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Placental Blood Flow and the Risk of Preterm Delivery

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Abstract

The goal of this analysis was to estimate the influence of variation in uterine artery and umbilical artery resistance indices (RI) measured across gestation on variation in the risk of preterm delivery (PTD). Analyses were carried out on data collected in a longitudinal study of 523 gravidas. Uterine and umbilical artery RIs were measured on three occasions during pregnancy (16 to 20 weeks gestation; 21 to 29 weeks gestation; and 30 to 36 weeks gestation). Data were analyzed using the Cox proportional hazards regression model. The primary outcome variable was birth prior to 37 weeks gestation. We found that for mothers who delivered preterm the mean uterine artery RI was consistently larger across all gestational ages, while the mean umbilical artery RI decreased significantly more slowly across gestation than for their term counterparts. In analyses pooled by type of delivery, we found that the hazard ratio (HR) for PTD was statistically significant for either uterine artery RI (HR = 2.26, 95% CI: 1.65, 3.11) or umbilical artery RI (HR = 3.47, 95% CI: 2.43, 4.95) after adjusting for statistically significant covariates. In stratified analyses, the hazard ratio for PTD was also positively associated with an increased uterine or umbilical artery RI in both spontaneous and indicated deliveries. Our data suggest that pregnancies with either a higher uterine or umbilical artery RI across gestation are more likely to be affected by PTD suggesting that disordered placentation resulting in compromised placental blood flow may be an important pathway to PTD.

Keywords

Preterm delivery; Doppler velocimetry; placental vascular resistance; Cox regression

Introduction

More than twelve percent of all births in the U.S. was preterm in the year 2006 [1]. Preterm delivery (PTD) is associated with 75 percent of all perinatal deaths in the U.S. and may result in substantial morbidity in those infants who survive [2]. Epidemiological and clinical studies have identified a number of environmental risk factors for prematurity. However, the physiological pathways that mediate the effects of these risk factors are not well characterized. The birth of a healthy infant at term depends on the establishment of the maternal-fetal vascular interface early in gestation and ongoing placental development during pregnancy [3].

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Accordingly, spontaneous preterm delivery is associated with histopathological evidence of disordered placentation [4-7]. Placentas from pregnancies complicated by PTD are found to have a greater degree of failure of physiologic transformation of the spiral arteries in the myometria and decidua of the placental bed than normal pregnant women at term [7]. These abnormalities may compromise placental blood flow and nutrient delivery to the developing fetus.

Doppler velocimetry provides insight into placental vascular development and is an important tool in the clinical management of pregnancies affected by abnormal placental blood flow [8-10]. Many cross-sectional studies have established that Doppler measures of abnormal uterine and umbilical artery blood flow at individual time points during pregnancy predict the risk of fetal morbidity and mortality [11-17]. However, few studies have adequately documented the relationship between variation in time-dependent measures of placental vascular flow and the risk of PTD. The goal of our study was to estimate the influence of variation in uterine artery and umbilical artery resistance indices measured at multiple time points across gestation on variation in the risk of preterm delivery (PTD).

Methods

Study Sample

Data were prospectively collected in a longitudinal study of multiethnic gravidas who presented for prenatal care over a three year period as part of the Behavior in Pregnancy Study conducted in public, private, and managed health-care settings associated with Cedars-Sinai Medical Center in Los Angeles, California [18]. The Cedars-Sinai Medical Center Institutional Review Committee approved the study. At the time of enrollment subjects were 18 years or older, less than 20 weeks pregnant with a singleton pregnancy, and intended to deliver at the study hospital. Informed consent was obtained at the initial visit. Subjects with multi-fetal pregnancies, major structural fetal abnormalities or prenatally diagnosed aneuploidy were excluded. Participants were seen at three study visits: Visit 1, 16 to 20 weeks gestation; Visit 2, 21 to 29 weeks gestation; and Visit 3, 30 to 36 weeks gestation. Data analyses were carried out on a cohort of 523 subjects who delivered a live infant between 22 and 44 weeks gestation and were measured for all relevant variables.

Data Collection and Study Variables

Baseline maternal characteristics were collected by review of medical records and questionnaire upon entry into the study [19]. These data included age, height, weight and self reports of ethnicity (only individuals categorized as Non-Hispanic White, African-American/Black, Hispanic were included in our analysis), years of education completed, source of medical payment, marital status, date of last menstrual period (LMP), prepregnancy weight, prior pregnancy history, current pregnancy history, maternal chronic illnesses, medications, alcohol, cigarette and other drug use. Maternal prepregnancy BMI was calculated using height and prepregnancy weight ($BMI = \text{weight}/\text{height}^2$).

At each of the follow-up visits, Doppler velocimetry was used to measure placental vascular blood flow using an ATL, HDI 3000 Ultrasound machine (Philips Medical Systems, the Netherlands). In particular, Doppler measurements were performed on the umbilical artery, and left and right proximal uterine artery. These measurements were obtained by one of five sonographers at a single site trained by and under the supervision of the project PI. Measurements on each uterine artery were obtained just proximal to the point where it crossed the internal iliac artery. For each Doppler waveform, the peak systolic (S) and end diastolic (D) velocity was measured three or four times. A reading more than twice, or less than half, the median of the measurements for an individual was excluded. Two related flow indices

[20,21], the resistance index ($RI = (S-D) / S$) and the pulsatility index ($PI = (S-D) / \text{mean velocity}$), were calculated. Since there may be laterality differences in uterine artery RI [22], a nested one-way analysis of variance was used to test the average difference between the left and right uterine artery RI. Since there were no significant differences ($p > 0.10$) between the average measurements on the two sides, the values of the left and right uterine artery RI for each individual were averaged together for each visit. The correlation between RI and PI is greater than 0.99 for each artery at each study visit. Since the PI is more difficult to determine, had more missing values, and does not provide any extra information [20], only data for the RI are presented here.

Infant variables, including date of delivery, type of delivery, birth weight (BW), and gender, were collected at delivery and abstracted from the medical record. Gestational age (GA) was estimated from the self-reported LMP. For 128 participants, a first trimester dating ultrasound was available. For 45 of these cases these two measures differed by >10 days, so the date determined from the first trimester ultrasound estimate was used to estimate GA. In all cases, our estimated GA was corroborated by ultrasound estimates at each follow-up visit. Preterm delivery (PTD) was defined as gestation lasting less than 37 completed weeks.

Statistical Analysis

SAS statistical software version 9.1 (SAS Institute, Cary, NC) was used for all data analyses. Data were analyzed using the Cox proportional hazards regression model using the PROC PHREG module to estimate the hazard ratios for covariates. The outcome event for our study was taken to be birth prior to 37 completed weeks gestation. Time zero was recorded as the date of the LMP and birth events were censored at 37 weeks (258 days) post-LMP using gestational age in days as the time scale. By definition, women are not at risk of PTD after 37 weeks post-LMP. Thus, the Cox model evaluates the hazard of a PTD. Ties were handled using the method of Efron [23]. In each analysis, the predictor variables, uterine artery RI or umbilical artery RI, were modeled as time-dependent covariates in the Cox regression [24]. The time dependence of the RI was described by a step-function which takes the value of the measurement at each visit and extends from the midpoint between the prior visit (or conception for the first visit) and the current visit to the midpoint between the current visit and the following visit (or to delivery for the last measure). Inspection of the Schoenfeld residuals did not demonstrate any consistent deviations to invalidate the proportional hazard assumption. Relevant analyses were stratified on type of delivery categorized as spontaneous delivery and indicated delivery, where the latter category included caesarean section and induced vaginal delivery.

Other covariates for predicting PTD, including ethnicity, maternal age, parity, marital status, education, source of payment, chronic illness and smoking, were treated as a time-independent (fixed) variables in the Cox model. We used a backward stepwise regression scheme to select the set of fixed covariates which best predicted the risk of PTD in each analysis. Covariates that did not significantly contribute to prediction of the risk of PTD at $p < 0.1$ were eliminated from the model in a stepwise iterative process. The final set of covariates in each strata were considered to be the most parsimonious set of fixed covariates for predicting PTD.

Results

Table 1 describes the cohort characteristics of the 523 participants. In our sample, 23.3% were individuals of Non-Hispanic White ethnicity, 32.3% were individuals of Hispanic ethnicity, and 44.4% were individuals of African-American ethnicity; 69.6% of infants were born by spontaneous delivery and 30.4% were born by indicated delivery, including caesarean section and induced vaginal delivery. Table 2 describes the characteristics of the 53 preterm deliveries in our cohort. Given the potential etiologic similarities and differences for spontaneous and

medically indicated preterm deliveries, we considered these two clinical subtypes of preterm births in our analyses [25,26]. We tested for significant differences between in the maternal characteristics of infants born by spontaneous or indicated delivery at the $p < 0.05$ level. By this criterion, only maternal educational level was significantly associated with type of delivery such that women with college or post-graduate education were significantly more likely to have an indicated delivery. There were no other statistically significant differences in the maternal characteristics between those women who delivered spontaneously and those who had an indicated delivery. The overall rate of PTD was 10.1%. The rate of PTD for infants born by spontaneous (8.8%) or indicated delivery (13.2%) was not significantly different. In addition, there was also no significant difference in gestational age at delivery or birthweight between the two groups.

Figure 1a and b plot the uterine and umbilical artery RI for term and preterm deliveries. We found that the mean RI for both uterine and umbilical arteries decreased steadily across all study visits from 112 days (16 weeks) to 287 days (41 weeks) gestation. In linear regression models, the relationships of both uterine and umbilical artery RI with gestational age were significantly different between preterm and term deliveries. The mean uterine artery RI showed a similar rate of decrease across gestation for preterm and term deliveries. However, the uterine artery RI was consistently larger across all gestational ages for mothers who delivered preterm (0.035 units, 95% CI: 0.044, 0.026). In contrast, the mean umbilical artery RI decreased significantly more slowly across gestation for preterm deliveries than for term deliveries. The relationships of the uterine and umbilical artery RI with gestational age in the linear regression models were not significantly different between spontaneous and indicated deliveries (data not shown).

Table 3 gives the results from the univariate proportional hazard regression models for predicting PTD that considered each of the time dependent (uterine and umbilical artery RIs) and time-independent (fixed) covariates separately. Among individuals with a spontaneous delivery, none of the fixed covariates were significant risk factors for PTD. In contrast, among individuals with an induced delivery or caesarean section, African-American race, older maternal age and smoking were each predictors of a significant increase in risk of PTD, while married women had a lower likelihood of PTD. We found that the hazard ratios associated with uterine and umbilical artery RI were large and statistically significant for both delivery types. We note that the estimate of the hazard ratio for indicated deliveries was larger than for spontaneous deliveries for both the uterine and umbilical artery RI. In univariate analyses pooled by type of delivery, a 2.3 fold increase in risk for PTD was associated with a 0.1 unit increase in uterine artery RI across gestation; while a 3.6 fold increase in risk for PTD was associated with a 0.1 unit increase in umbilical artery RI across gestation.

Table 4 gives the results from multivariable proportional hazard regression models in which we adjust the effects of uterine or umbilical artery RI for time-independent maternal covariates selected in the backward stepwise regressions. For the subset of spontaneous deliveries, the univariate uterine or umbilical artery RI model is sufficient since no covariates were found to significantly predict PTD when the backwards regression was carried out. Overall and in each delivery type stratum, we found that hazard ratios were statistically significant for both the uterine and umbilical artery RI after adjusting for significant fixed covariates. The magnitude of the effect sizes are similar, and in the case of the spontaneous deliveries, identical to the estimates from the univariate analyses presented in Table 3.

Discussion

We have shown that for mothers who delivered preterm the mean uterine artery RI was consistently larger across all gestational ages while the mean umbilical artery RI decreased

significantly more slowly across gestation than for their term counterparts (Figures 1a and 1b). We have estimated the influence of variation in uterine and umbilical artery RIs on variation in the risk of preterm delivery (PTD) using a proportional hazards model. Analyses using this model indicate that pregnancies with a higher uterine and umbilical artery RI are more likely to be affected by PTD (Tables 3 and 4). These results hold for both spontaneous delivery and indicated delivery. We suggest that our findings may arise from an underlying biological relationship between PTD and placental vascular dysfunction as discussed below.

Prior case-control studies examining the cross-sectional relationship between PTD and uterine artery Doppler indices measured only at single time points in pregnancy have reported contradictory results. Strigini *et al.* used Doppler velocimetry to measure the uterine artery systolic to diastolic ratio (S/D) in 417 women at 25–36 weeks of gestation and reported that the S/D was significantly higher in the 31 women with spontaneous PTD [27]. Similarly, Fonseca *et al.* found that the median uterine artery mean pulsatility index measured in singleton pregnancies at 22–24 weeks of gestation was significantly higher in 237 women who had a spontaneous delivery before 33 weeks than in 31,633 women delivering at or after 33 weeks [28]. However, Cobian-Sanchez *et al.* reported that the mean uterine artery RI measured between 18–23 weeks gestation in 72 singleton pregnancies that delivered before 34 weeks was not significantly different from that in 5472 patients who delivered at term [29]. Similarly, Soares *et al.* found that the mean uterine artery RI measured between 11–14 weeks in 73 singleton pregnancies with spontaneous preterm labor was not significantly different from that in 2417 pregnancies delivered at term [30].

Our study is among the first to document the relationship between variation in placental vascular resistance measured at multiple time points during pregnancy and the risk of PTD. Since PTD is a fundamentally time-dependent outcome, vulnerability to certain exposures may exist only if they occur in a particular gestational time frame (i.e. a “critical period”). As such, studies of PTD must carefully consider the time dimension in analytic models. Failure to account for the time-dependence of exposures and outcomes may lead to biased and erroneous results. The survival analysis (i.e. the Cox regression model) used here specifically addresses time-dependent exposures, outcomes, and differences in observation periods. In this context, the prospective cohort design of this study is ideally suited for measuring longitudinal data for the analysis of time-dependence of key variables over the course of gestation. Moreover, this design also ensures that an accurate estimate of gestational age can be determined, from both the date of a woman's LMP as well as from serial ultrasound examinations. However, the identification and recruitment of study participants early in pregnancy inherently limits study participation to a group of women who present for prenatal care and are able to attend multiple study visits. Women without prenatal care or with late, interrupted, or sporadic care are less likely to have been included.

Our Doppler measurements show that uterine and umbilical artery RI decrease with gestational age consistent with prior studies [21,31,32]. We find that the risk of PTD is associated with an increased resistance to flow in both of these arteries. It has been suggested that placental vascular compromise represents a unifying pathologic process that may explain a significant proportion of PTD [33]. Several pathophysiologic processes can compromise placental vascular function at different times during gestation leading to adverse pregnancy outcomes. These processes include acute inflammation, chronic inflammation, coagulopathy, and uteroplacental vascular lesions [33]. Accordingly, in case control studies, several types of histopathological evidence for disordered placentation, including umbilical and chorionic vasculitis, decidual vascular abnormalities, endovascular trophoblast, decidual vessel thrombosis, and fetal thrombotic vasculopathy are associated with PTD [7,34]. These pathologic changes may result in increased resistance to maternal intervillous flow and increased uterine artery RIs [35]. It is possible that the prolonged reduction in maternal intervillous flow,

may also result in a secondary reduction in placental stem villus flow that manifests as an increased resistance to flow in the umbilical artery [36]. In our study, the timing of the relationships between PTD and uterine and umbilical artery RI suggested in Figure 1 may reflect the consequences of these pathophysiologic processes. While our study is among the first to systematically analyze the contribution of the umbilical artery RI to the risk for PTD, our data are limited in providing a more detailed description of the interrelationship between uterine and umbilical artery RI. Future studies should address these issues.

Our results may also be important to consider in the context of the increased risk of PTD seen among African-American women in the U.S. Racial disparities in the rate of PTD among different ethnic groups in the U.S. have remained a vexing problem to clinicians, researchers and policy makers alike. We have previously shown that umbilical artery RI and its rate of change in the last trimester were significantly different among the White, Hispanic, and African-American ethnic groups [19]. As a potential etiologic mechanism, placental vascular dysfunction may offer one mechanism underlying disparities in PTD. In fact, in multivariate analyses we find that the hazard ratio associated with racial identity is reduced in models that include either uterine or umbilical artery RI. However, our current study was not designed or powered to address this issue. Nevertheless, our data conclusively demonstrate that pregnancies with a higher uterine or umbilical artery RI are more likely to be affected by PTD. These results suggest a more fundamental relationship between PTD and placental vascular dysfunction. As a potential etiologic mechanism, placental vascular dysfunction may offer many preventative and therapeutic possibilities for PTD in the future.

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References

1. Martin JA, Hamilton BE, Sutton PD, Ventura SJ, Menacker F, Kirmeyer S, Mathews TJ. Births: Final Data for 2006 National Vital Statistics Reports 2009;57(7):102.
2. Dusick AM. Medical outcomes in preterm infants. *Seminars in Perinatology* 1997;21(3):164–77. [PubMed: 9205973]
3. Regnault TR, Galan HL, Parker TA, Anthony RV. Placental development in normal and compromised pregnancies-- a review. *Placenta* 2002;23:S119–29. [PubMed: 11978069]
4. Arias F, Rodriguez L, Rayne SC, Kraus FT. Maternal placental vasculopathy and infection: two distinct subgroups among patients with preterm labor and preterm ruptured membranes. *Am J Obstet Gynecol* 1993;168(2):585–91. [PubMed: 8438933]
5. Arias F, Victoria A, Cho K, Kraus F. Placental histology and clinical characteristics of patients with preterm premature rupture of membranes. *Obstet Gynecol* 1997;89(2):265–71. [PubMed: 9015033]
6. Kim YM, Chaiworapongsa T, Gomez R, Bujold E, Yoon BH, Rotmensch S, Thaler HT, Romero R. Failure of physiologic transformation of the spiral arteries in the placental bed in preterm premature rupture of membranes. *Am J Obstet Gynecol* 2002;187(5):1137–42. [PubMed: 12439491]
7. Kim YM, Bujold E, Chaiworapongsa T, Gomez R, Yoon BH, Thaler HT, Rotmensch S, Romero R. Failure of physiologic transformation of the spiral arteries in patients with preterm labor and intact membranes. *Am J Obstet Gynecol* 2003;189(4):1063–9. [PubMed: 14586356]
8. Gagnon R, Van den Hof M. The use of fetal Doppler in obstetrics. *J Obstet Gynaecol Can* 2003;25(7):601–14. [PubMed: 12851673]quiz 15-6
9. Abramowicz JS, Sheiner E. Ultrasound of the Placenta: A Systematic Approach. Part II: Functional Assessment (Doppler). *Placenta* 2008;29(11):921–9. [PubMed: 18799213]
10. Abramowicz JS, Sheiner E. Ultrasound of the placenta: a systematic approach. Part I: Imaging. *Placenta* 2008;29(3):225–40. [PubMed: 18262643]

11. Krebs C, Macara LM, Leiser R, Bowman AW, Greer IA, Kingdom JC. Intrauterine growth restriction with absent end-diastolic flow velocity in the umbilical artery is associated with maldevelopment of the placental terminal villous tree. *Am J Obstet Gynecol* 1996;175(6):1534–42. [PubMed: 8987938]
12. Downing GJ, Maulik D, Phillips C, Kadado TR. In vivo correlation of Doppler waveform analysis with arterial input impedance parameters. *Ultrasound Med Biol* 1993;19(7):549–59. [PubMed: 8310551]
13. Prefumo F, Guven M, Ganapathy R, Thilaganathan B. The longitudinal variation in uterine artery blood flow pattern in relation to birth weight. *Obstet Gynecol* 2004;103(4):764–8. [PubMed: 15051571]
14. Ferrazzi E, Bulfamante G, Mezzopane R, Barbera A, Ghidini A, Pardi G. Uterine Doppler velocimetry and placental hypoxic-ischemic lesion in pregnancies with fetal intrauterine growth restriction. *Placenta* 1999;20(56):389–94. [PubMed: 10419803]
15. Ducey J, Schulman H, Farmakides G, Rochelson B, Bracero L, Fleischer A, Guzman E, Winter D, Penny B. A classification of hypertension in pregnancy based on Doppler velocimetry. *American Journal Of Obstetrics And Gynecology* 1987;157(3):680–5. [PubMed: 2957919]
16. Trudinger BJ, Giles WB, Cook CM. Uteroplacental blood flow velocity-time waveforms in normal and complicated pregnancy. *BR J OBSTET GYNAECOL* 1985;92(1):39–45. [PubMed: 3966989]
17. Papageorgiou AT, Yu CKH, Nicolaides KH. The role of uterine artery Doppler in predicting adverse pregnancy outcome. *Best Practice & Research Clinical Obstetrics & Gynaecology* 2004;18(3):383–96. [PubMed: 15183134]
18. Mancuso RA, Schetter CD, Rini CM, Roesch SC, Hobel CJ. Maternal Prenatal Anxiety and Corticotropin-Releasing Hormone Associated With Timing of Delivery. *Psychosom Med* 2004;66(5):762–9. [PubMed: 15385704]
19. Misra VK, Hobel CJ, Sing CF. Ethnic heterogeneity in the longitudinal effects of placental vascular blood flow on birthweight. *Am J Obstet Gynecol* 2008;198(1):72, e1–8. [PubMed: 17826729]
20. Thompson RS, Trudinger BJ, Cook CM. Doppler ultrasound waveform indices: A/B ratio, pulsatility index and Pourcelot ratio. *Br J Obstet Gynaecol* 1988;95(6):581–8. [PubMed: 3291936]
21. Thompson RS, Trudinger BJ, Cook CM. A comparison of Doppler ultrasound waveform indices in the umbilical artery--I. Indices derived from the maximum velocity waveform. *Ultrasound Med Biol* 1986;12(11):835–44. [PubMed: 2949412]
22. Kofinas AD, Penry M, Greiss FC Jr, Meis PJ, Nelson LH. The effect of placental location on uterine artery flow velocity waveforms. *Am J Obstet Gynecol* 1988;159(6):1504–8. [PubMed: 3061298]
23. Hertz-Picciotto I, Rockhill B. Validity and efficiency of approximation methods for tied survival times in Cox regression. *Biometrics* 1997;53(3):1151–6. [PubMed: 9333345]
24. Fisher LD, Lin DY. Time-dependent covariates in the Cox proportional hazards regression model. *Annual Review of Public Health* 1999;20(1):145–57.
25. Ananth CV, Getahun D, Peltier MR, Salihu HM, Vintzileos AM. Recurrence of spontaneous versus medically indicated preterm birth. *American Journal of Obstetrics and Gynecology* 2006;195(3):643–50. [PubMed: 16949395]
26. Savitz DA, Dole N, Herring AH, Kaczor D, Murphy J, Siega-Riz AM, T JM Jr, MacDonald Thaddeus L. Should spontaneous and medically indicated preterm births be separated for studying aetiology? *Paediatric & Perinatal Epidemiology* 2005;19(2):97–105. [PubMed: 15787884]
27. Strigini FA, Lencioni G, De Luca G, Lombardo M, Bianchi F, Genazzani AR. Uterine artery velocimetry and spontaneous preterm delivery. *Obstet Gynecol* 1995;85(3):374–7. [PubMed: 7862375]
28. Fonseca E, Yu CK, Singh M, Papageorgiou AT, Nicolaides KH. Relationship between second-trimester uterine artery Doppler and spontaneous early preterm delivery. *Ultrasound Obstet Gynecol* 2006;27(3):301–5. [PubMed: 16388510]
29. Cobian-Sanchez F, Prefumo F, Bhide A, Thilaganathan B. Second-trimester uterine artery Doppler and spontaneous preterm delivery. *Ultrasound Obstet Gynecol* 2004;24(4):435–9. [PubMed: 15343600]
30. Soares SC, Fratelli N, Prefumo F, Bhide A, Thilaganathan B. First-trimester uterine artery Doppler and spontaneous preterm delivery. *Ultrasound Obstet Gynecol* 2007;29(2):146–9. [PubMed: 17219368]

31. Campbell S, Diaz-Recasens J, Griffin DR, Cohen-Overbeek TE, Pearce JM, Willson K, Teague MJ. New doppler technique for assessing uteroplacental blood flow. *Lancet* 1983;1(8326 Pt 1):675–7. [PubMed: 6132039]
32. Goldkrand JW, Moore DH, Lentz SU, Clements SP, Turner AD, Bryant JL. Volumetric flow in the umbilical artery: normative data. *J Matern Fetal Med* 2000;9(4):224–8. [PubMed: 11048833]
33. Thorp JM. Placental Vascular Compromise: unifying the etiologic pathways of perinatal compromise. *Curr Probl Obstet Gynecol Fertil* 2001;24:203–20.
34. Salafia CM, Vogel CA, Vintzileos AM, Bantham KF, Pezzullo J, Silberman L. Placental pathologic findings in preterm birth. *Am J Obstet Gynecol* 1991;165(4 Pt 1):934–8. [PubMed: 1951558]
35. Brosens JJ, Pijnenborg R, Brosens IA. The myometrial junctional zone spiral arteries in normal and abnormal pregnancies: a review of the literature. *Am J Obstet Gynecol* 2002;187(5):1416–23. [PubMed: 12439541]
36. Sebire NJ. Umbilical artery Doppler revisited: pathophysiology of changes in intrauterine growth restriction revealed. *Ultrasound in Obstetrics and Gynecology* 2003;21(5):419–22. [PubMed: 12768548]

FIGURE 1a

FIGURE 1b **FIGURE 1.**

The gestational age dependence of a.) the uterine artery RI; and b.) the umbilical artery RI. Linear regression lines are shown for term (black) and preterm (red) deliveries. For the uterine artery RI, there is no significant difference in the regression coefficients for term and preterm deliveries; there is a 0.21 unit difference in the intercept of the regression lines ($P < 0.001$). For the umbilical artery RI, the regression coefficients for term ($\beta = -0.00147$; 95% CI: -0.00151, -0.00143) and preterm ($\beta = -0.00103$; 95% CI: -0.00084, -0.00123) deliveries are significantly different ($p < 0.01$).

Table 1

A description of the general characteristics of the sample studied.

	All Birth Types	Spontaneous	Indicated
Sample (No., %)	523	364	159
Preterm	53 (10.1)	32 (8.8)	21 (13.2)
Maternal Characteristics (No., %)			
Ethnicity			
Non-Hispanic White	122 (23.3)	77 (21.2)	45 (28.3)
Hispanic	169 (32.3)	126 (34.6)	43 (27.0)
African-American	232 (44.4)	161 (44.2)	71 (44.7)
Maternal Age			
≤ 30	331 (63.3)	237 (65.1)	94 (59.1)
> 30	192 (36.7)	127 (34.9)	65 (40.9)
Maternal BMI (kilograms/meters ²)			
≤ 26	344 (65.8)	248 (68.1)	96 (60.4)
> 26	173 (33.1)	112 (30.8)	61 (38.4)
Missing	6 (1.1)	4 (1.1)	2 (1.2)
Marital Status			
Married	261 (49.9)	172 (47.3)	89 (56.0)
Single	262 (50.1)	192 (52.7)	70 (44.0)
Highest Educational Level *			
High School or less	269 (51.4)	200 (55.0)	69 (43.4)
College or Post-Graduate	254 (48.6)	164 (45.0)	90 (56.6)
Source of Payment			
Government Assistance	246 (47.0)	173 (47.5)	73 (45.9)
Private Insurance	271 (51.8)	186 (51.1)	85 (53.5)
Missing	6 (1.2)	5 (1.4)	1 (0.6)
Diabetes			
Yes	20 (3.8)	6 (1.6)	14 (8.8)
No	501 (95.8)	356 (97.8)	145 (91.2)
Missing	2 (0.4)	2 (0.6)	---
Hypertension			
Yes	24 (4.6)	8 (2.2)	16 (10.1)
No	497 (95.0)	354 (97.2)	143 (89.9)
Missing	2 (0.4)	2 (0.6)	---
Parity			
Nulliparous	195 (37.3)	129 (35.4)	66 (41.5)
Multiparous	328 (62.7)	235 (64.6)	93 (58.5)
Smoking			
During Pregnancy	99 (18.9)	62 (17.0)	37 (23.3)
Not During Pregnancy	423 (80.9)	301 (82.7)	122 (76.7)
Missing	1 (0.2)	1 (0.3)	---
Infant Characteristics (mean, ±std)			
Gestational Age at Delivery (in days)	273.7 (16.0)	274.1 (15.5)	272.8 (17.1)

	All Birth Types	Spontaneous	Indicated
Birthweight (in grams)	3312.0 (599.3)	3295.6 (574.0)	3349.7 (654.0)

* Statistical significance of difference between type of delivery, spontaneous vs. induced ($p < 0.05$)

Table 2
Characteristics of preterm infants in the study sample.

	All Birth Types	Spontaneous	Indicated
Sample (%)	53 (10.1)	32 (8.8)	21 (13.2)
Maternal Characteristics (No., %)			
Ethnicity			
Non-Hispanic White	9 (17.0)	7 (21.9)	2 (9.5)
Hispanic	12 (22.6)	7 (21.9)	5 (23.8)
African-American	32 (60.4)	18 (56.2)	14 (66.7)
Maternal Age			
≤ 30	27 (50.9)	19 (59.4)	8 (38.1)
> 30	26 (49.1)	13 (40.6)	13 (61.9)
Maternal BMI (kilograms/meters ²)			
≤ 26	34 (64.2)	23 (71.9)	11 (52.4)
> 26	19 (35.8)	9 (28.1)	10 (47.6)
Marital Status			
Married	34 (64.2)	19 (59.4)	15 (71.4)
Single	19 (35.8)	13 (40.6)	6 (28.6)
Highest Educational Level			
High School or less	27 (50.9)	18 (56.2)	9 (42.9)
College or Post-Graduate	26 (49.1)	14 (43.8)	12 (57.1)
Source of Payment			
Government Assistance	29 (54.7)	16 (50.0)	13 (61.9)
Private Insurance	24 (45.3)	16 (50.0)	8 (38.1)
Diabetes			
Yes	2 (3.8)	---	2 (9.5)
No	50 (94.3)	31 (96.9)	19 (90.5)
Missing	1 (1.9)	1 (3.1)	---
Hypertension			
Yes	7 (13.2)	2 (6.3)	5 (23.8)
No	45 (84.9)	29 (90.6)	16 (76.2)
Missing	1 (1.9)	1 (3.1)	---
Parity			
Nulliparous	16 (30.2)	10 (31.3)	6 (28.6)
Multiparous	37 (69.8)	22 (68.7)	15 (71.4)
Smoking			
During Pregnancy	16 (30.2)	7 (21.9)	9 (42.9)
Not During Pregnancy	37 (69.8)	25 (78.1)	12 (57.1)
Type of Delivery *			
Spontaneous Vaginal	32 (60.4)	32 (100)	---
Induced Vaginal	14 (26.4)	---	14 (66.7)
Cesarean Section	7 (13.2)	---	7 (33.3)
Infant Characteristics (mean, ±std)			
Gestational Age at Delivery (in days)	238.3 (21.2)	237.0 (23.5)	240.3 (17.7)

	All Birth Types	Spontaneous	Indicated
Birthweight (in grams)	2239.3 (720.2)	2196.7 (711.0)	2304.2 (746.7)

* Statistical significance of difference between type of delivery, spontaneous vs. induced ($p < 0.05$)

Table 3

Univariate analysis of the relationship between preterm birth, maternal covariates, and resistance indices.

	All Birth Types Hazard Ratio (95% CI)	Spontaneous Hazard Ratio (95% CI)	Indicated Hazard Ratio (95% CI)
Race			
[†] Non-Hispanic White vs. African-American	1.94 (0.93, 4.06)	1.23 (0.51, 2.94)	4.93 * (1.12, 21.71)
[†] Non-Hispanic White vs. Hispanic	0.96 (0.40, 2.27)	0.60 (0.21, 1.71)	2.68 (0.52, 13.79)
Maternal Age			
[†] ≤ 30 vs. > 30	1.73 * (1.01, 2.97)	1.32 (0.65, 2.67)	2.50 * (1.04, 6.03)
BMI			
[†] ≤26.0 vs. > 26.0	1.12 (0.64, 1.97)	0.86 (0.40, 1.86)	1.49 (0.63, 3.51)
Marital Status			
[†] Single vs. married	0.54 * (0.31, 0.95)	0.76 (0.38, 1.54)	0.28 ** (0.11, 0.73)
Education			
[†] High school graduate or less vs. at least some college	1.02 (0.59, 1.74)	0.94 (0.47, 1.89)	1.02 (0.43, 2.43)
Source of Payment			
[†] Private insurance vs. government assistance	0.74 (0.43, 1.28)	0.93 (0.47, 1.87)	0.51 (0.21, 1.22)
Parity			
[†] Nulliparous vs. multiparous	1.39 (0.77, 2.50)	1.21 (0.57, 2.56)	1.81 (0.70, 4.67)
Smoking			
[†] Not smoked during pregnancy vs. smoked during pregnancy	1.91 * (1.06, 3.43)	1.39 (0.60, 3.21)	2.59 * (1.09, 6.15)
Umbilical Artery RI	3.58 ** (2.51, 5.12)	2.47 ** (1.41, 4.31)	3.97 ** (2.56, 6.15)
Uterine Artery RI	2.34 ** (1.71, 3.22)	2.02 * (1.28, 3.17)	2.62 ** (1.68, 4.10)

*
p ≤ 0.05**
p ≤ 0.001[†]
Reference group listed first

Table 4

Multiivariate analysis of the relationship between preterm delivery and resistance indices, after adjustment for maternal covariates.

	All Birth Types Hazard Ratio (95% CI)	Spontaneous Hazard Ratio (95% CI)	C-Section / Induced Hazard Ratio (95% CI)
<u>Umbilical Artery:</u>			
Maternal Age			
$\dagger \leq 30$ vs. > 30	2.52 * (1.37, 4.64)	---	4.14 * (1.61, 10.64)
Marital Status			
$\dagger$ Single vs. married	0.46 * (0.24, 0.87)	---	0.27 * (0.10, 0.73)
Umbilical Artery RI	3.47 ** (2.43, 4.95)	2.47 ** (1.41, 4.31)	4.10 ** (2.50, 6.74)
<u>Uterine Artery:</u>			
Maternal Age			
$\dagger \leq 30$ vs. > 30	2.21 * (1.20, 4.06)	---	3.19 * (1.28, 7.98)
Marital Status			
$\dagger$ Single vs. married	0.43 * (0.23, 0.81)	---	0.19 ** (0.07, 0.51)
Uterine Artery RI	2.26 ** (1.65, 3.11)	2.02 * (1.28, 3.17)	2.59 ** (1.63, 4.13)

*
p ≤ 0.05

**
p ≤ 0.001

$\dagger$
Reference group listed first