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Editorial

Prevention of spontaneous preterm birth: the role of sonographic cervical length in identifying patients who may benefit from progesterone treatment

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Introduction

The importance of progesterone in the maintenance of mammalian pregnancy is well established[1–18]. Similarly, a decline in progesterone action is believed to be central to the initiation of parturition in most mammalian species, including primates[5,7,8,12–14,19,20], although the precise mechanism for this in humans has not been elucidated[5,7,9,13,14,21–25].

Progestogen (a term that, like progestin, includes both 'natural' progesterone and synthetic compounds with progesterone action)[26] administration to prevent spontaneous miscarriage[27–39] and preterm birth[28,40–48] has been a subject of investigation for several decades. The use of progesterone in the first trimester of pregnancy to 'support corpus luteum function' is a well-established clinical practice[27,29,30,34,35,37,39,49]. Formulations of progesterone for this indication have been approved by the US Food and Drug Administration (FDA) (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm) and regulatory agencies in Europe and elsewhere[50].

Early trials of progestogens and meta-analyses

Emile Papiernik in France was the first to use progesterone for the prevention of preterm birth[40]. Subsequently, the results of individual clinical trials using progestogens for the prevention of preterm birth or recurrent miscarriage yielded contradictory results, as did the meta-analyses of such trials[49,51,52]. For example, the meta-analysis of Goldstein *et al.*[52] included trials employing several progestogens and could not demonstrate a beneficial effect of these compounds for the prevention of preterm birth. The meta-analysis of Keirse[51] focused only on studies of 17 alpha-hydroxyprogesterone caproate, examining its effect on different endpoints: 'early curtailment of gestation, whether by miscarriage (< 20 weeks or < 500 g) or by preterm birth (< 37 weeks)'. He found that 17 alpha-hydroxyprogesterone caproate reduced the rate of preterm labor, preterm birth and birth weight below 2500 g. Despite these encouraging results, little clinical research on the subject was conducted for nearly a decade. The reasons for this inactivity are unclear[53].

2003: Two trials rekindled the interest in progestogens to prevent preterm birth

In 2003, two trials were reported suggesting that daily vaginal progesterone administration (100 mg between 24 and 34 weeks of gestation)[46] and weekly injections of 17 alpha-hydroxyprogesterone caproate (250 mg intramuscularly between 16 and 36 weeks)[45] reduced the rate of preterm birth (≤ 37 weeks). The findings were highlighted in accompanying editorials[54,55]. Keirse wrote an interesting analysis of the trials, entitled 'Progesterone and preterm: seventy years of "déja vu" or "still to be seen?"'[56]. He expressed reservations about the power calculations of the trial that used vaginal progesterone. With respect to the trial using 17 alpha-hydroxyprogesterone caproate[45], Keirse proposed an alternative interpretation of the results: that placebo injections increased the rate of preterm birth in comparison to the synthetic progestogen. This argument was based on the unexpectedly high frequency of preterm birth in the placebo group (54.9% (84/153))[56]. He suggested that 17 alpha-hydroxyprogesterone caproate may not have been effective because the rate of preterm birth in the active drug group was 36.3% (111/306), akin to the

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baseline rate of preterm birth for a similar population[57] or the placebo group in another trial. Specifically, the power calculation of the trial was based on the 'Prediction of Prematurity' observational study and estimated that 37% of the women in the placebo group would deliver before 37 weeks[56,57]. Moreover, officials of the FDA analyzing this trial indicated that the rate of preterm birth in the active arm of the study (36.3%) was very similar to that in the placebo group of a similar study (http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4227S1-index.htm). This was the early phase of a similar clinical trial conducted by the same investigators that was discontinued because of concerns about quality control in the manufacturing of the active drug. (The FDA ordered a shutdown and a total recall of all drugs manufactured by this company[45]). The high rate of preterm delivery in the control group has been a subject of debate and the investigators who conducted the trial have argued that the population participating in the trial was at very high risk for preterm delivery based on obstetric history, ethnic composition and willingness to be randomized to a painful injection on a weekly basis. It has been suggested that the latter would apply largely to highly motivated patients, at substantial risk for preterm delivery.

After the publication of these trials[45,46], the flurry of activity that was expected[56] indeed occurred. Three new trials of progestogens to prevent preterm birth have since been reported[47,48,58] and more are in progress[59,60]. The results of recently reported randomized clinical trials[46–48,58] were unexpected because of conflicting results for vaginal progesterone administration in women with a history of spontaneous preterm birth[46,58] and negative results for 17 alpha-hydroxyprogesterone caproate in twin gestation[48]. A major development is the observation that vaginal progesterone reduces the risk of preterm birth (< 34 weeks) in women with a sonographic short cervix[47,61].

2007: Conflicting reports about the effectiveness of vaginal progesterone in preventing preterm birth

In this issue of the Journal, O'Brien *et al.* report the largest randomized clinical trial, in which patients with a history of a previous spontaneous preterm delivery were allocated to receive vaginal progesterone (90 mg per day) in a bioadhesive formulation/gel (which is currently approved by the FDA for progesterone supplementation or replacement during the course of assisted reproductive technologies) or placebo[58]. The primary endpoint was early preterm delivery (≤ 32 weeks). All patients underwent transvaginal sonography to determine cervical length at enrollment and at 28 weeks.

This multinational trial, involved 53 centers and 659 women with a singleton pregnancy, who were randomized, between 18 and 22 completed weeks of gestation, to receive daily treatment with vaginal progesterone gel or placebo (Replens®)[58]. Progesterone or placebo was self-administered until either delivery, 37 weeks of gestation, or the occurrence of premature rupture of membranes. Vaginal progesterone did not reduce the rate of preterm birth at ≤ 32, ≤ 35 or < 37 weeks of gestation. Moreover, there was no difference in neonatal and maternal outcomes between the groups. The results of this study conflict with those of the initial trial reported by da Fonseca *et al.*[46], which also used vaginal progesterone (100 mg daily, from 24 to 34 weeks in a non-bioadhesive formulation). In this trial, which included 142 women, the rate of preterm delivery at both < 37 weeks and < 34 weeks was significantly lower in women allocated to progesterone treatment than in those allocated to placebo (< 37 weeks, progesterone: 13.8% (10/72) vs. placebo: 28.5% (20/70); $P = 0.03$ and < 34 weeks, progesterone: 2.8% (2/72) vs. placebo: 18.6% (13/70); $P = 0.002$).

Why were there contradictory results in two trials which appear so similar in design?

Several differences between these two trials can be identified. First, the inclusion criteria differed. The initial trial of da Fonseca *et al.*[46] included patients with uterine malformations (3.5% (5/142) of the trial population) and patients who had had a cervical cerclage (2.8% (4/142) of the trial population). Such patients were excluded from the trial of O'Brien *et al.*[58]. While these conditions may confer a different risk for recurrent preterm delivery than does a previous history[62–66], it is difficult to attribute the difference in results of the two trials to this factor, because the total number of patients with uterine anomalies and cervical cerclage was small. Second, the two trials used a different formulation of micronized progesterone[67–71]: da Fonseca *et al.*[46] used a non-bioadhesive suppository (100 mg administered at night), while O'Brien *et al.*[58] used a bioadhesive gel (90 mg administered mostly in the morning). Whether the difference in dose and time of administration can account for the difference in results is unclear. Third, the trial of da Fonseca *et al.*[46] was conducted in Brazil, at the University of Sao Paulo, in a single center, while the study of O'Brien *et al.*[58] was multicenter. This may account for the apparent different frequencies of preterm deliveries in the placebo group of the trials (preterm birth before 37 weeks: 28.5% (20/70) in the da Fonseca *et al.* study[46], and 40.7% (123/302) in the study of O'Brien *et al.*[58]).

Can progestogens prevent preterm birth in twin gestation?

Multiple gestation is a risk factor for preterm birth[72–85]. Uterine overdistention has been implicated as a mechanism responsible for the excess rate of preterm delivery in this subset of patients[86–88]. Progesterone down-regulates the expression of contraction-associated proteins[89–94]. Therefore, it is possible that progestogens may reduce the rate of preterm birth in multiple gestations. Investigators have thus tested whether progestogens can prevent preterm birth in these pregnancies[42,47,48].

More than 25 years ago, Hartikainen-Sorri *et al.*[42] reported a placebo-controlled double-blind clinical trial of 17 alpha-hydroxyprogesterone caproate administration in 77 women with twin pregnancies enrolled between 28 and 33 weeks of gestation. Weekly intramuscular injection of 250 mg of 17 alpha-hydroxyprogesterone caproate or placebo were initiated at the time of enrollment and discontinued at 37 weeks of gestation or when labor occurred before term. The administration of 17 alpha-hydroxyprogesterone caproate did not reduce the rate of preterm birth (< 37 weeks) or perinatal morbidity.

This issue was revisited recently. Rouse *et al.*[48] reported a multicenter, placebo-controlled, double-blind, randomized clinical trial of 17 alpha-hydroxyprogesterone caproate for the prevention of preterm birth in twin pregnancies which included 655 women enrolled between 16 and 20 completed weeks of gestation. Patients were allocated to receive a weekly injection of 250 mg of 17 alpha-hydroxyprogesterone caproate or placebo until 34 completed weeks of gestation or delivery. The primary outcome was a composite of fetal death or delivery before 35 completed weeks of gestation, which occurred in 41.5% (135/325) of patients in the 17 alpha-hydroxyprogesterone caproate group and in 37.3% (123/330) of those in the placebo group (relative risk, 1.1 (95% CI, 0.9–1.3)). da Fonseca *et al.*[47] reported a subanalysis of their randomized trial of vaginal progesterone vs. placebo in 24 women with twin gestations and a short cervix (≤ 15 mm). Progesterone administration was associated with a non-significant reduction in the rate of preterm delivery. Collectively, the results of these studies indicate that prophylactic progestogen administration may not reduce the rate of preterm delivery in women with twin pregnancies. One explanation for this is the relatively low rate of spontaneous preterm birth in twin pregnancies at early gestational ages. It is possible that progestogens may benefit a subset of women with a twin gestation and a short cervix.

Sonographic cervical length to identify the patients who may benefit from progesterone treatment

Facchinetti *et al.*[95] reported the results of a randomized clinical trial in which women with preterm labor and intact membranes (25 to 33 + 6 weeks) were allocated to either observation or intramuscular administration of 341 mg of 17 alpha-hydroxyprogesterone caproate twice a week until 36 weeks of gestation or delivery, and sonographic cervical length was measured at discharge as well as 7 and 21 days later. Patients who received 17 alpha-hydroxyprogesterone caproate had a longer sonographic cervical length than had those in the observation group[95]. These findings, coupled with experimental data, suggest that progestogen may have major effects on the uterine cervix.

Two clinical lines of evidence support that cervical status may identify patients who could benefit from progestogen administration[47,61]. First, the recent randomized clinical trial reported by da Fonseca *et al.*[47] indicates that vaginal progesterone reduces the rate of preterm birth by 44% in women with a sonographic short cervix. Second, the study by DeFranco *et al.*[61], published in this issue of the Journal, suggests that patients with a short cervix may benefit from vaginal progesterone administration.

da Fonseca *et al.*[47] and The Fetal Medicine Foundation Second Trimester Screening Group reported a randomized, double blind, placebo-controlled trial in which women with a short cervix (≤ 15 mm by transvaginal ultrasound) between 20 and 25 weeks of gestation were allocated to daily vaginal administration of 200 mg of micronized progesterone or placebo (safflower oil) from 24 to 34 weeks. The frequency of spontaneous preterm delivery at < 34 weeks (primary endpoint for the trial) was significantly lower in the progesterone group compared with in the placebo group (19.2% (24/125) vs. 34.4% (43/125); $P = 0.007$). Importantly, a secondary analysis of this trial indicated that among women without a history of delivery before 34 weeks, the incidence of preterm birth was significantly lower in women receiving progesterone than in those allocated to placebo (17.9% (20/112) vs. 31.2% (34/109); relative risk, 0.57; 95% CI, 0.35 to 0.93; $P = 0.03$)). The trial was not designed to test whether progesterone administration could reduce neonatal morbidity, and such a reduction was not observed[47].

DeFranco *et al.*[61] report a retrospective analysis of the effect of vaginal progesterone on pregnancy outcome (preterm birth and infant outcome) as a function of cervical length. The hypothesis for this study was that the effect of prophylactic vaginal progesterone may vary according to cervical length. To test this concept, all patients eligible to participate in the trial of O'Brien *et al.*[58] underwent sonographic measurement of the cervix at the time of enrollment. Patients without a previous preterm birth and a cervical length of ≤ 25 mm were subjected to a separate randomization procedure (to vaginal progesterone or placebo) and were excluded from the main trial. The rationale for this was that the main trial tested the effect of vaginal progesterone on patients with a history of preterm delivery regardless of cervical length. However, after the completion of the main trial, nine patients had been enrolled in the 'short-cervix only' arm of the trial, rendering the analysis meaningless. Consequently, the investigators modified their initial plan so that the analysis included women enrolled in the main trial (and therefore with a history of previous preterm birth). The patient population was divided into quartiles according to cervical length at enrollment to test whether outcomes differed as a function of cervical length (the lowest quartile was a cervical length of ≤ 32 mm). Although there was a delay in delivery, progesterone administration did not result in a significant difference in outcome of patients in the lowest quartile.

DeFranco *et al.*[61] then explored the effect of vaginal progesterone as a function of cervical length using two new cut-offs: ≤ 30 mm and < 28 mm. For the cut-off of 30 mm, there was a trend for a longer randomization-to-delivery interval in women allocated to progesterone than in those allocated to placebo (Wilcoxon's $P = 0.043$,

log-rank $P = 0.057$). However, there was no difference in the frequency of preterm delivery ≤ 32 weeks. With the second cut-off (< 28 mm), patients who had received vaginal progesterone had a lower rate of spontaneous preterm delivery ≤ 32 weeks, although this was not observed for preterm delivery defined as ≤ 35 weeks or < 37 weeks. It is noteworthy that in women with a cervical length of ≤ 30 mm or < 28 mm, the frequency of newborn intensive care unit admission was lower in those who had received progesterone treatment than in those allocated to the placebo group. The same was the case for the duration of newborn intensive care unit stay[61]. This analysis provides the first hint that vaginal progesterone administration may improve infant outcome in properly selected patients. It is important to stress, however, that these conclusions must be considered tentative because they derive from a secondary analysis, which is intended to be hypothesis-generating[96]. Therefore, further investigation is necessary. Specifically, randomized clinical trials designed to test the effect of vaginal progesterone in women with a short cervix and powered to detect whether or not a difference in infant outcome can be demonstrated are now required.

What are the effects of progesterone on the uterine cervix?

Progesterone exerts biological effects not only in the myometrium and chorioamniotic membranes but also in the uterine cervix[94,95,97–103] (control of cervical ripening)[6,7,9]. Progesterone withdrawal (in rats, rabbits and sheep) or a decline in progesterone action (in guinea pigs and primates)[14] has been proposed as a key control mechanism for cervical ripening by Chwalisz and coworkers[7,104–106], Word *et al.*[107] and Mahendroo *et al.*[108,109]. Thus, a large body of evidence supports a role for progesterone in cervical ripening[95,107,110–116]. For example: (1) administration of antiprogestins to women in the mid-trimester and at term induces cervical ripening[107,117–121]; (2) administration of progesterone-receptor antagonists such as mifepristone (RU486) or onapristone to pregnant guinea pigs[105,122], old-world monkeys[123] and *Tupaja belangeri* induces cervical ripening[107]. It is interesting that cervical responsiveness to antiprogestins increases with advancing gestational age[107] and that their effects on the cervix are not always accompanied by changes in myometrial activity[107]. Indeed, Stys *et al.*[124] demonstrated a functional dissociation between the effects of progesterone in the myometrium and those in the cervix.

A frequent observation, in animals[122,123] as well as in humans[7], is that antiprogestins induce cervical ripening but not labor. Indeed, labor may not begin at all or may be delayed by days or weeks in humans after cervical ripening has been accomplished[107]. Collectively, this suggests that a major site of progesterone action may be the cervix. This realization is important because much of the emphasis in previous years has been on the effect of progesterone on the myometrium.

The precise mechanisms by which a blockade of progesterone action may induce cervical changes are complex and poorly understood. A decline in progesterone action probably causes cervical changes by inducing inflammation (leukocyte infiltration and production of chemokines[94] such as interleukin-8[98,99], nitric oxide[106,116,125], prostaglandins[98] and matrix-degrading enzymes[102,126,127]). It is also possible that cervical remodeling and ripening is influenced by NF-kB (nuclear factor-kappa B), a transcription factor which mediates the effect of certain proinflammatory cytokines such as IL-1β (interleukin 1β)[90,128–135] and TNF-α (tumor necrosis factor-α)[136–138]. This is important, because NF-kB can oppose progesterone action[89,93,129,132,139–141]. Thus, NF-kB provides a link between inflammation, a decline in progesterone action and cervical ripening.

The traditional understanding of the mechanisms of action of progesterone is that this hormone acts through nuclear receptors to induce genomic actions[25,142–151]. However, it is now clear that some of the actions of progesterone are induced through membrane receptors and non-genomic mechanisms[152–179]. The precise role of progesterone receptors, deoxyribonucleic acid (DNA)-binding properties and/or transcriptional activity in determining progesterone action on the cervix remains to be elucidated.

Another unresolved issue is why progesterone administration to pregnant women, who already have a very high concentration of circulating progesterone ($> 10^{-7}$ M)[107], would result in a therapeutic effect. In fact, it has been argued that the circulating concentration of progesterone in pregnant women is in excess of that required to saturate progesterone receptors[107]. However, these biochemical considerations were developed before the realization that progesterone has mechanisms of action that are independent of its nuclear receptors[162,180]. It is possible that the change in progesterone concentrations at the time of spontaneous parturition in the human occurs locally and not in the systemic circulation[181,182].

Short sonographic cervical length: a powerful predictor of preterm delivery

Cervical sonography is the best method to assess cervical length[63,183–188]. The shorter the sonographic cervical length in the mid-trimester, the higher the risk of spontaneous preterm labor/delivery[63,183–186]. There is no consensus as to what constitutes a sonographic short cervix. For example, Iams *et al.*[63] proposed that a cervix of ≤ 25 mm at 24 weeks of gestation increases the risk for spontaneous preterm delivery (relative risk, 6.19; 95% CI, 3.84–9.97). The prevalence of spontaneous preterm delivery (defined as < 35 weeks) was 4.3%, and the positive predictive value was 17.8% for a cervical length ≤ 25 mm at 24 weeks of gestation. Thus, most women with a short cervix and no history of previous preterm birth will deliver at term. Other investigators have proposed a cut-off of 15 mm[185,186], because a cervical length of ≤ 15 mm at or about 23 weeks is associated

with a nearly 50% risk of spontaneous preterm delivery at ≤ 32 weeks of gestation, when neonatal morbidity is substantial[185,186,189–197]. To *et al.*[188] developed a method with which to assess the risk of preterm delivery for individual patients using sonographic cervical length and other maternal risk factors, such as maternal age, ethnic group, body mass index, cigarette smoking and previous cervical surgery. Importantly, sonographic cervical length is the single most powerful predictor for preterm birth in the index pregnancy[187,188] and is far more informative than is a history of previous preterm birth[186,188,198]. This has implications for the selection of patients for future trials and for the interpretation of past trials. Specifically, all trials conducted to date[41,44–46,58], with the exception of one[47], identified patients for study based on a history of previous preterm birth. Such a strategy (selecting patients for treatment) would have a limited effect on the prevention of preterm delivery because most women who deliver preterm neonates do not have this history. Assessing the individual risk based on cervical length (and other clinical or biochemical markers) is an appealing alternative for future studies. Patients at increased risk for spontaneous preterm delivery because of a short cervix may benefit from progestogen prophylaxis. Moreover, it is possible that patients whose cervix shortens during the index pregnancy may be candidates for cervical cerclage in the absence of infection/inflammation[199,200].

Sonographic cervical length is not a screening test for spontaneous preterm delivery, because only a fraction of the patients who will have a spontaneous preterm birth have a short cervix in the mid-trimester. However, determination of cervical length is a powerful method for risk assessment.

The syndromic nature of a sonographic short cervix

Most women, as they progress in the third trimester of pregnancy towards the spontaneous onset of labor, undergo cervical ripening. As part of this process, their sonographic cervical length shortens. Therefore, shortening of the cervix is part of the common terminal pathway of parturition, which includes increased myometrial contractility, cervical ripening and membrane/decidual activation[18,88,201–203]. Unscheduled cervical ripening in the preterm gestation may occur in combination with activation of other components of the common terminal pathway or may be asynchronous[18,88,201–204] (Figure 1). Thus, the phenotype of preterm parturition syndrome (preterm labor with intact membranes, cervical insufficiency, preterm premature rupture of membranes, or a combination of these presentations) represents the recruitment of the different components of the uterine pathway of parturition[88].

A short cervix often occurs when there is cervical ripening; however, not all short cervices are ripened; hence, the observation that some women with a short cervix deliver at term. We have proposed that a short cervix is syndromic in nature and can be caused by multiple etiologies[205,206], such as: (1) the loss of connective tissue after a cervical operation such as conization[207–209] or loop electrical excision procedure (LEEP)[209]; (2) a congenital disorder such as cervical hypoplasia after diethylstilbestrol exposure[210–213]; (3) intrauterine infection[214,215]; (4) a decline in progesterone action[216]; and (5) a cervical disorder that manifests as the clinical presentation of 'cervical insufficiency'. Each of these different causes of the syndrome could be affected by genetic or environmental factors. Moreover, more than one mechanism of disease may be operative in a patient. The possibility of novel and as yet undiscovered mechanisms of disease must also be considered.

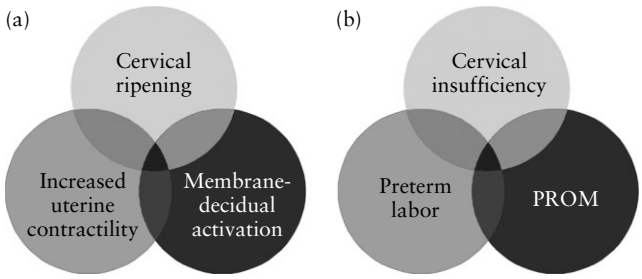

Figure 1 The common terminal pathway of preterm and term parturition (a) and the clinical manifestation of preterm activation (b). Modified from Romero *et al.*[88]. PROM, prelabor rupture of membranes.

Progesterone in women with a short cervix

Evidence suggests that the administration of vaginal progesterone[47,61] and 17 alpha-hydroxyprogesterone caproate[95] may be beneficial in patients with a short cervix or with clinically diagnosed cervical insufficiency[217]. However, the results of the most recent and promising randomized clinical trials[47,61], in which vaginal progesterone was administered to women with a sonographic short cervix, indicate that progesterone works in a subset of patients. For example, in the trial sponsored by The Fetal Medicine Foundation[47], the overall reduction of preterm birth in women with a cervical length of ≤ 15 mm was 44%. However, in women with an extremely short cervix (< 5 mm), progesterone administration was less effective (K. H. Nicolaides, pers. comm.). Why? One explanation is that women with a very short cervix may have already developed asymptomatic intrauterine infection and in such cases progesterone administration is ineffective. These patients may benefit from treatment with antibiotics and anti-inflammatory agents[195]. It is also possible that patients with an extremely short cervix have entered the irreversible phase of parturition, and intervention to prolong pregnancy would not be effective.

So far, evidence suggests that vaginal progesterone works in a subset of women with a cervical length ≤ 15 mm. However, the possibility must be considered that progesterone may work in women with a longer cervix. This would be consistent with the study of DeFranco *et al.*[61], which found that women with a cervix of < 28 mm and allocated to progesterone were more likely to deliver after 32 weeks. The implication of such

a finding is that progesterone may be effective in more women, as the frequency of a cervical length of ≤ 15 mm is 1.7%[47], while that of < 28 mm is about 10%[61,63] (an alternative is to use 25 mm as proposed by Iams *et al.*). This could expand the therapeutic range of progesterone (or progestogens if randomized clinical trials demonstrate effectiveness of 17 alpha-hydroxyprogesterone caproate in women with a sonographic short cervix).

The issue of risk must be considered carefully for any therapeutic intervention instituted during pregnancy. Questions of the safety of synthetic progestogens must be addressed[218], see also http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4227S1-index.htm. Follow-up information on infants exposed to progesterone during the second and third trimesters is necessary. The possibility that a sub-clinical insult may activate the cervical component of the pathway of parturition, resulting in a short cervix, and that prolongation of pregnancy with progestogens may come at a price, should not be overlooked[94].

Cervical ultrasound is a powerful tool in risk assessment for spontaneous preterm birth. It is simple to perform, inexpensive when performed at the time of second-trimester anomaly screening, informative, and can provide an estimate of risk for preterm delivery in primigravidae. We believe that measuring cervical length should be a standard part of sonographic examination in the mid-trimester. Other tools may help to refine the estimation of risk; for example, vaginal fibronectin[194,219], vaginal fluid analysis for other compounds[220], the collascope[221–224], amniotic fluid analysis[225–233], the presence/absence of amniotic fluid 'sludge'[197,234] and even genetic analysis of DNA variants of the progesterone receptor[19,235–237]. These may help to discriminate between patients who will respond to progestogens and those who will not. This could be an important step towards achieving 'personalized perinatal medicine' in the 21st century.

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