American Journal of Epidemiology
© The Author 2009. Published by the Johns Hopkins Bloomberg School of Public Health.
All rights reserved. For permissions, please e-mail: journals.permissions@oxfordjournals.org.
Vol. 170, No. 2
DOI: 10.1093/aje/kwp131
Advance Access publication June 9, 2009

Original Contribution

Placental Vascular Pathology Findings and Pathways to Preterm Delivery

R. Kelly, C. Holzman, P. Senagore, J. Wang, Y. Tian, M. H. Rahbar, and H. Chung

Initially submitted October 8, 2008; accepted for publication February 16, 2009.

The authors examined the associations between placental vascular findings and preterm delivery in 1,053 subcohort women (239 preterm, 814 term) from a Michigan pregnancy cohort study (1998–2004). Twenty-nine placental vascular variables from microscopic examinations were grouped into 5 constructs: 3 maternal constructs—obstructive lesions (MV-O), bleeding/vessel integrity (MV-I), and lack of physiologic conversion of maternal spiral arteries (MV-D)—and 2 fetal constructs—obstructive lesions (FV-O) and bleeding/vessel integrity (FV-I). Construct-specific scores were created by adding the number of positive findings and deriving a dichotomous variable to approximate the top quintile ("high") and bottom 4 quintiles ("not high") within each construct. In multivariate polytomous logistic regression models, medically indicated preterm delivery at <35 weeks was significantly associated with high scores for each of the vascular constructs; adjusted odds ratios ranged from 2.4 to 5.4. Spontaneous preterm delivery at 35–36 weeks was significantly associated with a high score on any 1 of 3 constructs: MV-I, MV-D, and FV-I. Spontaneous preterm delivery at <35 weeks was significantly associated with a high score on 2 or more of 3 constructs: MV-I, MV-D, and FV-I; adjusted odds ratios ranged from 4.1 to 7.4. These results support a role for various placental vascular lesions in medically indicated and spontaneous preterm delivery.

blood vessels; placenta; premature birth

Abbreviations: CI, confidence interval; OR, odds ratio; POUCH, Pregnancy Outcomes and Community Health.

Editor's note: *An invited commentary on this article appears on page 159, and the authors' response appears on page 162.*

Maternal vascular complications have been most consistently associated with medically indicated preterm delivery, but they may also contribute to preterm deliveries that result from premature rupture of membranes and spontaneous preterm labor (1–5). Studies of vascular pathways to preterm delivery have considered clinical signs/symptoms (6, 7), biomarkers (8–15), and placental pathology findings (4, 5, 16), all of which provide clues and unique challenges. Vasculature-related complications such as preeclampsia, gestational hypertension, intrauterine growth restriction, and overt bleeding are defined by extreme signs/symptoms that have potentially multiple causes, some distinct and some overlapping (2–4, 6, 17, 18). In addition, clinically diagnosed vascular complications most likely underrepresent vascular problems associated with preterm delivery, decreased fetal growth, and altered fetal development. Biomarkers such as thrombin (10, 15), fms-like tyrosine kinase 1 (12–14), vascular endothelial growth factor (8, 9), and placental growth factor (13, 14) have been linked to multiple clinically defined vascular complications in pregnancy, which may indicate common underlying etiologies or common sequelae following vascular damage.

Evaluation of placental vascular findings offers another avenue for uncovering vascular pathways. Studies have repeatedly shown that placental evidence of decidual vasculopathy or, more basically, uteroplacental vascular lesions are associated with preeclampsia, gestational hypertension,

Correspondence to Dr. Claudia Holzman, Department of Epidemiology, College of Human Medicine, Michigan State University, B601 West Fee Hall, East Lansing, MI 48824 (e-mail: cholzman@epi.msu.edu).

Table 1. Variability in Placental Vascular Pathology Groupings Used in Studies of Preterm Delivery, 1993–2003

Authors and Year (Ref. No.)	Placental Vascular Pathology
Arias et al., 1993 (2)	Maternal vascular pathology: unaltered spiral arteries containing recent or old organized thrombi, mural or occlusive, presence of uneven accelerated maturation of the chorionic villi, large numbers of multinucleated syncytial knots, and multiple placental infarcts.
Salafia et al., 1995 (19)	Decidual vasculopathy: aberrant conversion of spiral arteries, decidual vasculitis, and fibrinoid necrosis or atherosis.
	Uterine vascular insufficiency: villous infarcts, intervillous thrombi, gross or microscopic evidence of abruption, and villous lesions. Gross evidence of abruption was frank retroplacental clots with placental compression. Microscopically, abruption was diagnosed if retroplacental hemorrhage and basal plate destruction was accompanied by villous necrosis, trophoblast basophilia, and villous crowding.
Beebe et al., 1996 (1)	Histopathologic ischemic changes: villous agglutination, shrinkage of villi, numerically increased syncytiotrophoblastic knots, increased perivillous fibrin, infarcts, sclerotic or avascular villi, and fibrinoid material with abundant X cells.
	Placental infarcts: ischemic villous necrosis, diffuse fibrinoid material with abundant X cells, and, sometimes, ghost-like villi.
Ghidini et al., 1997 (20)	Uteroplacental vascular and related villous lesions: unaltered spiral arteries, fibrinoid necrosis and atheroma, abruptio placentae, villous infarcts, terminal villous fibrosis, increased syncytiotrophoblastic knotting, cytotrophoblast proliferation, villous hypovascularity, villous thrombus, and circulating fetal nucleated erythrocytes.
Kim et al., 2002 (4)	Aggregated vascular lesion: atherosis, fibrinoid necrosis of the decidual vessels, decidual vessel thrombosis, and fetal thrombotic vasculopathy (fibrin thrombi in chorionic or stem vessels).
Ogunyemi et al., 2003 (32)	Placental vascular pathology: placental infarction, placental abruption, villous fibrosis and sclerosis, vascular intimal hypertrophy, and decidual fibrinoid necrosis.
	Coagulation-related lesions: uteroplacental thrombosis, hemorrhagic endovasculitis, intervillous thrombosis, and intervillous fibrin deposits.

and fetal intrauterine growth restriction (19–21). Failed physiologic transformation of maternal spiral arteries and decidual vascular arthrosis were found to be more common in premature rupture of membranes and spontaneous preterm labor than in normal, term deliveries (4), but incorporating placental vascular findings into epidemiologic studies is also fraught with challenges. There are no ''gold'' standards demarcating ''normal'' from ''abnormal'' along the continuum of pathologic findings, and classification schemes for the different pathologic findings have been quite variable. One approach has been to focus on an individual placental vascular finding, such as failure of physiologic transformation of spiral arteries, and relate it to preterm delivery (3). Another has been to group multiple placental findings to characterize globally defined vascular complications such as abnormal placentation, uteroplacental ischemia, and hemorrhage, but across studies there are considerable inconsistencies in terminology, definitions, and findings used (Table 1). Few studies have empirically evaluated placental vascular findings to determine how often they co-occur (22, 23), and only 1 of these studies used both term and preterm placentas (22). Finally, investigators have primarily concentrated on maternal vascular pathology in relation to preterm delivery, so less is known about the influence of fetal vascular findings, alone or in combination with maternal vascular pathology (24–26).

The Pregnancy Outcomes and Community Health (POUCH) Study was a prospective cohort study designed to examine biologic and social factors associated with various pathways to preterm delivery. Here, data from a subcohort were used to explore the relation between vascular placental pathology and preterm delivery. Microscopic vascular findings in term and preterm placentas of subcohort women were divided into 5 groups, each representing a pathology-based latent construct. The goals of these analyses were to: 1) examine the extent to which the pathology-based constructs co-occur in the same placenta; 2) evaluate maternal characteristics for each of the 5 pathology-based constructs; and 3) assess relations between the pathology-based constructs and risk of spontaneous and/or medically indicated preterm delivery.

MATERIALS AND METHODS

Population and study design

The POUCH Study was a prospective cohort study designed to examine pathways to preterm delivery in 3,019 pregnant women (27). Between August 1998 and June 2004, pregnant women were recruited from 52 clinics in 5 Michigan communities. Women were enrolled in the 15th–27th week of pregnancy. Inclusion criteria included a singleton pregnancy with no known congenital anomaly, maternal age $\geq$15 years, prenatal screening of maternal serum α-fetoprotein at the 15th–22nd week of pregnancy, no prepregnancy history of diabetes mellitus, and competency in English. Women were recruited at the time of prenatal screening. All women with maternal serum α-fetoprotein levels greater than 2 multiples of the mean were invited to participate (7% of the cohort), because this biomarker had been linked to preterm delivery previously (28) and was of particular interest in the POUCH Study. Women with normal maternal serum α-fetoprotein levels were stratified by race/ethnicity and sampled into the cohort. Nineteen of the 3,038 women enrolled were lost to

follow-up (1998–2004), resulting in a cohort of 3,019 women. The study received institutional review board approval from Michigan State University, the Michigan Department of Community Health, and 9 community hospitals. Race/ethnicity-specific comparisons of the study cohort with birth certificate data from women delivering in the study communities showed that cohort participants closely resembled community women with regard to most maternal characteristics measured.

At enrollment, study participants were interviewed and biologic samples were obtained. For in-depth analyses, a subcohort ($n = 1{,}371$) was created which included all women who delivered preterm (<37 weeks' gestation), all women who delivered at term with elevated maternal serum α-fetoprotein levels (>2 multiples of the mean), and a sample of women who delivered at term with normal maternal serum α-fetoprotein levels, with oversampling of African-American women from this latter category. The subcohort sampling scheme was designed to maximize statistical power for studying at-risk subgroups. All subcohort analyses use sampling weights to reflect the sampling scheme, and therefore there is no bias introduced by oversampling certain subgroups. In the subcohort, prenatal and labor/delivery records were abstracted and delivered placentas were examined by a study placental pathologist. Placentas were retrieved for 88% (1,213 women) of the subcohort, and this analysis includes the first 1,053 placentas (239 preterm, 814 term) assessed in the subcohort to date.

Placental examination protocol

The POUCH Study placental examination protocol has been described elsewhere (27). Briefly, placentas were formalin-fixed and grossly examined by the study placental pathologist. Five full-thickness samples were taken from the disc: 1 at the cord insertion, 1 in grossly normal central tissue, 2 more from central tissue, and 1 from marginal tissue. The latter 3 samples were from grossly abnormal tissue if present. Four other samples were also taken: 2 umbilical cord samples and 2 extraplacental membrane samples from a membrane roll. Tissue samples were paraffin-embedded, sectioned, and stained with hematoxylin and eosin for microscopic assessment. The study's placental pathologist was blinded to gestational age at delivery, all clinical data, and gross examination findings during the microscopic examination.

Placental diagnostic coding tool

Placental microscopic findings were recorded with a computer-based data collection instrument adapted from that of Dr. Carolyn Salafia (Placental Analytics LLC, Larchmont, New York, and Institute for Basic Research, Staten Island, New York). The instrument is primarily descriptive, not diagnostic; it captures a large number of pathologic changes and their location, frequency, extent, and proximity to one another. Maternal vascular findings recorded on this instrument were organized using a scheme adapted from the Placental Diagnostic Coding Tool of Drs. Raymond Redline and Maureen Hack (October 31, 1996, revision; P. K. Senagore, Michigan State University, personal communication, 1999).

Table 2. Maternal Characteristics and Pregnancy Outcome in the Subcohort With Completed Placental Assessments ($n = 1{,}053$), Pregnancy Outcomes and Community Health Study, 1998–2004

Maternal Characteristic	No.	%	Weighted %[a]
Maternal age, years			
<20	167	15.9	13.8
20–29	592	56.2	56.5
≥30	294	27.9	29.7
Maternal education, years			
<12	213	20.2	16.9
12	301	28.6	27.4
>12	539	51.2	55.7
Race/ethnicity			
Non-Hispanic white	568	53.9	65.9
African-American	403	38.3	24.6
Other	82	7.8	9.5
Medicaid insurance			
Yes	567	53.9	48.0
No	485	46.1	52.0
Parity			
No previous livebirth	433	41.1	41.0
Previous livebirth with preterm delivery	59	5.6	4.4
Previous livebirth without preterm delivery	561	53.3	54.6
Gestational week at enrollment			
15–<20	154	14.6	13.8
20–<25	748	71.0	72.0
25–<27	151	14.4	14.2
Pregnancy outcome			
Term delivery	814	77.3	89.3
Spontaneous preterm delivery	163	15.5	7.4
Medically indicated preterm delivery	76	7.2	3.3

[a] Weighted for the subcohort sampling scheme; percentages reflect the distribution in the original cohort.

This adapted data summary tool was used to categorize findings into 5 conceptual groups, or pathology-based latent constructs: 1) maternal vascular–obstructive (MV-O) captures evidence of obstruction, as in major placental disc infarcts and decidual vessel atherosis; 2) maternal vascular–disturbance of integrity (MV-I) includes findings associated with retroplacental hemorrhage and bleeding in the decidua; 3) maternal vascular–developmental (MV-D) incorporates findings consistent with abnormal or incomplete trophoblast remodeling of maternal spiral arteries; 4) fetal vascular–obstructive (FV-O) represents findings related to large and small fetal vessel obstruction; and 5) fetal vascular–disturbance of integrity (FV-I) includes findings that suggest abnormalities of fetal villous blood flow such as fetal-to-maternal hemorrhage. The 5 groups initially consisted of 39 findings. The study pathologist reevaluated a 10% sample of placentas and rescored the 39 findings while blinded

Table 3. Spearman's Rank Correlation Coefficients and *P* Values for Correlations Between Pathology-based Vascular Construct[a] Scores[b], Pregnancy Outcomes and Community Health Study, 1998–2004

	MV-O		MV-I		MV-D		FV-O		FV-I	
	r_s	*P* Value	r_s	*P* Value	r_s	*P* Value	r_s	*P* Value	r_s	*P* Value
MV-O	1	NA								
MV-I	0.26	<0.0001	1	NA						
MV-D	0.03	0.35	0.03	0.32	1	NA				
FV-O	0.21	<0.0001	0.09	0.004	0.02	0.48	1	NA		
FV-I	0.06	0.04	0.17	<0.0001	0.05	0.11	0.04	0.20	1	NA

Abbreviation: NA, not applicable.

[a] Vascular constructs: FV-I, fetal vascular lesion–disturbance of integrity; FV-O, fetal vascular lesion–obstructive; MV-D, maternal vascular lesion–developmental; MV-I, maternal vascular lesion–disturbance of integrity; MV-O, maternal vascular lesion–obstructive.

[b] Continuous scores.

to results from the original placental assessments. Findings with a kappa (κ) value (a measure of concordance between the first and second scorings) below 0.40 were eliminated, leaving 29 total findings within the 5 pathology-based vascular constructs. Of the remaining 29 findings, 18 had κ's of 0.40–0.60 (moderate concordance) and 11 had κ's of 0.61–0.89 (excellent concordance).

Pregnancy outcome

Gestational age at delivery was calculated from the date of the last menstrual period. If the estimate based on the last menstrual period differed from an early ultrasound estimate by more than 2 weeks, ultrasound dates were given preference. Preterm delivery (<37 weeks' gestation) was subdivided into 2 commonly used clinical groupings: 1) spontaneous preterm delivery, which included women with spontaneous regular contractions that led to cervical changes (≥2 cm dilatation) and women with rupture of membranes prior to or at the onset of labor; and 2) medically indicated preterm delivery, which included women who delivered after induction of labor or by cesarean section before the onset of spontaneous regular contractions or membrane rupture. Women were assigned to one of these 2 groups based on a chart review protocol that included independent evaluations by obstetricians and by study labor and delivery nurses. Discrepancies were resolved with further review. Within the clinical subtypes, preterm delivery was further divided according to gestational week at delivery—that is, <35 weeks and 35–36 weeks—because pregnancy complications and clinical decisions to intervene vary as pregnancy progresses.

Table 4. Kappa Coefficients for Co-occurrence of High Pathology-based Vascular Construct[a] Scores[b], Pregnancy Outcomes and Community Health Study, 1998–2004

	MV-O	MV-I	MV-D	FV-O	FV-I
MV-O	1				
MV-I	0.16	1			
MV-D	0.08	0.04	1		
FV-O	0.12	0.04	0.02	1	
FV-I	−0.03	0.12	0.04	0.01	1

[a] Vascular constructs: FV-I, fetal vascular lesion–disturbance of integrity; FV-O, fetal vascular lesion–obstructive; MV-D, maternal vascular lesion–developmental; MV-I, maternal vascular lesion–disturbance of integrity; MV-O, maternal vascular lesion–obstructive.

[b] Dichotomous scores. Construct-specific scores were created by adding the number of positive findings and deriving a dichotomous variable to approximate the top quintile ("high") and bottom 4 quintiles ("not high") within each construct.

Maternal characteristics

Information on maternal educational level, Medicaid insurance status, parity, prepregnancy weight, height, and race/ethnicity were obtained through self-report at enrollment. Prepregnancy body mass index was calculated as weight in kilograms divided by height in meters squared and was divided into 3 groups: normal (18.5–24.9), overweight (25–29.9), and obese (≥30). Because of small numbers, underweight women ($n = 47$) were excluded from analyses involving body mass index, and the 82 women who were not African-American or white were grouped with whites (white/other), with whom they shared more similar risks of preterm delivery.

Analytic approach

Development of the pathology-based vascular construct scores. Each of the 29 vascular findings had a continuous score representing the number of samples per placenta in which the vascular pathology finding was present. Scores ranged from 0 to 2 when specifically considering findings within the extraplacental membrane samples, 0 to 5 for findings within each of the placental disc samples, and 0 to 7 when combining disc and extraplacental membrane samples. Data from women who delivered at term with normal maternal serum α-fetoprotein levels were used to determine the typical frequency distribution (number of positive samples per placenta) of each of the 29 vascular findings. The top quintile (or approximately) was

Table 5. Relation of Maternal Characteristics to Pathology-based Vascular Constructs[a] (Weighted Percentages[b]; $n = 1,053$), Pregnancy Outcomes and Community Health Study, 1998–2004

	MV-O		MV-I		MV-D		FV-O		FV-I	
	Not High[c]	High[c]	Not High	High	Not High	High	Not High	High	Not High	High
Race/ethnicity										
White/other	88	12	78	22	93	7	76	24*	60	40
African-American	90	10	82	18	80	20*	84	16	66	34
Maternal age, years										
<20	84	16	77	23	81	19*	75	25	64	36
20–29	90	10	80	20	91	9	80	20	62	38
≥30	88	12	79	21	92	8	75	25	57	43
Medicaid insurance										
Yes	88	12	81	19	88	12*	80	20	62	38
No	89	11	77	23	92	8	76	24	60	40
Parity										
No previous livebirth	84	16*	80	20	92	8	75	25	63	37
Previous livebirth with preterm delivery	93	7	77	23	94	6	79	21	62	38
Previous livebirth without preterm delivery	92	8	79	21	88	12	80	20	59	41
Body mass index[d]										
Normal (18.5–24.9)	88	12	78	22	94	6	79	21	64	36
Overweight (25–29.9)	88	12	80	20	89	11	76	24	59	41
Obese (≥30)	91	9	81	19	83	17*	76	24	56	44

* $P < 0.05$.

[a] Vascular constructs: FV-I, fetal vascular lesion–disturbance of integrity; FV-O, fetal vascular lesion–obstructive; MV-D, maternal vascular lesion–developmental; MV-I, maternal vascular lesion–disturbance of integrity; MV-O, maternal vascular lesion–obstructive.

[b] Weighted for the subcohort sampling scheme; percentages reflect the distribution in the original cohort.

[c] Construct-specific scores were created by adding the number of positive findings and deriving a dichotomous variable to approximate the top quintile ("high") and bottom 4 quintiles ("not high") within each construct.

[d] Weight (kg)/height $(m)^2$. Underweight women were excluded.

considered "high," and accordingly a vascular finding was scored as either "0" (not high) or "1" (high) for each placenta. We then summed the dichotomous vascular finding scores to obtain a pathology-based construct score. For example, the 7 findings in the MV-O construct were added to create a construct-specific score ranging from 0 to 7 for each placenta. Again, data from women who delivered at term with normal maternal serum α-fetoprotein levels were used to represent the typical frequency distributions of construct scores. Because of clumping in the distributions, the most uniform cutpoints for "high" across the constructs were the top 12th–21st percentiles. One construct (FV-I) had to be cut at the top 36th percentile. A dichotomous variable was created for each of the 5 pathology-based vascular constructs; "high" was at or above the cutpoint, and "not high" was below it. Using the 10% reevaluation method (as described above) with the 29 most reliable findings, the vascular construct κ's were in the range of moderate to excellent (for MV-O, $\kappa = 0.42$; for MV-I, $\kappa = 0.62$; for MV-D, $\kappa = 0.48$; for FV-O, $\kappa = 0.66$; and for FV-I, $\kappa = 0.64$).

Analyses using pathology-based vascular construct scores. Correlations between pathology-based vascular construct scores were determined in 2 ways. First, the score was modeled as a continuous variable and Spearman's rank correlation coefficients were obtained using PROC CORR in SAS (SAS Institute Inc., Cary, North Carolina). Second, the scores were modeled as a dichotomous variable (high and normal as defined above) and co-occurrence was assessed using the κ statistic.

We evaluated each pathology-based vascular construct (modeled as high/normal) in relation to maternal characteristics (χ^2 test) and in relation to risk of preterm delivery by using a polytomous logistic regression model (PROC SURVEYLOGISTIC in SAS) with a 5-level outcome variable: term (referent), 35–36 weeks with spontaneous preterm delivery, 35–36 weeks with medically indicated preterm delivery, <35 weeks with spontaneous preterm delivery, and <35 weeks with medically indicated preterm delivery. In these analyses, data were weighted to reflect oversampling of high maternal serum α-fetoprotein into the cohort and oversampling of preterm, high maternal serum α-fetoprotein, and African-American women into the subcohort. Because of the low-to-moderate correlations between the pathology-based vascular constructs, we also included all vascular constructs in a single polytomous logistic regression model to test their associations with preterm delivery after

accounting for the presence of other constructs. Significant ($P < 0.05$) construct interactions were observed for spontaneous preterm delivery but not medically indicated preterm delivery. To clarify these interactions, we used 2 separate polytomous regression models: 1 excluded spontaneous preterm delivery and had a 3-level outcome of term (referent), <35 weeks with medically indicated preterm delivery, and 35–36 weeks with medically indicated preterm delivery; the other excluded medically indicated preterm delivery and had a 3-level outcome of term (referent), <35 weeks with spontaneous preterm delivery, and 35–36 weeks with spontaneous preterm delivery. In a second version of these models, maternal characteristics related to preterm delivery in previous studies (race/ethnicity, parity, age, Medicaid insurance status, and body mass index) were added as potential confounders.

RESULTS

Table 2 shows the distributions of demographic and pregnancy-related factors in this subcohort sample. The table includes sampling weights to show the distributions of these same maternal characteristics in the POUCH Study cohort. Weighted and unweighted distributions were similar, except with regard to the characteristics used for subcohort sampling—that is, race/ethnicity and pregnancy outcome. In the subcohort sample, approximately 28% of participants were over 29 years of age, 51% had more than 12 years of education, 38% were African-American, 54% were insured by Medicaid, and 22.7% delivered preterm.

Correlations between pathology-based vascular construct scores measured on a continuous scale were generally weak to moderate in magnitude, with Spearman's rank correlation coefficients ranging from 0.02 to 0.26 (Table 3). Co-occurrence of vascular constructs was also tested using dichotomous variables (normal/high) and a κ statistic, which has a range of -1 to 1. The κ coefficients for the vascular constructs were all low, -0.03 to 0.16 (Table 4).

Maternal vascular obstructions, evidenced by a high MV-O score, were more common in primiparous women (Table 5). High FV-O scores, indicative of fetal vessel thrombosis, were observed more often in whites/others than in African Americans. A high MV-D score, consistent with poor conversion of spiral arteries, was associated with being African-American, under 20 years of age, insured by Medicaid, and obese. When all maternal characteristics were included in a single logistic regression model, a high MV-D score continued to be more prevalent in African-American women (adjusted odds ratio (OR) = 2.9, 95% confidence interval (CI): 1.8, 4.7), women under 20 years of age (adjusted OR = 2.9, 95% CI: 1.3, 6.7), overweight women (adjusted OR = 1.9, 95% CI: 1.1, 3.4), and obese women (adjusted OR = 3.2, 95% CI: 1.8, 5.5).

High scores for MV-O, MV-I, MV-D, FV-O, and FV-I were each associated with medically indicated preterm delivery at <35 weeks, with unadjusted odds ratios ranging from 2.9 to 6.5 (Table 6). MV-I and MV-D were also related to spontaneous preterm delivery at <35 weeks (unadjusted odds ratios were 2.2 and 2.7, respectively), and FV-I was associated with spontaneous preterm delivery at 35–36 weeks (unadjusted OR = 1.8). All pathology-based vascular constructs were placed in a single model after exclusion of spontaneous preterm deliveries. The adjusted odds ratios for medically indicated preterm delivery at <35 weeks were attenuated but remained statistically significant (Table 7). Following additional adjustment for maternal variables (i.e., parity, Medicaid status, race/ethnicity, age, and body mass index), there continued to be strong associations between medically indicated preterm delivery at <35 weeks and high scores for MV-O (OR = 3.1, 95% CI: 1.4, 6.9), MV-I (OR = 2.3, 95% CI: 1.0, 5.5), MV-D (OR = 2.8, 95% CI: 1.2, 6.6), FV-O (OR = 5.7, 95% CI: 2.3, 14), and FV-I (OR = 2.7, 95% CI: 1.2, 6.2). There were no statistically significant interactions ($P < 0.5$) among the vascular constructs in this model and no significant associations with medically indicated preterm delivery at 35–36 weeks.

A second series of analyses placed all vascular constructs into a single model after exclusion of medically indicated preterm delivery. These models showed significant interactions between MV-I, MV-D, and FV-I (Table 8). After adjustment for maternal characteristics, the presence of a high score on any 1 of these 3 vascular constructs significantly increased the risk of spontaneous preterm delivery at 35–36 weeks, with adjusted odds ratios ranging from 2.2 to 4.6. The presence of 2 or more high scores increased the risk of spontaneous preterm delivery at <35 weeks, with adjusted odds ratios ranging from 4.1 to 7.4. MV-O and FV-O were unrelated to spontaneous preterm delivery.

DISCUSSION

We found that a pathology-based system of grouping placental vascular findings into constructs offers insights into preterm delivery pathways. Separate consideration of the various vascular constructs was supported by 3 observations. First, the correlations between the pathology-based vascular construct scores were weak to moderate, suggesting that co-occurrence of these latent processes is not common. Second, there was considerable variation in the maternal characteristics associated with each of the vascular constructs. Third, some but not all constructs were related to spontaneous preterm delivery.

The MV-D construct was most closely linked to multiple maternal characteristics, including high body mass index, whereas the MV-O construct was associated only with primiparity. While inadequate maternal vessel remodeling can lead to placental obstructive lesions (29), our results suggest that there may be value in exploring upstream and downstream factors related to each of these constructs. The higher prevalence of fetal vascular obstruction (thrombosis) in whites/others compared with African Americans may reflect differential predispositions such as thrombophilias (30). There were no maternal characteristics significantly associated with maternal vessel bleeding. Acute placental abruptions, which are most evident through clinical presentation and/or gross pathology findings, are probably not sufficiently captured in this construct, which is defined only by microscopic placental findings.

Table 6. Associations Between Pathology-based Vascular Constructs[a] and Preterm Delivery ($n = 1{,}053$), Pregnancy Outcomes and Community Health Study, 1998–2004

Vascular Construct Group and Histopathologic Findings	Threshold No. of Tissue Samples per Placenta With Positive Findings[b]	Construct Scoring System	Gestational Week at Delivery							
			Medically Indicated Preterm Delivery				Spontaneous Preterm Delivery			
			<35		35–36		<35		35–36	
			Unadjusted OR[c]	95% CI	Unadjusted OR[c]	95% CI	Unadjusted OR[c]	95% CI	Unadjusted OR[c]	95% CI
MV-O										
Syncytial knots	≥3	+								
Villous infarcts	≥1	+								
Perivillous fibrin (not in Redline and Hack[d])	≥1	+								
Fibrinoid necrosis or atherosis in decidual vessels of basal plate	≥1	+								
Fibrinoid necrosis or atherosis in decidual vessels of membranes	≥1	+								
Noninflammatory necrosis of decidua in basal plate	≥1	+								
Noninflammatory necrosis of decidua in membranes	≥2	+								
Maximum MV-O score (minimum score for MV-O high[e])		7+ (3+)	3.8	1.6, 8.8	2.1	0.9, 4.5	0.5	0.1, 1.7	0.4	0.2, 1.0
MV-I										
Retroplacental blood with disruption/ compression	≥1	+								
Decidual hemorrhage in basal plate	≥1	+								
Pigment/hemosiderin-like in deciduas of membranes	≥1	+								
Pigment/hemosiderin-like in deciduas of basal plate	≥1	+								
Maximum MV-I score (minimum score for MV-I high[e])		4+ (2+)	3.7	1.7, 8.2	0.9	0.4, 2.0	2.2	1.1, 4.1	1.2	0.7, 2.0
MV-D										
Unaltered/abnormal decidual vessels in basal plate	≥2	+								
Unaltered/abnormal decidual vessels in membranes	≥2	+								
Mural hyperplasia of decidual vessels in membranes	≥1	+								
Maximum MV-D score (minimum score for MV-D high[e])		3+ (2+)	6.5	2.8, 15	2.2	1.0, 5.0	2.7	1.2, 5.9	1.8	1.0, 3.2
FV-O										
Fragmented red blood cells in small fetal vessels	≥1	+								
Nontrophokaryorrhexis in small fetal vessels	≥1	+								
Thrombi in large fetal disc vessels	≥1	+								
Luminal septation in large stem fetal vessels	≥1	+								
Hemorrhagic-mural disruption in large stem fetal vessels	≥1	+								
Fragmented red blood cells in large stem fetal vessels	≥1	+								
Nontrophokaryorrhexis in large stem fetal vessels	≥1	+								

Thrombi in chorionic plate fetal vessels	≥1	+									
Intimal fibrin cushion in chorionic plate fetal vessels	≥1	+									
Intimal fibrin cushion in large fetal disc vessels	≥1	+									
Avascular villi	≥2	+									
Maximum FV-O score (minimum score for FV-O high[e])		11+ (2+)	2.9	1.3, 6.4	0.9	0.4, 1.9	0.7	0.3, 1.6	0.5	0.3, 0.9	
FV-I											
Subchorionic hemorrhage (maternal dissecting hemorrhage)	≥1	+									
Villous stromal hemorrhage	≥1	+									
Villous edema	≥1	+									
Intervillous thrombus	≥2	+									
Maximum FV-I score (minimum score for FV-I high[e])		4+ (1+)	3.1	1.4, 6.8	1.7	0.9, 3.1	1.8	1.0, 3.3	1.8	1.2, 2.7	

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Vascular constructs: FV-I, fetal vascular lesion–disturbance of integrity; FV-O, fetal vascular lesion–obstructive; MV-D, maternal vascular lesion–developmental; MV-I, maternal vascular lesion–disturbance of integrity; MV-O, maternal vascular lesion–obstructive.

[b] Threshold based on the top quintile from the distribution of findings in term placentas with normal maternal serum α-fetoprotein levels.

[c] Weighted polytomous logit models with term delivery used as the referent category.

[d] Not listed in Redline and Hack's Placental Diagnostic Coding Tool (see text).

[e] Threshold based on the distribution of construct scores. Construct-specific scores were created by adding the number of positive findings and deriving a dichotomous variable to approximate the top quintile ("high") and bottom 4 quintiles ("not high") within each construct.

From a clinical perspective, preeclampsia, fetal distress, poor fetal growth, and placental abruption account for the majority of medically indicated preterm deliveries (6). It has been unclear whether all types of vascular pathology or only certain types drive the association with medically indicated preterm delivery. By building models that included all 5 pathology-based vascular constructs, we were able to show that each construct increased the risk of medically indicated preterm delivery at <35 weeks. The continued importance of the MV-D construct after adjustment for maternal obstructive lesions (e.g., infarcts and atherosis) suggests that developmental findings alone (abnormal or incomplete remodeling of maternal vessels) may be sufficient to trigger maternal complications (high blood pressure) that result in medically indicated preterm delivery.

Other investigators have reported an increased risk of spontaneous preterm delivery in association with placental findings such as uteroplacental vascular thrombosis, infarcts, absence of physiologic spiral artery change, and villous fibrosis (2–4). We found that among 3 of the 5 vascular constructs (MV-D, MV-I, and FV-I), there was an inverse "dose response" between the number of high construct scores and the timing of spontaneous preterm delivery—a clear indication that vascular constructs are important to both late and early spontaneous preterm delivery. The lack of association between vascular-obstruction constructs, maternal or fetal, and spontaneous preterm delivery may be due to the fact that in severe cases, medically indicated preterm delivery supersedes.

Comparisons across studies of preterm delivery-related vascular placental pathology are made difficult by 1) the variability in definitions and groupings of pathology findings and 2) geographic and secular trends in medically indicated preterm delivery, influenced both by the prevalence of indications and by variation in medical practices. In addition, previous studies have showed that interrater reliability for diagnosing histologic evidence of vasculature-related pathology is not high (22, 24, 31), perhaps because there is a lack of agreement as to what constitutes a critical mass of findings for the designation "positive."

Major strengths of this study include the sample, which was recruited from multiple community clinics and was shown to be highly comparable to community women giving birth during this period. The pathologist was blinded to all clinical information, which is not typical with referred placental examinations in perinatal medicine. We examined the distributions of placental vascular findings and constructs in term placentas as a means of determining what might be considered "normal." Often studies of placental vascular pathology compare subgroups of preterm births (16, 20, 32, 33), use high-risk term placentas as the reference group (1), or are conducted in teaching hospitals where patient populations overrepresent high-risk pregnancy conditions, even among term deliveries. Ten of the original 39 findings in our vascular scoring scheme were removed because they showed poor intrarater reliability. By refining our constructs, we were able to achieve κ's in the good-to-excellent range. Our next step will be to test the interrater reliability for this pathology-based vascular construct scoring tool.

Table 7. Associations Between Pathology-based Vascular Constructs[a] (High/Not High[b]) and Medically Indicated Preterm Delivery ($n = 890$[c]), Pregnancy Outcomes and Community Health Study, 1998–2004

	Gestational Week at Delivery							
	Model Including All 5 Vascular Constructs				Model Including All 5 Vascular Constructs Plus Maternal Characteristics[d]			
	<35		35–36		<35		35–36	
	Adjusted OR	95% CI	Adjusted OR	95% CI	Adjusted OR	95% CI	Adjusted OR	95% CI
MV-O	2.4	1.1, 5.5	2.1	0.9, 4.7	3.1	1.4, 6.9	1.7	0.9, 3.2
MV-I	2.7	1.2, 6.2	0.8	0.3, 1.8	2.3	1.0, 5.5	2.2	0.9, 5.2
MV-D	5.4	2.3, 13	2.0	0.9, 4.8	2.8	1.2, 6.6	0.8	0.3, 1.9
FV-O	2.7	1.2, 6.1	0.8	0.4, 1.8	5.7	2.3, 14	1.6	0.6, 4.1
FV-I	3.0	1.3, 6.8	1.7	0.9, 3.2	2.7	1.2, 6.2	0.8	0.4, 1.8

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Vascular constructs: FV-I, fetal vascular lesion–disturbance of integrity; FV-O, fetal vascular lesion–obstructive; MV-D, maternal vascular lesion–developmental; MV-I, maternal vascular lesion–disturbance of integrity; MV-O, maternal vascular lesion–obstructive.

[b] Construct-specific scores were created by adding the number of positive findings and deriving a dichotomous variable to approximate the top quintile ("high") and bottom 4 quintiles ("not high") within each construct.

[c] Term and medically indicated preterm deliveries only.

[d] Maternal characteristics related to preterm delivery in previous studies (race/ethnicity, Medicaid insurance, parity, maternal age, and body mass index (prepregnancy/at screening; weight (kg)/height $(m)^2$, continuous variable)).

A limitation of this study is that our approach required extensive effort to evaluate and score each placenta. However, our intent was not to supplant the hospital-based pathologists' diagnostic process, which is less time-consuming, encompasses pattern recognition, makes use of clinical information, and allows for expert interpretation of placental findings. Rather, we view our approach as a research tool that can aid in uncovering similarities and distinctions between the various vasculature-related pathways that affect pregnancy outcomes. In addition, note that placental

Table 8. Associations Between Pathology-based Vascular Constructs[a] (High/Not High[b]) and Spontaneous Preterm Delivery ($n = 977$[c]), Pregnancy Outcomes and Community Health Study, 1998–2004

			Gestational Week at Delivery							
			Model Including All 5 Vascular Constructs				Model Including All 5 Vascular Constructs Plus Maternal Characteristics[d]			
			<35		35–36		<35		35–36	
			Adjusted OR	95% CI	Adjusted OR	95% CI	Adjusted OR	95% CI	Adjusted OR	95% CI
MV-I	MV-D	FV-I								
+	−	−	1.3	0.4, 4.3	2.1	1.0, 4.5	1.5	0.5, 4.9	2.2	1.0, 4.7
−	+	−	2.3	0.5, 11	4.9	2.1, 11	2.1	0.4, 11	4.6	1.9, 11
−	−	+	1.0	0.4, 2.5	2.6	1.6, 4.4	1.2	0.5, 3.0	2.7	1.6, 4.6
+	+	−	3.1	0.3, 27	1.6	0.2, 15	3.2	0.3, 30	1.4	0.1, 13
+	−	+	4.0	1.7, 9.7	2.3	1.1, 5.0	4.8	2.0, 12	2.5	1.1, 5.3
−	+	+	4.5	1.4, 15	1.6	0.4, 5.7	4.1	1.2, 14	1.7	0.5, 6.3
+	+	+	4.8	0.9, 25	2.5	0.5, 13	7.4	1.3, 42	2.7	0.5, 15
MV-O			0.4	0.1, 1.5	0.4	0.2, 1.0	0.4	0.1, 1.4	0.4	0.2, 1.0
FV-O			0.8	0.3, 1.8	0.5	0.3, 1.0	0.8	0.3, 1.9	0.5	0.3, 1.0

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Vascular constructs: FV-I, fetal vascular lesion–disturbance of integrity; FV-O, fetal vascular lesion–obstructive; MV-D, maternal vascular lesion–developmental; MV-I, maternal vascular lesion–disturbance of integrity; MV-O, maternal vascular lesion–obstructive.

[b] Construct-specific scores were created by adding the number of positive findings and deriving a dichotomous variable to approximate the top quintile ("high") and bottom 4 quintiles ("not high") within each construct.

[c] Term and spontaneous preterm deliveries only.

[d] Maternal characteristics related to preterm delivery in previous studies (race/ethnicity, Medicaid insurance, parity, maternal age, and body mass index (prepregnancy/at screening; weight (kg)/height $(m)^2$, continuous variable)).

histopathologic findings, unlike blood biomarkers, cannot be compared between term and preterm deliveries at the same gestational week, and this too was a limitation.

In future analyses, we plan to assess the importance of individual placenta vascular findings within each vascular construct and, through sensitivity analyses, determine which if any can be excluded. Despite evidence that the vascular pathways leading to preterm delivery have some overlapping features (18), we have found with our results that separating vascular constructs may be informative as we move forward to examine biomarkers and upstream and downstream risk factors in greater depth.

ACKNOWLEDGMENTS

Author affiliations: Department of Epidemiology, College of Human Medicine, Michigan State University, East Lansing, Michigan (R. Kelly, C. Holzman, J. Wang, Y. Tian, H. Chung); Division of Human Pathology, College of Human Medicine, Michigan State University, East Lansing, Michigan (P. Senagore); Divisions of Epidemiology and Biostatistics, The University of Texas School of Public Health at Houston, Houston, Texas (M. H. Rahbar); and Biostatistics/Epidemiology/Research Design (BERD) Core, Center for Clinical and Translational Sciences, The University of Texas Health Science Center at Houston, Houston, Texas (M. H. Rahbar).

This study was supported by the National Institute of Child Health and Human Development and the National Institute of Nursing Research (grant R01 HD34543), the March of Dimes Foundation, Perinatal Epidemiological Research Initiative Program Grant 20-FY04-37 from the Thrasher Research Foundation (grant 02816-7), and the Centers for Disease Control and Prevention (grant U01 DP000143-01).

The authors thank Drs. Joseph Marshall and Lynn Reuss for medical chart reviews and Dr. Bertha Bullen for logistical oversight. They also thank the labor and delivery nurses for collection of placentas at the following participating hospitals: Borgess Medical Center, Bronson Methodist Hospital, Covenant HealthCare, Genesys Regional Medical Center, Hurley Medical Center, Ingham Regional Medical Center, McLaren Regional Medical Center, Sparrow Health System, and Spectrum Health.

Conflict of interest: none declared.

REFERENCES

1. Beebe LA, Cowan LD, Altshuler G. The epidemiology of placental features: associations with gestational age and neonatal outcome. *Obstet Gynecol*. 1996;87(5):771–778.
2. Arias F, Rodriquez L, Rayne SC, et al. Maternal placental vasculopathy and infection: two distinct subgroups among patients with preterm labor and preterm ruptured membranes. *Am J Obstet Gynecol*. 1993;168(2):585–591.
3. Kim YM, Bujold E, Chaiworapongsa T, et al. Failure of physiologic transformation of the spiral arteries in patients with preterm labor and intact membranes. *Am J Obstet Gynecol*. 2003;189(4):1063–1069.
4. Kim YM, Chaiworapongsa T, Gomez R, et al. Failure of physiologic transformation of the spiral arteries in the placental bed in preterm premature rupture of membranes. *Am J Obstet Gynecol*. 2002;187(5):1137–1142.
5. Salafia CM, Pezzullo JC, López-Zeno JA, et al. Placental pathologic features of preterm preeclampsia. *Am J Obstet Gynecol*. 1995;173(4):1097–1105.
6. Ananth CV, Vintzileos AM. Maternal-fetal conditions necessitating a medical intervention resulting in preterm birth. *Am J Obstet Gynecol*. 2006;195(6):1557–1563.
7. Ananth CV, Savitz DA, Luther ER, et al. Preeclampsia and preterm birth subtypes in Nova Scotia, 1986 to 1992. *Am J Perinatol*. 1997;14(1):17–23.
8. Levine RJ, Maynard SE, Qian C, et al. Circulating angiogenic factors and the risk of preeclampsia. *N Engl J Med*. 2004; 350(7):672–683.
9. Chaiworapongsa T, Espinoza J, Gotsch F, et al. The maternal plasma soluble vascular endothelial growth factor receptor-1 concentration is elevated in SGA and the magnitude of the increase relates to Doppler abnormalities in the maternal and fetal circulation. *J Matern Fetal Neonatal Med*. 2008;21(1): 25–40.
10. Chaiworapongsa T, Yoshimatsu J, Espinoza J, et al. Evidence of in vivo generation of thrombin in patients with small-for-gestational-age fetuses and pre-eclampsia. *J Matern Fetal Neonatal Med*. 2002;11(6):362–367.
11. Romero R, Nien JK, Espinoza J, et al. A longitudinal study of angiogenic (placental growth factor) and anti-angiogenic (soluble endoglin and soluble vascular endothelial growth factor receptor-1) factors in normal pregnancy and patients destined to develop preeclampsia and deliver a small for gestational age neonate. *J Matern Fetal Neonatal Med*. 2008; 21(1):9–23.
12. Shibata E, Rajakumar A, Powers RW, et al. Soluble fms-like tyrosine kinase 1 is increased in preeclampsia but not in normotensive pregnancies with small-for-gestational-age neonates: relationship to circulating placental growth factor. *J Clin Endocrinol Metab*. 2005;90(8):4895–4903.
13. Signore C, Mills JL, Qian C, et al. Circulating angiogenic factors and placental abruption. *Obstet Gynecol*. 2006;108(2): 338–344.
14. Thadhani R, Mutter WP, Wolf M, et al. First trimester placental growth factor and soluble fms-like tyrosine kinase 1 and risk for preeclampsia. *J Clin Endocrinol Metab*. 2004;89(2): 770–775.
15. Elovitz MA, Baron J, Phillippe M. The role of thrombin in preterm parturition. *Am J Obstet Gynecol*. 2001;185(5):1059–1063.
16. Goldenberg RL, Andrews WW, Faye-Petersen O, et al. The Alabama Preterm Birth Project: placental histology in recurrent spontaneous and indicated preterm birth. *Am J Obstet Gynecol*. 2006;195(2):792–796.
17. Ananth CV, Getahun D, Peltier MR, et al. Placental abruption in term and preterm gestations: evidence for heterogeneity in clinical pathways. *Obstet Gynecol*. 2006;107(4): 785–792.
18. Villar J, Carroli G, Wojdyla D, et al. Preeclampsia, gestational hypertension and intrauterine growth restriction, related or independent conditions? *Am J Obstet Gynecol*. 2006;194(4): 921–931.
19. Salafia CM, Ernst LM, Pezzullo JC, et al. The very low birthweight infant: maternal complications leading to preterm birth, placental lesions, and intrauterine growth. *Am J Perinatol*. 1995;12(2):106–110.

20. Ghidini A, Salafia CM, Pezzullo JC. Placental vascular lesions and likelihood of diagnosis of preeclampsia. *Obstet Gynecol*. 1997;90(4):542–545.
21. Corrêa RR, Gilio DB, Cavellani CL, et al. Placental morphometrical and histopathology changes in the different clinical presentations of hypertensive syndromes in pregnancy. *Arch Gynecol Obstet*. 2008;277(3):201–206.
22. Kramer MS, Chen MF, Roy I, et al. Intra- and interobserver agreement and statistical clustering of placental histopathologic features relevant to preterm birth. *Am J Obstet Gynecol*. 2006;195(6):1674–1679.
23. Salafia CM, Pezzullo JC, Ghidini A, et al. Clinical correlations of patterns of placental pathology in preterm pre-eclampsia. *Placenta*. 1998;19(1):67–72.
24. Redline RW, Boyd T, Campbell V, et al. Maternal vascular underperfusion: nosology and reproducibility of placental reaction patterns. *Pediatr Dev Pathol*. 2004;7(3):237–249.
25. Redline RW, Pappin A. Fetal thrombotic vasculopathy: the clinical significance of extensive avascular villi. *Hum Pathol*. 1995;26(1):80–85.
26. Sander CM, Gilliland D, Akers C, et al. Livebirths with placental hemorrhagic endovasculitis: interlesional relationships and perinatal outcomes. *Arch Pathol Lab Med*. 2002;126(2):157–164.
27. Holzman C, Bullen B, Fisher R, et al. Pregnancy outcomes and community health: the POUCH study of preterm delivery. *Paediatr Perinat Epidemiol*. 2001;15(suppl 2):136–158.
28. Waller DK, Lustig LS, Cunningham GC, et al. The association between maternal serum alpha-fetoprotein and preterm birth, small for gestational age infants, preeclampsia, and placental complications. *Obstet Gynecol*. 1996;88(5):816–822.
29. Redline RW. Placental pathology: a systematic approach with clinical correlations. *Placenta*. 2008;29(suppl A):S86–S91.
30. Dowling NF, Austin H, Dilley A, et al. The epidemiology of venous thromboembolism in Caucasians and African-Americans: the GATE Study. *J Thromb Haemost*. 2003;1(1):80–87.
31. Redline RW, Ariel I, Baergen RN, et al. Fetal vascular obstructive lesions: nosology and reproducibility of placental reaction patterns. *Pediatr Dev Pathol*. 2004;7(5):443–452.
32. Ogunyemi D, Murillo M, Jackson U, et al. The relationship between placental histopathology findings and perinatal outcome in preterm infants. *J Matern Fetal Neonatal Med*. 2003;13(2):102–109.
33. Salafia CM, Minior VK, Pezzullo JC, et al. Intrauterine growth restriction in infants of less than thirty-two weeks' gestation: associated placental pathologic features. *Am J Obstet Gynecol*. 1995;173(4):1049–1057.