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Placental Lesions Associated with Acute Atherosclerosis

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Abstract

Objective—Acute atherosclerosis is a lesion of the spiral arteries characterized by fibrinoid necrosis of the vessel wall, an accumulation of fat-containing macrophages, and a mononuclear perivascular infiltrate, which can be found in patients with preeclampsia, fetal death, small-for-gestational age (SGA), spontaneous preterm labor/premature prelabor rupture of membrane, and spontaneous mid-trimester abortion. This lesion is thought to decrease blood flow to the intervillous space which may lead to other vascular lesions of the placenta. The objective of this study was to test whether there is an association between acute atherosclerosis and placental lesions that are consistent with maternal vascular underperfusion, amniotic fluid infection, fetal vascular thrombo-occlusive disease or chronic inflammation.

Material and methods—A retrospective cohort study of pregnant women who delivered between July 1998 and July 2014 at Hutzel Women's Hospital/Detroit Medical Center was

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conducted examine 16,457 placentas. The frequency of placenta lesions (diagnosed using the criteria of the Perinatal Section of the Society for Pediatric Pathology) was compared between pregnancies with and without atherosclerosis.

Results—Among 16,457 women who were enrolled, 10.2% (1,671/16,457) were excluded, leaving 14,786 women who contributed data for analysis. Among them, the prevalence of acute atherosclerosis was 2.2% (326/14,786). Women with acute atherosclerosis were more than six times as likely as those without to have placental lesions consistent with maternal underperfusion (adjusted odds ratio- aOR: 6.7; 95% CI 5.2–8.6). To a lesser degree, acute atherosclerosis was also associated with greater risks of having either lesions consistent with fetal vascular thrombo-occlusive disease (aOR 1.7; 95% CI 1.2–2.3) or chronic chorioamnionitis (aOR 1.9; 95% CI 1.3–3), but not with other chronic inflammatory lesions, after adjusting for gestational age at delivery. In contrast, women with acute atherosclerosis were 60% less likely to have lesions consistent with amniotic fluid infection, adjusting for gestational age at delivery (aOR 0.4; 95% CI 0.3–0.5).

Conclusions—Acute atherosclerosis is associated with increased risks of having placental lesions consistent with maternal vascular underperfusion, and to a lesser extent, chronic chorioamnionitis and those consistent with fetal vascular thrombo-occlusive disease.

Keywords

amniotic fluid infection; chronic chorioamnionitis; chronic villitis; fetal vascular thrombo-occlusive disease; ischemic placental disease; maternal anti-fetal rejection; maternal underperfusion; pregnancy

Introduction

Acute atherosclerosis is a vascular lesion characterized by fibrinoid necrosis of the vessel wall, an accumulation of fat-containing macrophages, and a mononuclear perivascular infiltrate [1–50]. This lesion is usually identified in the spiral arteries which have not undergone physiologic transformation. Originally described in preeclampsia, acute atherosclerosis has also been found in other complications of pregnancy including spontaneous preterm labor (sPTL)/premature prelabor rupture of membrane (PPROM) [50], fetal death [50], gestational diabetes mellitus [5,15,24,50], gestational and chronic hypertension [15,24,27,28,50], systemic lupus erythematosus, and antiphospholipid antibody syndrome [14,24,31,34,37], intrauterine fetal growth restriction (IUGR) [13,16,19,20,22,32,50]. It is rarely observed in normal pregnancy [3,4,21,30,43,50]. The presence of acute atherosclerosis has also been associated with a more severe form of preeclampsia [4,46,50].

Acute atherosclerosis is considered to predispose to maternal vascular lesions of underperfusion (e.g. infarctions of the placenta) [51] and is thought to represent “ischemic placental disease” [52–57]. The relationship between acute atherosclerosis and vascular lesions of the placenta, however, has not been rigorously examined. The objective of this study is to determine the associations among acute atherosclerosis and histologic placental lesions consistent with maternal vascular underperfusion (MVU), fetal vascular thrombo-occlusive disease (FVTOD), chronic inflammation, or amniotic fluid infection (AFI).

Material and Methods

This retrospective cohort study includes pregnant women who delivered between July 1998 and July 2014 at Hutzel Women's Hospital/Detroit Medical Center and had pathologic examination of the placenta. All women provided written informed consent before specimen collection. The collection and utilization of the samples was approved by the Human Investigation Committee of Wayne State University and the IRB of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NIH/DHHS). The clinical definitions, classification of pregnancy complications and sample collection have been described in a previous report [50].

Placental Pathology

Tissue samples obtained from each placenta; one roll of chorioamniotic membranes and one of the umbilical cord. Two sections were taken from each the chorionic and basal plate. Tissues were formalin-fixed and embedded in paraffin. Five-micrometer sections of tissue blocks were stained with hematoxylin and eosin (H&E) and the slides were examined by perinatal pathologists masked to clinical outcomes. Acute atherosclerosis was diagnosed by the presence of fibrinoid necrosis of the spiral artery wall with the presence of lipid-laden macrophages in the lumen and a perivascular lymphocytic infiltrate [28]. Histopathological changes of the placenta were defined according to diagnostic criteria proposed by the Perinatal Section of the Society for Pediatric Pathology [51], which consists of 3 broad major categories: 1) lesions consistent with amniotic fluid infection; 2) maternal underperfusion; and 3) fetal vascular thrombo-occlusive disease.

1. Lesions associated with amniotic fluid infections (AFI) incorporate those that are consistent with a maternal response, including acute chorioamnionitis, and those that are consistent with a fetal response, including funisitis/acute chorion vasculitis. Acute chorioamnionitis is staged as follows: Stage 1 lesions include acute subchorionitis/acute chorionitis diagnosed when there are accumulations of neutrophils in the subchorionic zone and/or in the chorionic trophoblast layer of the extraplacental membranes; Stage 2 lesions are diagnosed when there are more than a few scattered neutrophils in the chorionic plate and membranous connective tissues and/or in the amnion; and Stage 3 lesions include necrotizing chorioamnionitis with a marked neutrophilic infiltrate with degenerating neutrophils (karyorrhexis), thickened eosinophilic amniotic basement membrane, and focal amnionic epithelial necrosis.

Funisitis is staged as follows: Stage 1 lesions include acute chorionic vasculitis/umbilical phlebitis, diagnosed when neutrophils are identified in the wall of any chorionic plate vessel or in the umbilical vein (a few neutrophils are usually present in Wharton's jelly but without aggregates or concentric bands of inflammatory cells); Stage 2 funisitis is diagnosed when neutrophils are seen in one or both umbilical arteries and/or the umbilical vein; and Stage 3 funisitis, or necrotizing funisitis, is diagnosed when neutrophils, cellular debris, and/or mineralization is present in a concentric band, ring, or halo around one or more umbilical vessels.

2. Lesions consistent with maternal vascular underperfusion are classified as: 1) villous changes, which are further subdivided into abrupt onset (remote villous infarcts, recent villous infarcts), gradual onset with intermediate duration (increased syncytial knots, villous agglutination, increased intervillous fibrin) or gradual onset with prolonged duration (decreased placental weight/increased fetoplacental weight ratio, distal villous hypoplasia); and 2) vascular lesions (persistent muscularization of basal plate arteries, mural hypertrophy of decidual arterioles, acute atherosclerosis of basal plate arteries and/or decidual arterioles). A change in the fetoplacental weight ratio criteria was not included in this study because the data was not available. Placental lesions consistent with maternal underperfusion were diagnosed if at least one pathologic lesion included in this category was present.
3. Lesions consistent with fetal vascular thrombo-occlusive disease (FVTOD) are also considered and are similarly classified as villous or vascular. Villous lesions of FVTOD are categorized as early, late or severe. Early villous lesions of FVTOD include villous stromal-vascular karyorrhexis (three or more foci of two or more terminal villi showing karyorrhexis of fetal cells with preservation of surrounding trophoblast). Late lesions of FVTOD consist of hyalinized avascular villi, either as exclusively small foci or variable sized foci, while severe lesions are consistent with fetal thrombotic vasculopathy with an average of 15 or more affected villi per slide.

Chronic placental inflammatory lesion diagnoses were recorded electronically for all women who enrolled in or beyond 2010. These include: 1) chronic chorioamnionitis; 2) villitis of unknown etiology and; 3) chronic deciduitis.

1. Chronic chorioamnionitis is diagnosed when lymphocytic infiltration into the chorionic trophoblast layer or chorioamniotic connective tissue is observed [58]. The severity of chronic chorioamnionitis is scored based upon two parameters. The extent of inflammation is graded 0 when there is no inflammation, 1 when there is more than two foci or patchy inflammation, and 2 when diffuse inflammation is present. The stage of inflammation is scored as stage 1 if amniotropic lymphocytic infiltration is limited to the chorionic trophoblast layer sparing the chorioamniotic connective tissue, and stage 2 if lymphocytic infiltration into the chorioamniotic connective tissue is noted.
2. Villitis of unknown etiology is defined as the presence of lymphohistiocytic infiltrate in varying proportion of the villous tree of placenta. When less than 10 villi are involved, the process is low grade and can be termed either focal (only one slide involved) or multifocal (more than one slide involved). High-grade chronic villitis, has more than 10 villi per focus and separated into patchy and diffuse subgroups with the latter subgroup being used when more than 5% of all distal villi are involved [59,60].
3. Chronic deciduitis is defined as the presence of lymphocytic infiltration into the decidua of the basal plate. The assessments are subsequently assigned numerical scores for statistical calculations: 0 for absence, 1 for maybe, and 2 for presence. Three other features of the chronic inflammatory infiltrate, when present, are also

scored by the pathologists: extent, scored as focal, multifocal, or diffuse (1, 2, or 3, respectively); severity, scored as mild, moderate or severe (1,2, or 3), plasma cells, scored as absent or present (0 or 1) [61].

Statistical analysis

The Kolmogorov-Smirnov test was used to assess the distributions of arithmetic data. The Kruskal-Wallis test for comparisons and the Mann-Whitney U test were used to make comparisons among and between groups for arithmetic variables. Chi-square or McNemar-Bowker tests were used for comparisons of categorical variables. Logistic regression models were fit to examine magnitudes of association, adjusting for gestational age at delivery. Statistical analysis was performed using SPSS 19 (IBM Corp, Armonk, NY) and SAS 9.3 (Cary, NC). A p value < 0.05 was considered statistically significant.

Results

Among 16,457 women who were enrolled and delivered at Hutzal Women's Hospital between July 1998 and July 2014, 10.2% (1,671/16,457) were excluded from this study because clinical information was incomplete, fetal anomalies, and multiple pregnancies, leaving 14,786 women who contributed data to this study. Among them, the prevalence of acute atherosclerosis was 2.2% (326/14,786). Women with acute atherosclerosis had a significantly higher median age, and greater frequencies of preeclampsia and fetal death, whereas the median birth weight and gestational age at delivery were significantly lower, when compared to women without acute atherosclerosis ($p < 0.001$). On the other hand, sPTB/PPROM occurred more frequently in women without acute atherosclerosis than in those with this lesion ($p < 0.001$) (Table I).

Placental lesions consistent with amniotic fluid infection, maternal vascular underperfusion (excluding atherosclerosis of basal plate arteries and/or decidual arterioles), and fetal vascular thromboocclusive disease were identified in 28% (4,122/14,715), 23.9% (3,537/14,786), and 8.9% (1,322/3,386) of the study population, respectively. Among the sub-cohort enrolled since 2010, for whom the presence or absence of chronic inflammatory lesions was recorded, the prevalence of chronic chorioamnionitis, chronic deciduitis and villitis of unknown etiology was 26% (881/3,386), 20.4% (692/3,386) and 16.7% (564/3,386), respectively (Table II).

Co-occurrence of Atherosclerosis with Acute and Chronic Placental Lesions

Placental findings consistent with maternal vascular underperfusion (excluding atherosclerosis of basal plate arteries and/or decidual arterioles) and fetal vascular thrombo-occlusive disease were found more commonly among women with acute atherosclerosis than in those without atherosclerosis [70.9% (231/326) vs. 22.9% (3,306/14,460), $p < 0.0001$; 14.4% (47/326) vs. 8.8% (1,275/14,460), $p = 0.0005$]. Among the sub-cohort with documented presence or absence of chronic inflammatory lesions, women with acute atherosclerosis also had chronic inflammatory lesions more frequently than those who did not. [59.4% (57/96) vs. 43.3% (1,424/3,290); $p = 0.002$]. In contrast, the frequency of placental lesions consistent with amniotic fluid

infection was significantly lower in patients with acute atherosclerosis than in those without [14.7% (48/326) vs. 28.3% (4,074/14,389); $p < 0.0001$] (Table II).

Magnitudes of association among acute atherosclerosis and other placental lesions

Table III shows the odds of having placental lesions among women with acute atherosclerosis compared to those without this lesion, adjusting for gestational age at delivery. Women with acute atherosclerosis were more than six times as likely as those without to have placental lesions consistent with maternal underperfusion than (adjusted odds ratio- aOR: 6.7; 95% CI 5.2–8.6). To a lesser degree, acute atherosclerosis was also associated with greater risks of having either lesions consistent with fetal vascular thrombo-occlusive disease (aOR 1.7; 95% CI 1.2–2.3) or chronic inflammatory lesions (aOR 2; 95% CI 1.3–3). The association between acute atherosclerosis and chronic inflammatory lesions was driven primarily by an increased risk among women with chronic chorioamnionitis, since the other chronic lesions were no longer associated after adjusting for gestational age at delivery. In contrast, women with acute atherosclerosis were 60% *less* likely to have lesions consistent with amniotic fluid infection, adjusting for gestational age at delivery (aOR 0.4; 95% CI 0.3–0.5).

Discussion

Principal findings of this study

1) acute atherosclerosis is associated with an increased risk of having placental lesions consistent with maternal vascular underperfusion, and to a lesser extent, chronic chorioamnionitis and those consistent with fetal vascular thrombo-occlusive disease. By contrast, the odds of having lesions consistent with amniotic fluid infection were significantly lower in women with acute atherosclerosis than in those without these lesions.

The Association Between Acute atherosclerosis and Placental Lesions Consistent with Maternal Underperfusion

Maternal lesions of underperfusion are thought to mediate utero-placental ischemia, which has been proposed as a mechanism of disease in preeclampsia [55,62–73], intrauterine growth restriction [55,62–64,66–68,71,74–79], fetal death [64,66,68,80,81] and abruptio placenta (ischemic placental disease) [52–57,64,66,68,82,83], preterm labor [64,66,68,84–90], preterm prelabor rupture of membranes [64,66,68,91,92], recurrent spontaneous abortion [17,93] and massive perivillous fibrin deposition [94–108]. It is important to clarify that the nosology of maternal vascular lesions consistent with underperfusion includes acute atherosclerosis, and that we examined its association with other villous and vascular lesions consistent with maternal vascular underperfusion.

Acute Atherosclerosis and Chronic Chorioamnionitis

During the course of allograft rejection, vascular lesions can be detected in the transplanted organ and they are characterized by the presence of foam cells, intimal sclerosis and myointimal hyperplasia leading to a narrow vascular lumen [109–115]. Typically, there is inflammatory cell infiltration (lymphocyte and macrophages) and extensive deposition of IgM, complement (C) 3 and C1q [111,116–120]. Immunohistochemistry studies have shown that IgM and C3 are detectable in decidual vessels with acute atherosclerosis but not in spiral

artery, which have undergone physiologic transformation [15,18,20,121–124]. Therefore, it is possible that in a subset of cases, acute atherosclerosis represents the morphologic expression of maternal anti-fetal rejection [26].

Chronic chorioamnionitis, the most common placental lesion in late spontaneous preterm birth [125], is characterized by maternal T cells infiltration of the chorion laeve, which can cause trophoblast apoptosis. This chronic placental lesion resembles allograft rejection [58]. We have previously reported that chronic chorioamnionitis is associated with anti-fetal HLA maternal sensitization [126] and complement deposition in umbilical vein endothelium [127], and this has been associated with a novel form of fetal systemic inflammation characterized by overexpression of T cell chemokines, such as CXCL-10 [125].

Parallels between acute atherosclerosis and the atheromatous lesions of atherosclerosis have been proposed [47–49,128]. Although both of these lesions are generally considered to reflect activation of the innate immune response (macrophages), there is accumulating evidence suggesting participation of the adaptive limb of the immune response as well [129–145]. Specifically, T lymphocytes have been detected in the early stages of atheroma formation and they persist as the lesions grow and eventually rupture [146]. Moreover, there is differential expression of three interferon gamma inducible CXC chemokines in atheromatous lesions, including: IFN-inducible protein 10 (CXCL10 or IP-10), monokine induced by IFN- γ (CXCL9 or Mig), and IFN-inducible T-cell α chemoattractant (CXCL11 or I-TAC) [146]. Mothers with chronic placental inflammation have higher concentrations of CXCL9, CXCL10 and CXCL11 than those without this lesion [147], and we have also demonstrated changes in the behavior of circulating T cells [89]. Therefore, it is tempting to hypothesize that circulating maternal T cells may participate in the genesis of acute atherosclerosis. Further studies are required to test this hypothesis.

Acute Atherosclerosis and Fetal Thrombo-occlusive Disease

The association between acute atherosclerosis and fetal thrombo-occlusive diseases is novel. Preeclampsia [147–156], preterm labor [157–162], and fetal death [163–169] were associated with thrombophilia. Inherited or acquired thrombophilic states have been implicated in the genesis of fetal thrombo-occlusive disease [40,111,115,170–174]. It is possible that a maternal thrombophilic state predisposes to acute atherosclerosis and if the condition is inherited by the fetus, to thrombotic lesions in the fetal circulation. The role of acquired excessive thrombin generation in acute atherosclerosis and fetal thrombo-occlusive disease requires further investigation.

Acute Atherosclerosis and Amniotic Fluid Infection

Accumulating evidence demonstrated that term parturition is associated with intra-amniotic infection and/or inflammation [175–188]. Patients with acute atherosclerosis were less likely to have placental lesions consistent with amniotic fluid infection. The most probable explanation for this is that atherosclerosis is most frequently observed in patients with preeclampsia and intrauterine growth restriction, which are frequent indications of cesarean delivery without labor; therefore, the lower frequency of placental lesions consistent with amniotic fluid infection might reflect that that patients without these lesions are more likely

to undergo labor, which is associated with the occurrence of placental lesions consistent with amniotic fluid infection [184,189].

Strengths and Limitations

Limitations of the study are those inherent in retrospective observational studies. We have previously reported the frequency of acute atherosclerosis in a large number of placentas using standard techniques employed by clinical pathologists in the United States (two sections of the basal plate, stained with H&E, and without the use of immunohistochemistry techniques to identify macrophages, lipids, smooth muscle and interstitial trophoblast). A wider sampling of the basal plate of the placenta, examination of a larger number of spiral arteries, and the use of special staining may yield insight into the frequency of acute atherosclerosis and associated placental lesions.

Conclusion

Acute atherosclerosis is associated with increased risks of having placental lesions consistent with maternal vascular underperfusion, and to a lesser extent, chronic chorioamnionitis and those consistent with fetal vascular thrombo-occlusive disease.

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Table I

Demographic and clinical characteristics of the study population

	Absence of atherosclerosis (n=14,460)	Presence of atherosclerosis (n=326)	P value
Maternal age (years)	24 (26.9–39)	26 (27.5–33.9)	<0.001
Body mass index (kg/m ²)	26.9 (22.7–32.9)	27.5 (23.3–32.8)	0.3
Race			
• African American	86.2% (12,450/14,460)	90.5% (294/326)	0.13
• Caucasian	7% (1,008/14,460)	4% (13/326)	
• Others	6.8% (977/14,460)	5.5% (19/326)	
Pregnancy outcomes			
• sPTB/PPROM	12.6% (1,818/14,460)	7.1% (23/326)	<0.001
• Preeclampsia	11.2% (1,598/14,460)	55.5% (181/326)	
• Fetal death	1.8% (266/14,460)	8% (26/326)	
• Normal pregnancy	47.9% (6,932/14,460)	8.9% (29/326)	
• Others	26.5% (3,831/14,460)	20.5% (67/326)	
Gestational age at delivery (weeks)	39 (37.1–40)	33.9 (29.6–38)	<0.001
Birthweight (g)	3080 (2,620–3,445)	1700 (936–2440)	<0.001

sPTB: spontaneous preterm birth, PPROM: preterm prelabor rupture of membrane

Data presented as median (interquartile) or % (n)

Table II

The frequency of other placental lesions in women with and without acute atherosclerosis

Placental lesions	Absence of atherosclerosis (n=14,460)	Presence of Atherosclerosis (n=326)	P value
Amniotic fluid infection (Any)	28.3% (4074/14389)	14.7% (48/326)	<0.001
• Maternal Response	26% (3,745/14,396)	14.4% (47/326)	<0.001
• Fetal Response	17.5% (2,527/14,409)	7.4% (24/326)	<0.001
Maternal underperfusion* (Any)	22.9% (3306/14460)	70.9% (231/326)	<0.0001
• Presence of villous changes	16.5% (2378/14460)	58% (189/326)	<0.001
• Presence of vascular lesions*	8.2% (1190/14460)	31.9% (104/326)	<0.001
Fetal thrombo-occlusive disease (Any)	8.8% (1275/14460)	14.4% (47/326)	0.0005
• Presence of villous changes	6.6% (943/14460)	3% (29/326)	0.09
• Presence of vascular lesions	2.7% (390/14460)	6.7% (22/326)	<0.001
Any chronic inflammatory lesion** (Any)	43.3% (1,424/3,290)	59.4% (57/96)	0.002
• Chronic chorioamnionitis	25.6% (843/3290)	39.6% (38/96)	0.002
• Chronic deciduitis	20.2% (664/3290)	29.2% (28/96)	0.03
• Villitis of unknown etiology	16.8% (551/3290)	13.5% (13/96)	0.41
[0]Note: * =excludes acute atherosclerosis of basal plate arteries and/or decidual arterioles ** =restricted to patients enrolled in or beyond year 2010, when the presence or absence of chronic inflammatory lesions was universally recorded.			

* Among women enrolled in or beyond 2010, when the presence or absence of chronic inflammatory lesions was universally recorded.

** Restricted to patients enrolled in or beyond year 2010, when the presence or absence of chronic inflammatory lesions was universally recorded.

Odds of having placental lesion (any of each group) among women with acute atherosclerosis relative to those without, adjusting for gestational age at delivery

Table III

	Adjusted odd ratios	95% CI	
Amniotic fluid infections	0.4	0.3	0.5
Maternal vascular underperfusion (excluding acute atherosclerosis of basal plate arteries and/or decidual arterioles)	6.7	5.2	8.6
Fetal thrombo-occlusive disease	1.7	1.2	2.3
Any chronic inflammatory lesion (chronic chorioamnionitis, deciduitis or villitis of unknown etiology) *	2.0	1.3	3.0
Chronic chorioamnionitis	1.9	1.3	3.0
Chronic deciduitis	1.5	0.9	2.3
Villitis of unknown etiology	1.2	0.6	2.1

*. Restricted to patients enrolled in or beyond year 2010, when the presence or absence of chronic inflammatory lesions was universally recorded; adjusted odd ratios: adjusted for gestational age at delivery