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EXPERT
REVIEWS

Cervical length for the prediction and prevention of preterm birth

Expert Rev. Obstet. Gynecol. 8(4), 345–355 (2013)**Mariarosaria Di Tommaso*¹ and Vincenzo Berghella²**¹*Division of Obstetrics and Gynecology, Department of Health Sciences, University of Florence, Viale Gaetano Pieraccini 24, 50139 Firenze, Italy*²*Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, Thomas Jefferson University, 834 Chestnut St. Suite 400, Philadelphia, PA 19107, USA**Author for correspondence: mariarosaria.ditommaso@unifi.it

The risk of early birth increases markedly with decreasing cervical length (CL) in both singleton and multiple pregnancies. Transvaginal ultrasound of CL can be useful in determining women that are at risk of preterm delivery and may be helpful in preventing unnecessary intervention. Appropriate technique is essential for correct results. Factors that affect the value of CL in the prediction of spontaneous preterm delivery include gestational age, patient obstetrical and medical history, symptoms and the number of fetuses. The value of CL consists of identifying high-risk women for therapeutic strategies, to reduce the rate of spontaneous preterm birth, such as progestogens, cervical cerclage and more recently, cervical pessary. Progestogens and cervical cerclage are more effective in gestations with prior preterm birth.

KEYWORDS: cerclage • cervical length • cervical pessary • prediction • preterm birth • progestogens

Recently, and for the first time in the past 30 years, the incidence of spontaneous preterm birth (sPTB) in the USA has decreased from 12.8% in 2006, to 11.7% in 2011 [1]. The reasons for this decrease are not well known, but in the last two decades, great efforts have been made in order to find an effective screening test to identify women that are at higher risk of sPTB. Although a major risk factor for sPTB is a previous sPTB, it is also recognized that the majority of women who have experienced sPTB did not have a previous sPTB in their history.

Predicting sPTB through study of the cervix is the conclusion of dozens of ultrasound studies, which show that the cervix starts to shorten weeks before delivery. The process begins at the internal os, and early detection of these changes can be crucial for intervention. By the time shortening is recognizable, a marked microstructural change has already occurred [2]. In fact, cervical softening is another critical process that precedes labor and sPTB, as well as cervical shortening. Recently, current data suggest that cervical microstructural changes also occur during specific stages of cervix remodeling: tissue hydration, collagen structure, and tissue elasticity all change progressively with cervical remodeling. Hydration increases, collagen disorganizes and elasticity (softness) increases before labor [3]. Traditionally, both shortening

and softening of the cervix have been evaluated by digital examination, which is subjective and suffers from a wide variability among examiners [4,5]. Moreover, the clinical usefulness of non-objective tests in assessing cervical softening is still limited by practical and economic issues. Ultrasound cervical sonography, in contrast, is supported by ample evidence as a method for assessing cervical length (CL) as a screening test in the prediction of sPTB [6,7].

The objectives of this review are to assess technical and clinical aspects of transvaginal cervical sonography; factors that affect the value of CL in the prediction of sPTB: gestational age, patient obstetrical and medical history, symptoms and the number of fetuses, and the value of CL in addressing therapeutic strategies to prevent PTB.

The authors searched PubMed, Ovid, EMBASE and Cochrane for all articles with key words 'cervical length', 'prediction of preterm birth', 'prevention of preterm birth', 'transvaginal ultrasound'. Preference was given to articles that were randomized trials or meta-analyses of such randomized studies.

Technical & clinical aspects of transvaginal cervical sonography

Transvaginal ultrasonography (TVU) CL assessment is the gold standard and preferred screening test for a short cervix. TVU is more

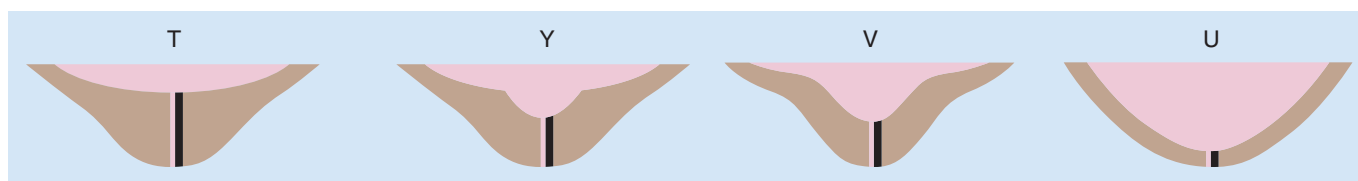


Figure 1. Black lines indicate the correct measurement of cervical length in the different shapes of cervical length: T, Y, V and U.

sensitive than transabdominal ultrasound. Transabdominal measurements overestimate CL by 8 mm among women with a short cervix, and have resulted in underdiagnosis of 57% of cases [8,9]. Transperineal or translabial ultrasound, a noninvasive technique, has also been proposed. However, it is limited because gas in the rectum may obstruct the view of the external os [10].

The appropriate technique to measure CL accurately using TVU requires the insertion of a clean probe covered by a condom in the anterior fornix of the vagina, after the woman has emptied her bladder [11]. When a sagittal long-axis view of the entire endocervical canal has been obtained, the probe can then be withdrawn slowly until the image loses its focus. At this point, slight pressure has to be given in order to obtain the image again, which should then be enlarged until the cervix occupies at least two-thirds of the screen and both the external and internal os are seen. Excessive pressure on the cervix can elongate it. CL has to be measured from the internal to the external os along the endocervical canal. It appears as a line of echodensity between the two ora. After obtaining three measurements, the shortest measurements in millimeters should be recorded. Then, a transfundal pressure for 15 s has to be applied before recording CL again at least three-times. TVU measurements are affected by the degree of pressure applied with the ultrasound transducer on the cervix, which can slightly change the orientation and measurements. TVU CL is not affected by maternal obesity, position of the cervix or shadowing from the fetal presenting part [12,13]. Maternal age, uterine contractions and cervical dynamic changes can also affect the measurement [14,15]. It has been reported that women younger than 20 years of age have longer cervixes than older women [14], and that uterine contractility and bowel peristalsis can modify CL by up to 5 mm [15].

The recommended scan time is at least 5 min, and the shortest and best CL has to be reported for clinical management [11]. The interobserver variability is 5–10% [16].

The rate of failed images of CL ranges between 10 and 20%, and skill is required for accurate TVU CL measurement [17,18]. It has also been suggested that providers need to be specifically trained in order to perform TVU CL [101,102]. In spite of statistically significant differences in CL between nulliparous and multiparous women, these differences are clinically unimportant [7].

The anatomic relationship of the sonographic internal os to the low uterine segment defines the shape of the sonographic junction, and it is qualitatively described as a T, Y, V or U [19].

Moving from a T to a U shape increases the severity of the finding. The TVU report may include funneling of the sonographic internal os, so that the following parameters may be reported: functional CL, which is the closed part of the cervix; funnel length, which is the open part of the cervix and funnel width

(FIGURE 1) [20]. Studies have established that progressive cervical effacements precede uterine contraction by several weeks in both normal and sPTB [21,22]. Overall, functional CL is the preferred method in establishing the risk of sPTB, considering that, if funneling is present, the CL is almost always short (FIGURE 2).

TVU can also help in recognizing other ultrasound risk indications for preterm delivery, including intra-amniotic sludge and choriodecidual separation [23,24]. Ultrasonography shows intra-amniotic sludge as suspended hyperechogenic material near the uterine cervix in the amniotic fluid. It could indicate intrauterine microbial invasion. Intra-amniotic sludge also represents an independent risk factor both for histologic chorioamnionitis and microbial colonization of the amniotic cavity; and for preterm premature membrane rupture and spontaneous preterm delivery. The combination of sludge and a CL <25 mm results in a higher risk for sPTB delivery at <28 and 32 weeks, than that of a short cervix alone. There is no sufficient evidence that intra-amniotic sludge alone can better the prediction accuracy already provided by CL [23].

The detachment of fetal membranes from the decidua, at the level of the internal os, 'the moon sign', is reported to be associated with an increased risk of premature preterm rupture of membranes and sPTB [25,26].

Factors that affect the value of CL for the prediction of spontaneous sPTB: gestational age, patient obstetrical & medical history, symptoms & number of fetuses

Gestational age

CL before 14 weeks is usually normal, except in women with a previous large cone biopsy or recurrent second trimester miscarriages. It is usually therefore not very effective to use TVU CL to screen for sPTB before 14 weeks, because at this gestational age CL can be falsely reassuring due to the endocervical canal continuity with the lower uterine segment. Nonetheless, the earlier in gestational age the short TVU CL is detected, the higher the percentage risk of preterm birth.

The biological variation of CL, as measured by endovaginal ultrasound in the second trimester of pregnancy, is normally distributed and resembles a normal bell-shaped curve. FIGURE 3 is a graphic summary of the longitudinal course of CL during singleton pregnancies, between 12 and 32 weeks [27]. At 24 weeks gestation, the 50th percentile is approximately 35 mm and the tenth and 19th percentiles are 25 and 45 mm, respectively. The tenth percentile is 25 mm at 24 weeks for a low-risk population. Using 25 mm as a cut off for CL in a low-risk population with a singleton pregnancy, the sensitivity and the positive prediction values for sPTB before 35 weeks gestation are 37 and 18%, respectively [7]. The relative risk of sPTB before 35 weeks is inversely related to TVU CL [7].

Patients with a CL <15 mm have an approximate 50% likelihood of preterm delivery <32 weeks, regardless of risk factors [28–30]. It is also possible to calculate the individual risk for sPTB based on CL and other risk factors [30].

In an unselected European population of 24,640 pregnant women screened at 20–25 weeks gestation, only 413 women (1.7%) women showed CL ≤15 mm [31]. In an unselected North American population of 32,091 pregnant women screened at 19–23 weeks gestation, 733 (2.3%) showed CL between 10 and 20 mm [32].

Although the measurement of CL has become a fundamental part of clinical practice, several obscure points remain and most women with a short cervix (especially without a history of sPTB) deliver at term without intervention. One explanation of the low sensitivities and positive predictive value of CL <25 mm is due to the fact that in a low-risk population, the incidence of sPTB is low.

Patient obstetrical & medical history

Patients with a history of sPTB show an increased risk of sPTB in subsequent pregnancies [16,33]. In the Preterm Prediction Study, Iams *et al.* reported that in patients with a prior spontaneous preterm birth, the recurrence risk of preterm birth varies widely according to both fetal fibronectin and CL at 22–24 weeks [34].

The best predictive value of CL is shown in a high-risk population with previous sPTB. Most women who deliver preterm, especially if they have had a previous sPTB, show CL <25 mm between 16 and 24 weeks. Short CL in pregnancy has been related to repetitive preterm birth and women with a short cervix during pregnancy are more likely to have had a previous sPTB [33,34]. The association between CL and sPTB is strongest in women with a prior sPTB, and this association is particularly evident when the previous sPTB occurred before 32 weeks [34–36].

TVU CL <3 cm between 24 and 30 weeks in women with history of sPTB is predictive of sPTB in both the two subtype groups of high-risk women: premature preterm rupture of membranes and intact membranes at the beginning of sPTB [37].

In a prospective, blinded observational study conducted in women with singleton pregnancies who had experienced at least one prior sPTB before 32 weeks, TVU CL less than 25 mm at 16–18 weeks gestation was a significant predictor of sPTB before 35 weeks. The sensitivity and the positive predictive value for sPTB before 35 weeks were 69 and 55%, respectively [38]. A history of more than one induced abortion is also a risk factor for short CL, with a relative risk for sPTB of 3.3 [39].

Besides previous sPTB, short CL during pregnancy can be the consequence of several factors: congenital malformations [40,41], previous surgery of the uterine cervix [42–44], subclinical intra-amniotic infection and/or inflammation [45–49] and cervical insufficiency [50,51].

Among congenital malformation groups, women pregnant with a unicornuate uterus have been reported to show the highest incidence of cervical shortening and sPTB [52]. The number of sPTB increases with the number of previous conizations [42].

In asymptomatic singleton pregnancies at 14–24 weeks with a short cervix of less than 25 mm, amniocentesis identifies microbial

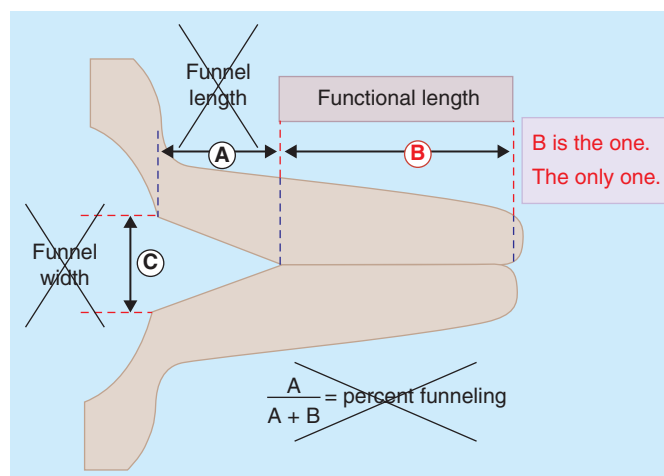


Figure 2. Measurements of the cervix with funneling.

(A) Funnel length, (B) functional length and (C) funnel width.

Adapted with permission from [20].

invasion in 9% of the women if *Mycoplasma* and *Ureaplasma* are also cultured for. Of those, 40% delivered before 32 weeks [53], underlying the relationship between inflammation/infection and sPTB.

Patients with symptoms of labor

In pregnancies with symptoms of spontaneous preterm labor (PTL), the clinical dilemma revolves around the issue of whether the woman is in true PTL requiring hospitalization and administration of tocolytics in order to prolong pregnancy for induction of fetal lung maturity. Symptoms consist of painful contractions and/or leaking fluid in the case of preterm premature rupturing of membranes, bleeding as an indicator of placental abruption, and fever as an indicator of chorioamnionitis. These women can be identified by TVU CL at presentation. The women with PTL at highest risk of PTB are those with a CL of <15 mm [54].

Ness proposes the use of a protocol in which the combination of TVU CL and fetal fibronectin is used for the management of women with threatened preterm labor at 24–34 weeks of gestation identifying women in whom treatment can provide benefit and optimizing use of resources (FIGURES 2 & 4) [55].

Amniocentesis and TVU CL were carried out in singleton pregnancies admitted in PTL, in order to examine the association between short CL and microbial invasion in the amniotic cavity. Microbial invasion, mainly *Ureaplasma urealyticum*, was found in 26% of the women with a CL of less than 15 mm, compared with 4% in those with a cervix of more than 15 mm, and 1.9% when the cervix length was more than 30 mm [56].

TVU appears to be safe in patients with preterm premature rupture of membranes and does not increase the risk of infection, although there are conflicting results about the predictive value of CL for latency [57,58]. A TVU CL <10 mm and cervical funneling >75% shows a predictive role for preterm premature rupture of membranes in high-risk patients [59]. There is a relation between TVU CL and vaginal bleeding during pregnancy.

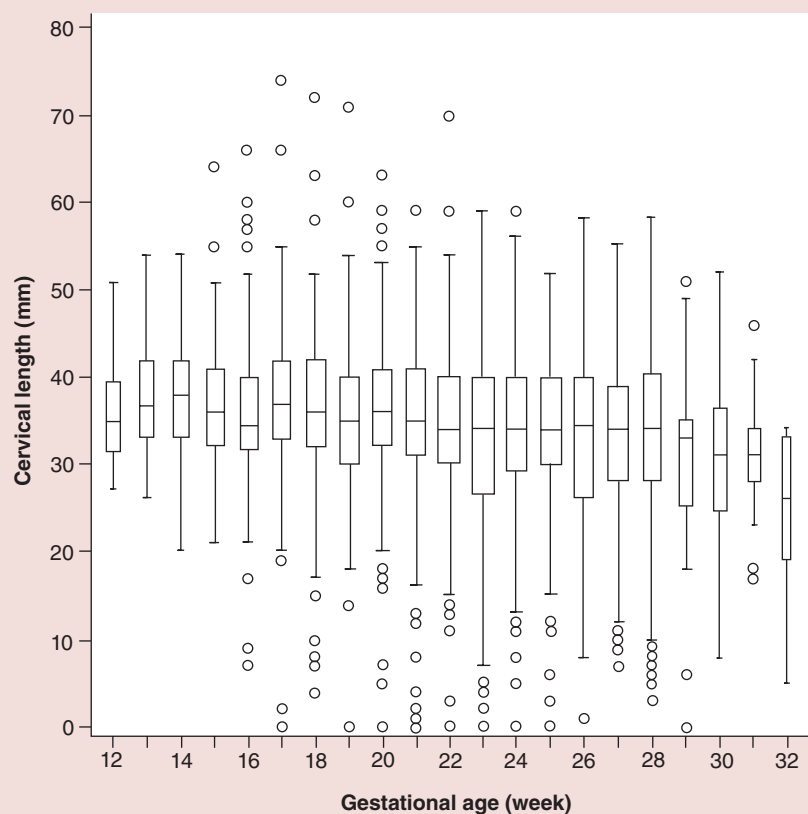


Figure 3. Cervical length by gestational age. The lower and upper edges of each box plot denote the 25th and 75th percentiles, respectively, and the horizontal line inside the box denotes the median. The vertical lines extend out up to 1.5-times the interquartile range (the height of the box). The width of each box plot is proportional to the square root of the number of measurements ($n = 2601$). Reproduced with permission from [27].

In women with threatened labor, the only independent predictors of delivery before 35 weeks are CL (OR: 0.84; 95% CI: 0.81–0.87) and vaginal bleeding (OR: 5.64; 95% CI: 2.20–14.42) [60].

Multiple gestation

Twin pregnancies represent a relevant but disproportionate part of all preterm births. For women carrying twins, a short cervix at 24 weeks is one of the most important risk factors associated with sPTB. In a prospective prediction study on women with twins, CL ≤ 25 mm measured at 24 weeks was significantly associated with sPTB at <32 , <35 and <37 weeks. When performed at 28 weeks, however, a short cervix was significantly associated with sPTB only at <35 weeks [61].

A systematic review and meta-analysis estimates CL accuracy in the prediction of sPTB in women with twin pregnancies, and supplies evidence that in twin pregnancies TVU CL at 20–24 weeks gestation is the best predictor of sPTB in asymptomatic women. Among asymptomatic women, a CL ≤ 20 mm at 20–24 weeks gestation predicts sPTB at <32 and <34 weeks gestation, whereas a CL ≤ 25 mm predicts preterm birth at <28 weeks gestation [62]. However, the negative predictive value

is quite low, so a normal CL is less accurate in predicting the absence of sPTB. CL is less accurate at predicting sPTB <37 weeks of gestation. In addition, in this group of patients, TVU CL has limited accuracy in predicting sPTB women in which the test is performed >24 weeks of gestation.

Among twin gestation women threatening preterm labor, the measurement of CL has minimal predictive accuracy for preterm birth <34 and <37 weeks of gestation [62]. There are limited data regarding the predictive accuracy of TVU CL performed <20 weeks of gestation [62].

Another systematic review and meta-analysis in asymptomatic women with multiple pregnancies confirms that second trimester CL is a predictor of preterm birth [63]. In advancing gestation, CL was reported to decrease more in triplet pregnancies than in twins [64]. Specifically, CL was predicted to decrease by 0.6 mm per week in singletons, 0.9 mm in twins and 1.2 mm in triplets (FIGURE 5). In a study of 63 triplets, a CL cut-off of 2 cm, prior to 28 weeks gestation, is significantly associated with sPTB [65].

The value of CL in addressing therapeutic strategies to prevent sPTB

The therapeutic strategies used to reduce the rate of sPTB are the use of progestogens, which includes 17α -hydroxy-progesterone caproate given intramuscularly and natural

progesterone given vaginally as a gel or as a suppository cervical cerclage and more recently, cervical pessary.

Progestogens

In the last decade, several randomized controlled trials assessing the effect of progestogens in reducing the rate of sPTB have been reported. In 2003, two studies demonstrated the role of progestogens in reducing the rate of sPTB in asymptomatic women at risk due to previous sPTB [66,67].

The action of progesterone and how it prevents sPTB has been the focus of various investigations. The most recognized mechanisms are generally the antiinflammatory effect, which interacts with the inflammatory process that induces sPTB, and a local increase of progesterone that balances the functional decrease leading to sPTB [68–70].

Specifically, Meis *et al.* using 17α -hydroxyprogesterone caproate (250-mg intramuscular injections weekly) in women with documented history of a singleton sPTB starting between 16 and 20 weeks gestation until 36 weeks or earlier delivery, demonstrated a reduction in the rate of recurrent spontaneous preterm delivery and in the likelihood of several complications

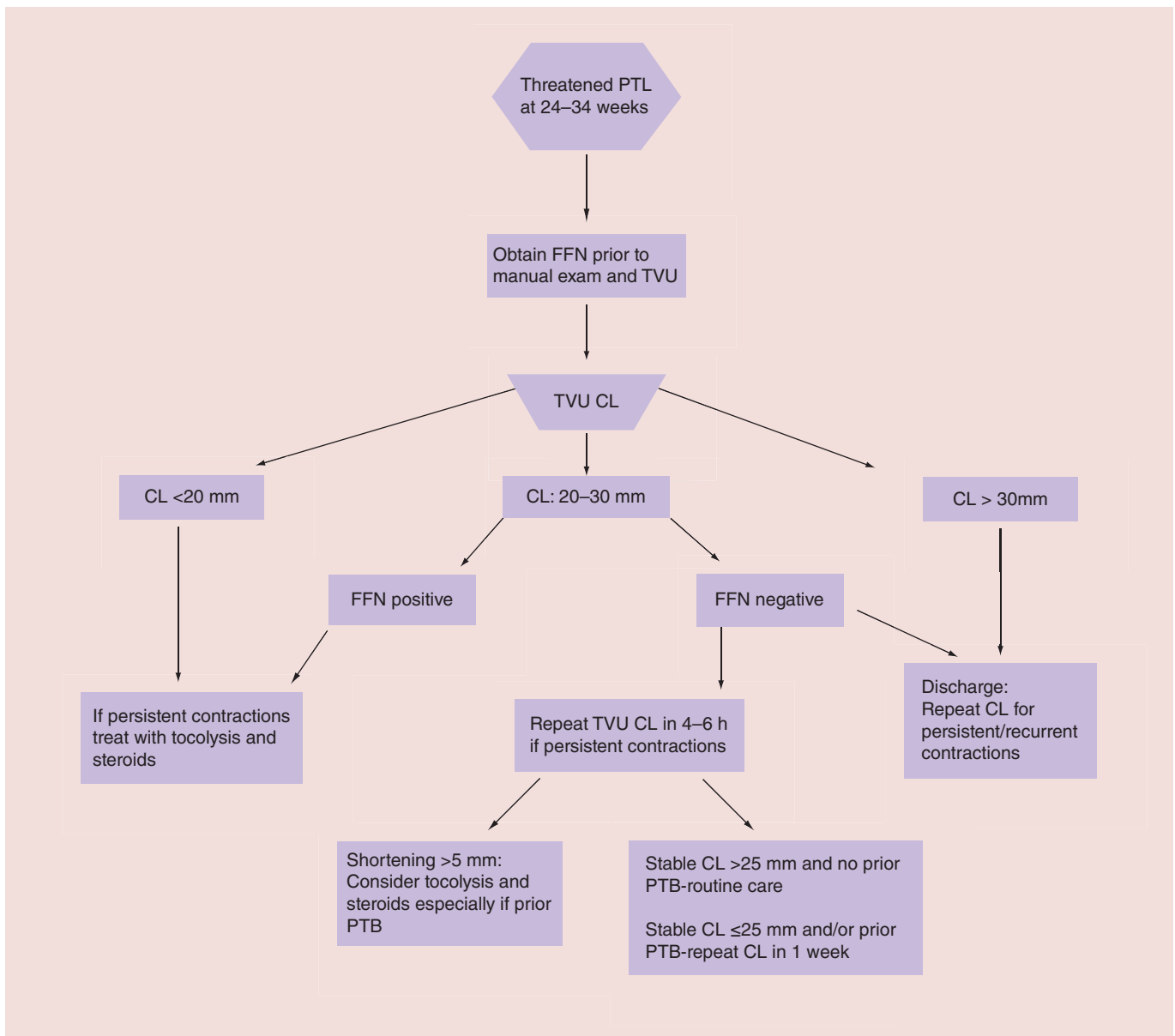


Figure 4. Management protocol using cervical length and fetal fibronectin for symptomatic patients with threatened preterm labor.

CL: Cervical length; FFN: Fetal fibronectin test; PTB: Preterm birth; PTL: Preterm labor; TVU: Transvaginal ultrasonography. Reproduced with permission from [55].

in their infants [66]. da Fonseca *et al.* used vaginal progesterone (100 mg daily) and monitored uterine contractions with an external tocodynamometer once a week for 60 min, between 24 and 34 weeks of gestation, on a population of high-risk women with a history of singleton sPTB. Here, prophylactic cervical cerclage and uterine malformation showed less frequent uterine contractions and preterm delivery [67]. In both of these studies, CL was not measured.

In 2007, O'Brien gave vaginal progesterone (90 mg daily) to women with a history of sPTB starting at 18 and 22 6/7 weeks gestation until 37 weeks or earlier delivery or premature rupture of membranes, and demonstrated that prophylactic treatment

with vaginal progesterone did not reduce the frequency of recurrent preterm birth ≤ 32 weeks in women with a history of spontaneous preterm birth. At admittance, the mean TVU CL was 37 mm [71]. In the same year, Fonseca *et al.*, for the first time showed that progesterone (micronized progesterone gel, 200-mg vaginally daily) was useful in reducing the rate of sPTB also in women without previous sPTB but with a very short CL (≤ 15 mm) between 20 and 23 6/7 weeks gestation. This study for the first time proposed a strategy of routine screening of pregnant women by TVU measurement of CL at 20–25 weeks in order to select women with a CL ≤ 15 mm that should undergo prophylactic administration of vaginal

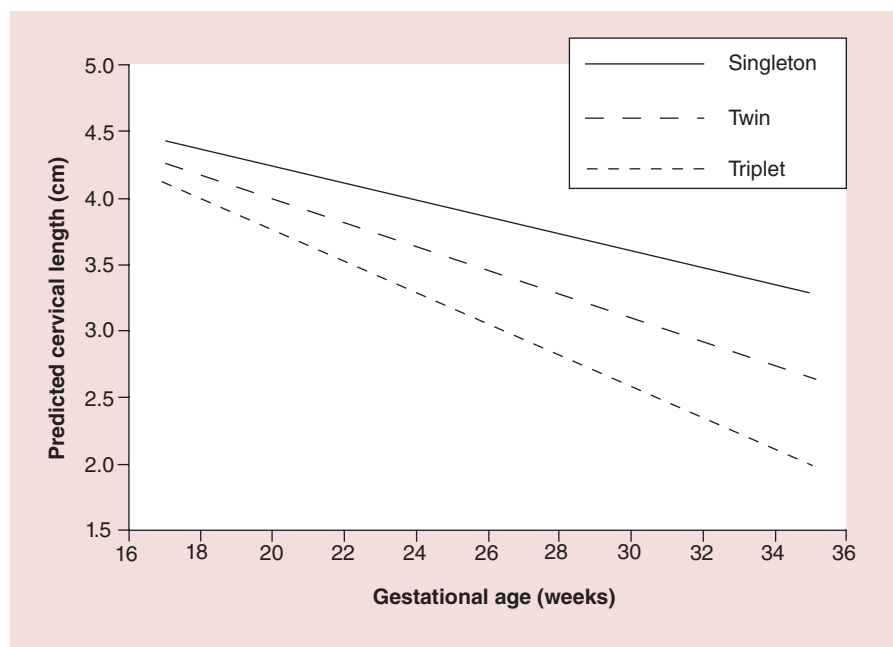


Figure 5. Predicted cervical length change among singleton, twin and triplet pregnancies, across gestation.

Reproduced with permission from [64].

micronized progesterone [31]. More recently, Hassan *et al.*, using vaginal progesterone gel (90 mg daily) between 20 and 23 + 6 gestation weeks until 36 + 6 weeks in singleton women with a short cervix (10–20 mm), showed a 45% reduction in the rate of preterm birth before 33 weeks gestation and with improved neonatal outcome [32].

The use of vaginal progesterone in asymptomatic women with a short cervix (≤ 25 mm) in the mid-trimester has been the subject of a recent meta-analysis that concluded that this strategy induces a 42% reduction in the rate of preterm birth before 33, 35, 34, 30 and 28 weeks gestation, and also 43% of composite neonatal mortality and morbidity [72]. The authors recommended TVU CL in all pregnant women between 19–24 weeks gestation (universal screening) and the use of vaginal progesterone for those with a short cervix (≤ 25 mm). There were no differences found regarding the efficiency of doses of 90–100 or 200 mg/day of vaginal progesterone.

To date, four proposed interventions using progestogens in order to reduce the rate of sPTB have been compared: no screening or treatments; universal screening to detect women with CL ≤ 15 mm who will receive 200 mg of vaginal progesterone from diagnosis until 33 weeks 6 days; high-risk screening using CL in woman at increased risk of sPTB to detect those with a short CL ≤ 15 mm who will be treated with vaginal progesterone gel and standardization of care using 19 α -hydroxyprogesterone acetate (weekly injections) in women with previous sPTB. An estimate has been made based on these four proposed strategies to reduce the rate of sPTB in order to see which is the most cost effective, and concluded that universal transvaginal screening for short CL and treatment with vaginal progesterone may be the most cost effective in the reduction of the risk of PTB [73].

On the basis of all these observations, the American College of Obstetricians Gynecologists has cautiously opened toward equal universal cervical screening in singleton gestations without prior PTB, and practitioners who decide to implement universal screening are recommended to follow one of the proposed protocols [31,32,62,68,69]. Pregnant patients at risk for sPTB, because of previous PTB in their history, are strongly recommended to take progesterone supplements starting at 16–24 weeks [74]. In woman with prior sPTB, if the TVU CL shortens to <25 mm at <24 weeks, cerclage may be offered. The Society for Maternal Fetal Medicine also proposed similar recommendations, and states that in singleton gestations, without prior PTB and short CL ≤ 20 mm at 24 weeks, vaginal progesterone, either 90 mg gel or a 200 mg suppository, is associated with a reduction in PTB and perinatal morbidity, and can be offered in these cases [75]. The algorithm

proposed by the Society for Maternal-Fetal Medicine for the use of progestogens in reducing the rate of PTB is shown in FIGURE 6.

Cervical cerclage

Cervical surveillance with sonography can select appropriate candidates who could benefit from cerclage. Ultrasound indicated cerclage has been reported to reduce the risk of recurrent PTB in singleton gestation with a short cervix. In contrast, with twins, cerclage is associated with a significantly higher incidence of sPTB and for this reason is contraindicated [76]. These data regarding ultrasound indicated cerclage has also been confirmed by a randomized clinical trial that demonstrated cervical cerclage is a therapeutic strategy in singleton pregnant women with a prior PTB that occurred at less than 34 weeks of gestation, when CL is less than 25 mm before 24 weeks of gestation. In women with a prior sPTB less than 34 weeks and CL less than 25 mm, cerclage reduced previable birth and perinatal mortality but did not prevent birth at less than 35 weeks, unless CL is less than 15 mm [77]. Meta-analysis of five randomized trials of cerclage versus no cerclage, which met strict inclusion criteria, that is, singleton pregnancy, short CL on TVU before 24 weeks gestation and previous sPTB before 35 weeks gestation, showed that in this select group, cerclage was associated with a significantly lower preterm birth (by 30%; relative risk [RR]: 0.70; 95% CI: 0.55–0.89) and perinatal morbidity and mortality (by 36%; RR: 0.64; 95% CI: 0.45–0.91) [78]. Clinical guidelines recommend ultrasound cervical cerclage in singleton gestation with prior sPTB if the TVU CL shortens to <25 mm before 24 weeks [74,75,79]. FIGURE 7 shows a care algorithm for asymptomatic women with multiple prior sPTB or spontaneous stillbirth [80].

Cervical pessary

Cervical pessary is a silicone device that has been used over the past 50 years to reduce the rate of sPTB [81]. Before 2012, more than 30 retrospective or case controlled studies showed that a cervical pessary can be used as a preventive strategy for patients at risk of sPTB [82,83]. In 2012, a randomized, controlled trial that investigated whether the insertion of the Arabin cervical pessary in singleton pregnant women with a TVU CL less than 25 mm at 20–23 weeks of gestation reduced the rate of early preterm delivery, showed a statistically significant reduction in spontaneous delivery before 34 weeks of gestation in the pessary compared with the expectant management groups, and no serious adverse effects associated with the use of a cervical pessary were reported. The authors suggested that although the mechanism of action of cervical pessary remains to be clarified, the positive effect of the use of a pessary relies on its mechanical ability to bend the cervix backwards, changing the uterocervical angle, which not only strengthens the cervical canal but also diminishes the contact of intact membranes with the vagina, somehow preserving its integrity [84]. More recently, the effectiveness of the use of Arabin cervical pessary in the reduction of the rate of sPTB has also been demonstrated in multiple pregnancy when the CL at 16–20 weeks is less than the 25th percentile, which corresponded to 38 mm [85].

Expert commentary

Recent research has clarified the best approach in measuring CL; the value of TVU CL in predicting PTBs when measured mid-trimester in asymptomatic patients, the use of TVU CL in screening patients with previous PTBs or second trimester losses in order to identify those that need therapeutic strategy and the usefulness of TVU CL in symptomatic singleton pregnancy to best select women for intervention such as tocolysis and induction of lung maturity.

CL is most accurately measured by TVU. In singleton pregnancy, the CL measured between 16 and 24 weeks of gestation is a good indicator of a pregnant woman's risk of PTB. CL is normally distributed, and decreases slightly from 24 weeks onward. At 24 weeks gestation, the average CL is 35 mm; the 25th percentile is 30 mm; the tenth percentile is 25 mm; the fifth percentile is 22 mm and the first percentile is 13 mm. The shorter the CL the higher the risk of PTB [7].

In pregnant patients at risk for previous sPTB prophylactic treatment with progestogens, both intramuscularly and

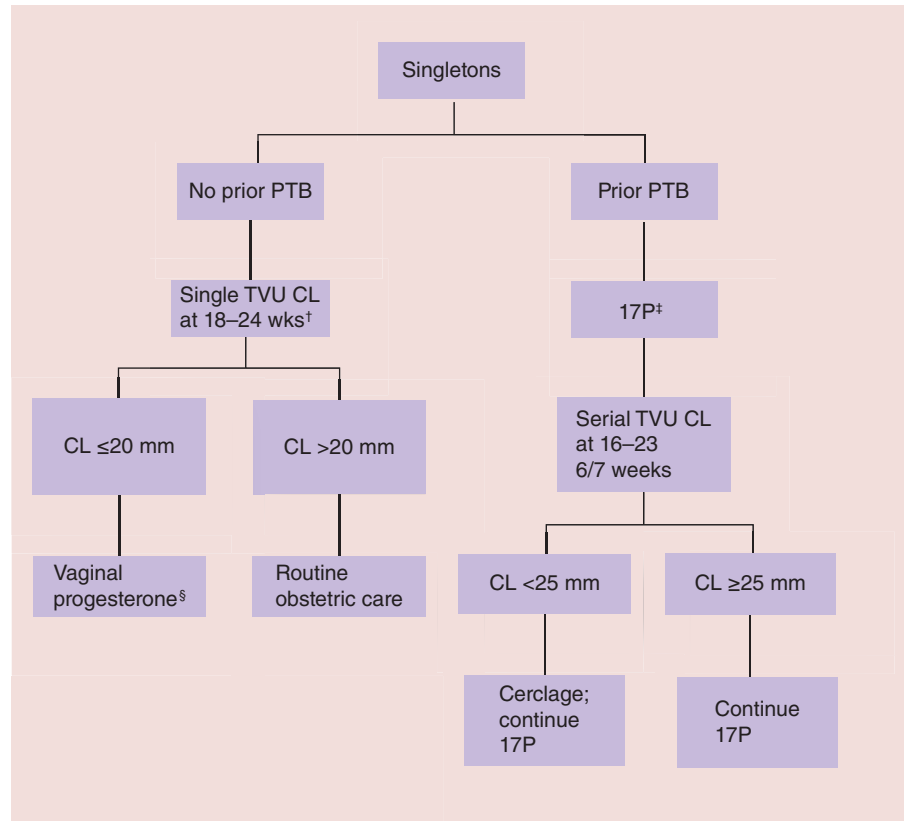


Figure 6. Algorithm for use of progestogen in prevention of preterm birth in clinical care both in women with and without prior spontaneous preterm birth.

†If TVU CL screening is performed.

‡17P 250 mg intramuscularly every week from 16–20 weeks to 36 weeks.

§e.g., daily 200-mg suppository or 90-mg gel from time of diagnosis of short CL to 36 weeks.

17P: 17 α -hydroxyprogesterone caproate; CL: Cervical length; PTB: Preterm birth; TVU: Transvaginal ultrasound.

Reproduced with permission from [75].

intravaginally has been shown to be effective [66,67]. In singleton women with a history of less than three early sPTB and/or second trimester losses, both weekly treatment with 17 α -hydroxyprogesterone caproate and monitoring CL every 2 weeks, starting at 16 weeks, is recommended. In these women, monitoring CL until 23 weeks, can identify women with CL <25 mm, and these women would be recommended cervical cerclage [66].

In singleton patients at risk of sPTB, vaginal administration of progesterone reduces the incidence of preterm delivery in the progesterone group to 13.8 (ten out of 72) and 28.5% (20 out of 70) in the placebo group ($p = 0.03$). Mean contraction frequency for each gestational week studied was significantly greater for the placebo group than the progesterone group [67].

In singleton symptomatic patients with no history of PTBs and or STL, CL screening can identify those who do not need tocolysis and steroids, versus those who need intervention. In particular, CL >30 mm that remains stable does not need any intervention, while women with CL between 20 and 30 mm combined with a positive fetal fibronectin test or CL <20 mm

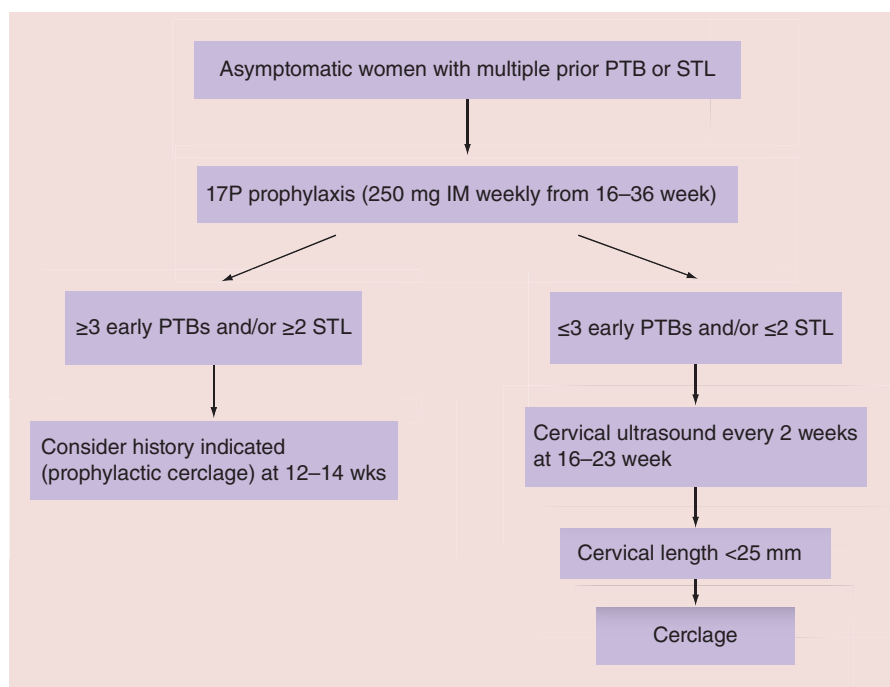


Figure 7. Care algorithm for asymptomatic women with multiple prior spontaneous preterm birth or second-trimester losses.

17P: 17 α -hydroxyprogesterone caproate; IM: Intramuscular; PTB: Preterm birth; STL: Second trimester losses.

should probably receive admission steroids for fetal maturation and tocolysis if contracting. Ultrasound indicated cervical cerclage in singleton gestation with prior sPTB is recommended if TVU CL shortens to less than 25 mm before 24 weeks [77].

Recently, promising data on the use of Arabin cervical pessary in reducing the rate of sPTB both in singleton and twin pregnancies

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have been reported, but more studies are necessary to confirm these results.

Five-year view

From the scientific point of view, in the future, randomized controlled studies using TVU CL as a screening test for patients at risk of sPTB will investigate the comparison of the efficacy of vaginal progesterone and cerclage and vaginal progesterone and pessary in the prevention of sPTB. The possibility of avoiding surgical procedures, such as a cerclage, is attractive and knowledge of the specific advantages of using a drug or mechanical device will help to identify the best customized treatment for each patient. Moreover, the possible cumulative effect of using combination approaches (e.g., progesterone and cerclage) should be explored. From the clinical point of view, TVU CL at 18–24 weeks will become an increasingly integral part of universal screening for sPTB offered to all of the pregnant population.

Financial & competing interests disclosure

Key issues

- Using cervical length (CL), the following three points ‘how’, ‘when’ and ‘what’ are defined as following: how: transvaginal ultrasonography (TVU) is the gold standard to investigate CL. When: between 16 and 24 weeks. What: CL less than 25 mm in singleton asymptomatic women with previous spontaneous preterm birth (sPTB). CL less than 20 mm in singleton asymptomatic women with no prior sPTB. CL less than 25 mm in twins asymptomatic women.
- The five important factors that affect the prevention of sPTB by using TVU CL are CL measurement, gestational age, number of fetuses, symptoms and other risk factors for sPTB such as patient obstetrical and medical history.
- The population categories in which TVU CL can be applied can be differentiated into asymptomatic and symptomatic pregnant women. In the group of asymptomatic patients, whether they are singleton with or without prior PTB, or multiples, the gestational age at which the test should be performed is 16–23 6/7 weeks.
- In symptomatic patients, whether they have cervical insufficiency or preterm labor or premature rupture of membranes or bleeding or more than one of these symptoms, the gestational age at which TVU CL is performed is usually between about 24 and 34 weeks.
- Pregnant patients at risk for sPTB, because of previous in their history, are strongly recommended to take a progestagen supplement starting at 16–24 weeks. In these women with prior sPTB, if the TVU CL shortens to <25 mm at <24 weeks, cerclage may be offered.
- In singleton gestations, without prior sPTB but with short CL ≤ 20 mm at 24 weeks, vaginal progesterone, either 90 mg gel or a 200 mg suppository, is associated with a reduction in PTB and perinatal morbidity, and can be offered in these cases.
- Clinical guidelines recommend ultrasound cervical cerclage in singleton gestation with prior sPTB if the TVU CL shortens to <25 mm before 24 weeks.
- The insertion of the Arabin cervical pessary in singleton pregnant women with a TVU CL less than 25 mm at 20–23 weeks of gestation reduced the rate of early sPTB before 34 weeks of gestation in a recent trial.

References

Papers of special note have been highlighted as:

• of interest

•• of considerable interest

- 1 Martin JA, Ventura SJ. Births: preliminary data for 2011. National vital statistics reports; vol 61 no 5. National Center for Health Statistics, Hyattsville, MD, USA. (2012).
- 2 Word RA, Li XH, Hnat M, Carrick K. Dynamics of cervical remodeling during pregnancy and parturition: mechanisms and current concepts. *Semin. Reprod. Med.* 25(1), 69–79 (2007).
- 3 Feltovich H, Hall TJ, Berghella V. Beyond cervical length: emerging technologies for assessing the pregnant cervix. *Am. J. Obstet. Gynecol.* 207(5), 345–354 (2012).
- 4 Holcomb WL Jr, Smeltzer JS. Cervical effacement: variation in belief among clinicians. *Obstet. Gynecol.* 78(1), 43–45 (1991).
- 5 Berghella V, Tolosa JE, Kuhlman K, Weiner S, Bolognese RJ, Wapner RJ. Cervical ultrasonography compared with manual examination as a predictor of preterm delivery. *Am. J. Obstet. Gynecol.* 177(4), 723–730 (1997).
- **Reports the proper technique of transvaginal ultrasonography (TVU) screening of the cervix for prediction of spontaneous preterm birth (sPTB), the optimal timing and frequency for measuring cervical length (CL) and the factors affecting prediction.**
- 6 Mella MT, Berghella V. Prediction of preterm birth: cervical sonography. *Semin. Perinatol.* 33(5), 317–324 (2009).
- 7 Iams JD, Goldenberg RL, Meis PJ *et al.* The length of the cervix and the risk of spontaneous premature delivery. National Institute of Child Health and Human Development Maternal Fetal Medicine Unit Network. *N. Engl. J. Med.* 334(9), 567–572 (1996).
- **In this multicenter, population-based study, the measure of CL and relation of this measurement to the risk of prematurity are reported.**
- 8 Hernandez-Andrade E, Romero R, Ahn H *et al.* Transabdominal evaluation of uterine cervical length during pregnancy fails to identify a substantial number of women with a short cervix. *J. Matern. Fetal Neonatal Med.* 25(9), 1682–1689 (2012).
- 9 Cicero S, Skentou C, Souka A, Nicolaides KH. Cervical length at 22–24 weeks of gestation: comparison of transvaginal and transperineal-translabial ultrasonography. *Ultrasound Obstet. Gynecol.* 17(4), 335–340 (2001).
- 10 Owen J, Neely C, Northen A. Transperineal versus endovaginal ultrasonographic examination of the cervix in the mid-trimester: a blinded comparison. *Am. J. Obstet. Gynecol.* 181(4), 780–783 (1999).
- 11 Berghella V, Bega G, Tolosa JE, Berghella M. Ultrasound assessment of the cervix. *Clin. Obstet. Gynecol.* 46(4), 947–962 (2003).
- 12 Doyle NM, Monga M. Role of ultrasound in screening patients at risk for preterm delivery. *Obstet. Gynecol. Clin. North Am.* 31(1), 125–139 (2004).
- 13 Leitich H, Brunbauer M, Kaider A, Egarter C, Husslein P. Cervical length and dilatation of the internal cervical os detected by vaginal ultrasonography as markers for preterm delivery: a systematic review. *Am. J. Obstet. Gynecol.* 181(6), 1465–1472 (1999).
- 14 Londero AP, Bertozzi S, Fruscalzo A, Driul L, Marchesoni D. Ultrasonographic assessment of cervix size and its correlation with female characteristics, pregnancy, BMI, and other anthropometric features. *Arch. Gynecol. Obstet.* 283(3), 545–550 (2011).
- 15 Meijer-Hoogveen M, Stoutenbeek P, Visser GH. Dynamic cervical length changes: preliminary observations from 30-minute transvaginal ultrasound recordings. *J. Matern. Fetal. Neonatal. Med.* 20(6), 481–486 (2007).
- 16 Sonek JD, Iams JD, Blumenfeld M, Johnson F, Landon M, Gabbe S. Measurement of cervical length in pregnancy: comparison between vaginal ultrasonography and digital examination. *Obstet. Gynecol.* 76(2), 172–175 (1990).
- 17 Mercer BM, Goldenberg RL, Moawad AH *et al.* The preterm prediction study: effect of gestational age and cause of preterm birth on subsequent obstetric outcome. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. *Am. J. Obstet. Gynecol.* 181(5 Pt 1), 1216–1221 (1999).
- 18 Goldberg J, Newman RB, Rust PF. Interobserver reliability of digital and endovaginal ultrasonographic cervical length measurements. *Am. J. Obstet. Gynecol.* 177(4), 853–858 (1997).
- 19 Timor-Tritsch IE, Boozarjomehri F, Masakowski Y, Monteagudo A, Chao CR. Can a 'snapshot' sagittal view of the cervix by transvaginal ultrasonography predict active preterm labor? *Am. J. Obstet. Gynecol.* 174(3), 990–995 (1996).
- 20 Berghella V, Kuhlman K, Weiner S, Teixeira L, Wapner RJ. Cervical funneling: sonographic criteria predictive of preterm delivery. *Ultrasound Obstet. Gynecol.* 10(3), 161–166 (1997).
- 21 Taipale P, Hiilesmaa V. Sonographic measurement of uterine cervix at 18–22 weeks' gestation and the risk of preterm delivery. *Obstet. Gynecol.* 92(6), 902–907 (1998).
- 22 Hibbard JU, Tart M, Moawad AH. Cervical length at 16–22 weeks' gestation and risk for preterm delivery. *Obstet. Gynecol.* 96(6), 972–978 (2000).
- 23 Kusanovic JP, Espinoza J, Romero R *et al.* Clinical significance of the presence of amniotic fluid 'sludge' in asymptomatic patients at high risk for spontaneous preterm delivery. *Ultrasound Obstet. Gynecol.* 30(5), 706–714 (2007).
- 24 Faye-Petersen OM. The placenta in preterm birth. *J. Clin. Pathol.* 61(12), 1261–1275 (2008).
- 25 Devlieger R, Scherjon SA, Oepkes D, Meerman R, Timmerman D, Vandembussche FP. Ultrasound visualization of fetal membrane detachment at the uterine cervix: the 'moon sign'. *Ultrasound Obstet. Gynecol.* 22(4), 431–432 (2003).
- 26 Lewi L, Hanssens M, Spitz B, Deprest J. Complete chorioamniotic membrane separation. Case report and review of the literature. *Fetal. Diagn. Ther.* 19(1), 78–82 (2004).
- 27 Berghella V, Roman A, Daskalakis C, Ness A, Baxter JK. Gestational age at cervical length measurement and incidence of preterm birth. *Obstet. Gynecol.* 110(2 Pt 1), 311–317 (2007).
- 28 Hassan SS, Romero R, Berry SM *et al.* Patients with an ultrasonographic cervical length < or = 15 mm have nearly a 50% risk of early spontaneous preterm delivery. *Am. J. Obstet. Gynecol.* 182(6), 1458–1467 (2000).
- **Shows that the use of vaginal progesterone in asymptomatic women with CL ≤ 25 mm in the midtrimester, reduces the risk of sPTB and improves neonatal morbidity and mortality.**
- 29 Vaisbuch E, Romero R, Erez O *et al.* Clinical significance of early (< 20 weeks) vs. late (20–24 weeks) detection of sonographic short cervix in asymptomatic women in the mid-trimester. *Ultrasound Obstet. Gynecol.* 36(4), 471–481 (2010).

- 30 Celik E, To M, Gajewska K, Smith GC, Nicolaides KH; Fetal Medicine Foundation Second Trimester Screening Group. Cervical length and obstetric history predict spontaneous preterm birth: development and validation of a model to provide individualized risk assessment. *Ultrasound Obstet. Gynecol.* 31(5), 549–554 (2008).
- 31 Fonseca EB, Celik E, Parra M, Singh M, Nicolaides KH; Fetal Medicine Foundation Second Trimester Screening Group. Progesterone and the risk of preterm birth among women with a short cervix. *N. Engl. J. Med.* 357(5), 462–469 (2007).
- 32 Hassan SS, Romero R, Vidyadhari D *et al.*; PREGNANT Trial. Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicenter, randomized, double-blind, placebo-controlled trial. *Ultrasound Obstet. Gynecol.* 38(1), 18–31 (2011).
- 33 Esplin MS, O'Brien E, Fraser A *et al.* Estimating recurrence of spontaneous preterm delivery. *Obstet. Gynecol.* 112(3), 516–523 (2008).
- 34 Iams JD, Johnson FF, Sonek J, Sachs L, Gebauer C, Samuels P. Cervical competence as a continuum: a study of ultrasonographic cervical length and obstetric performance. *Am. J. Obstet. Gynecol.* 172(4 Pt 1), 1097–1103; discussion 1104 (1995).
- 35 Goldenberg RL, Iams JD, Mercer BM *et al.* The preterm prediction study: the value of new vs standard risk factors in predicting early and all spontaneous preterm births. NICHD MFMU Network. *Am. J. Public Health* 88(2), 233–238 (1998).
- 36 Andrews WW, Copper R, Hauth JC, Goldenberg RL, Neely C, Dubard M. Second-trimester cervical ultrasound: associations with increased risk for recurrent early spontaneous delivery. *Obstet. Gynecol.* 95(2), 222–226 (2000).
- 37 Hutchens D. Use of transvaginal ultrasonography to predict preterm birth in women with a history of preterm birth. *Ultrasound Obstet. Gynecol.* 32(5), 640–645 (2008).
- 38 Owen J, Yost N, Berghella V *et al.*; National Institute of Child Health and Human Development, Maternal-Fetal Medicine Units Network. Mid-trimester endovaginal sonography in women at high risk for spontaneous preterm birth. *JAMA* 286(11), 1340–1348 (2001).
- 39 Visintine J, Berghella V, Henning D, Baxter J. Cervical length for prediction of preterm birth in women with multiple prior induced abortions. *Ultrasound Obstet. Gynecol.* 31(2), 198–200 (2008).
- 40 Rock JA, Roberts CP, Jones HW Jr. Congenital anomalies of the uterine cervix: lessons from 30 cases managed clinically by a common protocol. *Fertil. Steril.* 94(5), 1858–1863 (2010).
- 41 Anum EA, Hill LD, Pandya A, Strauss JF 3rd. Connective tissue and related disorders and preterm birth: clues to genes contributing to prematurity. *Placenta* 30(3), 207–215 (2009).
- 42 Ortoft G, Henriksen T, Hansen E, Petersen L. After conisation of the cervix, the perinatal mortality as a result of preterm delivery increases in subsequent pregnancy. *BJOG* 117(3), 258–267 (2010).
- 43 Fischer RL, Sveinbjornsson G, Hansen C. Cervical sonography in pregnant women with a prior cone biopsy or loop electrosurgical excision procedure. *Ultrasound Obstet. Gynecol.* 36(5), 613–617 (2010).
- 44 Roberts CP, Rock JA. Surgical methods in the treatment of congenital anomalies of the uterine cervix. *Curr. Opin. Obstet. Gynecol.* 23(4), 251–257 (2011).
- 45 Park KH, Hong JS, Kang WS, Shin DM. Transvaginal ultrasonographic measurement of cervical length in predicting intra-amniotic infection and impending preterm delivery in preterm labor: a comparison with amniotic fluid white blood cell count. *J. Perinat. Med.* 36(6), 479–484 (2008).
- 46 Romero R, Espinoza J, Gonçalves LF, Kusanovic JP, Friel L, Hassan S. The role of inflammation and infection in preterm birth. *Semin. Reprod. Med.* 25(1), 21–39 (2007).
- 47 Vaisbuch E, Hassan SS, Mazaki-Tovi S *et al.* Patients with an asymptomatic short cervix (≤ 15 mm) have a high rate of subclinical intra-amniotic inflammation: implications for patient counseling. *Am. J. Obstet. Gynecol.* 202(5), 433.e1–433.e8 (2010).
- 48 Vaisbuch E, Romero R, Mazaki-Tovi S *et al.* The risk of impending preterm delivery in asymptomatic patients with a nonmeasurable cervical length in the second trimester. *Am. J. Obstet. Gynecol.* 203(5), 446.e1–446.e9 (2010).
- 49 Kiefer DG, Keeler SM, Rust OA, Wayock CP, Vintzileos AM, Hanna N. Is midtrimester short cervix a sign of intraamniotic inflammation? *Am. J. Obstet. Gynecol.* 200(4), 374.e1–374.e5 (2009).
- 50 Schlembach D, Mackay L, Shi L, Maner WL, Garfield RE, Maul H. Cervical ripening and insufficiency: from biochemical and molecular studies to *in vivo* clinical examination. *Eur. J. Obstet. Gynecol. Reprod. Biol.* 144(Suppl. 1), S70–S76 (2009).
- 51 Ventolini G, Neiger R. Management of painless mid-trimester cervical dilatation: Prophylactic vs emergency placement of cervical cerclage. *J. Obstet. Gynaecol.* 28(1), 24–27 (2008).
- 52 Airoidi J, Berghella V, Sehdev H, Ludmir J. Transvaginal ultrasonography of the cervix to predict preterm birth in women with uterine anomalies. *Obstet. Gynecol.* 106(3), 553–556 (2005).
- 53 Hassan S, Romero R, Hendler I *et al.* A sonographic short cervix as the only clinical manifestation of intra-amniotic infection. *J. Perinat. Med.* 34(1), 13–19 (2006).
- 54 Tsoi E, Fuchs IB, Rane S, Geerts L, Nicolaides KH. Sonographic measurement of cervical length in threatened preterm labor in singleton pregnancies with intact membranes. *Ultrasound Obstet. Gynecol.* 25(4), 353–356 (2005).
- 55 Ness A. Prevention of preterm birth based on short cervix: symptomatic women with preterm labor or premature prelabor rupture of membranes. *Semin. Perinatol.* 33(5), 343–351 (2009).
- Reports the use of TVU CL in predicting sPTB in symptomatic women and improvement of the accuracy.
- 56 Gomez R, Romero R, Nien JK *et al.* A short cervix in women with preterm labor and intact membranes: a risk factor for microbial invasion of the amniotic cavity. *Am. J. Obstet. Gynecol.* 192(3), 678–689 (2005).
- 57 Carlan SJ, Richmond LB, O'Brien WF. Randomized trial of endovaginal ultrasound in preterm premature rupture of membranes. *Obstet. Gynecol.* 89(3), 458–461 (1997).
- 58 Rizzo G, Capponi A, Angelini E, Vlachopoulou A, Grassi C, Romanini C. The value of transvaginal ultrasonographic examination of the uterine cervix in predicting preterm delivery in patients with preterm premature rupture of membranes. *Ultrasound Obstet. Gynecol.* 11(1), 23–29 (1998).
- 59 Odibo AO, Berghella V, Reddy U, Tolosa JE, Wapner RJ. Does transvaginal ultrasound of the cervix predict preterm premature rupture of membranes in a high-risk population? *Ultrasound Obstet. Gynecol.* 18(3), 223–227 (2001).

- 60 Ramaeker DM, Simhan HN. Sonographic cervical length, vaginal bleeding, and the risk of preterm birth. *Am. J. Obstet. Gynecol.* 206(3), 224.e1–224.e4 (2012).
- 61 Goldenberg RL, Iams JD, Miodovnik M *et al.* The preterm prediction study: risk factors in twin gestations. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. *Am. J. Obstet. Gynecol.* 175(4 Pt 1), 1047–1053 (1996).
- 62 Conde-Agudelo A, Romero R, Hassan SS, Yeo L. Transvaginal sonographic cervical length for the prediction of spontaneous preterm birth in twin pregnancies: a systematic review and metaanalysis. *Am. J. Obstet. Gynecol.* 203(2), 128.e1–128.12 (2010).
- **Reports that TVU CL 20–24 weeks gestation is a good predictor of sPTB also in asymptomatic women with twin pregnancies.**
- 63 Lim AC, Hegeman MA, Huis In 't Veld MA, Opmeer BC, Bruinse HW, Mol BW. Cervical length measurement for the prediction of preterm birth in multiple pregnancies: a systematic review and bivariate meta-analysis. *Ultrasound Obstet. Gynecol.* 38(1), 10–17 (2011).
- 64 Meath AJ, Ramsey PS, Mulholland TA, Rosenquist RG, Lesnick T, Ramin KD. Comparative longitudinal study of cervical length and induced shortening changes among singleton, twin, and triplet pregnancies. *Am. J. Obstet. Gynecol.* 192(5), 1410–1415 (2005).
- 65 McElrath TF, Robinson JN, Ecker JL, Ringer SA, Norwitz ER. Neonatal outcome of infants born at 23 weeks' gestation. *Obstet. Gynecol.* 97(1), 49–52 (2001).
- 66 Meis PJ, Klebanoff M, Thom E *et al.*; National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. *N. Engl. J. Med.* 348(24), 2379–2385 (2003).
- 67 da Fonseca EB, Bittar RE, Carvalho MH, Zugaib M. Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: a randomized placebo-controlled double-blind study. *Am. J. Obstet. Gynecol.* 188(2), 419–424 (2003).
- 68 Sfakianaki AK, Norwitz ER. Mechanisms of progesterone action in inhibiting prematurity. *J. Matern. Fetal. Neonatal. Med.* 19(12), 763–772 (2006).
- 69 Zakar T, Hertelendy F. Progesterone withdrawal: key to parturition. *Am. J. Obstet. Gynecol.* 196(4), 289–296 (2007).
- 70 Zakar T, Mesiano S. How does progesterone relax the uterus in pregnancy? *N. Engl. J. Med.* 364(10), 972–973 (2011).
- 71 O'Brien JM, Adair CD, Lewis DF *et al.* Progesterone vaginal gel for the reduction of recurrent preterm birth: primary results from a randomized, double-blind, placebo-controlled trial. *Ultrasound Obstet. Gynecol.* 30(5), 687–696 (2007).
- 72 Romero R, Garite TJ, Kim MH *et al.* The new *American Journal of Obstetrics and Gynecology*, 5 years later: looking back and moving forward. *Am. J. Obstet. Gynecol.* 206(5), 364–373 (2012).
- **Reports the reduction of the risk of sPTB in asymptomatic women with short cervix by using vaginal progesterone.**
- 73 Cahill AG, Odibo AO, Allsworth JE, Macones GA. Frequent epidural dosing as a marker for impending uterine rupture in patients who attempt vaginal birth after cesarean delivery. *Am. J. Obstet. Gynecol.* 202(4), 355.e1–355.e5 (2010).
- 74 Practice bulletin no. 130: prediction and prevention of preterm birth. *Obstetrics and Gynecology* 120(4), 964–973 (2012).
- 75 Society Maternal Fetal Medicine Publication Committee, with the assistance of Vincenzo Berghella. Progesterone and preterm birth prevention: translating clinical trials data into clinical practice. *Am. J. Obstet. Gynecol.* 206(5), 376–386 (2012).
- **The Society of Maternal Fetal Medicine has cautiously moved towards a universal cervical screening in singleton gestations, without prior sPTB, and gives recommendations about the use of progestogens on the basis of the value of CL in singleton pregnancy.**
- 76 Berghella V, Odibo AO, To MS, Rust OA, Althuisius SM. Cerclage for short cervix on ultrasonography: meta-analysis of trials using individual patient-level data. *Obstet. Gynecol.* 106(1), 181–189 (2005).
- 77 Owen J, Hankins G, Iams JD *et al.* Multicenter randomized trial of cerclage for preterm birth prevention in high-risk women with shortened midtrimester cervical length. *Am. J. Obstet. Gynecol.* 201(4), 375.e1–375.e8 (2009).
- 78 Berghella V, Rafael TJ, Szychowski JM, Rust OA, Owen J. Cerclage for short cervix on ultrasonography in women with singleton gestations and previous preterm birth: a meta-analysis. *Obstet. Gynecol.* 117(3), 663–671 (2011).
- **Gives evidence about the use of ultrasound indicated cerclage to reduce the risk of recurrent sPTB in singleton gestation.**
- 79 Royal College of Obstetricians and Gynaecologists. Cervical cerclage. Green Top Guidelines n°60. (2011)
- 80 Iams JD, Berghella V. Care for women with prior preterm birth. *Am. J. Obstet. Gynecol.* 203(2), 89–100 (2010).
- 81 Cross R. Treatment of habitual abortion due to cervical incompetence. *Lancet* 274(7094), 127 (2013).
- 82 Newcomer J. Pessaries for the treatment of incompetent cervix and premature delivery. *Obstet. Gynecol. Surv.* 55(7), 443–448 (2000).
- 83 Arabin B, Halbesma JR, Vork F, Hübener M, van Eyck J. Is treatment with vaginal pessaries an option in patients with a sonographically detected short cervix? *J. Perinat. Med.* 31(2), 122–133 (2003).
- 84 Goya M, Pratcorona L, Merced C *et al.*; Pesario Cervical para Evitar Prematuridad (PECEP) Trial Group. Cervical pessary in pregnant women with a short cervix (PECEP): an open-label randomised controlled trial. *Lancet* 379(9828), 1800–1806 (2012).
- **The first randomized controlled trial on the use of cervical pessary in preventing sPTB in an at-risk population of women previously screened for TVU CL at the midtrimester scan.**
- 85 Liem SE, Bais J. Pessaries in multiple pregnancy as a prevention of preterm birth (ProTWIN): a randomized controlled trial. *Am J Obstet Gynecol.* 208(1), S2 (2013).

Websites

- 101 Online education. Cervical assessment. www.fetalmedicine.com/fmf/onlineeducation/05-cervical-assessment
- 102 Cervical Length Education & Review (CLEAR). www.perinatalquality.org