OBSTETRICS

Neonatal outcomes following preterm birth classified according to placental features

Janet M. Catov, PhD, MS; Christina M. Scifres, MD; Steve N. Caritis, MD; Marnie Bertolet, PhD; Jacob Larkin, MD; W. Tony Parks, MD

BACKGROUND: Preterm birth has staggering health implications, and yet the causes of most cases are still unknown. Placental features have been understudied as an etiology for preterm birth, and the association between placental pathologic lesions and neonatal outcomes are incompletely understood.

OBJECTIVE: We sought to characterize births according to placental pathology and relate these to adverse neonatal outcomes.

STUDY DESIGN: We studied 20,091 births (15,710 term and 4381 preterm) with placental evaluations. Births were classified according to the presence or absence of placental lesions consistent with malperfusion (vasculopathy, infarct, advanced villous maturation, perivillous fibrin, fibrin deposition) and intrauterine inflammation/infection (chorioamnionitis, funisitis, vasculitis). Outcomes were gestational week of delivery, birthweight z-score, neonatal respiratory distress syndrome, and intraventricular hemorrhage.

RESULTS: Among all preterm births, evidence of placental malperfusion was identified more often than inflammation/infection (50.6% vs 27.3%, $P < .0001$). Placental malperfusion was associated with reduced fetal growth (adjusted birthweight z-score, −0.83, $P < .0001$) and lesions of inflammation/infection were associated with earlier delivery (adjusted difference −2.08 weeks, $P < .0001$) than those with no lesions. When both placental lesions were present, earlier delivery (adjusted difference −2.28 weeks, $P < .0001$) and reduced fetal growth (adjusted birthweight z-score difference, −0.24, $P = .001$) were observed more often than when neither lesion was present. Findings were similar when restricted to cases of spontaneous preterm birth. Intraventricular hemorrhage was higher in preterm births with malperfusion lesions than cases with no lesions (7.6% vs 3.4%; odds ratio, 1.98; confidence interval, 1.18−3.32), accounting for gestational age and other covariates.

CONCLUSION: Placental pathology provides important insight into subtypes of preterm birth with adverse neonatal outcomes. Co-occurrence of malperfusion and inflammation/infection, especially among spontaneous preterm births, may be a novel pattern of placental injury linked to severe adverse outcomes.

Key words: neonatal outcomes, placenta, prematurity

Introduction

Preterm birth has staggering health implications. It is the leading cause of infant morbidity and mortality, with impairments affecting the lifelong health of offspring. The cause of most preterm birth is still unknown. It is well established that preterm birth, defined as delivery <37 weeks, is a complex, heterogeneous condition and classification of subtypes according to underlying etiology is essential to identify causal pathways. It has been common to classify cases according to clinical presentation as spontaneous (either spontaneous preterm labor or preterm premature rupture of membranes) and medically indicated. There are several concerns with this approach.[1-3] First, women may present with both contractions and ruptured membranes and clinical records may not be adequate to distinguish which came first. Second, medically indicated preterm births are influenced by clinical practice changes so this classification schema is not objective and not comparable across regions, countries, and time. Third, there is compelling evidence that the epidemiologic outcomes,[4-6] metabolic changes,[7,8] and abnormalities of implantation in indicated and spontaneous preterm births overlap.[9,10]

EDITORS' CHOICE

Alternative classification schemas have been proposed; placental microscopic and histopathology features have been suggested as valuable and perhaps essential tools to align preterm birth classification with underlying etiology.[3,11,12] Chorioamnionitis (intrauterine inflammation or infection detected in the placenta) is a precursor to many spontaneous preterm births, especially those occurring at early gestational ages.[13] Indicated preterm births are dominantly related to clinical conditions such as preeclampsia and growth restriction, and placental evidence of maternal malperfusion is abundant in these cases.[9] There is evidence, however, that the placental vascular lesions of maternal malperfusion also contribute to a third of spontaneous preterm birth cases.[9,10,14,15] There are a few reports that co-occurrence of both malperfusion and inflammation/infection is linked to severe neonatal health consequences,[16] but this has never been examined in a large cohort.

We utilized a clinical registry of 20,091 births delivered from 2008 through 2012 to classify subgroups of infants (15,710 delivered at term and 4381 delivered preterm) according to placental lesions indicating malperfusion or intrauterine inflammation/infection. We further examined the co-occurrence of these 2 lesion types, as comorbid pathologies may be of particular importance to neonatal health. We linked placental phenotypes to gestational age at

Cite this article as: Catov JM, Scifres CM, Caritis SN, et al. Neonatal outcomes following preterm birth classified according to placental features. Am J Obstet Gynecol 2017;216:411.e1-14.

0002-9378/free

http://dx.doi.org/10.1016/j.ajog.2016.12.022

delivery, fetal growth, respiratory distress syndrome, and intraventricular hemorrhage. These outcomes are highly relevant to immediate and long-term infant health, occur most often in preterm neonates, and are reliably available in medical records.

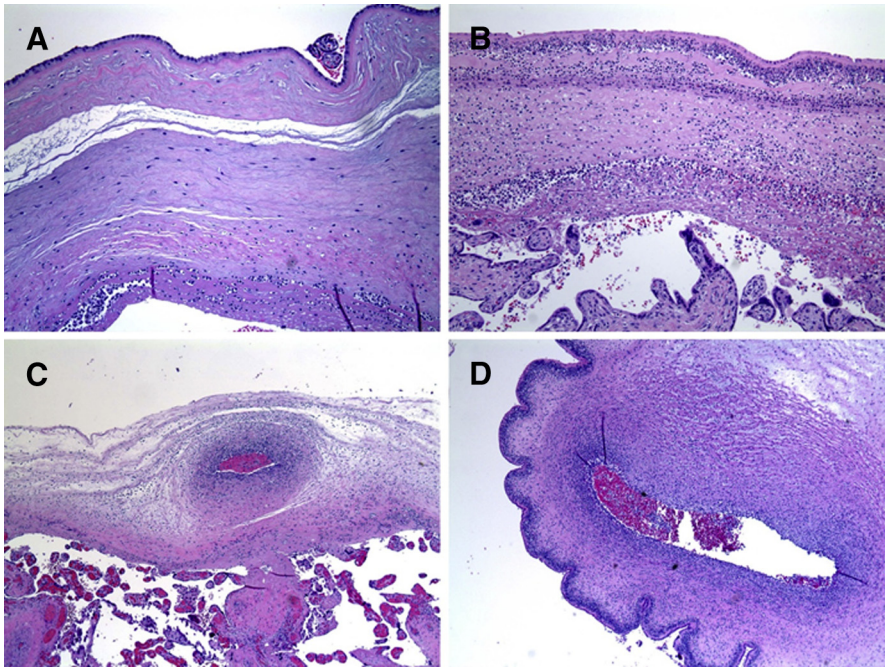
Materials and Methods

Delivery data were collected from the Magee Obstetric Medical and Infant database, which includes 300 variables for all deliveries at Magee-Womens Hospital in Pittsburgh, PA. Variables are derived from admitting services, *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes, medical record data abstraction, and ultrasound. Births occurring from 2008 through 2012 were selected for this study because, during this period, 2 placental pathologists (including W.T.P.) prepared all reports following a standardized protocol and used a uniform reporting approach and identical diagnostic criteria, provided in Supplemental Table 1. The University of Pittsburgh Institutional Review Board approved the project, which did not require informed consent as all data were deidentified (institutional review board no. PRO13020275).

A broad set of indications, based on the College of American Pathologists guidelines, warranted referral of a placenta for pathology evaluation during this period (Supplemental Table 1). In all, 44% of all deliveries and 92% of preterm births had placental pathology evaluation performed. Our placenta pathology matching and extraction process was described previously.[17] Briefly, we identified 30,716 placenta pathology reports from 2008 through 2012. Data were reformatted into Extensible Markup Language and then linked to the Magee Obstetric Medical and Infant database. Together with a placental pathologist (W.T.P.), we identified key words to capture all possible descriptions and diagnoses. A validation study demonstrated excellent sensitivity and specificity for placental lesions when this automated abstraction process was compared to manual record abstraction.[17] For the current analysis, we limited the study population to singleton live births, delivered between 20-42 completed weeks gestation, with a reported birthweight.

Presence of placental lesions was categorized according to proposed schemas[18,19] as maternal malperfusion (decidual vasculopathy, villous infarction, advanced villous maturation, increased perivillous fibrin deposition, increased intervillous fibrin deposition) and/or intrauterine inflammation/infection (acute chorioamnionitis, acute funisitis, acute vasculitis) (Figures 1-3 and Supplemental Table 2). Mild acute chorioamnionitis was defined as stage 1 (acute subchorionitis) with no accompanying chorionic plate vasculitis or umbilical cord vasculitis/funisitis. Severe acute chorioamnionitis was defined as higher stage acute chorioamnionitis (stage 2 or 3) and/or the presence of chorionic plate vasculitis or umbilical cord vasculitis/funisitis. A validation study (56 spontaneous, 19 medically indicated preterm, and 50 term births) compared the diagnosis of malperfusion and inflammation/infection on the clinical pathology reports to a review of the slides by a single pathologist blinded to all clinical information except gestational age (W.T.P.). There was excellent agreement (82%) between the clinical pathology reports and the review by the pathologist for inflammation/infection and good agreement (62%) for malperfusion lesions. Of note, the clinical report tended to underreport cases of malperfusion in both spontaneous and indicated preterm birth. Agreement was excellent for the malperfusion lesions among term births (82%). We also

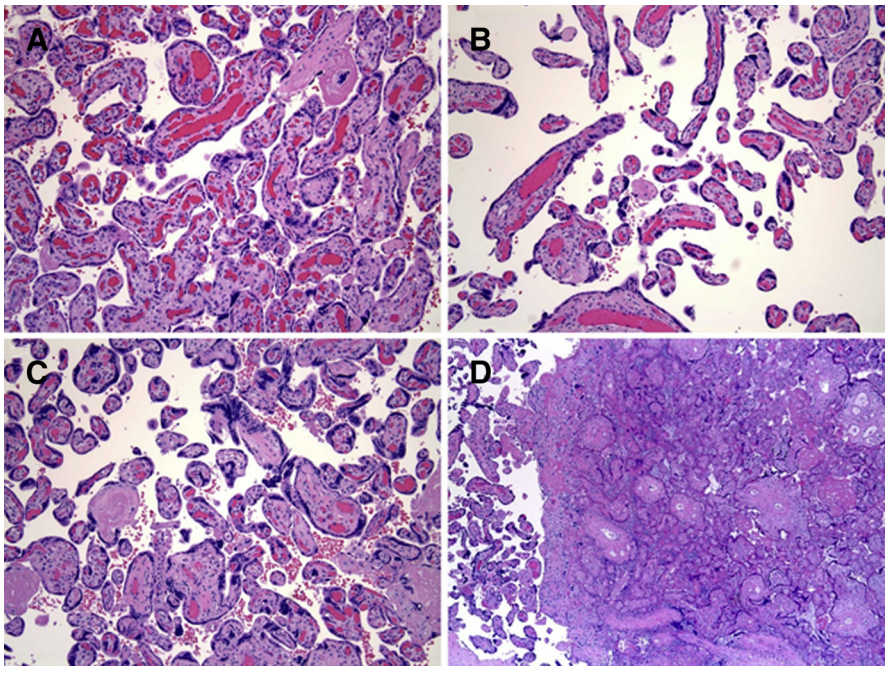
FIGURE 1
Acute inflammatory lesions



A, Mild acute chorioamnionitis (acute subchorionitis). Abundant neutrophils are present in subchorionic fibrin at bottom. Overlying chorion and amnion contain few neutrophils. **B**, Moderate to severe acute chorioamnionitis (stage 2, grade 1). Neutrophils are present at all levels of membranes, extending from subchorionic fibrin up to amnion. Thickening of amnion basement membrane is also evident. **C**, Acute vasculitis involving fetal chorionic plate vessels. Large numbers of neutrophils are noted to involve vessel wall and overlying chorion and amnion. **D**, Acute funisitis involving umbilical vein. Large numbers of neutrophils are noted to involve vessel wall. Dense infiltrate of neutrophils is also present just beneath amnionic surface of umbilical cord. (Hematoxylin-eosin stain; original magnifications: **A** and **B**, ×10; **C** and **D**, ×4.)

Catov et al. Placental features and preterm birth. Am J Obstet Gynecol 2017.

FIGURE 2
Lesions of maternal vascular malperfusion



A, Normal villi. Essentially unremarkable term villi. **B**, Accelerated (advanced) villous maturation. Villi manifest type of accelerated villous maturation termed "distal villous hypoplasia." These villi are substantially smaller than normal villi. They additionally appear longer and thinner with less frequent branching. **C**, Increased syncytial knots. Syncytial knots are found more frequently than expected on this villi. **D**, Old villous infarction. Bulk of villi underwent infarction previously. Villous trophoblast have lost their basophilia, and intravascular erythrocytes have all degenerated. Small rim of perivillous fibrin is present, particularly along left aspect of infarct. (Hematoxylin-eosin stain; original magnifications: **A** to **C**, ×10; **D**, ×4.)

Catov et al. Placental features and preterm birth. Am J Obstet Gynecol 2017.

evaluated placental weight as <10th percentile or >90th percentile for gestational week based on reference ranges created at our hospital.

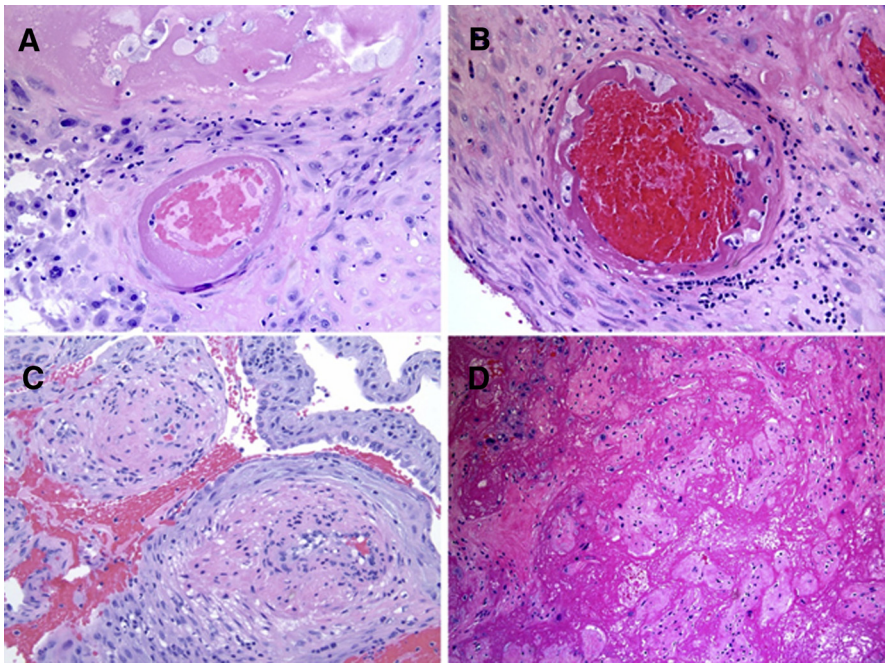
Gestational age in our data was based on the best clinical estimate at the time of delivery. Clinicians relied predominantly on first- and second-trimester ultrasound in conjunction with the last menstrual period. A validation study was conducted where a single obstetrician manually reviewed the medical records of 153 deliveries (n = 86 classified as term and n = 67 classified as preterm in our registry). The physician determined the best clinical estimate of gestational age at delivery based on date of last menstrual period, date of ultrasound, and gestational age at ultrasound. There was excellent agreement between the medical record and our registry (100% sensitivity for cases of preterm birth, and 96% specificity). For preterm birth <34 weeks, there was 100% sensitivity and 100% specificity.

Maternal race was self-reported as white, African American, Hispanic, Asian, and other. Numbers were too small to evaluate race/ethnicity groups other than white and African American, so all other groups were combined into 1 category. Absence of labor was identified via record abstraction. Covariates included maternal age at delivery, smoking during pregnancy, and primiparity. Maternal hypertension status was abstracted from the medical record using *ICD-9* codes and reported as chronic (including cases of superimposed preeclampsia [642.0, 642.1, 642.2, 642.7]), preeclampsia (de novo hypertension with proteinuria [642.4, 642.5, 642.6]; diagnostic criteria provided in Supplemental Table 3), or gestational (de novo hypertension without proteinuria [642.3]). Gestational diabetes screening was universal (94% in our data) and gestational diabetes was defined according to the criteria of Carpenter and Coustan.[20] Body mass index (BMI) (weight/height^2) was self-reported at the first prenatal visit and was available for 10,735 births (53%). We defined small for gestational age as fetal growth <10th percentile and large for gestational age as >90th percentile at each completed week of gestation, as recommended by the Global Reference Standard. This approach uses estimated fetal weights derived from ultrasound, accounts for race/ethnicity differences in mean birthweight, and identifies more fetal growth—related pathologies among preterm infants compared to birthweight-derived references.[21,22] Birthweight z-scores were created using the mean and SD of births in our complete registry occurring at each gestational week. Cases of respiratory distress syndrome (*ICD-9* codes 769, 770.6, 518.82; including bronchopulmonary dysplasia [770.7]), and intraventricular hemorrhage (772.10, 772.11, 772.12, 772.13, 431) were identified in the neonatal medical record.

Statistical methods

Maternal characteristics were compared among women with and without placental data and according to gestational age groups, using χ^2 and *t* tests. The prevalence of specific placental lesions was compared according to preterm birth groups, as was the co-occurrence of both malperfusion and inflammation/infection. We used linear regression to model the gestational age of delivery and birthweight z-score related to placental lesion groups (malperfusion only, inflammation/infection only, co-occurrence of malperfusion and inflammation/infection). Births with neither lesion were the referent. We then stratified by preterm birth status given the evidence that some placental lesions such as infarcts or chorioamnionitis occur at term as part of normal placental

FIGURE 3
Lesions of maternal vascular malperfusion: Vasculopathy



A, Decidual vasculopathy-fibrinoid necrosis of vessel walls. In lower central aspect of image is decidual vessel showing fibrinoid necrosis. Original smooth muscle wall has been replaced by bright, waxy fibrinoid material. Vessel along top of slide shows more diffuse fibrinoid deposition with foamy macrophages that characterize atherosis. **B**, Decidual vasculopathy-atherosis with fibrinoid necrosis. This vessel again shows dense fibrinoid deposition, but with addition of foamy macrophages within vessel wall. **C**, Decidual vasculopathy-mural hypertrophy of decidual arterioles. Presence of smooth muscle in walls of these vessels indicates absence of normal vascular remodeling necessary for normal pregnancy. Instead of undergoing fibrinoid necrosis, however, smooth muscle in this case has hypertrophied. **D**, Perivillous fibrin deposition. This image shows numerous villi entirely entrapped within dense fibrinoid material. While this entity may develop in context of maternal thrombophilia, its connection to maternal vascular malperfusion is less definitively established. (Hematoxylin-eosin stain; original magnifications: **A** to **C**, ×20; **D**, ×10.)

Catov et al. Placental features and preterm birth. Am J Obstet Gynecol 2017.

aging or as a result of labor. In contrast, these lesions may be pathologic when they occur <37 weeks' gestation. Models were also stratified according to clinical indication (spontaneous or indicated). Logistic regression models assessed the occurrence of neonatal respiratory distress syndrome or intraventricular hemorrhage according to placental lesion groups. Intraventricular hemorrhage was only evaluated in the preterm birth subset as 95% of cases occurred at preterm gestations. Covariates were selected a priori as race/ethnicity, maternal age, smoking, education, and prepregnancy BMI. Neonatal outcomes were then further adjusted for gestational age to determine if placental features may be on the pathway leading to earlier delivery and subsequent adverse neonatal outcomes.

Results

There were 45,638 singleton, live births from 2008 through 2012; 92% of preterm and 39% of term deliveries had placental evaluation. Births to younger women, those of African American race/ethnicity, with less than a high school education, higher prepregnancy BMI, and who smoked were more likely to have placental data (Supplemental Table 4). When limited to this group, as expected, those who delivered preterm were more likely to be African American, younger, to smoke, have a higher BMI, have less than a high school education, and have more pregnancy complications compared to term births (Table 1).

Women with preterm birth were more likely to have small-for-gestational-age placental weights (<10th percentile) compared to term births and rates increased as gestational age at delivery decreased (Table 2). Evidence of placental malperfusion lesions was more common among preterm compared to term births (50.6% vs 32.8%, $P < .0001$). Mild intrauterine inflammation/infection was highest in term births (19.6%) and severe intrauterine inflammation/infection was highest in extreme preterm birth (51%). Presence of the most specific malperfusion lesion, vasculopathy, was particularly high in moderate and extreme preterm compared to term births (17.9%, 13.1%, and 5.0%, respectively; $P < .0001$) as was presence of advanced villous maturation.

In general, birthweight was lower among births with malperfusion lesions alone or in combination with inflammation/infection (Table 3). After accounting for maternal race, age, smoking, education, and prepregnancy BMI, malperfusion lesions were associated with impaired fetal growth (term births, birth weight z score [BWz] difference −0.32; preterm births, BWz difference −0.48; $P < .0001$ for both). Presence of inflammation/infection at term was paradoxically associated with, on average, slightly longer gestations (difference 0.52 weeks, $P < .0001$) perhaps related to labor. Preterm births with inflammation/infection were delivered earlier (difference −2.08 weeks, $P < .0001$) but not smaller (BWz difference −0.01, $P = .909$) compared to preterm births with no lesions. Preterm births accompanied by both malperfusion and inflammation/infection, in contrast, were delivered earlier and smaller (gestational age difference −2.28 weeks, $P < .0001$; BWz difference −0.24, $P = .0006$). Results were quite similar when limited to spontaneous preterm births. For example, women with spontaneous preterm births and malperfusion coupled with inflammation delivered infants earlier (adjusted difference −2.70 weeks, $P < .0001$) and

TABLE 1
Maternal characteristics according to gestational age at delivery, n (%)

	Term 37–42 wk n = 15,710	Late PTB 34–36 wk n = 2745	Moderate PTB 28–33 wk n = 1238	Extreme PTB 20–27 wk n = 398	*P*
Age, y					<.0001
<20	1198 (7.6)	189 (6.9)	124 (10.0)	50 (12.6)	
20–29	7530 (47.9)	1335 (48.6)	629 (50.8)	214 (53.8)	
30–39	6476 (41.2)	1114 (40.6)	431 (34.8)	125 (31.4)	
≥40	506 (3.2)	107 (3.9)	54 (4.4)	9 (2.3)	
Race/ethnicity					.004
White	10,998 (73.1)	1924 (73.3)	867 (73.4)	251 (65.2)	
African American	3367 (22.4)	630 (24.0)	285 (24.1)	130 (33.8)	
Other	681 (4.5)	72 (2.7)	29 (2.5)	4 (1.0)	
Prepregnancy BMI, kg/m^2[a]					.005
<18.5	337 (3.9)	69 (4.8)	46 (7.9)	3 (2.3)	
18.5–<25	4097 (47.7)	657 (46.0)	266 (45.7)	56 (42.4)	
25–<30	2123 (24.7)	355 (24.9)	115 (19.8)	30 (22.7)	
≥30	2036 (23.7)	347 (24.3)	155 (26.6)	43 (32.6)	
Smoking[a]	2344 (17.0)	525 (21.8)	267 (24.9)	67 (19.9)	.060
Education[a]					<.0001
≤High school	4434 (32.1)	882 (36.5)	490 (45.8)	175 (52.9)	
College or some college	6918 (50.1)	1170 (48.4)	467 (43.7)	135 (40.8)	
>College	2469 (17.9)	366 (15.1)	112 (10.5)	21 (6.3)	
Diabetes					<.0001
Gestational	1648 (10.5)	269 (9.8)	120 (9.7)	13 (3.3)	
Preexisting (types 1 or 2)	172 (1.1)	84 (3.1)	32 (2.6)	1 (0.3)	
Hypertension					<.0001
Gestational	1211 (7.7)	108 (3.9)	42 (3.4)	8 (2.0)	
Preeclampsia	1649 (10.5)	509 (18.5)	301 (24.3)	45 (11.3)	
Chronic	149 (1.0)	139 (5.1)	111 (9.0)	22 (5.5)	
Fetal growth					<.0001
SGA	2124 (14.1)	459 (17.4)	378 (32.0)	113 (29.4)	
LGA	1924 (12.8)	409 (15.6)	106 (9.0)	49 (12.7)	
Neonatal respiratory distress syndrome	456 (2.9)				<.0001
Neonatal intraventricular hemorrhage	16 (0.1)	670 (24.4)	319 (25.8)	101 (25.4)	
No labor	1775 (11.3)	453 (16.5)	340 (27.5)	87 (21.9)	<.0001
Preterm clinical presentation		1021 (37.2)	518 (41.8)	102 (25.6)	
Spontaneous		495 (18.0)	758 (62.1)	290 (72.9)	<.0001
Medically indicated		32 (1.2)	183 (14.8)	115 (28.9)	<.0001

BMI, body mass index; *LGA*, large for gestational age; *PTB*, preterm birth; *SGA*, small for gestational age.

[a] BMI missing for 9356 (47%), smoking missing for 2489 (12%). education missing for 2452 (12%).

Catov et al. Placental features and preterm birth. Am J Obstet Gynecol 2017.

TABLE 2
Evidence of placental lesions, according to preterm birth status, n (%)

	Term 37–42 wk n = 15,710	Late PTB 34–36 wk n = 2745	Moderate PTB 28–33 wk n = 1238	Early PTB 20–27 wk n = 398	P[a]
Placental weight, g					<.0001
<10th Percentile	2975 (19.2)	583 (22.2)	511 (43.6)	123 (32.9)	
>90th Percentile	4094 (26.4)	593 (22.6)	164 (14.0)	71 (19.0)	
Malperfusion	5159 (32.8)	1250 (45.5)	782 (63.2)	184 (46.2)	<.0001
Vasculopathy	783 (5.0)	210 (7.7)	221 (17.9)	52 (13.1)	<.0001
Infarct	1983 (12.6)	359 (13.1)	283 (22.9)	58 (14.6)	<.0001
Advanced syncytial knots	1077 (6.9)	737 (26.9)	546 (44.1)	113 (28.4)	<.0001
Perivillous fibrin	2026 (12.9)	267 (9.7)	130 (10.7)	19 (4.8)	.003
Fibrin deposition	2389 (15.2)	366 (13.3)	190 (15.4)	33 (8.3)	.002
Intrauterine inflammation/infection—all	6493 (41.3)	553 (20.1)	394 (31.8)	265 (66.6)	<.0001
Chorioamnionitis, mild	3077 (19.6)	309 (11.3)	153 (12.4)	62 (16.6)	<.0001
Chorioamnionitis, severe	3416 (21.7)	244 (8.9)	241 (19.5)	203 (51.0)	
Intrauterine inflammation/infection—no labor[b]	214 (12.6)	30 (6.6)	28 (8.2)	20 (23.0)	<.0001
Chorioamnionitis, mild	133 (7.5)	19 (4.2)	14 (4.1)	7 (8.1)	<.0001
Chorioamnionitis, severe	81 (4.6)	11 (2.4)	14 (4.1)	13 (14.9)	
No lesions	4246 (27.0)	849 (30.9)	208 (16.8)	42 (10.6)	<.0001

PTB, preterm birth.

[a] χ^2 test; No labor; [b] n = 2655.

Catov et al. Placental features and preterm birth. Am J Obstet Gynecol 2017.

smaller (BWz difference −0.18, P = .012) compared to spontaneous preterm births with no lesions.

Given the importance of gestational age for newborn health, we then examined placental lesions in late (34-36 weeks), moderate (28-33 weeks), and extreme (20-27 weeks) preterm birth. Presence of malperfusion lesions combined with evidence of inflammation/infection increased as gestational age decreased (8.9% for late, 16.8% for moderate, and 27.5% for extreme preterm birth) (Figure 4, A). These trends were similar when limited to spontaneous preterm births (Figure 4, B). Of note, malperfusion was the most common lesion type detected in spontaneous late and moderate preterm births. As expected, malperfusion was the dominant pathology among indicated preterm births (Figure 4, C).

Placental malperfusion and/or inflammation were associated with higher risk of respiratory distress syndrome in both term and preterm neonates (Table 4). After accounting for gestational age, this association persisted in term births with placental lesions but not in preterm births. Rates of intraventricular hemorrhage were particularly high among women with preterm birth and malperfusion lesions, and this persisted after accounting for gestational age and other covariates (odds ratio, 1.98; 95% confidence interval, 1.18–3.32). Women with spontaneous or indicated preterm births accompanied by both malperfusion and inflammation/infection lesions had higher rates of intraventricular hemorrhage compared to those with no lesions (14.1%, 9.2%, and 3.4%, respectively) but risk estimates were attenuated after accounting for gestational age.

Comment

Our results demonstrate that placental pathology provides valuable insight into subtypes of preterm birth associated with severe neonatal risks. We highlight several important findings. First, placental malperfusion lesions were more common among pregnancies delivering preterm than lesions of inflammation/infection. Similarly, malperfusion lesions predominated in cases of spontaneous preterm birth. Second, our results suggest that co-occurrence of lesions of malperfusion and infection/inflammation affect as many as one third of extreme spontaneous preterm births and thus may be an important, yet heretofore unrecognized, phenotype. Third, these comorbid placental lesions were associated with earlier preterm birth accompanied by impaired fetal growth and severe neonatal complications and thus the long-term consequences may be profound. While these associations, as expected, were more modest when present at term our results raise the possibility that placental lesions may contribute to morbidity even among term births.

TABLE 3
Gestational age and birthweight z-score according to placental evidence of malperfusion and intrauterine inflammation/infection in term and preterm births, n = 20,091

		Malperfusion−/III− n = 7758		Malperfusion−/III+ n = 4958		Malperfusion+/III− n = 4628		Malperfusion+/III+ n = 2747	
Gestational age, wk, mean (SD)		38.0 (±2.4)		38.3 (±3.4)		36.9 (±3.2)		37.8 (±3.8)	
Birthweight z-score, mean (SD)		0.01 (±1.1)		0.01 (±1.0)		−0.31 (±1.1)		−0.18 (±1.1)	
			Beta[a]	*P* value	Beta[a]	*P* value	Beta[a]	*P* value
Gestational age, wk, difference								
Term	Referent		0.52	<.0001	−0.08	.033	0.49	<.0001
Preterm	Referent		−2.08	<.0001	−0.83	<.0001	−2.28	<.0001
Spontaneous preterm	Referent		−2.31	<.0001	−0.39	.062	−2.70	<.0001
Indicated preterm	Referent		−1.03	.021	−1.23	<.0001	−0.87	.034
Birthweight z-score, difference								
Term	Referent		0.06	.031	−0.32	<.0001	−0.15	<.0001
Preterm	Referent		−0.01	.909	−0.48	<.0001	−0.24	.0006
Spontaneous preterm	Referent		0.02	.773	−0.11	.060	−0.18	.012
Indicated preterm	Referent		−0.17	.285	−0.84	<.0001	−0.44	.003

III, intrauterine inflammation or infection.

[a] Models are adjusted for age, race/ethnicity, smoking, education, and prepregnancy body mass index.

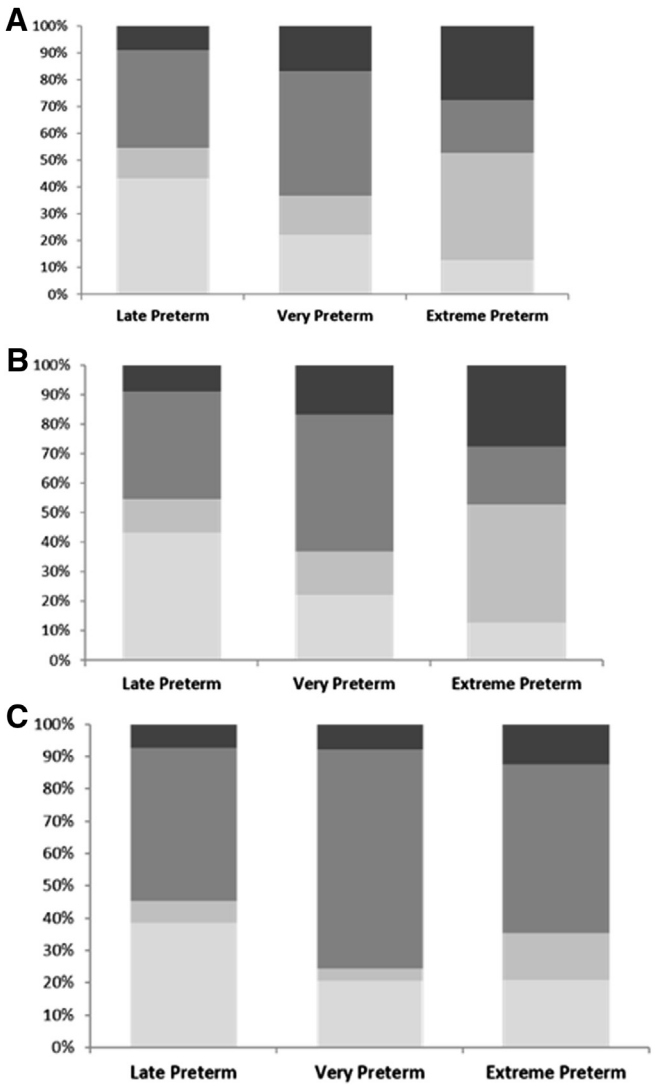
Catov et al. Placental features and preterm birth. Am J Obstet Gynecol 2017.

Normal placental function is critical to optimize fetal growth and development. Placentas are examined routinely following established guidelines.[23,24] These morphological and histopathological examinations can yield insight regarding morbidity and mortality in the fetus and offspring,[18] and yet placental data are included in only a handful of perinatal registries. The National Collaborative Perinatal Project, a multicenter pregnancy cohort of >50,000 US women recruited from 1959 through 1966, is perhaps the largest study, to date, to systematically collect placental characteristics.[25-27] The pathology approaches used >50 years ago, however, are not seamlessly applicable to current use. Certain features (eg, distal villous hypoplasia) were not diagnosed at that time, and villous infarction was primarily a macroscopic diagnosis, likely resulting in overdiagnosis. At least 1 contemporary hospital cohort and 3 prospective pregnancy cohorts have incorporated placental features into studies of stillbirth, preterm delivery, hypertensive disorders of pregnancy, and growth restriction.[9,28-33] To our knowledge, however, only 2 have characterized inflammatory and vascular lesions to phenotype preterm birth.[9,34]

Our results extend these observations by using placental features from a large contemporary clinical registry to classify term and preterm births according to the presence or absence of placental lesions typical of malperfusion and inflammation/infection. The severe neonatal morbidity associated with multiple placental lesions has been described in small case reports,[16] but, to date, there are very few reports regarding the prevalence of overlapping pathologies. Our clinical pathology data were able to characterize these cases. As the Human Placenta Project develops prenatal markers of placental function, our findings may help guide clinical management and the identification of biomarker and molecular profiles contributing to these phenomena.[35] For example, while chorioamnionitis is linked to higher risk of placental abruption,[36] it is unclear whether vascular and infectious pathways co-occur independently of one another or whether preexisting vascular impairments leave a placenta more susceptible to acute infection. There is also an emerging appreciation for the potential importance of sterile inflammation in the etiology of spontaneous preterm birth,[37] and the placental phenotypes that we have characterized may help to inform this line of inquiry.

Preterm birth has devastating consequences for immediate and long-term infant health. The sequelae linked to co-occurring placental injuries, as our results suggest, may be profound and thus the placenta may identify infants who need more intensive surveillance in the hospital as well as after discharge. There is evidence, for example, that acute chorioamnionitis, when detected together with chronic placental lesions such as villitis, is linked to pediatric neurologic impairments and that the risk may increase as the number of

FIGURE 4
Co-occurrence of placental malperfusion and intrauterine inflammation/infection



Proportion of co-occurrence of malperfusion and inflammation/infection lesions (light gray, neither lesion; medium gray, inflammation/infection only; dark gray, malperfusion only; black, malperfusion and inflammation/infection) among: **A**, all preterm births (n = 4381), **B**, spontaneous births (n = 2740), and **C**, medically indicated preterm births (n = 1641). Late preterm, 34-36 weeks; very preterm, 28-33 weeks; extreme preterm, 20-27 weeks.

Catov et al. Placental features and preterm birth. Am J Obstet Gynecol 2017.

distinct lesions increases.[38] Similarly, placental infection/inflammation is related to cerebral palsy in neonates weighing <1500 g[40] and the addition of placental features to a clinical prediction score developed for infants born <34 weeks may better predict neonatal morbidity than newborn physiologic risk evaluation alone.[41] The severity of infection/inflammation in the placenta increases as gestational age at delivery increases.[42] Our findings are consistent with this, and we can only speculate that this may be due to varying systemic or gestational age–specific immune competence.

Given the maternal vascular and metabolic adaptations required for successful placentation, the long-term maternal sequelae following placental abnormalities may also be distinct.[39] For example, there is evidence that maternal-fetal immune mediation of trophoblast invasion may be implicated in failed maternal vascular remodeling[43] as well as chronic placental inflammation leading to spontaneous preterm birth.[44] We may speculate that the group with placental evidence of malperfusion coupled with inflammation detected in our cohort may identify women with a preexisting morbidity that plays a role in pregnancy health and long-term maternal health. Could these, for example, be women with preexisting (perhaps preclinical) maternal disease? These questions warrant future investigation.

Our study is not without limitations. The placental pathology results utilized were derived from standard clinical reviews, and these may have varying reproducibility. The most severe lesions, however, such as vasculopathy and acute chorioamnionitis, are highly reproducible.[45-47] In addition, our validation study demonstrated that malperfusion may be underreported on clinical reports and therefore the importance of these lesions for neonatal health may be even greater than our estimates suggest. The most common malperfusion feature, advanced villous maturation, is known to have reporting variability. While there is evidence that the overall impression of a placental pathologist is superior to the detection of specific lesions for the diagnosis of malperfusion,[48] efforts to improve the diagnostic accuracy of these lesions are needed.[46,49] Our data were limited to cases that were referred for placental pathology review and although large, this group is higher risk compared to the general obstetric population. We anticipate, therefore, that the associations detected may underestimate of true risks. In addition, we acknowledge that the observed morphological changes in the preterm placenta may not be causal, and that similar features detected at term may not be pathologic. Future studies that can examine mechanisms related to the development of these lesions are needed to address these important questions. Of note, the prevalence of mild infection/inflammation at term is

TABLE 4
Odds of intraventricular hemorrhage on respiratory distress syndrome according to placental evidence of malperfusion and intrauterine inflammation/infection (III)+, stratified by spontaneous and indicated preterm birth

		Malperfusion - / III -	Malperfusion - / III +		Malperfusion + / III -		Malperfusion + / III +	
		n=7,758	n=4,958		n=4,628		n=2,747	
Respiratory distress syndrome	n (percent)		OR*	(95% CI)	OR*	(95% CI)	OR*	(95% CI)
Term	456 (2.9)	referent	1.38	(0.98, 1.95)	1.48	(1.02, 2.15)	1.54	(1.03, 2.31)
Preterm	1,543 (35.2)	referent	1.56	(1.14, 2.08)	1.32	(1.05, 1.65)	1.73	(1.29, 2.36)
Spontaneous Preterm	889 (32.5)	referent	1.82	(1.29, 2.58)	1.08	(0.78, 1.48)	1.96	(1.35, 2.82)
Indicated Preterm	654 (39.9)	referent	0.80	(0.40, 1.60)	1.47	(1.03, 2.08)	1.22	(0.66, 2.25)
Respiratory distress syndrome, adjusted for GA†			OR†	(95% CI)	OR†	(95% CI)	OR†	(95% CI)
Term		referent	1.54	(1.09, 2.19)	1.46	(1.00, 2.12)	1.71	(1.14, 2.58)
Preterm		referent	0.61	(0.41, 0.90)	0.91	(0.70, 1.17)	0.67	(0.46, 0.98)
Spontaneous Preterm		referent	0.66	(0.42, 1.04)	0.87	(0.61, 1.23)	0.62	(0.39, 0.98)
Indicated Preterm		referent	0.43	(0.18, 1.04)	0.91	(0.61, 1.35)	0.82	(0.41, 1.64)
Intraventricular hemorrhage	n (percent)		OR*	(95% CI)	OR*	(95% CI)	OR*	(95% CI)
Preterm	330 (7.5)	referent	1.49	(0.85, 2.62)	3.98	(2.48, 6.39)	3.88	(2.31, 6.53)
Spontaneous Preterm	214 (7.8)	referent	3.02	(1.50, 6.09)	1.92	(0.96, 3.86)	4.96	(2.53, 9.73)
Indicated Preterm	116 (7.1)	referent	0.56	(0.07, 4.60)	2.86	(1.29, 6.31)	3.10	(1.01, 9.48)
Intraventricular hemorrhage, adjusted for GA†			OR†	(95% CI)	OR†	(95% CI)	OR†	(95% CI)
Preterm		referent	0.69	(0.36, 1.35)	1.98	(1.18, 3.32)	1.71	(0.93, 3.14)
Spontaneous Preterm		referent	0.94	(0.42, 2.13)	1.81	(0.86, 3.71)	1.73	(0.81, 3.71)
Indicated Preterm		referent	0.19	(0.02, 1.95)	1.83	(0.79, 4.20)	2.55	(0.79, 8.16)

III, Intrauterine Inflammation or Infection; *OR*, odds ratio.

* Models are adjusted of age, race/ethnicity, smoking, education and pre-pregnacy BMI; † Models are additionally adjusted for gestational age (GA).

Catov et al. Placental features and preterm birth. Am J Obstet Gynecol 2017.

high in our cohort. We speculate that this is associated with labor, although we cannot account for length of labor in our data. This finding may also be due to the fact that our analysis is restricted to higher risk term births. In addition, our clinical definition of mild chorioamnionitis is more expansive and our criteria for severe chorioamnionitis is stricter compared to other studies. Thus our estimates regarding the occurrence of infection/inflammation among term births may differ from those reported by others.

Our results provide evidence that placental features may contribute valuable insight into subtypes of preterm birth with the most adverse neonatal complications. Malperfusion lesions may be more common than inflammation/infection, even among women with spontaneous preterm birth. Co-occurrence of malperfusion and inflammation/infection, especially among in spontaneous preterm birth, may constitute a unique pattern of placental injury associated with earlier delivery and thus severe adverse neonatal outcomes. Efforts to identify upstream and downstream profiles linked to these placental phenotypes can help identify causal pathways and ultimately clinical interventions to reduce the devastating burden of preterm birth. ■

References

1. Goldenberg RL, Gravett MG, Iams J, et al. The preterm birth syndrome: issues to consider in creating a classification system. Am J Obstet Gynecol 2012;206:113-8.

2. Kramer MS, Papageorghiou A, Culhane J, et al. Challenges in defining and classifying the preterm birth syndrome. Am J Obstet Gynecol 2012;206:108-12.

3. Villar J, Papageorghiou AT, Knight HE, et al. The preterm birth syndrome: a prototype phenotypic classification. Am J Obstet Gynecol 2012;206:119-23.

4. Hastie CE, Smith GC, Mackay DF, Pell JP. Maternal risk of ischemic heart disease following elective and spontaneous pre-term delivery: retrospective cohort study of 750,350 singleton pregnancies. Int J Epidemiol 2011;40:914-9.

5. Rich-Edwards JW, Klungsoyr K, Wilcox AJ, Skjaerven R. Duration of pregnancy, even at term, predicts long-term risk of coronary heart disease and stroke mortality in women: a population-based study. Am J Obstet Gynecol 2015;213:518.e1-8.

6. Catov JM, Wu CS, Olsen J, Sutton-Tyrrell K, Li J, Nohr EA. Early or recurrent preterm birth and maternal cardiovascular disease risk. Ann Epidemiol 2010;20:604-9.

7. Catov JM, Bodnar LM, Ness RB, Barron SJ, Roberts JM. Inflammation and dyslipidemia related to risk of spontaneous preterm birth. Am J Epidemiol 2007;166:1312-9.

8. Chatzi L, Plana E, Daraki V, et al. Metabolic syndrome in early pregnancy and risk of preterm birth. Am J Epidemiol 2009;170:829-36.

9. Kelly R, Holzman C, Senagore P, et al. Placental vascular pathology findings and pathways to preterm delivery. Am J Epidemiol 2009;170:148-58.

10. Romero R, Dey SK, Fisher SJ. Preterm labor: one syndrome, many causes. Science 2014;345:760-5.

11. Manuck TA, Esplin MS, Biggio J, et al. The phenotype of spontaneous preterm birth: application of a clinical phenotyping tool. Am J Obstet Gynecol 2015;212:487.e1-11.

12. Esplin MS. The importance of clinical phenotype in understanding and preventing spontaneous preterm birth. Am J Perinatol 2016;33:236-44.

13. Romero R, Espinoza J, Gonçalves L, Kusanovic J, Friel L, Hassan S. The role of inflammation and infection in preterm birth. Semin Reprod Med 2007;25:21-39.

14. Arias F, Rodriquez 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;168:585-91.

15. Germain AM, Carvajal J, Sanchez M, Valenzuela GJ, Tsunekawa H, Chuaqui B. Preterm labor: placental pathology and clinical correlation. Obstet Gynecol 1999;94:284-9.

16. Redline RW, Wilson-Costello D, Borawski E, Fanaroff AA, Hack M. The relationship between

placental and other perinatal risk factors for neurologic impairment in very low birth weight children. Pediatr Res 2000;47:721-6.
17. Catov JM, Peng Y, Scifres CM, Parks WT. Placental pathology measures: can they be rapidly and reliably integrated into large-scale perinatal studies? Placenta 2015;36:687-92.
18. Roescher AM, Timmer A, Erwich JJHM, Bos AF. Placental pathology, perinatal death, neonatal outcome, and neurological development: a systematic review. PLoS One 2014;9:e89419.
19. Zhao YJ, Zhang HJ, Li CX, Wu T, Shen XM, Zhang J. Selecting placental measures that have clinical implications in child development and diseases. Placenta 2014;35:178-87.
20. Carpenter M, Coustan D. Criteria for screening tests for gestational diabetes. Am J Obstet Gynecol 1982;144:768-73.
21. Ding G, Tian Y, Zhang Y, Pang Y, Zhang JS, Zhang J. Application of A global reference for fetal-weight and birthweight percentiles in predicting infant mortality. BJOG 2013;120:1613-21.
22. Mikolajczyk RT, Zhang J, Betran AP, et al. A global reference for fetal-weight and birthweight percentiles. Lancet 2011;377:1855-61.
23. Langston C, Kaplan C, Macpherson T, et al. Practice guideline for examination of the placenta—developed by the Placental Pathology Practice Guideline Development Task Force of the College of American Pathologists. Arch Pathol Lab Med 1997;121:449-76.
24. Cox P, Evans C. Tissue pathway for histopathological examination of the placenta: the Royal College of Pathologists; 2011 September.
25. Bodnar LM, Klebanoff MA, Gernand AD, et al. Maternal vitamin D status and spontaneous preterm birth by placental histology in the US Collaborative Perinatal Project. Am J Epidemiol 2014;179:168-76.
26. Salafia CM, Misra D, Miles JNV. Methodologic issues in the study of the relationship between histologic indicators of intraamniotic infection and clinical outcomes. Placenta 2009;30:988-93.
27. Salafia CM, Misra DP, Yampolsky M, Charles AK, Miller RK. Allometric metabolic scaling and fetal and placental weight. Placenta 2009;30:355-60.
28. McNamara H, Hutcheon JA, Platt RW, Benjamin A, Kramer MS. Risk factors for high and low placental weight. Paediatr Perinat Epidemiol 2014;28:97-105.
29. Hutcheon JA, McNamara H, Platt RW, Benjamin A, Kramer MS. Placental weight for gestational age and adverse perinatal outcomes. Obstet Gynecol 2012;119:1251-8.
30. Holzman C, Lin X, Senagore P, Chung H. Histologic chorioamnionitis and preterm delivery. Am J Epidemiol 2007;166:786-94.
31. Holzman C, Senagore PK, Wang JL. Mononuclear leukocyte infiltrate in extraplacental membranes and preterm delivery. Am J Epidemiol 2013;177:1053-64.
32. Pinar H, Goldenberg RL, Koch MA, et al. Placental findings in singleton stillbirths. Obstet Gynecol 2014;123:325-36.
33. Becroft DM, Thompson JM, Mitchell EA. Placental villitis of unknown origin: epidemiologic associations. Am J Obstet Gynecol 2005;192:264-71.
34. Holzman C, Bullen B, Fisher R, Paneth N, Reuss L. Pregnancy outcomes and community health: the POUCH study of preterm birth. Paediatr Perinat Epidemiol 2001;15:136-58.
35. Guttmacher AE, Maddox YT, Spong CY. The Human Placenta Project: placental structure, development, and function in real time. Placenta 2014;35:303-4.
36. Darby M, Caritis S, Shen-Schwarz S. Placental abruption in the preterm gestation: an association with chorioamnionitis. Obstet Gynecol 1989;74:88-92.
37. Behnia F, Menon KM. Mechanistic differences leading to infectious and sterile inflammation. Am J Reprod Immunol 2016;75:505-18.
38. Redline RW, O'Riordan MA. Placental lesions associated with cerebral palsy and neurologic impairment following term birth. Arch Pathol Lab Med 2000;124:1785-91.
39. Staff AC, Dechend R, Redman CWG. Review: preeclampsia, acute atherosis of the spiral arteries and future cardiovascular disease: two new hypotheses. Placenta 2013;34:S73-8.
40. Horvath B, Grasselly M, Bodecs T, Boncz I, Bodis J. Histological chorioamnionitis is associated with cerebral palsy in preterm neonates. Eur J Obstet Gynecol Reprod Biol 2012;163:160-4.
41. Chisholm KM, Heerema-McKenney A, Tian L, et al. Correlation of preterm infant illness severity with placental histology. Placenta 2016;39:61-9.
42. Torricelli M, Voltolini C, Toti P, et al. Histologic chorioamnionitis: different histologic features at different gestational ages. J Matern Fetal Neonatal Med 2014;27:910-3.
43. Roberts JM. Pathophysiology of ischemic placental disease. Semin Perinatol 2014;38:139-45.
44. Kim CJ, Romero R, Chaemsaithong P, Kim JS. Chronic inflammation of the placenta: definition, classification, pathogenesis, and clinical significance. Am J Obstet Gynecol 2015;213:S53-69.
45. Beebe LA, Cowan LD, Hyde SR, Altshuler G. Methods to improve the reliability of histopathological diagnoses in the placenta. Paediatr Perinat Epidemiol 2000;14:172-8.
46. 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;195:1674-9.
47. Simmonds M, Jeffery H, Watson G, Russell P. Intraobserver and interobserver variability for the histologic diagnosis of chorioamnionitis. Am J Obstet Gynecol 2004;190:152-5.
48. Redline RW, Boyd T, Campbell V, et al. Maternal vascular underperfusion: nosology and reproducibility of placental reaction patterns. Pediatr Dev Pathol 2004;7:237-49.
49. Senagore PK, Holzman CB, Parks WT, Catov JM. Working towards a reproducible method for quantifying placental syncytial knots. Pediatr Dev Pathol 2016;19:389-400.
50. Katzman PJ. Chronic inflammatory lesions of the placenta. Semin Perinatol 2015;39:20-6.
51. Redline R, Faye-Petersen O, Heller D, Qureshi F, Savell V, Vogler C. Amniotic infection syndrome: nosology and reproducibility of placental reaction patterns. Pediatr Dev Pathol 2003;6:435-48.
52. Redline RW, Ariel I, Baergen RN, et al. Fetal vascular obstructive lesions: nosology and reproducibility of placental reaction patterns. Pediatr Dev Pathol 2004;7:443-52.

Author and article information

From the Department of Obstetrics, Gynecology, and Reproductive Sciences, University of Pittsburgh School of Medicine, Pittsburgh, PA (Drs Catov, Caritis, Larkin, and Parks); Department of Epidemiology, University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA (Drs Catov and Bertolet); Magee-Womens Research Institute, Pittsburgh, PA (Drs Catov, Caritis, Larkin, and Parks); Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of Oklahoma Health Sciences Center, Oklahoma City, OK (Dr Scifres); and Department of Pathology, Magee-Womens Hospital of University of Pittsburgh Medical Center, Pittsburgh, PA (Dr Parks).

Received Sept. 14, 2016; revised Dec. 5, 2016; accepted Dec. 19, 2016.

Dr Parks is currently affiliated with the Department of Pathology, Dartmouth-Hitchcock Medical Center, Lebanon, NH.

Supported by a grant from the Commonwealth of Pennsylvania Department of Health (RFA-67-16) Maternal Lipids and Placental Function.

The authors report no conflict of interest.

Corresponding author: Janet M. Catov, PhD, MS. catovjm@upmc.edu

SUPPLEMENTAL TABLE 1
Indications for submission of placenta for pathologic examination[23]

1.	Multiple gestation
2.	Preterm delivery (<37 wk)
3.	Postterm delivery (42 completed wk)
4.	Fetal growth deviation (intrauterine growth restriction or macrosomia)
5.	Compromised fetal condition at delivery (eg, Apgar score of ≤4 at 5 min)
6.	Fetal anomaly
7.	Fetal distress
8.	Fetal demise
9.	Spontaneous recurrent pregnancy loss (>2 previous losses)
10.	Clinical concern for infection during pregnancy
11.	Maternal hemorrhage or severe anemia (Hgb <8 g/dL)
12.	Placenta previa
13.	Placental abruption
14.	Placenta accrete/increta/percreta
15.	Amniotic fluid abnormalities (polyhydramnios or oligohydramnios)
16.	Maternal disease/systemic disorder with clinical concerns for mother or infant: including but not limited to hypertensive disorders of pregnancy, diabetes mellitus, and autoimmune disorders
17.	History of substance abuse during pregnancy
18.	Meconium fluid or staining
19.	Any gross abnormality of placenta and/or umbilical cord
20.	Any infant transferred to NICU

Hgb, hemoglobin; *NICU*, neonatal intensive care unit.
Catov et al. Placental features and preterm birth. Am J Obstet Gynecol 2017.

SUPPLEMENTAL TABLE 2
Diagnostic criteria for placental lesions

Placental lesion	Diagnostic criteria[48,50-52]
Acute chorioamnionitis	A maternal response to infected amniotic fluid characterized by presence of linear accumulation of neutrophils within subchorionic fibrin or chorionic plate itself.
Acute vasculitis	A fetal response to infected amniotic fluid characterized by neutrophils within or emerging from vessels of fetal chorionic plate or umbilical cord.
Acute funisitis	Acute vasculitis of umbilical cord vessels in which neutrophils traverse through vessel wall into surrounding Wharton jelly.
Acute deciduitis	A significant linear accumulation of neutrophils within decidual tissues of placental basal plate or extraplacental membranes.
Decidual vasculopathy	Incomplete, pathologically abnormal remodeling of maternal vessels supplying placenta, with 4 often co-occurring manifestations. Absence of vascular remodeling is defined by presence of smooth muscle wall in at least 1 decidual vessel of placental basal plate. Mural hypertrophy of decidual arterioles is characterized by thickening of muscle wall of decidual vessel from any location, with thickened muscle wall leaving luminal diameter of $<$30% of total vessel diameter. Fibrinoid necrosis of vessel walls presents as waxy, intense red degeneration of at least 1 decidual vessel wall from any location. Atherosis is defined by presence of foamy macrophages within at least 1 decidual vessel wall. Fibrinoid necrosis and atherosis commonly co-occur.
Villous infarction	Devitalization of region of placental villi due to obstruction of underlying maternal blood flow. Characterized by geographically limited loss of staining, often with collapse of intervening maternal blood space.
Advanced (accelerated) villous maturation	Characterized by presence of at least 2 specific pathologic changes in villous architecture. Advanced villous maturation is typically characterized by increase in percentage of villi containing syncytial knot (increased syncytial knots), decrease in percentage of intermediate villi, and/or distal villous hypoplasia (zones of abnormally long, thin, unbranched terminal villi).
Perivillous fibrin deposition	Irregular zones of fibrinoid material tightly encasing entrapped villi. Small amount of perivillous fibrin is acceptable in upper third of placental parenchyma.
Intervillous fibrin deposition	Increased percentage (3% is upper limit) of small foci of fibrinoid material within or adjacent to villi.

Catov et al. Placental features and preterm birth. Am J Obstet Gynecol 2017.

SUPPLEMENTAL TABLE 3

Diagnostic criteria associated with *International Classification of Diseases, Ninth Revision* codes utilized

	Definition
Hypertension	
642	Benign essential hypertension in obstetric context
642.1	Hypertension secondary to renal disease in obstetric context
642.2	Hypertensive heart and renal disease in obstetric context
642.7	Chronic hypertension with superimposed preeclampsia
642.4	Mild to moderate preeclampsia
642.5	Severe preeclampsia
642.6	Eclampsia
642.3	Gestational hypertension
Respiratory distress syndrome	
769	Respiratory distress syndrome in newborn
770.6	Transitory tachypnea of newborn
518.82	Acute respiratory distress
770.7	Bronchopulmonary dysplasia of newborn
Intraventricular hemorrhage	
772.10	Hemorrhagic, newborn, intraventricular
772.11	Intraventricular hemorrhage of newborn, grade I
772.12	Intraventricular hemorrhage, grade II
772.13	Intraventricular hemorrhage, grade III
431	Intracerebral hemorrhage

Catov et al. Placental features and preterm birth. Am J Obstet Gynecol 2017.

SUPPLEMENTAL TABLE 4

Maternal characteristics of women with term and preterm births from 2008 through 2012, with and without placentas reviewed by pathology, percent

	Term, 37–42 wk			Preterm, 20–36 wk		
	No placental pathology n = 25,142	Placental pathology n = 15,710	*P*	No placental pathology n = 405	Placental pathology n = 4381	*P*
Age, y						<.01
<20	6.2	7.6	<.0001	8.2	8.2	
20–29	45.9	47.9		42.0	49.6	
30–39	45.1	41.2		46.9	38.3	
≥40	2.8	3.2		3.0	3.9	
Race/ethnicity						.02
White	77.8	73.1	<.0001	75.1	72.6	
African American	18.0	22.4		20.8	24.9	
Other	4.1	4.5		4.8	2.5	
Prepregnancy BMI, kg/m^2[a]						.18
<18.5	4.3	3.9	<.0001	4.4	5.5	
18.5–<25	57.6	47.7		50.2	45.6	
25–<30	22.1	24.7		26.1	89.4	
≥30	15.9	23.7		19.4	25.4	
Smoker	11.1	17.0	<.0001	18.5	22.5	.08
Education						<.01
≤High school	25.7	33.9	<.0001	31.7	40.4	
College or some college	52.4	42.2		50.1	46.5	
>College	21.9	16.8		18.2	13.1	

BMI, body mass index.

[a] BMI missing for n = 16,766 term births (41%) and n = 2416 preterm births (50%).

Catov et al. Placental features and preterm birth. Am J Obstet Gynecol 2017.