Failure of physiological transformation and spiral artery atherosclerosis: their roles in preeclampsia
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Uterine spiral arteries
The blood to the uterus is supplied by the uterine arteries, arising from the internal iliac arteries and joined by blood supply from the ovarian arteries. The uterine arteries deliver blood to the arcuate branches within the myometrium and thereafter to the radial arteries, which continue on as spiral arteries. The basal arteries branch from the distal ends of the radial arteries, supplying the basal portion of the endometrium. In contrast, the spiral arteries extend beyond the basal endometrial layer, supplying the outer functional layer. The outer layer of the endometrium undergoes hormone-dependent structural changes during the menstrual cycle. In pregnancy, this layer of the endometrium is transformed into a "decidua," destined to "fall off" (from the

Physiological transformation with remodeling of the uteroplacental spiral arteries is key to a successful placentation and normal placentation function. It is an intricate process that involves, but is not restricted to, complex interactions between maternal decidual immune cells and invasive trophoblasts in the uterine wall. In normal pregnancy, the smooth muscle cells of the arterial tunica media of uteroplacental spiral arteries are replaced by invading trophoblasts and fibrinoid, and the arterial diameter increases 5- to 10-fold. Poor remodeling of the uteroplacental spiral arteries is linked to early-onset preeclampsia and several other major obstetrical syndromes, including fetal growth restriction, placental abruption, and spontaneous preterm premature rupture of membranes. Extravillous endoglandular and endovenous trophoblast invasions have recently been put forth as potential contributors to these syndromes as well. The well-acknowledged disturbed extravillous invasion of maternal spiral arteries in preeclampsia is summarized, as are briefly novel concepts of disturbed extravillous endoglandular and endovenous trophoblast invasions.

Acute atherosclerosis is a foam cell lesion of the uteroplacental spiral arteries associated with poor remodeling. It shares some morphologic features with early stages of atherosclerosis, but several molecular differences between these lesions have also recently been revealed. Acute atherosclerosis is most prevalent at the maternal-fetal interface, at the tip of the spiral arteries. The localization of acute atherosclerosis downstream of poorly remodeled arteries suggests that alterations in blood flow may trigger inflammation and foam cell development. Acute atherosclerosis within the decidua basalis is not, however, confined to unremodeled areas of spiral arteries or to hypertensive disorders of pregnancy and may even be present in some clinically uneventful pregnancies. Given that foam cells of atherosclerotic lesions are known to arise from smooth muscle cells or macrophages activated by multiple types of inflammatory stimulation, we have proposed that multiple forms of decidual vascular inflammation may cause acute atherosclerosis, with or without poor remodeling and/or preeclampsia. Furthermore, we propose that acute atherosclerosis may develop at different gestational ages, depending on the type and degree of the inflammatory insult.

This review summarizes the current knowledge of spiral artery remodeling defects and acute atherosclerosis in preeclampsia. Some controversies will be presented, including endovascular and interstitial trophoblast invasion depths, the concept of 2-stage trophoblast invasion, and whether the replacement of maternal spiral artery endothelium by fetal endovascular trophoblasts is permanent. We will discuss the role of acute atherosclerosis in the pathophysiology of preeclampsia and short- and long-term health correlates. Finally, we suggest future opportunities for research on this intriguing utero-placental interface between the mother and fetus.

Key words: decidua, hypertension, immunology, pathophysiology, placenta, preeclampsia, pregnancy, spiral artery

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Latin word “decidere”) at the end of pregnancy. The spiral arteries, approximately 50 to 100 μm in diameter in the nonpregnant state, penetrate the inner part of the myometrium and are nonbranching end arteries with a corkscrew shape.2,3

Physiological transformation of spiral arteries
Approximately 30 to 60 uterine spiral arteries are estimated to supply the intervillous space of the placenta and maintain uteroplacental perfusion during pregnancy,3 but other studies suggest higher numbers.5,6 As pregnancy progresses, uteroplacental blood flow increases from 45 mL/min to 750 mL/min at term, a dramatic increase in blood flow that is necessary for maintaining adequate placental function1 and for meeting the high demands of the
growing fetus. These hemodynamic changes are facilitated by massive physiological transformation of the spiral arteries, also known as spiral artery remodeling. Expansive remodeling causes loss of smooth muscle cells and their rich autonomic innervation, which in turn leads to functional changes in arterial wall reactivity, enhanced vaso-dilation, and a major decrease in uterine vascular resistance. The physiological remodeling of the spiral arteries into highly diluted thin-walled vessels is vital to human pregnancy development.

At the start of pregnancy, spiral artery remodeling by endovascular trophoblasts has yet to begin. Before the establishment of the uteroplacental circulation during the first trimester of pregnancy, uterine glands provide histiotrophic nutrition for the fetus. Before 9 weeks’ gestation, endovascular (extravillous) trophoblast plugs limit maternal blood entry into the intervillous chambers. Plugging helps to maintain a state of physiological hypoxia early in the placentation process, favoring cytotrophoblast proliferation rather than functional changes in arterial wall reactivity, enhanced vaso-dilation, and a major decrease in uterine vascular resistance. The physiological remodeling of the spiral arteries into highly diluted thin-walled vessels is vital to human pregnancy development.

The physiological spiral artery remodeling process has been divided into 5 stages by Pijnenborg et al. (Figure 1). Stage 1 (decidua-associated early vascular remodeling) consists of endothelial vacuolization and swelling of individual muscle cells. Craven et al. highlighted that initial vascular remodeling occurs in the absence of trophoblast invasion, whereas others point out that complete pregnancy-associated spiral artery remodeling cannot occur without trophoblasts. In stage 2, interstitial trophoblasts invade stromal and perivascular tissue and induce further disorganization of the vascular smooth muscle and weakening of the elastic lamina of the arteries. In stage 3, endovascular extravillous trophoblasts enter from the spiral artery lumen into the vessel wall. Stage 4 (labeled by Pijnenborg as the physiological change) involves the incorporation of trophoblasts into the vessel wall, where a fibrinoid layer replaces the original vascular smooth muscle and elastic lamina. This loss of smooth muscle cells converts the arteries into flaccid conduits. Stage 5 involves maternal vascular repair with reendothelialization and subintimal thickening.

As reviewed previously, the local uterine lining’s (decidual) immune system is vital to spiral artery remodeling and thereby to successful placentation. There is increasing evidence for a role of both decidual natural killer (NK) cells and T cells (including regulatory T cells [Tregs]) in facilitating uteroplacental spiral artery remodeling. Placental extravillous trophoblasts (EVTs) invading the uterine spiral arteries are special in that they express only human leukocyte antigen (HLA)-C among the classical polymorphic class I HLAs, as reviewed by us. HLA-C expressed on EVT-s is a key molecule that can elicit immune responses by both decidual NK cells and T cells. It is therefore essential for a successful pregnancy that maternal-fetal immune tolerance toward HLA-C is well established. Appropriate remodeling requires successful interaction between these fetal HLA-C proteins, and killer cell immunoglobulin-like receptor (KIR) proteins, expressed on the maternal decidual NK cells. KIR genotypes have been shown to impact baby weight percentiles and preeclampsia rates worldwide. T cells and the adaptive immune system are also involved, as HLA-C incompatibility between the mother and fetus is associated with increased T-cell activation and generation of Tregs.

Decidual Tregs are essential to promoting maternal-fetal immune tolerance, a mechanism central to ensuring robust placentation and spiral artery remodeling. Tregs contribute to implantation and placental development by several mechanisms. These include preventing destructive effector T-cell responses to fetal antigens, regulating other decidual immune cells and thus promoting an anti-inflammatory environment, and by regulating maternal vascular changes through interaction with decidual NK cells. We previously reported that induction of Tregs ameliorated intrauterine growth restriction in a transgenic rat model of preeclampsia. Recently, in a mouse model, it was shown that Treg deprivation caused reduced maternal vascular adaptation in pregnancy. Insufficient numbers or impaired function of Tregs is linked to human reproductive disorders, such as preeclampsia and recurrent implantation failure or miscarriage. Studies in mice have also indicated that pregnancy imprints Tregs with protective memory to fetal antigens and that these memory Tregs persist and rapidly accumulate during a subsequent pregnancy.

Another important finding is that human decidual NK cells also possess some features of adaptive immunity. The decidual NK cells develop trained “memory” after a first pregnancy and differ from decidual NK cells from a first pregnancy in that they express higher levels of some receptors that interact with EVT-s and growth factors that are important for spiral artery remodeling, potentially promoting more efficient placentation in subsequent pregnancies. Immune cells with pregnancy-imprinted memory could be part of the reason why there is an additional risk of preeclampsia in first pregnancies. Perhaps the effects of these immune cells with pregnancy memory decline over time, which may explain why the protective benefit of a previous pregnancy conceived with the same partner is lost after a long interpregnancy interval. However, more research is needed to investigate these hypotheses.

**Dysfunctional spiral artery remodeling in preeclampsia**

A major contribution to the understanding of how failed spiral artery transformation contributes to the development of preeclampsia was made by Robertson and Brosens. In 1967, they reported that preeclampsia is associated with poor placentation, observed as shallow remodeling of the uteroplacental spiral arteries. Some scientific controversies remain regarding the dysfunctional nature of spiral artery remodeling.
in preeclampsia. One controversy has been Pijnenborg’s “2-wave” hypothesis of trophoblast invasion, based on hysterectomy specimens. This hypothesis has been refuted by Lyall, who concluded based on placental bed findings that continuous endovascular migration from decidual to myometrial arteries occurs, rather than 2 distinct trophoblast invasion waves. Furthermore, a common misunderstanding is that both the interstitial and endovascular depths of trophoblast invasion are altered in preeclampsia. Interstitial trophoblast invasion occurs before endovascular invasion; however, in preeclampsia, the interstitial trophoblast invasion depth remains normal, whereas the endovascular trophoblast invasion is more shallow than in normotensive pregnancies, as shown in detailed placental bed studies by Lyall et al.

Whether the superficial decidua basalis spiral arteries in preeclampsia are also severely affected by poor trophoblast invasion and failure of physiological transformation, as reported by Labarrere et al., is also debatable. This is not found in other decidua basalis studies. Differences among studies may however result from differences in patient selection, tissue collection techniques (including localization of biopsies from the placental bed and efficiency in spiral artery collection), assessment of smaller nutritional basal arteries vs wider uteroplacental spiral arteries, and immunohistochemical markers.

As Pijnenborg et al. point out, a misconception is that endovascular trophoblast invasion results in permanent replacement of maternal spiral artery endothelial cells by invading fetal trophoblasts. This concept was derived from findings by Zhou et al., showing that endovascular trophoblasts normally transform their adhesion receptor phenotype and begin to express endothelial markers, whereas those in preeclampsia fail to do so. As argued by Pijnenborg et al., maternal spiral artery endothelial cell replacement by trophoblasts is only temporary (Figure 1, stage 4), as these endovascular trophoblasts are then embedded intramurally and the spiral arteries are reendothelialized by maternal endothelial cells. In line with this, third-trimester immunohistochemical findings show that all spiral artery endothelial cells are cytokeratin negative and therefore unlikely trophoblast derived. We and others have confirmed this finding and further reported that these cells are positive for the endothelial cell markers CD31 and von Willebrand factor.

The failure of deep endovascular invasion and spiral artery remodeling, as observed in early-onset preeclampsia, was previously assumed to lead to placental underperfusion and thereby chronic hypoxia. A 2009 model by Burton et al. argued that flow volume is minimally affected by unsuccessful spiral artery remodeling but that the uteroplacental perfusion has a more pulsatile and higher pressure flow quality than normally remodeled arteries, partly because of the remaining contractile smooth muscle cells. This abnormal flow generates ischemia-reperfusion injury and placental oxidative stress rather than chronic hypoxia per se. Furthermore, placental endoplasmic reticulum (ER) stress is increased, and the unfolded protein response is activated by this abnormal flow. The dysfunctional placental perfusion results in adverse placental function and release of inflammatory placental factors. These factors mediate an excessive maternal inflammatory response, involving endothelial dysfunction and generalized vascular inflammation, resulting in the observed clinical maternal features of preeclampsia. These inflammatory factors are not fully defined but include syncytiotrophoblast microvesicles and angiogenic factors, contributing to an antiangiogenic imbalance in the maternal circulation (eg, elevated soluble fms-like tyrosine kinase 1 and low placental growth factor [PIGF]), as observed in early-onset preeclampsia and fetal growth restriction (FGR), both of which are placental syndromes characterized by inadequately remodeled spiral arteries.

Of note, poor placentation and risk of preeclampsia involve much more than inadequate trophoblast-associated spiral artery remodeling. Periconceptional endometrial function, early decidual vascular remodeling (before trophoblast invasion), and vascular plugging by trophoblasts all play a role. Obesity and other risk factors for preeclampsia affecting the inflammatory state of the endometrium likely confer risk partly through their effects on periconceptional endometrial function and spiral artery remodeling. Such risk factors may cause defective maturation of endometrial and decidual NK cells during the secretory phase and early pregnancy, also contributing to poor placentation.

**Extravillous trophoblast invasion failure: affecting more than the remodeling of uteroplacental spiral arteries?**

The acknowledged disturbed extravillous invasion of maternal spiral arteries in preeclampsia is summarized above. Recent studies have however also demonstrated extravillous glandular and extravillous endovenous invasions, occurring early on during placentation. It is possible that adverse regulation of these processes contributes to several obstetrical syndromes, including preeclampsia and FGR.

**The 2-stage model of preeclampsia: more than remodeling problems**

We have proposed that incomplete spiral artery remodeling along with other factors contributing to poor placentation is 1 of several pathways increasing the risk of preeclampsia. Poor placentation increases the risk of early severe placental dysfunction and “early-onset” preeclampsia, with concomitant FGR. “Late-onset” preeclampsia, without evidence of poor spiral artery remodeling and FGR, may be caused by overcrowding of the terminal villi in large placentas and also by senescent placentas. These pathways are however not mutually exclusive and may interact in causing placental dysfunction with cellular syncytiotrophoblast stress, resulting in the maternal syndromic signs of preeclampsia caused by...
generalized vascular inflammation. Hence, we propose that the pathways to early- and late-onset preeclampsia may differ in the time course and underlying causes but that the maternal signs of hypertension and other organ dysfunction (eg, proteinuria) are the same. This integrative concept takes into account that all pathways trigger placental (syncytiotrophoblast) stress and similar maternal responses but that FGR is more prevalent in early-onset preeclampsia as this preeclampsia form results mainly from early placental dysfunction with severe adverse effects on fetal growth.44,45 Our revised 2-stage model of preeclampsia accommodates most known risk factors, including chronic prepregnancy disease, primiparity, and other pregnancy-related risk factors (including multiples).17 First, maternal obesity, for instance, is a well-known risk factor for both preeclampsia and gestational hypertension,52 a finding that fits
Acute atherosis by Zeek and Assali in media. This finding was later termed atherosis.56 In 1945, Hertig described in 1945 spiral artery when? Acute atherosis: what, where, and when? Incomplete artery remodeling across several obesity is a risk factor for poor spiral sections, which is the compartment where the potential spiral artery remodeling problems are seen (eg, inadequate physiological remodeling and less deep endothelial trophoblast invasion).57,58 Acute atherosis lesions are usually focal,9,33,34 not necessarily affecting all spiral arteries, the entire circumference of a single artery, or its entire length. Apart from the placental bed, acute atherosis may be found in the decidua parietalis.56,58,59 where there is no physiological transformation of the spiral arteries. These lesions are however not found outside the uterus. Figure 2 (reproduced with permission from Fosheim35) shows examples of decidual acute atherosis in serial tissue section staining.

The time course of acute atherosis development is not definitively known, as longitudinal biopsies for histologic studies are infeasible. Decidual acute atherosis has been observed as early as the first trimester of pregnancy in women with chronic autoimmune diseases characterized by excessive inflammation (eg, systemic lupus erythematosus [SLE] with antiphospholipid syndrome).60 Delivery of the placenta is followed by gradual shedding of the remaining decidual tissue (where the lesion is most prevalent) over a few weeks, and the lesion likely regresses soon after delivery,18 as confirmed by small autopsy studies.36

The rate of acute atherosis is elevated in preeclampsia compared with that in normotensive pregnancies but not all preeclampsia pregnancies are affected.34,61–63 Acute atherosis also affects some pregnancies complicated by FGR or diabetes mellitus (without maternal hypertension),34,64 SLE and antiphospholipid syndrome,65 and even sometimes normotensive uncomplicated pregnancies.34,57,63,66 Our decidual basalis studies suggest that the foam cell lesions are much rarer in normotensive uncomplicated pregnancies than in preeclamptic pregnancies and that the lesions, when present, are smaller and affect fewer arteries.54 The reported rates of acute atherosis vary from 10% to 52% in preeclampsia and from 0.4% to 11% in normotensive pregnancies.34,61–63 This huge variation likely reflects differences in the populations investigated and the heterogeneous sampling techniques and diagnostic criteria.59 Acute atherosis assessment is not part of routine clinical practice because of the need for careful tissue sampling and the time-consuming morphologic and immunohistochemical investigations after delivery. Hitherto, there is no available noninvasive imaging strategy to reliably identify uteroplacental acute atherosis.

Various tissue sampling techniques have been used to investigate acute atherosis, including rare whole uterus specimens with placenta in situ (from postpartum hysterectomies),67 placental bed biopsies (including decidual and myometrial tissues),31,68 vacuum curettage of the placental bed (published by us in 1999),68–70 biopsies from the basal plate of the delivered placenta, and placental membranes (providing decidua parietalis, not the decidua basalis of the placental bed).61,68

As summarized in a state-of-the-art paper on optimizing sample collection for placental research,71 our technique of decidual vacuum suction of the placental bed during cesarean delivery68–70 represents the superior sampling method if one wishes to study the decidua basalis alone.71 Studies examining conventional placental tissue samples have found a higher frequency of acute atherosis in the fetal membranes, relative to tissue samples from the maternal surface of the placenta.51,72 However, the rate of acute atherosis is lower in fetal membranes when directly compared with vacuum-suctioned decidual tissue from the placental bed.59 This is not surprising, as most acute atherosis lesions are present in the decidua basalis.57,78 Advantages of the decidual vacuum suction methodology compared with that of traditional biopsies from the placental bed and maternal surface of the placenta include the following: (1) tissue yield is larger; (2) decidual tissue is collected from the whole placental bed in an unbiased way; and (3) it is easy and rapid and does not lead to short- or long-term complications when performed by experienced clinicians.68 One drawback is that the tissue lacks orientation, in contrast to placental bed biopsies. An issue that affects acute
Foam cells are not, however, specifically phagocytes and smooth muscle cells. Based on the ubiquity of perivascular infiltrate and fibrinoid, our simplified definition is based on identifying at least 2 adjacent foam cells in the spiral artery wall that are also CD68 positive. Other researchers, also acknowledging that all 3 classically required components of acute atherosclerosis are not always present, have used the terminology decidual vasculopathy for these spiral artery pathologies.

**Acute atherosclerosis in preeclampsia: why?**

The causes and consequences of acute atherosclerosis in preeclampsia and other obstetrical syndromes mediated by placental dysfunction are not completely understood. Although more rare and less extensive, the lesion’s presence in clinically uncomplicated pregnancies has also been an enigma. To shed light on the associations linking acute atherosclerosis and placental dysfunction, breaking down the characteristics of the lesion may be useful.

The immunohistochemical hallmark of acute atherosclerosis is CD68-positive subendothelial lipid-filled foam cells. CD68 is part of the scavenger receptor family and can bind and internalize oxidized low-density lipoprotein (LDL). Foam cells themselves are products of inflammatory stress, typically of the intima, and are characteristic of early stages of atherosclerosis. In atherosclerosis, foam cells have been shown to derive from both macrophages and smooth muscle cells. Foam cells are not, however, specific to atherosclerosis but may form in several inflammatory states (as reviewed in Staff et al). Like foam cells, myointimal cell proliferation and fibrinoid necrosis, the 2 other defining features of acute atherosclerosis, are also markers of arterial injury.

We have proposed that acute atherosclerosis may be the histologic manifestation of several decidual inflammatory mechanisms leading to arterial damage. These underlying mechanisms may vary in timing and intensity during a pregnancy, explaining the association of preeclampsia and a plethora of pregnancy complications with the lesion. This is in line with our 2-stage model of the complex preeclampsia syndrome, including heterogeneous pathways and risk factors for both early- and late-onset preeclampsia (summarized above in “Extravillous trophoblast invasion failure: affecting more than the remodeling of uteroplacental spiral arteries”).

In our model, acute atherosclerosis may not only be a consequence of placental dysfunction and the result of its underlying mechanisms but also be a risk factor for placental dysfunction, as illustrated in our 2014 model shown in Figure 3 (reproduced with permission from the *American Journal of Obstetrics & Gynecology*).

The mechanisms mediating placental dysfunction may also cause acute atherosclerosis, and vice versa. We propose several, potentially synergistic, pathways to acute atherosclerosis involving inflammatory, immunogenetic, and hemodynamic risks, as shown in Figure 4. Firstly, decidual inflammation may be a sufficient cause of acute atherosclerosis. We have put forward that uteroplacental acute atherosclerosis could develop at any stage of pregnancy in the setting of sufficient decidual inflammation, including in normotensive pregnancies. This is in line with findings that some women develop acute atherosclerosis very early in pregnancy, in situations of excessive prepregnancy and early pregnancy vascular inflammation, such as in SLE. This is not surprising, as it has become widely recognized that immunity and inflammation play a key role in the pathogenesis of arterial diseases affecting all wall layers of the arteries, at all levels of the arterial tree, including smaller vessels, where the spiral arteries belong to the latter group.

Secondly, immunologic mechanisms are likely important for acute atherosclerosis development. The localization of acute atherosclerosis is intriguing and may provide a clue to its origins. The lesion is found mainly in the tips of the spiral arteries, in the decidual end and is not found in other maternal arteries outside the uterine wall. We propose that the decidual spiral artery tips are particularly prone to arterial damage because of their colocalization with cells from a genetically distinct fetus, including invading extravillous trophoblasts. Dysregulated local maternal tolerization to these allo- genetic trophoblasts is likely 1 aspect of acute atherosis.

Finally, altered hemodynamics may lead to acute atherosclerosis. The localization of acute atherosis, usually downstream of unremodeled spiral arteries in the myometrial part of the spiral arteries, is also consistent with hemodynamic risk factors playing a role in its pathogenesis. Altered laminar blood flow caused by incomplete remodeling likely promotes endothelial shear stress, thus stimulating foam cell generation. This is similar to the formation of atherosclerotic lesions, tending to localize beyond arterial branching points in areas of altered blood flow patterns. We have suggested that the pathways outlined above, alone or in combination, may lead to a common endpoint, namely, inflammatory stimulation of foam cell formation, and thereby acute atherosclerosis.

Once present, the acute atherosclerosis lesions may themselves contribute to further placental dysfunction. Acute atherosclerosis narrows the spiral artery lumina, exacerbating dysfunctional uteroplacental flow. The greater the number of spiral arteries affected in a pregnancy, the more likely it is to lead to exacerbation of placental dysfunction, with oxidative and ER cellular stress responses, as seen in preeclampsia. The acute atherosclerosis lesions are also associated with an increased rate of local arterial thrombosis and thereby increased risk of downstream placental ischemia and infarctions. Clinically, acute atherosclerosis lesions in preeclampsia have been associated with more severe disease forms, including preterm delivery and FGR, both
well known to further increase the risk of premature cardiovascular disease after preeclampsia. This suggests a link between this short-term manifestation of uteroplacental arterial damage and chronic damage to the systemic maternal cardiovasculature.

**Acute atherosis: molecular pathways**

Acute atherosis was named after its morphologic resemblance of early atherosclerosis stages, but the lesions have several differing features and likely partly differing etiologies. We have previously argued that acute atherosis and atherosclerosis share inflammatory mechanisms for foam cell generation but that acute atherosis likely has additional, pregnancy-specific underlying mechanisms. As argued by us, although macrophage-derived foam cells represent a shared feature of acute atherosis and atherosclerotic lesions of larger arteries, the lesions differ with respect to time course (long vs short development), the size of the artery affected (acute atherosis only affects the small spiral arteries, in contrast to atherosclerosis affecting much larger arteries), and artery wall composition. Atherosclerotic lesions are more complex and develop plaques that may rupture.

The histologic similarities between acute atherosis and graft vascular disease have also been highlighted for several decades, although subendothelial foam cell lesions are less prominent in the latter. Fibrinoid necrosis and intimal hyperplasia are however a shared feature, and both types of lesions involve peri-vascular lymphocyte infiltration, complement, and immunoglobulin deposits. Strikingly, the arterial lesions of graft vascular disease and acute atherosis both occur at the boundaries between tissues from genetically distinct individuals, as reviewed by us. Both allograft rejection and preeclampsia correlate with the presence of circulating angiotensin II type 1 receptor agonistic autoantibody (AT1-AA), but our study did not find increased rates of this autoantibody in preeclampsia with acute atherosis compared with that of preeclampsia without acute atherosis. However, in line with the hypothesis that acute atherosis shares certain molecular pathways with graft vessel disease and acute atherosis, we have found presence of complement around uteroplacental decidual spiral arteries afflicted with acute atherosis.

When comparing decidual “tissue” features of preeclampsia and normotensive pregnancies, we previously demonstrated excessive tissue inflammation in preeclampsia, with increased content of lipids (total cholesterol, phospholipids, and triglycerides) and increased levels of 8-isoprostane, a marker of oxidative stress, and increased levels of 8-isoprostane, a marker of oxidative stress, and increased phospholipase A2 activity decidual tissue, the latter liberating 8-isoprostane from tissue phospholipids. We also showed in vitro that 8-isoprostane affects trophoblast function, including matrix metalloproteinase, NF-kappa B, and LOX-1 activities. Our renin-angiotensin system studies also demonstrated its local up-regulation in the decidua compared with that in placental...
tissues and a 5-fold up-regulation of decidual expression of the angiotensin II type 1 receptor in preeclampsia compared with that of normotensive pregnancies.84

As for comparing “cellular” features of acute atherosclerosis and early atherosclerosis, we have in our decidual studies found evidence of both differences and similarities. Most arterial injuries begin with endothelial dysfunction and activation,90 but in our recent study, immunohistochemical evidence of endothelial activation was lacking in most decidua basalis spiral arteries with acute atherosclerosis, with the absence of intercellular adhesion molecule 1 (ICAM-1) expression.35 Labarrere et al32 found evidence of ICAM-1 expression in decidua basalis spiral arteries with acute atherosclerosis, but the authors studied mainly nonremodeled arteries, in contrast to our work.35 We did however find other evidence of endothelial abnormalities in acute atherosclerosis lesions, characterized by weak CD31 staining, possibly secondary to cellular stress. Our findings35 and the findings of others66,91 of fibrinoid necrosis in acute atherosclerosis of the arterial wall (colored red by Martius scarlet blue [MSB] staining and gray-pink by periodic acid-Schiff [PAS] staining)34 are consistent with an altered local endothelial phenotype, likely leaking factors from the maternal circulation into the vessel wall, depositing fibrin or fibrinlike (fibrinoid) material. Our recent immunohistochemical investigations confirmed that perivascular infiltrates were not consistently present or large around all acute atherosclerosis lesions and that adaptive CD4 helper T cells may be involved, whereas the presence of Tregs (FOXP3+) was almost absent,73 again demonstrating similarities and discrepancies relative to early atherosclerosis lesions.92 The recent findings of a more prevalent proinflammatory macrophage phenotype in the decidua basalis with acute atherosclerosis and an intravascular monocyte source for macrophages in acute atherosclerosis93 support our hypothesis that both tissue-based and circulation-based cellular pathways lead to decidual acute atherosclerosis.18

Similarities among the circulating biomarkers also exist between acute atherosclerosis and atherosclerosis. Another of our recent papers suggests that older women with decidual acute atherosclerosis (both preeclamptic and normotensive pregnancies) have a lipidemic profile resembling that of patients with atherosclerosis, including elevated levels of apolipoprotein B and LDL.94 Furthermore, we recently showed that the presence of decidual acute atherosclerosis or other evidences of placental dysfunction (eg, low levels of PlGF) was associated with dysregulated patterns of circulating cardiovascular disease—related multiplex biomarkers at delivery,95 supporting our model of potentially shared mechanisms.

**Acute atherosclerosis and long-term maternal health**

Pregnancy is seen as a stress test for future maternal health, and preeclampsia is associated with 2- to 8-fold increased risk of cardiovascular death.81 We have suggested that the subset of women who develop acute atherosclerosis lesions in pregnancy may have increased risk of atherosclerotic disease later in life.81,83 Acute atherosclerosis may represent an accelerated atherosclerotic process, driven by the dramatic physiological changes that occur in pregnancy. We have proposed that diagnosing acute atherosclerosis thereby could aid in better targeting preeclamptic women at higher risk of long-term cardiovascular disease,76 and our findings of dyslipidemia in the follow-up of older pregnant women with acute atherosclerosis support this notion.94 This concept has also been followed up by Veerbeek et al96 and Stevens et al,97 the latter study demonstrating an adverse cardiovascular risk profile at 7 months after delivery in women with a history of preeclampsia and decidual vasculopathy. However, both short- and long-term studies of acute atherosclerosis are potentially hampered with the challenges in obtaining enough tissue for optimal diagnosis of decidual acute atherosclerosis.59

**FIGURE 4**

Multiple pathways to the decidua parietalis acute atherosclerosis formation

We propose several, potentially synergistic, pathways to acute atherosclerosis, involving inflammatory, immunogenetic, and hemodynamic risks.18,65,76 Staff. Failure of physiological transformation and spiral artery atherosclerosis in preeclampsia. Am J Obstet Gynecol 2022.
Early stages of atherosclerosis are reversible, and statins have been shown to confer antiatherogenic and anti-inflammatory effects in large clinical trials. We have therefore put forward that use of statins in established pre eclampsia may ameliorate acute atherosclerosis, thereby improving uteroplacental perfusion and pregnancy outcome. In support of this, small clinical studies of statins used in women with antiphospholipid syndrome presenting with preeclampsia or FGR have shown promising results with improved uteroplacental perfusion, although randomized trials are lacking. Whether postpartum statins or other pharmacologic anti-inflammatory interventions (eg, metformin) following preeclampsia or acute atherosclerosis would be useful to women in delaying atherosclerosis progression and improving long-term cardiovascular health is neither known nor tested.

Remaining enigmas of acute atherosclerosis

We are still far from understanding all molecular, immunologic, genetic, and environmental mechanisms leading to the different clinical presentations of the placental syndromes, including pre eclampsia and acute atherosclerosis. Areas that merit more research are preimplantation heterogeneity, the decidua-related (trophoblast-independent) vascular remodeling processes, trophoblast invasion routes (arterial, venous, and glandular), decidual and immune cell interactions, and cytokine and growth factor production before and during trophoblast invasion. The cellular precursors of acute atherosclerosis foam cells may include trophoblast cells in addition to activated macrophages and smooth muscle cells and should be further detailed. Emerging studies demonstrating accelerated placental aging in early-onset preeclampsia and atherogenicity are worth pursuing, also in the setting of other placental syndromes with remodeling defects. As argued previously, preeclampsia represents a complex and multifaceted syndrome, as it involves several genomes; the maternal (oocyte and uterine), paternal, and fetal genomes. Dissecting its molecular pathology and interaction with environmental and modifiable risk factors is likely to uncover biologic understanding relevant to many human diseases, in addition to refining our conceptions and models of preeclampsia.

Finally, whether acute atherosclerosis in pregnancy truly correlates with excessive cardiovascular risk is still an intriguing topic for further investigation.

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