Acute Atherosis of the Uterine Spiral Arteries: Clinicopathologic Implications

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Acute atherosis was first described in 1945 by Hertig1 and was named by Zeek and Assali.2 Acute atherosis is unique vascular changes observed in non-transformed spiral arteries of the placenta. The histologic findings of acute atherosis, including fibrinoid necrosis, inflammatory cell infiltration of the vessel walls and collection of subendothelial lipid-laden macrophages,1,49 are similar to those of early-stage atherosclerosis of the coronary and other larger arteries, as well as allograft rejection.27,50 Acute atherosis is rare in normal pregnancy,25,22,31,42 but is frequently observed in abnormal pregnancies, such as preeclampsia, small for gestational age (SGA), fetal death, spontaneous preterm labor and preterm premature rupture of membranes.2,4,5,7,13,16-19,21,25,24,26-31,40-42,44-48,51 The etiology and pathogenesis of preeclampsia is complicated and remains unclear, despite its role as one of the leading causes of maternal and neonatal morbidity and mortality in pregnancy. Failure of physiologic remodeling of the spiral arteries is a main cause of preeclampsia, and these arteries are prone to develop acute atherosis.52 Moreover, accumulating evidence suggests that women with a history of preeclampsia exhibit a high prevalence of major cardiovascular risk factors.53-57 This gives rise to the question of whether acute atherosis in the placenta is related to possible future cardiovascular disease in the mother.

This review describes (1) spiral artery changes in normal and abnormal placentation during pregnancy, (2) histologic findings of acute atherosis, (3) acute atherosis frequency in normal and abnormal pregnancies, (4) placental lesions associated with acute atherosis, (5) possible pathogenic mechanisms of acute atherosis, and (6) clinical implications of acute atherosis.

POOR PLACENTATION AND ACUTE AHEROSIS

Normal physiologic transformation of the uterine spiral arter...
ies during early pregnancy is considered a foundation of successful pregnancy. The spiral arteries are normally transformed into large dilated vessels, with dramatic structural changes to the vessel wall. The key findings of normal transformation of the spiral arteries are (1) dilatation of the lumen, (2) trophoblast invasion into the vessel wall, and (3) replacement of the muscular and elastic tissue of the arterial wall by a thick fibrinoid material (Fig. 1A). These changes maximize the delivery of maternal blood to the intervillous space of the placenta, so that a sufficient blood supply through transformed spiral arteries enables the transfer of enough nutrition and oxygen from the mother to the fetus. Maternal blood from dilated spiral arteries meets fetal blood in the intervillous space, while the intervillous space drains blood back to the utero-placental veins. For successful placentation, trophoblast invasion from the maternal-fetal interface to the myometrium through the decidua during the first 3 months of pregnancy is critical.

Poor placentation is defined as the failure of physiologic transformation of spiral arteries and appears to arise from an inadequate or shallow trophoblast invasion. Poor placentation is also a leading cause of preeclampsia and other abnormal pregnancies, such as spontaneous abortion, SGA, preterm labor and preterm PROM. In preeclampsia, spiral arteries of the myometrial segment of the uterus fail to achieve physiologic transformation and retain thick walls and a narrow lumen; this is believed to be the main cause of uteroplacental ischemia (Fig. 1B). Uteroplacental ischemia can lead to the production of anti-angiogenic factors, such as soluble fms-like tyrosine kinase 1 and endoglin, which can induce endothelial dysfunction and eventually predispose the pregnancy to preeclampsia. Spiral arteries that fail to achieve physiologic transformation are prone to develop acute atherosis.

**HISTOLOGIC CHARACTERISTICS AND TOPOGRAPHIC DISTRIBUTION OF ACUTE ATHEROSIS**

Histologic findings of acute atherosis consist of the presence of fibrinoid necrosis of the artery wall, a subendothelial collection of lipid-laden macrophages, and vascular or perivascular lymphocytic infiltration in non-transformed uterine spiral arteries (Fig. 2A). Lipids in the spiral arteries with acute atherosis are stained red with oil-red O (Fig. 2B).

Acute atherosis was more frequently observed in the spiral arteries of the decidua (parietalis or basalis) of the placenta than in the decidual or myometrial segments of the placental bed. The depth of acute atherosis is associated with the severity of preeclampsia. Briefly, the presence of atherosis in the myometrial segment is associated with a severe form and an earlier onset of preeclampsia than those without this lesion in the myometrial segment.

**FREQUENCY OF ACUTE ATHEROSIS**

Acute atherosis used to be considered a characteristic finding of spiral arteries of patients with preeclampsia and has been reported to occur in 5% to 40% of patients with preeclampsia. The variable frequency of acute atherosis may be explained by the following reasons: (1) variation in the number of tissue sections taken (size of sample), (2)
location of tissue sections, (3) variation in tissue staining methods (hematoxylin and eosin [H&E] staining only or additional immunohistochemical staining) for the diagnosis of acute atherosis, and (4) differences in the pathologist’s diagnostic skill. In a previous study with over 14,000 placenta samples using only H&E staining for the diagnosis of acute atherosis and taking an average of two sections from each placenta based on routine histology laboratory tasks, the prevalence of acute atherosis in uncomplicated pregnancies was 0.4% and the frequency of acute atherosis varied based on the specific obstetrical syndrome: preeclampsia, 10%; fetal death, 9%; mid-trimester spontaneous abortion, 2.5%; SGA neonates without preeclampsia, 1.7%; and spontaneous preterm labor, 1.2%. Acute atherosis is associated with more severe disease, earlier onset of preeclampsia, and a greater frequency of SGA neonates in patients with preeclampsia.51,80

PLACENTAL LESIONS ASSOCIATED WITH ACUTE ATHEROSIS

A previous study found that acute atherosis is associated with an increased risk of placental lesions consistent with maternal underperfusion, fetal vascular thrombo-occlusive disease and chronic chorioamnionitis, but not with other chronic inflammatory lesions.81

The correlation between acute atherosis and chronic chorioamnionitis indicates the presence of circulating maternal T cells and adaptive immune response may also play a role in the genesis of acute atherosis.73,77,78,91

In chronic chorioamnionitis, maternal T cells infiltrating the chorion laeve cause trophoblast apoptosis, which resembles allograft rejection.92 Chronic chorioamnionitis is also associated with anti-fetal HLA maternal sensitization53 and complement deposition in the umbilical vein endothelium,94 which has been associated with a novel form of fetal systemic inflammatory response characterized by the over-expression of T-cell chemokines such as CXCL10.95

Higher concentrations of CXCL9, CXCL10, and CXCL11 have been found in mothers with chronic placental inflammation compared to those without.92 Similarly, T lymphocytes have been detected in the early stages of atheroma formation.96 Moreover, differential expression of three interferon (IFN) gamma-inducible CXC chemokines, IFN-inducible protein 10 (CXCL10 or IP-10), monokine induced by IFN-y (CXCL9 or Mig) and IFN-inducible T-cell α chemoattractant (CXCL11 or I-TAC) were found in atherosclerosis.96

PATHOGENESIS OF ACUTE ATHEROSIS

Multiple factors including excessive decidual inflammation,45,46,47 immune dysregulation at the maternal-fetal interface27 and immunological mismatch between the mother and fetus27 have been proposed as causes or initiators of acute atherosis.

Recently, Staff et al.48 suggested four serial mechanisms for the development of acute atherosis, with excessive decidual inflammation as the final common pathway: (1) shear flow stress caused by abnormal blood flow in inadequately remodeled spiral arteries, (2) decidual inflammation, including maternal allo-reactivity to feto-paternal HLA-C or minor histocompatibility antigens, (3) background (systemic) maternal inflammatory stress secondary to the changes induced by pregnancy and preeclampsia, and (4) maternal genetic predisposition (for example, polymorphism in regulator of G protein signaling 2).

Elevation of signs of intravascular inflammation have been reported in both normal98-101 and abnormal pregnancies, such as
spontaneous preterm labor with intact membranes,102-108 preterm PROM,109-114 preeclampsia,115-117 SGA,26-28 SGA,119,120,121,122 preeclampsia,26-28,94 and pyelonephritis.99,135-137 Since chronic vascular inflammation is one of the main causes of atherosclerosis and acute atherosclerosis, the possibility of activation of cholesterol crystal-induced inflammation in macrophages138 should be investigated as an important link between cholesterol metabolism and acute atherosclerosis.

**THE CLINICAL IMPLICATIONS OF ACUTE ATHEROSIS**

Maternal serum lipid level of patients with acute atherosclerosis in the placenta
In atherosclerosis, medium-sized and large arteries fueled by lipids, as well as the deposition of excess cholesterol in the blood stream, initiate atherogenesis.139 Similarly, acute atherosclerosis in non-transformed uterine spiral arteries also show variable amounts of lipid deposition in the wall of spiral arteries, and it is stained red with oil-red O staining (Fig. 2B). Moreover, serum triglycerides are about 50% higher in pre eclamptic women than in normal pregnant women. However, there are no differences in other lipid profiles, including total cholesterol and high-density lipoprotein.31,160-162 Whether there are differences in low-density lipoprotein remains controversial.143-145,163

Acute atherosclerosis and future cardiovascular risk
Accumulating evidence suggests that women with a history of preeclampsia show a high prevalence of major cardiovascular risk factors.53-57 Similarities between preeclampsia and atherosclerosis, as well as between acute atherosclerosis of the spiral arteries and coronary atherosclerosis, have been observed. Intravascular inflammation,98,118,120,164,165 changes in lipid metabolism,162,166-168 and macrophage infiltration of the intima and media are seen in both acute atherosclerosis and atherosclerosis.27,169,170 Therefore, hyperlipidemia and abnormal lipid metabolism combined with intravascular inflammation can defect endothelial cell function and may lead to atherosclerosis in non-pregnant women who have a past history of preeclampsia.52-79 We recommend that women who have a past history of preeclampsia be considered at high risk for cardiovascular disease and recommend implementation of regular screenings and prevention programs.

**CONCLUSION**

The presence and deeper location of acute atherosclerosis is associated with worse pregnancy outcomes, more severe disease, earli-er onset, and a greater frequency of SGA neonates in patients with preeclampsia. Moreover, the idea that acute atherosclerosis in the placenta may increase the risk of future cardiovascular disease in women with a history of preeclampsia is of growing concern. Therefore, placental examination is crucial for investigation of pregnancy complications and outcomes, and accurate placental pathology based on universal diagnostic criteria in patients with abnormal pregnancies is essential for clinicopathologic correlation.

**Conflicts of Interest**
No potential conflict of interest relevant to this article was reported.

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