Universal Cervical Screening and Vaginal Progesterone to Prevent Preterm Birth

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Introduction

Preterm birth is recognized as the leading cause of perinatal morbidity and mortality worldwide. It is defined as one that occurs between fetal viability and 37 completed weeks of gestation (1-4). A common view is to treat preterm birth as a single condition. Yet, this may occur after the spontaneous onset of labor or may be “indicated” – resulting from induced preterm labor or preterm cesarean delivery for maternal complications (e.g. preeclampsia) or fetal disease (e.g. intrauterine growth restriction, congenital anomalies) (3, 5-9). Moreover, spontaneous preterm birth is a syndrome caused by multiple etiologies (these have been discussed elsewhere) (10). One cause is a decline in progesterone action, leading to cervical ripening. A sonographic short cervical length is a powerful predictor of spontaneous preterm delivery – the shorter the length in the midtrimester, the higher the risk (11-14). Evidence from randomized clinical trials and meta-analyses have shown that vaginal progesterone is an effective method to prevent preterm birth in those with a short cervix (15-16). This chapter will describe the prediction of spontaneous preterm birth using cervical length in the midtrimester and its prevention with vaginal progesterone, and discuss the concept of universal cervical length screening.

The Common Pathway of Parturition

Both preterm and term labor share a common terminal pathway. We have defined this “common pathway of parturition” as the anatomic, biochemical, endocrinologic, and clinical events that occur in both term and preterm labor (17-22). The common pathway consists of uterine (maternal and fetal) and extraterine components. The uterine components include increased uterine contractility, cervical ripening, and decidual/membrane activation (17,18). There are methods available to detect activation of each of these components of the common pathway. For example, changes in the cervix may lead to symptoms of vaginal pressure, and this may be detected by digital examination to document dilatation and effacement of the cervix. However, studies have shown that transvaginal sonography (vs. digital examination of the cervix to assess dilatation and effacement) is more accurate to predict the risk of preterm birth (11,23). Indeed, the most important advancement in diagnosing preterm labor has been the introduction of transvaginal sonography (11, 24-26). Ultrasound can assess cervical changes, because a short cervix is often a sign of effacement in progress.

A fundamental concept is that activation of the components of the common pathway appears clinically as an acute event. However, there is evidence that such activation has a long subclinical phase. For example, a patient with a short cervix in the midtrimester has a 50% risk of delivering a preterm neonate before 33 weeks of gestation, and the condition is “silent” clinically for weeks prior to the onset of preterm labor or preterm prelabor rupture of membranes (PPROM) (27). As a result, this long subclinical phase allows implementation of methods to predict preterm delivery (e.g. sonographic cervical length) and interventions to prevent it (28).
**Syndromic Nature of a Sonographic Short Cervix**

A short cervix is syndromic in nature, and may be the result of multiple conditions which are reviewed here (10, 22, 29). A sonographic short cervix may evolve into “cervical insufficiency”, or place the patient at risk for early spontaneous preterm birth.

1. **Risk factors for a short cervix**: a low body mass index (< 19.8 kg/m²), maternal age (< 20 years; > 35 years), and ethnicity (African-American or Afro-Carribean) are associated with a shorter cervical length (30). A combination of environmental and genetic factors may also play a role in determining cervical length. Polymorphisms in the genes encoding for transforming growth factor-β1 (TGF-β1) and collagen 1A1 (COL1A1) have been associated with cervical insufficiency (31, 32).

2. **History of prior preterm birth**: studies have reported a relationship between history of a prior preterm birth and cervical length in a subsequent pregnancy (33, 34). Guzman et al. observed that the frequency of a short cervix (length < 20 mm) or progressive shortening of the cervix to a length < 20 mm was associated with gestational age at delivery in the prior pregnancy (33). Iams et al. performed a cross-sectional study of cervical length in women with a prior preterm delivery ≤ 26 weeks, 27 to 32 weeks, and 33 to 35 weeks of gestation compared to women with “cervical incompetence”, and a normal control group delivered at term (34). There was a strong relationship between cervical length in the index pregnancy and prior obstetrical history.

3. **Congenital short cervix**: cervical hypoplasia after in-utero exposure to diethylstilbestrol (DES) has been reported (35-42), along with dysgenesis of the cervix (fragmented cervix with separations of segments and a thin, fibrous core) (43-46). These are rare disorders, and in most cases, have an unknown etiology.

4. **Cervical surgery**: cervical procedures, such as conization (47-51) or loop electrosurgical excision procedure (LEEP) (47-48), in which there is a loss of connective tissue, may lead to a short cervix.

5. **Intra-amniotic infection/inflammation**: a sonographic short cervix may be the only clinical manifestation of an intra-amniotic infection. Hassan et al. reported that in asymptomatic women with a cervical length < 25 mm in the midtrimester (without cervical dilation), 9% (5/57) had microbiologically proven intra-amniotic infection (52). The microorganisms that were isolated included *Ureaplasma urealyticum* and *Fusobacterium* spp.

Intra-amniotic inflammation (an elevation in amniotic fluid proinflammatory cytokines or chemokines) has also been reported in women having a sonographically short cervix in the midtrimester. Of 45 asymptomatic patients with a midtrimester cervical length ≤ 15 mm, intra-amniotic inflammation (amniotic fluid matrix metalloproteinase-8 concentration > 23 ng/mL) was demonstrated in 22% (n=10), and this was associated with an adverse pregnancy outcome (53). Patients with intra-amniotic
inflammation had a shorter median diagnosis-to-delivery interval than those without this condition, and 40% of those with intra-amniotic inflammation delivered within 7 days from the amniocentesis (53). Kiefer et al. reported an association between midtrimester cervical length \( \leq 5 \text{ mm} \) and increased amniotic fluid concentrations of the cytokine interleukin-6 (IL-6), and the chemokine monocyte chemotactic protein-1 (MCP-1) (54). A subsequent study of patients with a midtrimester cervical length \( \leq 25 \text{ mm} \) confirmed these findings, in which the amniotic fluid MCP-1 concentration was predictive of spontaneous preterm delivery (55).

Even in patients with the clinical diagnosis of cervical insufficiency (which may be considered part of the spectrum of disorders that shortens the cervix), the frequency of intra-amniotic infection/inflammation has been reported to be nearly 50% (56-58).

6. **Cervical insufficiency**: The term “cervical insufficiency” has replaced “cervical incompetence”, defined as the inability of the cervix to retain a pregnancy in the absence of contractions or labor (59). Cervical insufficiency has traditionally been applied to women with a history of recurrent midtrimester abortions and/or early preterm deliveries, in which the fundamental process is thought to be “failure of the cervix to remain closed during pregnancy” (60). Women often present with symptoms of vaginal pressure, and there is painless cervical dilatation. Unfortunately, there is no objective diagnostic test to identify patients at risk for cervical insufficiency, either before, or during early pregnancy. Thus, this is a clinical diagnosis (29).

7. **Suspension of progesterone action**: progesterone is a natural sex steroid produced by the corpus luteum, and then the placenta during pregnancy. It is a key hormone in the maintenance of pregnancy, and a decline in progesterone action has been implicated in the control of cervical ripening (61-63) and preterm labor (64-66). The role for progesterone in cervical ripening is supported by the following evidence: 1) administration of a progesterone receptor antagonist (RU486 or mifepristone) to women in the midtrimester and at term will ripen the cervix (63,67-71); and 2) administration of progesterone receptor antagonists (RU486 or onapristone) to pregnant guinea pigs (72-73), Old World monkeys (74), and *Tupaia belangeri* induces cervical ripening (63) and also labor.

With advancing gestational age, the cervical responsiveness to progesterone antagonists increases, and the effect on the cervix is not always accompanied by changes in myometrial activity (63). A functional dissociation between the effects of progesterone on the cervix and myometrium has been shown (75). In pregnant ewes, maternal progesterone supplementation at parturition inhibited uterine contractions, but not an increase in cervical compliance, demonstrating the independence of these two events (75).

Based upon the actions of progesterone, it is not surprising that investigators have explored the use of this hormone for the prevention of preterm birth (see below). The effect of vaginal progesterone in the prevention of preterm birth is believed to be related
to a pharmacologic correction of the decline or suspension of progesterone action, which is clinically manifest as a sonographically short cervix (28).

**How Should the Sonographic Cervical Examination be Performed to Assess the Risk for Preterm Delivery?**

When compared to a digital examination, sonographic evaluation of the cervix is less invasive, and is a more precise and objective method to assess cervical status (76). Transvaginal ultrasound is considered the “gold standard” to diagnose a short cervix during pregnancy (Figure 1), and its advantages (accuracy and acceptability for patients) have been described previously (11, 30, 77-86). The reported inter- and intra-observer variability of transvaginal sonography is < 5% (or 2 – 4 mm) (14,30). Using the transvaginal approach, definition of cervical anatomy is optimal with visualization of the cervix in all cases. More than 90% of women report experiencing either no, or only mild discomfort or embarrassment (30, 87), and transvaginal examination is even preferred to digital examination by most patients. The method of transvaginal sonographic examination of the cervix has been described elsewhere (28).

While several continue to propose that transabdominal cervical length assessment can be used to identify women with a short cervix (88-89), this approach is not recommend for several reasons. Visualization of the cervix using transabdominal sonography requires a distended maternal bladder to provide an acoustic window (90). Yet, even despite a full bladder, clear definition of anatomical landmarks is not always possible (91-92). To et al. reported that successful visualization of the cervix is a function of the volume of urine within the maternal bladder (93). When the urine volume was < 50 mL, the cervix was visualized in only 42% of women. Additionally, when the cervical length was < 20 mm (a length associated with an increased risk for preterm birth), visualization using transabdominal sonography occurred in only 13% of cases (93). A recent study comparing transabdominal to transvaginal sonography determined that a transabdominal measurement of cervical length was unable to identify 57% of cases with a short cervix (< 25 mm) as determined by transvaginal sonography (94). Therefore, many women with a true short cervix would be missed if they only underwent a transabdominal sonogram. It has also been reported that a distended bladder can compress and artificially increase the cervical length (Figure 2) (90, 93, 95, 96), thus leading to the underdiagnosis of a short cervix (Figure 3). Finally, when using transabdominal ultrasound, the image quality of the cervix is lower (than with transvaginal ultrasound) since there is greater distance between the probe and the cervix. When fetal parts are located close to the cervix, this can also obscure visualization.

In conclusion, screening for a short cervix using transabdominal sonography would underdiagnose this condition. This is important, because by not diagnosing a short cervix, this could preclude patients from receiving effective and safe therapy for the prevention of preterm birth, such as vaginal progesterone. Therefore, the use of transabdominal sonography is not appropriate to identify patients who should undergo a subsequent transvaginal ultrasound to diagnose a short cervix (94). Transvaginal
Cervical Length and the Risk for Preterm Delivery in Asymptomatic Patients

In the 1980’s, studies on the cervix using ultrasound began (26, 95, 97-103). Sonographic cervical length is a powerful predictor of spontaneous preterm delivery – the shorter the length in the midtrimester, the higher the risk (11-14). One of the earliest reports evaluating the relationship between a sonographic short cervix and the risk for spontaneous preterm birth was conducted by Andersen et al. (11). In this study, 113 women were evaluated by digital examination of the cervix, along with transabdominal and transvaginal sonography to evaluate cervical length. Endovaginal sonographic cervical length predicted an increased preterm delivery risk, regardless of parity or obstetrical history. However, transabdominal sonographic measurement of cervical length was not predictive of preterm delivery (11).

A curvilinear relationship exists between cervical length and the likelihood of preterm birth, as reported by Andersen et al. (11) and later confirmed by others (12, 13, 27). These results have also been reported by other investigators in both low- and high-risk patients (12, 13, 14, 27, 34, 82, 83, 104-117).

As part of a prospective study of screening tests to predict spontaneous preterm birth, conducted by the Maternal Fetal Medicine Network of the National Institute of Child Health and Human Development (NICHD), Iams et al. reported the relationship between cervical length and the risk of preterm delivery (13). A total of 2915 low-risk asymptomatic patients were examined by transvaginal sonography at 24 weeks of gestation, and then at 28 weeks of gestation to calculate the risk of delivery prior to 35 weeks. The relative risk of preterm delivery according to the distribution of cervical length values at 24 weeks of gestation is shown in Figure 4 (13). The association between cervical length and the risk for preterm delivery was evident across the entire range of cervical lengths. The diagnostic indices for different cutoff values of cervical length, funneling, and Bishop score are shown in Table 1.

Heath et al. later reported an important series of studies examining the value of cervical sonography in screening for preterm birth (12,30,118). In a low-risk population of 2567 women, cervical length was measured by transvaginal sonography at 23 weeks of gestation (12). Women with a prior history of preterm birth, of Afro-Caribbean origin, young maternal age (< 20 years), and low body mass index had a short cervix when compared to those without these risk factors. Yet, when logistic regression analysis was performed to examine the contribution of these parameters to the prediction of preterm birth (≤ 32 weeks), a short cervix was the only predictor of outcome (12). These findings suggest that demographic and clinical risk factors for preterm birth may operate through a short cervix. In this study, a cervical length of ≤ 15 mm at 23 weeks of gestation identified 60% of those who subsequently had a spontaneous preterm birth ≤ 32 weeks, and 80% of those who had a spontaneous preterm birth at ≤ 30 weeks (12).
Hassan et al. conducted a retrospective cohort study of 6877 women who underwent cervical sonography between 14 and 24 weeks of gestation (27). The authors confirmed that a short cervix increases the risk for preterm delivery. Additionally, the later in the midtrimester that sonographic examinations were performed (closer to 24 weeks of gestation), the greater was the predictive performance of cervical length for preterm delivery. The diagnostic indices of sonographic cervical length in low-risk, asymptomatic pregnant women according to different cervical length cutoffs are depicted in Table 2.

Sonographic cervical length is not a screening test for spontaneous preterm delivery, since only some patients who will have a spontaneous preterm birth have a short cervix in the midtrimester. However, sonographic cervical length is a method for risk assessment for spontaneous preterm delivery. It is the single most powerful predictor for preterm birth in the index pregnancy (27,120), and is far more informative than a history of prior preterm birth (27,121,122). This has implications in the selection of patients for future clinical trials, and also identifies those women who may benefit from vaginal progesterone administration to reduce the rate of spontaneous preterm birth (123).

**Sonographic Short Cervix and Vaginal Progesterone to Prevent Preterm Birth**

Two randomized clinical trials support that cervical length may identify women who could benefit from vaginal progesterone administration (123, 124). Fonseca et al., on behalf of the Fetal Medicine Foundation Second Trimester Screening Group, conducted a randomized, double blind, placebo-controlled trial in which women with a short cervix (≤15 mm by transvaginal sonography) between 20-25 weeks of gestation were allocated to either vaginal progesterone (200 mg of micronized progesterone daily) or placebo (safflower oil). The duration of treatment was from 24 to 34 weeks of gestation (123). The primary endpoint for this trial was the frequency of spontaneous preterm delivery < 34 weeks of gestation. Women receiving vaginal progesterone had a lower rate of preterm delivery < 34 weeks than those in the placebo group [19.2% (24/125) vs. 34.4% (43/125); p = 0.007]. The rate of adverse events was similar in the placebo and progesterone groups. A secondary analysis of the trial by Fonseca et al. 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 receiving placebo [17.9% (20/112) vs. 31.2% (34/109); relative risk (RR) 0.57, 95% confidence interval (CI) 0.35 – 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 (123). Twin gestations were also included in this trial; however, the number was small (n=24) (123).

The second trial examining the effects of vaginal progesterone on the rate of preterm birth in women with a sonographic short cervix was the PREGNANT trial (124). Hassan et al. conducted a multicenter, randomized, double-blind, placebo-controlled trial that enrolled asymptomatic women with a singleton gestation and a sonographically short cervix (10 – 20 mm) at 19 to 23-6/7 weeks of gestation. Women were randomly allocated to receive vaginal progesterone gel (90 mg) or placebo daily, starting between 20 and 23
+6/7 weeks of gestation until 36 +6 weeks of gestation, rupture of membranes, or delivery (whichever occurred first). The primary endpoint was preterm birth < 33 weeks of gestation. Women who received vaginal progesterone had a significantly lower rate of preterm birth < 33 weeks of gestation than those receiving placebo (8.9% vs. 16.1%; RR 0.55, 95% CI 0.33 – 0.92; p = 0.02; when adjusted for pooled study site and a history of prior preterm birth, RR 0.54, 95% CI 0.33 – 0.89, p = 0.01). It was estimated that 14 women having a short cervical length between 10 – 20 mm would need to be treated with vaginal progesterone to prevent one case of preterm birth < 33 weeks of gestation. Vaginal progesterone was also associated with a significant reduction in the rate of preterm birth < 28 weeks of gestation (5.1% vs. 10.3%; RR 0.50, 95% CI 0.25 – 0.97; p = 0.04) and < 35 weeks of gestation (14.5% vs. 23.3%; RR 0.62, 95% CI 0.42 – 0.92; p = 0.02).

In terms of infant outcome, neonates born to women allocated to receive vaginal progesterone had a significantly lower frequency of respiratory distress syndrome (RDS) than those receiving placebo (3% vs. 7.6%; RR 0.39, 95% CI 0.17 – 0.92, p = 0.03). The number needed to treat to prevent one case of RDS was 22. The reduction in RDS remained significant after adjusting for pooled study site and a history of preterm birth (RR 0.40, 95% CI 0.17 – 0.94, p = 0.03). It is noteworthy that the frequency of adverse events was similar in women allocated to vaginal progesterone and placebo, and there was no evidence of a potential safety signal (124).

The conclusion of the PREGNANT trial was that the administration of vaginal progesterone gel to women with a sonographic short cervix in the midtrimester was associated with a 45% reduction in the risk of preterm birth < 33 weeks of gestation and improved neonatal outcomes.

Because there were additional studies to the two described above, an individual patient meta-analysis of five randomized controlled trials was recently conducted (125). This is a specific type of systematic review in which original research data from each participant in a study are obtained directly from the investigators in a trial (126). This method is considered the “gold standard” to summarize evidence across clinical trials, since it offers several advantages (both statistically and clinically) over conventional meta-analyses that use aggregated data (127).

In this individual patient meta-analysis, the primary objective was to determine whether the use of vaginal progesterone in asymptomatic women with a short cervix in the midtrimester (≤ 25 mm) reduces the rate of preterm birth, and improves neonatal morbidity and mortality (125). The prespecified primary outcome was preterm birth at less than 33 weeks of gestation. Secondary outcomes included: preterm birth at < 37, < 36, < 35, < 34, < 30, and < 28 weeks of gestation; RDS; birth weight < 1500 grams; admission to the neonatal intensive care unit (NICU); and use of mechanical ventilation. Perinatal morbidity/mortality (secondary outcome measure) was assessed using a composite outcome, which was defined as the occurrence of any of the following events: RDS, intraventricular hemorrhage, necrotizing enterocolitis, proven neonatal sepsis, or neonatal death.
There were five high quality studies included, for a total of 775 women and 827 infants (123, 124, 128-130). Treatment with vaginal progesterone was associated with a significant reduction in the rate of preterm birth < 33 weeks of gestation (RR 0.58, 95% CI 0.42 – 0.80) (Figure 5). Vaginal progesterone treatment was also associated with a significant reduction in the rate of preterm birth < 35 weeks of gestation (RR 0.69, 95% CI 0.55 – 0.88), < 28 weeks of gestation (RR 0.50, 95% CI 0.30 – 0.81), RDS (RR 0.48, 95% CI 0.30 – 0.76), birth weight < 1500 grams (RR 0.55, 95% CI 0.38 – 0.80), admission to NICU (RR 0.75, 95% CI 0.59 – 0.94), requirement for mechanical ventilation (RR 0.66, 95% CI 0.44 – 0.98), and composite neonatal morbidity and mortality (RR 0.57, 95% CI 0.40 – 0.81) (125).

Subgroup analysis on the effect of vaginal progesterone was only performed for the primary outcome of preterm birth < 33 weeks of gestation, and for the secondary outcome of composite neonatal morbidity and mortality. The following results have clinical implications (125):

1. A daily dosage of 90 – 100 mg of progesterone was equivalent to a daily dosage of 200 mg in both the reduction of preterm birth and composite neonatal morbidity and mortality.
2. Vaginal progesterone was equally effective in women having a short cervix both without a history of prior preterm birth and those with a history of prior preterm birth, in reducing preterm birth < 33 weeks of gestation and composite neonatal morbidity and mortality.
3. No differences were shown in the effect of progesterone as a function of cervical length in women with a short cervix (< 25 mm) for the prevention of preterm birth or reduction of neonatal morbidity and mortality (as determined by a test of interaction).

Therefore, the collective evidence suggests that vaginal progesterone prevents preterm delivery at less than 33 weeks of gestation in women with a midtrimester short cervix, and this is also associated with a reduction in neonatal morbidity. Based upon the results of the individual patient meta-analysis (125), the indication for vaginal progesterone can also be extended to women with a history of spontaneous preterm birth who have a short cervix.

**Vaginal Progesterone to Prevent Preterm Birth in Twin Gestations**

An important question is whether vaginal progesterone prevents preterm delivery in twin gestations (131). Three randomized clinical trials have explored this question (without considering cervical length); two used vaginal progesterone (90 mg daily, in a bioadhesive gel) (132,133), while the third trial used 200 mg in the form of vaginal progesterone pessaries (130). All trials have been negative, and a logical question is whether a larger dose of vaginal progesterone for the prevention of preterm birth is required in twin gestations. Recently, Serra et al. conducted a randomized controlled double-blind multicenter trial in which women with dichorionic, diamniotic twin
gestations were randomized at 20 weeks of gestation to either placebo, or two different doses of vaginal progesterone in daily pessaries (one group received 200 mg, and the other group received 400 mg). (134). The primary end point of the study was preterm birth < 37 weeks of gestation. The rate of preterm birth at < 37, < 34, < 32, and < 28 weeks of gestation was not significantly different among the three groups. The frequency of a sonographic short cervix (< 25 mm) in this trial was low (1.7%; 5/290), and this may be one explanation for the negative results.

There are two observations from the trial of Serra et al. which should be noted (134). First, a higher dosage (400 mg vs. 200 mg) of vaginal progesterone did not yield efficacy. Second, higher doses of progesterone appeared to have side effects. A dose-dependent trend (non-significant) was noted towards a higher incidence of intrahepatic cholestasis among women treated with progesterone (134). Therefore, it is wise to use the lowest effective dose, even for a natural hormone that is present in high concentrations in the peripheral blood during pregnancy.

It is clear that regardless of the reason for lack of effectiveness of vaginal progesterone for the prevention of preterm delivery in twin gestations, further randomized clinical trials in unselected twin gestations does not seem justified (131). The question is whether randomized clinical trials have not focused on the specific population that could benefit from this treatment. A sonographic short cervix is also a powerful predictor of preterm birth in twin gestations (135,136). Indeed, the same cervical length confers a greater risk for preterm birth in twin, than in singleton pregnancies. A cervical length of ≤ 15 mm in singletons confers a 50% risk for preterm delivery at < 32 weeks of gestation (27), while the same risk is conferred to twin gestations by a cervical length of ≤ 25 mm (135). A systematic review and meta-analysis of twin gestations reported that among asymptomatic women, a cervical length ≤ 20 mm (at 20 – 24 weeks of gestation) was a major predictor of preterm birth < 32 and < 34 weeks of gestation (with pooled positive likelihood ratios of 10.1 and 9.0, respectively) (136). Thus, the question arises as to whether vaginal progesterone administered to women with dichorionic twin gestations and a short cervix can prevent preterm birth.

In the individual patient meta-analysis described above (125), a subgroup analysis in twin gestations with a cervical length of ≤ 25 mm was performed. Vaginal progesterone was associated with a non-significant trend towards reduction in the rate of preterm birth < 33 weeks of gestation (30.4% vs. 44.8%; RR 0.70, 95% CI 0.34 – 1.44). Yet, vaginal progesterone did lead to a significant reduction in composite neonatal morbidity and mortality (23.9% vs. 39.7%; RR 0.52, 95% CI 0.29 – 0.93). It is important to note that the observations are based upon a small number of patients; thus, the 30% decrease may not have reached statistical significance due to the small sample size. However, composite neonatal morbidity and mortality was significant when the sample size was larger.

It is clear that a properly designed randomized controlled trial in twin gestations is needed to determine the efficacy of vaginal progesterone to prevent preterm birth and neonatal morbidity and mortality in women with a short cervix (28,125,131).
17-alpha-hydroxyprogesterone Caproate in Women with a Short Cervix

“Progestogen” is a term which includes natural and synthetic compounds with progesterone-like action (137). 17-alpha-hydroxyprogesterone is a natural progestogen produced by the human body, and is abbreviated 17OHP. However, 17-alpha-hydroxyprogesterone caproate is a synthetic progestogen, and the human body does not produce the caproate molecule. The main reason for adding the caproate molecule is to prolong the half-life of the compound. However, this change alters the structure of the molecule, and could result in modifications of the pharmacologic or physiologic properties of the drug.

Recently, a multicenter randomized controlled trial was conducted in nulliparous women with a singleton gestation between 16 and 22 +3/7 weeks of gestation, and a cervical length < 30 mm (10th percentile in this population) (138). Women were randomized to receive weekly 250 mg intramuscular injections of 17-alpha hydroxyprogesterone caproate (17OHP-C) through 36 weeks, or an identical appearing placebo. The primary outcome was preterm birth < 37 weeks of gestation. Of 15,435 total women screened, 1588 (10.3%) had a cervical length < 30 mm. After 657 women had been randomized (n=327 17OHP-C and n=330 placebo), the study was ended by the Data Safety Monitoring Board after a planned interim analysis revealed that further enrollment was unlikely to demonstrate a significant difference between the study groups (138). There was no difference in the frequency of preterm birth < 37 weeks between the 17OHP-C and placebo groups (25.1% vs. 24.2%; RR 1.03, 95% CI 0.79 – 1.35). Moreover, there was no difference in the rate of preterm delivery < 35 weeks (13.5% vs. 16.1%; RR 0.84, 95% CI 0.58 – 1.21), or at < 32 weeks of gestation (8.6% vs. 9.7%; RR 0.88, 95% CI 0.54 – 1.43).

Subgroup analysis did not show any benefit from 17OHP-C in women with either a cervical length of < 15 mm, or at 10 – 20 mm (138). Based upon such evidence, weekly 17OHP-C intramuscular administration cannot be recommended for nulliparous patients having a short cervical length < 30 mm.

17 alpha-hydroxyprogesterone Caproate to Prevent Preterm Delivery in Women with a Prior History of Preterm Birth

Meis et al. conducted a double-blind, placebo-controlled trial of women with a history of prior spontaneous preterm birth in which women were enrolled at 16 to 20 weeks of gestation, and assigned to receive either weekly injections of 250 mg of 17OHP-C or an inert oil placebo (139). Injections were continued until delivery, or 36 weeks of gestation. The primary outcome was preterm delivery < 37 weeks of gestation. Treatment with 17OHP-C significantly reduced the risk of delivery at < 37 weeks of gestation (36.3% vs. 54.9%; RR 0.66, 95% CI 0.54 – 0.81). There was also a significant reduction in the rate of preterm delivery < 35 and < 32 weeks of gestation (139).
However, the results of this study have been the topic of question due to issues of efficacy and safety. Keirse has questioned the results because of the unexpectedly high frequency of preterm birth in the placebo group (54.9%; 84/153) (140). He has suggested that 17OHP-C may not have been effective because the rate of preterm birth in this group was 36.3% (139), which is similar to the baseline rate of preterm birth (37%) for a similar population (141), and the placebo group in another trial by the same investigators. In fact, the power calculation of the Meis et al. trial was based on observed rates of prematurity in a study by the Maternal-Fetal Medicine Units Network (141). The power calculation estimated that 37% of the women in the placebo group would deliver before 37 weeks of gestation (139-141). Similarly, FDA Officials analyzing this trial also indicated that the rate of preterm birth in the 17OHP-C group (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; see below).

It is not widely known that an initial randomized placebo-controlled study (with a target enrollment of 500 women) known as “17P-IF-001” was conducted by the Maternal-Fetal Medicine Units Network. The purpose of this study was to test the effectiveness and safety of 17OHP-C in the prevention of preterm birth < 37 weeks of gestation. However, after 150 women had been enrolled and treated, the study was prematurely ended because of a study drug recall, secondary to quality control issues. In women allocated to receive placebo, the rate of preterm delivery was 38.5% (15/39), while such rate was 43.1% (28/65) in those allocated to receive 17OHP-C (non-significant results). Yet, 38.5% is much lower than the 54.9% in the trial of Meis et al.(139).

As stated above, the high rate of preterm delivery in the control group (54.9%) has been the subject of debate. The investigators of this trial (139) have argued that the participants were at very high risk for preterm delivery based upon obstetrical history, ethnicity, and willingness to be randomized to a painful weekly injection. It has been suggested that the latter would apply mainly to highly motivated patients who were at substantial risk for preterm delivery. Yet, if this is the actual explanation for the high rate of preterm delivery in the control group (54.9%), this argument goes against the trial’s external validity. For example, if the rationale is that 17OHP-C is only effective in African-American women with bacterial vaginosis and more than one preterm birth (which were allegedly overrepresented in the control group), and who are strongly motivated to receive weekly intramuscular injections, then it is valid to ask whether 17OHP-C should be administered to women with a prior preterm birth, but do not have the other poor prognostic factors used to explain the high rate of preterm delivery in the control group (28).

An important issue with the administration of any drug is one of safety. Meis et al. reported an excess of miscarriages and stillbirths in those receiving 17OHP-C. Yet, this was not statistically significant. This finding was not discussed in the paper, in the Editorial which followed (142), or in subsequent articles and opinions of professional organizations (143-145). On August 29, 2006, this matter was first brought up by the medical officer of the FDA when reviewing the results of the trial at the Advisory
Committee meeting (146). A slide was produced by the FDA which indicated that women receiving 17OHP-C in the midtrimester had a higher rate of fetal and neonatal death in the first 66 days of treatment, than in those receiving placebo. This observation is known as a “safety signal” in pharmacovigilance. A safety signal is a non-statistical increase in the rate of adverse events during exposure to a drug (147). Data and Safety Monitoring Committees are appointed for several reasons; one is to monitor for adverse events or safety signals that may lead to termination of a trial due to unexpected risks. It is noteworthy that the FDA approval of the commercial preparation of 17OHP-C includes a warning that administration of this agent may increase the frequency of gestational diabetes and other complications, and requires physicians to inform potential patients of the numerically nonsignificant increase in the rate of stillbirth and spontaneous abortions. The interested reader can view the package insert: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021945s000lbl.pdf). Both the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) have recommended that patients be counseled appropriately and sign an informed consent when receiving 17OHP-C (Letter to Members, Friday, April 29, 2011).

The FDA has approved administration of 17OHP-C to prevent preterm birth in women with a prior history under Subpart H of the Code of Federal Regulations, which is a regulatory pathway used when the decision is based on a surrogate endpoint (delivery < 37 weeks of gestation), and further studies are necessary. Currently in the U.S., another randomized clinical trial of 17OHP-C is underway; women with a prior history of preterm birth will be allocated to receive either placebo or 17OHP-C. The primary endpoint is preterm delivery < 35 weeks of gestation. The originally predicted date for conclusion has been changed from October 2013 until 2016. Something to consider is that if professional organizations and regulatory agencies are truly convinced that 17OHP-C is effective, is it ethical to randomize women with a history of prior preterm delivery to receive a placebo? Another issue is a report that 17OHP-C may increase perinatal mortality. A recent double-blind, randomized clinical trial in mothers with triplet gestations who were randomly assigned to weekly injections of 250 mg 17OHP-C or placebo reported 13 midtrimester fetal losses in the treatment group (vs. none in the placebo group) (148). In France, a recent randomized controlled trial conducted in asymptomatic women with a twin gestation and short cervix (≤ 25 mm) reported that the rate of early preterm delivery (< 32 weeks of gestation) was significantly greater in patients given 17OHP-C compared to the placebo group (29% vs. 12%; p = 0.007) (149). Moreover, neonatal morbidity was slightly higher in the 17OHP-C group (but not significant). If the randomized clinical trial currently taking place in the U.S. is completed and yields negative results, the FDA has the authority to change the approval status of 17OHP-C.

An interesting clinical scenario is if a patient undergoing weekly injections of 17OHP-C (due to a prior history of preterm birth) is diagnosed with a short cervix (< 25 mm) in the midtrimester (28). The question is whether the patient should continue receiving 17OHP-C, or should this be discontinued and the patient switched to vaginal progesterone or undergo cerclage placement? 17OHP-C administration has not been
shown to be effective in women having a short cervix, and therefore, this agent should not be continued. No evidence also exists that 17OHP-C should be combined with vaginal progesterone and thus, this strategy cannot be recommended. Based upon the safety concerns of 17OHP-C, we recommend that the best strategy is to discontinue 17OHP-C, and begin treatment with vaginal progesterone, since this has proven to be effective in women with a short cervix and history of preterm birth (28,158).

**Patients with a Short Cervix, Prior Preterm Birth, and Singleton Gestation**

*(Cervical Cerclage vs. Vaginal Progesterone)*

There is evidence that patients with a sonographically short cervix (< 25 mm) and a prior history of preterm birth may benefit from placement of a cervical cerclage (150). Such evidence is derived from a meta-analysis of five randomized clinical trials of women diagnosed with a short cervix prior to 24 weeks of gestation, in which cerclage was compared to expectant management (151-155). Women receiving a cerclage had a lower rate of preterm birth < 35 weeks of gestation (primary outcome) than the no cerclage group [28.4% (71/250) vs. 41.3% (105/254); RR 0.70, 95% CI 0.55 – 0.89]. Cerclage placement also reduced preterm birth < 37, < 32, < 28, and < 24 weeks of gestation. Regarding composite perinatal morbidity and mortality, this was significantly reduced in the cerclage vs. no cerclage group (15.6% vs. 24.8%; RR 0.64, 95% CI 0.45 – 0.91). Recently, two professional organizations have recommended that cerclage may be considered for the treatment of women with a singleton gestation, prior spontaneous preterm birth, and short cervical length (< 25 mm) at < 24 weeks of gestation (156-157).

Hence, there are two interventions that may reduce the rate of preterm delivery in patients with a history of preterm birth and a short cervix (< 25 mm): vaginal progesterone administration or cervical cerclage. Yet, this situation could create a dilemma for physicians and patients about the optimal choice of treatment. There are no randomized controlled trials comparing vaginal progesterone and cervical cerclage directly for the prevention of preterm birth in women with a midtrimester sonographic short cervix, singleton gestation, and history of prior spontaneous preterm birth (158). In the absence of such evidence, indirect meta-analysis has emerged as an accepted and valid method for the comparison of competing interventions with the use of a common comparator (159-162). Such indirect meta-analysis of randomized clinical trials comparing vaginal progesterone vs. placebo, and cerclage vs. expectant management in patients with a singleton gestation, history of preterm birth, and midtrimester cervical length < 25 mm was recently performed (158). The conclusion was that the efficacy of both interventions (cervical cerclage or vaginal progesterone) is similar in the prevention of preterm birth or adverse perinatal outcomes, and patients can thus be treated with either intervention (Table 3). Consideration of patient/physician preference and costs should be taken into account. For example, vaginal progesterone administration requires patient compliance. Placement of a cervical cerclage requires anesthesia and surgery, and has been associated with complications (e.g. bleeding, rupture of membranes) (28).

**Universal Cervical Screening, Vaginal Progesterone, and Cost Effectiveness**
Cervical sonography is a powerful tool in performing risk assessment for spontaneous preterm birth. It is simple to perform, safe, acceptable, reproducible, informative, inexpensive (when performed at the time of the second trimester fetal anatomy survey), and can provide an estimate of risk in primigravid women. Due to the current availability of a treatment strategy for women with a short cervix (vaginal progesterone), the question arises whether we should actively search for this population of women, or if we should restrict offering vaginal progesterone to those women whose short cervix has been detected incidentally (163). As described in recent Editorials (15,164), universal cervical length screening fulfills all of the general principles outlined by the World Health Organization (WHO) for a good screening tool (165). It screens for an important adverse outcome (preterm birth), uses an acceptable and suitable screening test (transvaginal sonography), and there is an effective treatment (vaginal progesterone) available to those identified by screening (Table 4) (163, 166).

Therefore, we (and others) believe that measuring cervical length should be part of the standard sonographic examination in the midtrimester of pregnancy (15,164,167-169). For screening to be effective, however, sonographic examinations should be performed using proper transvaginal technique to yield accurate results, and continuing quality control and monitoring should be implemented (166,167). Transabdominal cervical length screening cannot be recommended for reasons discussed previously. To ensure quality, the Perinatal Quality Foundation of the U.S. has obtained consensus from multiple organizations and teamed with experts to produce the Cervix Length Education and Image Review (CLEAR) website (170), which provides education on cervical length measurements, a web-based examination, and cervical length image review. It has been recommended that clinicians should refrain from screening at different gestational ages, and refrain from “stretching” the definition of a short cervical length to include measurements > 25 mm (167). Performing cervical sonography outside of the studied gestational age (18 – 24 weeks) and applying treatment to women outside studied cervical length ranges may potentially result in adverse unintended consequences (166).

Adoption of universal cervical length assessment is currently being considered as a preterm birth prevention strategy (171). Guidelines from the Society for Maternal-Fetal Medicine state that although universal cervical length screening remains controversial, “implementation of such a screening strategy should be viewed as reasonable, and can be considered by individual practitioners; third-party payers should not deny reimbursements for this screening” (166). An evidence-based algorithm for prediction and prevention of preterm birth based on transvaginal ultrasound cervical screening and selected interventions can be offered (166).

Routine assessment of the risk for preterm birth using cervical ultrasound, along with vaginal progesterone for those with a short cervix, has been shown to be cost-effective and cost-saving (172, 173). A recent economic analysis evaluated different strategies to reduce the rate of preterm delivery, including: 1) identifying patients at risk according to previous history; 2) sonographic examination of the cervix; and 3) treatment modalities, including cervical cerclage, 17-alpha hydroxyprogesterone caproate, and vaginal progesterone (172). The authors concluded that universal assessment of cervical
length by transvaginal sonography followed by vaginal progesterone administration was the most cost-effective approach (172). Universal cervical ultrasound screening in singletons is predicted to result in a reduction of approximately 100,000 preterm births (<37 weeks) annually in the United States (172), or about 20% of all preterm births. Similarly, universal cervical screening and vaginal progesterone administration to those with a short cervix would lead to a cost savings of $19 million per 100,000 pregnant woman, or $500-750 million per year in the United States alone (28,173). Recently, the cost-effectiveness of vaginal progesterone treatment for the prevention of preterm birth over a wide range of short cervical length measurements was determined (174). Vaginal progesterone was found to be an effective and inexpensive intervention, with the greatest reduction in preterm birth observed in the 10 – 14 mm cervical length group. Based upon these considerations, the state of Michigan has implemented universal cervical screening and treatment with vaginal progesterone. Other investigators support and recommend this policy as well (167, 168).

In conclusion, patients with a short cervix (10 – 20 mm) should be offered vaginal progesterone to prevent preterm birth and to lead to an improvement in neonatal outcomes. Universal cervical screening by transvaginal ultrasound in the midtrimester followed by the use of vaginal progesterone appears to be cost-effective, and allows the prevention of preterm delivery in nulliparous women (172, 173). However, this approach is only one of the solutions for the prevention of preterm birth. Interventions can only be expected to be successful if they interrupt the specific pathway leading to preterm delivery (28). Future clinical trials of preventive methods should be intelligently designed by keeping this concept in mind.
References:


127. Stewart LA, Parmar MK. Meta-analysis of the literature or of individual patient data: is there a difference? Lancet 1993;341:418-22.


140. Keirse MJ. Progesterone and preterm: seventy years of "deja vu" or "still to be seen"? Birth 2004;31:230-5.


161. Wells GA, Sultan A, Chen L, Khan M, Coyle D. Indirect evidence: indirect treatment comparisons in meta-analysis. Ottawa, Canada: Canadian Agency for Drugs and Technologies in Health; 2009.


Figure 1: Transvaginal ultrasound of the cervix (length 37.1 mm). This is the “gold standard” for the performance of cervical examinations during pregnancy. Note that visualization of cervical anatomy and measurement of cervical length is optimal.
Figure 2: Transabdominal ultrasound performed in a patient with a full bladder and preterm prelabor rupture of membranes (PPROM). The bladder is causing compression and artificial lengthening of the cervix (length 36.8 mm). A pool of amniotic fluid is seen in the vaginal vault surrounding the external cervical os. The region of the internal os is not well visualized and is obscured by the fetal head.
Figure 3: Same patient as in Figure 2, but with the bladder emptied and transvaginal sonography performed. Note that the true cervical length is much shorter (17.3 mm).
Figure 4: Distribution of subjects among percentiles for cervical length measured by transvaginal ultrasonography at 24 weeks of gestation (solid line) and relative risk of spontaneous preterm delivery before 35 weeks of gestation according to percentiles for cervical length (bars). The risks among women with values at or below the 1st, 5th, 10th, 25th, 50th, and 75th percentiles for cervical length are compared with the risk among women with values above the 75th percentile.

Source: Reference 13
Figure 5: Effect of vaginal progesterone on preterm birth < 33 weeks of gestation (individual patient meta-analysis of five randomized controlled trials)

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative risk (fixed) (95% CI)</th>
<th>Vaginal progesterone n/N</th>
<th>Placebo n/N</th>
<th>Weight (%)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fonseca 2007</td>
<td>[0.58 (0.36-0.92)]</td>
<td>22/125</td>
<td>38/125</td>
<td>45.4</td>
<td></td>
</tr>
<tr>
<td>O’Brien 2007</td>
<td>[0.40 (0.05-3.13)]</td>
<td>1/12</td>
<td>4/19</td>
<td>3.7</td>
<td></td>
</tr>
<tr>
<td>Rode 2011</td>
<td>[1.20 (0.40-3.63)]</td>
<td>3/7</td>
<td>5/14</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>Hassan 2011</td>
<td>[0.55 (0.33-0.92)]</td>
<td>21/235</td>
<td>36/223</td>
<td>44.1</td>
<td></td>
</tr>
<tr>
<td>Cetingoz 2011</td>
<td>[0.33 (0.04-2.91)]</td>
<td>1/9</td>
<td>2/6</td>
<td>2.9</td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td>[0.58 (0.42-0.80)]</td>
<td>48/388</td>
<td>85/387</td>
<td>100.0</td>
<td></td>
</tr>
</tbody>
</table>

Source: Reference 125
Table 1: Diagnostic indices and predictive values of cervical length, funneling and Bishop score for prediction of preterm delivery before 35 weeks of gestation*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cervix at 24 wk</th>
<th>Cervix at 28 wk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤20 mm</td>
<td>≤25 mm</td>
</tr>
<tr>
<td>% Sensitivity</td>
<td>23.0</td>
<td>37.3</td>
</tr>
<tr>
<td>% Specificity</td>
<td>97.0</td>
<td>92.2</td>
</tr>
<tr>
<td>% Positive predictive value</td>
<td>25.7</td>
<td>17.8</td>
</tr>
<tr>
<td>% Negative predictive value</td>
<td>96.5</td>
<td>97.0</td>
</tr>
</tbody>
</table>

* The rate of spontaneous delivery before 35 weeks of gestation was 4.3% among the women examined at 24 weeks, and 3.3% among those examined at 28 weeks of gestation

Source: Reference 13
Table 2: Diagnostic indices of sonographic cervical length in low-risk, asymptomatic pregnant women according to different cervical length cutoffs

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n</th>
<th>Gestation (weeks)</th>
<th>Cutoff (mm)</th>
<th>Definition of PTD (weeks)</th>
<th>Prevalence of PTD (%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andersen et al.</td>
<td>1990</td>
<td>113</td>
<td>&lt; 30</td>
<td>&lt; 39</td>
<td>&lt; 37</td>
<td>15</td>
<td>76</td>
<td>59</td>
<td>25</td>
<td>93</td>
</tr>
<tr>
<td>Tongione et al.</td>
<td>1995</td>
<td>730</td>
<td>26–30</td>
<td>≤ 35</td>
<td>&lt; 37</td>
<td>12</td>
<td>66</td>
<td>62</td>
<td>20</td>
<td>93</td>
</tr>
<tr>
<td>Iams et al.</td>
<td>1996</td>
<td>2915</td>
<td>24</td>
<td>&lt; 20</td>
<td>&lt; 35</td>
<td>4</td>
<td>23</td>
<td>97</td>
<td>26</td>
<td>97</td>
</tr>
<tr>
<td>Taipale et al.</td>
<td>1998</td>
<td>3694</td>
<td>18–22</td>
<td>≤ 25</td>
<td>&lt; 37</td>
<td>2</td>
<td>6</td>
<td>100</td>
<td>39</td>
<td>99</td>
</tr>
<tr>
<td>Hillesmaa et al.</td>
<td>1998</td>
<td>23</td>
<td>14–24</td>
<td>≤ 15</td>
<td>≤ 32</td>
<td>1.5</td>
<td>58</td>
<td>99</td>
<td>52</td>
<td>99</td>
</tr>
<tr>
<td>Hassan et al.</td>
<td>2000</td>
<td>6877</td>
<td>14–24</td>
<td>≤ 15</td>
<td>≤ 32</td>
<td>3.6</td>
<td>8</td>
<td>99</td>
<td>47</td>
<td>97</td>
</tr>
</tbody>
</table>

NPV = negative predictive value; PPV = positive predictive value; PTD = preterm delivery

Source: Reference 119
Table 3: Results of an indirect patient meta-analysis of randomized clinical trials comparing vaginal progesterone vs. placebo and cerclage vs. expectant management in women with singleton gestations, history of preterm birth, and midtrimester cervical length < 25 mm

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Indirect comparison: vaginal progesterone vs. cerclage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>Preterm birth &lt; 32 weeks</td>
<td>0.70 (0.33 – 1.50)</td>
</tr>
<tr>
<td>Preterm birth &lt; 28 weeks</td>
<td>0.71 (0.27 – 1.88)</td>
</tr>
<tr>
<td>Preterm birth &lt; 35 weeks</td>
<td>0.88 (0.51 – 1.52)</td>
</tr>
<tr>
<td>Preterm birth &lt; 37 weeks</td>
<td>1.19 (0.82 – 1.74)</td>
</tr>
<tr>
<td>Perinatal mortality</td>
<td>1.05 (0.30 – 3.64)</td>
</tr>
</tbody>
</table>

For the test of association

Source: Modified from reference 158
Table 4: Cervical length as a screening test in singleton gestations

<table>
<thead>
<tr>
<th>Characteristic of screening test</th>
<th>Comments</th>
<th>TVU fulfills criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease is clinically important</td>
<td>PTB: no. 1 cause of perinatal mortality and morbidity in developed countries; associated with 1 million deaths annually worldwide</td>
<td>Yes</td>
</tr>
<tr>
<td>Disease is clearly defined</td>
<td>Birth &lt;37 wk</td>
<td>Yes</td>
</tr>
<tr>
<td>Disease prevalence is well known</td>
<td>12% in United States, about 10% worldwide</td>
<td>Yes</td>
</tr>
<tr>
<td>Disease natural history is known/recognizable</td>
<td>First cervical changes associated with inter PTB occur at internal os, and can only be detected early by ultrasound</td>
<td>Yes</td>
</tr>
<tr>
<td>Screening</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screening technique well described</td>
<td>Described in several articles</td>
<td>Yes</td>
</tr>
<tr>
<td>Screening is safe and acceptable</td>
<td>TVU is safe even in woman with PPROM; 90% of women would have TVU again; &lt;2% have severe pain</td>
<td>Yes</td>
</tr>
<tr>
<td>Screening has reasonable cutoff identified</td>
<td>20 mm is 5th percentile, 25 mm is 10th percentile in general US population</td>
<td>Yes</td>
</tr>
<tr>
<td>Results are reproducible (reliable)</td>
<td>&lt;10% intraobserver and interobserver variability</td>
<td>Yes; extremely important to control quality of TVU CL</td>
</tr>
<tr>
<td>Results are accurate (valid)</td>
<td>Better than manual examination; predictive in all populations studied</td>
<td>Yes</td>
</tr>
<tr>
<td>Intervention, cost-effectiveness, and feasibility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>“Early” intervention is effective</td>
<td>Two positive randomized trials both reported that using vaginal progesterone for short TVU CL is effective in preventing preterm birth</td>
<td>Yes</td>
</tr>
<tr>
<td>Screening and treating abnormalities is cost-effective</td>
<td>Two cost-effectiveness articles published</td>
<td>Yes, in fact cost-saving</td>
</tr>
<tr>
<td>Facilities for screening are readily available</td>
<td>All pregnancies are offered ultrasound for fetal anatomy screening at around 18-24 wk</td>
<td>Yes, but must be properly organized</td>
</tr>
<tr>
<td>Facilities for treatment are readily available</td>
<td>Vaginal progesterone is easily administered as outpatient</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Source: Reference 167