Acute Atherosis Lesions at the Fetal-Maternal Border: Current Knowledge and Implications for Maternal Cardiovascular Health

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Decidua basalis, the endometrium of pregnancy, is an important interface between maternal and fetal tissues, made up of both maternal and fetal cells. Acute atherosis is a uteroplacental spiral artery lesion. These patchy arterial wall lesions containing foam cells are predominantly found in the decidua basalis, at the tips of the maternal arteries, where they feed into the placental intervillous space. Acute atherosis is prevalent in preeclampsia and other obstetric syndromes such as fetal growth restriction. Causal factors and effects of acute atherosis remain uncertain. This is in part because decidua basalis is challenging to sample systematically and in large amounts following delivery. We summarize our decidua basalis vacuum suction method, which facilitates tissue-based studies of acute atherosis. We also describe our evidence-based research definition of acute atherosis. Here, we comprehensively review the existing literature on acute atherosis, its underlying mechanisms and possible short- and long-term effects. We propose that multiple pathways leading to decidual vascular inflammation may promote acute atherosis formation, with or without poor spiral artery remodeling and/or preeclampsia. These include maternal alloreactivity, ischemia-reperfusion injury, preexisting systemic inflammation, and microbial infection. The concept of acute atherosis as an inflammatory lesion is not novel. The lesions themselves have an inflammatory phenotype and resemble other arterial lesions of more extensively studied etiology. We discuss findings of concurrently dysregulated proteins involved in immune regulation and cardiovascular function in women with acute atherosis. We also propose a novel hypothesis linking cellular fetal microchimerism, which is prevalent in women with preeclampsia, with acute atherosis in pregnancy and future cardiovascular and neurovascular disease. Finally, women with a history of preeclampsia have an increased risk of premature cardiovascular disease. We review whether presence of acute atherosis may identify women at especially high risk for premature cardiovascular disease.

Keywords: acute atherosis, inflammation, decidua basalis, preeclampsia, tolerance, cardiovascular disease, placenta, microchimerism

INTRODUCTION

Arterial lesions specific to the spiral arteries at the fetal-maternal border were first reported in 1945 (1). These lesions were later termed acute atherosis, described as lipid-laden foam cells within the intima, surrounded by fibrinoid necrosis and perivascular immune cell infiltrate (2, 3). Acute atherosis is associated with lower birthweight (4) and lower placental weight (5), and some studies show that acute atherosis may be correlated with an antiangiogenic profile (6, 7), all three of which are indicators of placental dysfunction. Moreover, the well documented high concomitance of acute atherosis and preeclampsia and other obstetric syndromes suggests shared underlying mechanisms (8–25).

Causal factors and effects of acute atherosis during pregnancy, as well as the long-term effects on maternal cardiovascular health, remain uncertain. There are several constraints on studying the acute atherosis lesions histologically. Systematic sampling of the decidua in large amounts following delivery is quite difficult, and a uniform, evidence-based research definition of acute atherosis lesions is historically lacking. As discussed below, both issues have been addressed by us (22, 26). However, even when these constraints are overcome, only a subset of the decidua can realistically be evaluated in any morphological tissue study, thus one can only with certainty determine the presence of acute atherosis, and never the definitive absence.

Acute Atherosis Sampling Methodology

The ideal method for studying the impact of decidual acute atherosis on placental function requires specimens of a challenging nature; there are today only some very rare hysterectomy specimens of severely preeclamptic women with the placenta still *in situ* (27). In one such published case report, acute atherosis of spiral arteries with severe narrowing of the vascular lumen were associated with substantial infarcted areas in the overlying parts of the placenta (28). Moreover, in this case the lesions could be traced as deeply as the inner myometrium, implying that the severity of the placental defects may be related to the depth of the lesions. It is also noteworthy in this study that remodeling of the placental bed spiral arteries, including the myometrial segments, was absolutely normal in a few invaded spiral arteries at the very center of the placental bed. This suggests that non-invaded, more laterally situated vessels run a higher risk of developing acute atherosis, again highlighting the need for uniform sampling of relevant tissues for the study of acute atherosis, preferably of the whole placental bed.

Several methods have been employed for sampling decidua basalis for research purposes. These include placental bed biopsies (29), biopsies from the basal plate of delivered placentas (30), and our method of vacuum suctioning the placental bed (31). Of these sampling methods, placental bed punch or knife biopsy is the most invasive, but has the advantage of providing myometrium, which is needed if the goal is to study spiral artery remodeling or other features of this tissue (32). Biopsies from delivered placentas is the least invasive sampling method, and will yield moderate samples of decidua basalis

tissue. However, if the goal is to study decidua basalis alone, our vacuum suction technique is the superior method (32–34).

The vacuum suction technique is performed during caeserean section, after delivery of the placenta, by applying vacuum suction to the uterine wall. This method has the advantages of an unbiased sampling and a large tissue yield. It is also time efficient and without danger to maternal health (34). One drawback is that tissue orientation is lost due to suctioning. Still, the vacuum suction method provides tissue applicable for acute atherosis research. We showed that higher rates of acute atherosis detection was achieved using vacuum suction samples, as compared to routinely sampled basal surface placental tissue and fetal membrane roll biopsies from the same pregnancies (33). The rate of decidual acute atherosis is thus likely underestimated in most studies, and we recommend using the vacuum suction technique if the goal is to study the lesions independent of tissue orientation. Our large Oslo Pregnancy Biobank, consisting of decidual tissue collected during elective cesarean section, along with placental tissue biopsies, fetal (umbilical artery as well as umbilical vein) and maternal blood samples, amniotic fluid, and maternal muscle and fat tissue biopsies, has enabled multiple studies comparing the presence of decidual acute atherosis and dysregulated features of other anatomical compartments (20–26, 31, 33, 35–41).

Nonuniformity in Acute Atherosis Definitions

Historically, a uniform definition of acute atherosis has been lacking. This may have led to discrepancies in reported rates of acute atherosis across pregnancy groups. In addition, differences in patient populations studied as well as in tissue collection and evaluation methodology (e.g. antibody selection) may have contributed. Moreover, clear definitions of perivascular infiltrate (PVI) and fibrinoid necrosis have been lacking. We set out to address these issues by attempting to establish an evidence-based research definition of acute atherosis (22). After examining 278 decidua basalis samples, we observed that perivascular leukocyte infiltrates and increased fibrinoid did not always correlate with adjacent foam cell lesions. Instead, we concluded that these are features of the decidual pathology of preeclampsia, while CD68^{+} foam cells are an essential aspect of acute atherosis (**Figure 1**). Thus, we proposed that acute atherosis should be diagnosed solely by the presence of foam cell lesions, defined as two or more intramural, adjacent, vacuolated CD68^{+} cells. Nonetheless, throughout this review, we will include studies with other acute atherosis diagnosis criteria as well.

ACUTE ATHEROSIS ETIOLOGY

Hertig, who first described acute atherosis, proposed that vessel damage followed by lipophage infiltration is what initiates acute atherosis lesion development (1). Endothelial injury has long been suspected as integral to decidual lesion development by others as well (42). However, the lack of an association between acute
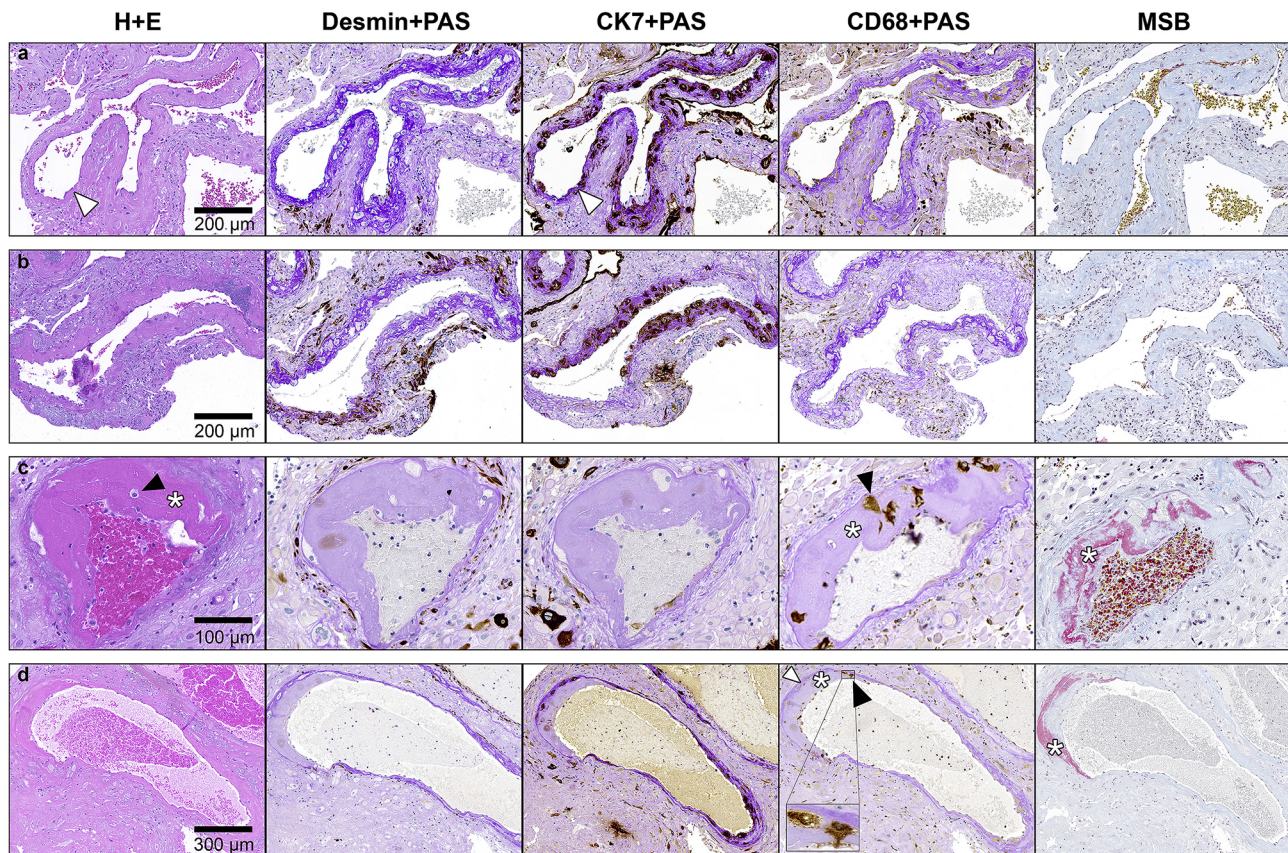
FIGURE 1 | Staining of serial FFPE sections of decidua basalis tissue to identify spiral arteries. Slides are stained with (from left to right) Hematoxylin + Eosin (H + E), desmin and Periodic acid–Schiff (PAS), cytokeratin 7 (CK7) and PAS, CD68 + PAS and Martius Scarlet Blue (MSB). Representative images of **(A)** spiral artery from a normotensive control with complete physiological transformation, characterized by presence of CK7-positive trophoblasts and intramural fibrinoid (bright purple upon PAS staining, white arrowhead) in the vessel wall, and complete absence of intramural smooth muscle cells (no desmin stain). **(B)** Spiral artery from a preeclampsia patient with partial physiological transformation characterized by intramural fibrinoid, trophoblasts and areas with traces of mural smooth muscle cells (desmin-positive). **(C)** Spiral artery with acute atherosis from same sample as in **(B)**, lacking bright purple fibrinoid and CK7-positive trophoblasts in the vessel wall. Traces of intramural smooth muscle cells (desmin positive) are seen. Fibrinoid necrosis is visible as a grey-pink material in the vessel wall (asterisk), which stains red upon MSB staining (asterisk). Erythrocytes in the lumen of the AA artery stains red-brown upon MSB staining. Intramural CD68-positive foam cells are present (black arrowhead). **(D)** Spiral artery from a preeclampsia patient with almost complete physiological transformation – evident by the lack of desmin-positive smooth muscle cells and the presence of CK7-positive trophoblasts – yet acute atherosis lesion is present (asterisk; fibrinoid necrosis, black arrowhead; foam cells, white arrowhead; purple physiological fibrinoid). Inset; higher power inset of foam cells. Reprinted from Fosheim et al. (35), with permission from the journal *Placenta*.

atherosis and the severity and duration of hypertension, or antihypertensive treatment, implies that hemodynamic forces alone are not adequate for lesion development (43). Similar to the heterogeneity of preeclampsia, acute atherosis is likely a multifactorial pathology with several pathways leading to an adverse uterovascular phenotype endpoint. We now have access to 75 years of research into the nature of the histological lesions known as acute atherosis, but have not finished elucidating the complexity of its etiological and mechanistic molecular constituents.

One such potential constituent, however, may be endothelin-1 (ET-1) (44). ET-1 is a highly potent vasoconstrictor (45). It is upregulated by mechanical stretch (46) and hypoxia (47), and plasma ET-1 is elevated in preeclampsia and gestational hypertension (48, 49). It exerts its effects by binding G-protein coupled receptors on vascular smooth muscle cells and endothelial cells (50), a byproduct of which may be intracellular lipid accumulation (51, 52). Thus, ET-1 may be a common trigger for lipid accumulation within endothelial cells in acute atherosis and in hepatocytes in the associated rare disease, acute fatty liver of pregnancy (44).

Another vasoconstrictor of interest is angiotensin II, which may play a role in the pathogenesis of atherosclerosis (53). We have postulated a role in acute atherosis for activating antibodies against the angiotensin II type 1 receptor (AA-AT_1), after demonstrating a clear association between AA-AT_1 and preeclampsia (54–56). Based on our cesarean delivery population, we were unable to demonstrate any association between AA-AT_1 and acute atherosis (21). However, angiotensin

II is known to work synergistically with ET-1 (57), and studying both of these vasoconstrictor systems simultaneously would shed more light on the possible involvement of G-protein cascades in acute atherosis development.

The regulator of G protein signaling 2 (RGS2) likely has implications for ET-1 and AA-AT$_1$ signaling (58). Interestingly, we have observed an association between acute atherosis and a genotype associated with lower RGS2 expression (38). If G-protein cascades indeed cause intracellular lipid accumulation, as proposed by Coffey (44), we would expect early acute atherosis lesions to contain lipid-laden endothelial or vascular muscle cells. Accordingly, arterial lesions containing vacuolated endothelial cells and myofibroblasts have been observed in first-trimester curetted endometrium samples from therapeutic and spontaneous abortions (59, 60). A higher incidence of such lesions was observed in primigravida as compared to multigravida (60). Primigravidity is associated with an increased risk of preeclampsia (36, 61), often considered due to excessive inflammation, although evidence is lacking (62). Whether these lesions are precursors to full-blown acute atherosis, and whether lipid accumulation within endothelial cells and myofibroblasts is indeed the insult that catalyzes intramural immune cell infiltration, remains to be investigated.

Acute atherosis shares morphological features with *early* atherosclerotic lesions, which is recognized as an inflammatory disease of the arterial walls (63). Both lesions present with increased numbers of intimal macrophages, lipid-laden foam cells, lipoprotein(a) throughout the vessel walls and extracellular droplets of lipid as well as similar expression of intracellular lipid-handling proteins (41, 64–67). Moreover, both acute atherosis and atherosclerosis are associated with preeclampsia and other states of systemic inflammation (68, 69).

However, there are several differences between acute atherosis and atherosclerosis. Firstly, vessel caliber differs enormously. Atherosclerosis is found in major arteries with a thick intimal layer, and the vessels are supplied with oxygen and nutrients from the vasa vasorum (70). Notably, the vasa vasorum may be instrumental as a source of lipids in the development of atherosclerosis (71–73). Spiral arteries are much smaller and do not have an external blood supply. Preeclampsia is associated with elevated lipid content in decidua basalis tissue, which may act as a source of lipid compounds for lesion development (26). Moreover, acute atherosis is not associated with *plasma* lipid contents, further indicating a local rather than a systemic excess of lipids (23). Secondly, research into the molecular composition of acute atherosis versus atherosclerosis reveals several dissimilarities. For instance, we have observed no LOX-1 positive endothelial cells or foam cells within the lesions of spiral arteries (41), while this lipid scavenger receptor is a key contributor to atherosclerotic development (74). Finally, endothelial activation is important in atherosclerosis (75), whereas evidence is conflicting with regards to endothelial status in acute atherosis. Although one study reported endothelial and interstitial extravillous trophoblast ICAM-1 expression in placentas with acute atherosis (76), we were unable to detect any ICAM-1 expression within the acute atherosis lesions (35). Moreover, the endothelial lining of the artery wall is often destroyed in acute atherosis and there is evidence of leakage of fibrin-like material from the circulation into the vessel walls (35, 42, 77). Accordingly, in a study of women with preeclampsia, we demonstrated elevated levels of thrombomodulin – a marker of endothelial dysfunction (78) or damage (79) – in those who had concomitant acute atherosis (39).

Acute atherosis is not found outside of the uterus (80). The lesions are focal and patchy, mainly localized downstream in the circulation, at the tips of the decidua basalis spiral arteries. The major remodeling problems occur upstream in the myometrium (67, 80). Yet, there is a link between acute atherosis formation and poor remodeling, as lesions are commonly found downstream of inadequately remodeled spiral arteries (77). The fully remodeled decidual segment of the spiral artery may be considered as being somewhat "naked" and is then likely more at risk for attacks both from the inside (by luminal, circulating factors) as well as from the outside (by components in the surrounding decidual tissue) in addition to being especially exposed to ischemia-reperfusion injury due to turbulent blood flow. Specifically, we postulate that these areas are especially exposed to local inflammatory signaling molecules. This may be compounded by their unique local environment close to the semi-allogenic fetal cells and the resulting inflammatory changes, potentially explaining why this uteroplacental location seems to be a prerequisite for the development of these particular atherosis lesions.

Inflammation does indeed appear to be clearly linked to acute atherosis development. Spiral arteries affected by acute atherosis contain huge deposits of IgM, as well as smaller amounts of IgG and IgA within the arterial wall. In addition to immunoglobulins, complement component 3 (C3) is often observed within acute atherosis lesions (81–86). In addition, early immunohistochemistry studies of the leukocyte infiltrate demonstrated T lymphocytes in acute atherosis (87). We later expanded on these findings, demonstrating increased concentrations of CD3^{+}, CD8^{+} and CD3^{+}CD8^{-} intramural T cells in the walls of spiral arteries with acute atherosis compared to arteries from samples without acute atherosis (37). Higher numbers of CD3^{+} and CD3+CD8^{-} T cells were also observed in the surrounding perivascular space. Furthermore, a study by Gill and colleagues conducting flow cytometry of basal plate samples demonstrated higher numbers of M1-macrophages in acute atherosis, displaying a pro-inflammatory phenotype (88). Fluorescence staining revealed M1-macrophage localization within vessel walls of spiral arteries affected by acute atherosis. Interestingly, a recent study from India showed that the incidence of acute atherosis – after exclusion of placental associated syndromes like fetal growth restriction, pregnancy hypertension and diabetes – was significantly higher in asymptomatic or mildly symptomatic SARS-CoV-2 positive pregnant women as compared to SARS-CoV-2 negative pregnant women (89). Finally, another support of acute atherosis representing an inflammatory lesion is its resemblance to systemic vasculitis, a general term applied to inflammation of vessel walls that progresses to fibrinoid necrosis (90, 91).

MANY ROADS TO DECIDUAL INFLAMMATION

We hypothesize that several mechanisms may trigger acute atherosis. Our hypothesis places inflammation at the center of lesion and as the final common pathway converged upon by these different triggers (69). We believe these mechanisms may act individually or in concert to produce acute atherosis, as illustrated in **Figure 2**.

Maternal Alloreactivity

Human pregnancy is a dynamic balancing act for the maternal immune system. The fetal allograft must peacefully coexist with the maternal immune and cardiovascular systems, whilst the
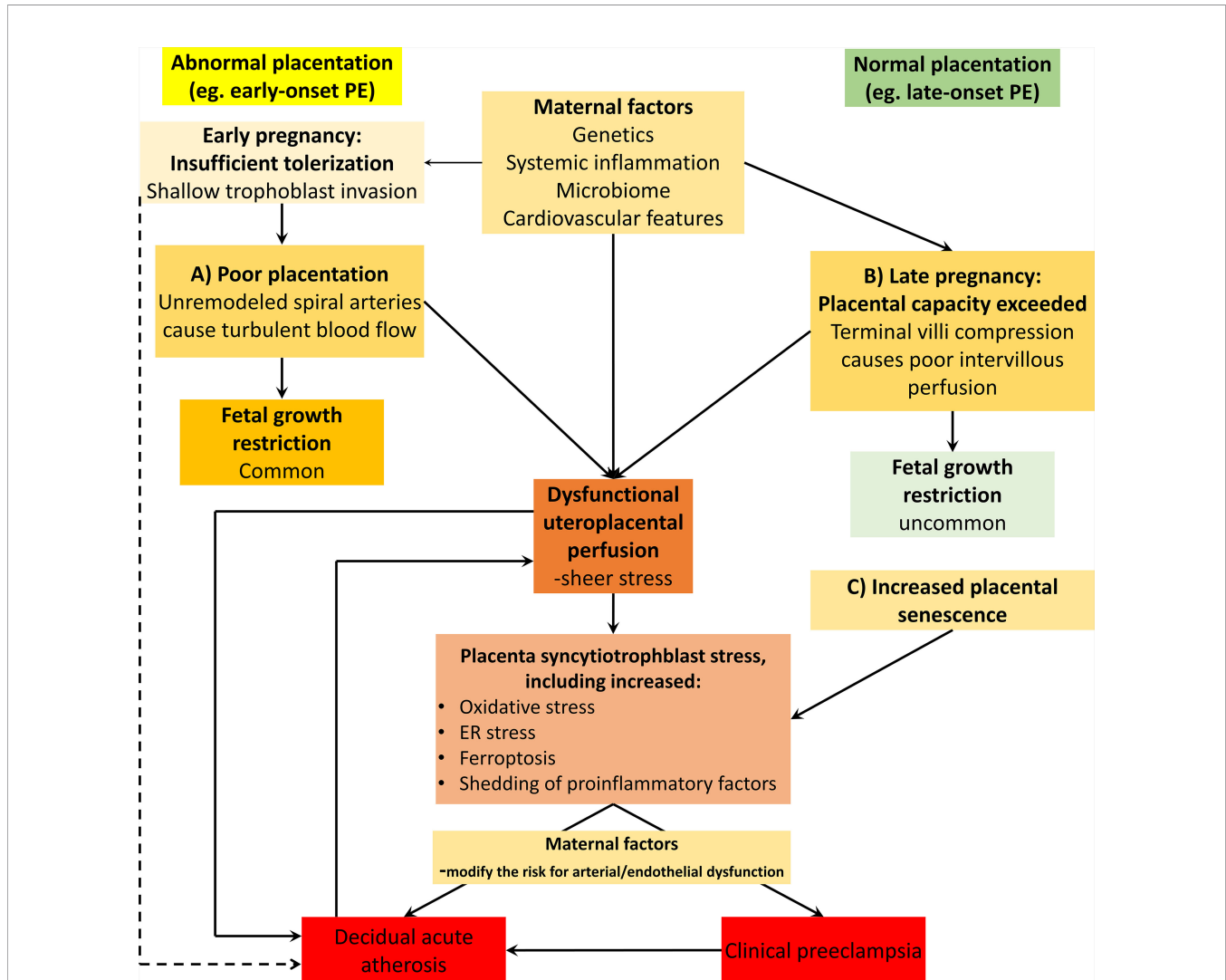
FIGURE 2 | Acute atherosis presence across the several forms of placental syndrome forms. Acute atherosis has been found in several forms of placental syndromes, many of these associated with spiral artery remodeling deficiencies, including early-onset preeclampsia (PE) (illustrated on the left side of the Figure). This figure also illustrates our concepts of how acute atherosis may be present also in late forms of preeclampsia (illustrated on the right side of the Figure), or indeed in any other forms of placental dysfunction without spiral artery remodeling defects. Preplacentation factors impacts the early and ensuing placentation processes, and includes both fetal-maternal tolerization processes as well as endometrial health (92). In this model, acute atherosis is seen as a consequence of any form of placental dysfunction and its underlying mechanisms (69). The triggers include both the uteroplacental malperfusion pathway secondary to spiral artery remodeling problems (as in early-onset preeclampsia) as well as the late-onset preeclampsia forms with other causes of placental malperfusion and syncytiotrophoblast stress (92, 93). Furthermore, this model also proposes that acute atherosis itself may represent a risk factor for placental dysfunction and preeclampsia. This is in line with acute atherosis developing very early in women with excessive vascular inflammation, such as in systemic lupus erythematosus, who also have a high risk for developing early-onset preeclampsia, severe fetal growth restriction and intrauterine death, all severe clinical aspects of placental dysfunction. The line from the tolerization box to acute atherosis illustrate how HLA-C/KIR interactions and alterations in level of immune-dampening molecules such as sHLA-G could contribute to lesion promotion at the maternal-fetal interface, as discussed in this review. The maternal factors promoting the clinical forms of preeclampsia (e.g. early- and late-onset) as well as atherosis development include cardiovascular, inflammatory and metabolic factors. Also, any form of clinical preeclampsia, with excessive circulation of proinflammatory factors and hypertension may add to the risk for atherosis development, although hypertension in itself is not a mandatory requirement.

mother and fetus simultaneously remain protected against microbial infections. Under any other circumstances, immune cells would quickly target genetically foreign tissue. However, a cascade of immune-modulating molecules acting throughout pregnancy enable the conceptus to evade rejection until parturition. The innate immune system is strengthened, while adaptive immunity is weakened (94). Serial blood samples collected at different time points during pregnancy have revealed precise timing of particular immunological changes (95). Aghaeepour and colleagues suggest deviations from this "immune clock of human pregnancy" could indicate pregnancy-related pathologies.

The fetus inherits half of its genetic material from the mother, and the other half from the father. Given the extremely high variability in major histocompatibility complex (MHC) genetics, it is unlikely that the paternally inherited fetal MHC alleles are identical to the maternally inherited fetal MHC alleles. Fetal trophoblasts circumvent this obstacle and avoid rejection by local maternal immune cells by not expressing most classical MHC class I or class II surface molecules (96). They do, however, express human leukocyte antigen (HLA) C and the non-classical MHC molecules HLA-G, HLA-E and HLA-F (96–98). HLA-C and HLA-G attenuate immune activation by binding to killer immunoglobulin like receptors (KIR), which are abundantly expressed on maternally derived immune cells (99, 100). KIR activation prevents cytotoxicity by alloreactive T-cells (101), and may induce apoptosis of activated T-cells and NK cells (102, 103). Invading extravillous trophoblasts rely on these KIR/HLA-interactions to avoid immune cell attacks. In fact, there is a positive correlation between the amount of surface HLA-G expression and the depth of trophoblast invasion into the decidua (104).

Several factors may influence these tolerogenic pathways. As HLA-C is the only polymorphic histocompatibility antigen expressed by fetal cells at the fetal-maternal interface, paternal HLA-C genotype is particularly important. In fact, HLA-C mismatched pregnancies are characterized by a higher percentage of activated maternal T-cells (105). Moreover, the combination of fetal HLA-C and maternal killer immunoglobulin like receptor (KIR) genotypes may greatly predispose pregnancies to preeclampsia (106). We have expanded on this finding by showing that the combination of fetal HLA-C2 with the maternal KIR-B haplotype was significantly associated with acute atherosis in preeclampsia (25).

Similarly, inadequate induction of tolerance by HLA-G is detrimental to pregnancy health (107). Membrane bound HLA-G expression is lower on trophoblasts from preeclamptic placentas (108, 109). Circulating soluble HLA-G (sHLA-G) is also lower in preeclampsia throughout all trimesters, compared to pregnancies that remain normotensive (110). We have shown that maternal sHLA-G inversely correlates with the level of placental dysfunction, the latter evaluated by maternal levels of the antiangiogenic factor sFlt-1, or by the sFlt-1/PlGF ratio (36), and that fetal polymorphisms in the 3'UTR region of HLA-G are associated with presence of acute atherosis in preeclampsia (24). Our hypothesis is that these polymorphisms lead to altered HLA-

G expression in the decidua basalis, affecting local fetal-maternal immune tolerance and in turn promoting development of acute atherosis. Failure to establish fetal-maternal tolerance may also influence trophoblast invasion into the decidua. These extravillous trophoblasts are involved in the plugging and remodeling of uteroplacental spiral arteries in early pregnancy (80).

Ischemia-Reperfusion Injury

The first 10 weeks of pregnancy, the spiral arteries extending from the placenta to the endometrial surface of the decidua are effectively plugged, and the fetus exists in a state of physiological hypoxia (111, 112). At the end of the first trimester, the maternal vessels of the decidua open up and the placenta is submerged in maternal blood (111). This marks a dramatic shift in the fetoplacental exposure to the maternal cardiovascular and system.

Throughout pregnancy, uteroplacental blood flow increases, reaching up to 750 ml/minute at term, about 25% of maternal cardiac output (113). At the same time, the approximate 5-fold increase in diameter of the terminal coils of fully remodeled spiral arteries dramatically slows down the speed of the blood entering the intervillous space (111). Failure of proper spiral artery remodeling results in downstream placental malperfusion. The retention of smooth muscle within the arterial wall likely causes ischemia-reperfusion injury (114), and not impaired flow volume nor uteroplacental hypoperfusion. In addition, we argue that placental malperfusion may not be exclusively secondary to failure of spiral artery remodeling. Failed remodeling may be considered an "external" cause of placental malperfusion and is typically seen in early-onset preeclampsia. Late-onset preeclampsia affects a greater rate of women than the early-onset form, and spiral artery remodeling is rarely affected. In this setting, malperfusion may be caused by two "internal" pathways. In the one pathway, placental senescence causes a syncytiotrophoblast stress response as the pregnancy progresses towards term and thereafter. The other pathway occurs with particularly large placentas, such as in multiple gestations, in which compression leads to placental congestion and thereby malperfusion (93, 115). The ensuing disturbances in calcium-homeostasis may cause endoplasmic reticulum stress and initiate the unfolded protein response, ultimately leading to cell death (116, 117). Moreover, intracellular buildup of reactive oxygen species induces upregulation and secretion of the proinflammatory cytokines TNF and IL-1b (118, 119). ER stress and oxidative stress in placental tissues are both features of preeclampsia (31, 117, 120), and may also play a role in the strongly associated acute atherosis lesion development.

High pressure and turbulent blood flow may also damage the endothelial lining of the terminal coils of spiral arteries, as well as syncytiotrophoblasts coating placental villi. Analysis of hemodynamic forces on vascular endothelial cells has shown that disturbed blood flow and continuous low grade shear stress acting on the arterial wall may promote atherogenesis (121). This is in line with the increased incidence of atherosclerotic lesions at arterial branch points or sections with high curvature (122, 123). Endothelial cells possess surface molecules capable of detecting shear stress and inducing gene transcription through the Ras-

MAP kinase signaling pathway (124). Among several changes in gene expression is a transient upregulation of the monocyte chemotactic protein 1 (MCP-1) (125). Overexpression of MCP-1 attracts macrophages and may induce infiltration into vessel walls (126). Interestingly, endothelial MCP-1 is upregulated in preeclampsia (127, 128), possibly due to atherogenic blood flow, and could possibly be involved in CD68^{+} cell recruitment to the sites of lesion development (129, 130).

Ferroptosis is a recently discovered mode of iron-dependent cell death (131, 132). Lipoxygenases and other enzymes may induce ferroptosis in a controlled manner (133). In addition, and more relevant to the topic at hand, ferroptosis may occur due to iron dysregulation and free-radical chain reactions, leading to hydroxyl and peroxyl radicals (133). Recently, ferroptosis has gained attention as a possible target against ischemia-reperfusion injury (134–136). Thus, ferroptosis may play a role in early-onset preeclampsia following incomplete spiral artery remodeling. Interestingly, huge amounts of iron have been observed in atherosclerotic lesions (137), and lipid peroxidation is known to play a significant role in atherogenesis (138). Moreover, animal experiments have shown alleviation of atherosclerosis through inhibition of ferroptosis (139). However, the role of iron-dependent cell death due to ischemia-reperfusion in acute atherosis development remains to be investigated.

Preexisting Systemic Inflammation

Systemic inflammation is associated with many chronic diseases, such as obesity, diabetes mellitus and cardiovascular disease, as reviewed in (140–142). Considering that even normal pregnancy is associated with elevated systemic inflammation (143), one would expect heightened baseline inflammation to be associated with higher rates of obstetric complications linked to the maternal immune system. This is indeed what is observed. Obesity, diabetes mellitus and high blood pressure are all substantial risk factors for miscarriage (144–146), preeclampsia (92, 147) and fetal neurodevelopmental disorders (148–150). In line with the effects of other chronic inflammatory conditions on pregnancy, pregnant women with autoimmune disease experience higher rates of hypertensive disorders of pregnancy, intrauterine growth restriction, preterm delivery and autism spectrum disorder in their offspring (151–154). Interestingly, autoimmune disorders are also commonly observed in association with acute atherosis (155, 156). In fact, lesions have been observed as early as the first trimester in women with systemic lupus erythematosus (157).

Microbial Infection

Many tissues first thought to be sterile have been shown to harbor dormant bacteria. This includes blood (158, 159), seminal fluid (160) and possibly the placenta (161) – although this latter claim is disputed (162). The source of these bacteria may be the gut (163), the oral cavity (164) or the urinary tract (165). The iron dysregulation and dormant microbes hypothesis proposes these bacteria may be resuscitated from dormancy by free iron and manifest a diverse range of chronic inflammatory diseases previously thought to not possess infectious properties such as preeclampsia and atherosclerotic disease (166). Viable bacteria release lipopolysaccharide (LPS) or lipoteichoic acid (LTA). This initiates a cascade of immune responses, including a dramatic upregulation of many circulating cytokines and other acute phase signaling molecules like serum amyloid A1 (SAA1) and C-reactive protein (167, 168). As extensively reviewed by Kell and Kenny, there are several lines of evidence pointing towards microbial contribution in the development of preeclampsia (169). There is high co-occurrence between bacterial infections and preeclampsia. Examples include *Chlamydia pneumoniae* (170, 171) and *Helicobacter pylori* (172). Several biomarkers associated with preeclampsia have also been linked to microbial infections, including sFlt-1/PlGF ratio (173, 174) and SAA1 (167). In support of the concept that preeclampsia development has a microbial component, is the virtual absence of preeclampsia in pregnancies with *Toxoplasma gondii* infection treated with anti-microbial medication (spiramycin) (175). Kell and others have also argued for the existence of a microbial component in atherosclerosis with quite compelling evidence (159, 166, 176). Patients with chronic bacterial infections are substantially more at risk for atherosclerosis (177, 178), and LPS is regularly used to generate animal models of the disease (179, 180). Moreover, atherosclerotic plaques contain bacterial DNA (181, 182) and elevated levels of iron (180), adding credence to the iron dysregulation and dormant microbes hypothesis. The similarities to atherosclerosis have led others to speculate that an infectious trigger underlies the development of acute atherosis as well (183, 184). However, this matter remains unsettled.

A NEW HYPOTHESIS LINKING CELLULAR FETAL MICROCHIMERISM WITH ACUTE ATHEROSIS IN PREGNANCY AND FUTURE CARDIOVASCULAR AND NEUROVASCULAR DISEASE

Cellular fetal microchimerism (cFMC) arises when cells of fetal origin are transferred to maternal blood and tissues during pregnancy (185). These cells are known to possess stem cell-like properties, capable of differentiating into endothelial cells, smooth muscle cells and even leukocytes (186, 187). During pregnancy, a lot of fetal material leaks into maternal circulation. While cell free fetal DNA and other debris is rapidly cleared following delivery (188) and likely completely absent from maternal systems postpartum, cFMC may persist for decades. In fact, fetal cells have been observed in maternal circulation up to 27 years postpartum, indicating that these cells may inhabit maternal systems throughout life (189). Restorative as well as detrimental effects have been attributed to cFMC, possibly tied to fetal-maternal histocompatibility (185). Of particular interest in the context of this review is the apparent detrimental effect of cFMC on autoimmunity (190, 191). The trigger has been proposed to be a maternal alloimmune response towards fetal cells expressing foreign HLA surface peptides (191). By far the majority of patients diagnosed with autoimmune disorders are women (192), which could partly be due to the acquisition of fetal cells during pregnancy.

In comparison to healthy pregnancies, circulating fetal microchimeric cells are more prevalent in pregnancies complicated by preeclampsia (193, 194) or severe fetal growth restriction combined with impaired placental perfusion (195). If this is due to increased cell transfer, reduced clearance or reduced migration from maternal blood into maternal tissues is unclear (185, 196). We hypothesize that when the placenta is dysfunctional, fetal cells leak more freely across into maternal blood and subsequently other tissues. These cells may then inhabit maternal vessels, in the presence or absence of endothelial damage, and induce a maternal anti-fetal immune response towards the vascular endothelium. This could explain the association between male cFMC and an increased cardiovascular mortality hazard ratio (197). However, this last observation was based on a total of only 5 cardiovascular deaths. A recent study on a much larger cohort found that male-origin microchimerism was associated with *reduced* risk of ischemic heart disease as well as no association between microchimerism and ischemic stroke (198).

Microchimerism is not unique to pregnancy. Low levels of donor cells may be acquired following solid organ transplantation (199). The presence of such microchimerism has been linked to graft acceptance (200) as well as graft rejection (201). As with autoimmune diseases and cFMC, the effect of donor microchimerism may depend on how well the host tolerates the graft. Interestingly, vascular lesions have been observed in arteries surrounding transplanted organs following kidney transplant rejection (202), after liver transplantation (203) and after heart transplantation (204). These lesions are characterized by large amounts of lipids, IgM and C3 (205), and thus bear striking resemblance to acute atherosis.

Our novel hypothesis states that placental dysfunction leads to augmented cFMC. If persistent in the circulation or alternatively engrafted in maternal endothelium, these semi-allogenic cells could cause further inflammation, particularly in vessel walls, and initiate development of inflammatory arterial lesions such as acute atherosis. As cFMC persist decades after pregnancy, there may be a role for these cells in the pathogenesis of chronic cardiovascular and neurovascular disease in the long term as well. We believe this hypothesis merits further testing in translational clinical studies.

CLINICAL TRANSLATION

During Pregnancy

Acute atherosis is associated with arterial thrombosis, placental infarction and perinatal death (22, 28, 30, 206, 207). This has led researchers to propose aspirin as a possible treatment for acute atherosis (208). Aspirin is an effective prophylactic treatment against thrombosis (209). Outside of pregnancy, aspirin is widely used for primary and secondary prevention of atherosclerotic CVD (210). Daily low-dose aspirin started during the first trimester has shown a substantially reduced risk of preeclampsia in women at high risk (211–213). Whether this effect is related to a reduced tendency of blood clot formation, and how this may relate to acute atherosis, remains to be investigated.

Acute atherosis lesions may also effectively reduce the diameter of uteroplacental spiral arteries, causing aberrant blood flow (69, 111). The evidence of this latter claim is, however, conflicting. Supporting this, an early study of only 6 cases showed a trend between acute atherosis and high uterine artery pulsatility index, which could reflect obstructed spiral artery blood flow (214). Furthermore, another research group showed that acute atherosis is associated with a higher incidence of placental lesions characteristic of maternal vascular hypoperfusion (215). Placental lesions are also associated with abnormal uterine velocimetry measurements among women with intrauterine fetal growth restriction (216). In contrast to these findings, one study found no association between uterine artery pulsatility index and acute atherosis (217). The reasons for these discrepant findings may be that the spiral arteries are not visualized directly by Doppler studies, but rather indirectly by studying the blood flow of the larger uterine arteries (214, 216–218). Uterine and spiral arteries differ much in structure, size and function. Uterine artery ultrasonography has historically been viewed as a reflection of spiral artery remodeling (219), but recent studies indicate that the radial arteries, as well as the maternal vascular system, may have a larger impact on uterine artery waveforms than the spiral arteries (218). Doppler ultrasonography is hence unlikely a reliable tool for diagnosing uteroplacental acute atherosis.

Postpartum: Targeting the Women at Highest Risk of Premature Cardiovascular Disease?

We have put forth the hypothesis that women with concomitant preeclampsia and acute atherosis are at especially high risk for developing atherosclerosis and premature cardiovascular disease (130). If pregnancy is a physiological stress test (220, 221), then preeclampsia is an unmasking of compromised maternal cardiovascular health. Time and time again preeclampsia has been linked to future maternal cardiovascular disease in one form or another (222–230). The severity of preeclampsia also correlates with ischemic heart disease incidence rate (231). Moreover, fetal manifestations of placental dysfunction, such as intrauterine growth restriction, further add to maternal risk of cardiovascular disease (232). Abnormal placentation also associates with infertility or subfertility, both of which are associated with poor long-term cardiovascular health (233, 234). As described above, acute atherosis may disturb placental perfusion (69, 111), and is associated with low birth weight (4) and low placental weight (5). Acute atherosis may thus play a role in producing and/or exacerbating maternal and fetal symptoms of placental dysfunction, associated with high cardiovascular disease risk.

There are striking similarities between acute atherosis and atherosclerosis, indicative of shared pathophysiology. We know that preeclampsia is associated with a substantial atherosclerotic load (235). Compared to normotensive women and women with gestational hypertension, women with preeclampsia have higher carotid intima-media thickness (CIMT) (236, 237) – increasingly used as a surrogate marker for preclinical atherosclerosis (238). In some studies, these differences remained evident up to 18 months postpartum (236, 237). However, other studies with longer follow-up did not corroborate these findings (239, 240).

Notably, one study unexpectedly reported *thinner* CIMT 7 Years postpartum in women with preeclampsia compared to controls (241). Instead, they found increased intima thickness as well as intima-media ratio in cases versus control. The authors suggest that these measures are preferable to the conventional CIMT for assessing cardiovascular disease risk in women with a history of preeclampsia. As lesions of the placental bed manifest during a shorter time span compared to atherosclerosis (possibly due to the proximity to the foreign fetus and the excessive inflammation of pregnancy), acute atherosis may possibly be used as an indicator of women with excessive atherosclerotic load (130).

Several studies have examined the link between decidual lesions and subsequent cardiovascular health. Two retrospective cohort studies by the same research group have revealed long-term cardiovascular consequences of decidual vasculopathy (242, 243). Decidual vasculopathy was in these studies defined by vascular fibrinoid necrosis and lipid-filled foam cells in the vascular wall, thus sharing some of the features traditionally used for acute atherosis (244). The first study examined cardiovascular parameters 2-74 months postpartum in women whose index pregnancies were complicated by preeclampsia. Women with concomitant decidual vasculopathy and preeclampsia had higher diastolic blood pressure, lower left ventricular stroke volume and higher total peripheral vascular resistance as compared to women with only preeclampsia (243). Decidual vasculopathy did, however, not correlate with circulating lipids or thrombophilia postpartum. The second study demonstrated a higher prevalence of chronic hypertension several years postpartum in women who had concomitant decidual vasculopathy and preeclampsia, compared to women who only had preeclampsia. These results remained significant after correcting for chronic hypertension before index pregnancy (242).

A small study comprising only 3 cases of acute atherosis showed higher levels of triglycerides and low-density lipoprotein in these women on the first day postpartum as compared to women without acute atherosis (245). Our group conducted a larger study where we also measured triglycerides and cholesterols (among other circulating biomarkers) the day of cesarean section. We observed no differences in circulating cardiovascular biomarkers between women with acute atherosis and women without. However, when restricting the analyses to women of advanced maternal age (age 36-44) we observed significantly elevated low-density lipoprotein and ApoB in women with acute atherosis (20). These studies highlight the potential use of acute atherosis in targeting women at particularly high risk of cardiovascular disease – a concept promoted by us and others previously (246, 247). Utilizing the more readily detected maternal vascular malperfusion lesions of the placenta has also been suggested (248), although some claim

cardiovascular disease risk should be linked with atherosclerotic lesions of the uteroplacental artery instead of decidual basal artery or placental lesions (249).

FUTURE RESEARCH OPPORTUNITIES

As outlined above, there is substantial evidence backing up the concept of acute atherosis as a pregnancy-specific inflammatory arterial lesion. However, many uncertainties regarding acute atherosis remain. Firstly, the risk factors and triggers that initiate lesion development have not been fully elucidated, though there seems to be a consensus among researchers that endothelial damage is part of it. Damage could stem from ischemia-reperfusion injury, infections or excessive activation of G-protein cascades, to name a few. Further research into the molecular constituents of acute atherosis – in particular early lesion stages – could shed some light on this issue. Secondly, there are many candidates for drivers of inflammation and lesion development following endothelial insult. Further knowledge of which pathways play a substantial role could guide the development of prophylactic treatments of obstetric syndromes tightly associated with acute atherosis. This includes our suggestion of testing whether the use of anti-atherogenic statins during severe preeclampsia or fetal growth restriction, such as in women with systemic lupus, may ameliorate acute atherosis, improve uteroplacental perfusion and enhance pregnancy outcome (69). Thirdly, the long-lasting implications of pregnancy affected by acute atherosis on maternal health need further research. There is a clear lack of studies with hard endpoints to show if acute atherosis, as we have proposed, can be used to identify women at substantial risk for premature cardiovascular disease and death.

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DPJ wrote the review. HEF, GMJ, IKF, KM, PA-K, RD, MS, and ACS revised the manuscript and gave expert scientific input on its content. All authors contributed to the article and approved the submitted version.

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