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Editorial

Interventions for women with mid-trimester short cervix: which ones work?

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Introduction

Two of the most significant advances in obstetrics over the last 20 years are (1) the discovery that a short mid-trimester cervix on transvaginal ultrasound is the most powerful predictor of preterm birth (PTB), for both high- and low-risk women[1–3], thus enabling universal cervical length screening[4]; and (2) the introduction of potentially promising treatments for the prevention of PTB in women with a short cervix. In women with a short mid-trimester cervix, randomized controlled trials (RCTs) have used progestogens, cervical cerclage and, lately, cervical pessary as PTB prevention strategies. The aims of this Editorial are to review Level-I evidence regarding the effectiveness of interventions in women identified as having a short cervix on mid-trimester ultrasound, discuss the challenges remaining and outline areas for future research.

Progestogens

The evidence is clear with respect to the use of progestogens in asymptomatic women with short mid-trimester cervix: synthetic progestogens are not effective, whereas natural vaginal progesterone seems to be quite effective, in reducing preterm births. Two trials that randomized women to weekly intramuscular injections of 17α-hydroxyprogesterone caproate did not show any benefit, regardless of the participant's risk[5,6]. In contrast to synthetic progestogens, there is evidence that natural progesterone, in the form of vaginal capsules or gel, for PTB prevention in women with a singleton pregnancy and short cervix appears to be associated with substantial reduction not only in PTB ≤ 34 weeks but also in neonatal morbidity.

The first RCT to use vaginal progesterone (200 mg capsule nightly) in the general population of women with short cervical length (≤ 15 mm) was reported by Fonseca *et al.*[7]. They found that vaginal progesterone significantly reduced the rate of spontaneous PTB < 34 weeks (19.2% *vs* 34.4%; relative risk (RR), 0.56 (95% CI, 0.36–0.86)) but the reduction in neonatal morbidity was not significant (8.1% *vs* 13.8%; RR, 0.59 (95% CI, 0.26–1.25)). The historical significance of this RCT is that it paved the way for screening of the general population, among whom the majority of PTBs occur. The second trial to use vaginal progesterone (90 mg gel daily) in women with short cervical length (10–20 mm) was reported by Hassan *et al.*[8]. The results were even more promising than those of Fonseca's[7] because, in addition to the reduction in PTB, it was the first trial to show significant improvement in neonatal outcomes in women with a short cervix treated with vaginal progesterone. Treated patients, as compared with placebo patients, had a 45% reduction in the primary outcome of PTB < 33 weeks (8.9% *vs* 16.1%; RR, 0.55 (95% CI, 0.33–0.92)), 50% reduction in PTB < 28 weeks (5.1% *vs* 10.3%; RR, 0.50 (95% CI, 0.25–0.97)) and 38% reduction in PTB < 35 weeks (14.5% *vs* 23.3%; RR, 0.62 (95% CI, 0.42–0.92))[8]. In the treated group, there was significant improvement in neonatal outcomes including reduced rates of respiratory distress syndrome (3.0% *vs* 7.6%; RR, 0.39 (95% CI, 0.17–0.92)), any neonatal morbidity or mortality event (7.7% *vs* 13.5%; RR, 0.57 (95% CI, 0.33–0.99)) and birth weight < 1500 g (6.4% *vs* 13.6%; RR, 0.47 (95% CI, 0.26–0.85))[8].

The RCTs by Fonseca *et al.*[7] and Hassan *et al.*[8] were unique because they focused on women with a short mid-trimester cervix. Three additional trials focused on high-risk patients, using varying concentrations of vaginal progesterone (90–100 mg daily) and cervical length cut-offs ranging from 25 to 32 mm[9–11]. These three trials focused primarily on high-risk patients, based on historical factors such as history of spontaneous PTB, uterine malformation, twin pregnancy, positive cervicovaginal fibronectin or a short cervix. The largest and most recent of the three trials (OPPTIMUM)[11] involved a very heterogeneous population from 65 UK National Health Service hospitals and one Swedish hospital. Candidates for inclusion were women with singleton pregnancy who had previous spontaneous PTB ≤ 34 weeks, cervical length ≤ 25 mm, or positive fetal fibronectin combined with other risk factors (i.e. history of PTB, second-trimester pregnancy loss, preterm prelabor rupture of membranes or history of a cervical procedure)[11]. In this heterogeneous population, with a compliance rate of only 69%, the investigators could not demonstrate a benefit of vaginal progesterone in reducing the primary obstetric outcome (fetal death or PTB < 34 weeks), neonatal composite outcome (death, brain injury or bronchopulmonary dysplasia) or childhood outcome at 22–26 months of age (Bayley-III cognitive composite score). However, among

patients with a short cervix (≤ 25 mm) there was a non-significant reduction in PTB ≤ 34 weeks (24.8% *vs* 32.2%; RR, 0.77 (95% CI, 0.52–1.14))[11]. The number of women with a short cervix in the OPPTIMUM trial[11] was comparable to that of Fonseca *et al.*[7], but was much less than that of Hassan *et al.*[8]. To clarify further the evidence for the benefit of vaginal progesterone, Romero *et al.* performed two meta-analyses, one before[12] and one after[13] the OPPTIMUM trial, thus including its data, with similar positive results. Using the same primary outcome as in the OPPTIMUM trial, they found that vaginal progesterone significantly decreased the risk of PTB ≤ 34 weeks or fetal death compared with placebo (18.1% *vs* 27.5%; RR, 0.66 (95% CI, 0.52–0.83))[13]. The study also found that, in singleton pregnancies with a short cervix (≤ 25 mm), vaginal progesterone reduced the risks of PTB occurring at < 28 to < 36 weeks, respiratory distress syndrome, composite neonatal morbidity and mortality, birth weight < 1500 g and admission to the neonatal intensive care unit[13]. Importantly, no differences in neurodevelopmental outcomes at 2 years of age were found between the progesterone and placebo groups. Romero *et al.* concluded that clinicians should continue to offer mid-trimester cervical length screening at 18–24 weeks in women with a singleton pregnancy and offer vaginal progesterone to those with cervical length ≤ 25 mm[13].

The efficacy of vaginal progesterone in women with twins and a short mid-trimester cervix is reported in this issue by Romero *et al.* who performed an individual patient data meta-analysis using data from six randomized controlled trials; it was found that administration of vaginal progesterone to this group of women significantly decreased the risk of PTB < 34 weeks by approximately 30% and, in addition, it decreased neonatal mortality and composite neonatal morbidity/mortality by approximately 50%[14].

In our opinion, considering the data altogether, it appears that there is strong evidence for the benefit of vaginal progesterone in women with a short mid-trimester cervix. However, tantalizing questions remain regarding the best group of candidates, as defined by the degree of cervical shortening, the optimal dose of progesterone and possible short- and long-term side effects. The two trials that focused on treating only women with short cervix used different cervical length cut-offs of < 15 mm[7] and 10–20 mm[8]. The other three trials that included women with a short cervix used cervical length cut-offs ranging from 25 to 32 mm[9–11], whereas traditionally, a short cervix is defined as < 25 mm[15]. The individual and aggregate meta-analyses demonstrated that vaginal progesterone is effective in women with a cervical length ≤ 25 mm[13,14]. However, it should be noted that all trials used a single static cervical length cut-off for intervention.

From serial observations in clinical practice, we have noticed that some patients with a short cervix will develop progressive cervical shortening and others will remain stable. Unfortunately, both of these groups of patients have been grouped together in the aforementioned trials so that we have no information regarding the presence or absence of progressive cervical shortening prior to randomization. It is possible that the beneficial effects of progesterone could be attributed to women with progressive cervical shortening. Hopefully, future studies will determine the optimal group of candidates on which to focus treatment. Although the trials used different doses of progesterone, ranging from 90 to 200 mg[7–11], an individual patient data meta-analysis[12] showed that there was no difference in the efficacy of vaginal progesterone according to the dose administered. In the meta-analysis of twin gestations with a short cervix, a dose of 400 mg daily appeared to be more effective, as compared to 100 mg or 200 mg, but this should be interpreted with caution given the small number of patients in the subgroup analyses[14]. Also, a careful prospective evaluation for not only short- but also long-term side effects beyond 2 years of age is necessary. So far, trials have shown that there is better short-term perinatal outcome, and no difference in long-term neurodevelopment at 2 years of age, in pregnancies with a short cervix treated with vaginal progesterone, as compared with controls.

As intra-amniotic inflammation is observed in a significant proportion of women with a short cervix (approximately 10%)[16], it is conceivable that some pregnancies with short cervix and intra-amniotic inflammation may be prolonged by the use of progesterone and that the long-term childhood morbidity in such cases may be increased. We hope that future studies will be able to address this important question.

Cerclage

The first trial that focused on high-risk pregnant women with a short cervix (< 25 mm) used cervical cerclage as the mode of treatment[17]. Despite the initial encouraging results of this RCT, which had a very small number of subjects[17], three subsequent RCTs involving many more patients produced negative results[18–20]. A meta-analysis of the aforementioned four trials performed 40 subgroup analyses, taking into consideration not only gestational age at delivery but also factors such as singletons, twins, history of prior PTB, second-trimester fetal loss, history of cone biopsy, number of prior dilations and evacuations, cervical funneling, gestational age at cervical shortening and degree of shortening[21]. Of the 40 subgroup comparisons, six were statistically significant with five of the six comparisons having upper limit estimates of the 95% confidence intervals of 0.92–0.99. The authors concluded that in the subgroup analyses, cerclage was associated with a significant reduction in PTB among women, who in addition to a short cervix, had a prior PTB (RR, 0.61 (95% CI, 0.40–0.92)) or second-trimester pregnancy loss (RR, 0.57 (95% CI, 0.33–0.99)), and recommended a well-powered RCT in this group of patients[21]. Four years later, Owen *et al.*[22] reported the

results of a multicenter RCT using cerclage for PTB prevention in women with short mid-trimester cervix (< 25 mm) and a history of spontaneous PTB between 17 + 0 and 33 + 6 weeks' gestation. The authors found that cerclage did not prevent PTB < 35 weeks (primary outcome) but was associated with its reduction if cervical length was < 15 mm (secondary outcome)[22]. In other words, the results of the trial were negative. At face value, one can conclude that cerclage does not work for women with prior spontaneous PTB who have a cervical length of 15–24 mm. If one were to accept the results of the planned secondary analysis in this trial[22] then cerclage remains effective in reducing PTB among women with a cervical length < 15 mm. However, as women who had visible membranes on speculum examination were excluded, it is highly likely that many patients with very short cervix (i.e. < 5 mm) may have been deemed ineligible, and hence excluded from the trial. Thus, if cerclage works, its benefits are confined to a very small subset of women with a history of spontaneous PTB or second-trimester pregnancy loss who have a mid-trimester cervical length of 5–14 mm. Therefore, from the point of view of the general population, the role of cerclage as a prevention strategy for PTB remains very limited, at best.

It is worth commenting on the sequence of events that may have led to the trial by Owen *et al.*[22]. This trial was carried out as a result of the findings of the multiple subgroup analyses of a prior meta-analysis, rather than the traditional 'other way around' of pooling small RCTs to draw a conclusion from the evidence. In our view, from a statistical perspective, when undertaking a meta-analysis, one should ensure that the meta-analysis preserves (or reduces) both Type I and Type II errors. An accumulation of studies in a meta-analysis will almost always decrease the Type II error, and hence increase the power to detect treatment efficacy, but attention to Type I error is often pushed to the wayside. Performing a meta-analysis with several underpowered subgroup analyses will inflate the Type I error. While such subgroup analyses may compromise the statistical power, they will just as likely compromise Type I error too.

Cervical pessary

The third modality that has been attempted recently for preventing PTB in women with a short cervix is cervical pessary. In our view, the evidence regarding the use of pessaries in women with short mid-trimester cervix appears inconclusive for both singleton and twin gestations. For singleton gestations with a short mid-trimester cervix, we evaluated three trials that used cervical pessary. The first reported trial by Goya *et al.*, which used the Arabin pessary in asymptomatic singleton gestations with a short cervix (≤ 25 mm), reported a significant reduction in PTB < 34 weeks in those with pessary compared with those with expectant management (6% *vs* 27%; OR, 0.18 (95% CI, 0.08–0.37))[23]. The authors hypothesized that the mechanism by which the pessary works is by supporting 'the immunologic barrier between the chorioamnion-extraovular space and the microbiological flora as cerclage has been postulated to do'[23]. This hypothesis, if true, would argue against the potential benefit of the pessary given the poor record of cerclage in women with a short cervix. A subsequent smaller trial by Hui *et al.*[24], which used cervical length cut-off < 25 mm, and a considerably larger trial by Nicolaides *et al.*[25], which used cervical length cut-off ≤ 15 mm, reported negative results (PTB < 34 weeks: 9.4% *vs* 5.5%; OR, 1.80 (95% CI, 0.40–7.96) by Hui *et al.*[24] and 12.0% *vs* 10.8%; OR, 1.12 (95% CI, 0.75–1.69) by Nicolaides *et al.*[25]). However, it is worth noting that the rates of PTB < 34 weeks in the control groups of Goya *et al.*[23] and Nicolaides *et al.*[25] were significantly different (27.0% in Goya *et al.*[23] *vs* 10.8% in Nicolaides *et al.*[25]; RR, 2.49 (95% CI, 1.75–3.54)). Given the differences in cervical length used in the two trials (≤ 25 *vs* ≤ 15 mm), one would expect the control group in Goya *et al.* to have lower PTB rate; however, the opposite occurred. This observation suggests that there was considerable heterogeneity or dissimilarity between these two populations. Interestingly, the same pattern of differences in the control groups was also noted in the cervical pessary trials of these two investigators in women with twin gestations and a short cervix (discussed below).

The first trial using cervical pessary for prevention of PTB in unselected asymptomatic women with multiple pregnancy was reported by Liem *et al.*[26]. In this trial, the primary outcome was composite poor perinatal outcome (stillbirth, periventricular leukomalacia, severe respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular hemorrhage, necrotizing enterocolitis, neonatal sepsis and neonatal death); PTB was one of the secondary outcomes. Overall, the pessary did not improve composite perinatal outcome or gestational age at birth; however, a secondary analysis showed that, among women with a mid-trimester cervical length < 38 mm, who received the pessary, poor perinatal outcome was less frequent and PTB rates < 28 and < 32 weeks were lower when compared with the control group. These findings were an impetus for two subsequent trials in twin gestation[27,28]. The largest trial was reported by Nicolaides *et al.* in unselected twin gestations ($n = 1180$; 590 in each group) and had negative results as there was no difference between the pessary and control groups in terms of PTB or any other adverse perinatal outcome[27]. In addition, a *post-hoc* subgroup analysis of 214 women with a short cervix (≤ 25 mm) did not show any benefit among those who received the pessary ($n = 106$) and those who did not ($n = 108$); the rates of spontaneous PTB < 34 weeks were 31.1% and 25.9%, respectively (RR, 1.20 (95% CI, 0.78–1.83))[27]. Goya *et al.*[28] reported a smaller trial in twin gestations focusing specifically on those with a short cervix (≤ 25 mm) and found significant benefit of the pessary in terms of less frequent spontaneous PTB < 34 weeks (16.2% *vs* 39.4%; RR, 0.41 (95% CI, 0.22–0.76)) for

those who received the pessary ($n = 68$) compared with those who did not ($n = 66$); however, there was no difference in neonatal morbidity or mortality between the two groups. The discrepant results between the latter two trials were attributed by Goya[28] to a high rate of pessary removal < 34 weeks and the lack of a training program for pessary insertion and follow-up in the Nicolaides trial. However, in our view, it appears that the populations were, once again, highly heterogeneous given the discrepant rates of PTB < 34 weeks between the control groups of these two trials (39.4% in Goya *et al.*[28] *vs* 25.9% in Nicolaides *et al.*[27]). For all the aforementioned reasons, it is our belief that the evidence regarding the use of pessary in women with a short cervix is inconclusive, in both singleton and twin gestations, due to differences in the studied populations and perhaps in training in pessary insertion.

Unsolved challenges

Altogether, the evidence suggests that there is progress in preventing PTB and that the most effective intervention is in women with singleton pregnancy and a short mid-trimester cervix, regardless of their risk status, by vaginal progesterone. However, we still face some serious challenges relating to (1) the accuracy of cervical length measurements in the setting of universal screening, (2) the appropriateness of universal screening in countries with low PTB rate, and (3) the very small impact in reducing PTB rate by current interventions.

Data on the association between a short cervix and PTB are consistent in showing that approximately 30% of women with a singleton pregnancy and a cervical length ≤ 25 mm (the 10th centile in some populations[15]) in the mid-trimester will deliver preterm and that these patients account for 25–45% of women with a spontaneous PTB[1,12,13,15,29,30]. However, most studies on cervical length screening come from 'expert' centers and/or research settings. It remains to be seen if the aforementioned detection rates can be achieved by universal screening of all populations. In a study in which physicians were asked to send their ultrasound images of the cervix for certification, it was found that 25% of assessments did not meet published quality criteria[31]. The quality of images in the clinical setting may be even worse considering that participants of this study most likely sent their 'best' images. New technology may work but might only be available for use by experts, of which there are not many. Training and accreditation are essential. Given the above information, it seems likely that the overall effectiveness of universal cervical length screening may be limited in settings without continuous quality control.

Another issue to consider before introducing universal screening is that the incidence of a short cervix (≤ 25 mm) seems to vary considerably between populations. For instance, in Sweden, a mid-trimester cervical length ≤ 25 mm is seen only in 0.5% of the population[32]. Another example is in The Netherlands, where a mid-trimester cervical length ≤ 30 mm, measured twice, corresponds to the 0.7th centile; 20 234 patients had to be screened in order to identify 151 patients with a persistently 'short' cervix (≤ 30 mm)[33]. The randomized trial in this population of low-risk singleton pregnancies, using this cervical length as a cut-off, and comparing vaginal progesterone (200 mg capsule daily) *vs* placebo had negative results (non-significant reduction in PTB < 32 weeks and < 34 weeks)[33]. In countries with a very low incidence of a short cervix or PTB, for which universal screening is not cost-effective, consideration may be given to use cervical length only in symptomatic patients with threatened preterm labor to assess the need for hospitalization, tocolytics or corticosteroids. For asymptomatic patients, risk-based strategies may be more appropriate. In risk-based strategies, mid-trimester cervical length evaluation is restricted to high-risk patients such as parous women with a previous PTB and risk-based screening of nulliparous women based on ethnicity, previous cervical surgery and smoking. By using such a policy, the number of cervical sonograms may be reduced by two-thirds; however, such a policy may reduce the detection of women delivering preterm by one-third[34], which may be acceptable in countries with low PTB rates. In contrast to the aforementioned North European populations, in the USA, where there is a high rate of PTB (approximately 10% in 2013[35]), universal cervical length screening has been found to be cost-effective as compared with risk-based screening or no screening[36]. Universal screening and vaginal progesterone administration to women with a short mid-trimester cervix in the USA, regardless of risk status or prior history, has been reported to prevent one case of PTB < 34 weeks for every 125 women screened and one case of major neonatal morbidity or mortality for every 225 women screened, which translates into an annual reduction of approximately 30 000 PTBs < 34 weeks and 17 500 cases of major neonatal morbidity or mortality[4].

Although vaginal progesterone seems to reduce the rate of PTB < 34 weeks in women with a singleton pregnancy and a short cervix, the effect on the overall PTB rate is limited. An analysis of trends and potential reductions with PTB interventions in 39 countries with very high human development index concluded that five combined interventions may decrease the rate of PTB by no more than 5%[37]. The possible impact of our current interventions in reducing PTB, based on assumptions from published data[13,14,37–39], is depicted in Figure 1. We did not include cerclage as one of the prevention strategies because women with a short cervix and prior history of PTB or second-trimester pregnancy loss may be treated with vaginal progesterone. Unfortunately, current interventions can prevent only approximately 8% of the total number of PTBs (Figure 1). Therefore, despite considerable progress in the prevention of PTB in women with a short cervix by vaginal progesterone, serious challenges remain.

As shown in Figure 1, in order to have a clinically meaningful impact in reducing PTB, future research efforts should focus on the following four groups of patients:

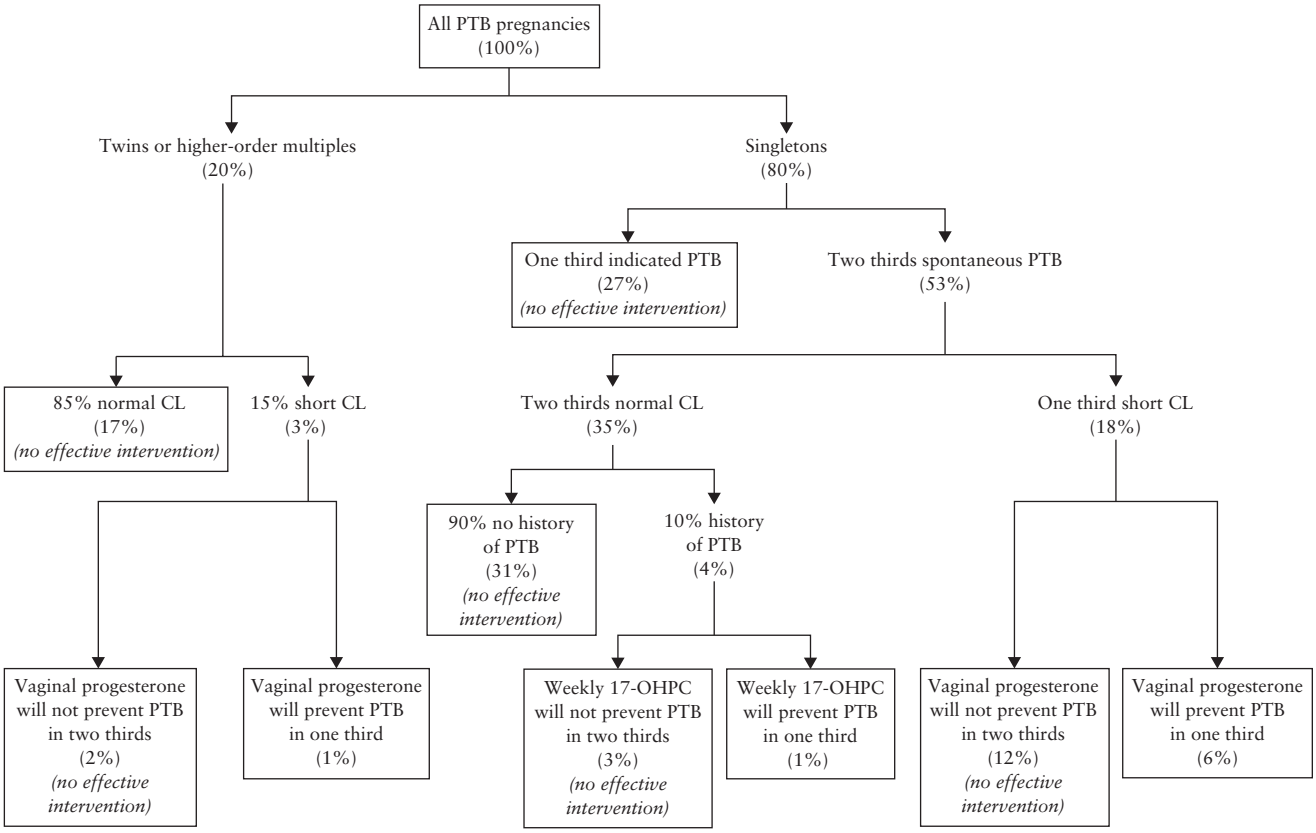

Figure 1 Impact of current interventions for preterm birth (PTB), including universal cervical length (CL) screening, on rate of PTB < 34 weeks (percentages in boxes represent those from initial 100%). 17-OHPC, intramuscular 17α-hydroxyprogesterone caproate.

(1) multiple pregnancies, since only a small proportion will respond to vaginal progesterone; (2) those with indicated PTB; (3) those with short mid-trimester cervical length who do not respond to vaginal progesterone; and (4) those with normal mid-trimester cervical length who develop spontaneous PTB. We have a huge task ahead of us because, if we are to have a meaningful impact on reducing PTB, future studies should focus on all four groups. Investigators will need to keep in mind that our interventions, or combinations of interventions, should take into consideration the etiological pathways of PTB, since we already have data to suggest that the pathways may define the success or failure of our chosen treatments[40,41].

In our opinion, without taking into consideration the etiology of each individual threatened preterm episode, we will only produce 'hit and miss' treatments. In the meantime, it makes sense to offer universal cervical length screening, with or without[42] the use of transvaginal ultrasound, and offer treatment with vaginal progesterone in women with singleton pregnancy and short mid-trimester cervix in countries with high PTB rate, such as the USA. For countries with low PTB rates, such as North European countries, a more conservative approach of risk-based screening and offering vaginal progesterone to those with a singleton pregnancy and a short cervix seems reasonable.

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