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Review

Risk assessment and management to prevent preterm birth

B. Koullali [a, *], M.A. Oudijk [a], T.A.J. Nijman [b], B.W.J. Mol [c], E. Pajkrt [a]

[a] Department of Obstetrics and Gynaecology, Academic Medical Center, Amsterdam, The Netherlands
[b] Department of Obstetrics and Gynaecology, University Medical Center, Utrecht, The Netherlands
[c] Robinson Research Institute, School of Paediatrics and Reproductive Health, University of Adelaide, Adelaide, Australia

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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.

* Corresponding author. Address: Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands. Tel.: +31 20 56 61973.
E-mail address: b.koullali@amc.nl (B. Koullali).

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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

[19]. Bacteriuria is considered to be associated with obstetric complications such as preterm birth and low birth weight in low risk pregnant women in various studies [20,21]. However, a more recent prospective cohort study with an embedded randomized controlled trial (RCT) by Kazemier et al. did not confirm the association between asymptomatic bacteriuria and preterm birth in uncomplicated singleton pregnancies (OR: 1.5; 95% CI: 0.6–3.5) [22].

2.2.1.3. Cervical length. The risk of spontaneous preterm birth is increased in women with a mid-pregnancy short cervix [23–25]. In low risk singleton pregnancies with a mid-pregnancy cervical length of ≤35 mm and without any known risk factors, the risk of spontaneous preterm birth before 37 weeks of gestation is 13% (RR: 2.35; 95% CI: 1.42–3.89). This risk is inversely proportional to the size of the cervix, with a shorter cervix predicting a higher risk. Once the cervix is <26 mm the risk of preterm birth will be more than double (RR: 6.19; 95% CI: 3.84–9.97) [24]. Although a short cervical length is associated with a higher risk for preterm birth, change in transvaginal sonographic cervical length over time does not appear to be a clinically useful test to predict preterm birth [26].

Cervical length measurements can be performed by using transabdominal or transvaginal ultrasound. In contrast to transabdominal ultrasound evaluation of the cervix, transvaginal cervical ultrasonography has been shown to be a reliable and reproducible method to assess the cervical length and is the gold standard for cervical length measurement [27]. In addition, transvaginal evaluation of the cervix is safe and well accepted by women [28].

The role of mid-pregnancy screening for short cervical length in a low risk population is currently being debated while not routinely recommended [29]. Limiting cervical length screening for short cervical length to women with one or more identified risk factors decreases the number of transvaginal ultrasound examinations and increases the specificity from 62.8% to 96.5%. However, this results in nearly 40% of women with short cervix not being detected. Before the introduction of a universal screening program, it is important to be aware of potential limiting factors, such as a high number needed to screen to prevent one preterm birth [30], and the poor image qualities of many cervical length measurements. This could lead to over-diagnosis of cervical shortening and possible unnecessary interventions such as bed rest and hospitalization [31]. Developing an optimal screening and treatment program is a challenging yet important task for clinical investigators.

2.2.1.4. Fetal fibronectin. Fetal fibronectin is a glycoprotein found in amniotic fluid, membranes, and in placental tissue which is normally present in low concentrations in cervical and vaginal secretions between 18 and 34 weeks of gestation. Although its exact function is unclear, it appears to act as an adhesive glue between fetal membranes and the decidua. It is hypothesized that fetal fibronectin is released through mechanical and infection-mediated damage to the membranes or placenta prior to birth. Elevated concentrations of fetal fibronectin indicate an increased likelihood of (preterm) delivery [32], making it one of the most effective predictors of preterm birth in all pregnant populations, including low and high risk singleton and twin pregnancies, and especially in women with symptoms of preterm labour [33].

A prospective study with 2929 low risk singleton pregnancies evaluated the correlation between positive fetal fibronectin and the prediction of spontaneous preterm birth in low risk singleton pregnancies, finding an association between a positive test and preterm birth (sensitivity 63%, specificity 98%, resulting in a positive predictive value of 13%) [34]. An additional study confirmed this association, particularly in women with a short cervix [35]. Abbott et al. performed a prospective observational cohort study in which they evaluated quantitative fetal fibronectin concentration in asymptomatic women at high risk of spontaneous preterm birth. Quantitative measurement of fetal fibronectin improved the accuracy for defining risk of spontaneous preterm birth in high risk asymptomatic women [36].

2.3. High risk pregnancies

2.3.1. Women with a multiple pregnancy

As more than 50% of all women with twin pregnancies deliver at <37 weeks of gestation, women with multiple gestation contribute to 20% of all preterm births and to an even larger proportion of preterm children [37,38].

2.3.1.1. Bacterial vaginosis. In contrast to low risk singleton pregnancies, the presence of bacterial vaginosis in twin pregnancies appears not to be associated with an additional increased risk of spontaneous preterm birth. A meta-analysis performed by Conde-Agudelo et al. reported that the presence of bacterial vaginosis has very low predictive values for spontaneous preterm birth at <32, <35, and <37 weeks of gestation with sensitivities and specificities, between 0–23% and 78–92%, with corresponding likelihood ratios of positive and negative tests ranging between 0.6–1.8 and 0.9–1.2, respectively [39].

2.3.1.2. Cervical length. There are conflicting results regarding cervical length measurements and the prediction of preterm birth in twin gestations. Conde-Agudelo et al. reported in a meta-analysis that a mid-pregnancy cervical length measurement is considered as a good predictor of spontaneous preterm birth (pooled sensitivities and specificities of 39% and 96%, and likelihood ratios of positive and negative tests of 10.1 and 0.64, respectively, for preterm birth <32 weeks) [38]. In addition, various studies report that a cervical length of >35 mm in women with a twin pregnancy is associated with a low risk of 4% for preterm delivery [40,41]. In contrast, Pagani et al. showed that, despite an independent association between cervical length and preterm birth (OR: 0.94; 95% CI: 0.90–0.99), a mid-pregnancy cervical length measurement is a poor predictor of preterm birth <32 weeks in asymptomatic twin gestations [42].

A meta-analysis by Kindinger et al. showed that prediction of preterm birth in twin gestations depends on both cervical lengths and the gestational age at screening. The authors conclude that the best prediction of preterm birth ≤28 weeks is provided by screening at ≤18 weeks, and prediction of birth between 28 and 36 weeks by screening at ≥24 weeks. It is therefore recommended to screen twins ≤18 weeks for cervical length shortening [43].

2.3.1.3. Fetal fibronectin. A meta-analysis by Conde-Agudelo et al. on the accuracy of fetal fibronectin test in predicting preterm birth in 1009 asymptomatic women with twin pregnancies included a total of 11 studies and found only limited accuracy in predicting preterm birth before 32, 34, and 37 weeks of gestation (pooled sensitivities and specificities between 33–39% and 80–94%, and likelihood ratios of positive and negative tests ranged from 2.0–5.1 and 0.7–0.8, respectively) [44]. In addition, two retrospective cohort studies found similar disappointing results for the prediction of preterm birth before 32 weeks of gestation in asymptomatic women [45,46].

2.3.2. Women with a previous preterm birth

The most important risk factor for preterm birth is a previous preterm birth. Women with a history of spontaneous preterm birth are considered as high risk and they have an average risk of 20% (range: 15.8–30.2%) of recurrence of spontaneous preterm birth before 37 weeks [47]. The risk increases with a lower gestational age at index pregnancy and the number of spontaneous preterm births [48].

2.3.2.1. Cervical length. Many studies evaluating screening for short cervical length in women with a prior preterm birth have been performed. In this high risk group, a cervical length <25 mm is associated with an increased risk of preterm birth in a subsequent pregnancy (RR: 4.5; 95% CI: 2.7–7.6) [49]. Women with a previous preterm birth should be screened with serial cervical length measurements before 24 weeks of gestation, as some may benefit from interventions to prevent preterm birth when a short cervix is found [49].

2.3.2.2. Fetal fibronectin. In a prospective study by Iams et al. on predictors of spontaneous preterm birth in singleton gestations, the relationship between fetal fibronectin and recurrence rate of spontaneous preterm birth was assessed. The study compared 378 women with a prior spontaneous preterm birth before 37 weeks of gestation to 904 women without a history of spontaneous preterm birth. This study concluded that fetal fibronectin was the best single predictor in women with a history of preterm birth, with a short cervical length also contributing independently to the recurrence risk. The recurrence risk was 64% in women with a positive fetal fibronectin test and a cervical length of ≤25 mm, compared to 25% when the fetal fibronectin test was negative [25]. Romero et al. found dissimilar results in a retrospective cohort of 176 patients with a prior spontaneous preterm birth. These authors did not find a similar association between fetal fibronectin and recurrent preterm birth in patients with a history of spontaneous preterm birth (OR: 0.647; 95% CI: 0.043–9.759) [50].

There is no hard evidence endorsing the clinical value of fetal fibronectin tests in asymptomatic singleton pregnancies so far [51].

3. Risk reduction

Interventions aiming at risk reduction of spontaneous preterm birth vary between different populations, including low and high risk singleton and twin pregnancies. This section reviews preventive interventions to reduce the risk of spontaneous preterm birth.

3.1. General

3.1.1. Maternal characteristics

Clearly, ethnicity and socio-economic status are fixed characteristics, making these factors unsuitable for preventive interventions; however, this information may be of great value in providing perinatal care adjusted to an individual woman's risk profile.

For maternal overweight and obesity, there is no evidence that exercise during pregnancy reduces the risk of preterm birth [52]. Available data even suggest that insufficient gestational weight gain and gestational weight loss may increase the risk of preterm delivery (OR: 1.38; 95% CI: 1.12, 1.71). Because of this association with preterm birth, for women with a low BMI and for overweight women it is recommended not to lose weight during pregnancy [53].

The relationship between IVF and preterm birth has been demonstrated in various studies; we therefore advise performing IVF only in those women with a sound medical indication. In addition, it is recommended to perform a single embryo transfer which gives a lower rate of preterm birth compared to a double or multiple embryo transfer [6].

Various studies propose that there is a relationship between interpregnancy interval and preterm birth, suggesting that there is an optimal interval between pregnancies and that spacing pregnancies appropriately might help to prevent these adverse perinatal outcomes. The World Health Organization recommends a minimum interpregnancy interval of two years based on the available information and evidence. However, it has been hypothesized that this association is confounded by unknown maternal factors, which would counter the suggestion of an optimal interval.

3.1.2. Medical history

Whether treatment of periodontal disease decreases the risk of preterm birth remains uncertain since several studies report conflicting and inconclusive findings. An RCT from 2009 included 1087 women with periodontal disease who were randomly assigned to dental treatment or no additional care (control group) during pregnancy. This study did not find a reduction in the preterm birth rate in the treatment group (OR: 1.05; 95% CI: 0.7–1.58) [54]. In 2010, a meta-analysis found similar results and showed no difference in preterm birth when periodontal disease was treated (OR: 1.15; 95% CI: 0.95–1.40) [55]. In contrast, a meta-analysis from 2011 showed that periodontal treatment significantly decreased preterm birth (OR: 0.65; 95% CI: 0.45–0.95) [56]. A meta-analysis from 2012 did not find this association, but a subgroup analysis of women at high risk for preterm birth showed a decrease in the preterm birth rate (RR: 0.66; 95% CI: 0.54–0.80) [57]. Treatment of periodontal disease solely for the purpose of reducing the risk of preterm birth should therefore not be recommended, as results are conflicting. However, consideration of treatment after pregnancy is advisable for dental reasons.

The risk of progression of CIN to invasive cervical cancer during pregnancy is minimal and a significant number regresses spontaneously postpartum. Treatment of CIN with cervical surgery during pregnancy is associated with preterm birth and with a high rate of recurrence or persistence. Therefore, these data suggest that cervical surgery in cases of CIN should be postponed until after delivery and that the only indication for therapy during pregnancy is invasive cancer [10,58]. Furthermore, large excisional treatment should be avoided when CIN is detected during the reproductive age of a woman. It is recommended to excise the entire lesion while preserving as much healthy cervical tissue as possible [12].

3.1.3. Smoking

Since smoking is associated with an increased risk for preterm birth, all women should be advised to quit smoking before pregnancy or early in pregnancy. A prospective cohort study from 2009 examined pregnancy outcomes of 1992 non-smokers, 261 women who had stopped smoking before 15 weeks of gestation, and 251 smokers. There were no differences in preterm birth between non-smokers and women who had stopped smoking (OR: 1.03; 95% CI: 0.49–2.18). Continuing smokers had significantly higher rates of spontaneous preterm birth (OR: 3.21; 95% CI: 1.42–7.23). This study indicates that stopping smoking early in pregnancy reduces the risk of preterm birth to the level of non-smokers [13].

Potentially all the above-mentioned general risk factors are interrelated. Women of lower socio-economic status tend to have a higher BMI, appear to smoke more frequently, and will probably have worse body and dental hygiene. Thus, reduction in preterm birth may potentially be achieved by tailor-made education

programmes creating awareness not just in the general population, but more especially in the lower educated.

3.2. Low risk pregnancies

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

3.2.1.1. Bacterial vaginosis. The association of bacterial vaginosis and preterm birth resulted in the hypothesis that screening for and treatment of bacterial vaginosis might reduce the preterm birth rate. In a meta-analysis from 2011, treatment with clindamycin was associated with a significantly reduced risk of preterm birth before 37 weeks (pooled RR: 0.60; 95% CI: 0.42–0.86) [59]. On the contrary, a Cochrane review from 2013 including 21 trials reported a reduced risk of late miscarriage (RR: 0.20; 95% CI: 0.05–0.76); however, no effect on the preterm birth rate before 37 weeks of gestation (RR: 0.88; 95% CI: 0.71–1.09) was seen when asymptomatic bacterial vaginosis was treated [60].

3.2.1.2. Treatment of asymptomatic bacteriuria. In a recent study from 2015, 248 out of 4283 low risk women were screened positive for asymptomatic bacteriuria, of whom 40 were randomly assigned to treatment with nitrofurantoin and 45 to placebo. No difference in preterm birth was observed when asymptomatic bacteriuria was treated (risk difference: −0.4; 95% CI: −3.6 to 9.4) [22].

3.2.1.3. Treatment of short cervix. Many strategies and interventions to prevent preterm birth in low risk women with a short mid-pregnancy cervix have been investigated. We discuss the cervical cerclage, pessary, and progesterone.

- Cerclage. A cervical cerclage is a surgical procedure that involves occlusion of the cervix by means of a cervical suture or stitch, which is performed under general or spinal anaesthesia as proposed by Shirodkar in 1955 [61] and by McDonald in 1957 [62]. Cervical cerclage aims to give mechanical support to the cervix and to keep the cervix closed during pregnancy.
  In asymptomatic singleton pregnancies without a prior preterm birth with a short cervix of <25 mm, cerclage has not been shown to be of benefit in the reduction of preterm birth (RR: 0.76; 95% CI: 0.52–1.15) [63,64]. This was confirmed by a meta-analysis from 2010 showing no reduction in preterm birth in 344 women with an asymptomatic short cervix <25 mm [65].
- Pessary. The cervical pessary is a soft and flexible silicone device, used since 1959 in women with recurrent miscarriage [66]. Although the exact mechanism of the cervical pessary remains unknown, it has been hypothesized that the pessary relieves direct pressure on the internal cervical os by changing the position of the cervical canal and distributing the weight of the pregnant uterus [67]. Hence, it may prevent premature dilatation of the cervix and premature rupture of the membranes. Another possible mechanism is that the pessary might support the immunological barrier between chorioamnion-extraovular space and the vaginal microbiological flora [68].
  The largest RCT evaluating the effect of a cervical pessary in women with a short cervical length was the Spanish PECEP trial from 2012. In this study, 385 women with a singleton pregnancy and a cervical length of ≤25 mm at ~20 weeks of gestation were randomized either to a cervical pessary or to expectant management. This trial showed that a cervical pessary reduces the risk of spontaneous preterm birth before 37 weeks of gestation (OR: 0.19; 95% CI: 0.12–0.30), spontaneous preterm birth before 34 weeks (OR: 0.18; 95% CI: 0.08–0.37) and improves neonatal outcome (RR: 0.14; 95% CI: 0.04–0.39) [68]. A Chinese study from 2013 with 108 randomized singleton pregnancies did not reproduce these results, and did not find a positive effect of the pessary (RR: 0.96; 95% CI: 0.81–1.14) [69].
- Progesterone. It has been suggested that progesterone plays an important role in maintaining pregnancy. Progesterone has suppressive actions on the immune system and lymphocyte proliferation and activity. In addition, progesterone suppresses the activity of uterine smooth muscle to ensure maintenance of pregnancy [70,71]. Progesterone concentration in peripheral blood decreases before the onset of labour in most mammalian species, but this mechanism is not described in humans. The hypothesis of the working mechanism of progesterone is based on the cervical ripening action of progesterone antagonists, which leads to cervical shortening [72].
  A Cochrane meta-analysis from 2013 including 36 studies with a total of 8523 women shows that the use of vaginal progesterone reduces the risk of preterm birth before 34 weeks (RR: 0.64; 95% CI: 0.45–0.90) and before 28 weeks of gestation (RR: 0.59; 95% CI: 0.37–0.93) in women with a singleton pregnancy and a short cervix (<25 mm) [73]. In addition, another meta-analysis from 2012 shows a reduction in composite adverse neonatal outcome when vaginal progesterone is used in singleton pregnancies with a cervical length of ≤25 mm [74].
  The use of vaginal progesterone appears to be cost-effective when screening for short cervical length in a low risk population [75].

3.3. High risk pregnancies

3.3.1. Women with a multiple pregnancy

3.3.1.1. Cerclage. A Cochrane review from 2014 concludes that there is currently no evidence available that a cerclage is an effective intervention for preventing preterm births and improving perinatal and neonatal outcomes [76]. A meta-analysis from 2015 assessed the effect of ultrasound-indicated cerclage and found no effect on the preterm birth rate (before 37 weeks OR: 1.13; 95% CI: 0.17–8.66; before 28 weeks 1.66; 0.62–4.01) [77]. Both the Cochrane review and the meta-analysis indicate an increased rate of very low birth weight and respiratory distress syndrome in twin gestations with a short cervical length and a cerclage [76,77]. However, these results are based on limited data and large trials concerning this issue remain necessary.

3.3.1.2. Pessary. Liem et al. performed a large RCT including 808 twin gestations to assess the effect of a pessary in twin gestations. Overall the pessary did not improve neonatal outcome; however, in a subgroup of women with a cervix <38 mm (p25), neonatal outcome was improved (RR: 0.40; 95% CI: 0.19 0.83), and preterm birth rates <28 and <34 weeks were decreased in the pessary group [78]. An RCT recently performed by Goya et al. evaluated the effect of a pessary in twin pregnancies and a cervical length of ≤25 mm. A reduction in spontaneous preterm birth before 34 weeks of gestation was observed (16.2% versus 25.7%; $P < 0.0001$) [79]. Nicolaides et al. performed a trial to evaluate the effect of a pessary on twin pregnancies. No benefit was present in the reduction of preterm birth <34 weeks (RR: 1.054; 95% CI: 0.787–1.413) or neonatal outcome (RR: 1.094; 95% CI: 0.851–1.407). A subgroup analysis of women with a cervical length of ≤25 mm also showed no benefit from the cervical pessary on the preterm birth rate or neonatal outcome [80].

These conflicting results may be due to the difference in gestational age at which the pessary was inserted between the studies. In studies where the pessary was inserted at an earlier gestational age, the effect seems to be present. Future research is needed to

give more information about the optimal time and cervical length of intervention.

3.3.1.3. Progesterone. Dodd et al. concluded in a meta-analysis that there is no effect of both 17α-hydroxyprogesterone caproate and vaginal progesterone in multiple pregnancies on pregnancy outcome [73]. Another meta-analysis from 2014, including 13 trials with 3768 twin gestations, found no effect of progesterone in unselected women with an uncomplicated twin gestation. However, vaginal progesterone reduced adverse perinatal outcomes in women with a cervical length of <25 mm (RR: 0.56; 95% CI: 0.42–0.75) [81]. An RCT also published in 2015 included 288 twin pregnancies of which 194 women were allocated to weekly 17α-hydroxyprogesterone caproate. There was no reduction in preterm birth, whereas there was a significant reduction in composite neonatal outcome (OR: 0.53; 95% CI: 0.31–0.90) [82].

The conflicting findings of various studies assessing the effect of progesterone in twin and multiple pregnancies may be due to the range of cervical lengths in women, since there is evidence that progesterone reduces preterm birth in twin pregnancies with a short cervical length [81]. This implies that future studies should focus on women who may benefit from the interventions to prevent preterm birth [83].

3.3.2. Women with a previous preterm birth

3.3.2.1. Bacterial vaginosis: antibiotics. A Cochrane meta-analysis by Brocklehurst et al. showed no effect of the use of antibiotics in women with a history of preterm birth and bacterial vaginosis (RR: 0.57; 95% CI: 0.22–1.50) [60]. However, Thinkhamrop et al. performed a meta-analysis to assess the effect of antibiotic prophylaxis during the second and third trimester on adverse pregnancy outcome and morbidity. A reduction in preterm delivery in the subgroup of pregnant women with a prior preterm birth and bacterial vaginosis during the current pregnancy was observed (RR: 0.64; 95% CI: 0.47–0.88) [84].

There is still no clear evidence whether the use of antibiotics is effective in the prevention of preterm birth in this subgroup.

3.3.2.2. Progesterone. The preventive effect of progesterone in the reduction of spontaneous preterm birth in women with a history of spontaneous preterm birth has been thoroughly investigated. Dodd et al. performed a meta-analysis including 11 studies encompassing 1899 singletons with a prior spontaneous preterm birth to assess the benefits of progesterone administration for the prevention of preterm birth. There was a significant reduction in spontaneous preterm birth before 34 weeks (RR: 0.31; 95% CI: 0.14–0.69) and of perinatal mortality (RR: 0.50; 95% CI: 0.33–0.75) in the progesterone group. There is no strong evidence for a difference in effectiveness between the different routes of administration of progesterone; therefore, it is recommended to offer women with a prior spontaneous preterm birth either vaginal progesterone (gel capsules 200 mg daily of vaginal gel 90 mg daily) or 17α-hydroxyprogesterone caproate intramuscular (250 mg weekly) starting between 16 and 24 weeks of gestation, until 36 (intramuscular) or 37 (vaginal) weeks of gestation [51,73].

3.3.2.3. Cerclage: history indicated. Primary cerclage, also elective cerclage, is considered to be effective in the prevention of preterm birth in women with a cervical insufficiency. Cervical insufficiency is characterized by progressive shortening and dilatation of the cervix before 24 weeks of gestation without signs of preterm labour, and is associated with mid-trimester pregnancy loss. However, due to the lack of objective findings and clear criteria, the clinical diagnosis of cervical insufficiency remains challenging.

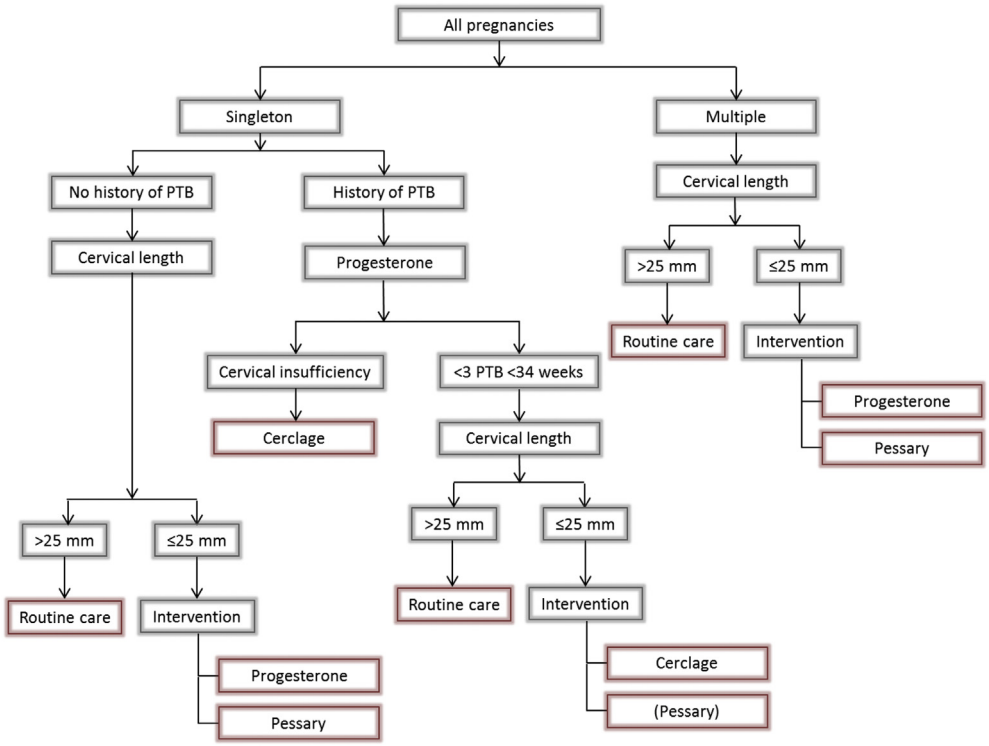

Fig. 1. Algorithm for all pregnancies as a tool to identify possible interventions to prevent preterm birth (PTB).

Primary cerclages have been studied in several RCTs and meta-analyses. The first RCT from 1984 included 194 women with a singleton pregnancy and high risk of preterm birth, and showed no benefit of cervical cerclage compared to conservative treatment in the reduction of preterm birth, neonatal morbidity, and neonatal mortality [85]. Similar results were found in another RCT including 506 women; however, this study included women at moderate risk for preterm birth and excluded women at high risk [86]. The largest trial was performed with 1292 women with singleton pregnancies published in 2003, which showed a significant reduction in preterm birth before 33 weeks of gestation (13% versus 17%; $P = 0.03$). An increased incidence of postpartum fever in the cerclage cohort was found in this study [87]. In addition, a meta-analysis from 2003 demonstrated that an elective cervical cerclage had a significant effect in preventing spontaneous preterm birth before 34 weeks of gestation, yet the authors recommended further research with a focus on the identification of women who would benefit most from cerclage [88]. Based on current, yet limited, clinical information, an elective history-indicated cerclage should be limited to patients with a history of one or more unexplained second-trimester deliveries in the absence of painful cervical dilation or labour [64]. However, the indication for a history-indicated cerclage may vary between, and even within, countries worldwide.

3.3.2.4. Short cervix

- Cerclage: ultrasound-indicated. The effectiveness of cervical cerclage in women with a high risk of spontaneous preterm birth based on their history of previous spontaneous preterm birth and mid-pregnancy short cervix, and ultrasound-indicated cerclage, has been studied in a number of trials. A meta-analysis from 2011 included 504 women with a prior preterm birth and short cervix (<25 mm) receiving a cerclage. The authors observed a reduction in both preterm birth (before 37 weeks of gestation RR: 0.70, 95% CI 0.58–0.83; 35 weeks: 0.70, 055–0.89; 32 weeks: 0.66, 0.48–0.91; 28 weeks: 0.64, 0.43–0.96) and in composite perinatal mortality and morbidity (0.64, 0.45–0.91) [89]. A Cochrane review of 2012 also concluded that cerclage is associated with a reduction in preterm birth before 37 weeks of gestation (RR: 0.80; 95% CI: 0.69–0.95), before 34 weeks (0.79; 0.68–0.93) and before 28 weeks (0.80; 0.64–1.00). Yet, no significant effect on perinatal death nor on composite outcome of perinatal mortality and morbidity was reported in this review [90]. Szychowski et al. assessed the optimal cervical length for placing an ultrasound-indicated cerclage and concluded that cerclage is beneficial in women with shortened cervical length <25 mm when placed between 16 and 24 weeks of gestation [91].

- Pessary. When the pessary was first described in 1959, it was used in women with habitual abortions and possible cervical incompetence. In addition, the PECEP study from 2012 included 11% of women with at least one prior preterm birth. This study compared expectant management with pessary treatment in women with a short cervix, showing a significant decrease in preterm birth in the intervention (pessary) group; however, no subgroup analysis was performed for women with a previous preterm birth [68]. There are currently no recent large studies available with information on the effectiveness of a pessary in women with a previous preterm birth. There are ongoing RCTs evaluating the effect of a cervical pessary in women at risk of preterm birth based on their obstetric history.

Practice points

- Identification of risk factors early in pregnancy is an essential component of clinical obstetric care, since early interventions may be effective to reduce the risk of preterm birth. Preconceptional counselling regarding these factors may further reduce the risk of preterm birth.
- Differentiation between low risk and high risk pregnancies is important to assess the best strategy of preventing preterm birth (Table 1).
- In low risk singleton women without a history of preterm birth, cervical length measurements may be of value to identify women at risk for preterm birth; however, the number needed to screen is relatively high. When a mid-trimester measurement of the cervix of ≤25 mm is detected, women can be offered treatment with either vaginal progesterone 200 mg or a cervical pessary (see also Fig. 1).
- In multiple pregnancies, cervical length measurement may be of value to identify women at higher risk for preterm birth. Both vaginal progesterone and a cervical pessary may be beneficial to reduce the risk of preterm birth in twin pregnancies with a mid-trimester short cervical length; however, optimal timing of intervention should be investigated (see also Fig. 1).
- Women at high risk for a preterm birth, i.e. women with one or more preterm births in their history, should be offered routine progesterone starting at 16 weeks of gestation until 36 weeks. In addition, serial cervical length screening is indicated between 16 and 24 weeks of gestation. In case of a cervix <25 mm, ultrasound-indicated cerclage is recommended. The pessary is being evaluated in this subgroup of women. In women with cervical insufficiency, i.e. women with one or more mid-pregnancy deliveries in the absence of signs of labor, a history-indicated cerclage might be considered (see also Fig. 1).

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