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

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Abstract

Objective—Acute atherosclerosis 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 atherosclerosis in the great obstetrical syndromes is unknown. The purpose of this study was to determine the frequency and topographic distribution of acute atherosclerosis 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 atherosclerosis 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 atherosclerosis was compared among the different groups.

Results—1) The prevalence of acute atherosclerosis in uncomplicated pregnancies was 0.4% (29/6,961) based upon examination of nearly 7,000 placentas; 2) the frequency of acute atherosclerosis 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 PPRM; 3) among patients with preeclampsia, those with acute atherosclerosis 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 atherosclerosis 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 atherosclerosis 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 atherosclerosis [44,46,47,50–54].

Although acute atherosclerosis 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 atherosclerosis 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 atherosclerosis may occur in other complications of pregnancy; yet, the frequency of acute atherosclerosis 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 atherosclerosis 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 atherosclerosis 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 10th and 90th 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 PPRM.

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 $\geq$ 140 mmHg and/or diastolic blood pressure $\geq$ 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 $\geq$ 140 or $\geq$ 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 < 10th 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

Atherosclerosis 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 atherosclerosis 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 atherosclerosis according to pregnancy outcome

Acute atherosclerosis 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 atherosclerosis 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 atherosclerosis

Acute atherosclerosis 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 atherosclerosis 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 atherosclerosis 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 atherosclerosis in uncomplicated pregnancies was 0.4% based upon examination of nearly 7,000 placentas; 2) the frequency of acute atherosclerosis 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 atherosclerosis 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 atherosclerosis and clinical severity of preeclampsia

We report herein that the presence of acute atherosclerosis 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 atherosclerosis and depth of the process in the spiral arteries

Topographically, acute atherosclerosis is typically present in spiral arteries with failure of physiologic transformation, 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 atherosclerosis affects the distal segment of the spiral arteries. It is possible that the presence of atherosclerosis 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 atherosclerosis

The interested reader is referred to recent reviews on the pathophysiology of acute atherosclerosis [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 atherosclerosis [81]. The relative contributions of each of these mechanisms have not been determined.

We report herein acute atherosclerosis 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 atherosclerosis in the susceptible patient.

The frequency of atherosclerosis 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 atherosclerosis, 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 atherosclerosis 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. Atherosclerosis 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 atherosclerosis 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 atherosclerosis 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 atherosclerosis in future studies.

Conclusion

Acute atherosclerosis 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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References

1. Hertig AT. Vascular pathology in the hypertensive albuminuric toxemias of pregnancy. *Clinics*. 1945;602–14.
2. Sexton LI, Hertig AT, et al. Premature separation of the normally implanted placenta; a clinicopathological study of 476 cases. *Am J Obstet Gynecol*. 1950; 59:13–24. [PubMed: 15408710]
3. Zeek PM, Assali NS. Vascular changes in the decidua associated with eclamptogenic toxemia of pregnancy. *Am J Clin Pathol*. 1950; 20:1099–109. [PubMed: 14783095]
4. Maqueo M, Chavezazuela J, Dosaldelavega M. Placental Pathology in Eclampsia and Preeclampsia. *Obstet Gynecol*. 1964; 24:350–6. [PubMed: 14207329]
5. Driscoll SG. The pathology of pregnancy complicated by diabetes mellitus. *Medical Clinics of North America*. 1965; 49:1053–67.
6. Robertson WB, Brosens I, Dixon HG. The pathological response of the vessels of the placental bed to hypertensive pregnancy. *J Pathol Bacteriol*. 1967; 93:581–92. [PubMed: 6054058]
7. Brosens IA, Robertson WB, Dixon HG. The role of the spiral arteries in the pathogenesis of preeclampsia. *Obstet Gynecol Annu*. 1972; 1:177–91. [PubMed: 4669123]
8. Brosens I, Renaer M. On the pathogenesis of placental infarcts in pre-eclampsia. *J Obstet Gynaecol Br Commonw*. 1972; 79:794–9. [PubMed: 4651288]
9. Emmrich P, Birke R, Godel E. Morphology of myometrial and decidual arteries in normal pregnancy, in toxemia of pregnancy, and in maternal diabetes (author's transl). *Pathol Microbiol (Basel)*. 1975; 43:38–61.
10. De Wolf F, Robertson WB, Brosens I. The ultrastructure of acute atherosclerosis in hypertensive pregnancy. *Am J Obstet Gynecol*. 1975; 123:164–74. [PubMed: 1163579]
11. Robertson WB, Brosens I, Dixon G. Uteroplacental vascular pathology. *Eur J Obstet Gynecol Reprod Biol*. 1975; 5:47–65. [PubMed: 1053577]
12. Robertson WB, Brosens I, Dixon G. Maternal uterine vascular lesions in the hypertensive complications of pregnancy. *Perspect Nephrol Hypertens*. 1976; 5:115–27. [PubMed: 1005030]
13. De Wolf F, Brosens I, Renaer M. Fetal growth retardation and the maternal arterial supply of the human placenta in the absence of sustained hypertension. *Br J Obstet Gynaecol*. 1980; 87:678–85. [PubMed: 7426529]
14. Abramowsky CR, Vegas ME, Swinehart G, et al. Decidual vasculopathy of the placenta in lupus erythematosus. *N Engl J Med*. 1980; 303:668–72. [PubMed: 6995842]

15. Kitzmiller JL, Watt N, Driscoll SG. Decidual arteriopathy in hypertension and diabetes in pregnancy: immunofluorescent studies. *Am J Obstet Gynecol.* 1981; 141:773–9. [PubMed: 7032298]
16. Sheppard BL, Bonnar J. An ultrastructural study of utero-placental spiral arteries in hypertensive and normotensive pregnancy and fetal growth retardation. *Br J Obstet Gynaecol.* 1981; 88:695–705. [PubMed: 7248226]
17. De Wolf F, Carreras LO, Moerman P, et al. Decidual vasculopathy and extensive placental infarction in a patient with repeated thromboembolic accidents, recurrent fetal loss, and a lupus anticoagulant. *Am J Obstet Gynecol.* 1982; 142:829–34. [PubMed: 6801984]
18. Hustin J, Foidart JM, Lambotte R. Maternal vascular lesions in pre-eclampsia and intrauterine growth retardation: light microscopy and immunofluorescence. *Placenta.* 1983; 4(Spec No):489–98. [PubMed: 6369298]
19. Althabe O, Labarrere C, Telenta M. Maternal vascular lesions in placentae of small-for-gestational-age infants. *Placenta.* 1985; 6:265–76. [PubMed: 4022955]
20. Labarrere C, Alonso J, Manni J, et al. Immunohistochemical findings in acute atherosclerosis associated with intrauterine growth retardation. *Am J Reprod Immunol Microbiol.* 1985; 7:149–55. [PubMed: 3893171]
21. Labarrere C, Althabe O. Chronic villitis of unknown etiology and maternal arterial lesions in preeclamptic pregnancies. *Eur J Obstet Gynecol Reprod Biol.* 1985; 20:1–11. [PubMed: 4029472]
22. Khong TY, De Wolf F, Robertson WB, et al. Inadequate maternal vascular response to placentation in pregnancies complicated by pre-eclampsia and by small-for-gestational age infants. *Br J Obstet Gynaecol.* 1986; 93:1049–59. [PubMed: 3790464]
23. McFadyen IR, Price AB, Geirsson RT. The relation of birthweight to histological appearances in vessels of the placental bed. *Br J Obstet Gynaecol.* 1986; 93:476–81. [PubMed: 3707878]
24. Labarrere CA, Catoggio LJ, Mullen EG, et al. Placental lesions in maternal autoimmune diseases. *Am J Reprod Immunol Microbiol.* 1986; 12:78–86. [PubMed: 3812855]
25. Khong TY, Pearce JM, Robertson WB. Acute atherosclerosis in preeclampsia: maternal determinants and fetal outcome in the presence of the lesion. *Am J Obstet Gynecol.* 1987; 157:360–3. [PubMed: 3618685]
26. Labarrere CA. Acute atherosclerosis. A histopathological hallmark of immune aggression? *Placenta.* 1988; 9:95–108. [PubMed: 3283724]
27. Frusca T, Morassi L, Pecorelli S, et al. Histological features of uteroplacental vessels in normal and hypertensive patients in relation to birthweight. *Br J Obstet Gynaecol.* 1989; 96:835–9. [PubMed: 2765429]
28. Khong TY. Acute atherosclerosis in pregnancies complicated by hypertension, small-for-gestational-age infants, and diabetes mellitus. *Arch Pathol Lab Med.* 1991; 115:722–5. [PubMed: 2064534]
29. Meekins JW, Pijnenborg R, Hanssens M, et al. A study of placental bed spiral arteries and trophoblast invasion in normal and severe pre-eclamptic pregnancies. *Br J Obstet Gynaecol.* 1994; 101:669–74. [PubMed: 7947500]
30. Meekins JW, Pijnenborg R, Hanssens M, et al. Immunohistochemical detection of lipoprotein(a) in the wall of placental bed spiral arteries in normal and severe preeclamptic pregnancies. *Placenta.* 1994; 15:511–24. [PubMed: 7997451]
31. Salafia CM, Parke AL. Placental pathology in systemic lupus erythematosus and phospholipid antibody syndrome. *Rheum Dis Clin North Am.* 1997; 23:85–97. [PubMed: 9031376]
32. Brosens I, Dixon HG, Robertson WB. Fetal growth retardation and the arteries of the placental bed. *Br J Obstet Gynaecol.* 1977; 84:656–63. [PubMed: 911717]
33. Gerretsen G, Huisjes HJ, Elema JD. Morphological changes of the spiral arteries in the placental bed in relation to pre-eclampsia and fetal growth retardation. *Br J Obstet Gynaecol.* 1981; 88:876–81. [PubMed: 7272259]
34. Nayar R, Lage JM. Placental changes in a first trimester missed abortion in maternal systemic lupus erythematosus with antiphospholipid syndrome; a case report and review of the literature. *Hum Pathol.* 1996; 27:201–6. [PubMed: 8617465]
35. Hayati AR, Azizah A, Wahidah A. Incidence of acute atherosclerosis in complete molar pregnancy. *Malays J Pathol.* 1998; 20:113–4. [PubMed: 10879273]

36. Khong TY, Hague WM. The placenta in maternal hyperhomocysteinaemia. *Br J Obstet Gynaecol.* 1999; 106:273–8. [PubMed: 10426649]
37. Ogishima D, Matsumoto T, Nakamura Y, et al. Placental pathology in systemic lupus erythematosus with antiphospholipid antibodies. *Pathol Int.* 2000; 50:224–9. [PubMed: 10792786]
38. Sebire NJ, Rees H, Paradinas F, et al. Extravillous endovascular implantation site trophoblast invasion is abnormal in complete versus partial molar pregnancies. *Placenta.* 2001; 22:725–8. [PubMed: 11597192]
39. Moldenhauer JS, Stanek J, Warshak C, et al. The frequency and severity of placental findings in women with preeclampsia are gestational age dependent. *Am J Obstet Gynecol.* 2003; 189:1173–7. [PubMed: 14586374]
40. Faye-Petersen, O.; Heller, DS.; Joshi, VV. Histologic lesions of the placenta: villi, fetal stem arteries, intervillous space and maternal arteries in decidua. In: Faye-Petersen, O.; Heller, DS.; Joshi, VV., editors. *Handbook of Placental Pathology.* 2. United Kingdom: Taylor & Francis; 2006. p. 53-78.
41. Harsem NK, Roald B, Braekke K, et al. Acute atherosclerosis in decidua: not associated with systemic oxidative stress in preeclampsia. *Placenta.* 2007; 28:958–64. [PubMed: 17218009]
42. Fox, H.; Sebire, NJ. Histological abnormalities of the placenta. In: Fox, H.; Sebire, NJ., editors. *Pathology of the Placenta.* 3. China: ELSEVIER; 2007. p. 147-86.
43. Brosens, I.; Khong, TY. Defective spiral artery remodeling. In: Pijnenborg, R.; Brosens, I.; Romero, R., editors. *Placental Bed Disorders.* Cambridge, UK: Cambridge University Press; 2010. p. 11
44. Staff AC, Dechend R, Pijnenborg R. Learning from the placenta: acute atherosclerosis and vascular remodeling in preeclampsia—novel aspects for atherosclerosis and future cardiovascular health. *Hypertension.* 2010; 56:1026–34. [PubMed: 20956732]
45. Stevens DU, Al-Nasiry S, Bulten J, et al. Decidual vasculopathy in preeclampsia: lesion characteristics relate to disease severity and perinatal outcome. *Placenta.* 2013; 34:805–9. [PubMed: 23827236]
46. Staff AC, Dechend R, Redman CW. Review: Preeclampsia, acute atherosclerosis of the spiral arteries and future cardiovascular disease: two new hypotheses. *Placenta.* 2013; 34 (Suppl):S73–8. [PubMed: 23246096]
47. Staff AC, Johnsen GM, Dechend R, et al. Preeclampsia and uteroplacental acute atherosclerosis: immune and inflammatory factors. *J Reprod Immunol.* 2014; 101–102:120–6.
48. Staff AC, Redman CW. IFPA Award in Placentology Lecture: preeclampsia, the decidual battleground and future maternal cardiovascular disease. *Placenta.* 2014; 35 (Suppl):S26–31. [PubMed: 24411701]
49. Mitchell RN. Graft vascular disease: immune response meets the vessel wall. *Annu Rev Pathol.* 2009; 4:19–47. [PubMed: 18717641]
50. Danesh J, Collins R, Appleby P, et al. Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. *JAMA.* 1998; 279:1477–82. [PubMed: 9600484]
51. Ross R. Atherosclerosis—an inflammatory disease. *N Engl J Med.* 1999; 340:115–26. [PubMed: 9887164]
52. Yudkin JS, Kumari M, Humphries SE, et al. Inflammation, obesity, stress and coronary heart disease: is interleukin-6 the link? *Atherosclerosis.* 2000; 148:209–14. [PubMed: 10657556]
53. Galkina E, Ley K. Immune and inflammatory mechanisms of atherosclerosis. *Annu Rev Immunol.* 2009; 27:165–97. [PubMed: 19302038]
54. Libby P. Inflammation in atherosclerosis. *Arterioscler Thromb Vasc Biol.* 2012; 32:2045–51. [PubMed: 22895665]
55. Khong TY, Liddell HS, Robertson WB. Defective haemochorial placentation as a cause of miscarriage: a preliminary study. *Br J Obstet Gynaecol.* 1987; 94:649–55. [PubMed: 3620413]
56. Dommissie J, Tiltman AJ. Placental bed biopsies in placental abruption. *Br J Obstet Gynaecol.* 1992; 99:651–4. [PubMed: 1390469]

57. Kim YM, Chaiworapongsa T, Gomez R, et al. Failure of physiologic transformation of the spiral arteries in the placental bed in preterm premature rupture of membranes. *Am J Obstet Gynecol.* 2002; 187:1137–42. [PubMed: 12439491]
58. Kim YM, Bujold E, Chaiworapongsa T, et al. Failure of physiologic transformation of the spiral arteries in patients with preterm labor and intact membranes. *Am J Obstet Gynecol.* 2003; 189:1063–9. [PubMed: 14586356]
59. Ball E, Bulmer JN, Ayis S, et al. Late sporadic miscarriage is associated with abnormalities in spiral artery transformation and trophoblast invasion. *J Pathol.* 2006; 208:535–42. [PubMed: 16402350]
60. Pijnenborg R, Vercruysse L, Hanssens M. The uterine spiral arteries in human pregnancy: facts and controversies. *Placenta.* 2006; 27:939–58. [PubMed: 16490251]
61. Brosens I, Pijnenborg R, Vercruysse L, et al. The “Great Obstetrical Syndromes” are associated with disorders of deep placentation. *Am J Obstet Gynecol.* 2011; 204:193–201. [PubMed: 21094932]
62. Pijnenborg R, Vercruysse L, Brosens I. Deep placentation. *Best Pract Res Clin Obstet Gynaecol.* 2011; 25:273–85. [PubMed: 21212025]
63. Sibai BM, Ewell M, Levine RJ, et al. Risk factors associated with preeclampsia in healthy nulliparous women. The Calcium for Preeclampsia Prevention (CPEP) Study Group. *Am J Obstet Gynecol.* 1997; 177:1003–10. [PubMed: 9396883]
64. Seeds JW. Impaired fetal growth: definition and clinical diagnosis. *Obstet Gynecol.* 1984; 64:303–10. [PubMed: 6379528]
65. Alexander GR, Himes JH, Kaufman RB, et al. A United States national reference for fetal growth. *Obstet Gynecol.* 1996; 87:163–8. [PubMed: 8559516]
66. Ogge G, Chaiworapongsa T, Romero R, et al. Placental lesions associated with maternal underperfusion are more frequent in early-onset than in late-onset preeclampsia. *J Perinat Med.* 2011; 39:641–52. [PubMed: 21848483]
67. Espinoza J, Romero R, Mee Kim Y, et al. Normal and abnormal transformation of the spiral arteries during pregnancy. *J Perinat Med.* 2006; 34:447–58. [PubMed: 17140293]
68. Ustun Y, Engin-Ustun Y, Kamaci M. Association of fibrinogen and C-reactive protein with severity of preeclampsia. *Eur J Obstet Gynecol Reprod Biol.* 2005; 121:154–8. [PubMed: 16054955]
69. Venkatesha S, Toporsian M, Lam C, et al. Soluble endoglin contributes to the pathogenesis of preeclampsia. *Nat Med.* 2006; 12:642–9. [PubMed: 16751767]
70. Hirashima C, Ohkuchi A, Matsubara S, et al. Alteration of serum soluble endoglin levels after the onset of preeclampsia is more pronounced in women with early-onset. *Hypertens Res.* 2008; 31:1541–8. [PubMed: 18971528]
71. Redman CW, Sargent IL. Immunology of pre-eclampsia. *Am J Reprod Immunol.* 2010; 63:534–43. [PubMed: 20331588]
72. Hertig A, Fort J, Lefevre G, et al. Soluble endoglin in preeclamptic patients with or without HELLP syndrome. *Am J Obstet Gynecol.* 2010; 202:594, e1–4. [PubMed: 20430360]
73. Boij R, Svensson J, Nilsson-Ekdahl K, et al. Biomarkers of coagulation, inflammation, and angiogenesis are independently associated with preeclampsia. *Am J Reprod Immunol.* 2012; 68:258–70. [PubMed: 22626009]
74. Ozler A, Turgut A, Sak ME, et al. Serum levels of neopterin, tumor necrosis factor-alpha and Interleukin-6 in preeclampsia: relationship with disease severity. *Eur Rev Med Pharmacol Sci.* 2012; 16:1707–12. [PubMed: 23161044]
75. Peracoli JC, Bannwart-Castro CF, Romao M, et al. High levels of heat shock protein 70 are associated with pro-inflammatory cytokines and may differentiate early- from late-onset preeclampsia. *J Reprod Immunol.* 2013; 100:129–34. [PubMed: 24051131]
76. Pinheiro MB, Martins-Filho OA, Mota AP, et al. Severe preeclampsia goes along with a cytokine network disturbance towards a systemic inflammatory state. *Cytokine.* 2013; 62:165–73. [PubMed: 23523008]
77. Xiao JP, Yin YX, Gao YF, et al. The increased maternal serum levels of IL-6 are associated with the severity and onset of preeclampsia. *Cytokine.* 2012; 60:856–60. [PubMed: 22921280]

78. Schonkeren D, van der Hoorn ML, Khedoe P, et al. Differential distribution and phenotype of decidual macrophages in preeclamptic versus control pregnancies. *Am J Pathol.* 2011; 178:709–17. [PubMed: 21281803]
79. Quinn KH, Lacoursiere DY, Cui L, et al. The unique pathophysiology of early-onset severe preeclampsia: role of decidual T regulatory cells. *J Reprod Immunol.* 2011; 91:76–82. [PubMed: 21782252]
80. Kimura C, Watanabe K, Iwasaki A, et al. The severity of hypoxic changes and oxidative DNA damage in the placenta of early-onset preeclamptic women and fetal growth restriction. *J Matern Fetal Neonatal Med.* 2013; 26:491–6. [PubMed: 23035823]
81. Kvehaugen AS, Melien O, Holmen OL, et al. Single nucleotide polymorphisms in G protein signaling pathway genes in preeclampsia. *Hypertension.* 2013; 61:655–61. [PubMed: 23339167]
82. Sacks GP, Studena K, Sargent K, et al. Normal pregnancy and preeclampsia both produce inflammatory changes in peripheral blood leukocytes akin to those of sepsis. *Am J Obstet Gynecol.* 1998; 179:80–6. [PubMed: 9704769]
83. Naccasha N, Gervasi MT, Chaiworapongsa T, et al. Phenotypic and metabolic characteristics of monocytes and granulocytes in normal pregnancy and maternal infection. *Am J Obstet Gynecol.* 2001; 185:1118–23. [PubMed: 11717644]
84. Brenner B. Haemostatic changes in pregnancy. *Thromb Res.* 2004; 114:409–14. [PubMed: 15507271]
85. Watts DH, Krohn MA, Wener MH, et al. C-reactive protein in normal pregnancy. *Obstet Gynecol.* 1991; 77:176–80. [PubMed: 1988876]
86. Gervasi MT, Chaiworapongsa T, Naccasha N, et al. Phenotypic and metabolic characteristics of maternal monocytes and granulocytes in preterm labor with intact membranes. *Am J Obstet Gynecol.* 2001; 185:1124–9. [PubMed: 11717645]
87. Pitiphat W, Gillman MW, Joshipura KJ, et al. Plasma C-reactive protein in early pregnancy and preterm delivery. *Am J Epidemiol.* 2005; 162:1108–13. [PubMed: 16236995]
88. Gotsch F, Romero R, Kusanovic JP, et al. The anti-inflammatory limb of the immune response in preterm labor, intra-amniotic infection/inflammation, and spontaneous parturition at term: a role for interleukin-10. *J Matern Fetal Neonatal Med.* 2008; 21:529–47. [PubMed: 18609361]
89. Kim MA, Lee BS, Park YW, et al. Serum markers for prediction of spontaneous preterm delivery in preterm labour. *Eur J Clin Invest.* 2011; 41:773–80. [PubMed: 21299551]
90. Laudanski P, Raba G, Kuc P, et al. Assessment of the selected biochemical markers in predicting preterm labour. *J Matern Fetal Neonatal Med.* 2012; 25:2696–9. [PubMed: 22646705]
91. Cruciani L, Romero R, Vaisbuch E, et al. Pentraxin 3 in maternal circulation: an association with preterm labor and preterm PROM, but not with intra-amniotic infection/inflammation. *J Matern Fetal Neonatal Med.* 2010; 23:1097–105. [PubMed: 20121391]
92. Stampalija T, Chaiworapongsa T, Romero R, et al. Soluble ST2, a modulator of the inflammatory response, in preterm and term labor. *J Matern Fetal Neonatal Med.* 2014; 27:111–21. [PubMed: 23688338]
93. Ismail MA, Zinaman MJ, Lowensohn RI, et al. The significance of C-reactive protein levels in women with premature rupture of membranes. *Am J Obstet Gynecol.* 1985; 151:541–4. [PubMed: 3976754]
94. Yoon BH, Jun JK, Park KH, et al. Serum C-reactive protein, white blood cell count, and amniotic fluid white blood cell count in women with preterm premature rupture of membranes. *Obstet Gynecol.* 1996; 88:1034–40. [PubMed: 8942849]
95. Gervasi MT, Chaiworapongsa T, Naccasha N, et al. Maternal intravascular inflammation in preterm premature rupture of membranes. *J Matern Fetal Neonatal Med.* 2002; 11:171–5. [PubMed: 12380672]
96. Loukovaara MJ, Alfthan HV, Kurki MT, et al. Serum highly sensitive C-reactive protein in preterm premature rupture of membranes. *Eur J Obstet Gynecol Reprod Biol.* 2003; 110:26–8. [PubMed: 12932866]
97. Moghaddam Banaem L, Mohamadi B, Asghari Jaafarabadi M, et al. Maternal serum C-reactive protein in early pregnancy and occurrence of preterm premature rupture of membranes and preterm birth. *J Obstet Gynaecol Res.* 2012; 38:780–6. [PubMed: 22435496]

98. Gulati S, Agrawal S, Raghunandan C, et al. Maternal serum interleukin-6 and its association with clinicopathological infectious morbidity in preterm premature rupture of membranes: a prospective cohort study. *J Matern Fetal Neonatal Med.* 2012; 25:1428–32. [PubMed: 22098613]
99. Vince GS, Starkey PM, Austgulen R, et al. Interleukin-6, tumour necrosis factor and soluble tumour necrosis factor receptors in women with pre-eclampsia. *Br J Obstet Gynaecol.* 1995; 102:20–5. [PubMed: 7833306]
100. Hamai Y, Fujii T, Yamashita T, et al. Evidence for an elevation in serum interleukin-2 and tumor necrosis factor-alpha levels before the clinical manifestations of preeclampsia. *Am J Reprod Immunol.* 1997; 38:89–93. [PubMed: 9272206]
101. Conrad KP, Miles TM, Benyo DF. Circulating levels of immunoreactive cytokines in women with preeclampsia. *Am J Reprod Immunol.* 1998; 40:102–11. [PubMed: 9764352]
102. Redman CW, Sacks GP, Sargent IL. Preeclampsia: an excessive maternal inflammatory response to pregnancy. *Am J Obstet Gynecol.* 1999; 180:499–506. [PubMed: 9988826]
103. Sabatier F, Bretelle F, D'Ercole C, et al. Neutrophil activation in preeclampsia and isolated intrauterine growth restriction. *Am J Obstet Gynecol.* 2000; 183:1558–63. [PubMed: 11120528]
104. Gervasi MT, Chaiworapongsa T, Pacora P, et al. Phenotypic and metabolic characteristics of monocytes and granulocytes in preeclampsia. *Am J Obstet Gynecol.* 2001; 185:792–7. [PubMed: 11641653]
105. Teran E, Escudero C, Moya W, et al. Elevated C-reactive protein and pro-inflammatory cytokines in Andean women with pre-eclampsia. *Int J Gynaecol Obstet.* 2001; 75:243–9. [PubMed: 11728484]
106. Chaiworapongsa T, Romero R, Yoshimatsu J, et al. Soluble adhesion molecule profile in normal pregnancy and pre-eclampsia. *J Matern Fetal Neonatal Med.* 2002; 12:19–27. [PubMed: 12422905]
107. Chaiworapongsa T, Gervasi MT, Refuerzo J, et al. Maternal lymphocyte subpopulations (CD45RA+ and CD45RO+) in preeclampsia. *Am J Obstet Gynecol.* 2002; 187:889–93. [PubMed: 12388971]
108. Velzing-Aarts FV, Muskiet FA, van der Dijs FP, et al. High serum interleukin-8 levels in afro-caribbean women with pre-eclampsia. Relations with tumor necrosis factor-alpha, duffy negative phenotype and von Willebrand factor. *Am J Reprod Immunol.* 2002; 48:319–22. [PubMed: 12516654]
109. Serin IS, Ozelcik B, Basbug M, et al. Predictive value of tumor necrosis factor alpha (TNF-alpha) in preeclampsia. *Eur J Obstet Gynecol Reprod Biol.* 2002; 100:143–5. [PubMed: 11750953]
110. Belo L, Santos-Silva A, Caslake M, et al. Neutrophil activation and C-reactive protein concentration in preeclampsia. *Hypertens Pregnancy.* 2003; 22:129–41. [PubMed: 12908997]
111. Levine RJ, Qian C, Leshane ES, et al. Two-stage elevation of cell-free fetal DNA in maternal sera before onset of preeclampsia. *Am J Obstet Gynecol.* 2004; 190:707–13. [PubMed: 15042003]
112. Kocyigit Y, Atamer Y, Atamer A, et al. Changes in serum levels of leptin, cytokines and lipoprotein in pre-eclamptic and normotensive pregnant women. *Gynecol Endocrinol.* 2004; 19:267–73. [PubMed: 15726915]
113. Freeman DJ, McManus F, Brown EA, et al. Short- and long-term changes in plasma inflammatory markers associated with preeclampsia. *Hypertension.* 2004; 44:708–14. [PubMed: 15452036]
114. Kim YM, Romero R, Oh SY, et al. Toll-like receptor 4: a potential link between “danger signals,” the innate immune system, and preeclampsia? *Am J Obstet Gynecol.* 2005; 193:921–7. [PubMed: 16157088]
115. Braekke K, Holthe MR, Harsem NK, et al. Calprotectin, a marker of inflammation, is elevated in the maternal but not in the fetal circulation in preeclampsia. *Am J Obstet Gynecol.* 2005; 193:227–33. [PubMed: 16021084]
116. Enquobahrie DA, Williams MA, Qiu C, et al. Maternal plasma transforming growth factor-beta1 concentrations in preeclamptic and normotensive pregnant Zimbabwean women. *J Matern Fetal Neonatal Med.* 2005; 17:343–8. [PubMed: 16147848]
117. Jonsson Y, Ruber M, Matthiesen L, et al. Cytokine mapping of sera from women with preeclampsia and normal pregnancies. *J Reprod Immunol.* 2006; 70:83–91. [PubMed: 16388854]

118. Kusanovic JP, Romero R, Hassan SS, et al. Maternal serum soluble CD30 is increased in normal pregnancy, but decreased in preeclampsia and small for gestational age pregnancies. *J Matern Fetal Neonatal Med.* 2007; 20:867–78. [PubMed: 17853188]
119. Sharma A, Satyam A, Sharma JB. Leptin, IL-10 and inflammatory markers (TNF-alpha, IL-6 and IL-8) in pre-eclamptic, normotensive pregnant and healthy non-pregnant women. *Am J Reprod Immunol.* 2007; 58:21–30. [PubMed: 17565544]
120. Laskowska M, Laskowska K, Leszczynska-Gorzelak B, et al. Comparative analysis of the maternal and umbilical interleukin-8 levels in normal pregnancies and in pregnancies complicated by preeclampsia with intrauterine normal growth and intrauterine growth retardation. *J Matern Fetal Neonatal Med.* 2007; 20:527–32. [PubMed: 17674266]
121. Sibai B, Romero R, Klebanoff MA, et al. Maternal plasma concentrations of the soluble tumor necrosis factor receptor 2 are increased prior to the diagnosis of preeclampsia. *Am J Obstet Gynecol.* 2009; 200:630, e1–8. [PubMed: 19306961]
122. Ogge G, Romero R, Chaiworapongsa T, et al. Leukocytes of pregnant women with small-for-gestational age neonates have a different phenotypic and metabolic activity from those of women with preeclampsia. *J Matern Fetal Neonatal Med.* 2010; 23:476–87. [PubMed: 19916874]
123. Soto E, Romero R, Richani K, et al. Preeclampsia and pregnancies with small-for-gestational age neonates have different profiles of complement split products. *J Matern Fetal Neonatal Med.* 2010; 23:646–57. [PubMed: 19900030]
124. Szarka A, Rigo J Jr, Lazar L, et al. Circulating cytokines, chemokines and adhesion molecules in normal pregnancy and preeclampsia determined by multiplex suspension array. *BMC Immunol.* 2010; 11:59. [PubMed: 21126355]
125. Xie C, Yao MZ, Liu JB, et al. A meta-analysis of tumor necrosis factor-alpha, interleukin-6, and interleukin-10 in preeclampsia. *Cytokine.* 2011; 56:550–9. [PubMed: 22019000]
126. Twina G, Sheiner E, Shahaf G, et al. Lower circulation levels and activity of alpha-1 antitrypsin in pregnant women with severe preeclampsia. *J Matern Fetal Neonatal Med.* 2012; 25:2667–70. [PubMed: 22746289]
127. Stampalija T, Chaiworapongsa T, Romero R, et al. Maternal plasma concentrations of sST2 and angiogenic/anti-angiogenic factors in preeclampsia. *J Matern Fetal Neonatal Med.* 2013; 26:1359–70. [PubMed: 23488689]
128. Sahin S, Ozakpinar OB, Eroglu M, et al. The impact of platelet functions and inflammatory status on the severity of preeclampsia. *J Matern Fetal Neonatal Med.* 2014; 1–6. [PubMed: 25208229]
129. Labarrere C, Manni J, Salas P, et al. Intrauterine growth retardation of unknown etiology. I. Serum complement and circulating immune complexes in mothers and infants. *Am J Reprod Immunol Microbiol.* 1985; 8:87–93. [PubMed: 4025671]
130. Labarrere CA, Althabe OH. Intrauterine growth retardation of unknown etiology: II. Serum complement and circulating immune complexes in maternal sera and their relationship with parity and chronic villitis. *Am J Reprod Immunol Microbiol.* 1986; 12:4–6. [PubMed: 3777310]
131. Johnston TA, Greer IA, Dawes J, et al. Neutrophil activation in small for gestational age pregnancies. *Br J Obstet Gynaecol.* 1991; 98:105–6. [PubMed: 1998619]
132. Johnson MR, Anim-Nyame N, Johnson P, et al. Does endothelial cell activation occur with intrauterine growth restriction? *BJOG.* 2002; 109:836–9. [PubMed: 12135223]
133. Coata G, Pennacchi L, Bini V, et al. Soluble adhesion molecules: marker of pre-eclampsia and intrauterine growth restriction. *J Matern Fetal Neonatal Med.* 2002; 12:28–34. [PubMed: 12422906]
134. Tjoa ML, van Vugt JM, Go AT, et al. Elevated C-reactive protein levels during first trimester of pregnancy are indicative of preeclampsia and intrauterine growth restriction. *J Reprod Immunol.* 2003; 59:29–37. [PubMed: 12892901]
135. Cetin I, Cozzi V, Pasqualini F, et al. Elevated maternal levels of the long pentraxin 3 (PTX3) in preeclampsia and intrauterine growth restriction. *Am J Obstet Gynecol.* 2006; 194:1347–53. [PubMed: 16647920]
136. Girardi G, Yarilin D, Thurman JM, et al. Complement activation induces dysregulation of angiogenic factors and causes fetal rejection and growth restriction. *J Exp Med.* 2006; 203:2165–75. [PubMed: 16923853]

137. Laskowska M, Laskowska K, Leszczynska-Gorzela B, et al. Maternal and umbilical sTNF-R1 in preeclamptic pregnancies with intrauterine normal and growth retarded fetus. *Hypertens Pregnancy*. 2007; 26:13–21. [PubMed: 17454214]
138. Erez O, Romero R, Hoppensteadt D, et al. Tissue factor and its natural inhibitor in pre-eclampsia and SGA. *J Matern Fetal Neonatal Med*. 2008; 21:855–69. [PubMed: 19065458]
139. Duff P. Pyelonephritis in pregnancy. *Clin Obstet Gynecol*. 1984; 27:17–31. [PubMed: 6368078]
140. Gilstrap LC 3rd, Lucas MJ. Urinary tract infections in women. *Curr Opin Obstet Gynecol*. 1990; 2:643–8. [PubMed: 2130963]
141. Soto E, Richani K, Romero R, et al. Increased concentration of the complement split product C5a in acute pyelonephritis during pregnancy. *J Matern Fetal Neonatal Med*. 2005; 17:247–52. [PubMed: 16147833]
142. Kim YM, Romero R. Cover Image. *Am J Obstet Gynecol*. 2014;212. [PubMed: 25223243]
143. Alnaes-Katjavivi P, Lyall F, Roald B, et al. Placenta. 2013; 34:A11, abstract P1.1.

Figure 1.

Acute atherosclerosis 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 atherosclerosis 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, PPRM: 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 atherosclerosis

	Preeclampsia without atherosclerosis (n=1598)	Preeclampsia with atherosclerosis (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)	0.75
• Caucasian	6.4% (103)	6.1% (11)	
• 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)	<0.001
• Severe preeclampsia	43.4% (694)	50.8% (92)	
• 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 atherosclerosis according to histologic sections examined in the placenta and placental bed biopsies

Location of acute atherosclerosis	Frequency of atherosclerosis % (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