

Original Contribution

Pregnancy Disorders That Lead to Delivery Before the 28th Week of Gestation: An Epidemiologic Approach to Classification

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Epidemiologists have grouped the multiple disorders that lead to preterm delivery before the 28th week of gestation in a variety of ways. The authors sought to identify characteristics that would help guide how to classify disorders that lead to such preterm delivery. They enrolled 1,006 women who delivered a liveborn singleton infant of less than 28 weeks' gestation at 14 centers in the United States between 2002 and 2004. Each delivery was classified by presentation: preterm labor (40%), prelabor premature rupture of membranes (23%), preeclampsia (18%), placental abruption (11%), cervical incompetence (5%), and fetal indication/intrauterine growth restriction (3%). Using factor analysis (eigenvalue = 1.73) to compare characteristics identified by standardized interview, chart review, placental histology, and placental microbiology among the presentation groups, the authors found 2 broad patterns. One pattern, characterized by histologic chorioamnionitis and placental microbe recovery, was associated with preterm labor, prelabor premature rupture of membranes, placental abruption, and cervical insufficiency. The other, characterized by a paucity of organisms and inflammation but the presence of histologic features of dysfunctional placentation, was associated with preeclampsia and fetal indication/intrauterine growth restriction. Disorders leading to preterm delivery may be separated into two groups: those associated with intrauterine inflammation and those associated with aberrations of placentation.

abruptio placentae; fetal growth retardation; inflammation; obstetric labor, premature; placentation; pre-eclampsia; premature birth; uterine cervical incompetence

Abbreviations: ELGAN, Extremely Low Gestational Age Newborns; IUGR, intrauterine growth restriction; pPROM, prelabor premature rupture of membranes.

Editor's note: An invited commentary on this article appears on page 990, and the authors' response is on page 993.

The burdens on families and society associated with extreme premature delivery have prompted efforts to find ways to reduce the occurrence of this disorder (1–4). Some epidemiologists suggest that, if different clinical presentations share etiologies, then grouping them together maximizes the power of epidemiologic studies (5–7) and can recommend common therapeutic interventions. Others feel that, until the evidence is

stronger, it is best to study individual entities (2, 8–10). Finally, some are not yet convinced there is an advantage either way (4).

Our large prospective study of pregnancies that ended with a livebirth before the 28th week of gestation allowed us to explore the heterogeneity/homogeneity of clinically defined subgroups of these pregnancies. In addition to the traditional information about maternal demographic and clinical characteristics, we gathered details about placental microbiology and histology. These additional data provided insight into the intrauterine conditions that existed prior to delivery, thereby helping us classify the antecedent conditions associated with extremely preterm delivery.

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Table 1. Distribution of Demographic Characteristics of the Mothers Classified by the Complication Preceding Delivery Before the 28th Week, 14 US Centers, 2002–2004

Maternal Characteristic	Pregnancy Complication ^a						P Value
	Preterm Labor	Prelabor Premature Rupture of Membranes	Preeclampsia	Abruption	Cervical Insufficiency	Fetal Indication	
Identity							
White	48	48	49	61	49	53	0.02
Black	35	36	36	28	38	41	
Other	17	16	16	11	13	6	
Hispanic, yes	14	15	11	15	17	6	0.56
Age, years							
<21	22	18	11	24	17	9	0.003
21–35	63	60	74	58	72	81	
>35	14	22	15	18	11	9	
Years of education							
<12	22	21	16	28	22	16	0.002
12 (high school)	28	32	27	30	27	45	
>12–<16	26	25	28	17	24	26	
16 (college)	15	17	20	14	18	3	
>16	9	6	9	11	9	10	
Marital status, single	57	52	42	49	51	53	0.26
Support ^b							
Self	63	59	69	49	57	88	0.02
Partner	63	66	70	67	65	66	0.73
Family, friends	25	21	15	28	24	19	0.29
State, Social Security, etc.	33	30	25	27	22	31	0.14
Insurance ^b							
Health maintenance organization	50	49	60	47	59	50	0.15
Medicaid	52	50	43	50	41	53	0.30
Maximum no. of subjects	399	230	183	115	47	32	

^a All numbers (except those in the bottom row) are column percentages.^b May be in more than one category.

MATERIALS AND METHODS

During the years 2002–2004, 1,249 women delivering before 28 weeks' gestation at 1 of 14 participating institutions in 11 cities in 5 states consented to participate in the Extremely Low Gestational Age Newborns (ELGAN) Study, which was designed to identify characteristics and exposures that increase the risk of structural and functional neurologic disorders. Approximately 260 (17%) women were either missed or did not consent to participate. Because the epidemiology of preterm delivery in singleton pregnancies differs from that of multiple gestation pregnancies (11), we limited our study to the 1,006 (81%) singleton deliveries (Table 1). Each of the individual institutional review boards approved the enrollment and consent processes.

Demographic and pregnancy variables

After delivery, a trained research nurse interviewed each mother in her native language using a structured questionnaire. The medical record provided information about events following admission.

The clinical circumstances that led to each maternal admission and ultimately to each preterm delivery were operationally defined by using data from the maternal interview and data abstracted from the medical record. Preterm labor was defined as progressive cervical dilation with regular contractions and intact membranes. The diagnosis of prelabor premature rupture of membranes (pPROM) was defined as the presence of vaginal pooling with either documented nitrazine-positive testing or ferning prior to

regular uterine activity. Preeclampsia was defined as new-onset hypertension and proteinuria of sufficient severity to warrant delivery for either a maternal or fetal indication/intrauterine growth restriction (IUGR). For a diagnosis of cervical insufficiency, a woman had to present with cervical dilation of greater than 2 cm, in the absence of membrane rupture and detected or perceived uterine activity. Prolapse of the fetal membranes was not required. Placental abruption was defined as presentation with a significant amount of vaginal bleeding (either documented in the medical record or a postpartum hematocrit of $<24\%$) and a clinical diagnosis of placental abruption in the absence of cervical change. Painful uterine contractions were not required. Among the presentations in the category of fetal indication/IUGR were nonreassuring fetal testing, oligohydramnios, Doppler abnormalities of umbilical cord blood flow, and severe intrauterine growth restriction based on antepartum ultrasound examination. For the purposes of this study, the initial complication that caused presentation to medical attention is the focus of analysis. Complications that occurred after presentation were not considered independent and as such were not assumed to have a separate etiology.

Newborn variables

The gestational age estimates were based on a hierarchy of the quality of available information. Most desirable were estimates based on the dates of embryo retrieval or intrauterine insemination or an ultrasound examination before the 14th week of gestation (62%). When these were not available, reliance was placed sequentially on an ultrasound examination at 14 or more weeks (29%), menstrual dating without ultrasound confirmation (7%), and gestational age recorded in the log of the neonatal intensive care unit (1%). The birth weight z score is the number of standard deviations the infant's birth weight is above or below the median weight of infants at the same gestational age in a standard data set (12).

Placentas

Delivered placentas were placed in a sterile examination basin and transported to a sampling room. Eighty-two percent of the samples were obtained within 1 hour of delivery.

Details about the microbiologic and histologic analyses are presented elsewhere (13, 14). Briefly, midway between the cord insertion and the edge of the placental disk, a piece of chorion and the underlying trophoblastic tissue was obtained under sterile conditions, placed in liquid nitrogen, and then stored at -80°C . In the central microbiology laboratory, frozen samples were allowed to thaw at room temperature, homogenized, diluted, and plated on selective and nonselective media. After incubation, the various colony types were enumerated, isolated, and identified by established criteria (15).

In keeping with the guidelines of the College of American Pathologists' conference (16), representative sections were taken from all abnormal areas, as well as routine sections of the umbilical cord, a membrane roll, and full-thickness sections from the center and a paracentral zone of the placental

disk. After exercises were completed to minimize observer variability, placentas were reviewed at each site by a study pathologist, who completed a structured data collection form without knowledge of clinical details.

Data analysis

The main generalized null hypothesis that we evaluated is that pregnancy disorders leading to preterm delivery do not differ in demographic, clinical, microbiologic, or histologic characteristics. We tested this hypothesis in our search for the antecedents of each of the 6 pregnancy disorders. All P values presented are based on chi-squared analyses for homogeneity.

We also explored the possibility that common features characterize groups of these pregnancy disorders leading to preterm delivery. In our search for groups of pregnancy disorders, we relied on nonhierarchical cluster approaches and chose factor analysis (with varimax rotation) because it is the most transparent, identifying and quantifying interrelations and the structural basis for what is common to each factor as well as what is common to each disorder.

For the correlation matrix that served as the basis in this paper, we selected all 15 variables from Tables 1–5 that distinguished one pregnancy disorder from the rest. Four of these are demographic variables: maternal identification as White, maternal age <21 years, maternal education less than college, and self and/or spouse support; 6 are clinical characteristics: any tobacco during pregnancy, body mass index of $\geq 30 \text{ kg/m}^2$, primigravidity, conception assistance, self-report of vaginitis during pregnancy, and the prescription of an antibiotic prior to hospitalization; 3 are newborn characteristics: birth weight z score of <-2 , gestational age of <25 weeks, and male gender; 2 are histologic characteristics of the placenta: grade 3+ chorionic plate inflammation and increased syncytial knots; and 3 are bacteriologic characteristics of the placenta: recovery of an organism, recovery of a vaginal organism, and more than one organism recovered.

Another factor analysis (not shown), based on only 9 variables that discriminated 2 or more pregnancy disorders from the rest, provided a first factor (eigenvalue = 1.52) similar to that obtained with 15 variables and with similar discriminating information.

RESULTS

Sociodemographic characteristics of the mother

Overall, preterm labor accounted for the largest proportion (40%) and fetal indication/IUGR accounted for the smallest proportion (3%) of deliveries. In between were pPROM (23%), preeclampsia (18%), placental abruption (11%), and cervical insufficiency (5%). Among the deliveries in our sample, abruption tended to occur preferentially among Whites, women less than 21 years of age, and women who did not graduate from high school. Similarly, fetal indication/IUGR occurred most commonly among women who identified themselves as Black and among women who did not rely on a partner, family, or friends for financial support (Table 1).

Table 2. Distribution of Clinical Characteristics of Women Classified by the Pregnancy Complication Associated With Delivery Before the 28th Week, 14 US Centers, 2002–2004

Maternal Characteristic	Pregnancy Complication ^a						P Value
	Preterm Labor	Prelabor Premature Rupture of Membranes	Preeclampsia	Abruption	Cervical Insufficiency	Fetal Indication	
Smoking ^b							
Prepregnancy	31	32	21	36	30	23	0.005
During pregnancy	17	22	11	26	11	16	0.001
Passive	36	30	29	41	14	30	<0.001
Prepregnancy body mass index, kg/m ²							
<18.5	11	9	2	9	2	13	<0.001
18.5–<25	48	46	40	52	44	31	
25–<30	21	20	25	21	27	22	
≥30	20	26	33	19	27	34	
Gravidity, primigravida	40	26	47	40	23	26	<0.001
Years since last pregnant							
< 1	18	17	20	32	24	13	0.21
1–2	29	31	24	29	30	26	
> 2	54	52	56	40	45	61	
Trying to get pregnant, yes	40	40	53	33	47	32	0.09
Conception assistance, any ^b	5	6	5	8	9	6	<0.001
This pregnancy ^b							
Fever	7	7	4	7	9	19	0.78
Vaginitis	15	14	10	12	18	13	0.04
Urinary tract infection	18	14	23	14	20	19	0.09
Periodontal	3	2	1	0	2	6	0.74
Predelivery highest white blood cell count >20,000	21	25	19	21	16	13	0.28
Medication ^b							
Any	86	86	93	89	91	97	0.05
Antibiotic	32	31	30	33	42	42	0.03
Maximum no. of subjects	399	230	183	115	47	32	

^a All numbers (except those in the bottom row) are column percentages.^b May be in more than one category.

Clinical characteristics and exposures of the pregnancy

Smoking, both prior to and during pregnancy, was least common among women delivering pregnancies complicated by preeclampsia. Exposure to passive smoke was relatively uncommon in our sample among women presenting with cervical insufficiency. Among those delivering at less than 28 weeks' gestation, a high prepregnancy body mass index (i.e., body mass index of ≥ 30 kg/m²) was most common among women with the complications of preeclampsia and fetal indication/IUGR. Preeclampsia was overrepresented among primigravidas and women with intended pregnancies, although placental abruption and cervical insufficiency were most common among women who sought conception

assistance. The rate of vaginitis was higher among women who presented with cervical insufficiency. These women and women who presented with fetal indication/IUGR were most likely to have received an antibiotic at some point prior to admission (Table 2).

Newborn characteristics

Preeclampsia and fetal indication/IUGR were observed at older gestational ages. Birth weight and, even more prominently, birth weight *z* scores were lower among the pregnancies complicated by preeclampsia and fetal indication/IUGR. Male babies were overrepresented among deliveries complicated by cervical insufficiency, and female babies were overrepresented among those delivered in the setting

Table 3. Distribution of Newborn's Characteristics Classified by the Complication That Preceded Delivery, 14 US Centers, 2002–2004

Newborn's Characteristics	Pregnancy Complication ^a						P Value
	Preterm Labor	Prelabor Premature Rupture of Membranes	Preeclampsia	Abruption	Cervical Insufficiency	Fetal Indication	
Gestational age, weeks							
23	13	10	2	8	7	3	<0.001
24	21	15	12	27	24	3	
25	23	21	15	19	22	29	
26	20	24	34	26	29	32	
27	23	31	37	20	18	32	
Birth weight, g							
≤750	38	36	69	41	31	81	<0.001
>750–1,000	45	42	25	41	40	13	
>1,000–1,250	15	21	6	16	27	6	
>1,250	3	2	0	2	2	0	
Birth weight z score ^b							
<–2	1	1	29	5	0	42	<0.001
<–1	6	11	42	7	0	29	
–1 to 1	79	77	28	73	80	23	
>1	11	10	1	13	20	3	
>2	2	1	0	3	0	3	
Sex, male	58	53	45	54	71	52	0.03
Died, yes	17	16	20	18	16	23	0.06
Maximum no. of infants	399	230	183	115	47	32	

^a All numbers (except those in the bottom row) are column percentages.^b Birth weight z score based on the standard of Yudkin et al. (12).

of preeclampsia. The mortality rate was highest among infants of pregnancies complicated by preeclampsia and fetal indication/IUGR, even after controlling for maternal race, gestational age, and a complete course of antenatal steroids (Tables 3 and 4).

Table 4. Odds Ratios (Point Estimates and 95% Confidence Intervals) for Neonatal Death Associated With Each Pregnancy Disorder Adjusting for Gestational Age, Receipt of a Complete Course of Antenatal Steroids, and Maternal Race, 14 US Centers, 2002–2004

Pregnancy Disorder	Neonatal Death	
	Odds Ratio	95% Confidence Interval
Fetal indication/intrauterine growth restriction	2.6	1.0, 7.0
Preeclampsia	2.1	1.1, 4.1
Prelabor premature rupture of membranes	1.4	0.7, 2.6
Preterm labor	1.1	0.6, 1.9
Cervical insufficiency	1.0	0.4, 2.7
Abruption	1.0	Referent

Placenta histology

A total of 943 (94%) of the placentas were available for histologic examination. Inflammation in the chorionic plate, the fetal membranes, and the umbilical cords was most frequent in placentas delivered after pPROM and cervical insufficiency, somewhat less frequent in placentas delivered after preterm labor and placental abruption, and least frequent in placentas delivered after preeclampsia and for fetal indication/IUGR.

Placentas of pregnancies complicated by preeclampsia and fetal indication/IUGR were most likely to have infarcts and an abundance of syncytial knots, both of which are considered indicators of poor placentation (Table 5).

Placenta microbiology

Compared with the placentas of pregnancies complicated by preeclampsia or fetal indication/IUGR, those delivered of pregnancies complicated by preterm labor, pPROM, placental abruption, and cervical insufficiency were much more likely to harbor an organism, especially those common to the vagina (i.e., *Prevotella bivia*, *Lactobacillus* spp., *Peptostreptococcus magnus*, or *Gardnerella vaginalis*). More than 30% of the placentas of these pregnancies harbored multiple

Table 5. Distribution of Histologic Characteristics of the Placentas of Pregnancies Classified by the Complication Preceding Delivery, 14 US Centers, 2002–2004

Placenta Histologic Characteristic	Pregnancy Complication ^a						P Value
	Preterm Labor	Prelabor Premature Rupture of Membranes	Preeclampsia	Abruption	Cervical Insufficiency	Fetal Indication	
Inflammation							
Chorionic plate ^b	33	49	2	19	39	7	<0.001
Membranes ^c	32	52	1	17	36	6	<0.001
Neutrophils in fetal stem vessels	29	57	2	22	45	7	<0.001
Umbilical cord vasculitis ^d	17	40	0	14	33	3	<0.001
Thrombosis of fetal stem vessels	5	9	3	7	5	10	0.13
Infarct	12	12	46	18	11	35	<0.001
Increased syncytial knots	9	10	59	9	11	42	<0.001
Decidual hemorrhage/fibrin	23	16	16	29	11	27	0.002
Total no. of placentas	375	209	172	111	45	31	

^a All numbers (except those in the bottom row) are column percentages.

^b Count: >20 neutrophils/20×.

^c Numerous large or confluent foci of inflammation.

^d Neutrophils in perivascular Wharton's jelly.

organisms. In contrast, only one-quarter of pregnancies delivered for preeclampsia or fetal indication/IUGR had any microorganism present, and the majority of these tended to be single-organism culture.

To assess the magnitude of possible contamination, we conducted separate analyses of placentas delivered by cesarean section (data not shown). The rate of vaginal organ-

ism recovery from placentas delivered following labor, pPROM, placental abruption, and cervical insufficiency, although reduced, remained many times higher than the rate among placentas from preeclampsia and fetal indication/IUGR pregnancies (Table 6).

Table 6. Percentage of All Placentas From Each Pregnancy Complication That Harbored the Organism or Group of Organisms Specified, 14 US Centers, 2002–2004

Microorganism	Pregnancy Complication ^a						P Value
	Preterm Labor	Prelabor Premature Rupture of Membranes	Preeclampsia	Abruption	Cervical Insufficiency	Fetal Indication	
Any organism	58	69	26	55	59	25	<0.001
Any anaerobe	36	34	18	38	25	18	0.001
Any aerobe	35	47	11	37	50	18	<0.001
Any <i>Mycoplasma</i>	19	21	0	10	7	0	<0.001
No. of organisms isolated							
0	42	31	74	45	41	75	<0.001
1	24	30	21	24	25	14	
≥2	34	38	4	32	34	11	
Skin organisms ^b	23	26	17	25	16	25	0.31
Vaginal organisms ^c	24	17	1	19	16	4	<0.001
Total no. of placentas	338	191	160	101	44	28	

^a All numbers (except those in the bottom row) are column percentages.

^b *Corynebacterium* spp., *Propionibacterium* spp., *Staphylococcus* spp.

^c *Prevotella bivia*, *Lactobacillus* spp., *Peptostreptococcus magnus*, *Gardnerella vaginalis*.

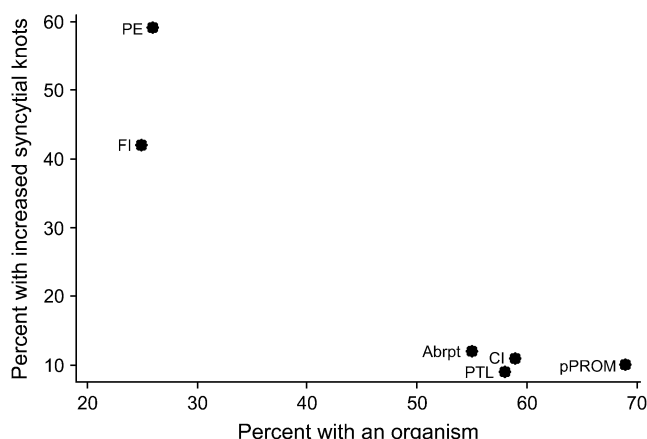


Figure 1. Comparison of pregnancy disorders by frequency of infection/inflammation and frequency of impaired placentation, 14 US Centers, 2002–2004. The percentage of placentas that harbored an organism is on the x-axis, and the percentage of placentas with increased syncytial knots is on the y-axis. The cluster of preeclampsia (PE) and fetal indication/intrauterine growth restriction (FI) is far removed from the cluster consisting of preterm labor (PTL), prelabor premature rupture of membranes (pPROM), placenta abruption (Abtpt), and cervical insufficiency (CI).

Visual display

We plotted the frequency of organism recovery along the x-axis (as an indicator of infection/inflammation) and the frequency of finding increased syncytial knots along the y-axis (as an indicator of impaired placentation). As expected from Tables 5 and 6, preeclampsia and fetal indication/IUGR cluster together far removed from the cluster of preterm labor, pPROM, placenta abruption, and cervical insufficiency. A plot of the percentage of placentas that harbored an organism on one axis and the percentage of placentas with grade 3+ chorionic plate inflammation on the other axis also clearly separated these two groups as did a plot of the percentage of placentas with grade 3+ chorionic plate inflammation on one axis and the percentage of placentas with increased syncytial knots on the other axis (not shown) (Figure 1).

Factor analysis

The first factor, with an eigenvalue of 1.73, was positively associated with organism recovery from the placenta, placental inflammation, and early gestational age and negatively associated with growth restriction and the finding of syncytial knots (Table 7). The second factor, with an eigenvalue of 1.07, was negatively associated with younger maternal age, lower educational attainment, and primiparity but positively associated with self and/or partner support. The third factor, with an eigenvalue of 0.60, was negatively associated with not attending or completing college but positively associated with identification as White, self and/or partner support, primiparity, and fertility treatment.

Table 7. Loadings of Maternal, Neonatal, Histologic, and Microbiologic Characteristics on Factors Obtained With Varimax Rotation,^a 14 US Centers, 2002–2004

	Factor		
	1	2	3
Mother identifies herself as White	−0.009	0.108	0.407
Maternal age <21 years	0.028	−0.629	−0.174
Maternal education less than college	0.051	−0.204	−0.526
Self and/or partner support	−0.048	0.386	0.273
Smoking during pregnancy	0.001	−0.003	−0.183
Body mass index >30	−0.030	0.193	−0.120
First pregnancy	−0.032	−0.423	0.232
Any fertility treatment	0.052	0.100	0.303
Birth weight z score <−2 ^b	−0.247	−0.046	0.091
Gestational age <25 weeks	0.259	0.023	−0.136
Male baby	0.050	0.086	0.029
Vaginal infection during pregnancy	0.061	0.067	−0.174
Antibiotic prescribed	0.056	0.035	0.016
Recovery of an organism	0.681	0.046	−0.058
Recovery of a vaginal organism	0.604	−0.050	−0.002
More than one organism recovered	0.763	−0.030	0.016
Grade 3+ chorionic plate inflammation	0.260	0.189	−0.124
Increased syncytial knots	−0.249	−0.029	0.135

^a A method for rotating axes of a plot such that the eigenvectors remain orthogonal as they are rotated.

^b Birth weight z score based on the standard of Yudkin et al. (12).

The mean first factor scores of each pregnancy complication can be divided into 2 groups (Table 8). One, characterized by high negative scores, identifies preeclampsia and fetal indication/IUGR. The other, characterized by low to moderate positive scores, identifies preterm labor, pPROM, placental abruption, and cervical insufficiency. The mean second and third factor scores did not provide additional information that discriminated 2 or more pregnancy disorders from the rest.

DISCUSSION

Our search for the antecedents of pregnancy disorders that lead to preterm delivery fueled our search for features common to these disorders. Although the 6 pregnancy disorders that lead to delivery much before term have distinct clinical presentations, our findings suggest that they can be divided into 2 broad groups on the basis of common characteristics. One group, characterized by the presence of infection and inflammation and the absence of indicators of impaired placentation, includes preterm labor, pPROM, placental abruption, and cervical insufficiency. “Spontaneous” preterm delivery has been defined as the group of entities that are neither maternal nor fetal indication/IUGR, and it typically includes complications such as preterm labor and

Table 8. Mean Factor Scores of Each Pregnancy Complication, 14 US Centers, 2002–2004

Factor	Complication Preceding Preterm Delivery					
	Preterm Labor	Prelabor Premature Rupture of Membranes	Preeclampsia	Abruption	Cervical Insufficiency	Fetal Indication
1	0.178	0.249	−0.665	0.104	0.156	−0.572
2	−0.055	0.154	−0.056	−0.109	0.167	0.092
3	−0.032	−0.152	0.218	0.067	−0.072	−0.001

pPROM. We prefer, however, to group these causes of preterm delivery under the description “inflammatory,” because it more accurately summarizes the observations made in this analysis, and to include placental abruption and cervical insufficiency under this umbrella.

The other group, characterized by infarcts and increased syncytial knots in the placenta, the relative absence of inflammation, and a higher neonatal mortality rate, includes preeclampsia and the entity identified as fetal indication/IUGR. The presence of increased syncytial knots and infarcts has been viewed as evidence of maternal-placental insufficiency (17, 18). Low-birth-weight *z* scores, another indicator of placental function, are characteristic of infants delivered for fetal indication/IUGR and preeclampsia (19, 20). Intrauterine growth restriction has been attributed to a restricted arteriolar supply of the uterine-placental interface (21). Delivery for preeclampsia and fetal indication/IUGR has been labeled “indicated” or “nonspontaneous” delivery. We, however, prefer to identify this group with the more pathophysiologically accurate term of “placental dysfunction.”

This study is unique in culturing placental stroma rather than amniotic fluid or fetal membranes. Nevertheless, the results are similar, recovering a diverse group of organisms with no one organism or class of organisms predominating (22–24). We also observed that vaginal microorganisms occur preferentially in the placentas of women with preterm labor, pPROM, placental abruption, and cervical insufficiency regardless of whether delivery is vaginal or abdominal, suggesting that these organisms are not merely contaminants associated with the route of delivery but are biologically significant.

Our study is not unique in finding elevated frequencies of histologic inflammation in placentas from pregnancies complicated by preterm labor and pPROM (25, 26), nor is it unique in finding evidence that placental abruption is characterized by inflammatory processes (27–29). However, our observations allow us to go the next step and suggest that the patterns of histologic changes and microbes recovered from placentas after both cervical insufficiency and abruption are similar to those of placentas delivered after preterm labor or pPROM.

We observed that demographic variables discriminate among the 6 pregnancy complications. As others have also observed, we found that maternal age (30–33), educational attainment (34), and race (35, 36) differ by cause of preterm delivery. Unlike others, we did not find that marital status

(37, 38) and limited financial resources (39, 40) discriminate among the causes of preterm delivery.

Characteristics that are more specific to the physiology of the pregnancy itself such as maternal smoking, body mass index, and conception assistance also discriminate among the 6 disorders that lead to preterm delivery. Consistent with prior work, we observed that smoking was associated with reduced risk of preeclampsia (41, 42) and an increased risk of pPROM and placental abruption (8, 43–45). Similarly, we confirmed a positive association between increased body mass index and both fetal indication/IUGR and preeclampsia (46, 47).

Our data support the hypothesis that the intrauterine environment influences the risk of mortality in the preterm neonate (48). Neonatal mortality was higher in pregnancy disorders associated with placental dysfunction than in those disorders associated with intrauterine inflammation.

In summary, we have found support for classifying the disorders leading to delivery well before term in 2 broad groups. What we call the “inflammatory” group and others call “spontaneous preterm delivery” includes preterm labor, pPROM, placental abruption, and cervical insufficiency and is characterized by evidence of infection and inflammation. The “placental dysfunction” group, otherwise classified as “indicated delivery,” includes preeclampsia and fetal indication/IUGR and is characterized by the relative absence of inflammation and the presence of infarcts, as well as increased syncytial knots in the placenta. Further work will be needed to suggest whether intervening at a point before the final common pathway of each group can potentially reduce the burdens that these disorders place on families and society.

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