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The Frequency of Acute Atherosis in Normal Pregnancy and Preterm Labor, Preeclampsia, Small for Gestational Age, Fetal Death and Midtrimester Spontaneous Abortion

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Abstract

Objective—Acute atherosis is characterized by subendothelial lipid-filled foam cells, fibrinoid necrosis and perivascular lymphocytic infiltration. This lesion is generally confined to non-transformed spiral arteries and is frequently observed in patients with preeclampsia. However, the frequency of acute atherosis in the great obstetrical syndromes is unknown. The purpose of this study was to determine the frequency and topographic distribution of acute atherosis in placentas and placental bed biopsy samples obtained from women with normal pregnancy and those affected

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by the “great obstetrical syndromes”. We also examined the relationship between acute atherosis and pregnancy outcome in patients with preeclampsia.

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 conducted to examine 16,345 placentas. Patients were classified into the following groups: 1) uncomplicated pregnancy; 2) spontaneous preterm labor and preterm prelabor rupture of membranes (PPROM); 3) preeclampsia; 4) gestational hypertension; 5) small for gestational age; 6) chronic hypertension; 5) fetal death; 6) spontaneous abortion; and 7) others. A subset of patients had placental bed biopsy. The incidence of acute atherosis was compared among the different groups.

Results—1) The prevalence of acute atherosis in uncomplicated pregnancies was 0.4% (29/6,961) based upon examination of nearly 7,000 placentas; 2) the frequency of acute atherosis was 10.2% (181/1,779) in preeclampsia, 9% (26/292) in fetal death, 2.5% (3/120) in midtrimester spontaneous abortion, 1.7% (22/1,298) in small for gestational age neonates, and 1.2% (23/1,841) in spontaneous preterm labor and PPROM; 3) among patients with preeclampsia, those with acute atherosis had significantly more severe disease, earlier onset, and a greater frequency of small-for-gestational age neonates than in those without the lesion ($p < 0.05$ all); 4) the lesion was more frequently observed in the decidua (parietalis or basalis) than in the decidual segment of the spiral arteries in patients with placental bed biopsies.

Conclusions—Acute atherosis is rare in normal pregnancy, and occurs more frequently in patients with pregnancy complications, including preeclampsia, spontaneous preterm labor, preterm PROM, midtrimester spontaneous abortion, fetal death, and SGA.

Keywords

atherosclerosis; CD68; fibrinoid; foam cells; macrophage; spiral artery

Introduction

Acute atherosis is a unique lesion observed in the spiral arteries characterized by fibrinoid necrosis of the vessel wall, which is often accompanied by the collection of foamy, fat-laden macrophages beneath the intima of the arteries and an inflammatory infiltrate of the vessel wall [1–48]. The similarities with lesions observed in early stages of atherosclerosis and allograft rejection (i.e. kidney transplants) [26,49] suggest that intravascular inflammation and hyperlipidemia might be responsible for the generation of atherosis [44,46,47,50–54].

Although acute atherosis was originally described in the spiral arteries of patients with preeclampsia [2–4,6–12,15–18,20,22,23,25–30,39–41,43–47], this lesion is not specific, and has been reported in normal pregnancy [3,4,21,30,41], as well as those complicated by diabetes mellitus [5,15,24], gestational and chronic hypertension [15,24,27,28], systemic lupus erythematosus, and antiphospholipid antibody syndrome [14,24,31,34,37], as well as intrauterine fetal growth restriction (IUGR) [13,16,19,20,22,32]. The prevalence of acute atherosis in spontaneous midtrimester abortion, spontaneous preterm labor, preterm prelabor rupture of membranes (PPROM), and unexplained fetal death, however, is unknown.

Failure of physiologic transformation was originally described in preeclampsia, but is also observed in many of the "great obstetrical syndromes" [55–62]. Therefore, it is possible that acute atherosis may occur in other complications of pregnancy; yet, the frequency of acute atherosis in the great obstetrical syndromes is lacking and its association with adverse pregnancy outcomes remains unclear [3,4,15,23,25,27,41,45]. The purpose of this study was to determine the frequency and the topographic distribution of acute atherosis in the placentas and placental bed biopsy samples obtained from women with normal pregnancies and those affected by the great obstetrical syndromes. We also examined the relationship between acute atherosis and pregnancy outcomes in patients with preeclampsia.

Material and Methods

We undertook a retrospective cohort study of 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. From this cohort, a subset had placental bed biopsies performed at the time of Cesarean delivery. The following groups were excluded from this study: 1) fetal congenital anomaly; 2) multiple gestations; 3) missing clinical data; and 4) indicated/elective abortion. All women provided written informed consent prior to the collection of placentas and placental bed biopsy samples. 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).

Clinical Definitions

Term delivery without obstetrical complications—Patients without medical or surgical complications of pregnancy who delivered a normal term (≥37 weeks) neonate whose birth weight was between the 10^{th} and 90^{th} percentile for gestational age.

Spontaneous preterm labor (sPTL)—Patients between 20–36 6/7 weeks of gestation who presented with spontaneous labor and intact membranes and delivered prior to 37 weeks of gestation.

Preterm prelabor rupture of membranes (PPROM)—PPROM was diagnosed in the presence of the following criteria: 1) delivery < 37 weeks of gestation; 2) history of leaking of fluid from the vagina; and 3) positive pooling of vaginal fluid and positive nitrazine test. A positive ferning test was considered confirmatory, but not necessary, for the diagnosis of PPROM.

Preeclampsia (PE)—Defined as new onset hypertension developing after 20 weeks of gestation (systolic or diastolic blood pressure ≥140 or ≥90 mmHg, respectively, measured at two different time points, 4 hours to 1 week apart) in the presence of proteinuria (≥300 mg in a 24 hour urine collection, or two random urine specimens obtained 4 hours to 1 week apart demonstrating ≥ 1+ protein by dipstick, or one dipstick demonstrating ≥ 2+ protein) [63]. Severe preeclampsia was defined as previously described [63]. Patients with preeclampsia were also classified as "early" (≤34 weeks) or "late" (>34 weeks) preeclampsia according to the gestational age at delivery. Chronic hypertension with

superimposed preeclampsia was diagnosed in women with hypertension documented before 20 weeks of gestation with a new-onset proteinuria or in women with hypertension and proteinuria at < 20 weeks of gestation with a sudden increase in proteinuria, blood pressure in women whose hypertension was previously well controlled, thrombocytopenia and elevated liver transaminase enzymes [63].

Gestational hypertension: defined as a systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg on at least two determinations 4 hours to one week apart without proteinuria (dipstick < 1+ or 24 hour urine protein < 300 mg).

Chronic hypertension—Women with hypertension (systolic or diastolic blood pressure ≥ 140 or ≥ 90 mmHg, respectively, measured at two different time points, 4 hour to 1 week apart) before 20 weeks of gestation or those who reported a history of hypertension.

Small-for-gestational age (SGA)—Neonates with birth weight < 10^{th} percentile for gestational age, according to the reference range [64,65].

Fetal death: defined as death of the fetus after 20 weeks of gestation diagnosed by ultrasound examination. Fetuses with known congenital and/or chromosomal abnormalities were excluded. This group was classified according to clinical circumstances into: 1) unexplained fetal death (n=4); 2) fetal death with preeclampsia (n=14); and 3) others which included abruptio placentae (n=8).

Spontaneous abortion: fetal loss between 10 and 20 completed weeks of gestation.

Others—This group included indicated preterm delivery due to fetal/maternal conditions which were not included following groups above, such as abruptio placentae, placenta previa, placenta accreta and pregnancy with maternal underlying medical conditions.

Each patient with pregnancy complications was classified according to a mutually exclusive schema which placed priority in the following order: 1) fetal death; 2) pregnancy- associated hypertension (preeclampsia, gestational hypertension, preeclampsia superimposed chronic hypertension and chronic hypertension); 3) spontaneous preterm birth (sPTL and PPROM); and 4) others. The SGA group in the current study included patients with SGA neonates without fetal death, pregnancy associated hypertension and spontaneous preterm birth. Hence, a pregnancy that was affected by preeclampsia, yet resulted in a fetal death, would be grouped in the fetal death study group rather than in the preeclampsia study group.

Placental specimens

After delivery, placentas were transported to the laboratory and examined by trained personnel according to methods previously described by our group [66]. Tissue samples obtained from each placenta included 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. In a small subset of patients, placental bed biopsy

specimens were obtained at the time of cesarean delivery according to techniques previously described [67].

Criteria for histopathologic diagnosis

Atherosis was diagnosed by the presence of fibrinoid necrosis of the spiral artery wall with presence of lipid laden macrophages in the lumen and a perivascular lymphocytic infiltrate [28]. Figure 1 shows a normal spiral artery and several examples of acute atherosis with fibrinoid necrosis, foamy macrophages, and inflammatory infiltration of the vessel wall.

Statistical analysis

The Kolmogorov-Smirnov test was used to assess the distributions of arithmetic data. The Kruskal-Wallis test 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. Statistical analysis was performed using SPSS 19 (IBM Corp, Armonk, NY, USA) and SAS 9.3 (Cary, NC, USA). A p value < 0.05 was considered statistically significant.

Results

Among 16,345 women who were enrolled and delivered at Hutzel Women's Hospital between July 1998 and July 2014, 9.5% (1,559/16,345) were excluded from this study due to the following: clinical information was incomplete [4.2% (694/16,345)], fetal anomalies [1.9% (304/16,345)], or multiple pregnancies [3.4% (561/16,345)], leaving 14,786 cases for analysis. Among these, 47.1% (6,961/14,786) had normal term delivery, 12.5% (1,841/14,786) had spontaneous preterm delivery or PPROM, 12% (1,779/14,786) were diagnosed with preeclampsia, 10.8% (1,597/14,786) had gestational hypertension, 8.8% (1,298/14,786) had small-for-gestational age neonates, and 4.7% (698/14,786) had chronic hypertension. The frequency of pregnancy complications in this study is described in Table I. A total of 543 placental bed biopsies were available for examination.

Frequency of atherosis according to pregnancy outcome

Acute atherosis was more frequently identified in patients with preeclampsia [10.2% (181/1779), fetal death [8.9% (26/292)], midtrimester spontaneous abortion [2.5% (3/120)], chronic hypertension without preeclampsia [2.3% (16/698)], SGA alone [1.7% (22/1298)], gestational hypertension [1.3% (20/1597)], spontaneous preterm labor and PPROM [1.2% (23/1841)] and others [3% (6/200)] than in those with uncomplicated pregnancies [0.4% (29/6961)] ($p<0.001$ for all) (Figure 2).

Among patients with preeclampsia (n=1779), those with acute atherosis had a higher frequency of preterm delivery, a lower median birth weight, higher frequencies of small for gestational age, severe preeclampsia and early preeclampsia than in those without this lesion (Table II).

The topographic distribution of acute atherosis

Acute atherosis was observed more frequently in the decidua parietalis (chorioamniotic membranes) and the basal plate of the placenta (Table III). There was a significantly higher frequency of acute atherosis lesions in the placenta (both basal plate and chorioamnion) than in placental bed biopsies (both decidua and myometrial segment) ($p < 0.001$) (Table III). Among women with preeclampsia, patients with acute atherosis lesions in the myometrial segment from placental bed biopsy (n=19/71) had a significantly lower median (IQR) gestational age at delivery (weeks) than those without this lesion in the myometrial segment (n=53/71) [27.4 (25.3–30.7) vs. 31.9 (28.6–35.6); p=0.005], indicating that the depth of the lesion is associated with the severity of preeclampsia.

Discussion

Principal Findings

1) The prevalence of acute atherosis in uncomplicated pregnancies was 0.4% based upon examination of nearly 7,000 placentas; 2) the frequency of acute atherosis varied with the specific obstetrical syndrome – preeclampsia, 10%; fetal death, 9%; midtrimester spontaneous abortion, 2.5%; small-for-gestational age neonates (without preeclampsia), 1.7%; spontaneous preterm labor, 1.2% and; 3) among patients with preeclampsia, those with acute atherosis had a more severe form, earlier onset, and a greater frequency of small-for-gestational age neonates; 4) the lesion was more frequently observed in the decidua (parietalis or basalis) of placental specimens than in the decidual segment of the spiral arteries in patients with placental bed biopsies.

Relationship between acute atherosis and clinical severity of preeclampsia

We report herein that the presence of acute atherosis is associated with severe and early preeclampsia, an observation that is consistent with other reports [4,45]. The link probably reflects the association among severe intravascular inflammation [68–77], immune dysregulation [78–80] in patients with early-onset and severe disease and the degree of defective deep placentation of spiral arteries [61] in this subpopulation of patients.

The distribution of acute atherosis and depth of the process in the spiral arteries

Topographically, acute atherosis is typically present in spiral arteries with failure of physiologic tranformation, usually in the decidual segment [11,28,29,48]. However, the lesion has also been observed in the myometrial section of the spiral arteries. The observations reported in this study are in keeping with those in the literature indicating that acute atherosis affects the distal segment of the spiral arteries. It is possible that the presence of atherosis in the myometrial segment is indicative of more extensive disease, which would be clinically manifested as early and severe preeclampsia.

Possible mechanisms implicated in the genesis of acute atherosis

The interested reader is referred to recent reviews on the pathophysiology of acute atherosis [44,46–48]. Briefly, the mechanisms implicated include: 1) shear flow stress caused by abnormal blood flow in inadequate remodeled spiral arteries; 2) decidual inflammation

induced by an immune response to trophoblasts or danger signals in the decidua; 3) an exaggerated systemic maternal inflammatory response which creates conditions similar to those observed in atherosclerosis and favors the generation of arterial wall lesions; 4) maternal genetic predisposition, given that a polymorphism in RGS2 (regulator of G protein signaling) increases the risk of preeclampsia and acute atherosis [81]. The relative contributions of each of these mechanisms have not been determined.

We report herein acute atherosis can be observed in unexplained fetal death, spontaneous midtrimester abortion, spontaneous preterm birth and PPROM. Normal pregnancy is characterized by physiologic intravascular inflammation, demonstrated by a change in the immunophenotype of granulocytes and monocytes, and increased production of reactive oxygen species [82,83], as well as an increase in acute phase reactants during normal pregnancy (fibrinogen [84], C-reactive protein [85], etc.). In complications of pregnancy such as spontaneous preterm labor with intact membranes, [86–92], PPROM [93–98], preeclampsia [99–128], SGA [103,118,120,122,129–138], and pyelonephritis [83,139–141], intravascular inflammation is increased compared to normal pregnancy. These observations support the hypothesis that an exaggerated intravascular inflammatory response may play a role in the genesis of acute atherosis in the susceptible patient.

The frequency of atherosis in preeclampsia reported in the present study is lower than that typically observed in other studies [4,6,7,9–12,15–18,22,23,25–30,39,41,44,45], yet prevalence ranging from 5% to 40% has been reported. The lower prevalence reported herein might be attributable to differences in case-definition, or since most prior studies performed a deliberate search for acute atherosis, and ours involved data collected during the course of ongoing research and clinical care, ascertainment bias may have inflated prior estimates.

Strengths and Limitations

The frequency of any lesion in histopathologic studies is a function of sampling of the organ, the definition of the lesion, the methods used for staining of tissues and recognizing specific features (such as macrophages, fibrinoid necrosis, the deposition of lipids, etc.). The findings of this study reflect the practice of placental pathology worldwide. We used H&E, as this is the standard immunohistochemical staining. In previous reports in which we have focused on the study of the placental bed, we used Periodic Acid Schiff (PAS) to detect fibrinoid necrosis and cytokeratin to identify interstitial trophoblast [57,58,67]. Neither of these methods was used in this study. The original description of atherosis included the presence of lipid-laden macrophages within the spiral arteries. Macrophage markers such as CD-68, as well as immunohistochemistry staining to identify lipids (oil-red O, sudan black B, etc.), [142] could be used to identify macrophages and lipid deposition in future studies. Staining for smooth-muscle actin could be used to determine whether there is loss of the smooth muscle in the spiral arteries. Atherosis typically occurs in physiologically non-transformed spiral arteries in which the smooth muscle in the media has not been replaced by fibrinoid. As studies of the Human Placenta Project move forward, a more in-depth characterization of acute atherosis and other lesions can be undertaken by increasing the number of sections - particularly those of the basal plate of the placenta. Alnaes-Katjavivi et

al. emphasized that the standard definition of acute atherosis lacks quantitative criteria, and could be subject to observer bias, and proposed new diagnostic criteria using quantitative methods [143]. We agree that such an approach would be useful in assessing the frequency and clinical significance of acute atherosis in future studies.

Conclusion

Acute atherosis is rare in normal pregnancy, occurs more frequently in patients with pregnancy complications including: preeclampsia, spontaneous preterm labor, preterm PROM, midtrimester spontaneous abortion, fetal death, and SGA, and is associated with poorer pregnancy outcomes in women with preeclampsia.

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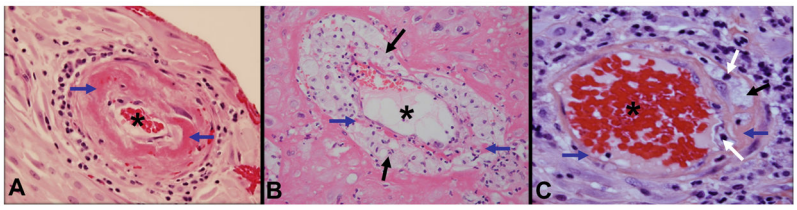

Figure 1.

Acute atherosis in the decidual segment of spiral arteries (Hematoxylin and Eosin, x400). A) Fibrinoid necrosis (blue arrow) and few chronic inflammatory cells within the vessel wall but no macrophages; B) Mainly lipid-laden macrophages (black arrows) with minor fibrinoid necrosis (blue arrow) in the vessel wall and; C) Fibrinoid necrosis (blue arrow) with lipid-laden macrophages (black arrow) as well as chronic inflammatory cells (white arrows) in the vessel wall and perivascular areas. * lumen of spiral artery.

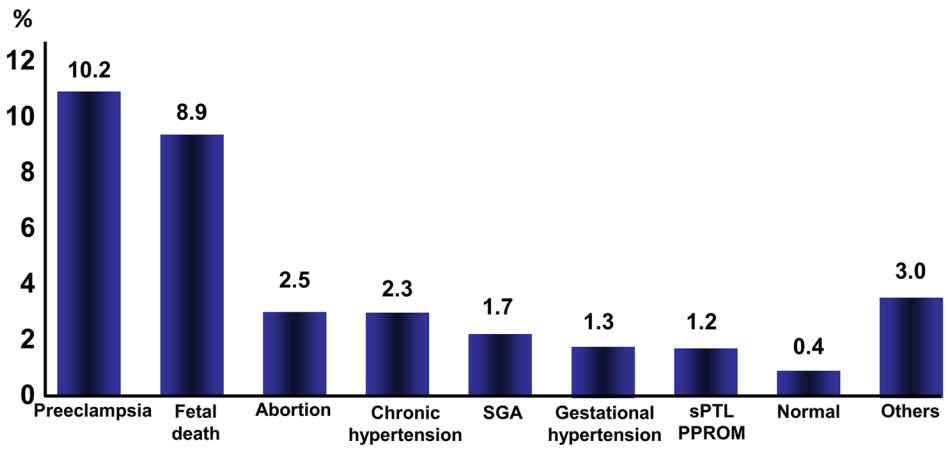

Figure 2.

Frequency of acute atherosis according to pregnancy outcomes. Each patient with pregnancy complications was classified according to a mutually exclusive schema. Abortion: midtrimester abortion, SGA: small-for-gestational age, sPTL: spontaneous preterm labor, PPROM: preterm prelabor rupture of membranes. SGA group included patients with SGA neonates without fetal death, pregnancy associated hypertension and spontaneous preterm birth. Comparison between each pregnancy complication and term delivery: $p < 0.001$ for all.

Table 1

Clinical Diagnosis of Patients Included in the Study

Pregnancy outcomes	N	%
Uncomplicated pregnancy	6961	47.1%
Spontaneous preterm labor and PPROM	1841	12.5%
Preeclampsia	1779	12%
Gestational hypertension	1597	10.8%
Small for gestational age	1298	8.8%
Chronic hypertension	698	4.7%
Fetal Death	292	2%
Mid-trimester spontaneous abortion	120	0.8%
Others	200	1.4%
Total	14786	100%

Each patient with pregnancy complications was classified according to a mutually exclusive schema; PPROM: preterm premature rupture of membranes, SGA group included patients with SGA neonates without fetal death, pregnancy associated hypertension and spontaneous preterm birth.

Table 2

Clinical characteristics and pregnancy outcome of patients with preeclampsia according to the presence or absence of acute atherosis

	Preeclampsia without atherosis (n=1598)	Preeclampsia with atherosis (n=181)	P value
Maternal age (years)	25 (20–31)	27 (22–34)	<0.01
Frequency of nulliparous women	33% (481)	26% (31)	0.1
BMI (kg/m^2)	29.4 (24.6–36.1)	28.2 (24–35)	0.07
Race			
• African American	88.4% (1413)	87.3% (158)	
• Caucasian	6.4% (103)	6.1% (11)	0.75
• Other	5.1% (82)	6.6% (12)	
Gestational age at delivery (weeks)	37.7 (35.6–39.3)	32.6 (29–36.3)	<0.01
Birthweight (kg)	2795 (2175–3280)	1705.5 (914.3–2592.5)	<0.01
Small for gestational age	29.1% (463)	44.2 (80)	0.004
Severity of preeclampsia			
• Mild preeclampsia	30.7% (490)	11.6% (21)	
• Severe preeclampsia	43.4% (694)	50.8% (92)	<0.001
• Superimposed preeclampsia	25.9% (414)	37.6% (68)	
Early preeclampsia (delivery ≤ 34 weeks)	16 % (255)	56.4% (102)	<0.001

Data presented as median (interquartile) or percent (n); BMI: body mass index

Table 3

Distribution of acute atherosis according to histologic sections examined in the placenta and placental bed biopsies

Location of acute atherosis	Frequency of atherosis % (n)
Chorioamniotic membranes	75.5% (246/326)
Basal plate of placenta	72.1% (235/326)
Basal plate or chorioamnion	97.2% (317/326)
Decidua in placental bed biopsies	53.8% (56/104)
Myometrium in placental bed biopsies	23.8% (25/101)

P value = 0.5; comparison between basal plate and chorioamnion in membranes

P value < 0.001; comparison between basal plate or chorioamnion and placental bed biopsies