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Screening for spontaneous preterm birth and resultant therapies to reduce neonatal morbidity and mortality: A review

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A B S T R A C T

Despite considerable effort aimed at decreasing the incidence of spontaneous preterm birth, it remains the leading cause of perinatal morbidity and mortality. Screening strategies are imperfect. Approaches used to identify women considered by historical factors to be low risk for preterm delivery (generally considered to be women with singleton pregnancies without a history of a previous preterm birth) as well as those at high risk for preterm birth (those with a previous preterm birth, short cervix, or multiple gestation) continue to evolve. Herein, we review the current evidence and approaches to screening women for preterm birth, and examine future directions for clinical practice. Further research is necessary to better identify at-risk women and provide evidence-based management.

1. Introduction

Preterm birth (PTB) continues to be one of the leading causes of perinatal morbidity and mortality worldwide [1–3]. The majority (two-thirds) of PTB cases are attributed to spontaneous PTB (SPTB); the remaining one-third are medically indicated, due to maternal or fetal complications [4]. SPTB is classically defined as birth between $20^{0/7}$ and $37^{0/7}$ weeks gestation following the spontaneous onset of labor, preterm prelabor rupture of membranes, or premature dilation of the cervix (cervical insufficiency) [5]. Recently, however, some experts have recognized that some spontaneous deliveries late in the mid-second trimester (e.g. $16^{0/7}$ to $19^{6/7}$), classically considered to be miscarriages, may also be SPTB due to similarities to classical SPTB with regard to risk factors, presentation, and recurrence. Infants born preterm require prolonged hospitalizations and are at high risk of adverse outcomes, including respiratory difficulty, neurodevelopmental sequelae, necrotizing enterocolitis, feeding difficulties, blindness, deafness, and intraventricular hemorrhage. Preterm infants are also at a higher risk of death both during the neonatal period and up to age five years when compared to infants delivered at term [2,6]. Hence, the health needs of premature infants can be extensive and lifelong, both for the family and society as a whole, and PTB constitutes a major public health problem.

Roughly 11% of infants worldwide are born preterm; of these, the majority of cases occur in low-income countries [7]. PTB continues to be one of the most common pregnancy-related complications in the USA. Though the rate of preterm birth declined modestly in the USA from 2008 to 2014 to 9.57%, this rate rose between 2014 and 2015 to 9.63% [8]. This recent rise was most significant among non-Hispanic black women – a group with an already substantially higher rate of PTB compared to other races. Despite its overall recent downtrend, the rate of PTB remains high, and neonatal and infant mortality associated with PTB and subsequent low birth weight is estimated at 104.6 infant deaths per 100,000 in 2014 in the USA alone [1].

Given the significant societal implications of PTB in the USA and worldwide, considerable attention has been placed on identifying those women at highest risk, focusing on SPTB because it constitutes the majority of premature deliveries. Unfortunately, SPTB is a heterogeneous condition, with multiple underlying etiologies. The greatest risk factor for SPTB is a history of previous SPTB. However, beyond this, due to the heterogeneity of the condition and variety of underlying etiologies and risk factors, the prediction of PTB is challenging. Known epidemiologic risk factors for SPTB, along with the odds of PTB based on each risk factor, are shown in Table 1 [4,9,10]. Though some demographic and baseline patient characteristics provide insight into women that may benefit from closer surveillance, maternal history and historical risk factors traditionally have poor efficacy at identifying women destined to deliver preterm [21]. The objective of this review is to evaluate the current

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Table 1
Risk factors associated with spontaneous preterm birth.

Risk factor	RR for PTB <37 weeks gestation (95% CI as applicable)	Ref.
Previous preterm birth of a singleton gestation	2.62 (1.99–3.44)[a]	[11]
Short interpregnancy interval (<6 months)	1.40 (1.24–1.58)	[12]
Underweight pre-pregnancy BMI	1.32 (1.10–1.57)	[13]
Low socio-economic status	1.66 (1.06–2.61)	[11]
Non-Hispanic black race	1.68 (1.06–2.67)	[11]
Congenital uterine malformation – canalization defects (e.g. uterine septum)	2.14 (1.48–3.11)	[14]
Congenital uterine malformation – unification defects (e.g. unicornuate, bicornuate)	2.97 (2.08–4.23)	[14]
Maternal smoking	1.27 (1.21–1.33)	[15]
Cocaine abuse	3.53 (1.65–7.56)	[16]
Opioid abuse	2.86 (1.11–7.36)	[16]
Family history of PTB	1.35 (1.12–1.63)[b]	[17,18]
Pregnancy-specific risk factors		
Shortened mid-trimester cervical length <2.50 cm	6.9 (4.3–11.1)[c]	[19]
Placental abruption or vaginal bleeding in the first or second trimester	1.62 (1.22–2.17)	[11]
Carriage of male fetus	1.51 (1.02–2.24)[b]	[20]

RR, relative risk; PTB, preterm birth; CI, confidence interval; BMI, body mass index.
[a] Risk depends on other factors that cannot be characterized in the table, such as number of prior preterm births and gestational age of previous preterm births.
[b] Data presented are odds ratios (95% CI).
[c] For preterm birth <35 weeks gestation.

literature surrounding screening modalities for prediction of SPTB in singleton pregnancies. Screening for PTB in multiple gestations encompasses different underlying pathophysiology and is therefore outside the scope of this article. Early detection of pregnancies at highest risk for SPTB may hold promise in the implementation of therapeutic management options and secondary prevention of morbidities associated with SPTB.

2. Current methods of screening for preterm birth

2.1. Ultrasonographic cervical length assessment

A short mid-trimester cervical length is one of the strongest risk factors for SPTB, as studies have consistently shown that the risk of SPTB is inversely proportional to the length of the cervix (Fig. 1) [11,22]. Transvaginal ultrasound measurement of cervical length is safe, reliable, and highly reproducible when performed by trained providers [23]. Formal training and certification is available through several online educational programs (e.g. the Perinatal Quality Foundation's Cervical Length Education and Review (CLEAR) program (https://clear.perinatalquality.org/), the Fetal Medicine Foundation's cervical assessment certificate of competence, and others [24]). Though proponents of transvaginal ultrasound argue that this approach more accurately identifies a short cervical length compared with transabdominal ultrasound [25,26] and that image quality does not vary with fetal position and maternal body habitus [24,27,28], others argue that a two-step approach where the cervix is visualized transabdominally first and transvaginal cervical length is performed only if it appears <30 or 35 mm may also be adequate [29].

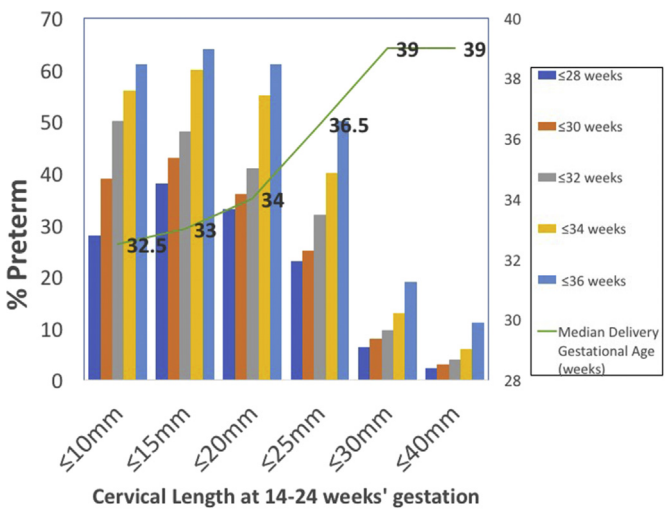

Fig. 1. Proportion of women delivering preterm at various gestational age cut-offs according to the mid-trimester cervical length (based on $n = 6877$ women) [12].

In the mid-trimester (16–24 weeks gestation), a transvaginal cervical length <25 mm is considered "short," as 25 mm corresponds to the 10th percentile for this gestational age [22]. Even among women who have a "normal" cervical length, the risk of SPTB remains inversely proportional to the length of the cervix in mid-pregnancy. Mercer et al. estimated that for each increase of 1 mm in the length of the cervix, the odds for SPTB was 0.91 (RR: 0.89–0.93) [11]. Furthermore, the risk of SPTB is higher if the cervix is found to be short earlier in pregnancy (e.g. a short cervix first detected at 18 weeks gestation carries a higher risk for SPTB compared with a short cervix first detected at 22 weeks gestation). Ultimately, the risk of SPTB in the setting of a short cervical length depends on the a-priori risk of SPTB. The risk is therefore highest among those with a prior SPTB and a short cervix [30]; this combination confers a relative risk for SPTB of 3.3 [31]. By contrast, in women without a prior SPTB, the risk is lower, but still significant.

Because the resultant risk for SPTB if a short cervical length is detected differs by pregnancy history, cervical length screening recommendations set forth by professional societies also differ based on these baseline characteristics. In women with a prior SPTB <37 weeks gestation, both the Society for Maternal–Fetal Medicine and the American College of Obstetricians and Gynecologists recommend screening with serial cervical length from $16^{0/7}$ to $24^{0/7}$ weeks gestation. Unfortunately, evidence is conflicting regarding the utility, feasibility, and cost-effectiveness of universal transvaginal cervical length screening in low-risk populations. Though many institutions have implemented universal cervical length screening protocols, evidence regarding the effectiveness of this approach continues to evolve.

Most recently, Esplin et al. [32] reported results from a multicenter, prospective observational cohort that included 9410 nulliparous singleton pregnancies. Transvaginal cervical length assessments were performed twice, at least 4 weeks apart, between

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