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Risk Factors for Uteroplacental Vascular Compromise and Inflammation

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Abstract

Objective—To identify potentially modifiable risk factors of placental injury reflecting maternal uteroplacental vascular compromise (UPVC) and acute and chronic placental inflammation.

Study design—A prospective epidemiologic study was conducted. A total of 1270 placentas were characterized by gross and microscopic examination. Placental pathology was coded for features of amniotic fluid infection syndrome (AFIS), chronic villitis, UPVC, and fetal vascular obstructive lesions. Odds ratios between UPVC, the acute and the chronic inflammatory lesions, and risk factors of interest were calculated.

Results—After adjusting for confounders, women with a history of preterm birth had 1.60 times the odds of chronic inflammation (95% CI: 1.10, 2.55). Women with a previous elective termination had 3.28 times the odds of acute inflammation (95% CI: 1.89, 5.70). The odds of chronic villitis increased with parity, while the odds of AFIS decreased with parity.

Conclusion—We have identified several predictors of UPVC, AFIS and chronic villitis. Further studies are needed to examine whether interventions to alter UPVC, AFIS and chronic villitis will lead to improved pregnancy outcomes.

Keywords

inflammation; pathology; placenta; preterm

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Condensation We have identified several risk factors for placental pathology and inflammation that could aid in our understanding of preterm birth.

Introduction

Preterm delivery is a major cause of perinatal morbidity and mortality, resulting in a significant amount of medical resources being allocated for perinatal health care.[1-3] Efforts to predict, prevent or delay the occurrence of preterm birth have had marginal success.[4-7] Because of this, there is great interest in ascertaining the etiology of preterm delivery so that effective preventative measures can be developed. One area of study that has garnered such attention is the contribution of maternal uteroplacental vascular compromise (UPVC) and inflammation (both as amniotic fluid infection syndrome (AFIS) and as chronic villitis) as a potential pathway to preterm birth. Certain placental histopathologic findings have been associated with preterm birth and have been helpful in predicting outcomes for preterm infants.[8-11] Identifying predictors of placental pathology that are potentially modifiable could result in reducing the risk of preterm delivery.

Potential risk factors for placental pathology and preterm delivery include tobacco use[12], pregnancy complications, reproductive and medical history, and socioeconomic and psychosocial attributes.[13] How these influences affect the placenta and contribute to early delivery is poorly understood. Large epidemiologic studies addressing this question have been lacking. Our goal was to prospectively study a large representative population of women to evaluate what impact these factors of interest have on the placenta. We will examine the role of known and suspected risk factors for preterm birth in relation to UPVC and inflammation representing both AFIS and chronic villitis.

Materials and Methods

Placentas were obtained from women participating in the Pregnancy, Infection and Nutrition (PIN) study at the University of North Carolina-Chapel Hill. A total of 2006 women were enrolled at a prenatal clinic visit before 20 weeks gestation at the University of North Carolina medical clinics from January of 2001 to November of 2005. Of the 2006 women enrolled, 1847 (92.1%) were eligible to donate placentas, of whom 1542 (76.9%) were recruited. We obtained placentas from 1270 (63.3%) of these women. Demographic and medical information was obtained through a series of telephone and face-to-face interviews, questionnaires, and medical chart review. The basic study protocol for PIN has been described in detail elsewhere.[14] This study was approved by the Institutional Review Board at the University of North Carolina at Chapel Hill.

Placental pathology was characterized by gross and microscopic examination of the placenta and decidua, assigning histopathology to one of three categories as outlined by Salafia: inflammation (AFIS and chronic villitis) and uteroplacental vascular lesions.[15-18] Details regarding categorization of uteroplacental vascular pathology have been previously described.[19] For the purposes of this study, AFIS was considered present when there was any fetal inflammatory response (i.e., umbilical vasculitis, funisitis, or fetal chorionic vasculitis); these lesions have been shown to be present in <1% of uncomplicated term births.[20] Chronic inflammation was diagnosed by the presence of chronic villitis, inflammation of placental villi remote from the basal plate. UPVC was diagnosed in cases via two routes: 1. All placentas with at least one non-marginal placental infarct (>2 cm from the nearest margin) >1 cm^3 in volume. 2. Cases with summary scores of histology items of syncytial knotting, syncytial basophilia, villous fibrosis and excess perivillous fibrin deposition with cytotrophoblast proliferation (each scored on a 0-4 scale as previously described [15-18]) greater than the birth cohort median value of 7. Fetal vascular obstructive lesions included chorionic and fetal stem vessel mural thrombi, the “hemorrhagic endovasculitis” group of lesions and avascular villi present in clumps of >50 villi. All placentas were examined by a single expert pathologist (CS), who was blinded to the patient characteristics when reviewing the placental pathology. For

purposes of analysis, UPVC and AFIS and chronic villitis was coded as present vs. not present for each of the four categories: AFIS, chronic villitis, UPVC, and fetal vascular obstructive pathology.

Potential risk factors for placental pathology considered in the analyses included maternal age (≥ 35 years vs. < 35 years), race (black vs. non-black), poverty to income ratio (PIR), maternal education, marital status, smoking during pregnancy, pre-pregnancy body mass index (BMI) (< 19.8, 19.8-26.0, 26.1-29.0, > 29.0), pregnancy induced hypertension (PIH), chronic hypertension, gestational diabetes (GDM), pre-pregnancy diabetes, preeclampsia, previous elective termination, previous miscarriage, previous preterm birth, and parity. GDM was defined as 2 or more abnormal values on a 3-hour glucose tolerance test (fasting ≥ 95, 1 hr ≥ 180, 2 hr ≥ 155, 3 hr ≥ 140). A previous preterm birth was defined as any birth reported by the patient occurring greater than 2 weeks before her scheduled due date. PIH was defined as an elevation in systolic blood pressure ≥ 30 mm Hg, an elevation in diastolic blood pressure ≥ 15 mm Hg, or a blood pressure ≥ 140/90 noted 2 times at least 6 hours apart. Preeclampsia was defined as PIH with either 300 mg of protein noted in a 24 hour urine collection or 1+ protein noted on a urine dipstick 2 times at least 6 hours apart. Simple associations between UPVC, AFIS and chronic villitis and covariates were analyzed and are presented in Table 1.

Two sets of analyses were performed: one to examine the single primary pathology as determined by the pathologist and another to examine the presence or absence of any type of placental pathology, as multiple pathologies were often identified. Using generalized estimating equations to control for within subject correlation of multiple pathology types, we calculated unadjusted odds ratios (ORs) between placental pathology and covariates.[21-22] Placental pathology was coded as a multivariate response variable with four types (presence or absence of acute inflammation, chronic inflammation, maternal vascular pathology, and fetal vascular pathology). Our model used interaction terms to allow the association between each covariate and placental pathology to differ by type of UPVC, AFIS and chronic villitis. Unadjusted results for the patient's primary placental pathology are presented in Table 2. Associations found to be statistically significant at the 0.20 level were included in the final model, obtained using backward elimination. The final adjusted model for primary pathology included PIH, age, maternal smoking during pregnancy, PIR, and previous elective termination. Adjusted results are presented in Table 3. Further analysis was conducted based on the presence of any placental pathology that was noted.

Results

A total of 1270 placentas were available for examination. As Table 1 indicates, the sample was predominately white, upper income, college educated, < 35 year old women. Approximately 8.5%, 18.6%, 19.4%, and 14.5% of placentas had AFIS, chronic villitis, maternal vascular pathology, and fetal vascular pathology as the primary placental pathology, respectively (Table 1). Among examined placentas, 27.1%, 56.1%, 83.3% and 53.3% had some evidence of AFIS, chronic villitis UPVC, and fetal vascular pathology present, respectively. However, our blinded pathologist (CS) assigned a final primary pathology as stated above.

We observed unadjusted relationships between the following: AFIS and maternal age, marital status, previous elective termination, previous preterm birth, and smoking during pregnancy; chronic inflammation and PIR, marital status, and previous preterm birth; UPVC and maternal age, PIR, race, smoking during pregnancy, chronic hypertension, PIH, preeclampsia, and GDM; and fetal vascular pathology and PIR, smoking during pregnancy, chronic hypertension, and PIH (Table 1).

Table 2 describes unadjusted odds ratios between these factors of interest and the placental pathology types. Women reporting a history of a preterm birth had 1.53 (95% CI: 1.01, 2.32) times the odds of chronic villitis. Women who smoked during pregnancy had 1.81 (95% CI: 1.04, 3.17) times the odds of AFIS. Previous elective termination was associated with 2.19 (95% CI: 1.42, 3.40) times the odds of AFIS. Chronic hypertension was associated with 1.95 (95% CI: 1.20, 3.18) times the odds of fetal vascular pathology. PIH was associated with 1.48 (95% CI: 1.10, 2.01) and 1.71 (95% CI: 1.22, 2.40) times the odds of UPVC and fetal vascular compromise, respectively. Women with preeclampsia had an elevated risk (OR: 1.83; 95% CI: 1.05, 3.28) of having UPVC.

The final adjusted model for primary placental pathology is presented in Table 3. After adjustment, women with a history of preterm birth continued to have increased odds (OR: 1.60; 95% CI: 1.10, 2.55) of chronic villitis, while women with previous births seemed to be protected against AFIS (OR: 0.44; 95% CI: 0.26, 0.74). Women with a previous elective termination had increased (OR: 3.28; 95% CI: 1.89, 5.70) odds of AFIS. Maternal smoking during pregnancy was no longer a significant predictor of AFIS, with an odds ratio of 1.64 (95% CI: 0.85, 3.14), but these results are still suggestive of a potential association. PIH was significantly associated with 1.44 (95% CI: 1.01, 2.07) and 1.61 (95% CI: 1.10, 2.37) times the odds of UPVC and fetal vascular pathology.

Further analyses were conducted to explore the relationship between parity and acute or chronic inflammation. When compared against primaparous mothers, the odds of chronic villitis increased with parity in a monotonic fashion (Figure 1). Conversely, the odds of AFIS decreased with parity (Figure 2).

Finally, unadjusted and adjusted odds ratios were calculated between confounders and the presence of any placental pathology that was noted histologically. Significant associations that were identified were essentially the same as those noted in the analysis of the primary placental pathology.

Comment

In this prospective epidemiologic study, we identified several factors associated with UPVC, AFIS and chronic villitis in a large representative population of pregnant women. To our knowledge, this is the largest study conducted addressing how risk factors for preterm birth affect placental pathology. The most significant findings we noted were those dealing with both AFIS and chronic villitis. A previous elective termination, smoking, and a low PIR were all risk factors for AFIS. Increased odds of chronic villitis were seen with a history of a prior preterm delivery or a prior term delivery. However, increasing parity was protective against AFIS. Finally, women with PIH were more likely to have both UPVC and fetal vascular placental lesions.

Both AFIS and chronic villitis of the placenta are common findings in preterm delivery. Recently, Ghidini and Salafia[8] evaluated the placentas from 413 women delivering before 32 weeks gestation. Women with a history of a previous preterm delivery had more AFIS and chronic villitis than women without a history of preterm delivery that delivered at a similar gestational age. In a similar study by Goldenberg et al[9], 457 placentas from women with both spontaneous and indicated preterm births were analyzed. They noted that AFIS was more common in spontaneous preterm births than indicated preterm births, but chronic villitis was more common in indicated preterm delivery. In our subjects, those who reported a history of having a preterm delivery were at significantly greater risk of having chronic villitis in a subsequent pregnancy.

One of the strongest associations that we noted was the increased risk of AFIS in women with a history of an elective termination. Whether or not elective terminations place women at risk for future preterm deliveries is a matter of significant debate. Two recent studies did not find an increased risk of preterm delivery in patients with a history of a mid-trimester dilation and evacuation[23] or in those with a history of a medical abortion.[24] However, other studies have shown increased rates of preterm delivery following induced abortions.[25-27] In fact, Henriet et al[25] reported that the risk of preterm delivery increased with the number of previous induced abortions. In this study, we do not have information regarding the specific method used to induce the abortion. Because of this, we are not able to determine what contribution this had on the increased rate of AFIS seen in our women with a history of an elective termination. However, this finding does suggest a potential causal pathway to preterm delivery in women with a history of induced abortion if such an association truly exists.

Another interesting finding of this study was the effect of parity on AFIS and chronic villitis. While the risk of AFIS decreased with increasing parity, the risk of chronic villitis rose with each subsequent delivery. The effect of parity on placental pathology is not well described in the literature. However, a study by Lagadari et al[28] did address this issue in a mouse model. They proposed that the benefits of multiparity could be explained by the presence of a protective layer of macrophages found between the decidua and trophoblast layers. In their study, these placental macrophages were found in greater number in multiparous mice compared to their primparous counterparts. The authors suggest the protective effects of these cells could be the result of the secretion of various growth factors and regulators of trophoblast function. Because macrophages represent an important part of the immune system that protects against infection, they may play an important role in placental inflammation. In our study, increasing parity was associated with decreased risk for acute placental inflammation. It may be that the increased chronic inflammation associated with parity provides some immunologic protection against infection. Obviously, more studies are needed to specifically address how parity modulates the number and function of macrophages and on the immune system itself.

Lastly, we noted an association between PIH and vascular lesions of the placenta. This is in keeping with other studies that have also shown more UPVC in pregnancies complicated by hypertensive disorders.[9,29] In women with indicated preterm births, this is often a common finding and differs from the AFIS and chronic villitis associated with spontaneous preterm delivery.[8-9]

In summary, UPVC, AFIS and chronic villitis may play an important role in both spontaneous and indicated preterm delivery. In this study, there were several risk factors for preterm birth significantly associated with pathologic lesions of the placenta. Future research is needed to determine how much these risk factors contribute to these specific pathologic entities. Whether or not interventions aimed at altering UPVC, AFIS and chronic villitis will lead to improved pregnancy outcomes remains an unanswered question.

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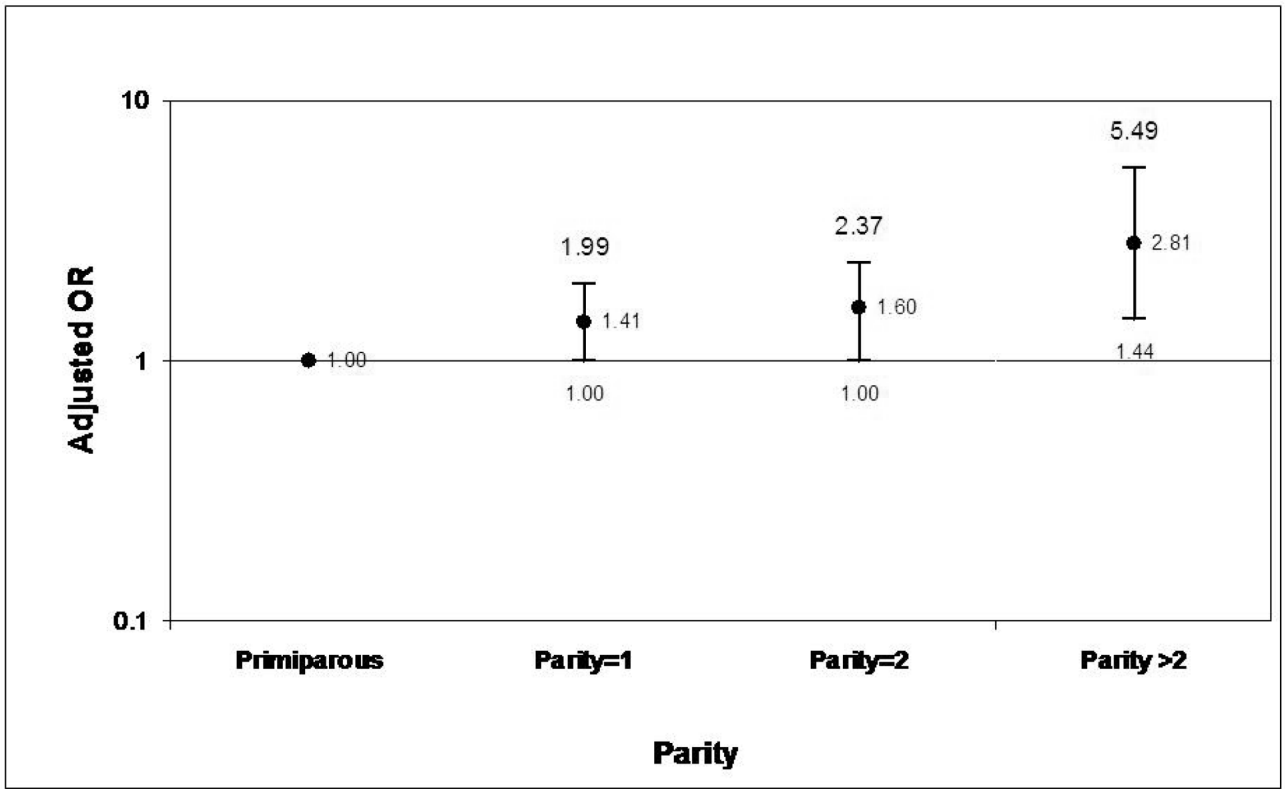

Figure 1. Adjusted ORs for Chronic Villitis According to Parity.*
*Adjusted for pregnancy induced hypertension, age, maternal smoking during pregnancy, poverty to income ratio percent, and previous elective termination.

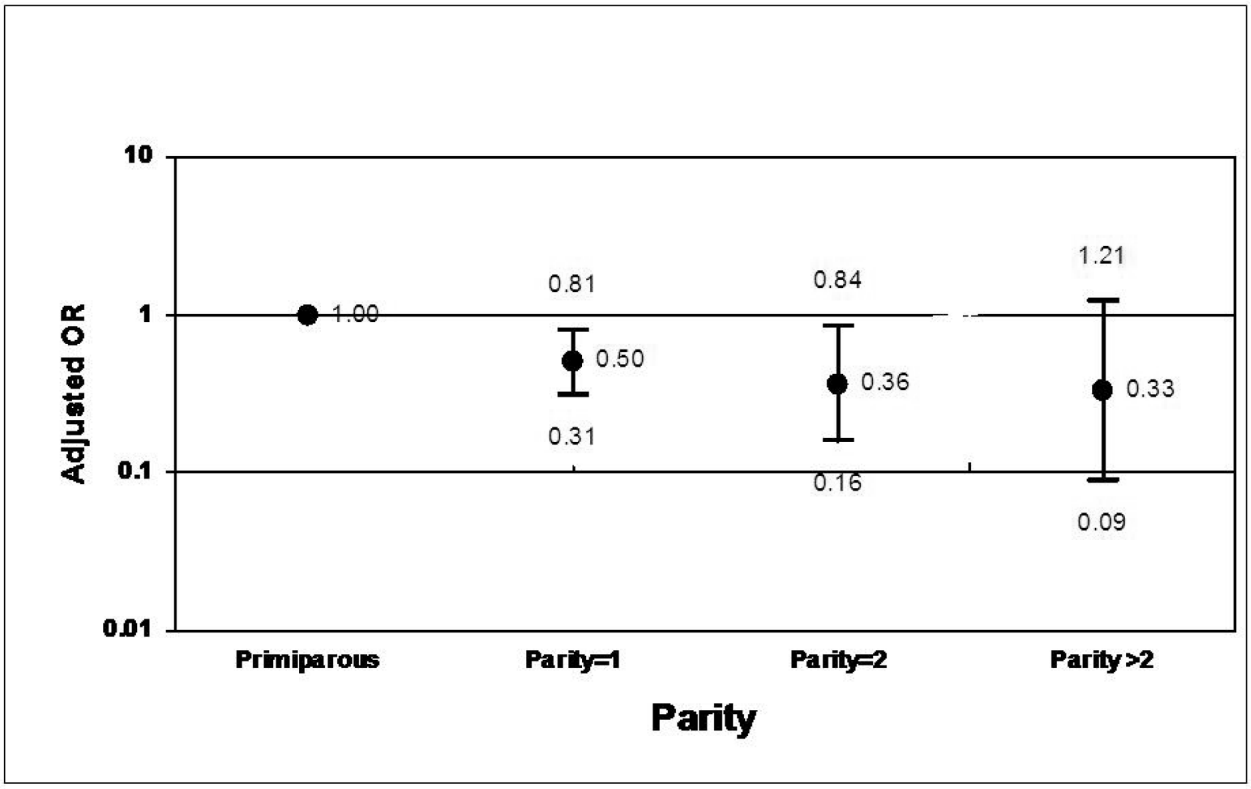

Figure 2. Adjusted ORs for AFIS According to Parity.*

*Adjusted for pregnancy induced hypertension, age, maternal smoking during pregnancy, poverty to income ratio percent, and previous elective termination.

TABLE 1

Prevalence of primary pathology type, according to demographic and medical factors.

Variable	Sample size(n)	Percent of sample (%)	AFIS(%)	Chronic villitis(%)	Maternal vascular pathologic condition (%)	Fetal vascular pathologic condition (%)
Total	1270	-	8.5	18.6	19.4	14.5
Age (y)						
<35	1070	84.2	9.2	18.6	18.6	14.0
≥35	200	15.8	4.5	18.5	23.5	17.0
Race						
White (including other)	1033	81.3	7.7	19.1	18.6	14.9
African American	237	18.7	11.7	16.5	22.8	12.7
Maternal education						
≤High school	258	20.5	11.2	20.0	19.0	14.7
Some college	242	19.0	8.3	17.4	24.0	12.8
≥College	770	60.5	7.7	15.3	18.0	15.7
PIR (%)						
<100	166	13.8	12.6	12.6	21.7	15.7
100-199	142	11.7	9.9	16.9	16.9	12.6
≥200	907	74.5	7.3	20.3	19.1	11.3
Mother's marital status						
Married	958	75.2	7.0	19.7	18.4	14.9
Single, widowed, divorced, separated	312	24.8	13.1	15.1	22.4	13.1
Previous pregnancy						
None	399	31.5	10.8	17.5	21.8	15.0
≥1	864	68.5	7.5	19.1	18.1	14.4
Previous elective termination						
No	1037	82.1	7.2	19.4	19.3	14.3
Yes	226	17.9	14.6	15.0	19.0	15.9
Previous preterm birth						
No	1127	89.2	9.0	17.8	19.0	15.2
Yes	136	10.8	4.4	25.0	21.3	9.6
Previous miscarriage						
No	924	73.0	9.2	18.5	18.9	14.3
Yes	339	27.0	6.8	18.9	20.1	15.3

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Variable	Sample size(n)	Percent of sample (%)	AFIS(%)	Chronic villitis(%)	Maternal vascular pathologic condition (%)	Fetal vascular pathologic condition (%)
Body mass index (kg/m^2)[a]						
<19.8	180	14.3	8.3	16.1	21.7	18.4
19.8-26.0	640	51.1	8.9	18.3	17.8	12.5
26.1-29.0	142	11.3	4.2	20.4	22.5	16.9
>29.0	289	23.3	9.7	20.4	20.0	15.5
Chronic hypertension						
No	1166	92.0	9.0	18.7	18.9	13.6
Yes	99	8.0	3.0	18.2	26.3	24.2
PIH						
No	950	75.0	9.0	18.2	17.8	12.6
Yes	315	25.0	7.0	20.0	24.4	20.0
Preeclampsia						
No	1208	95.5	8.9	18.6	19.0	14.4
Yes	57	4.5	1.8	19.3	29.8	15.8
GDM						
No	1223	96.3	8.7	18.4	19.2	14.5
Yes	47	3.7	4.3	25.5	25.5	12.8
Diabetes mellitus						
No	1216	96.0	8.9	18.5	19.2	14.6
Yes	49	4.0	0.0	22.4	24.5	12.2
Mother smoked during pregnancy						
No	1045	89.3	7.9	19.1	18.2	13.5
Yes	126	10.7	13.5	13.5	23.0	18.2
Infant’s gender						
Female	596	46.9	7.7	17.1	19.6	16.1
Male	672	53.1	9.2	20.3	19.2	13.1

[a]Institute of Medicine (National Research Council) categories.

TABLE 2

Unadjusted ORs for primary placental pathologic condition, according to demographic and medical factors.

Variable	*P* value for test of association between risk factor and placental pathologic condition	OR			
		AFIS (95% CI)	Chronic villitis (95% CI)	Maternal vascular pathologic condition (95% CI)	Fetal vascular pathologic condition (95% CI)
Age (y)	.0573				
<35		Reference	Reference	Reference	Reference
≥35		0.46 (0.23, 0.92)	0.99 (0.67, 1.45)	1.33 (0.93, 1.91)	1.25 (0.83, 1.87)
Race	.1093				
White (including other)		Reference	Reference	Reference	Reference
African American		1.59 (1.01, 2.50)	0.83 (0.57, 1.21)	1.28 (0.91, 1.81)	0.82 (0.54, 1.25)
Maternal education	.3637				
≤High school		1.51 (0.95, 2.41)	0.84 (0.58, 1.21)	1.05 (0.73, 1.51)	0.84 (0.56, 1.28)
Some college		1.08 (0.64, 1.84)	0.72 (0.49, 1.07)	1.43 (1.01, 2.02)	1.08 (0.72, 1.61)
≥College		Reference	Reference	Reference	Reference
PIR (%)	.0714				
<100		1.83 (1.08, 3.08)	0.56 (0.35, 0.92)	1.16 (0.78, 1.74)	0.77 (0.47, 1.26)
100-199		1.39 (0.76, 2.54)	0.80 (0.50, 1.27)	0.86 (0.54, 1.37)	0.68 (0.39, 1.18)
>200		Reference	Reference	Reference	Reference
Mother's marital status	.0055				
Married		0.50 (0.33, 0.76)	1.40 (0.99, 1.99)	0.79 (0.58, 1.08)	1.17 (0.81, 1.71)
Single, divorced widowed, separated		Reference	Reference	Reference	Reference
Body mass index (kg/m^2)	.3222				
<19.8		0.93 (0.51, 1.69)	0.86 (0.55, 1.34)	1.28 (0.85, 1.93)	1.58 (1.01, 2.46)
19.8-26.0		Reference	Reference	Reference	Reference
26.1-29.0		0.45 (0.19, 1.07)	1.15 (0.73, 1.81)	1.35 (0.87, 2.35)	1.43 (0.87, 2.35)
>29.0		1.08 (0.67, 1.74)	1.13 (0.80, 1.60)	1.14 (0.80, 1.62)	1.27 (0.86, 1.89)
Smoking during pregnancy	0.0842				
No		Reference	Reference	Reference	Reference
Yes		1.81 (1.04, 3.17)	0.66 (0.39, 1.13)	1.35 (0.87, 2.10)	1.43 (0.88, 2.33)
Previous birth	.1519				
None		Reference	Reference	Reference	Reference
≥1		0.67 (0.45, 1.01)	1.11 (0.82, 1.51)	0.79 (0.59, 1.06)	0.95 (0.68, 1.32)

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Variable	*P* value for test of association between risk factor and placental pathologic condition	OR AFIS (95% CI)	Chronic villitis (95% CI)	Maternal vascular pathologic condition (95% CI)	Fetal vascular pathologic condition (95% CI)
Previous preterm birth	.0128				
No		Reference	Reference	Reference	Reference
Yes		0.46 (0.20, 1.07)	1.53 (1.01, 2.32)	1.15 (0.75, 1.78)	0.59 (0.32, 1.07)
Previous miscarriage	.6872				
No		Reference	Reference	Reference	Reference
Yes		0.71 (0.44, 1.15)	1.021 (0.74, 1.40)	1.07 (0.78, 1.46)	1.08 (0.76, 1.53)
Previous elective termination	.0313				
No		Reference	Reference	Reference	Reference
Yes		2.19 (1.42, 3.40)	0.74 (0.50, 1.09)	0.98 (0.68, 1.42)	1.14 (0.77, 1.69)
Chronic hypertension	.0109				
No		Reference	Reference	Reference	Reference
Yes		0.31 (0.10, 0.98)	0.93 (0.55, 1.59)	1.47 (0.92, 2.36)	1.95 (1.20, .018)
PIH	.0073				
No		Reference	Reference	Reference	Reference
Yes		0.75 (0.46, 1.22)	1.13 (0.81, 1.53)	1.48 (1.10, 2.01)	1.71 (1.22, 2.40)
Preeclampsia	.0133				
No		Reference	Reference	Reference	Reference
Yes		0.18 (0.03, 1.34)	1.05 (0.54, 2.06)	1.83 (1.02, 3.28)	1.12 (0.54, 2.32)
Prepregnancy diabetes mellitus	.1097				
No		Reference	Reference	Reference	Reference
Yes		Insufficient Data	1.22 (0.62, 2.41)	1.10 (0.54, 2.27)	0.46 (0.20, 1.03)
GDM	.3450				
No		Reference	Reference	Reference	Reference
Yes		0.47 (0.11, 1.96)	1.53 (0.78, 2.99)	1.45 (0.74, 2.83)	0.86 (0.36, 2.07)
Infant’s gender	.2145				
Female		Reference	Reference	Reference	Reference
Male		1.21 (0.81, 1.80)	0.91 (0.61, 1.07)	0.97 (0.73, 1.28)	0.78 (0.57, 1.07)

Table 3

Adjusted ORs for primary placental pathologic, according to demographic and medical factors.[a]

Variable	*P* value for test of association between risk factor and placental pathologic condition	OR AFIS (95% CI)	Chronic villitis (95% CI)	Maternal vascular pathologic condition (95% CI)	Fetal vascular pathologic condition (95% CI)
Age (y)	.1079				
< 35		Reference	Reference	Reference	Reference
≥35		0.55 (0.26, 1.18)	0.87 (0.58, 1.33)	1.64 (1.11, 2.41)	1.16 (0.74, 1.83)
PIR (%)	.0864				
>200		Reference	Reference	Reference	Reference
100-200		1.03 (0.51, 2.10)	0.75 (0.44, 1.29)	0.79 (0.46, 1.36)	0.60 (0.32, 1.12)
<100		1.93 (1.05, 3.56)	0.55 (0.32, 0.94)	1.03 (0.63, 1.69)	0.74 (0.40, 1.36)
Smoking during pregnancy	.1343				
No		Reference	Reference	Reference	Reference
Yes		1.64 (0.85, 3.14)	0.75 (0.41, 1.37)	1.32 (0.78, 2.24)	1.76 (1.00, 3.11)
Previous birth	.0025				
None		Reference	Reference	Reference	Reference
≥1		0.44 (0.26, 0.74)	1.34 (0.94, 1.92)	0.67 (0.47, 0.96)	1.01 (0.68, 1.51)
Previous preterm birth	.0218				
No		Reference	Reference	Reference	Reference
Yes		0.50 (0.19, 1.30)	1.60 (1.10, 2.55)	1.17 (0.70, 1.94)	0.52 (0.26, 1.04)
Previous elective termination	.0032				
No		Reference	Reference	Reference	Reference
Yes		3.28 (1.89, 5.70)	0.67 (0.43, 1.04)	1.13 (0.74, 1.72)	1.20 (0.76, 1.89)
PIH	.0659				
No		Reference	Reference	Reference	Reference
Yes		0.93 (0.55, 1.58)	1.12 (0.77, 1.62)	1.44 (1.01, 2.07)	1.61 (1.10, 2.37)
Preeclampsia	.1077				
No		Reference	Reference	Reference	Reference
Yes		0.21 (0.02, 1.84)	1.22 (0.57, 2.58)	0.99 (0.47, 2.08)	0.55 (0.21, 1.42)

[a] Adjusted for PIH, age, maternal smoking during pregnancy, PIR percent, and previous elective termination.