Chapter 2

Individualizing the risk for preterm birth; an overview of the literature

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Abstract

Preterm birth is the most important cause of perinatal morbidity and mortality worldwide and ranks among the top 10 of global causes of burden of disease. Since treatment of threatened preterm delivery has limited effectiveness, the focus is on primary and secondary prevention.

Identification of risk indicators in early pregnancy provides the opportunity for preventive measures. To determine the potential impact of individualised risk indicators on the prediction of preterm birth, we reviewed the literature on this topic.

Risk indicators for spontaneous preterm birth can be categorized in five groups; characteristics of the individual (ethnicity/race), characteristics of the fetus (fetal gender, fetal number and chorionicity), obstetric history (history of preterm birth), modifiable risk indicators (social status, life style, infection), and signs of early labour; potential predictors (sonographic markers, biomarkers). Risk for preterm birth can be seen as a continuous transition from one state to the other. The number of studies that integrate these data is limited.

2

Introduction

Preterm birth is the most important cause of perinatal morbidity and mortality in obstetric practice[1]. Preterm birth is traditionally defined as a delivery that occurs before 37 completed weeks of gestation. The preterm birth rate has been reported as an estimated 14.9 million, 11.1% of all live births worldwide, ranging from approximately 5% in some European countries to 18% in several African countries. More than 60% of preterm births take place in south Asia and sub-Saharan Africa, where 52% of the global live births take place. Preterm birth also affects developed countries, USA, for instance is one of the ten countries with the highest numbers of preterm births[2]. 45–50% of preterm births worldwide are estimated to be idiopathic, 30% are related to preterm prelabour rupture of membranes (PPROM) and another 15–20% are ascribed to medically indicated or elective preterm deliveries[3]. Its impact on public health has resulted in broad attention to this topic in scientific research. Preterm birth was recently ranked in the top 10 causes of global burden of disease, justifying its reduction to become a main goal of the global community[4]. Treatment of threatened preterm birth has limited effectiveness, as antenatal administration of corticosteroids is the only intervention proven to improve neonatal outcome[5]. Since prevention seems to be more effective than treatment, the medical world is searching for tools to identify women at risk for spontaneous preterm birth. Several prediction models have been proposed including variables such as maternal indicators, for instance age, anthropometry and medical history, pregnancy characteristics like vaginal bleeding, markers early in pregnancy by physical examination and biological markers to predict spontaneous preterm birth. Although these predictive indicators are usually not classified, we hypothesize that their origin and nature is clearly different. Some indicators are a non-modifiable characteristic of the woman (including ethnicity and medical and obstetric history) or the fetus (including fetal gender, fetal number and chorionicity). Other indicators are modifiable, including smoking, ovarian stimulation, number of embryos transferred, life style and infection. Finally, indicators which are essentially signs of early labour and among which a short cervical length and fetal fibronectin, should be considered. Preterm birth can be the result of three obstetrical circumstances: 1) preterm labour with intact membranes; 2) preterm prelabour rupture of membranes (PROM); and 3) 'indicated' preterm birth, which occurs when maternal or fetal indications require delivery before 37 weeks of gestation[6]. The aim of the current manuscript is to provide an overview of current knowledge on risk indicators for

spontaneous preterm birth (1,2), defined as delivery before 37 weeks in singleton pregnancies. Since the multitude of different risk indicators makes it impossible to discuss them all, we decided to make a selection of risk indicators, based on their importance stated in current literature. We subsequently categorized risk indicators into characteristics of the individual women, fetal characteristics and obstetric history as well as modifiable indicators (infection socio-economic status) and signs of early labour; potential predictors. Our general approach was not to repeat searches of the literature, but rather aim to complete existing reviews and discuss the literature from the perspective of impact of individualized risk indicators.

Characteristics of the individual woman

Ethnicity/race
Sheaf *et al*. recently reviewed the literature on ethnic and racial disparities in the risk of preterm birth[7]. Ethnic/racial disparities in the risk of preterm birth were clearly pronounced among black women. Black ethnicity/race was associated with an increased risk of preterm birth when compared with whites (range of adjusted odds ratios [OR]: 0.6–2.8; pooled OR: 2.0; 95% CI: 1.8–2.2). For an overview of associations between different risk indicators and preterm birth see Table 1.

Table 1. Overview of associations between different risk indicators and preterm birth expressed in Risk Ratio's

Risk indicators	Risk Ratio	95% Confidence Interval
Black ethnicity	2.0[*1]	1.8 - 2.2
Body mass index	0.96	0.66 - 1.4
Pregnancy weight gain	1.8	1.5 - 2.3
Short maternal height	1.8	1.3 - 2.5
History of SPTB[*2]	3.6[*1]	3.2 - 4.0
Bacterial vaginosis	2.2[*1]	1.5 - 3.1
Asymptomatic bacteriuria	1.1[*1]	0.8 - 1.5
Periodontitis	1.6	1.1 - 2.3
Low socio-economic status	1.9	1.7 - 2.2
Cervical length	2.9	2.1 - 3.9
Fetal Fibronectin	4.0	2.9 - 5.5
Chlamydia	2.2	1.0 - 4.8

[*1] Associations are Relative Risks or Odds Ratio's [*2] Spontaneous preterm birth

For Asian and Hispanic ethnicity/race, there was no significant association with the range of adjusted ORs being 0.6–2.3 and 0.7–1.5, respectively. When considering the above risk assessments, one should realize that these were based on traditional definitions of preterm birth, in other words, delivery before 37 weeks, and that those curves of normalcy were constructed on populations with predominantly Caucasian women. Both the distribution of duration of pregnancy and the consequences of preterm birth in black women differ from those in Caucasian women. This was demonstrated by another recent paper of Schaaf *et al.* showing that subsequent odds of adverse neonatal outcome were significantly lower for children born from African women (OR: 0.51; 95% CI: 0.41–0.64) than for European whites[8]. The majority of studies described in this review where from the USA, concerning African-Americans and Africans. In addition, the risk of preterm birth was reduced in African black and South and Central American black women compared with non-Hispanic American black women. These data indicate that black women with an identified non-US family ancestry and/or foreign-born maternal nativity have significantly lower risk of preterm birth as compared with American black women[9].

BMI

In a systematic review published in 2005, Honest *et al.* found pre-pregnancy BMI (<20, 20–30 and >30 kg/m^2) to be a poor predictor of preterm birth before 37 weeks' gestation (likelihood ratio (LR): 0.96–1.75) as were pregnancy weight gain (LR: 1.8; 95% CI: 1.5–2.3) and short maternal height <25% quartile of the population or below 152 cm (LR: 1.8; 95% CI:

1.3–2.5). The review showed that routine antenatal maternal anthropometric measurements were not useful in predicting the risk of preterm birth before 37 weeks' gestation[10].

Cnattingius *et al.* found the risk of spontaneous extremely preterm delivery to be increased with BMI among obese women (BMI ≥30) in Sweden. The risk of extreme preterm delivery between 22 and 27 week of gestation with a BMI of 40 or greater was 0.52% (OR: 3.0; 95% CI: 2.28–3.92)[11].

Fetal characteristics

Fetal gender

Epidemiologic studies have shown that pregnancies carrying a male fetus have a higher incidence of preterm birth, and this male-female difference is more prominent in early preterm birth[12].

Fetal number & chorionicity

Multiple gestations result in 15–20% of all preterm births. Nearly 60% of twin are born preterm. Using the data from National Centre for Health Statistics, about 50% of preterm births were indicated; one-third of the births were spontaneous and 10% of the births occurred after preterm premature rupture of the membranes (PPROM)[13]. Of twin gestations with symptoms of preterm labour, about 22–29% of the pregnancies will deliver within 7 days[13]. Nearly all higher multiple gestations will result in preterm delivery. Uterine over distension, resulting in contractions and PPROM, is believed to be the causative mechanism for the rate of increased spontaneous preterm births[14]. The dichorionic triamniotic triplets have a higher risk of delivery at <30 weeks of gestation (OR: 4.6; 95% CI: 1.6–11.8) compared to trichorionic triplets. The dichorionic triamniotic triplets have a 5.5-fold higher risk of adverse perinatal outcome predominantly because of twin–twin transfusion syndrome and premature rupture of membranes (PROM), followed by spontaneous preterm birth[15].

Obstetric history

A history of preterm birth stands out as one of the most important historical risk indicators for subsequent preterm birth. Although our search did not show any reviews about history of preterm birth as an individual risk indicator, there is consensus about the impact of a history of preterm birth, with a doubled risk of renewed preterm birth after an earlier preterm birth[16]. Women with early spontaneous preterm births (i.e., <32 weeks) are far more likely to have recurrent spontaneous preterm births, indicating a dose-response effect (OR: 3.6; 95% CI: 3.2–4.0)[17–19]. The frequency of pregnancies complicated by PROM is 2–3.5%, but account for 30–40% of preterm deliveries and therefore a leading clinically identifiable cause of preterm birth[6]. Several investigators confirmed the high recurrence rate of preterm PROM; Mercer *et al,* described that among multiparous women, a previous preterm birth due to preterm PROM was the primary risk factor for preterm PROM in a subsequent pregnancy[20]. In addition, prior spontaneous preterm delivery caused by PPROM and preterm labour is significantly associated with similar outcomes in the current gestation[17]. The mechanism responsible for the association spontaneous preterm delivery and PPROM has not been elucidated. However, it is likely that persistent or recurrent intrauterine infections as a result might explain the increased risk of recurrence of spontaneous preterm births. Goldenberg *et al.* examined the free membranes, umbilical cord and chorionic

plate of placentas from women after spontaneous preterm birth and described an acute inflammation in 74%[17]. In addition, women with indicated preterm births following induced labour or caesarean section before the term date on maternal or fetal indication tend to repeat such births,[17,18] and are also at increased risk of spontaneous preterm birth. The later might be explained by the presence of risk indicators such as maternal age or maternal ethnicity, that contributed both to the need of medical intervention in the first pregnancy and to the pathogenesis of spontaneous preterm birth in the next pregnancy[21]. The underlying disorder and its severity of causing indicated preterm births, such as pre-eclampsia, hypertension or haemolysis, elevated liver enzymes, low platelets (HELLP) syndrome, frequently persists between pregnancies (OR: 7.8; 95% CI: 6.7–9.0) and is responsible for the rate of recurrence[22,23].

Modifiable indicators

Infection
Infection is thought to be one of the primary biologic pathways leading to preterm birth[23]. The risk of preterm birth is increased in specific infections such as bacterial vaginosis, chlamydia trachomatis and asymptomatic bacteriuria (ASB). In a systematic review Leitich *et al.* reviewed the literature and found bacterial vaginosis to double the risk of preterm birth
(OR: 2.2; 95% CI: 1.5–3.1)[24]. Abnormal genital tract flora at 26–32 weeks gestation is associated with a doubled preterm birth risk (OR: 1.4–2), whereas abnormal genital tract flora at 7–16 weeks gestation is associated with a fivefold increased risk (OR: 5–7.5)[25]. Genitourinary infection with chlamydia is also associated with preterm birth (OR: 2)[26].
The relationship between ASB and preterm birth is controversial; in a large cohort study no association was found between spontaneous preterm birth and ASB (OR: 1.07; 95% CI: 0.78–1.46)[27]. A Cochrane review on the effectiveness of antibiotic treatment for ASB failed to show a significant reduction of preterm delivery with the use of antibiotics (OR: 0.37; 95% CI: 0.10–1.36)[28]. A short cervix may predispose to ascending intrauterine infection by shortening the distance between microorganisms in the lower genital tract and chorioamniotic membranes. Vaisbuch *et al.* found women with a mid-trimester having a short cervical length have intra-amniotic inflammation. The risk of preterm delivery within seven days for these patients is 40%[29]. The sonographic finding of amniotic fluid 'sludge' (dense

aggregates of particulate matter in the amniotic fluid close to the internal cervical os) is associated with microbial invasion of the amniotic cavity, chorioamnionitis in patients with spontaneous preterm labour and intact membranes[30]. The presence of maternal periodontal disease is associated with an increased risk of preterm birth. In a review, 18 out of 25 studies showed a significant association between periodontal disease and increased risk of adverse pregnancy outcome (OR: 1.10–20.0)[31]. The mechanism through which periodontitis is thought to increase preterm birth remains uncertain. It is suggested that either by causing low-grade bacteremia, which lodges in the decidua, chorion and amnion or by releasing endotoxin into the maternal circulation, which triggers intrauterine inflammation and preterm birth or by releasing cytokines and other inflammatory products, which then triggers preterm birth. Meta-analysis found that periodontal treatment significantly lowered preterm birth (OR: 0.65; 95% CI: 0.45–0.93) and low birth weight (OR: 0.53; 95% CI: 0.31–0.92) rates while there was a non-significant difference for stillbirth (OR: 0; 95% CI: 0.43–1.2)[32]. The pathway through which different kinds of infections are related to preterm birth remains unclear. Several hypothesis about the infection pathway have been proposed, including ascending infection from the vagina to the uterus leading to intra-amniotic infection, haematogenous infection through the placenta, retrograde spread through the fallopian tubes or iatrogenic introduction of infections at the time of invasive procedures, causing intra-uterine infection leading to preterm birth[22]. Intra-amniotic infection is a clear risk for preterm birth, treatment of intra-amniotic infection has not yet been established so prevention of intra-amniotic infection is paramount. Prevention of infections in the lower genital tract are most likely associated with improved pregnancy outcomes by reducing intra-amniotic infection rates. Systemic increase of inflammatory mediators by infections such as periodontitis may raise the amount of inflammatory mediators like PGE2 and cytokines and cause preterm birth in this way[33].

Socio-economic status
Published estimates of the incidence of preterm birth from around the world have been affected by a variety of indicators, such as the method of assessment of gestational age, the completeness of birth registrations and policies on the viability of extremely preterm births and their documentation. Smith et al., studied socio-economic status and preterm birth in the UK from 1994 until 2003 in a cohort of 7185 births. The maternal deprivation status defined by a multidomain measure based on census and administrative data concerning seven domains including

income, employment, health deprivation and disability, education skills, barriers to housing, crime and living environment. They found that the women from the most deprived decile were at nearly twice the risk of very preterm birth compared to those from the least deprived decile (risk ratio [RR]: 1.9; 95% CI: 1.7–2.2)[34]. Other modifiable risk indicators associated with socio-economic status, for example, nutritional status, risk of infection are also involved in the aetiology of preterm birth.

Signs of early labour; potential predictors

In the previous paragraphs, we have described risk indicators for preterm birth that are present before the occurrence of preterm labour. In our opinion, some risk indicators that are observed before the moment that clinical symptoms of preterm birth become apparent, are in fact signs of the onset of labour, instead of an independent indicator.

Sonographic markers; cervical length

Shortening of the cervix is predictive of preterm birth. A short cervix, generally defined as a cervix <3.0 cm observed in second trimester transvaginal ultrasonography, doubles the risk of preterm birth (RR: 2.0; 95% CI: 1.2–3.3)[35]. The risk of preterm birth increases as cervical length decreases, and for each increase of the cervical length by 1 mm, the risk of preterm birth decreases (RR: 0.91; 95% CI: 0.89– 0.93) [35]. Similarly, the shorter the cervical length cut-off, the higher the likelihood ratio (LR) for preterm birth. At a cut-off value of 25 mm, the LR was 2.9 (95% CI: 2.1–3.9) at 20–24 weeks gestation[36]. Cervical insufficiency caused by congenital cervical weakness, surgery or trauma has been implicated as causal for some preterm births preceded by short cervical length; however, distinguishing cervical insufficiency from cervical shortening attributable to other causes has proven difficult, and the exact contribution of each individual cause to preterm birth is unknown[37]. Other causes for preterm birth preceded by short cervical length are intra-amniotic infection and PPROM[29]. A short cervix at an early gestational age increases the risk of preterm birth[38]. As stated, the question remains whether cervical length is in itself a risk indicator for preterm birth or if a short cervical length is just a first sign of preterm labour. If the latter proves true, serial cervical length measurements showing a shortening of cervical length might be more valuable in the prediction of preterm birth than a single measurement at 20 weeks of gestation. Short cervical length was mentioned here in the section; signs of early labour, because of our hypothesis that it might be a symptom instead of an indicator. This does not take

away the knowledge that short cervical length is modifiable by progesterone as shown by Meis *et al.*, da Fonseca *et al.* and Hassan *et al.*[39–41].

Biomarkers associated with increased preterm birth risk

One of the most investigated biomarker predicting preterm birth identified to date is fetal fibronectin. The presence of this glycoprotein in cervicovaginal secretion is a marker of choriodecidual disruption[42]. Usually, fetal fibronectin is absent from cervicovaginal secretions from 24 weeks' gestation until near term. However, in a study by Goldenberg *et al.* 3–4% of women undergoing routine screening at 24–26 weeks' gestation tested positive, and these women had a substantially increased risk of preterm birth[42,43]. A positive cervical or vaginal fetal fibronectin test at 22–24 weeks predicted more than half of the spontaneous preterm births at <28 weeks (sensitivity: 0.63)[42]. The relative risk for a positive fetal fibronectin test versus negative test was 59. The specificity in this study was 96–98%, whereas the positive predictive value rose from 13–36% as the gestational age at which preterm birth occurred increased from <28 to <37 weeks. Compared with a negative fetal fibronectin test the relative risk for spontaneous preterm birth after a positive fetal fibronectin test varied substantially by testing period and by the definition of spontaneous preterm birth, but always remained >4 and statistically significant. Other studies among asymptomatic women with a positive fibronectin also confirmed an increased risk of preterm birth before 34 weeks' gestation (pooled LR: 4.0; 95% CI: 2.9–5.5). The corresponding summary LR for negative results was 0.78 (0.72–0.84)[44]. For clinical care, an important characteristic of the fetal fibronectin test is its negative predictive value[45]. Several meta-analyses have reported on the usefulness of single biomarkers such as fetal fibronectin, a-fetoprotein, C-reactive protein, IL-6, estriol and IGFBP-1, other systematic reviews and meta-analyses have reported lack of effectiveness of single biomarkers in preterm birth prediction[46]. Menon *et al.* made an overview of literature on biomarkers in the last four decades and reviewed 217 studies looking at a total of 116 biomarkers, concluding that there was no biomarker that stood out as a predictor for preterm birth. However, a combination of several biomarkers and clinical parameters might increase the sensitivity and specificity of biomarkers. Studies of biomarkers have enhanced the understanding of the pathways of disease leading to spontaneous preterm birth, few biomarkers have shown clinical benefit[46]. Ongoing research is performed on the aetiology specific biomarkers and panels of potential biomarkers in serum and cervicovaginal fluid[47–49].

Prediction models

In the 1970s, studies on individual risk assessment for preterm birth were first introduced. Honest et al. reviewed the literature on risk assessment tools and found 19 articles, reporting on a total of 67,390 women, evaluating 12 different risks coring systems. Quality characteristics of an ideal study, like blinding and consecutive enrolment, were often missing from the included studies, none of the studies fulfilled all criteria for a high quality study and there was substantial heterogeneity between their accuracy estimates. Birth before 37 weeks' gestation was most often used as the reference standard. The estimates for the likelihood ratios varied widely among the different studies. In asymptomatic women, predicting spontaneous preterm birth before 37 weeks' gestation with the help of risk scoring early in pregnancy has a wide range of accuracy[50]. Honest *et al.* concluded that in order to make tools that are applicable in clinical practice, there is a need for better quality information of the tools and new tools should be developed with more robust methods[50]. To *et al.* and Celik *et al.* used logistic regression methods to develop prognostic models[51,52]. These models included data on patient history as well as ultrasound results for cervical length measurements. Celik *et al.* included 58,807 women in their study cohort. Their model was based on information on only patient history and maternal characteristics (maternal age, race, height, weight, smoking status, history of cervical surgery and obstetric history) and showed areas under the receiver operating characteristic curve between 0.61 and 0.69. When cervical length was included in their model, it showed even better performance. Beta *et al.* found that addition of biomarkers did not to improve the predictive performances of their model[53]. Unfortunately previously described models for predicting preterm birth, are not ready for actual implementation in current patient care[54]. Systematic reviews have shown that test accuracy for predicting preterm birth overall is disappointing. Until now, the most important risk indicator seems to be previous preterm birth, and treatment with progestagens has found to be effective in these women[55]. A problem however is that most preterm births occur in nulliparous women, urging the need for identification of other risk indicators[56]. As several preventive strategies have been evaluated for asymptomatic women in early pregnancy including periodontal care, fish oil, progesterone and antibiotics for ASB, there is a need for better risk stratification[57].

Expert commentary

Our review of the literature indicates some important insights. First, we should distinguish modifiable risk indicators from non-modifiable indicators. The latter category can be epigenetic, but is at present influenced by race. We hypothesize that ethnicity/race is not a risk indicator, but rather an expression of a total different biology in women with different ethnicity/race. In fact, most currently developed and used curves of normalcy are based on a predominantly white population. The same applies to our definition of disease, in other words, delivery. Indeed, the risk that a black baby is harmed by a delivery at for example 36 weeks is probably different from that of a white baby. Consequently, the definition of preterm birth should be individually adjusted, but this is not yet the case. A second issue is the fact that some risk indicators are in fact early signs of the start of labour. We hypothesize, for example, that shortening of the cervix and the presence of fetal fibronectin are such early signs.

The focus of research in the area of preterm birth is shifting from finding individual risk indicators toward understanding the biological process in which all these risk indicators play a role, taking into account that biological processes differ between ethnical groups and even between males and females. Advanced technology might take research a step further towards finding the link between all individual risk indicators in epigenetic predisposition. Several risk indicators are associated with preterm birth and although it seems that many risk indicators are interrelated, for instance, infection and nutritional status play a role in socio-economic status and short cervical length, is associated with a higher risk of intra-amniotic infection[28,58]. The link has not been unravelled yet. Combining these individual risk indicators might increase insight in the aetiology of preterm birth.

Five-year view

Recently, Chang *et al.* published an article in which the trend and potential reduction in preterm birth was discussed[60]. Trends in preterm birth prevalence rates from countries, where this data were available and qualitatively good, were assessed. Subsequently they estimated the effect of interventions to reduce the preterm birth rates. The interventions consisted of smoking cessation, progesterone, cerclage, decrease in non-medically indicated caesarean delivery and induction of labour and limit multiple embryo transfer in assisted reproductive technology. For all the included countries together, a risk reduction of 0.5% was predicted, from 9.6–9.1%. This shows that even with the implementation of seemingly valid interventions

only little progress is made, emphasizing how little we now about the whole cascade involved in preterm birth. Of course, the cause of preterm birth is unlike in different areas of the world changing from multiple embryo transfer in assisted reproductive technology in the west to infection in undeveloped countries. Preterm birth complications are placed on the 8th place in the global burden of disease list. The way forward includes improved individualized classification for the causes of preterm birth, allowing for early diagnosis and better risk stratification, followed by development of new preventive interventions based on understanding of the underlying aetiology.

Key issues

- Preterm birth is the most important cause of perinatal morbidity and mortality worldwide, and ranks among the top 10 of global causes of burden of disease.
- Systematic reviews have shown that test accuracy for predicting preterm birth overall is disappointing.
- The risk indicators and indicators for preterm labour can be categorized in five groups; characteristics of the individual (ethnicity/race), fetal characteristics (fetal gender, fetal number and chorionicity) obstetric history (history of preterm birth), modifiable risk indicators (social status, BMI, infection) and signs of early labour; potential predictors (sonographic markers and biomarkers).
- Black ethnicity/race, fetal male gender are seen as risk indicators for preterm birth, one should realize, risk assessments are based on traditional definitions of preterm birth, in other words, delivery before 37 weeks, and that those curves of normalcy are made on populations
- Within majority of Caucasian women. So it is important to take into account individual biological pathways.
- Infection and socio-economic status are modifiable risk indicators for preterm birth.
- Shortening of the cervix and the presence of fetal fibronectin has been shown to be predictive of preterm birth. These indicators were seen as risk indicator but can actually be seen as first symptoms of preterm birth.
- Studies of biomarkers have improved the understanding of the mechanisms of disease leading to spontaneous preterm birth, but so far only fetal fibronectin has shown clinical usefulness.
- Previously described models for predicting preterm birth, are not ready for actual implementation in current patient care.

· Even with the implementation of seemingly valid interventions only little progress is made, in reducing the number of preterm births.
· The way forward includes improved individualized classification for the causes of preterm birth, allowing for early diagnosis and better risk stratification, followed by development of new preventive interventions based on understanding of the underlying aetiology.

Statement of contribution

MO wrote the first draft of the paper. AV, BK, MH, EP, BM and CG critically revised the manuscript for important intellectual content. All authors approved of the final version of the manuscript to be submitted.

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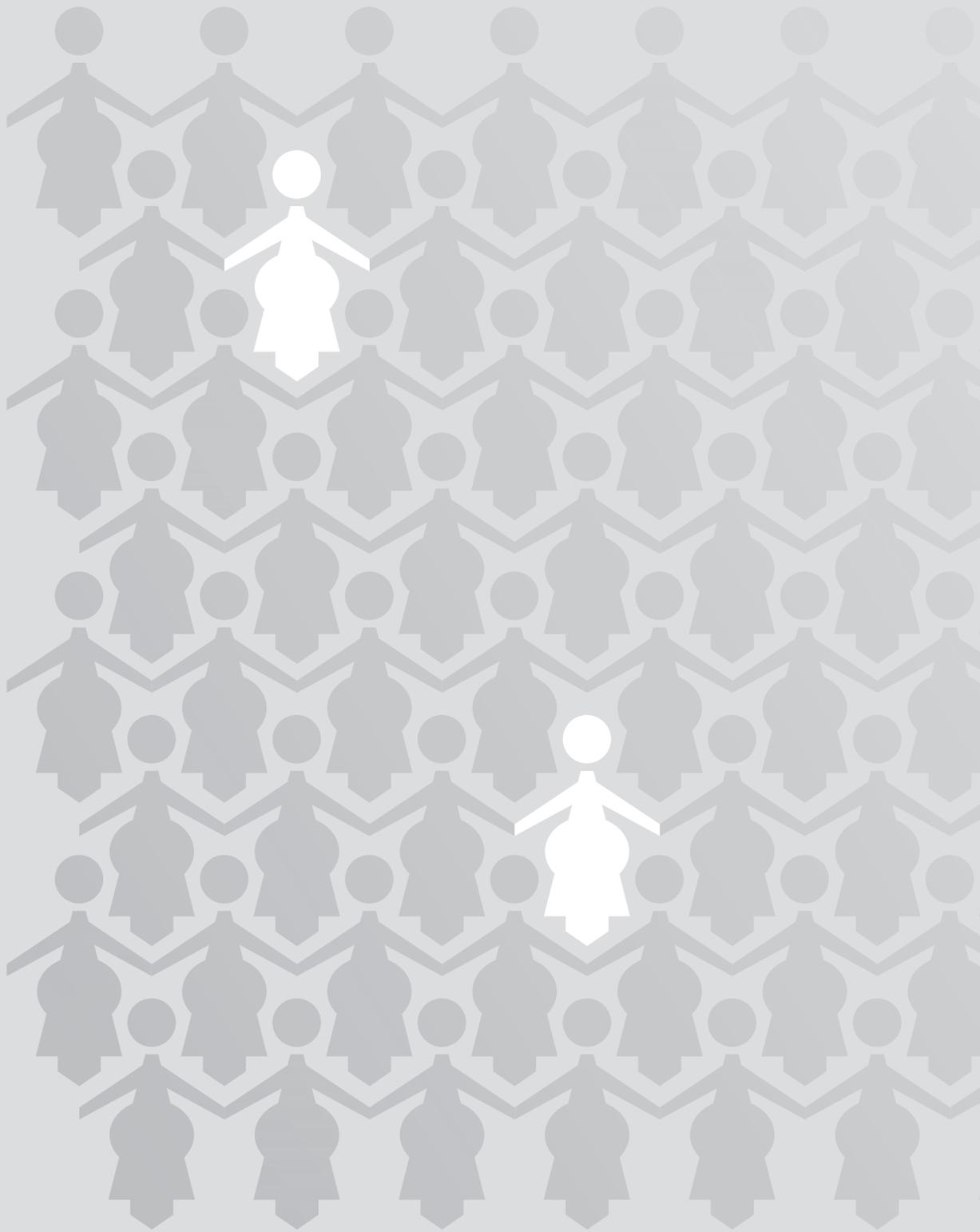
Part two:

Who is at risk for preterm birth?