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# The Phenotype of Spontaneous Preterm Birth: Application of a Clinical Phenotyping Tool

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## Abstract



***Author Affiliation Notes:***

Since the study was conducted, Dr. Manuck has moved to the University of North Carolina- Chapel Hill Department of Obstetrics and Gynecology Division of Maternal Fetal Medicine (Chapel Hill, NC). Dr. Bukowski has moved to Yale University School of Medicine, Division of Maternal Fetal Medicine (New Haven, CT).



**Conflict of Interest/Disclosure Statement**: Dr. Sean Esplin serves on the scientific advisory board and holds stock in Sera Prognostics, a private company that was established to create a commercial test to predict preterm birth and other obstetric complications. The remaining authors report no conflict of interest.

**Presentation**: This study will be presented in part at the 35th Annual Society of Maternal Fetal Medicine Meeting (February 2015, San Diego, CA) as an oral concurrent presentation (final abstract ID #14).

**Objective—**Spontaneous preterm birth (SPTB) is a complex condition that is likely a final common pathway with multiple possible etiologies. We hypothesized that a comprehensive classification system could appropriately group women with similar STPB etiologies, and provide an explanation, at least in part, for the disparities in SPTB associated with race and gestational age at delivery.

**Study Design—**Planned analysis of a multicenter, prospective study of singleton SPTB. Women with SPTB < 34 weeks were included. We defined 9 potential SPTB phenotypes based on clinical data, including infection/inflammation, maternal stress, decidual hemorrhage, uterine distention, cervical insufficiency, placental dysfunction, premature rupture of the membranes, maternal comorbidities, and familial factors. Each woman was evaluated for each phenotype. Delivery gestational age was compared between those with and without each phenotype. Phenotype profiles were also compared between women with very early (20.0–27.9 weeks) SPTB vs. those with early SPTB (28.0–34.0 weeks), and between African-American and Caucasian women. Statistical analysis was by t-test and chi-square as appropriate.

**Results—**The phenotyping tool was applied to 1025 women with SPTB who delivered at a mean 30.0 (+/− 3.2) weeks gestation. Of these, 800 (78%) had ≥2 phenotypes. Only 43 (4.2%) had no phenotypes. The 281 women with early SPTB were more likely to have infection/inflammation, decidual hemorrhage, and cervical insufficiency phenotypes (all $p \leq 0.001$). African-American women had more maternal stress and cervical insufficiency but less decidual hemorrhage and placental dysfunction compared to Caucasian women (all $p < 0.05$). Gestational age at delivery decreased as the number of phenotypes present increased.

**Conclusions—**Precise SPTB phenotyping classifies women with SPTB and identifies specific differences between very early and early SPTB and between African-Americans and Caucasians.

### Keywords

spontaneous preterm birth; preterm phenotype; racial disparity

## INTRODUCTION

Preterm birth (PTB) complicates approximately 12% of pregnancies, but is responsible for the majority of neonatal death and long-term morbidity amongst non-anomalous newborns in the United States.[1,2] In recent years, clinicians and researchers have sought to identify causes and outline effective prematurity prevention and treatment strategies, with variable success. Although the overall rate of PTB has decreased slightly in the United States, this reduction has been mainly in late PTB; the rate of early PTB (<34 weeks gestation) has remained constant.[3] Increased utilization of resources in early life, increased need for early intervention services, and reduced school performance are more common among survivors of preterm birth, resulting in significant societal costs.[4–6]

A multitude of poorly understood mechanisms are necessary for pregnancy maintenance and the normal transition to labor.[7,8] The initiation of preterm parturition also remains poorly understood, but multiple potential causes and triggers are thought to result in the final common pathway of PTB. The phenotype of PTB refers to the biochemical and physical characteristics of the mother, fetus, and/or placenta that lead to, and/or are present at the

time of, delivery.[7,9] When activated or altered prematurely any of these processes, either alone or in combination, may lead to premature parturition.

Many traditional PTB classification systems stratify preterm deliveries by gestational age at delivery (early vs. late) or general clinical presentation (e.g., spontaneous preterm labor, preterm premature rupture of membranes [PPROM], and iatrogenic [indicated] preterm birth).[10,11] These classifications are broad and are unlikely to be sufficiently precise to define the underlying etiologies responsible for PTB.

Recently, experts have proposed more sophisticated classification systems. According to Goldenberg et al. the most useful classification system will incorporate antenatal factors (e.g. maternal infections, short cervical length, polyhydramnios), delivery clinical presentation (e.g., contractions, bleeding, advanced cervical dilation), and relevant laboratory/pathological exam findings.[8] In 2012, Villar, et al. proposed a PTB phenotype classification that incorporates 5 components – maternal conditions, fetal conditions, placental conditions, signs of parturition initiation, and the pathway to delivery. However, this classification system has not been validated or used in practice.[7]

We concur that the optimal classification system should incorporate the clinical phenotype (defined as one or more characteristics of the mother, fetus, and/or placenta, and the delivery presentation) with genetic and biochemical markers.[9] Due to the heterogeneous nature of SPTB, it is likely that more than one phenotype may be present for each individual preterm delivery.

We hypothesized that a comprehensive SPTB classification system could be developed to characterize an individual's PTB phenotype, and this phenotype could be used to identify specific differences between women with early and later SPTB. Such a system could facilitate future attempts to identify underlying etiologies of SPTB and provide a basis for studies of new intervention strategies.

## MATERIALS and METHODS

This is a planned analysis of a multicenter, prospectively collected case-control study of women enrolled in the Eunice Kennedy Shriver National Institute for Child Health and Human Development Genomic and Proteomic Network for Preterm Birth Research. Briefly, women were recruited across eight clinical sites from November 2007 through January 2011. Cases consisted of women who delivered singleton pregnancies between 20.0–33.9 weeks gestation following the spontaneous onset of labor (PTB cases). Women with preterm premature rupture of membranes (PPROM) who labored and delivered prior to 34 weeks were also included as cases. Women with iatrogenic or medically indicated preterm deliveries (e.g., due to pre-eclampsia or growth restriction) were excluded. A concomitant diagnosis of pre-eclampsia was not an exclusion, provided that the woman had spontaneous onset of preterm labor as defined above.

Clinical and demographic data were collected by trained research nurses. Research nurses conducted in-person interviews with participants and abstracted additional clinical and demographic data from medical records. Participating women were interviewed prior to

hospital discharge from their delivery encounter whenever possible, and all interviews were performed within 14 days of delivery. Data collected included demographics, medical, social, family, and obstetric histories, obstetric course and complications during the current pregnancy (including intrapartum course, mode of delivery, and neonatal outcomes). Women also completed questionnaires to evaluate anxiety (Beck anxiety index), depression (Beck depression inventory), and perceived stress (Perceived stress scale).[12] In addition, participants were asked to indicate their attitude and the attitude of their partner with respect to pregnancy. This study was approved by the Institutional Review Board at each center, and written, informed consent was obtained from all participants.

A phenotyping tool was designed by the authors (MSE, TAM, MWV) to group maternal social, demographic, family history, and obstetric factors into 9 potential underlying SPTB categories. These categories include: (1) Infection/inflammation, (2) decidual hemorrhage, (3) maternal stress, (4) cervical insufficiency, (5) uterine distention, (6) placental dysfunction, (7) premature rupture of the membranes (PROM), (8) maternal comorbidities, and (9) familial factors (Table 1). Within each of the 9 categories, clinical factors were classified as providing strong, moderate, and possible evidence of the phenotype. Any of the listed criteria were sufficient for phenotype classification; it was not required that all criteria be met within each classification (Table 1). A phenotype profile was assigned to each woman by assessing whether she met criteria for each of the 9 phenotypes. Next, the phenotype profiles of women with very early PTB (delivering the current gestation at 20.0–27.9 weeks gestation) were compared to those with early PTB (delivery 28.0–33.9 weeks gestation). Finally, we examined phenotype profiles by self-reported race/ethnicity.

Statistical analysis was performed using STATA version 12.1 (College Station, TX). Comparisons were made using student’s t-test, chi-square, ANOVA, and the Pearson correlation coefficient as appropriate.

## RESULTS

The phenotyping tool (Table 1) was applied to 1025 women with SPTB <34 weeks gestation, including 281 with very early SPTB (20.0–27.9 weeks gestation). Basic demographics and baseline characteristics, compared by delivery gestational age epoch, are shown in Table 2. The majority of women (800, 78%) met criteria for more than one phenotype, although 43 (4%) had no evidence of any phenotypes (Table 3). We observed an inverse relationship between the number of phenotypes and gestational age at delivery, as those with multiple phenotypes delivered earliest ($r^2$=−0.110, p<0.001, Table 3).

The number and percentage of women with each of the 9 clinical phenotypes, and the corresponding mean delivery gestational age are shown in Table 4. The maternal stress phenotype was most common; more than half of all women with SPTB had strong, moderate, or possible evidence of maternal stress. Infection/inflammation (38%), PPROM (35%), familial (32%), and decidual hemorrhage (31%) were the next most common phenotypes.

Women with any evidence of cervical insufficiency delivered, on average, more than 2.5 weeks earlier than those without any evidence of cervical insufficiency. Those with any evidence of decidual hemorrhage, and those with any evidence of inflammation or infection also delivered significantly earlier (1.0 weeks and 0.7 weeks, respectively) compared to those without evidence of the phenotype (Table 4). Women with strong evidence of decidual hemorrhage or cervical insufficiency delivered at the earliest gestational ages. For other phenotypes, women delivered *later* with the phenotype than without it. For example, those with strong evidence of maternal co-morbidities or familial phenotypes delivered between 0.5 and 0.8 weeks later than those who did not.

The distribution of phenotypes among women with very early SPTB (20.0–27.9 weeks gestation) and early SPTB (28.0–33.6 weeks gestation) were compared, and several differences noted (Table 5). Among women with very early SPTB, the distributions of phenotypes differed from the overall cohort. Although maternal stress remained the most common phenotype (60%) and was similar between gestational age epochs, infection/inflammation (47% vs. 35%, $p<0.001$) and decidual hemorrhage (39% vs. 28%, $p<0.001$), and cervical insufficiency (25% vs. 7%, $p<0.001$) were substantially more common among those with very early SPTB (all $p\leq0.001$, Table 5).

Finally, we evaluated phenotype profiles based on self-reported race. More than 90% of women in this cohort were self reported African-American or Caucasian, and therefore we limited this portion of the analysis to these two groups. The 234 African-American women delivered approximately one week earlier than the 696 Caucasian women (29.2 vs. 30.2 weeks gestation, $p<0.001$). Placental pathology was available for only 2 African-American women (compared with 176 Caucasian women, $p<0.001$). Therefore, placental pathology result information was removed from the phenotype definitions for this portion of the analysis (Table 6). Among the modified phenotype profiles, there were significant differences between African-American and Caucasian women (Table 6). African-American women were significantly more likely to have maternal stress, strong evidence of cervical insufficiency, possible evidence of PPROM, while they were less likely to have any evidence of decidual hemorrhage, any evidence of placental dysfunction, or moderate evidence of uterine distension compared to Caucasians (Table 6).

## COMMENT

We have described and defined specific SPTB phenotypes, and have successfully used this classification system to group a large cohort of women with SPTB < 34.0 weeks gestation. We found that nearly all women with PTB had at least one phenotype, and the majority had some evidence of at least two distinct phenotypes. Additionally, we found that phenotypes vary with delivery gestational age and self-reported maternal race. Phenotype classification provides more detailed information beyond delivery gestational age.

Recently, there has been a concerted effort to develop classification system to refine the phenotype of SPTB. As part of the 2009 Global Alliance to Prevent Prematurity and Stillbirth Conference, several groups of investigators have proposed a new method for classifying PTB.[7–9] The classifies both induced and spontaneous PTB, describes factors that

arise from fetal and maternal conditions, and distinguishes between preterm delivery following ‘idiopathic’ preterm labor vs. PPROM. Some patterns have been identified using this approach. For example, African-American women have been noted to have an increased incidence of PPROM. In contrast, idiopathic preterm labor has been found to predominate among Caucasian populations.[13] However, the difference between SPTB due to preterm labor versus that due to PPROM may reflect other demographic considerations (such as ready access to transportation to arrive at the hospital before rupture of the membranes). Instead of broadly classifying women into these categories, we have sought to provide more specific possible etiologic explanations for seemingly ‘idiopathic’ preterm labor and PPROM. Although PPROM remains as one of the 9 phenotypes in our system, we have considered 8 other categories, which can be combined along with PPROM to characterize an individual’s PTB profile.

We found distinct differences when comparing phenotype profiles of African- American and Caucasian women. Previous studies have suggested that the racial disparity in rates of adverse pregnancy outcomes (namely, PTB), may be due to differences in maternal stress and/or inflammatory response.[14,15] Indeed, our finding of differences in the incidence of the maternal stress phenotype between African-American and Caucasian women is consistent with these prior reports. We did not appreciate a difference between African-American and Caucasian women with regards to infectious phenotype, but were limited by the incomplete placental pathology data for this phenotype in particular.

From our data it is clear that multiple etiologies lead to the ultimate downstream clinical SPTB phenotype. Thus, we believe that previous, less specific approaches may be insufficient to identify groups of women who may have similar genotypic causes of PTB. Incomplete and/or imprecise phenotype characterization may in part explain why genetic (including genome wide association) studies have failed to consistently identify genetic factors associated with SPTB.[9] We believe that our proposed phenotype definitions will allow clinicians and researchers to more accurately group women by possible underlying PTB etiology, which may facilitate future identification of group-specific interventions.[8]

Our study has several strengths. All women were identified and enrolled prospectively with standardized data collection. Enrollment of women occurred at 3 major perinatal centers in distinctly different geographic settings across the United States, increasing the generalizability of our results. SPTB was strictly defined prior to patient enrollment. We included only women with SPTB less than 34 weeks; capturing those premature neonates at highest risk for long-term sequelae of prematurity. Our phenotyping tool improves upon other previously proposed PTB classification systems by providing more specific classification, yet was applied using readily available data. The tool did not limit the classification of women into only one phenotype, and allowed for overlapping SPTB etiologies, necessary due to the complexity of the disease itself.

Our study should be interpreted with several limitations in mind. Phenotype definitions are complex and somewhat subjective. In some situations (e.g., family history), we elected to include variables traditionally considered to be ‘risk factors’ in our phenotype definitions, in order to group women likely to have similar etiologic determinants of PTB. Although this

was a planned analysis, clinical and biologic data were not collected specifically for phenotype classification. Clinical data were collected at delivery and in the immediate postpartum time period, precluding analysis of antenatal factors that could be followed serially (such as cervical length measurements over time). Although questionnaire instructions specify for participants to report average stress over the past month, our finding of a high proportion of women with the maternal stress phenotype may reflect the timing of questionnaire administration, rather than life events/general stress and anxiety in the month prior to birth. We were limited by the inclusion criteria of the initial cohort; for example, multiple gestation pregnancies would meet criteria for the uterine distension phenotype, but since this cohort was limited to singletons, multiples were excluded from the phenotype definitions. Additionally, the data available for each woman varied, and precluded a more complete comparison between African-American and Caucasian women. In general, incomplete data likely resulted in under-classification of some women, but would favor the null hypothesis. We were also unable to incorporate biomarkers (e.g. c-reactive protein, neutrophil count, inflammatory cytokines) or genotype, which have been previously correlated in some groups of women with SPTB.[16–19]

In this cohort, a relatively small number of women had evidence of cervical insufficiency. Given that the majority of participants did not have an antenatal cervical length assessment, and those with a cervical cerclage in situ were excluded from the main study, these findings are not unanticipated. Also, because only a small subset of women had placental pathology results available, there was likely under-classification of women into the inflammation/infection and decidual hemorrhage phenotypes. Nonetheless, we found that a considerable proportion of women had evidence of infection/inflammation (37.9%) or decidual hemorrhage (30.8%), despite these limitations. Specific application of this tool prospectively would likely identify that cervical insufficiency, and to a lesser extent, inflammation/infection and decidual hemorrhage, have a greater contribution to SPTB than we have found in the present study.

Although our classification system is more specific than prior systems, additional refinement will doubtless occur. Incorporation of prospective, longitudinal data collection throughout gestation, integration of biomarkers, and inclusion of maternal and/or fetal genetic data are necessary to more specifically define and distinguish each phenotype. We found that many women had evidence of several phenotypes; although this may reflect the multifactorial nature of SPTB, it is also possible that further refinement of the phenotype classification system may reduce these overlaps. A standardized approach to SPTB evaluation will provide an opportunity to enhance ongoing research and increase understanding of the etiology(ies) of SPTB. This tool may also be useful when applied to all women with PTB, regardless of indication, given the high probability of overlap between ‘spontaneous’ and ‘iatrogenic’ prematurity.

Future research should validate these results in another patient population, and investigate the relationship between clinical phenotype and response to preterm birth preventative or treatment strategies in subsequent pregnancies. Additionally, neonatal outcomes should be examined by PTB phenotype. Consideration could also be given to application of the phenotyping tool to late preterm and/or early term deliveries to provide additional

information regarding labor across the full spectrum of gestational ages. Additional consideration could be given to creating individual phenotype ‘scores,’ by assigning a numeric point value to individual criteria within each phenotype, this may more accurately determine the ‘level of evidence’ each woman demonstrates for each phenotype. Prospective application of this phenotyping tool will provide a basis for more accurate sub-classification of women who are more likely to share underlying environmental and/or genetic etiologies of prematurity. Future studies should also assess whether this classification tool enhances the ability of high throughput screens to uncover changes (e.g., gene expression) in a manner than uncovers genuine biology.

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Data collected at participating sites of the GPN were transmitted to Yale University, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the GPN, Dr. Heping Zhang (DCC Principal Investigator) had full access to the clinical data in the study and takes responsibility for the integrity of the data.

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## Table 1

Spontaneous preterm birth clinical phenotype classification system.

| Phenotype | Strong Evidence | Moderate Evidence | Possible Evidence |
|---|---|---|---|
| **Infection / Inflammation**[a] | - Histologic chorioamnionitis or funisitis<br>- Positive placental culture or presence of placental viral inclusions | - Clinical chorioamnionitis requiring intrapartum antibiotic treatment<br>- Placental pathology positive for deciduitis, villitis, microabscess, arteritis, and/or phlebitis | - Clinical endometritis requiring postpartum antibiotic treatment<br>- Major antenatal maternal systemic infection (pneumonia, pyelonephritis, pancreatitis, hepatitis)<br>- Symptomatic urinary tract infection<br>- Sexually transmitted disease diagnosed at any time during pregnancy (chlamydia, gonorrhea, trichomoniasis, HIV) |
| **Decidual Hemorrhagea** | - Hemosiderin deposits or tightly adherent clot on placental pathology<br>- At least 25% hemorrhage on fetal or maternal interface on placental pathology | - Placental pathology demonstrating 1–25% or unspecified percentage of hemorrhage on fetal or maternal interface<br>- Active vaginal bleeding plus at least one of the following - non-reassuring fetal heart tones, uterine tenderness, or uterine tachysystole<br>- Clinical diagnosis of abruption requiring delivery | - Trauma to abdomen or motor vehicle accident during pregnancy<br>- Vaginal bleeding during pregnancy, not otherwise specified<br>- Placenta previa |
| **Maternal Stress** | - Moderate to severe depression/anxiety requiring medication treatment during pregnancy | - Beck Depression Index score indicates severe depression<br>- Perceived stress score = ‘very high’ or life stressors questionnaire indicated ‘severe distress’ | - Mild to moderate depression/anxiety not requiring medication treatment<br>- Illicit drug use or current binge alcohol use during pregnancy<br>- High risk socioeconomic risk factor: income less than poverty level, less than a high school degree |
| **Cervical Insufficiency** | - Cervical dilation ≥2 cm prior to 28 weeks | - Cervical length <1.50 cm prior to 28 weeks | - Cervical length 1.50–2.50 cm prior to 28 weeks |

| Phenotype | Strong Evidence | Moderate Evidence | Possible Evidence |
|---|---|---|---|
| | gestation in the absence of labor<br>Cervical length <0.5 cm prior to 28 weeks in the absence of labor<br>At least one pregnancy loss prior to 24 weeks gestation due to painless cervical dilation | gestation in the absence of labor<br>- Cervical length 1.50–2.5cm prior to 28 weeks gestation AND hourglassing membranes/marked funneling | gestation in the absence of labor<br>- History of cervical conization procedure or loop electro-excision procedure |
| **Uterine Distension**[a] | n/a | - Polyhydramnios (4-quadrant AFI >25cm or single deepest pocket >8cm)<br>- Birthweight >90% for gestational age) | - Sonographically confirmed presence of uterine fibroids<br>- Placental weight >90% for gestational age |
| **Placental Dysfunction**[a] | - Birthweight <3% for gestational age and gender<br>- Placental weight <3% for gestational age<br>- At least 25% placental infarction on pathology<br>- Reverse end diastolic | - Birthweight <10% for gestational age and gender<br>- Placental weight <10% for gestational age<br>- Absent end diastolic flow on cord Doppler prior to delivery<br>- Any placental infarction with no percentage listed or <25% on placental pathology<br>- Four quadrant amniotic fluid index <5cm or single deepest pocket <2cm on ultrasound<br>- Pre-eclampsia without severe features | - Velamentous cord insertion on placental pathology |
| **Preterm premature rupture of membranes** | - Preterm, premature rupture of membranes diagnosed with sterile speculum examination, dye test, or amnisure at least 48 hours prior to the onset of labor | - Preterm, premature rupture of membranes diagnosed with sterile speculum examination, dye test, or amnisure 12–48 hours prior to the onset of labor | - History of PPROM and delivery less than 37 weeks in a prior pregnancy |
| **Maternal Co-morbidities** | - Class B or higher diabetes mellitus<br>- Chronic hypertension<br>- Systemic lupus erythematosus - Antiphospholipid antibody syndrome<br>- Chronic renal failure or insufficiency | - Gestational diabetes in the current gestation<br>- Other medical condition affecting a major organ system, not otherwise specified – i.e. pulmonary disease, renal disease, autoimmune disease, history of seizures | n/a |
| **Familial** | - At least one first degree relative with history of | - At least one first degree relative with history of medically indicated preterm birth | - At least one second degree relative with history of medically |

| Phenotype | Strong Evidence | Moderate Evidence | Possible Evidence |
|---|---|---|---|
| | spontaneous preterm birth | - At least one second degree relative with history of spontaneous preterm birth | indicated preterm birth |

[a] Placental pathology was available for only 195 women (19%). When pathologic evidence of each phenotype was noted, it was included in the classification. The frequency of placental pathology availability did not vary with gestational age epoch.

## Table 2

Demographic and baseline characteristics.

| | Very Early Spontaneous Preterm Birth 20.0–27.9 weeks N=281 | Early Spontaneous Preterm Birth 27.0–33.9 weeks N=744 | P-value |
|---|---|---|---|
| **Maternal age (mean, +/− SD)** | 25.3 (5.8) | 25.7 (6.0) | 0.422 |
| **Maternal Race**<br>**White**<br>**Black**<br>**Other** | 174 (61.9)<br>84 (29.9)<br>23 (8.2) | 522 (70.2)<br>150 (20.2)<br>72 (9.7) | 0.004 |
| **Hispanic ethnicity** | 63 (22.4) | 148 (19.9) | 0.372 |
| **Married (n, %)** | 122 (43.4) | 390 (52.4) | 0.010 |
| **Nulliparous (n, %)** | 141 (50.2) | 340 (45.7) | 0.200 |
| **Prior preterm delivery <37 weeks gestation (n, %)** | 69 (24.6) | 222 (29.8) | 0.094 |
| **Maternal pre-pregnancy BMI ($kg/m^2$, mean +/− SD)** | 27.1 (7.2) | 25.4 (6.5) | <0.001 |
| **Cigarette use during pregnancy** | 54 (19.2) | 138 (18.6) | 0.807 |
| **Delivery gestational age, weeks (mean +/− SD)** | 25.5 (1.6) | 31.7 (1.7) | <0.001 |

**Table 3**

Mean gestational age at delivery (+/− SD) stratified by number of distinct phenotypes.

| Total Count of Distinct Phenotypes | Number of Women | Mean Delivery Gestational Age |
|---|---|---|
| 0 | 43 (4.2) | 30.7 (3.2) |
| 1 | 182 (17.8) | 30.5 (2.9) |
| 2 | 273 (26.6) | 30.1 (3.3) |
| 3 | 296 (28.9) | 29.9 (3.2) |
| 4 | 148 (14.4) | 29.5 (3.3) |
| 5 | 64 (6.2) | 29.8 (3.3) |
| 6 | 15 (1.5) | 28.4 (3.0) |
| 7 | 4 (0.4) | 30.5 (2.7) |

## Table 4

Percentage of cases with some evidence of each of the 9 proposed phenotypes, and mean delivery gestational age (+/− SD) among those with and without each phenotype.

| Phenotype | Number of SPTB Cases with Phenotype (from total n=1025) | Delivery Gestational Age (weeks, +/− SD) with Phenotype | Delivery Gestational Age (weeks, +/− SD) without Phenotype | p-value |
|---|---|---|---|---|
| **Infection / Inflammation** | | | | |
| Strong Evidence | 86 (8.4) | 29.1 (3.4) | 30.1 (3.2) | 0.006 |
| Moderate Evidence | 98 (9.6) | 28.3 (3.6) | 30.2 (3.1) | <0.001 |
| Possible Evidence | 272 (26.5) | 29.9 (3.2) | 30.0 (3.2) | 0.620 |
| Any Evidence | 388 (37.9) | 29.6 (3.4) | 30.3 (3.1) | <0.001 |
| **Decidual Hemorrhage** | | | | |
| Strong Evidence | 4 (0.4) | 27.6 (4.0) | 30.0 (3.2) | 0.131 |
| Moderate Evidence | 150 (14.6) | 29.4 (3.4) | 30.1 (3.2) | 0.008 |
| Possible Evidence | 202 (19.7) | 29.1 (3.5) | 30.2 (3.1) | <0.001 |
| Any Evidence | 316 (30.8) | 29.3 (3.5) | 30.3 (3.1) | <0.001 |
| **Maternal Stress** | | | | |
| Strong Evidence | 47 (4.6) | 31.3 (2.7) | 29.9 (3.2) | 0.005 |
| Moderate Evidence | 306 (29.9) | 30.1 (3.3) | 30.0 (3.2) | 0.646 |
| Possible Evidence | 422 (41.2) | 29.6 (3.2) | 30.3 (3.2) | 0.001 |
| Any Evidence | 580 (56.6) | 29.8 (3.2) | 30.2 (3.2) | 0.081 |
| **Cervical insufficiency** | | | | |
| Strong Evidence | 68 (6.6) | 27.1 (2.6) | 30.2 (3.2) | <0.001 |
| Moderate Evidence | 51 (5.0) | 28.2 (2.7) | 30.1 (3.2) | <0.001 |
| Possible Evidence | 22 (2.2) | 28.0 (2.5) | 30.0 (3.2) | 0.003 |
| Any Evidence | 119 (11.6) | 27.7 (2.7) | 30.3 (3.2) | <0.001 |
| **Uterine distension** | | | | |
| Strong Evidence | -- | -- | -- | -- |
| Moderate Evidence | 175 (17.1) | 30.2 (2.8) | 30.0 (3.3) | 0.448 |
| Possible Evidence | 43 (4.2) | 30.3 (3.0) | 30.0 (3.2) | 0.539 |
| Any Evidence | 212 (20.7) | 30.2 (2.9) | 30.0 (3.3) | 0.418 |
| **Placental dysfunction** | | | | |
| Strong Evidence | 39 (3.8) | 30.8 (3.0) | 30.0 (3.2) | 0.114 |
| Moderate Evidence | 84 (8.2) | 30.2 (3.4) | 30.0 (3.2) | 0.643 |
| Possible Evidence | 55 (5.4) | 30.2 (3.3) | 30.0 (3.2) | 0.639 |
| Any Evidence | 122 (11.9) | 30.0 (3.4) | 30.0 (3.2) | 0.855 |
| **PPROM** | | | | |
| Strong Evidence | 211 (20.6) | 30.0 (3.0) | 30.0 (3.3) | 0.950 |

| Phenotype | Number of SPTB Cases with Phenotype (from total n=1025) | Delivery Gestational Age (weeks, +/− SD) with Phenotype | Delivery Gestational Age (weeks, +/− SD) without Phenotype | p-value |
|---|---|---|---|---|
| Moderate Evidence | 141 (149 | 30.6 (3.2) | 29.9 (3.2) | 0.014 |
| Possible Evidence | 49 (4.8) | 29.7 (3.0) | 30.0 (3.2) | 0.440 |
| Any Evidence | 362 (35.3) | 30.2 (3.1) | 29.9 (3.3) | 0.078 |
| **Maternal Co-morbidities** | | | | |
| Strong Evidence | 87 (8.5) | 30.7 (2.7) | 29.9 (3.3) | 0.029 |
| Moderate Evidence | 182 (17.8) | 30.4 (3.1) | 29.9 (3.2) | 0.040 |
| Possible Evidence | -- | -- | -- | -- |
| Any Evidence | 216 (21.1) | 30.3 (3.1) | 29.9 (3.2) | 0.102 |
| **Familial** | | | | |
| Strong Evidence | 227 (22.2) | 30.4 (3.0) | 29.9 (3.3) | 0.023 |
| Moderate Evidence | 143 (14.0) | 29.9 (3.4) | 30.0 (3.2) | 0.801 |
| Possible Evidence | -- | -- | -- | -- |
| Any Evidence | 331 (32.3) | 30.2 (3.2) | 29.9 (3.2) | 0.113 |

## Table 5

Comparison of the number and percentage of women with each phenotype among women with SPTB.

| Phenotype | Very Early Spontaneous Preterm Birth 20.0–27.9 weeks n=281 | Early Spontaneous Preterm Birth 28.0–33.9 weeks N=744 | p-value |
|---|---|---|---|
| **Infection / Inflammation** | | | |
| Strong Evidence | 33 (11.7) | 53 (7.1) | 0.017 |
| Moderate Evidence | 48 (17.1) | 50 (6.7) | <0.001 |
| Possible Evidence | 83 (29.5) | 189 (25.4) | 0.181 |
| Any Evidence | 131 (46.6) | 257 (34.5) | <0.001 |
| **Decidual Hemorrhage** | | | |
| Strong Evidence | 3 (1.1) | 1 (0.13) | 0.033 |
| Moderate Evidence | 50 (17.8) | 100 (13.4) | 0.079 |
| Possible Evidence | 76 (27.1) | 126 (16.9) | <0.001 |
| Any Evidence | 109 (38.8) | 207 (27.8) | 0.001 |
| **Maternal Stress** | | | |
| Strong Evidence | 8 (2.9) | 39 (5.2) | 0.102 |
| Moderate Evidence | 80 (28.5) | 226 (30.4) | 0.552 |
| Possible Evidence | 132 (47.0) | 290 (39.0) | 0.020 |
| Any Evidence | 168 (59.8) | 412 (55.4) | 0.204 |
| **Cervical insufficiency** | | | |
| Strong Evidence | 49 (17.4) | 19 (2.6) | <0.001 |
| Moderate Evidence | 25 (8.9) | 26 (3.5) | <0.001 |
| Possible Evidence | 11 (3.9) | 11 (1.5) | 0.016 |
| Any Evidence | 70 (24.9) | 49 (6.6) | <0.001 |
| **Uterine distension** | | | |
| Strong Evidence | -- | -- | -- |
| Moderate Evidence | 49 (17.4) | 126 (16.9) | 0.849 |
| Possible Evidence | 10 (3.6) | 33 (4.4) | 0.532 |
| Any Evidence | 58 (20.6) | 154 (20.7) | 0.984 |
| **Placental dysfunction** | | | |
| Strong Evidence | 8 (2.9) | 31 (4.2) | 0.325 |
| Moderate Evidence | 23 (8.2) | 61 (8.2) | 0.994 |
| Possible Evidence | 14 (5.0) | 41 (5.5) | 0.738 |
| Any Evidence | 33 (11.7) | 89 (12.0) | 0.923 |
| **PPROM** | | | |
| Strong Evidence | 52 (18.5) | 159 (21.4) | 0.311 |
| Moderate Evidence | 32 (11.4) | 109 (14.7) | 0.176 |

| Phenotype | Very Early Spontaneous Preterm Birth 20.0–27.9 weeks n=281 | Early Spontaneous Preterm Birth 28.0–33.9 weeks N=744 | p-value |
|---|---|---|---|
| Possible Evidence | 14 (5.0) | 35 (4.7) | 0.852 |
| Any Evidence | 86 (30.6) | 276 (37.1) | 0.052 |
| **Maternal Co-morbidities** | | | |
| Strong Evidence | 14 (5.0) | 73 (9.8) | 0.013 |
| Moderate Evidence | 36 (12.8) | 146 (19.6) | 0.011 |
| Possible Evidence | -- | -- | -- |
| Any Evidence | 46 (16.4) | 170 (22.9) | 0.023 |
| **Familial** | | | |
| Strong Evidence | 51 (18.2) | 176 (23.7) | 0.058 |
| Moderate Evidence | 41 (14.6) | 102 (13.67 | 0.716 |
| Possible Evidence | -- | -- | -- |
| Any Evidence | 84 (29.9) | 247 (33.2) | 0.313 |
| **None of the above phenotypes** | 8 (2.9) | 35 (4.7) | 0.186 |

## Table 6

Percentage of SPTB cases based on race with some evidence of each of the 9 proposed phenotypes.

| Phenotype | African American N=234 | Caucasian N=696 | p-value |
|---|---|---|---|
| **Infection / Inflammation** | | | |
| Strong Evidence[a] | -- | -- | -- |
| Moderate Evidence[b] | 12 (5.1) | 56 (8.1) | 0.138 |
| Possible Evidence | 65 (27.8) | 176 (25.3) | 0.452 |
| Any Evidence[b] | 75 (32.1) | 217(31.2) | 0.803 |
| **Decidual Hemorrhage** | | | |
| Strong Evidence[a] | -- | -- | -- |
| Moderate Evidence[b] | 20 (8.6) | 56 (8.1) | 0.809 |
| Possible Evidence | 31 (13.3) | 156 (22.4) | 0.002 |
| Any Evidence[b] | 49 (20.9) | 243 (34.9) | <0.001 |
| **Maternal Stress** | | | |
| Strong Evidence | 1 (0.4) | 45 (6.5) | <0.001 |
| Moderate Evidence | 68 (29.1) | 211 (30.3) | 0.717 |
| Possible Evidence | 128 (54.7) | 243 (34.9) | <0.001 |
| Any Evidence | 154 (65.8) | 365 (52.4) | <0.001 |
| **Cervical insufficiency** | | | |
| Strong Evidence | 24 (10.3) | 39 (5.6) | 0.014 |
| Moderate Evidence | 14 (6.0) | 34 (4.9) | 0.511 |
| Possible Evidence | 3 (1.3) | 16 (2.3) | 0.342 |
| Any Evidence | 36 (15.4) | 74 (10.6) | 0.051 |
| **Uterine distension** | | | |
| Strong Evidence | -- | -- | -- |
| Moderate Evidence | 25 (10.7) | 130 (18.7) | 0.005 |
| Possible Evidence[b] | 10 (4.3) | 5 (0.7) | <0.001 |
| Any Evidence[b] | 35 (15.0) | 134 (19.3) | 0.140 |
| **Placental dysfunction** | | | |
| Strong Evidence[b] | 0 (0) | 4 (0.6) | 0.245 |
| Moderate Evidence[b] | 9 (3.9) | 19 (2.7) | 0.387 |
| Possible Evidence[b] | 0 (0) | 32 (4.6) | 0.001 |
| Any Evidence[b] | 9 (3.9) | 53 (7.6) | 0.046 |
| **PPROM** | | | |
| Strong Evidence | 48 (20.5) | 145 (20.8) | 0.917 |
| Moderate Evidence | 35 (15.0) | 93 (13.4) | 0.540 |

| Phenotype | African American N=234 | Caucasian N=696 | p-value |
|---|---|---|---|
| Possible Evidence | 17 (7.3) | 27 (3.9) | 0.035 |
| Any Evidence | 85 (36.3) | 245 (35.2) | 0.756 |
| **Maternal Co-morbidities** | | | |
| Strong Evidence | 24 (10.3) | 50 (7.2) | 0.133 |
| Moderate Evidence | 35 (15.0) | 127 (18.3) | 0.251 |
| Possible Evidence | -- | -- | -- |
| Any Evidence | 50 (21.4) | 144 (20.7) | 0.825 |
| **Familial** | | | |
| Strong Evidence | 60 (25.6) | 149 (21.4) | 0.180 |
| Moderate Evidence | 38 (16.2) | 90 (12.9) | 0.204 |
| Possible Evidence | -- | -- | -- |
| Any Evidence | 86 (36.8) | 216 (31.0) | 0.106 |
| **None of the above phenotypes** | 11 (4.7) | 30 (4.3) | 0.801 |

[a] This category relies entirely on placental pathology data, and a disproportionate amount of missing data were present for African-American women, therefore this comparison could not be made.

[b] Calculated without placental pathology data in definition.