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PLACENTAL LESIONS ASSOCIATED WITH MATERNAL UNDERPERFUSION ARE MORE FREQUENT IN EARLY-ONSET THAN IN LATE-ONSET PREECLAMPSIA

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Abstract

Objective—Preeclampsia (PE) has been classified into early- and late-onset disease. These two phenotypic variants of PE have been proposed to have a different pathophysiology. However, the gestational age cut-off to define ‘early’ versus ‘late’ PE has varied among studies. The objective of this investigation was to determine the prevalence of lesions consistent with maternal underperfusion of the placenta in patients with PE as a function of gestational age.

Study design—A nested case-control study of 8,307 singleton pregnant women who deliver after 20 weeks of gestation was constructed based on a cohort. Cases were defined as those with PE (n=910); controls were pregnant women who did not have a hypertensive disorder in pregnancy (n=7,397). The frequency of maternal underperfusion of the placenta (according to the criteria of the Society for Pediatric Pathology) was compared between the two groups. Logistic regression was used for analysis. Estimated relative risks were calculated from adjusted odds ratios.

Results—1) The prevalence of lesions consistent with maternal underperfusion was higher in patients with PE than in the control group [43.3% vs. 15.9%; unadjusted odds ratio 4.0 (95% CI 3.5–4.7); P<0.001]; 2) the estimated relative risk of maternal underperfusion lesions in PE was higher than in the control group; 3) the lower the gestational age at delivery, the higher the relative risk for these lesions; 4) early-onset PE, regardless of the gestational age used to define it (<32, 33, 34, 35 or 37 weeks) had a significantly higher frequency of placental lesions consistent with maternal underperfusion than late-onset PE (p<0.001 for all).

Conclusions—1) The earlier the gestational age of preeclampsia at delivery, the higher the frequency of placental lesions consistent with maternal underperfusion; 2) our data suggests that demonstrable placental involvement as determined by pathologic examination differs in early- and late-onset preeclampsia; and 3) this phenomenon appears to be a continuum, and we could not

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identify a clear and unambiguous gestational age at which lesions consistent with underperfusion would not be present.

Keywords

maternal underperfusion; placental infarction; gestational age; classification; villous changes

INTRODUCTION

Preeclampsia (PE) is one of the “great obstetrical syndromes” [12,118,119,121]. This specific pregnancy disorder can be the result of multiple mechanisms of disease [9,10,13,16,20,21,25,32–36,42,43,46,47,53,56,57,59,64–66,70,78,80–82,84,87,88,91,102,105,111,112,116,120,123,129,134,136,144,154], is adaptive in nature [2,15,44,96,97,113,135] and has a long subclinical phase [19,22,63,67,68,98,100,122,125,140,145]. Due to its syndromic nature, several attempts have been made to classify patients with PE into distinct subgroups in order to improve understanding of its pathophysiology [148–150,153], predict maternal/fetal complications [4,27,89,124,126] and to develop individualized preventive or therapeutic interventions [11,23,128,138].

Redman et al. [109] proposed to distinguish PE into two broad categories, maternal and placental, based on its main etiologic factors. In placental PE, the problem arises from a placenta that is under hypoxic conditions, whereas in maternal PE, it arises from the interaction between a normal placenta and maternal factors that are susceptible to microvascular damage. However, the most common presentation is that which involves the maternal system, as well as the placenta [109].

PE is clinically classified as mild or severe [3] according to the severity of signs and symptoms, and the presence of maternal and fetal complications. Another commonly-used classification divides PE into early- and late-onset based on the gestational age at diagnosis or delivery [28,101]. This simple approach has prognostic value since; early-onset PE has a significantly higher risk of maternal and fetal complications [86,101,141,153]. Moreover, early onset PE is associated with a greater prevalence of placental lesions [85].

Several gestational age cut-offs have been used to define early- versus late-onset PE [4,27,28,148–150,153]. One reason to differentiate early from late PE is that neonatal outcomes are largely dependent upon gestational age at delivery [39,137]. It remains unclear, however, whether these cut-offs reflect a different mechanism of disease or the contribution of placental and/or maternal factors.

The histologic examination of the placenta, umbilical cord, and chorio-amniotic membranes can provide insights into the pathophysiology of different complications of pregnancy [8,58,60–62,73]. The Perinatal Section of the Society for Pediatric Pathology has proposed a classification [107] of placental lesions based on available evidence of their association with pathological processes and/or pregnancy outcomes. Such classification consists of 3 broad major categories: 1) lesions consistent with amniotic fluid infection; 2) lesions consistent with maternal vascular underperfusion; and 3) lesions consistent with fetal vascular thrombo-occlusive disease.

The aim of this study was to determine the prevalence of pathologic findings suggestive of maternal underperfusion of the placenta. We chose to focus on these lesions given that amniotic fluid infection is extremely rare in PE [30] and that placental ischemia [5,71,74,132,155] due to maternal underperfusion has been considered the key mechanism of disease in PE for several decades.

MATERIALS AND METHODS

Study design

A retrospective nested case-control study of women who deliver after 20 weeks of gestation was constructed from a cohort of 19,041 women with singleton pregnancies who delivered at the Sótero del Río Hospital, Santiago, Chile, between December 1997 and July 2007. Patients with PE or chronic hypertension with superimposed PE were included in the study group, while the control group was composed of all patients without any hypertensive complications of pregnancy. Exclusion criteria were: multiple gestations, known fetal anomalies, unavailability of the placenta for pathologic examination, lack of neonatal data and absence of adequate data to document an accurate diagnosis of PE (hypertension and proteinuria). All women provided written informed consent to the collection of biological samples and clinical data. The study was approved by the Institutional Review Boards of the participating institute and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD/NIH/DHHS).

Clinical definitions

PE was defined as the new onset of hypertension that developed after 20 weeks of gestation (systolic or diastolic blood pressure ≥ 140 or ≥ 90 mm Hg, 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 containing $\geq 1+$ by dipstick or one dipstick demonstrating $\geq 2+$ protein)[1]. Chronic hypertension with superimposed PE was diagnosed in women with hypertension documented before 20 weeks of gestation by the appearance of previously absent proteinuria, or a sudden increase in proteinuria if already present in early gestation. Patients were defined as controls if they did not have any sign of hypertensive disease during pregnancy (including gestational hypertension, chronic hypertension, PE and eclampsia).

Placental pathology

Tissue samples obtained from the placenta, fetal membranes and umbilical cord were fixed in formalin and embedded in paraffin. Sections of tissue blocks were stained with hematoxylin and eosin and all the slides were examined by a perinatal pathologist (C.J.K.). Histopathological changes of the placenta were defined according to diagnostic criteria proposed by the Perinatal Section of the Society for Pediatric Pathology [107], which consists of 3 broad major categories: lesions consistent with amniotic fluid infection, maternal vascular underperfusion, and fetal vascular thrombo-occlusive disease. Findings consistent with maternal 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. It is noteworthy that these criteria are based on the constellation of placental findings observed in PE and/or fetal growth restriction. These conditions have been demonstrated to be associated with reduced uteroplacental blood flow by experiments using radioisotopes [71,72,92] or three-dimensional power Doppler indices (vascularization index, vascularization flow index and flow index) [48,50]. These placental lesions are not necessarily created by reduced uteroplacental blood supply directly.

The prevalence of placental lesions consistent with maternal underperfusion in cases and controls who delivered at different gestational age was assessed. As the definition of early and late PE is not uniform across studies, different cut-offs of gestational age were used to compare the prevalence of placental lesions between early-onset and late-onset PE.

Statistics

A Mann-Whitney U test was utilized for comparison of continuous variables between groups. The χ^2 test was used to compare the proportion of placental lesions in the two groups. Multiple logistic regression was applied to estimate the association between PE and placental lesions consistent with maternal underperfusion at different gestational age intervals adjusting for parity, body mass index and tobacco use. The adjusted odds ratios with 95% confident interval (CI) derived from logistic regression were transformed into estimated relative risks (RR) according to the formula proposed by Zhang and Yu [161]. Analysis was conducted with SPSS V.15 (SPSS Inc., Chicago, IL). A p value <0.05 was considered significant.

Results

Among 19,041 women who were enrolled and delivered at the Sotero del Rio Hospital between December 1997 and July 2007, 1031 (5.4%) were excluded from this study because of inadequate information concerning blood pressure and/or proteinuria, leaving 18,010 cases for analysis. Among these, 14,243 (79.1%) did not have any evidence of hypertensive disease during pregnancy, 1,369 (7.6%) developed gestational hypertension, 648 (3.6%) had chronic hypertension, 1,415 (7.9%) were diagnosed with PE, and 335 (1.9%) with PE superimposed on chronic hypertension.

The results of pathologic examination of the placenta were available for 9,175 subjects. Cases ($n=910$) were patients who developed PE ($n=743$) and those who had PE superimposed on chronic hypertension ($n=167$). Patients with gestational hypertension ($n=590$) and those with chronic hypertension without superimposed PE ($n=278$) were excluded from subsequent analysis. The control group consisted of patients who did not have any hypertensive disease ($n=7,397$). Table 1 displays the demographic and clinical characteristics of the 2 groups.

The prevalence of pathologic findings consistent with maternal underperfusion was significantly higher in the PE group than in the control group [43.3% (94/910) vs. 15.9% (1,179/7,397), unadjusted odds ratio 4.0 (95% CI 3.5–4.7), estimated RR 2.8 (95% CI 2.5–3.0); $p<0.001$]. The frequency of lesions consistent with fetal thrombo-occlusive disease was also higher in PE than in the control group [15.9% (145/910) vs. 13.2% (978/7,397); $p=0.03$]. In contrast, the prevalence of placental lesions consistent with amniotic infection was higher in the control group than in the PE group [18.2% (1346/7397) vs. 7.9% (73/910); $p<0.001$].

Table 2 displays the distribution of each lesion suggestive of maternal underperfusion in the two groups: every lesion was significantly more common in the placenta of patients with PE than of that in the control group (all $p<0.05$). In the PE group, syncytial knots were the most frequent finding consistent with maternal underperfusion (26.7%). Remote and recent villous infarctions (i.e. abrupt onset villous changes) were found in 9.9% and 4.2% of placentas from patients with PE, respectively, while mural hypertrophy of decidual arterioles was the rarest lesion (3%).

In the PE group, the prevalence of placental findings consistent with maternal underperfusion gradually decreased with advancing gestational age: ranging from 100% at

less than 25 weeks, to 13% at more than 41 weeks of gestation (Table 3). The estimated RR after adjusting for maternal BMI, parity and cigarette smoking also gradually decreased with gestation, remaining statistically significant at every gestational age interval between 25.1 and 40.9 weeks (Table 3). In fact, the estimated RR decreased from 3.1 (95% CI 1.8–3.8) at 25–26 weeks to 2.2 (95% CI 1.7–2.6) at 39–40 weeks. When we included gestational age as a continuous independent variable (without dividing into each week) and allowed interaction between PE and gestational age, the effect of PE on the log-odds of lesion (and relative risk) decreases at a constant pace as a function of gestational age (0.14 unit per week; $p=1.11E^{-09}$) (see Figure I).

The prevalence of histological findings of placental underperfusion was significantly higher in early- when compared to late-onset PE, regardless of the gestational age cut-off used to define such disorders (Table 4).

DISCUSSION

Principal findings of this study

1) the prevalence of placental lesions consistent with maternal underperfusion was significantly higher in pregnancies complicated with PE than in the placentas of patients in the control group at all gestational ages (range 25.1–40.9 weeks of gestation); 2) the prevalence of placental lesions consistent with maternal underperfusion decreased gradually and continuously with gestational age in the PE group, while in the control group this change was small; 3) the estimated relative risk of maternal underperfusion of the placenta associated with PE decreased continuously with gestational age, but was still statistically significantly higher than that in the control group until term; and 4) the prevalence of placental lesions consistent with maternal underperfusion was higher in early- than in late-onset PE, regardless of which gestational age cut-off was chosen to define the two conditions.

Evidence in support of the different pathophysiology between early- and late-onset preeclampsia

The classification of PE into early- and late-onset carries an obvious prognostic value, as early onset disease is associated with a higher perinatal and maternal morbidity and mortality than late onset disease. Indeed, the risk of small for gestational age newborns is higher with early-onset disease [93,150,158,159], and neonatal morbidity and mortality in pregnancies with PE are mainly related to gestational age at delivery [39,41,137,157]. Early-onset PE is also associated with an increased maternal prevalence of metabolic syndrome later in life [89,141] and mortality from cardiovascular disease [40,55,86,106,139]. Moreover, the risk of ischemic heart disease and stroke in later life is more strongly associated with the gestational age at onset of PE than with the severity of PE [7].

Several lines of evidence support the hypothesis that early- and late-onset PE may have different etiologies. First, several recognized risk factors for PE seem to have a different effect on early- and late-onset PE. For example, maternal history of PE in a previous pregnancy [94], chronic hypertension [94], and use of drugs to induce ovulation [103] predispose to early-onset disease more often than to late-onset disease, while self-reported tobacco use during pregnancy has a protective effect towards late- but not early-onset PE [94].

Second, an increasing number of biochemical markers have been shown to be differentially associated with early- or late-onset disease. Early-onset PE is characterized by increased placental plasminogen activator inhibitor (PAI)-1 to PAI-2 ratio (indicative of trophoblastic dysfunction) and higher placental concentration of 8-iso-prostaglandin $F_{2\alpha}$, a marker of

oxidative stress [156]. Early-onset PE is also characterized by a higher degree of systemic inflammation compared to late-onset. Indeed, the plasma concentration of elastase (a soluble marker of neutrophil activation) is significantly higher in patients with early-onset PE, but not those with late-onset PE, compared with gestational age-matched controls [49]. Early-onset, but not late-onset PE, is also associated with increased serum concentration of retinol binding protein-4 [147], an adipokine involved in obesity-associated insulin resistance and inflammation. In contrast, serum concentrations of adiponectin, an adipokine with anti-inflammatory activity, was reported to be increased only in late-onset PE [77].

Similarly, several angiogenic/anti-angiogenic factors and markers of placental function show different behavior in early-onset compared to late-onset PE. Cross-sectional [17,26,27,77] and longitudinal studies [18,63,67,68,125] have demonstrated a higher plasma soluble vascular endothelial growth factor receptor-1 (sVEGFR-1, or sFlt-1) concentration in early-onset PE than late-onset disease. A low plasma concentration of the angiogenic factor, placental growth factor (PlGF) [38,114,142,143,146], or low plasma PlGF/soluble endoglin (sEng) ratio [63] in the midtrimester are a better predictor of early-onset PE, rather than late-onset PE. Moreover, a case-control study also showed that the sFlt-1/PlGF ratio was increased in patients with early-onset compared with late-onset PE [68,77]. First trimester serum concentration of Placental Protein 13 (PP13), a protein mainly produced by the syncytiotrophoblast, is significantly increased in women who subsequently developed preterm PE [90,122,140], while it had limited value in predicting term PE [122]. Even when maternal risk factors, first trimester biophysical markers (mean arterial blood pressure, mean uterine artery pulsatility index) and biochemical markers (Pregnancy Associated Plasma Protein (PAPP)-A, PlGF, PP13, soluble endoglin (sEng), Inhibin-A, Activin-A, Pentraxin-3, P-Selectin) are integrated in a single algorithm, the diagnostic performance of the screening model is much higher for early- (delivery before 34 weeks) than for intermediate- (delivery between 34 and 37 weeks) or late-PE (delivery after 37 weeks) (sensitivity 90%, 80% and 60%, respectively, at the false positive rate of 5%) [4].

A third line of evidence supporting the hypothesis that early-onset and late-onset PE are different disorders derive from the observations of the results in uterine artery Doppler velocimetry in the first [6,83,98,100,104] or second [14,99,160] trimester for the identification of patients who subsequently develop PE. This methodology has a higher accuracy predicting early- rather than late-onset PE. Abnormally high impedance to blood flow in the uterine arteries has been associated with failure of physiological transformation of the spiral arteries [1,14,37,69,75,95,130,152]. Inadequate remodeling of the spiral arteries may induce placental hypoxia and oxidative stress, followed by the release of placental factors (such as sVEGFR-1 [76,79], sEng [151], pro-inflammatory cytokines [9,51,127], and trophoblast debris [52–54,59,110]) which have been implicated in the mechanisms of disease of PE, including maternal intravascular systemic inflammation [24,108,133], leukocyte activation [42,129], and endothelial cell dysfunction [29,115–117]. The association between increased impedance to blood flow in the uterine arteries and early-onset PE, therefore, suggests a greater contribution of placental underperfusion preceding early-onset PE than late-onset disease.

Different histologic findings of the placenta in early and late-onset preeclampsia

An additional evidence in support of the differences between early- and late-onset PE arises from the heterogeneity of placental lesions observed between the two. Salafia *et al.* reported a significantly higher prevalence of lesions related to utero-placental vascular pathology as well as chronic inflammation [131] (i.e. chronic uteroplacental vasculitis and chronic villitis) in early-onset PE requiring delivery between 22 and 32 weeks of gestation (n=76, compared to gestational age-matched controls (n=353); this study, however, did not examine the distribution of placental lesions in PE at various gestational ages. In a morphometric study

of the placenta from 69 patients, Egbor *et al* observed a significant reduction in the volume and surface of the terminal villi in the placentas of patients with early-onset PE delivering before 34 weeks compared to gestational age-matched controls, while no changes were demonstrable in the placentas of patients with PE who delivered after 34 weeks [31]. Differences in the placental pathology between early and late-onset PE were confirmed in a small case-control study showing higher rates of placental infarctions, decidual arteriopathy and villous hypermaturation in early-onset than in late-onset PE [149]. Moldenhauer *et al.* reported that the prevalence of lesions consistent with maternal underperfusion, such as decidual arteriopathy, infarctions, and hypermaturity of villi, among patients with PE was higher at early gestational ages, while the same lesions were significantly less frequent and did not correlate with gestational age in the control group [85].

The finding that the lower the gestational age at delivery, the greater the prevalence of placental lesions consistent with maternal underperfusion supports the hypothesis that placental ischemic changes play a greater role in the pathogenesis of early-onset PE than in the late-onset phenotype. Indeed, the prevalence of pathologic findings consistent with maternal underperfusion in the PE group decreased with gestational age at delivery, being as high as 75% at 25–26 weeks, declining to slightly more than half of the cases (55%) at 33–34 weeks, and to about one-third of the cases (34%) at 39–40 weeks. It is noteworthy that although the prevalence of these lesions in PE gradually decreased with gestational age until term, these lesions were still significantly associated with PE in patients who were at term. The prevalence of placental lesions consistent with maternal underperfusion was roughly twice in PE than in controls at term. Consequently, it was not possible to identify a single gestational age cut-off which completely discriminates early- from late-onset PE on the basis of the presence or absence of placental lesions indicative of underperfusion. The frequency of placental lesions consistent with maternal underperfusion for early-onset PE was significantly higher than late-onset PE for each gestational age cut-off examined in this study (32, 33, 34, 35 and 37 weeks).

Early- and late-onset PE: a similar etiology with different contributions from the underperfused placenta

An alternative interpretation of these findings is that both early- and late-onset PE have a similar etiology with different contributions from maternal and placental factors. The extent of the ‘conflict’ or ‘miscommunication’ between the mother and fetus would dictate the extent of the uterine supply line and the frequency of placental lesions consistent with maternal underperfusion. The different phenotypes of PE would be the result of adaptive mechanisms that allow successful negotiation between the interests of the mother and the fetus. Early-onset PE may reflect the most severe form of this conflict, while late-onset PE results from a milder one. The contribution of placental lesions consistent with maternal underperfusion to the pathophysiology of PE decreases as a function of advancing gestational age. This is consistent with the hypothesis that other factors (i.e. maternal systemic inflammation), rather than the placenta alone, may play a significant role in late-onset PE [109]. However, it must be emphasized that placental lesions consistent with maternal underperfusion may be one of several consequences of shallow trophoblastic invasion and inadequate transformation of the spiral arteries. The placenta is a very complex organ, whose functions are only partially understood today. Therefore, it is not possible to draw conclusions about the placental origin of the PE syndrome on the basis of surgical examination of the placenta alone.

Strengths and limitations of the study

This is the largest study to examine the association between placental pathologic findings and PE. The availability of such a large sample size allows examination of the differences in

placental lesions of PE at various gestational ages. The fact that all placentas were examined with a well-defined standardized protocol greatly increases the internal validity of the results. However, a few potential limitations must be acknowledged. First, the criteria used to diagnose placental lesions consistent with maternal underperfusion may be too broad, since it requires the presence of only one subtype of lesions. The prevalence of placental underperfusion observed herein would be lower if more than one subtype of lesions were required for the diagnosis. Second, as the results of this study are based on patients from a single medical center with a large Hispanic population, the external validity of these findings remains to be confirmed in other populations. Third, the retrospective nature of this study may introduce selection bias towards more pathologic cases because of the unavailability of the placenta for examination or missing diagnostic information in some patients in the control group. Finally, the placenta is a large organ, and the accurate assessment of placenta pathology may require the use of morphologic techniques which are not generally employed in surgical pathology. For example, a quantitative method to determine the extent of vascular underperfusion is highly desirable and needed. Yet, such an approach would be very labor intensive, and is not part of routine examination of the placenta.

Conclusions

The findings of this study demonstrate that the frequency of placental lesions consistent with maternal underperfusion are higher in early- than in late-onset PE, and that the prevalence of these lesions gradually decreases with advancing gestational age. Therefore, an abrupt change in the frequency of these lesions could not be detected. One interpretation of our findings is that the more severe the vascular disorder associated with underperfusion, the earlier the presentation and severity of PE. However, this phenomenon appears to be a continuum, and we could not identify a clear and unambiguous gestational age at which lesions consistent with underperfusion would not be present. We propose that multiple mechanisms of disease can cause PE, and that there is a common pathway clinically expressed by the presence of hypertension and proteinuria. The molecular counterpart of the common pathway remains to be defined.

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Figure I. Graphic representation of odds ratio (OR) and relative risks (RR) for the effect of preeclampsia (vs. control) on the presence of placental lesion consistent with “maternal underperfusion” as a function of gestational age.

Table 1

Demographic and clinical characteristics of the study population.

	Controls (n = 7,397)	Preeclampsia (n=910)	p-value
Maternal Age (years)	25 (13–46)	25 (13–47)	0.2
Maternal BMI (kg/m²)	23.7 (14.9–49.3)	25.0 (15.2–45.0)	<0.001
Nulliparous	3,093 (41.8%)	504 (55.4%)	<0.001
PE in a previous pregnancy[#]	108 (2.4%)	66 (14.9%)	<0.001
Tobacco use			
- No	6,431 (86.9%)	818 (89.9%)	
- Yes	954 (12.8%)	59 (9.7)	0.004
- Unknown	12 (0.2%)	4 (0.4%)	
GA at delivery (weeks)	39.3 (20–42.9)	37.8 (24.7–42.1)	<0.001
Birthweight (grams)	3,280 (150–5,800)	2,840 (410–4,650)	<0.001
Birthweight <10th percentile	724 (9.8%)	165 (18.1%)	<0.001

Values are expressed as median (range) or number (percent)

GA: gestational age

[#] the analysis includes only parous cases

* reference range from Gonzalez et al [45]

Table 2

Distribution of specific placental lesions consistent with maternal underperfusion in the study population.

	Control (n = 7,397)	PE (n=910)	p
Villous changes			
Abrupt onset			
- Remote villous infarctions	3.7%	9.9%	<0.001
- Recent villous infarctions	0.4%	4.2%	<0.001
Gradual onset			
- Intermediate duration			
Increased syncytial knots	6.8%	26.7%	<0.001
Villous agglutination	1.9%	7.6%	<0.001
Increased intervillous fibrin	4.9%	11.6%	<0.001
- Prolonged duration			
Distal villous hypoplasia	0.9%	10.1%	<0.001
Vascular lesions			
- Persistent muscularization of basal plate arteries	1.4%	3.8%	<0.001
- Mural hypertrophy of decidual arterioles	0.3%	3.0%	<0.001
- Acute atherosclerosis of basal plate arteries and/or decidual arterioles	0.2%	5.2%	<0.001

PE: preeclampsia

Table 3

Prevalence of placental findings consistent with maternal underperfusion in uncomplicated pregnancies (Controls) and preeclampsia (PE) stratified by gestational age at delivery

GA (weeks)	N	Maternal underperfusion		Adjusted OR (95% CI)	Estimated RR (95% CI)
		Controls % (n/N)	PE % (n/N)		
≤ 25.0	102	21 (21/100)	100 (2/2)	Not available	Not available
25.1–26.9	80	25 (17/68)	75 (9/12)	11.1 (2.4–50.4)	3.1 (1.8–3.8) *
27.0–28.9	101	22 (17/78)	70 (16/23)	10.3 (3.2–33.7)	3.4 (2.2–4.1) *
29.0–30.9	161	22 (28/128)	73(24/33)	8.8 (3.5–22.4)	3.2 (2.3–3.9) *
31.0–32.9	194	25 (36/146)	73(35/48)	8.2 (3.7–17.9)	2.9 (2.2–3.4) *
33.0–34.9	468	20 (74/379)	55 (52/89)	6.3 (3.8–10.6)	3.1 (2.4–3.6) *
35.0–36.9	721	18 (103/560)	47(75/161)	3.5 (2.4–5.2)	2.4 (1.9–3.0) *
37.0–38.9	1,976	14 (244/1,692)	35 (99/284)	3.0 (2.2–4.1)	2.3 (1.9–2.9) *
39.0–40.9	3,740	15 (530/3,505)	34 (79/235)	2.7 (2.0–3.7)	2.2 (1.7–2.6) *
≥ 41.0	764	15 (109/741)	13 (3/23)	0.8 (0.2–2.9)	0.8 (0.2–2.3)

-GA: gestational age at delivery

-The prevalence of placental lesions consistent with maternal underperfusion is presented as percent (number)

- Adjusted odds ratio (OR) was derived from logistic regression adjusted for maternal BMI, parity and smoking

- Estimated relative risks (RR) were calculated from adjusted OR using the method of Zhang and Yu [161].

* p<0.001

Table 4

Frequency of early and late-onset preeclampsia (PE) for each gestational age cut-off and prevalence of placental lesions consistent with maternal underperfusion in each subgroup.

GA cut-off for early-onset PE (weeks)	Early PE n (%)	Late PE n (%)	Maternal underperfusion	
			Early PE (%)	Late PE (%)
<32	89 (9.8)	821 (90.2)	76% *	40%
<33	118 (13)	792 (87)	73% *	39%
<34	161 (17.7)	749 (82.3)	70% *	38%
<35	207 (22.7)	703 (77.3)	67% *	36%
<37	213 (40.4)	542 (59.6)	58% *	33%

GA: gestational age at delivery;

*
p<0.001