OBSTETRICS

The phenotype of spontaneous preterm birth: application of a clinical phenotyping tool

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

STUDY DESIGN: This was a planned analysis of a multicenter, prospective study of singleton SPTBs. Women with SPTB at <34 weeks' gestation were included. We defined 9 potential SPTB phenotypes based on clinical data: infection/inflammation, maternal stress, decidual hemorrhage, uterine distention, cervical insufficiency, placental dysfunction, premature rupture of the membranes, maternal comorbidities, and familial factors. Each woman's condition 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' gestation) SPTB vs those with early SPTB (28.0-34.0 weeks' gestation) and between African American and white women. Statistical analysis was by *t* test and χ^2 test, as appropriate.

RESULTS: The phenotyping tool was applied to 1025 women with SPTBs who delivered at a mean 30.0 ± 3.2 (SD) weeks' gestation. Of these, 800 women (78%) had ≥2 phenotypes. Only 43 women (4.2%) had no phenotypes. The 281 women with early SPTBs were more likely to have infection/inflammation, decidual hemorrhage, and cervical insufficiency phenotypes (all $P \leq .001$). African American women had more maternal stress and cervical insufficiency but less decidual hemorrhage and placental dysfunction compared with white women (all $P < .05$). Gestational age at delivery decreased as the number of phenotypes that were present increased.

CONCLUSION: Precise SPTB phenotyping classifies women with SPTBs and identifies specific differences between very early and early SPTB and between African American and white women.

Key words: phenotype, preterm, racial disparity, spontaneous preterm birth

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Preterm birth (PTB) complicates approximately 12% of pregnancies but is responsible for most neonatal deaths 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 PTB, which results 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

TABLE 1
Spontaneous preterm birth clinical phenotype classification system

	Evidence		
Phenotype	**Strong**	**Moderate**	**Possible**
Infection /inflammation[a]	Histologic chorioamnionitis or funisitis	Clinical chorioamnionitis that requires intrapartum antibiotic treatment	Clinical endometritis that requires postpartum antibiotic treatment
	Positive placental culture or presence of placental viral inclusions	Placental pathologic evidence positive for deciduitis, villitis, microabscess, arteritis, and/or phlebitis	Major antenatal maternal systemic infection (pneumonia, pyelonephritis, pancreatitis, hepatitis)
			Symptomatic urinary tract infection
			Sexually transmitted disease diagnosed at any time during pregnancy (chlamydia, gonorrhea, trichomoniasis, HIV)
Decidual hemorrhage[a]	Hemosiderin deposits or tightly adherent clot on placental pathologic evaluation	Placental pathologic evidence demonstrating 1-25% or unspecified percentage of hemorrhage on fetal or maternal interface	Trauma to abdomen or motor vehicle accident during pregnancy
	At least 25% hemorrhage on fetal or maternal interface on placental pathologic evaluation	Active vaginal bleeding plus at least 1 of the following events:	Vaginal bleeding during pregnancy, not otherwise specified
		(1) Nonreassuring fetal heart tones, uterine tenderness, or uterine tachysystole	Placenta previa
		(2) Clinical diagnosis of abruption that requires delivery	
Maternal stress	Moderate-to-severe depression/anxiety that requires medication treatment during pregnancy	Beck Depression Index score that indicates severe depression	Mild to moderate depression/anxiety not requiring medication treatment
		Perceived stress score "very high" or life stressors questionnaire indicated "severe distress"	Illicit drug use or current binge alcohol use during pregnancy
			High risk socioeconomic risk factor: income less than poverty level, less than a high school degree
Cervical insufficiency	Cervical dilation ≥2 cm at <28 weeks' gestation in the absence of labor	Cervical length <1.50 cm at <28 weeks' gestation in the absence of labor	Cervical length 1.50-2.50 cm at <28 weeks' gestation in the absence of labor
	Cervical length <0.5 cm at <28 weeks' gestation in the absence of labor	Cervical length 1.50-2.5 cm at <28 weeks' gestation AND hourglassing membranes/marked funneling	History of cervical conization procedure or loop electro-excision procedure

Manuck. The clinical phenotype of spontaneous preterm birth. Am J Obstet Gynecol 2015. *(continued)*