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Review

Risk assessment and management to prevent preterm birth

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SUMMARY

Preterm birth is the most important cause of neonatal mortality and morbidity worldwide. In this review, we review potential risk factors associated with preterm birth and the subsequent management to prevent preterm birth in low and high risk women with a singleton or multiple pregnancy. A history of preterm birth is considered the most important risk factor for preterm birth in subsequent pregnancy. General risk factors with a much lower impact include ethnicity, low socio-economic status, maternal weight, smoking, and periodontal status. Pregnancy-related characteristics, including bacterial vaginosis and asymptomatic bacteriuria, appear to be of limited value in the prediction of preterm birth. By contrast, a mid-pregnancy cervical length measurement is independently associated with preterm birth and could be used to identify women at risk of a premature delivery. A fetal fibronectin test may be of additional value in the prediction of preterm birth. The most effective methods to prevent preterm birth depend on the obstetric history, which makes the identification of women at risk of preterm birth an important task for clinical care providers.

1. Introduction

Preterm birth, defined as delivery before 37 weeks of gestation, is an important complication of both singleton and multifetal pregnancies worldwide. Children born preterm are at increased risk of mortality and are more likely to have long-term neurological and developmental disorders than those born at term. The incidence of preterm birth varies between countries with a range of 5–13%, resulting in 15 million preterm deliveries worldwide each year. More than 60% of all preterm births occur in Sub-Saharan Africa and South(-eastern) Asia. The highest rates are found in South-eastern and South Asia where 13.4% of the children are born preterm. The preterm birth rate in Europe ranges from 5% to 10%, where relatively low rates are observed in Scandinavian countries and relatively high rates occur in Cyprus and Hungary. Of the 1.2 million preterm births that occur in high income countries, more than 0.5 million (42%) occur in the USA where the estimated preterm birth rate is 11–12% [1].

Mortality and morbidity rates of babies born preterm increase with decreasing gestational age. The worldwide incidence of preterm birth at <32 weeks is 16% of all preterm births. Although survival rates have greatly improved in recent years for children born very (<32 weeks) and extremely (<28 weeks) preterm, mortality and morbidity are highest among these children, especially in low income countries. Mortality and morbidity rates in late preterm births (32–37 weeks) are less pronounced, though they remain substantial compared to rates in children born at term.

The identification of women at risk is important, as several treatment strategies have been effective in the reduction of spontaneous preterm birth. For an accurate risk assessment, several factors may be taken into account including general risk factors, obstetric history and specific pregnancy-related risk factors (Table 1). This article aims to review potential risk factors associated with preterm birth and the subsequent management to prevent preterm birth in both low and high risk singleton and multiple pregnancies.

2. Risk factors

2.1. General

2.1.1. Maternal characteristics

Ethnicity, socio-economic status, and body mass index (BMI; kg/m^2) all seem to be associated with poor pregnancy outcome including preterm birth.

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Table 1
Risk factors for preterm birth and possible interventions.

	Risk factor	Intervention
Maternal characteristics	Low socio-economic status	Information
	Ethnicity	Information
	Smoking	Stop smoking
	Low body mass index	Lifestyle, nutrition information
	Periodontitis	Referral to dentist
Medical history	Cervical surgery (LEEP/conization)	Information
	Uterus anomaly	Information
Obstetrical history	Preterm birth	Progesterone
	Pregnancy loss >16 weeks GA	Progesterone
	Cervical insufficiency	History indicated cerclage (singletons)
Current pregnancy	Mode of conception (in-vitro fertilization)	Information
	Multiple pregnancy	Information
	Short cervix in women without a history of PTB (singleton and twin pregnancies)	Progesterone or pessary
	Short cervix in women with a history of PTB (singleton pregnancies only)	Ultrasound-indicated cerclage (or pessary)

LEEP, loop electrosurgical excision procedure; GA, gestational age; PTB, preterm birth.

Several studies report a positive association between certain ethnic groups and preterm birth. Women classified as African and Afro-Caribbean are considered to be at high risk for preterm birth (odds ratio (OR): 2.0; 95% confidence interval (CI): 1.8–2.2) when compared to Caucasian women as well as women of low socio-economic and low educational status [2,3]. It should not be excluded that the physiological duration of pregnancy in women of different ethnicities is different, and that African and Afro-American women have a shorter duration pregnancy. Indeed, preterm children from Afro-Caribbean women do better when born preterm as compared to women from other ethnicities [4].

Furthermore, as compared to normal-weight women, higher preterm birth rates are observed in women with both low BMI (OR: 1.35; 95% CI: 1.14–1.60) and in overweight and obese women (1.26; 1.15–1.37 for BMI 25–30). The higher the BMI, the higher the risk, especially for extreme preterm birth (1.58; 1.39–1.79 for BMI 30–35; 2.01; 1.66–2.45 for BMI 35–40; and 2.99; 2.28–3.92 for BMI ≥40) [5]. The mechanism by which these maternal demographics are related to preterm birth remain unclear.

In addition to these general maternal characteristics, it is known that singleton pregnancies after in-vitro fertilization (IVF) are at increased risk of preterm birth (risk ratio (RR): 2.13; 95% CI: 1.26–3.61) [6]. Additionally, previous studies indicate that either a short or a long interval between pregnancies is associated with adverse perinatal outcomes, including preterm birth; however, whether this association is confounded remains unclear [7,8].

2.1.2. Medical history

Maternal periodontal disease is associated with preterm birth (RR: 1.6; 95% CI: 1.1–2.3), and the risk seems to increase when periodontal disease progresses during pregnancy, potentially due to haematogenous transmission of oral microbial pathogens and release of inflammatory mediators and prostaglandins into the maternal circulation [9].

Cervical surgery after cervical intraepithelial neoplasia (CIN) is also associated with preterm birth. Various studies have shown that the increased risk is due to the cervical surgery, especially when performed during pregnancy, and does not seem to be related to the neoplasia itself [10,11]. Castanon et al. observed that large excisional treatment (>15 mm) of cervical transformation zone is associated with a doubling of the risk of preterm birth (RR: 2.04; 95% CI: 1.41–2.96). This risk does not decrease with increasing time to conception. This implies that all women who have had cervical surgery with large excisions of the cervical transformation zone should be closely monitored during pregnancy [12].

2.1.3. Smoking

Smoking is strongly related to preterm birth (OR: 3.21; 95% CI: 1.42–7.23) and this risk is directly correlated to the number of cigarettes smoked per day [13]. It has been hypothesized that smoking is associated with a systemic inflammatory response, leading to preterm birth. The association between smoking and preterm birth appears to be stronger for very preterm birth (<32 weeks) than for moderate preterm birth (≥32 weeks) [14].

Previous studies report that 20–40% of smokers quit smoking during pregnancy; of those, the majority quits early in pregnancy. Women with low education, women who started smoking at a young age, heavy smokers, women exposed to passive smoking, and multiparous women are more at risk for continued smoking during pregnancy [14].

The assessment of risk factors varies between different pregnancy populations. In this review we discuss the following subgroups: low risk pregnancies, i.e. women with a singleton pregnancy without a history of preterm birth; and high risk pregnancies, i.e. women with a multiple pregnancy and women with a history of preterm birth.

2.2. Low risk pregnancies

2.2.1. Women with singleton pregnancy without a history of preterm birth

2.2.1.1. Bacterial vaginosis. Bacterial vaginosis is an abnormal vaginal condition that results from an overgrowth of atypical micro-organisms in the vagina, including *Gardnerella vaginalis*, *Prevotella* spp., *Bacteroides* spp., *Mobiluncus* spp., Gram-positive cocci, and genital mycoplasma [15]. The presence of at least three of the following four criteria is considered to be consistent with the presence of bacterial vaginosis: vaginal pH >4.5, clue cells on saline wet mount, release of a fish amine odour on addition of 10% KOH to a drop of vaginal discharge, and abnormal vaginal discharge [16]. A scoring system of vaginal smears to diagnose bacterial vaginosis was described by Nugent et al., in 1991. The Nugent score is based on a weighted combination of the different micro-organisms on wet mount, ranging from 0 to 10 [17].

A meta-analysis from 2003, which included 18 studies and 20,232 low risk singleton pregnancies showed that bacterial vaginosis during pregnancy is associated with an increased risk of miscarriage (RR: 9.91; 95% CI: 1.99–49.34) and preterm birth (2.19; 1.54–3.12) [18].

2.2.1.2. Asymptomatic bacteriuria. Asymptomatic bacteriuria is defined as the presence of significant bacteriuria without symptoms of a urinary tract infection, occurring in 5–10% of pregnancies