth restriction, hypoxia, oxidative stress, preeclampsia, trophoblast, uteroplacental arteries, vasoconstriction

Preeclampsia remains a leading cause of maternal and perinatal morbidity and mortality. It is characterized by new onset of hypertension and proteinuria at ≥20 weeks of gestation and involves several organs, including the kidneys, liver, and brain.[1]

Cardinal features of this disorder include incomplete physiological vascular remodeling in the placental bed and aberrant angiogenesis, the severity of which may determine clinical presentation.[2] Indeed, circulating levels of angiogenic and antiangiogenic proteins correlate well with disease severity, have a prognostic value, and may be useful in the triage of women with suspected preeclampsia.[3]

An important mechanism implicated in the pathogenesis of preeclampsia is defective deep placentation, characterized, among other features, by the persistence of the endothelium in uteroplacental spiral arteries. More than 30 years ago, Yanagisawa et al[4] presented unequivocal evidence that injured endothelial cells increase the contractile sensitivity of isolated vessels.

From the Faculty of Medicine, Catholic University of Leuven (Dr I. Brosens), and Life Institute for Fertility and Embryology (Dr Puttemans), Leuven, Belgium; the Division of Biomedical Sciences, Warwick Medical School, Coventry, United Kingdom (Drs J. Brosens and Muter); and the Department of Gynecology, Obstetrics, and Urology, Sapienza, University of Rome, Rome, Italy (Dr Benagiano).

Received Aug. 26, 2018; revised Jan. 11, 2019; accepted Jan. 31, 2019.

Dr Muter and Dr Brosens are supported by Tommy's National Miscarriage Research Centre.

The authors report no conflict of interest.

Corresponding author: Ivo Brosens MD, PhD. Ivo.brosens@med.kuleuven.be

0002-9378/$36.00

https://doi.org/10.1016/j.ajog.2019.01.239

Roberts et al[5] were among the first to reflect on the role of endothelial dysfunction in the placental bed and wrote, "Inasmuch as endothelial cell injury reduces the synthesis of vaso-relaxing agents, increases the production of vasoconstrictors, impairs synthesis of endogenous anticoagulants, and increases procoagulant production, these cells are likely to be implicated in the pathophysiology of preeclampsia."

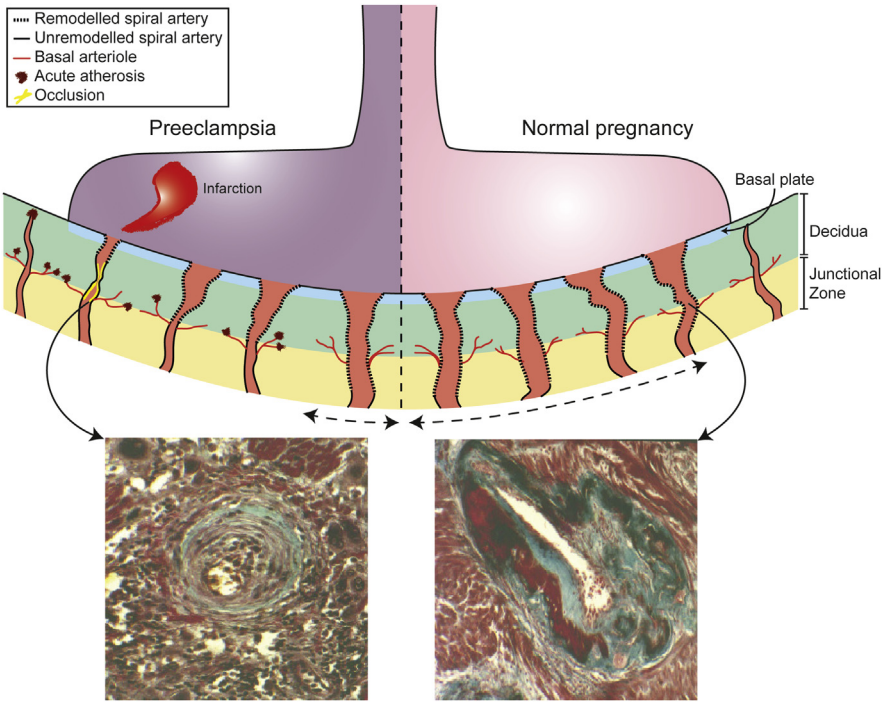
Redman and Sargent[6] stressed that the presence of the placenta is both necessary and sufficient to cause preeclampsia. They argued that placental microfragments are continuously shed into the maternal circulation as part of the physiological renewal of the syncytiotrophoblast. This placental debris in turn activates the maternal endothelium, either directly or indirectly, through the effects of proinflammatory mediators on peripheral blood granulocytes and monocytes, generating the systemic inflammatory response of normal pregnancy.

A glaring consequence of spiral artery disease and placental stress in preeclampsia is that the maternal burden of trophoblastic debris may be increased, more inflammatory, or both. Furthermore, maternal antiinflammatory defenses may be compromised by preexisting metabolic disorders, such as obesity, accelerating the clinical presentation of preeclampsia.

Koopmans et al[7] investigated microvascular endothelial function in women with fetal growth restriction and demonstrated abnormal endothelium-dependent vasodilation in nonobese, normotensive women with fetal growth restriction. While these observations support the role of endothelial cell dysfunction in fetal growth restriction, they also highlight that clinical manifestations of preeclampsia likely depend on the severity of the pathological stimulus, the ability to mount a compensatory response, or both.

The seminal studies from Furchgott and Zawadzki[8] demonstrated the obligatory role of endothelial cells in controlling vascular tone. In addition, endothelial inflammation and injury lead to leukocyte extravasation, thrombosis, and atherosclerosis[9-11] (ie, pathological features relevant to

FIGURE 1
Normal uteroplacental arteries and severe atherosclerotic lesion



The top panel depicts the uteroplacental arteries in normal pregnancy and preeclampsia. Physiological transformation of the spiral arteries in normal pregnancy encompasses both the decidual and junctional zone segments of the vessels. By contrast, spiral artery remodeling in preeclampsia tends to be confined to the decidual portion of the vessels, although fully transformed arteries can be present in the center of the placenta bed. Also depicted are atherosis of terminal basal and spiral arterioles in preeclampsia, an occlusive atherosclerotic lesion underlying a peripheral placental infarction, and unremodeled arteries outside the placental bed. The *dotted horizontal lines* indicate the extent of successful spiral artery remodeling in preeclampsia and normal pregnancy. The bottom panels show a severe atherosclerotic lesion in a junctional zone spiral artery at term (left panel, Masson's trichome stain, original magnification, ×112) vs a physiologically transformed placental bed artery (right panel, Masson's trichome stain, ×80).

Brosens. Persistent endothelium in preeclampsia. Am J Obstet Gynecol 2019.

the uteroplacental vasculature in preeclampsia).

Here we explore the evidence that implicates activated endothelial cells following incomplete spiral artery remodeling as key drivers of a chain reaction that ultimately results in the clinical syndrome of preeclampsia.

Spiral arteries in pregnancy

In pregnancy, 3 types of spiral arteries are distinguished.[12] First, there are large, tortuous funnel-shaped spiral arteries, which are the de facto vessels supplying the intervillous space. They undergo physiological changes and are visible to the naked eye in cesarean hysterectomy specimens when the placenta is carefully removed from the placental bed, although, because of their size and distended state, they can be mistaken for veins. Also, the severed terminations of these vessels adherent to the basal plate of the placenta can be distinguished, albeit with some difficulty, from veins.

Second, there are the basal arteries, seen only on histological sections, which are small branches, measuring approximately 100 μm in diameter, of the radial or spiral arteries; they ramify in the inner myometrium (also termed the junctional zone) and terminate in the decidua basalis but do not open into the intervillous space.

Third, there are the spiral arteries outside the placental bed, again seen only on histology; they do not undergo physiological changes but terminate in the decidua vera or parietalis. These vessels play no part in the blood supply to the placenta itself but may nourish the chorionic aspect of the membranes. The extent of physiological changes in the arteries of the placental bed differs between normal and preeclamptic pregnancies as depicted schematically in Figure 1.

Physiological changes in uteroplacental arteries

Deep hemochorial placentation involves extravillous trophoblast invasion of the decidua and the myometrial junctional zone[13] and requires physiological transformation (ie, remodeling) of the uteroplacental spiral arteries in the placental bed.[14] Physiological transformation, which starts in the decidua and extends into the junctional zone segment of the vessels, results in complete loss of the arterial wall, including the endothelium, the intima, and the musculoelastic structures. Upon the loss of the original arterial structure, a new vessel wall is formed by the deposition of fibrinoid material and fibrous tissue. Ultimately, progressive remodeling of ~50 spiral arteries into large sinusoidal vessels makes it possible for the placenta to meet the metabolic demands of the growing fetus throughout pregnancy.[15]

Physiological spiral artery remodeling

The action of trophoblast on the wall of uteroplacental arteries was first investigated in 12 placental bed biopsies obtained by hysterotomy or hysterectomy between the 14th and 22nd week of gestation.[16] In early pregnancy, extravillous trophoblast cells differentiate from the outer layer of the cytotrophoblastic shell, move retrogradely into the lumen of endometrial capillaries and the terminal spiral arterioles, and erode and infiltrate the subendothelial space of the tunica intima of the maternal arteries.

Expression of surface-bound complement component 1q on decidualizing

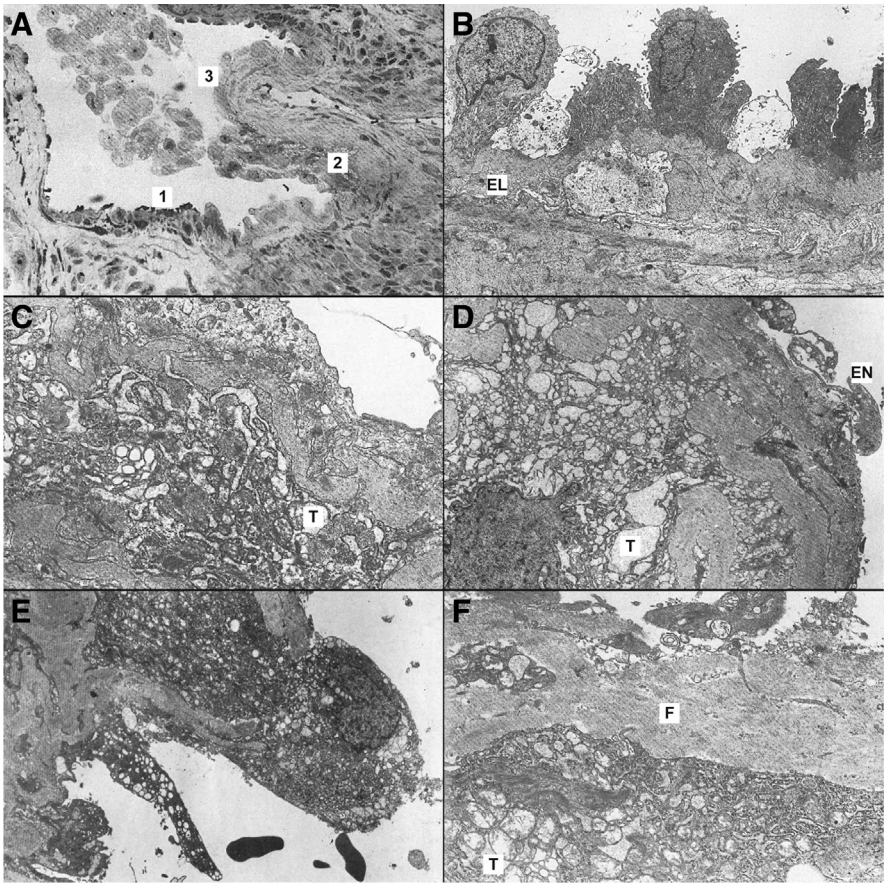
endothelial cells has been shown to promote adhesion of endovascular trophoblasts and their migration through the interendothelial cell junctions of spiral arteries.[17] This process creates defects in the endothelial lining, leakage of plasma into the vessel wall, disruption of the internal elastic lamina, and some fibrinoid degeneration of the media. While intramural trophoblast cells do not appear to infiltrate the media, the altered intima is overgrown by endothelium.

Remarkably, disruption of the endothelial lining is seldom accompanied by deposition of platelets and fibrin and generally does not elicit a thrombotic reaction. As suggested by Jogee et al,[18] this could be accounted for by local prostacyclin production by intramural trophoblast cells. Nevertheless, even normal pregnancies, mural and even occlusive thrombosis are occasionally encountered in arteries at the periphery of the placental bed, although thrombotic and inflammatory responses to vessel damage, pivotal characteristics of pathological processes, are kept within bounds.

In the vessel wall, trophoblast cells are always surrounded by and separated from the other cellular constituents by a band of fibrinoid material. Ultrastructural observations support the hypothesis that this intercellular fibrinoid material is partly the result of apocrine trophoblast secretions.[19] These physiological changes account, at least in part, for the remarkable luminal distension of uteroplacental arteries during the second and third trimesters of pregnancy.

Away from the vessels, intimate contact between trophoblast and decidua in the basal plate is accompanied by cellular degradation, necrosis, and fibrinoid deposition. As pregnancy advances, extravillous trophoblast cells penetrate the decidua to reach the junctional zone. A striking feature is that the cellular degeneration observed in the decidua is virtually absent in junctional zone myometrium, although intimate interactions between maternal and fetal cells are maintained. In the junctional zone, trophoblastic cells appear as multinuclear giant cells. Resident smooth muscle cells seem remarkably unperturbed by the presence of these fetal cells and tissue necrosis is absent.

FIGURE 2
Electron microscopy of transforming spiral arteries



Electron microscopy of transforming spiral arteries during midpregnancy showing the destruction of the endothelial lining. **A,** Epon-embedded section, 1 μm thick, showing a spiral artery with the 3 different modifications during the second trimester (12—20 weeks) of pregnancy (original magnification, ×160). **B**, Translucent cytoplasmic fragments are observed in between hypertrophic endothelial cells as well as fenestrations in the interstitial EL (×5400). **C**, Trophoblastic cell (T) in the tunica intima of a vessel in the early stages of physiological remodeling with intact overlying endothelium. **D**, EN disruption overlying a trophoblast cell (×5400). **E**, A large intraluminal trophoblastic cell continuous with luminal cells and loss of maternal endothelium (×14,400). **F**, A totally disrupted endothelium without evidence of thrombosis or fibrin deposition. A thick layer of F material overlies intimal T (×14,400). Adapted from De Wolf et al. (1980).[16]

EL, elastic lamina; *EN*, endothelial; *F*, fibrinoid; *T*, trophoblast.

Brosens. Persistent endothelium in preeclampsia. Am J Obstet Gynecol 2019.

Endothelial disintegration

Endothelial changes in uteroplacental arteries are rarely observed in placental bed biopsies for the obvious reason that the endothelium progressively disappears during the physiological transformation in pregnancy.[20] In a detailed study of the ultrastructure of placental bed spiral arteries in early pregnancy, De Wolf et al[21] concluded that trophoblast cells replace the maternal endothelium in the decidual portions of the spiral artery in normal pregnancy.

At the beginning of the second trimester, the uteroplacental spiral arteries harbor trophoblastic cells in the intima and the overlying endothelium is disrupted (Figure 2). The remarkable

TABLE 1
Ultrastructure of placental bed spiral arteries between 8 and 18 weeks of gestation

Variables	Gestation (wks) 8	10	16–18
Number of arteries	85	132	69
Ultrastructural characteristics			
Swollen endothelium	13	28	4
Intimal vacuolation	40	70	81
Medial basophilic cells	3	24	6
Perivascular trophoblast	19	33	59
Endovascular trophoblast	0	1	32
Disruption of the media			
0, none	55	18	10
1, mild	27	63	33
2, severe	18	17	57

Adapted from Pijnenborg et al.[22] Note that a variety of morphological features can be found not only in different spiral arteries of the same placental bed but also in different segments of the same artery.

Brosens. Persistent endothelium in preeclampsia. Am J Obstet Gynecol 2019.

structural alterations in the wall of spiral arteries are preceded by an initial stage in which hypertrophied and focally overlapping endothelial cells line the vessel wall. These endothelial cells contain a great number of ribosomes, a well-developed rough endoplasmic reticulum, and many pinocytotic vesicles beneath the cell membrane. Translucent cytoplasmic fragments containing pinocytotic vesicles, as well as few organelles, are often found in between hypertrophied cells.[19] Based on morphological criteria, the granular and fibrillar material that lines the remodeled vessels are characteristic of fibrin, whereas the embedded cells are indistinguishable from trophoblasts.

It has also been suggested that part of the fibrinoid material is derived from the degeneration of trophoblastic cells in the arterial wall. At any rate, these structural modifications of the arterial wall are probably the direct consequence of invasion by trophoblast; they are more pronounced in the decidual compared with the junctional zone portion of the spiral arteries, although the mechanisms that drive remodeling are likely the same for both segments.

Pijnenborg et al[22] examined a collection of pregnant uteri, obtained between 8 and 18 weeks of gestation, part of a much larger collection held in the Department of Obstetrics and Gynecology at the University of Bristol (Bristol, United Kingdom). The material included 8 specimens at 8 weeks, 12 at 10 weeks, and 7 obtained between 16 and 18 weeks of pregnancy (Table 1).

The investigation focused on the pattern of endovascular trophoblast cell migration, which appears to occur in 2 waves: the first wave encompasses the decidual segments of the spiral arteries up to approximately 10 weeks of gestation, and the second involves the myometrial segments of the same arteries from 14 weeks onward. Outside the placental bed, endothelial swelling is rare, but intimal vacuolation is common and increases with gestational age as is also the case in placental arteries. Around 10 weeks, the endothelium is significantly more swollen inside compared with outside the placental bed.

In specimens obtained between 16 and 18 weeks of gestation, much of the endothelium is already replaced by endovascular trophoblast and disruption of the intima precludes reliable morphometric assessment of endothelial changes. Taken together, these observations indicate that the endothelium of uteroplacental arteries disappears progressively during the second trimester of a normal pregnancy.

Pathogenesis of preeclampsia

Roberts and Gammill[23] proposed more than a decade ago a 2-stage model of preeclampsia. Stage 1 involves reduced placental perfusion, which drives the fetal syndrome. Reduced placental perfusion, in some but not all women, is translated into stage 2, representing the maternal syndrome of preeclampsia. Based on our reappraisal of the role of persistent endothelium in the uteroplacental vasculature, as well as recent observations by numerous other investigators (Table 2), we propose that the clinical manifestations of preeclampsia are the result of disease progression through 3 sequential stages.

Stage 1: defective spiral artery remodeling and endothelial retention

Many decades ago while studying the role of the spiral arteries in the pathogenesis of preeclampsia, Brosens et al[24] were puzzled by the apparent lack of large uteroplacental vessels in the myometrial junctional zone of the placental bed of affected women. A review of placental bed biopsies and cesarean hysterectomy specimens from 300 normotensive and 58 preeclamptic pregnancies, including 22 cases of preeclampsia superimposed on preexisting essential hypertension, demonstrated that physiological changes in preeclampsia tend to be restricted to the decidual segment of the spiral arteries (Figure 1).[25]

Lack of remodeling of the junctional zone portion of the spiral arteries is commonly referred to as defective deep placentation.[14] Several hypotheses have been formulated to explain the pathogenesis of defective deep placentation, including impaired trophoblast invasion,[26-28] specific combinatory interactions between polygenic maternal killer immunoglobulin-like receptors

TABLE 2
Expanding the Roberts' hypothesis on the pathogenesis of preeclampsia[a]

Stage 1: endothelium activation in uteroplacental arteries
• Roberts et al (1989).[5] In the absence of physiological spiral artery changes, the endothelial lining likely persists and not only retains the capacity of vasoconstrictors production from the onset of pregnancy but also causes an increase with the growth of the uterine vascular capacity.
• McCarthy et al (1993).[52] Endothelium-dependent relaxation is impaired in the arteries of women with preeclampsia, but endothelium-independent relaxation is unaffected.
• Labarrere et al (2017).[34] Failure of spiral artery transformation is associated with interstitial extravillous trophoblast and arterial endothelial activation in the placental basal plate along with increased frequency of atherosis.
Stage 2: placental stress
• Seligman et al (1994).[53] Circulating nitrite levels are decreased in preeclampsia, suggesting that diminished nitric oxide synthesis contributes to the pathophysiological changes.
• Lyall et al (1996).[54] Increased serum concentrations of total nitrites, an index of nitric oxide synthesis, in the maternal and fetal circulations in preeclampsia may limit platelet aggregation or represent a compensatory response to improve blood flow.
• Ishihara et al (2002).[55] Decreased expression of B-cell lymphoma-2 protein may render syncytiotrophoblast more vulnerable to apoptosis in preeclampsia.
• Redman et al (2014).[56] Abnormal placental perfusion and stressed syncytiotrophoblast both contribute to the pathogenesis of early- and late-onset preeclampsia. But the early variant is caused by an extrinsic cause, defective placentation, whereas the late variant is due to an intrinsic cause, microvillous overcrowding, impeding intervillous perfusion and increasing intervillous hypoxia as placental growth.
• Burton and Jauniaux (2017).[57] Impaired formation of the cytotrophoblastic shell in response to a suboptimal endometrial environment in early pregnancy may compromise extravillous trophoblast differentiation, have an impact on the timing and spatial configuration of onset of the maternal arterial circulation and increase the risk of bleeding. Formation of intrauterine hematomas may act as a source of oxidative stress.
• Sultana et al (2018).[58] Accelerated cellular senescence in the placenta, characterized by permanent cell cycle exit and secretion of inflammatory mediators, contributes to the pathophysiology of preeclampsia and other obstetrical disorders.
Stage 3: angiogenic imbalance and clinical manifestations of preeclampsia
• Redman et al (1999).[59] Preeclampsia arises when a universal maternal intravascular inflammatory response to pregnancy decompensates, which may occur because either the stimulus or the maternal response is too strong. Thus, there is no specific cause for the disorder, which can be better considered as the extreme end of the range of maternal adaptation to pregnancy, and poor placentation is not the cause of preeclampsia but merely a powerful predisposing factor.
• Chaiworapongsa et al (2004).[49] Elevated concentrations of sVEGFR-1 correlate with the severity of preeclampsia.
• McKeeman et al (2004).[50] There is a definite association between elevated sFlt-1 concentrations and the onset of preeclampsia.
• Moore Simas et al (2007).[60] In women with a high-risk pregnancy, serum sFlt1 and its ratio with PGF is predictive of preeclampsia, although more studies are needed.
• Vaisbuch et al (2011).[61] Eclampsia is associated with higher circulating concentrations of sVEGFR-1 and soluble endoglin and lower concentrations of PGF, indicating a shared pathogenic pathway with preeclampsia.
• Agrawal et al (2018).[48] A meta-analysis and systematic review of the role of sFlt-1 and PGF ratio in the prediction of preeclampsia concludes that measuring such a ratio may help in decision making, treatment stratification, and better resource allocation.

PGF, placental growth factor; *sFlt-1*, soluble vascular endothelial growth factor receptor-1; *sVEGFR-1*, soluble vascular endothelial growth factor receptor-1.

[a] Only a limited selection of important studies was tabulated because of space limitations.

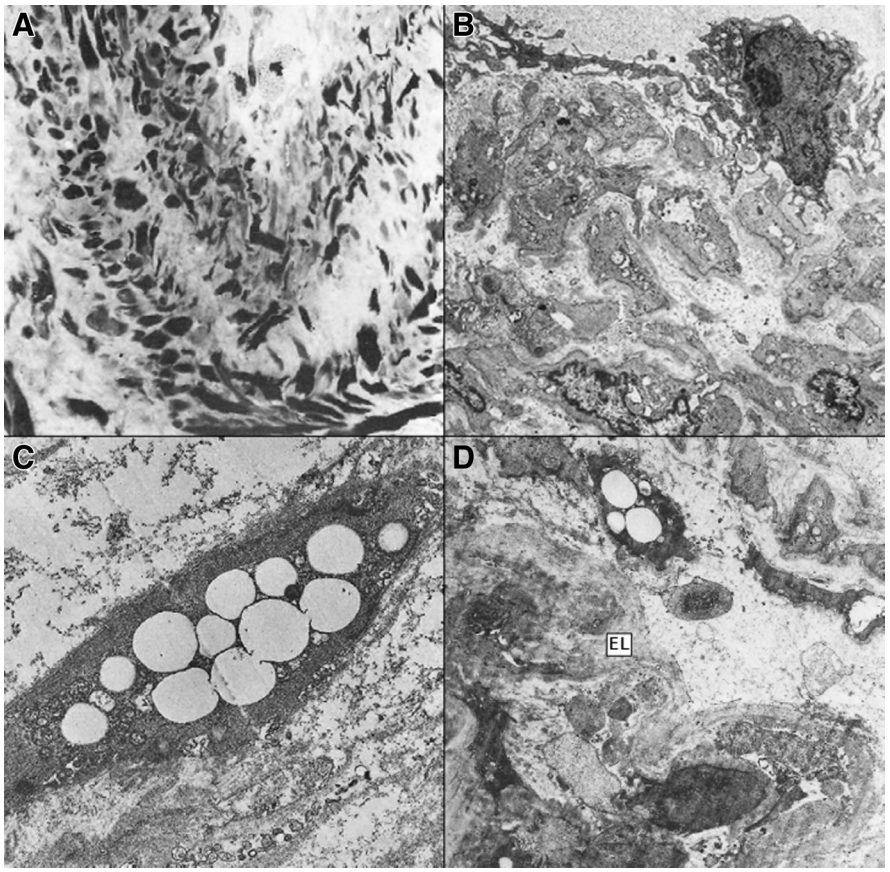
Brosens. Persistent endothelium in preeclampsia. Am J Obstet Gynecol 2019.

and fetal human leukocyte antigens,[29] lack of uterine preconditioning and impaired decidualization,[30-32] and pre-existing maternal metabolic and cardiovascular disease.[33]

Arterionecrosis is a common finding in the late stages of accelerated or malignant systemic hypertension; consequently, arterial lesions of systemic hypertension can be interpreted as a response to the hemodynamic disturbances of that condition.

Preeclampsia is also associated with a necrotic process in the uteroplacental spiral arteries as acute hypertension can provoke similar lesions in the maternal vessels of the pregnant uterus. This is due to the presence in all the segments of arteries and arterioles of areas with retained endothelium, intima, and musculoelastic wall (Figure 3). Consequently, these vessels retain the ability to respond to pathological cues, not only producing local arteriopathy but also generating vasomotor stimuli. Thus, the persistence of activated endothelial cells that release vasoconstrictive agents is likely responsible for accelerating the disease during the second trimester of pregnancy.

FIGURE 3
Electron microscopic analysis of placental bed biopsy



Electron microscopic analysis of placental bed biopsy obtained at cesarean delivery in women with preeclampsia. **A**, A deciduomyometrial artery in the placental bed (original magnification, ×620). **B**, Focal disruption of the endothelium and haphazard proliferation of myointimal cells in the tunica intima (×4500). **C**, Myointimal cell with a more advanced degree of fat accumulation. Note the 4 lower vacuoles are appearing to be fusing (×12,000). **D**, Atherosis showing proliferation of myointimal cells, one containing lipid and (bottom) medial necrosis. The internal El separating the intima from the media is partially disrupted and associated with deposits of electron-dense material (×6875). Adapted from De Wolf et al (1975).[21]

El, elastic lamina.

Brosens. Persistent endothelium in preeclampsia. Am J Obstet Gynecol 2019.

In line with these conjectures, Labarrere et al[34] demonstrated recently that impaired spiral artery remodeling in the placental basal plate is associated with endothelial activation, defined by intercellular adhesion molecule-1 expression along with increased frequency of spiral artery atherosis. Notably, severe atherosclerotic lesions in the deeper segments of the arteries can develop in preeclamptic pregnancies with a speed not observed outside the uterus as well as seemingly reverse spontaneously following pregnancy.

Sheppard and Bonnar[35] purported that physiological transformation of the uteroplacental arteries is not always restricted to the decidual segment in pregnancies complicated by preeclampsia or fetal growth restriction. Indeed, remodeled junctional zone arteries have been observed in cesarean hysterectomy specimens with placenta in situ from women with hypertensive disease, although they are invariably confined to the very center of the placental bed.[36]

Stage 2: placental oxidative stress

It seems logical to assume that failure to establish an adequate uteroplacental blood flow leads to relative hypoxia in trophoblastic tissue, thereby eliciting an oxidative stress response in the whole placenta. This phenomenon likely attenuates the invasiveness of trophoblast further and compromises placental villous angiogenesis. The final result is an abnormally reactive and poorly developed fetoplacental vasculature. Increased oxidative stress has a negative impact on vascular reactivity, blood flow, and the delivery to the fetus of both oxygen and nutrients.[37]

Failure of the physiological conversion of maternal spiral arteries also has important rheological consequences. Indeed, Burton et al[38] have shown that in the absence of the physiological conversion, blood will enter the intervillous space as a turbulent jet at rates of 1-2 m/sec, further compounding placental hypoxia. They speculated that turbulence damages the villous architecture and creates cystic lesions that are visible on ultrasound. Because the spiral arteries retain their smooth muscle layer in preeclampsia, they are vulnerable to spontaneous vasoconstriction and ischemia-reperfusion injury, leading to further oxidative damage and cell death.

Several investigators have focused on putative factors that may trigger oxidative stress pathways in the placenta. For example, circulating endothelin-1 levels are high in pregnancies complicated with preeclampsia, and, at least in vitro, endothelin-1 compromises trophoblast viability by increasing cellular oxidation.[39]

Maynard et al[40] reported that excessive placental production of the soluble Fms-like tyrosine kinase receptor-1 (sFlt-1), which antagonizes proangiogenic factors such as vascular endothelial growth factor and placental growth factor, contributes to the pathogenesis of preeclampsia. Other investigators found that accumulation of advanced oxidation protein products drives the expression of

soluble sFlt-1 in trophoblast cells.[41,42] Likewise, accumulation of advanced glycation end products in extravillous trophoblast and endothelial cells has also been linked to increased reactive oxygen species production and upregulation of sFlt-1 expression.[43,44]

Stage 3: biochemical and clinical manifestations of preeclampsia

Compelling experimental evidence indicates that endotheliosis in the systemic, renal, cerebral, or hepatic circulations perturbs the balance of endothelium-derived vasodilators (eg, nitric oxide, prostacyclin, and endothelium-derived hyperpolarizing factor) and vasoconstrictors (eg, endothelin-1 and thromboxan-A2), leading to increased vasoconstriction, hypertension, and other manifestation of preeclampsia.[45]

A host of genetic, demographic, and environmental risk factors purportedly act upstream of endothelial dysfunction through a variety of mechanisms, including aberrant expression of uteroplacental integrins, cytokines, and matrix metalloproteinases (MMPs). These molecular defects in turn are implicated in impaired maternal immune tolerance, apoptosis of invasive trophoblast, inadequate spiral arteries remodeling, reduced uterine perfusion pressure, and placental ischemia/hypoxia.

Increased expression of MMP-2 and MMP-9 in response to sustained estrogens and progesterone signaling during pregnancy has been implicated in vasodilatation, placentation, and uterine expansion. In pathological pregnancies, decreased levels of vascular MMP-2 and MMP-9 may compromise spiral artery remodeling and reduce uterine perfusion pressure.[46,47] This in turn may cause an imbalance between antiangiogenic (sFlt-1 and soluble endoglin) and proangiogenic (vascular endothelial growth factor and placental growth factor) factors or stimulate the expression of inflammatory mediators, reactive oxygen species, and agonistic autoantibodies against angiotensin-II type 1 receptor.[48-51] These circulating factors target endothelial and vascular smooth muscle cells, causing generalized vascular dysfunction, increased vasoconstriction, and hypertension in pregnancy.

Conclusions

The critical role of placental stress in the pathogenesis of preeclampsia explains why the disease regresses spontaneously following the removal of the placenta. In an effort to elucidate the primary driver of placental stress, we focused on the putative role of persistent endothelial cells in the uteroplacental spiral arteries. Normal pregnancy is associated with progressive loss of the endothelial cell lining in spiral arteries, a process integral to establishing a uteroplacental vasculature that can meet the increasing metabolic demands of the fetus throughout gestation.

Loss of endothelium in the decidual and junctional zone segments of the uteroplacental arteries is compensated for by the formation of a prominent fibrofibrinoid layer in which discrete trophoblastic cells are embedded. Although failure of physiological transformation in the spiral arteries has been extensively documented in preeclampsia, the role of persistent endothelial cells is often neglected.

Based on a reappraisal of the available evidence, we propose that persistence and damage of endothelial cells cause pathological vascular reactivity of uteroplacental vessels during the second trimester of pregnancy, which in turn accelerates local arteriopathy, amplifies placental stress and results in early-onset preeclampsia. Whether uterine endothelial dysfunction outside the placental bed contributes to pregnancy disorders warrants further investigation. ■

REFERENCES

1. Chaiworapongsa T, Chaemsaithong P, Yeo L, Romero R. Pre-eclampsia part 1: current understanding of its pathophysiology. Nat Rev Nephrol 2014;10:466–80.
2. Chaiworapongsa T, Chaemsaithong P, Korzeniewski SJ, Yeo L, Romero R. Pre-eclampsia part 2: prediction, prevention and management. Nat Rev Nephrol 2014;10:531–40.
3. Levine RJ, Maynard SE, Qian C, et al. Circulating angiogenic factors and the risk of preeclampsia. N Engl J Med 2004;350:672–83.
4. Yanagisawa M, Kurihara H, Kimura S, et al. A novel potent vasoconstrictor peptide produced by vascular endothelial cells. Nature 1988;332:411–5.
5. Roberts JM, Taylor RN, Musci TJ, Rodgers GM, Hubel CA, McLaughlin MK. Preeclampsia: an endothelial cell disorder. Am J Obstet Gynecol 1989;161:1200–4.
6. Redman CW, Sargent IL. Placental debris, oxidative stress and pre-eclampsia. Placenta 2000;21:597–602.
7. Koopmans CM, Blaauw J, van Pampus MG, Rakhorst G, Aarnoudse JG. Abnormal endothelium-dependent microvascular dilator reactivity in pregnancies complicated by normotensive intrauterine growth restriction. Am J Obstet Gynecol 2009;200:66.e1–6.
8. Furchgott RF, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature 1980;288:373–6.
9. Cines DB, Pollak ES, Buck CA, et al. Endothelial cells in physiology and in the pathophysiology of vascular disorders. Blood 1998;91:3527–61.
10. Croce K, Libby P. Intertwining of thrombosis and inflammation in atherosclerosis. Curr Opin Hematol 2007;14:55–61.
11. Jaakkola K, Nikula T, Holopainen R, et al. In vivo detection of vascular adhesion protein-1 in experimental inflammation. Am J Pathol 2000;157:463–71.
12. Robertson WB, Brosens IA, Dixon HG. Placental bed vessels. Am J Obstet Gynecol 1973;117:294–5.
13. Pijnenborg R, Vercruysse L, Brosens I. Deep placentation. Best Pract Res Clin Obstet Gynaecol 2011;25:273–85.
14. Brosens I, Pijnenborg R, Vercruysse L, Romero R. The "Great Obstetrical Syndromes" are associated with disorders of deep placentation. Am J Obstet Gynecol 2011;204:193–201.
15. Pijnenborg R, Dixon G, Robertson WB, Brosens I. Trophoblastic invasion of human decidua from 8 to 18 weeks of pregnancy. Placenta 1980;1:3–19.
16. De Wolf F, De Wolf-Peeters C, Brosens I, Robertson WB. The human placental bed: electron microscopic study of trophoblastic invasion of spiral arteries. Am J Obstet Gynecol 1980;137:58–70.
17. Bulla R, Agostinis C, Bossi F, et al. Decidual endothelial cells express surface-bound C1q as a molecular bridge between endovascular trophoblast and decidual endothelium. Mol Immunol 2008;45:2629–40.
18. Jogee M, Myatt L, Moore P, Elder MG. Prostacyclin production by human placental cells in short-term culture. Placenta 1983;4:219–30.
19. De Wolf F, Brosens I, Robertson W. Ultrastructure of uteroplacental arteries. Contrib Gynecol Obstet 1982;9:86–99.

20. Brosens I, Robertson WB, Dixon HG. The physiological response of the vessels of the placental bed to normal pregnancy. J Pathol Bacteriol 1967;93:569–79.
21. De Wolf F, De Wolf-Peeters C, Brosens I. Ultrastructure of the spiral arteries in the human placental bed at the end of normal pregnancy. Am J Obstet Gynecol 1973;117:833–48.
22. Pijnenborg R, Bland JM, Robertson WB, Brosens I. Uteroplacental arterial changes related to interstitial trophoblast migration in early human pregnancy. Placenta 1983;4: 397–413.
23. Roberts JM, Gammill HS. Preeclampsia: recent insights. Hypertension 2005;46:1243–9.
24. Brosens IA, Robertson WB, Dixon HG. The role of the spiral arteries in the pathogenesis of preeclampsia. Obstet Gynecol Annu 1972;1: 177–91.
25. Brosens JJ, Pijnenborg R, Brosens IA. The myometrial junctional zone spiral arteries in normal and abnormal pregnancies: a review of the literature. Am J Obstet Gynecol 2002;187: 1416–23.
26. Kaufmann P, Black S, Huppertz B. Endovascular trophoblast invasion: implications for the pathogenesis of intrauterine growth retardation and preeclampsia. Biol Reprod 2003;69: 1–7.
27. Lyall F, Bulmer JN, Duffie E, Cousins F, Theriault A, Robson SC. Human trophoblast invasion and spiral artery transformation: the role of PECAM-1 in normal pregnancy, preeclampsia, and fetal growth restriction. Am J Pathol 2001;158:1713–21.
28. Naicker T, Khedun SM, Moodley J, Pijnenborg R. Quantitative analysis of trophoblast invasion in preeclampsia. Acta Obstet Gynecol Scand 2003;82:722–9.
29. Hiby SE, Walker JJ, O'Shaughnessy KM, et al. Combinations of maternal KIR and fetal HLA-C genes influence the risk of preeclampsia and reproductive success. J Exp Med 2004;200:957–65.
30. Brosens JJ, Parker MG, McIndoe A, Pijnenborg R, Brosens IA. A role for menstruation in preconditioning the uterus for successful pregnancy. Am J Obstet Gynecol 2009;200: 615.e1–6.
31. Garrido-Gomez T, Dominguez F, Quinonero A, et al. Defective decidualization during and after severe preeclampsia reveals a possible maternal contribution to the etiology. Proc Natl Acad Sci USA 2017;114:E8468–77.
32. Gellersen B, Brosens JJ. Cyclic decidualization of the human endometrium in reproductive health and failure. Endocr Rev 2014;35: 851–905.
33. Brosens I, Muter J, Ewington L, et al. Adolescent preeclampsia: pathological drivers and clinical prevention. Reprod Sci 2018: 1933719118804412.
34. Labarrere CA, DiCarlo HL, Bammerlin E, et al. Failure of physiologic transformation of spiral arteries, endothelial and trophoblast cell activation, and acute atherosis in the basal plate of the placenta. Am J Obstet Gynecol 2017;216: 287.e1–16.
35. Sheppard BL, Bonnar J. An ultrastructural study of utero-placental spiral arteries in hypertensive and normotensive pregnancy and fetal growth retardation. Br J Obstet Gynaecol 1981;88:695–705.
36. Brosens I, Renaer M. On the pathogenesis of placental infarcts in pre-eclampsia. J Obstet Gynaecol Br Commonw 1972;79:794–9.
37. Myatt L. Role of placenta in preeclampsia. Endocrine 2002;19:103–11.
38. Burton GJ, Woods AW, Jauniaux E, Kingdom JC. Rheological and physiological consequences of conversion of the maternal spiral arteries for uteroplacental blood flow during human pregnancy. Placenta 2009;30: 473–82.
39. Fiore G, Florio P, Micheli L, et al. Endothelin-1 triggers placental oxidative stress pathways: putative role in preeclampsia. J Clin Endocrinol Metab 2005;90:4205–10.
40. Maynard SE, Min JY, Merchan J, et al. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. J Clin Invest 2003;111:649–58.
41. Huang QT, Zhang M, Zhong M, et al. Advanced glycation end products as an upstream molecule triggers ROS-induced sFlt-1 production in extravillous trophoblasts: a novel bridge between oxidative stress and preeclampsia. Placenta 2013;34:1177–82.
42. Huang QT, Wang SS, Zhang M, et al. Advanced oxidation protein products enhances soluble Fms-like tyrosine kinase 1 expression in trophoblasts: a possible link between oxidative stress and preeclampsia. Placenta 2013;34: 949–52.
43. Chekir C, Nakatsuka M, Noguchi S, et al. Accumulation of advanced glycation end products in women with preeclampsia: possible involvement of placental oxidative and nitrative stress. Placenta 2006;27:225–33.
44. Guo ZJ, Niu HX, Hou FF, et al. Advanced oxidation protein products activate vascular endothelial cells via a RAGE-mediated signaling pathway. Antioxid Redox Signal 2008;10: 1699–712.
45. Possomato-Vieira JS, Khalil RA. Mechanisms of endothelial dysfunction in hypertensive pregnancy and preeclampsia. Adv Pharmacol 2016;77:361–431.
46. Dias-Junior CA, Chen J, Cui N, et al. Angiogenic imbalance and diminished matrix metalloproteinase-2 and -9 underlie regional decreases in uteroplacental vascularization and feto-placental growth in hypertensive pregnancy. Biochem Pharmacol 2017;146:101–16.
47. Chen J, Khalil RA. Matrix metalloproteinases in normal pregnancy and preeclampsia. Prog Mol Biol Transl Sci 2017;148:87–165.
48. Agrawal S, Cerdeira AS, Redman C, Vatish M. Meta-analysis and systematic review to assess the role of soluble FMS-like tyrosine kinase-1 and placenta growth factor ratio in prediction of preeclampsia: the SaPPPhirE study. Hypertension 2018;71:306–16.
49. Chaiworapongsa T, Romero R, Espinoza J, et al. Evidence supporting a role for blockade of the vascular endothelial growth factor system in the pathophysiology of preeclampsia. Young Investigator Award. Am J Obstet Gynecol 2004;190:1541–7; discussion 1547-50.
50. McKeeman GC, Ardill JE, Caldwell CM, Hunter AJ, McClure N. Soluble vascular endothelial growth factor receptor-1 (sFlt-1) is increased throughout gestation in patients who have preeclampsia develop. Am J Obstet Gynecol 2004;191:1240–6.
51. Wallukat G, Homuth V, Fischer T, et al. Patients with preeclampsia develop agonistic autoantibodies against the angiotensin AT1 receptor. J Clin Invest 1999;103: 945–52.
52. McCarthy AL, Woolfson RG, Raju SK, Poston L. Abnormal endothelial cell function of resistance arteries from women with preeclampsia. Am J Obstet Gynecol 1993;168: 1323–30.
53. Seligman SP, Buyon JP, Clancy RM, Young BK, Abramson SB. The role of nitric oxide in the pathogenesis of preeclampsia. Am J Obstet Gynecol 1994;171:944–8.
54. Lyall F, Greer IA, Young A, Myatt L. Nitric oxide concentrations are increased in the feto-placental circulation in intrauterine growth restriction. Placenta 1996;17:165–8.
55. Ishihara N, Matsuo H, Murakoshi H, Laoag-Fernandez JB, Samoto T, Maruo T. Increased apoptosis in the syncytiotrophoblast in human term placentas complicated by either preeclampsia or intrauterine growth retardation. Am J Obstet Gynecol 2002;186: 158–66.
56. Redman CW, Sargent IL, Staff AC. IFPA Senior Award Lecture: making sense of pre-eclampsia—two placental causes of preclampsia? Placenta 2014;35(Suppl): S20–5.
57. Burton GJ, Jauniaux E. The cytotrophoblastic shell and complications of pregnancy. Placenta 2017;60:134–9.
58. Sultana Z, Maiti K, Dedman L, Smith R. Is there a role for placental senescence in the genesis of obstetric complications and fetal growth restriction? Am J Obstet Gynecol 2018;218:S762–73.
59. Redman CW, Sacks GP, Sargent IL. Preeclampsia: an excessive maternal inflammatory response to pregnancy. Am J Obstet Gynecol 1999;180:499–506.
60. Moore Simas TA, Crawford SL, Solitro MJ, Frost SC, Meyer BA, Maynard SE. Angiogenic factors for the prediction of preeclampsia in high-risk women. Am J Obstet Gynecol 2007;197:244.e1–8.
61. Vaisbuch E, Whitty JE, Hassan SS, et al. Circulating angiogenic and antiangiogenic factors in women with eclampsia. Am J Obstet Gynecol 2011;204:152.e1–9.