Ultrasonographic Assessment of the Cervix for Prediction of Spontaneous Preterm Birth in Singleton Pregnancies

Zorán Belics¹ , Zoltán Papp²

ABSTRACT

Spontaneous preterm birth remains a major cause of neonatal morbidity and mortality across the world. Hence, there is an urgent need to find and implement diagnostic methods and interventions that can reduce this public health treat. The ultrasonographic assessment of the cervix is one tool that can be utilized to identify women at increased risk who may be candidates for preventive interventions. There are three main characteristics of the cervix, which can be evaluated during the ultrasound examination of the cervix: cervical length (CL), funneling and cervical gland area. Cervical shortening is one of the first steps in the processes leading to labor and can precede labor by several weeks. Because shortening begins at the internal cervical os and progresses caudally, it is often detected on ultrasound examination before it can be appreciated on physical examination. This is equally true for funneling and cervical gland area (CGA), which cannot be assessed with the physical examination. Based on previous experiences, the timing and frequency of ultrasonographic assessment of the cervix is primarily based on the patient's prior obstetric history (low-risk women are screened once at 18–24 weeks of gestation; high-risk population usually begins screening at about 16 weeks of gestation and the frequency depends on the measurement result). Classically the diagnosis of short cervix is defined when the CL is less than or equal to 25 mm at these gestational weeks, with the best prediction for PTB obtained at 16–24 weeks of gestation. The CL measurement, evaluation of funneling and CGA together increased the sensitivity of cervical screening for PTB and appeared to be powerful predictor of PTB before 32 weeks gestation. Generally, the importance of positive test is to try to recognize cervical changes on time, to plan the adequate therapy, to prepare for sufficient intrauterine transport, and to administered course of antenatal corticosteroid therapy to women at risk for PTB reduced the incidence and severity of respiratory distress syndrome (RDS) and mortality in offspring. Many interventions (bed rest, lifestyle intervention, cervical cerclage, pessary, progesterone, indomethacin, antibiotics, etc.) have been proposed in an attempt to prevent PTB depending on risk classification.

Keywords: Digital examination, Perinatal morbidity, Perinatal mortality, Pregnancy, Prematurity, Transabdominal ultrasound, Transvaginal ultrasound.

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INTRODUCTION

Preterm birth (PTB) is a syndrome with a variety of causes and underlying factors, which resulting contraction of the uterus and changes in the cervix (effacement and dilation).

Preterm birth is defined by World Health Organization as all births before 37 completed weeks of gestation or fewer than 259 days since the first day of a woman's last menstrual period,¹ usually divided into spontaneous and provider-initiated PTBs. About 70–80% of PTBs are spontaneous. Globally, prematurity is the leading cause of perinatal mortality and morbidity, an estimated 15 million newborns are born too early every year (more than 1 in 10 newborns). In addition to its significant contribution to mortality (PTB is a risk factor in over 50% of all neonatal deaths), the effect of PTB amongst some survivors may continue throughout life, impairing neurodevelopmental functioning through increasing the risk of cerebral palsy, learning impairment and visual disorders, and affecting long-term physical health with a higher risk of disease.² These effects exert a heavy burden on families (families—providing care for preterm infants), society, and the health system.³

Thereby, there is an urgent need to find and implement diagnostic methods and interventions that can reduce this public health treat.

RISK FACTORS FOR SPONTANEOUS PRETERM BIRTH

The following are risk factors for spontaneous PTB (sPTB):

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- Demographic factors (low socioeconomic status, low level of education, single marital status, and maternal age under 18 years or over 35 years)
- Lifestyle issues⁴
- Reproductive history [previous sPTB (Table 1), use of assisted reproductive technologies]^{5–7}
- Antepartum bleeding and rupture of membranes
- Cervical or uterine factors (cervical insufficiency, uterine congenital anomalies, fibroids, and previous excisional cervical treatment)^{7–10}
- Fetal or intrauterine factors (multifetal gestation, fetal anomaly, and polyhydramnios)

Table 1: Risk of recurrent spontaneous preterm birth in a second pregnancy

	Risk of PTB in next pregnancy (%)	Risk of PTB before 28 weeks of gestation (%)
No prior PTB	9	0.23
Prior PTB	22	
Prior PTB at 23–27 weeks		5
Prior PTB at 28–34 weeks		3
Prior PTB at 35–36 weeks		1

PTB, preterm birth

Source: 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 1999;181(5 Pt 1):1216–1221

- Infection (chorioamnionitis, bacteriuria, periodontal disease, and current bacterial vaginosis with a prior PTB)^{7,11,12}
- Inadequate prenatal care, low prepregnancy weight, and poor weight gain in pregnancy.¹³

However, there are many cases where women who deliver preterm do not have any known risk factors.⁷

Uterine Cervix

During the pregnancy, the primary biomechanical function of the cervix is to maintain the fetus within the uterus. Furthermore, the uterine cervix serves two major functions—(1) it retains its physical integrity by remaining firm and close during pregnancy, (2) despite a progressive increase in the size of the uterine distension. At the end of pregnancy, during the preparation for labor and delivery, the cervix softens and becomes more distensible, a process called cervical ripening. These active chemical and physical changes are required for cervical dilation, labor, and delivery of a fetus.

Critical problems can occur when the timing and extent of the cervical biomechanical changes are altered. Specifically, premature softening, shortening, and dilation occur in cases of sPTB. The underlying pathophysiology of these changes is poorly understood and the cause of preterm cervical shortening is often unclear.

Ultrasound Assessment of the Cervix during Pregnancy

Ultrasound evaluation of the cervix during pregnancy has been the focus of much research during the past decades. There are three main characteristics of the cervix, which can be evaluated during the ultrasound examination of the cervix:

- Cervical length (CL)
- Funneling
- Cervical gland area.

Cervical shortening (i.e., effacement) is one of the first steps in the processes leading to labor and can precede labor by several weeks. Because effacement begins at the internal cervical os and progresses caudally,^{14,15} it is often detected on ultrasound examination before it can be appreciated on physical examination. This is equally true for funneling and cervical gland area (CGA), which cannot be assessed with the physical examination.

Evaluation of the Uterine Cervix—Techniques

There are essentially four methods that can be used to evaluate the uterine cervix—(1) digital examination, (2) transabdominal ultrasound, (3) translabial (transperineal) ultrasound, and (4) transvaginal sonography (TVS).

- **Digital examination:** The digital examination is the most extensive evaluation of the cervix, assessing dilatation, position, consistency, and length. It is always accessible, but this subjective and nonspecific examination is limited especially in its ability to establish accurately the CL. It also cannot detect changes at the internal cervical os and the upper portion of the cervical canal. However, for PTB screening, the positive predictive value of digital examination is only 0–27%.¹⁶
- **Transabdominal ultrasound:** The first attempts at evaluating the cervix in the 1970s were performed with transabdominal sonography (TAS) (Fig. 1). Unfortunately, it was very soon recognized that this technique does not have sufficient performance which has been attributed to multiple factors, including:
 - The bladder often needs to be filled to obtain a good image, resulting in elongation of the cervix and masking of any funneling of the internal os;
 - Fetal parts can obscure the cervix, especially after 20 weeks;
 - The distance from the probe to the cervix results in degraded image quality; and
 - Obesity and manual pressure interfere with the image.¹⁷

The sensitivity for PTB prediction using the TAS is 8.2%.¹⁸ Summarizing, measurement of the cervix using TAS is more comfortable for the patient but has more limitations than TVS. Therefore, transabdominal ultrasound should not be used for the assessment of the uterine cervix, even as a screening test.

- **Transperineal ultrasound:** This ultrasound technique also known as translabial (TPS or TLS) was first described in France in the early 1980s. It is performed with the patient in a dorsal lithotomy position and it does not require bladder filling. Elevation of the hips during the examination can be used to improve image.

Fig. 1: Transabdominal view of the cervix and lower uterine segment of a patient scanned at the 18th week of her pregnancy

Fig. 2: Transvaginal view of the cervix and lower uterine segment of a patient scanned at the 20th week of her pregnancy

Fig. 3: Transvaginal view of the cervix, the transducer is placed into the anterior fornix

Fig. 4: A longitudinal view of the cervix (transvaginal view—21th week of gestation)

During the examination, the gloved transducer is placed on the perineum and rotated until the complete cervical canal and the internal and external os can be identified. Because the placement of the probe is further away from the cervix, there is a reduction in the detail in which the cervix is seen, especially when there are gases in the rectum. Generally, performing the transperineal ultrasound examination is more difficult than TVS. In cases with a short cervix, this modality tends to overestimate the true CL. Therefore, it is a dissatisfactory alternative to TVS, but in cases in which TVS should be avoided, such as in those with preterm prelabor rupture of membranes, the use of TPS can be advantageous.

- **Transvaginal ultrasound:** In general, the cervix should be assessed by TVS (Fig. 2). The first studies of the human cervix using TVS are from late 1980s. Cervical measurements using this technique are more reproducible and reliable than those obtained by TAS and more sensitive for prediction of PTB.^{19,20} It is also important to note that all randomized trials supporting the efficacy of

treatment of women with a short cervix used TVS to measure CL.^{21–23}

Transvaginal sonography is performed with the patient in a dorsal lithotomy position. A clean transvaginal probe covered by a condom is inserted into the anterior fornix of the vagina.

Some clinicians find the cervix is easier to locate sonographically, if a digital examination is performed first as gel from the examiner's glove left in the cervical canal makes the external os more echogenic. The same effect can be result, if the gel is placed on top of the covered transducer.

Practical points for the TVS technique are:

- The patient should empty her bladder prior to the examination.
- Ultrasound gel is placed on a transvaginal probe before covering it with a specialized probe cover, usually condom and then more ultrasound gel is placed on top of the cover.
- The transvaginal transducer is gently placed into the anterior fornix until the cervix is visualized, while avoiding excessive pressure on the anterior cervical lip (Fig. 3). The image of the cervix is enlarged to fill at least one-half of the ultrasound screens and oriented so that cephalad is to the left of the screen. Fetal membranes in the cervical canal or beyond the cervix should be noted, if present.
- A longitudinal view of the cervix should be obtained (Fig. 4).
- The amniotic fluid in the lower uterine segment is assessed and then the lowest edge of the empty maternal bladder. The internal os is then located, often just below this edge.
- Duration of the examination should be 3–5 minutes²⁴—the cervix is not a static structure and the length can vary. Therefore, sufficient time should be allowed for the examination to detect these changes. It may be helpful to press manually on the uterus or to ask the patient to push downwards to assess the cervical stability. Some even suggest that during the examination the patient stands, with the ultrasound probe inside the vagina. Abdominal pressure applied to the fundus for 15 seconds can aid the examination by revealing a “dynamic” cervix (i.e., the development of short CL in a cervix seemingly initially of normal length).^{25,26}

Limitations and Pitfalls

Although TVS of the cervix is usually straightforward, there can be a technical or anatomic difficulty that may be encountered in approximately 25% of examined patients.²⁷

Generally, the following limitations and pitfalls can lead to suboptimal examination and measurement of cervix, typically resulting in overestimation.

- **Full bladder:** A bladder that is not completely empty can exert pressure on the cervix and mask possible funneling or opening of the internal os.
- **Excessive pressure:** Placing excessive pressure on the cervix during the examination is a common mistake in performing transvaginal ultrasound (TVU)—this can mask funneling and/or opening the internal os and elongate the cervix due to compression of the anterior cervical lip and lower uterine segment. It can be easily identified by excessive echogenicity of the cervix.
- **Not allowing enough time to view dynamic changes:** Measuring CL too quickly is common and can result in an accurate measurement.
- **Uterine contractions:** Contractions during the examination can cause a false impression of a long cervix, likewise may mimic the appearance of funneling of the internal cervical os with a normal residual CL.
- **Underdevelopment of the lower uterine segment:** Before 14 weeks, the lower uterine segment is difficult to differentiate from the endocervical canal (Fig. 5), because the gestational sac has not reached a sufficient size to completely expand the lower part of the uterus. Placenta previa may create this same problem, resulting in an artificially increased CL.
- If the lower uterine segment is underdeveloped, it can be difficult to identify the true internal os, and some myometrium may be included in the CL measurement. This should be suspected when the cervix appears longer than 50 mm or the internal os is cephalad above the bladder reflection.²⁸ A difference in echotexture between myometrium and true cervical stroma often can be appreciated during real-time scanning and provides a means for differentiating between the two structures.

Fig. 5: Transvaginal view of the cervix and lower uterine segment of a patient scanned at the 13th week of gestation—the lower uterine segment is difficult to differentiate from the endocervical canal and internal os

- Prior cervical surgery may alter the appearance of the cervix, making the identification of measurement landmarks difficult.
- **Air bubbles:** Hasty placement of ultrasound gel into the transducer cover may generate small air bubbles that create a poor image.

WHAT TO MEASURE

Cervical Length

Cervical length measurement using TVS is an essential part of assessing the risk of preterm delivery, because cervical shortening (i.e., effacement) is one of the first steps in the processes leading to labor and can precede labor by several weeks. At midgestation, it provides a useful method, a decrease in CL is predictive of sPTB (Table 2), with the highest risk in women with early and substantial cervical shortening.^{14,15,29} Because shortening begins at the internal cervical os,^{14,15,29} it is often detected on ultrasound examination, especially on TVS before it can be appreciated on physical examination. In women, who present with threatened spontaneous preterm labor, TVS measurement of CL can help to distinguish between “true” and “false” spontaneous preterm labor. Moreover, the identification of women with a short cervix and adequate treatment can reduce the frequency of PTB, and these procedures can be cost-effective,^{30,31} but the major remaining question about CL ultrasound screening is how to best define or select women who could benefit from this test.

Cervical length measurements at 16–22 weeks’ gestation form a normal bell-shaped curve, with 27 mm corresponding to the 5th percentile, 30 mm to the 10th percentile, and 45 mm to the 90th percentile.³² For singleton gestations at about 20 weeks without a prior sPTB, the centiles for three CL thresholds are approximately:

- 15 mm—0.5th centile
- 20 mm—1st centile
- 25 mm—2nd–3rd centile.

The definition of short cervix varies according to the gestational age at cervical measurement (cervix normally shortens after 22 weeks) and the outcome of interest (gestational age of the PTB).^{32–34} The median CL after 32 weeks is 33 mm vs 37–35 mm at 21–32 weeks and 38.5 mm before 21 weeks (Table 3).

Cervical length is not significantly affected by parity, race or ethnicity, or maternal height.^{14,29,33–40}

Table 2: Relative risk is in comparison to women whose cervical lengths were above the 75th percentile. Data from an asymptomatic general obstetrical population evaluated between 22 weeks and 30 weeks of gestation with exclusion of women with multiple gestations, fetal anomalies, cerclage, or placental previa

Cervical length (mm)	Centile	Relative risk of PTB	Confidence interval
≤35	50	2.35	1.42–3.89
≤30	25	3.79	2.32–6.19
≤26	10	6.19	3.84–9.97
≤22	5	9.49	5.95–15.15
≤13	1	13.99	7.89–24.78

PTB, preterm birth

Source: 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 1996;334(9):567–572

Table 3: Percentile values for CL between 17 weeks and 32 weeks of gestation

Group (GW)	Percentiles						
	5	10	25	50	75	90	95
17–20 GW	33.00	34.00	37.00	38.50	41.00	44.00	45.00
21–24 GW	29.00	30.00	34.50	37.00	39.00	41.00	43.00
25–28 GW	27.00	28.00	33.00	35.00	37.00	40.00	41.40
29–32 GW	26.50	28.00	31.00	33.00	36.50	39.00	40.00

Source: Arisoy R, Yayla M. Transvaginal sonographic evaluation of the cervix in asymptomatic singleton pregnancy and management options in short cervix. J Pregnancy 2012;2012:201628

Fig. 6: Ultrasound of normal cervix with equal thickness of anterior and posterior cervical lips. Calipers should be placed correctly

Practical points for the TVS cervix length measurement technique are:

- The patient should empty her bladder prior to the examination, because the patient having a full bladder can increase artificially the CL. To et al.³⁴ showed that the mean difference between CL measured when the patient's bladder is empty and that measured when the bladder is full is about 4 mm. In addition, a full bladder can obscure the presence of cervical funneling by compressing the two halves of the funnel together.
- The transvaginal transducer is gently placed into the anterior fornix until the cervix is visualized.
- A longitudinal view of the cervix should be obtained. The cervix should be measured along its longitudinal axis, which may be different from the patient's longitudinal axis. The cervical canal, in most cases, is a fairly thin line. It may have a thin layer of hypoechoic contents.
- Calipers should be placed correctly (Fig. 6). Cervical measurement is obtained by placing calipers at the external and the internal os. In 95% of cases, the difference between two measurements obtained by the same sonographer or by two different sonographers is about 4 mm.³² CL should only be determined from images in which the lowermost edge of the empty maternal bladder and the internal and external os are visible, and when the anterior and posterior lips of the cervix are of approximately equal thickness. If the cervix appears asymmetric (thin anteriorly and thicker posteriorly), this suggests excessive probe pressure.
- Evaluation of CL in a patient with a curved cervix can be performed in either of two ways:
 - The length of a single, straight line from the internal to external os can be measured.
 - The sum of two separate, straight lines joined at an angle along the curved length of cervix is determined: this sum is used for the CL if the distance between the angle and a straight line from the internal to external os is more than 5 mm (Fig. 7) as it may provide a more accurate measurement.²⁶
- The tracing the cervical canal is avoided because it introduces unpredictable operator variation. A curved cervix usually means a long cervix and thus a low risk for PTB, while a short cervix is usually straight.
- If there is funneling, the caliper should be placed at the apex of the funnel (Fig. 8). Excess pressure on the cervix can artificially increase its apparent length. This can be avoided by first obtaining an apparently satisfactory image, withdrawing the probe until the image blurs, and then reapplying only enough pressure to restore the image.
- When three measurements have been obtained that satisfy measurement criteria and vary by less than 10%, the shortest of these is chosen and recorded as the "shortest best." Choosing the shortest of three excellent images reduces interobserver variation.
- Duration of the examination should be 3–5 minutes.
- If a short (or shorter) CL is seen after application of fundal pressure, the length of the residual closed portion of the cervix

Fig. 7: Evaluation of cervical length in a patient with a curved cervix. If the widest distance ("A"—red arrow) between the dashed yellow lines is greater than 5 mm, use the sum of "B" and "C" as the best measurement of cervical length. If less than or equal to 5 mm, use "D" as the best measurement of cervical length

Fig. 8: Funnel length should not be measured or recorded as it is not an independent predictor of preterm labor risk when the closed length of the cervical canal is considered. *Source:* Berghella V. (2017). Second-trimester evaluation of cervical length for prediction of spontaneous preterm birth in singleton gestations. [online] UpToDate. Available from: <https://www.uptodate.com/contents/second-trimester-evaluation-of-cervical-length-for-prediction-of-spontaneous-preterm-birth-in-singleton-gestations> [Accessed June 2018]

is taken three times, with the shortest length recorded in millimeters as the best estimate of the true length of the cervix. This length best correlates with duration of pregnancy. Only one measurement should be reported—the shortest best CL (mm) of all measurements taken.

Three-dimensional Cervical Assessment

Recent developments in ultrasonography (US) technology make possible the acquisition of 2D data in a 3D volume, which are presented in a variety of orthogonal multiplanar displays in which sagittal, axial, and coronal views of the cervix are shown simultaneously (Fig. 9). These techniques make possible visualization of anatomic planes that are simply impossible with 2D technique (the 3D TVU is the unique imaging method capable of obtaining a true coronal plane by direct correlation of the views in a multiplanar display), but further research works are needed to evaluate whether this additional information has any impact in clinical management. Furthermore, the measurement of CL with 3D sonography is longer than with the 2D approach. According to Bega et al.⁴¹ the 2D US has been ineffective for defining the true sagittal plane of uterine cervix in a considerable number of studies, since differences of 5–15 mm in the CL measured by both methods were detected. Towner et al.⁴² in a study published in 2004, reported larger uterine cervix length measured at 3D US than at 2D US. Severi et al.⁴³ also found a significant difference ($p < 0.001$) between CL measured with 2D ultrasound (37.6 mm) and 3D ultrasound (39.8 mm). A correct, midsagittal plane was more accurately determined with 3D in contrast to 2D ultrasound.⁴³ Considering the differences between the 2D and 3D methods of examination in the biometry measurement, the cervical 3D US may be added to the battery of examinations presently being utilized for cervical evaluation in the screening for PTB, aiming at improving the prematurity prognosis. However, from these and mentioned reasons further researches with a higher number of cases are necessary for confirming these results.

Fig. 9: 3D ultrasound image (transvaginal view) of the uterine cervix in multiplanar display simultaneously showing sagittal, axial, and coronal planes

Diagnosis of Short Cervix

The diagnosis of short cervix is defined when the CL is less than or equal to 25 mm at these gestational weeks, with the best prediction for PTB obtained at 16–24 weeks of gestation. On the other hand, in women diagnosed with a short cervix (≤ 25 mm), a change in CL on subsequent ultrasound examinations appears to impact the risk of PTB.^{44,45} Although CL less than or equal to 25 mm in the second trimester is reliably associated with an increased risk of sPTB, with a particularly strong relationship when it occurs before 24 weeks of gestation or in women with a prior PTB, especially before 32 weeks.^{14,15,29,32,35,46,47} However, there is no threshold value below, which the patient always delivers preterm. Iams et al. demonstrated that cervical ultrasound measurement at approximately 24 weeks and thus did not alter management based on this finding, delivery at less than 35 weeks occurred in 18% of women with CL below the 10th percentile (25 mm) and approximately 50% of those with CL below the 1 percentile (13 mm).¹⁴

A stable or longer CL at a subsequent examination is associated with a lower risk for sPTB than initially predicted, while a shorter CL increases the risk of PTB.

Best Gestation Age and Frequency of Examination

The timing and frequency of CL measurement on is primarily based on the patient's prior obstetric history:

- Low-risk women are screened once at 18–24 weeks of gestation.⁴⁸
- High-risk population usually begins screening at about 16 weeks of gestation and the frequency depends on the measurement result (Flowchart 1). According to literature data, there is a proof that serial screening is effective in this population.^{26,49}

Reproducible measurement of CL becomes possible usually when the cervix normally becomes distinct from the lower uterine segment,⁵⁰ at approximately 14 weeks of gestation. CL measurements before 14 weeks of gestation have limited clinical value.^{50,51} However, in some particularly high-risk pregnancies, such as those with prior second-trimester losses and/or large (or

Flowchart 1: Approach to sonographic screening of cervical length in pregnancy and management of pregnant women with a short cervix. (TVU, transvaginal ultrasound). *Source:* Berghella V. (2017) Second-trimester evaluation of cervical length for prediction of spontaneous preterm birth in singleton gestations. [online] UpToDate. Available from: <https://www.uptodate.com/contents/second-trimester-evaluation-of-cervical-length-for-prediction-of-spontaneous-preterm-birth-in-singleton-gestations> [Accessed June 2018]

multiple) excisional biopsies, cervical shortening has been seen as early as 10–13 weeks of gestation and was associated with a high risk of second-trimester loss.⁵⁰ After 30 weeks, CL measurement is not useful for predicting PTB because the cervix physiologically starts to shorten at this time, even in women destined to deliver at term, so the diagnosis of short cervix obtained at 16–24 weeks of gestation has the best prediction for PTB.

Furthermore, CL measurements performed in nonpregnant women are not useful for predicting PTB.⁵²

Patients Identification

Selection for sonographic CL screening is still controversial. There have been numerous studies in the subject, which evaluated the predictive accuracy of CL measurement for PTB in many different populations. Population characteristics that could affect the performance of the test include the proportion of singleton vs multiple gestation, symptomatic vs asymptomatic women, intact membranes vs ruptured membranes, prior PTB vs no prior PTB, prior term birth vs no prior term birth, and prior cervical surgery vs no prior cervical surgery.^{14,26} In 2001, Iams and associates demonstrated low sensitivity (39.1%) for the detection of women at risk for PTB among low-risk pregnant women posing the question thus there is a rationality to use it to screen low-risk population.⁵³ A 2013 Cochrane

review did not find sufficient evidence to recommend routine CL measurement as a screening test for all pregnant women.⁵⁴

The relevant data suggested that in low-risk population (singleton gestations and no prior PTB), the sensitivity of a short cervix for subsequent PTB is between 35% and 45% in the absence of intervention,¹⁴ with the positive predictive between 20% and 30%.⁵⁵ Sensitivity is much higher in high-risk populations; Owen et al. demonstrated that sensitivity of the screening test among women with a prior PTB is 70%.²⁶ On the other hand, Son et al. introduced a universal transvaginal CL screening program where the universal CL screening was associated with a significant decrease in the frequency of PTB, furthermore, the effect size for the reduction in PTB was similar in nulliparous and multiparous women with previous term births. Miller and associates demonstrated that limiting CL screening to women with historical risk factors for PTB would miss about 40% of women with a short cervix, and thus at risk for PTB.⁵⁶ Nevertheless, according to presented data, the overall value of universal CL screen continues to be debated.⁵⁶

Multiple Gestation

The prediction of PTB in multiple gestation using traditional clinical means is limited. Compared with singleton pregnancies, twin pregnancies that deliver at term have been shown to have a similar CL

Fig. 10: Cervix with funneling (transvaginal view), showing funnel length "A", functional length "B", and funnel width "C"

at 14–19 weeks of gestation but have a progressively much shorter cervix after 20 weeks of gestation.⁵⁷ Unfortunately, the predictive value of CL measurement in twins between 24 weeks and 34 weeks of gestation is low.⁵⁸ Likewise, the sensitivity of CL measurement to predict which triplet gestations will deliver preterm is low.⁵⁹ From the available data it can be concluded that CL measurement is not a sensitive screening test for prediction of PTB in multiple gestation, although they are at increased risk of PTB.⁶⁰

There are a few national organizations, which recommend cervix length measurement guidelines. Of these:

- *American College of Obstetricians and Gynecologists (ACOG)*: In a practice bulletin on PTB, ACOG neither mandated universal routine CL screening in women without a prior PTB nor recommended against such screening.⁶¹ However, in women undergoing obstetrical ultrasound examination, ACOG has recommended that the cervix be examined when technically feasible.⁶²
- *Society for Maternal-Fetal Medicine (SMFM)*: The SMFM recommends routine TVU CL screening between 16 weeks and 24 weeks of gestation for women with a singleton pregnancy and history of prior sPTB.⁶³ They consider screening reasonable for women with a singleton pregnancy and no history of prior sPTB but have not recommended routine screening for this population. They suggest not performing routine CL screening for women with a cervical cerclage, multiple gestation, preterm premature rupture of membranes (PPROM), or placenta previa.

Funneling

The disruption of the internal os, as documented by funneling (internal os width >5 mm), is a significant risk factor for adverse perinatal outcome (i.e., preterm labor, chorioamnionitis, abruption, rupture of the membranes, and serious neonatal morbidity and mortality) (Fig. 10). Several authors have suggested that funneling is an early sign of cervical incompetence.^{64–67} Funneling has been variably defined according to the depth of protrusion¹⁴ and/or the ratio of the funnel depth to the length of funnel plus the remaining closed cervix.²⁵ As the cervix effaces, the relationship between the lower uterine segment and the axis of the cervical canal also changes. Zilianti first reported an observation that the cervix goes through a typical sequence in cervical shape prior to preterm delivery, which he described by the phrase "Trust Your Vaginal

Fig. 11: Progression of cervical effacement at the internal cervical os from completely uneffaced (T) to completely effaced (U). Source: Zilianti M, Azuaga A, Calderon F, et al. Monitoring the effacement of the uterine cervix by transperineal sonography: a new perspective. J Ultrasound Med. 1995;14(10):719–724

Ultrasound" (Fig. 11).³⁹ "T" represents the normal relationship of the area where the endocervical canal meets the uterine cavity (Fig. 12), whereas "U" represents almost complete effacement and signifies the highest risk for PTB (Fig. 13). The shape of the funnel (U or V), percent funneling, and the depth and width of the funnel have all been described as methods of assessing cervical funneling. In high-risk women, the progression to a U-shaped funnel has been associated with an increased risk of preterm delivery.⁶⁴ Thus, the relationship between cervical funneling and PTB remains unclear. However, when funneling is present with a normal residual CL, it is usually related to a contraction of the lower uterine segment and has little to no clinical significance.

Ultrasonographic Assessment

Good scanning technique is essential, as excessive pressure with the probe, or presence of a distended bladder may artificially narrow the canal. Preferably, a transvaginal scan is recommended for accurate assessment of CL and measurement of funneling.

Fig. 12: "T" represents the normal relationship of the area where the endocervical canal meets the uterine cavity (transvaginal view)

Fig. 13: "U" represents almost complete effacement and signifies the highest risk for preterm birth (transvaginal view)

Fig. 14: Measurement of the cervix with funneling. Source: Berghella V, Kuhlman K, Weiner S, et al. Cervical funneling: sonographic criteria predictive of preterm delivery. *Ultrasound Obstet Gynecol* 1997;10(3):161–116

Measurement Criteria

- **Percentage funneling:** Funnel length/(functional CL + funnel length) (Fig. 14)
- **Shape of funneling:** V-shaped or U-shaped. It appears that U-shaped funneling has higher risk of preterm delivery compared with a V-shaped funnel⁶⁴
- **Depth and width of the funnel:** V-shaped funnel has a depth with no width; however, U-shaped funnel has the width as an important parameter.

The presence of all criteria gives a high-positive predictive value of 82% for PTB.⁶⁸ However, the most predictive variable is percentage funneling, which is proposed to be used for PTB risk assessment.⁶⁸

Cervical Gland Area

An accurate diagnosis of preterm labor cannot be made solely on these criteria, as the shortening of the CL represents one of many signs of cervical maturation. In addition, funnel formation is often affected by uterine contractions and cannot be considered a reliable predictor of threatened preterm labor unless the uterine contractions are taken into account. Thus guiding, Sekiya et al. during ultrasound (TVS) observation of the pregnant cervix identify the CGA surrounding the cervical canal (Fig. 15).⁶⁹ In 1988, Sekiya et al. demonstrated that this area could be found in most women, whether they were pregnant or not, but it could not be detected in patients with a mature cervix which includes those threatened by preterm labor or those with cervical incompetence.⁶⁹ They found highly significant correlations between the detection rate of CGA and CL, CGA and cervical maturation index, and CL and cervical maturation index.⁶⁹

The CGA was defined as the sonographically hyperechoic or hypoechoic zone surrounding the cervical canal (Fig. 15), which probably corresponds to the histological CGA. This zone is consistently seen until 31 weeks of gestation.⁷⁰ The detection rate of CGA during the TVS between 16 weeks and 31 weeks of gestation is about 80%.^{69–72} Nondetection of CGA could correspond to the beginning of the uterine cervix maturation.^{69,71,72}

In the light of the available data, the absence of CGA at second trimester US appeared to be new and powerful predictor of PTB before 32 weeks gestation.^{69–73} Asakura et al. reported that short CL (<20 mm) with absent CGA represents an independent predictor for PTB. However, the absence of the CGA as a new marker for the risk of PTB has to be confirmed by further investigations.⁷²

Amniotic Fluid Sludge

The sonographic finding of dense aggregates of particulate matter in the amniotic fluid close to the internal cervical os, known as amniotic fluid sludge (AFS). AFS may represent clusters of bacteria and inflammatory cells, it is possible that the presence of AFS may represent chronic intra-amniotic infection.⁷⁴ However, the clinical implications of the presence of this ultrasonographic finding in these patients are unknown.

Figs 15A and B: Cervical gland area (CGA) surrounding the cervical canal (arrows and blue area)

Amniotic fluid sludge is an independent risk factor for spontaneous preterm delivery at less than 28 weeks, less than 32 weeks, and less than 35 weeks of gestation. Kusanovic et al. presented that the combination of AFS and a short cervix (<25 mm) confers a higher risk for spontaneous preterm delivery at less than 28 and less than 32 weeks than that conferred by a short cervix alone.⁷⁵

CLINICAL ASPECTS

For the ultrasonographic assessment of the cervix to be judged cost-effective, there must be an effective intervention to prevent PTB if the test is positive.

Generally, the importance of positive test is to try to recognize cervical changes on time, to plan the adequate therapy, to prepare for sufficient intrauterine transport, and to administered course of antenatal corticosteroid therapy to women at risk for PTB reduced the incidence and severity of respiratory distress syndrome (RDS) and mortality in offspring.

Many interventions have been proposed in an attempt to prevent PTB depending on risk classification.

Bed Rest

Long ago bed rest and hydration are often recommended in an attempt to prevent PTB in women at high risk. While bed rest improves uteroplacental blood flow and can lead to a slight increase in birth weight, there is no evidence that it decreases the incidence of PTB,^{76–78} even in women with a short cervix.⁷⁹ However, bed rest appears to increase the risk of thromboembolic events, has clear negative psychosocial effects, and leads to deconditioning.^{25,80}

Lifestyle Interventions

Clinicians should consider the available evidence and the patient's individual circumstances when making lifestyle recommendations as there are social, psychological, financial, and medical side effects associated with these interventions. Lifestyle interventions (cessation of work and physical exercise, abstinence from sexual intercourse, and bed rest or limited activity) have not been adequately evaluated by well-designed studies. Although there are inadequate data on the safety of coitus in women at risk for PTB because of previous PTB or preterm cervical ripening.⁸¹

Cervical Cerclage

Cervical cerclage is an old, easily performed procedure for treatment of true cervical incompetence.⁸² Dijkstra et al. found that the mean $\pm$ standard deviation precerclage CL was 27.2 ± 10.3 mm and after cerclage was 34.1 ± 9.9 mm ($n = 80$, $p < 0.001$). The increase in CL after cerclage is not predictive of term delivery.⁸³ Until recently, cerclage was the only intervention studied to prevent PTB in asymptomatic women with short CL. Rust et al. randomized 113 women with CL less than 25 mm or more than equal to 25% funneling measured between 16 weeks and 24 weeks to either modified bed rest or cerclage. No significant differences between two groups regarding risk of PTB less than 34 weeks or perinatal death were noted.⁸⁴ To et al. also sampled 47,123 asymptomatic women and identified a cervix of 15 mm or less in 470, of whom 54% were randomized to either cervical cerclage or expectant management. No significant differences in the rate of PTB less than 33 weeks or in perinatal or maternal morbidity or mortality were noted. Subgroup analysis of the utility of cerclage in the high-risk population, based on maternal history, was not performed.⁸⁵

Based on the data published in the subject, cerclage is not indicated in low-risk patients. A case-controlled study found that cerclage does not reduce PTB in low-risk women with short CL compared with rest alone. Owen and coworkers in a multicenter randomized trial screened high-risk women for short cervix, and randomly assigned to cerclage if CL was less than 25 mm. They find that in women with a prior sPTB less than 34 weeks and CL less than 25 mm, cerclage reduced previsible birth and perinatal mortality but did not prevent birth less than 35 weeks, unless CL was less than 15 mm.⁴⁹ The systematic meta-analysis by Berghella et al. has shown that cerclage, when performed in high-risk women with a singleton gestation and CL less than 25 mm, seems to have a similar effect regardless of the degree of cervical shortening, including CL 16–24 mm, as well as CL less than or equal to 5.9 mm.⁸⁶

Moreover, the effectiveness of cervical cerclage remains unclear and the literature is unable to establish a clinical population in which cerclage may be of true benefit.⁸⁷

Pessary

Vaginal pessaries are intended to alter the axis of the cervical canal and displace the weight of the uterine contents away from the

cervix. By changing the angle of the cervix in relation to the uterus, the pessary also obstructs the internal os and thus may provide protection against ascending infection.

Use of a pessary in women with a short CL has been proposed as an effective, inexpensive, and easy to implement method for prolonging pregnancy, but efficacy is not supported by the body of literature.

Progesterone

Progesterone's role in the treatment and prevention of PTB is still uncertain. A Cochrane meta-analysis from 2005 showed that intramuscular progesterone is associated with a reduction in risk of PTB before 37 gestational weeks.⁸⁸ Recent data [including data from the dOes Progesterone Prophylaxis to prevent preterm labor IMprove oUtoCoMe? (OPPTIMUM study)] show that vaginal progesterone supplementation reduced the risk of PTB and neonatal morbidity and mortality in singleton gestations with midtrimester short cervix (≤ 25 mm), without any deleterious effects on neurodevelopmental outcome.^{89,90} Compared with placebo, vaginal progesterone:

- Reduced PTB
- Reduced RDS
- Reduced composite neonatal morbidity and mortality
- Reduced birthweight less than 1,500 g
- Reduced admission to the neonatal intensive care unit.⁹¹

Intramuscular injections of synthetic progestogen—hydroxyprogesterone caproate (250 mg)⁹² as active prophylaxis, compared with the placebo group, significantly reduced the risk of delivery at all gestational ages studied:

- Less than 37 weeks (36% vs 55%),
- Less than 35 weeks (21% vs 31%)
- Less than 32 weeks (11% vs 20%).

Meis et al. also demonstrated that infants from progesterone supplemented pregnancies had less perinatal morbidity, with significantly reduced rates of necrotizing enterocolitis, intraventricular hemorrhage, and need for supplemental oxygen. In addition, the data show that there was no evidence of virilization of female offspring, which is a theoretic concern of this therapy.⁹²

The effect of hydroxyprogesterone caproate on cervical ripening is less clear.⁹³ The safety of hydroxyprogesterone caproate in pregnancy has been supported by several clinical trials^{51,92,94} and epidemiologic studies.^{95,96} Although some studies have reported a nonstatistical increase in risk of miscarriage and stillbirth in pregnancies exposed to progestins,^{52,92,96} others could not confirm this observation or observed a nonstatistical decrease in these risks.^{97,98} This association requires further study.⁹⁹ Additionally, Silver et al. later Carmichael et al. found that pregnancy-related intake of progestins was associated with increased hypospadias risk.^{100,101} Even if confirmed, this risk is limited to exposure prior to 11 weeks of gestation and thus is not relevant to women with prior preterm delivery, as they will receive the drug after 16 weeks of gestation.⁹¹

Progesterone preparations and doses: Natural or micronized progesterone:

- *Natural progesterone* is typically administered daily and vaginally. The advantage of vaginal progesterone is its high uterine bioavailability since uterine exposure occurs before the first pass through the liver. Moreover, binding

to progesterone receptors, glucocorticoid receptors, or expression of progesterone-responsive genes is no greater with 17-alpha hydroxyprogesterone caproate than with natural progesterone.¹⁰² Doses of 90–400 mg have been effective, beginning as early as 18 weeks of gestation.

- *Micronized progesterone:* There are two main types of micronized progesterone—(1) vaginal tablet (100 mg) or (2) vaginal gel (90 mg). Both preparations are commercially available, but not approved for prevention of PTB in cervical shortening. The Food and Drug Administration (FDA) analyses indicated that progesterone gel was not associated with a reduction in PTB among women with a short CL at any gestational age, with a treatment difference of only—2.4% in favor of progesterone gel compared to placebo at less than or equal to 32 6/7 weeks gestation, but the drug was safe in this population.¹⁰³

Indomethacin

Indomethacin therapy for asymptomatic women with a short cervix (≤ 25 mm) at 14–27 weeks who did not receive a cerclage did not reduce sPTB s less than 35 weeks, but appeared to reduce PTB s less than 24 weeks.¹⁰⁴ Further research including a larger number of pregnancies and a randomized trial design is necessary to further clarify the effectiveness, as well as the risks, of this therapy.

Antibiotics

A short CL has also been associated with infection. Unfortunately, there is insufficient evidence to recommend antibiotics for women with cervical insufficiency, based on poor obstetrical history, short TVU CL, or dilated cervix on physical examination.¹⁰⁵ The antibiotics treatment is indicated in the presence of AFS, which suggests subclinical infection and an increased risk of preterm delivery.^{75,106}

THERAPEUTICAL APPROACHES ACCORDING TO RISK CLASSIFICATION

Singleton Low Risk

Orzechowski et al. found that in a universal transvaginal ultrasonogram CL screening program, the incidence of a CL 20 mm or less was 1.1% in women with singleton gestations without prior sPTB.¹⁰⁷ The incidence of sPTB was similar among women undergoing transvaginal CL screening compared with those not screened. For women with singleton pregnancies and no history of prior PTB, Orzechowski et al. screens for a short cervix (≤ 25 mm) with a single examination at 18–24 weeks (Flowchart 1).^{107,108} Because the rate is slightly higher in nulliparas than in multiparas without a prior PTB,¹⁰⁷ the same screening protocol is proposed for both groups.

Treatment Options

- *Pessary* is an effective, inexpensive, and easy to implement method for prolonging pregnancy, but there is no true evidence of efficacy of this treatment.
- *Cervical cerclage* does not appear to be effective for women with a short cervix who have not had a prior PTB.¹⁰⁹
- Vaginal progesterone supplementation reduced the risk of PTB and neonatal morbidity and mortality in singleton gestations with midtrimester short cervix (≤ 25 mm).⁸⁹
- *Bed rest* does not prolong pregnancy and increases the risk for thromboembolic events.

Singleton High Risk

Women with a prior PTB are at high risk for recurrence. However, a woman with clinical factors for PTB who has a normal CL (≥ 25 mm) between 18 weeks and 22 weeks of gestation has a risk of PTB of less than 10%, which represents a significant reduction in risk and can prevent unnecessary interventions in these women.¹⁷ Contrariwise, the sensitivity of TVS CL measurement to detect which high-risk women will deliver preterm is about 60%, much higher, than in low-risk women, as so as the positive predictive value.

Treatment Options

- *Cerclage* placement reduces the frequency of recurrent PTB.¹⁰⁹
- Daily treatment with *vaginal progesterone* is a reasonable alternative to the combination of cerclage and hydroxyprogesterone caproate.¹¹⁰
- An alternative approach is to substitute vaginal progesterone for intramuscular hydroxyprogesterone caproate in women with a history of PTB who develop a short cervix. Some clinicians perform an amniocentesis to assess for subclinical infection before placing a cerclage in women with a short cervix.⁹¹

Singleton Pregnancy, No Prior PTB, but Risk Factors for Preterm Birth

For women with singleton pregnancies and risk factors for PTB but no prior PTB, Orzechowski et al. treat women with a short cervix with vaginal progesterone, similar to the approach for any woman without a previous PTB (Flowchart 1).^{107,108}

CONCLUSION

- Transvaginal sonography for cervical assessment is one of the best techniques for predicting PTB, furthermore the use of TVS of the cervix has been found to be safe and acceptable to patients.
- *Cervical length*: The length of closed cervix between the internal os and external os. It should only be determined from images in which the lowermost edge of the empty maternal bladder and the internal and external os are visible, and when the anterior and posterior lips of the cervix are of equal thickness.
- The diagnosis of short cervix is defined by CL less than or equal to 25 mm at 16–24 weeks of gestation.
- A gradual decline in CL is a normal finding after 28–32 weeks of gestation. However, a decrease in CL in the second trimester is predictive of sPTB, and the risk increases as CL decreases.
- The routine TVS screening for short cervix in singleton pregnancies is suggested, as long as an appropriate intervention to reduce the risk of PTB is available.
- Screening frequency should depend on severity of obstetric history—serial TVS of the cervix having a better predictive accuracy.
- For a low-risk woman with a singleton gestation and CL less than or equal to 25 mm before 25 weeks, vaginal progesterone supplementation is suggested.
- Cerclage does not prevent PTB in this population. The benefit of placing a pessary has not been adequately studied.
- High-risk women who develop CL less than or equal to 25 mm may have cervical insufficiency. These women are initially administered progesterone (hydroxyprogesterone caproate by intramuscular injection) based on their past pregnancy history

and then offered the addition of a cerclage upon identification of a short cervix.

- Cervical length measurement is an insensitive screening test for prediction of PTB in multiple gestations, and no intervention has been proven beneficial in preventing PTB in multiple gestations with short CL.
- In high-risk women, the progression to a U-shaped funnel has been associated with an increased risk of PTB. However, when funneling is present with a normal residual CL, it is usually related to a contraction of the lower uterine segment and has little to no clinical significance.
- There are significant correlations between the detection rate of CGA and CL, CGA and cervical maturation index, and CL and cervical maturation index. The absence of CGA at second trimester US appeared to be new and powerful predictor of PTB before 32 weeks gestation.
- The cervical 3D US may be added to the battery of examinations presently being utilized for cervical evaluation in the screening for PTB, but further researches are necessary for confirming its success.
- The CL measurement, evaluation of funneling and CGA together increased the sensitivity of cervical screening for PTB and appeared to be powerful predictor of PTB before 32 weeks gestation.

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REFERENCES

1. WHO. WHO: recommended definitions, terminology and format for statistical tables related to the perinatal period and use of a new certificate for cause of perinatal deaths. Modifications recommended by FIGO as amended October 14, 1976. *Acta Obstet Gynecol Scand* 1977;56(3):247–253.
2. Rogers LK, Velten M. Maternal inflammation, growth retardation, and preterm birth: insights into adult cardiovascular disease. *Life Sci* 2011;89(13–14):417–421. DOI: 10.1016/j.lfs.2011.07.017.
3. Blencowe H, Lee AC, Cousens S, et al. Preterm birth associated neurodevelopmental impairment estimates at regional and global level for 2010. *Pediatr Res* 2013;74(Suppl 1):17–34. DOI: 10.1038/pr.2013.204.
4. Rodrigues T, Rocha L, Barros H. Physical abuse during pregnancy and preterm delivery. *Am J Obstet Gynecol* 2008;198(2):171–176. DOI: 10.1016/j.jajog.2007.05.015.
5. Caughey AB, (2007). Definition, incidence, significance and demographic characteristics of preterm birth. [online] UpToDate. Available from: <http://www.uptodate.com/contents/demographic-factors-in-preterm-birth> [Accessed June 2018].
6. Lockwood CJ, (2007) Overview of preterm labor and delivery. [online] UpToDate. Available from: <http://www.uptodate.com/contents/fetal-fibronectin-for-prediction-of-preterm-labor-and-delivery> [Accessed June 2018].
7. Robinson JN, Norwitz E, (2007). Risk factors for preterm labor and delivery. [online] UpToDate. Available from: <https://www.uptodate.com/contents/preterm-birth-risk-factors-and-interventions-for-risk-reduction> [Accessed Jun 2018].
8. Crane JM, Delaney T, Hutchens D. Transvaginal ultrasonography in the prediction of preterm birth after treatment for cervical intraepithelial neoplasia. *Obstet Gynecol* 2006;107(1):37–44. DOI: 10.1097/01.AOG.0000192169.44775.76.

9. Arbyn M, Kyrgiou M, Simoons C, et al. Perinatal mortality and other severe adverse pregnancy outcomes associated with treatment of cervical intraepithelial neoplasia: meta-analysis. *BMJ* 2008;337(sep18 1):a1284. DOI: 10.1136/bmj.a1284.
10. Jolley JA, Wing DA. Pregnancy management after cervical surgery. *Curr Opin Obstet Gynecol* 2008;20(6):528–533. DOI: 10.1097/GCO.0b013e328317a411.
11. Dasanayake AP, Gennaro S, Hendricks-Muñoz KD, et al. Maternal periodontal disease, pregnancy, and neonatal outcomes. *MCN Am J Matern Child Nurs* 2008;33(1):45–49. DOI: 10.1097/01.NMC.0000305657.24613.47.
12. Yudin MH, Money DM, SOGC Infectious Diseases Committee Screening and management of bacterial vaginosis in pregnancy. SOGC clinical Practice guideline no. 211, August 2008. *J Obstet Gynaecol Can* 2008;30(8):702–716. DOI: 10.1016/S1701-2163(16)32919-X.
13. Viswanathan M, Siega-Riz AM, Moos MK, et al. Outcomes of maternal weight gain. *Evid Rep Technol Assess (Full Rep)* 2008;168:1–223.
14. 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* 1996;334(9):567–572. DOI: 10.1056/NEJM199602293340904.
15. Owen J, Yost N, Berghella V, et al. Can shortened midtrimester cervical length predict very early spontaneous preterm birth? *Am J Obstet Gynecol* 2004;191(1):298–303. DOI: 10.1016/j.ajog.2003.11.025.
16. Blondel B, Le Coutour X, Kaminski M, et al. Prediction of preterm delivery: is it substantially improved by routine vaginal examinations? *Am J Obstet Gynecol* 1990;162(4):1042–1048. DOI: 10.1016/0002-9378(90)91312-Z.
17. Berghella V, Bega G, Tolosa JE, et al. Ultrasound assessment of the cervix. *Clin Obstet Gynecol* 2003;46(4):947–962. DOI: 10.1097/00003081-200312000-00026.
18. 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* 2000;182(6):1458–1467. DOI: 10.1067/mob.2000.106851.
19. 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* 2012;25(9):1682–1689. DOI: 10.3109/14767058.2012.657278.
20. Saul LL, Kurtzman JT, Hagemann C, et al. Is transabdominal sonography of the cervix after voiding a reliable method of cervical length assessment? *J Ultrasound Med* 2008;27(9):1305–1311. DOI: 10.7863/jum.2008.27.9.1305.
21. Hassan SS, Romero R, Vidyadhari D, et al. 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* 2011;38(1):18–31. DOI: 10.1002/uog.9017.
22. Goya M, Pratcorona L, Merced C, et al. Cervical pessary in pregnant women with a short cervix (PECEP): an open-label randomised controlled trial. *Lancet* 2012;379(9828):1800–1806. DOI: 10.1016/S0140-6736(12)60030-0.
23. Althuisius SM, Dekker GA, Hummel P, et al. Cervical incompetence prevention randomized cerclage trial: emergency cerclage with bed rest versus bed rest alone. *Am J Obstet Gynecol* 2003;189(4):907–910. DOI: 10.1067/S0002-9378(03)00718-X.
24. Kagan KO, Sonek J. How to measure cervical length. *Obstet Gynecol* 2015;45(3):358–362. DOI: 10.1002/uog.14742.
25. Berghella V, Owen J, MacPherson C, et al. Natural history of cervical funneling in women at high risk for spontaneous preterm birth. *Obstet Gynecol* 2007;109(4):863–869. DOI: 10.1097/01.AOG.0000258276.64005.ce.
26. Owen J, Yost N, Berghella V, et al. Mid-trimester endovaginal sonography in women at high risk for spontaneous preterm birth. *JAMA* 2001;286(11):1340–1348. DOI: 10.1001/jama.286.11.1340.
27. Yost NP, Bloom SL, Twickler DM, et al. Pitfalls in ultrasonic cervical length measurement for predicting preterm birth. *Obstet Gynecol* 1999;93(4):510–516. DOI: 10.1097/00006250-199904000-00008.
28. Iams JD, Johnson FF, Sonck J, et al. Cervical competence as a continuum: a study of ultrasonographic cervical length and obstetric performance. *Am J Obstet Gynecol* 1995;172(4 Pt 1):1097–1103. DOI: 10.1016/0002-9378(95)91469-2.
29. Hibbard JU, Tart M, Moawad AH. Cervical length at 16–22 weeks' gestation and risk for preterm delivery. *Obstet Gynecol* 2000;96(6):972–978. DOI: 10.1097/00006250-200012000-00020.
30. Cahill AG, Odibo AO, Caughey AB, et al. Universal cervical length screening and treatment with vaginal progesterone to prevent preterm birth: a decision and economic analysis. *Am J Obstet Gynecol* 2010;202(6):548.e1–8. DOI: 10.1016/j.ajog.2009.12.005.
31. Werner EF, Han CS, Pettker CM, et al. Universal cervical-length screening to prevent preterm birth: a cost-effectiveness analysis. *Ultrasound Obstet Gynecol* 2011;38(1):32–37. DOI: 10.1002/uog.8911.
32. Heath VCF, Southall TR, Souka AP, et al. Cervical length at 23 weeks of gestation: relation to demographic characteristics and previous obstetric history. *Ultrasound Obstet Gynecol* 1998;12(5):304–311. DOI: 10.1046/j.1469-0705.1998.12050304.x.
33. Greco E, Gupta R, Syngelaki A, et al. First-trimester screening for spontaneous preterm delivery with maternal characteristics and cervical length. *Fetal Diagn Ther* 2012;31(3):154–161. DOI: 10.1159/000335686.
34. To MS, Skentou C, Cicero S, et al. Cervical assessment at the routine 23-weeks' scan: problems with transabdominal sonography. *Ultrasound Obstet Gynecol* 2000;15(4):292–296. DOI: 10.1046/j.1469-0705.2000.00094.x.
35. Taipale P, Hiilesmaa V. Sonographic measurement of uterine cervix at 18–22 weeks' gestation and the risk of preterm delivery. *Obstet Gynecol* 1998;92(6):902–907. DOI: 10.1016/S0029-7844(98)00346-9.
36. Kushnir O, Vigil DA, Izquierdo L, et al. Vaginal ultrasonographic assessment of cervical length changes during normal pregnancy. *Am J Obstet Gynecol* 1990;162(4):991–993. DOI: 10.1016/0002-9378(90)91302-S.
37. Andersen HF, Nugent CE, Wanty SD, et al. Prediction of risk for preterm delivery by ultrasonographic measurement of cervical length. *Am J Obstet Gynecol* 1990;163(3):859–867. DOI: 10.1016/0002-9378(90)91084-P.
38. Zorzoli A, Soliani A, Perra M, et al. Cervical changes throughout pregnancy as assessed by transvaginal sonography. *Obstet Gynecol* 1994;84(6):960–964.
39. Zilianti M, Azuaga A, Calderon F, et al. Monitoring the effacement of the uterine cervix by transperineal sonography: a new perspective. *J Ultrasound Med* 1995;14(10):719–724. DOI: 10.7863/jum.1995.14.10.719.
40. Gramellini D, Fieni S, Molina E, et al. Transvaginal sonographic cervical length changes during normal pregnancy. *J Ultrasound Med* 2002;21(3):227–232. DOI: 10.7863/jum.2002.21.3.227.
41. Bega G, Lev-Toaff A, Kuhlman K, et al. Three-dimensional multiplanar transvaginal ultrasound of the cervix in pregnancy. *Ultrasound Obstet Gynecol* 2000;16(4):351–358. DOI: 10.1046/j.1469-0705.2000.00184.x.
42. Towner D, Boe N, Lou K, et al. Cervical length measurements in pregnancy are longer when measured with three-dimensional transvaginal ultrasound. *J Maternal Fetal Neonat Med* 2004;16(3):167–170. DOI: 10.1080/jmf.16.3.167.170.
43. Severi FM, Bocchi C, Florio P, et al. Comparison of two-dimensional and three-dimensional ultrasound in the assessment of the cervix to predict preterm delivery. *Ultrasound Med Biol* 2003;29(9):1261–1265. DOI: 10.1016/S0301-5629(03)01011-1.
44. Moroz LA, Simhan HN. Rate of sonographic cervical shortening and the risk of spontaneous preterm birth. *Am J Obstet Gynecol* 2012;206(3):234.e1–5. DOI: 10.1016/j.ajog.2011.11.017.
45. Iams JD, Cebrik D, Lynch C, et al. The rate of cervical change and the phenotype of spontaneous preterm birth. *Am J Obstet Gynecol* 2011;205(2):130. DOI: 10.1016/j.ajog.2011.05.021.

46. Berghella V, Roman A, Daskalakis C, et al. Gestational age at cervical length measurement and incidence of preterm birth. *Obstet Gynecol* 2007;110(2 Pt 1):311–317. DOI: 10.1097/01.AOG.0000270112.05025.1d.
47. Crane JM, Hutchens D. Transvaginal sonographic measurement of cervical length to predict preterm birth in asymptomatic women at increased risk: a systematic review. *Ultrasound Obstet Gynecol* 2008;31(5):579–587. DOI: 10.1002/uog.5323.
48. Conde-Agudelo A, Romero R. Predictive accuracy of changes in transvaginal sonographic cervical length over time for preterm birth: a systematic review and metaanalysis. *Am J Obstet Gynecol* 2015;213(6):789–801. DOI: 10.1016/j.ajog.2015.06.015.
49. 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* 2009;201(4):375.e1–8. DOI: 10.1016/j.ajog.2009.08.015.
50. Berghella V, Talucci M, Desai A. Does transvaginal sonographic measurement of cervical length before 14 weeks predict preterm delivery in high-risk pregnancies? *Ultrasound Obstet Gynecol* 2003;21(2):140–144. DOI: 10.1002/uog.28.
51. Conoscenti G, Meir YJ, D'Ottavio G, et al. Does cervical length at 13–15 weeks' gestation predict preterm delivery in an unselected population? *Ultrasound Obstet Gynecol* 2003;21(2):128–134. DOI: 10.1002/uog.47.
52. Uldmire J. Sonographic detection of cervical incompetence. *Clin Obstet Gynecol* 1988;31(1):101–109. DOI: 10.1097/00003081-198803000-00012.
53. Iams JD, Goldenberg RL, Mercer BM, et al. The preterm prediction study: can low-risk women destined for spontaneous preterm birth be identified? *Am J Obstet Gynecol* 2001;184(4):652–655. DOI: 10.1067/mob.2001.111248.
54. Berghella V, Baxter JK, Hendrix NW. Cervical assessment by ultrasound for preventing preterm delivery. *Cochrane Database Syst Rev* 2013(1):CD007235. DOI: 10.1002/14651858.CD007235.pub3.
55. Mella MT, Berghella V. Prediction of preterm birth: cervical sonography. *Semin Perinatol* 2009;33(5):317–324. DOI: 10.1053/j.semper.2009.06.007.
56. Miller ES, Tita AT, Grobman WA. Second-trimester cervical length screening among asymptomatic women: an evaluation of risk-based strategies. *Obstet Gynecol* 2015;126(1):61–66. DOI: 10.1097/AOG.0000000000000864.
57. Kushnir O, Izquierdo LA, Smith JF, et al. Transvaginal sonographic measurement of cervical length. Evaluation of twin pregnancies. *J Reprod Med* 1995;40(5):380–382.
58. Wennerholm UB, Holm B, Mattsby-Baltzer I, et al. Fetal fibronectin, endotoxin, bacterial vaginosis and cervical length as predictors of preterm birth and neonatal morbidity in twin pregnancies. *Br J Obstet Gynaecol* 1997;104(12):1398–1404. DOI: 10.1111/j.1471-0528.1997.tb11010.x.
59. Guzman ER, Walters C, O'reilly-Green C, et al. Use of cervical ultrasonography in prediction of spontaneous preterm birth in triplet gestations. *Am J Obstet Gynecol* 2000;183(5):1108–1113. DOI: 10.1067/mob.2000.108875.
60. 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* 1996;175(4 Pt 1):1047–1053. DOI: 10.1016/S0002-9378(96)80051-2.
61. Committee on Practice Bulletins—Obstetrics. The american college of obstetricians and gynecologists. Practice bulletin no. 130: prediction and prevention of preterm birth. *Obstet Gynecol* 2012;120(4):964–973. DOI: 10.1097/AOG.0b013e3182723b1b.
62. Committee on Practice Bulletins—Obstetrics and the American Institute of Ultrasound in Medicine. Practice bulletin no. 175: ultrasound in pregnancy. *Obstet Gynecol* 2016;128(6):e241–e256. DOI: 10.1097/AOG.0000000000001815.
63. McIntosh J, Feltovich H, Berghella V, et al. Society for Maternal-Fetal Medicine (SMFM), electronic address: Pubs@SMFM.org, the role of routine cervical length screening in selected high- and low-risk women for preterm birth prevention. *Am J Obstet Gynecol* 2016;215(3):B2–B7. DOI: 10.1016/j.ajog.2016.04.027.
64. Podobnik M, Bulić M, Smiljanec N, et al. Ultrasonography in the detection of cervical incompetency. *J Clin Ultrasound* 1988;13(6):383–391. DOI: 10.1002/jcu.1870160604.
65. Michaels WH, Montgomery C, Karo J, et al. Ultrasound differentiation of the competent from the incompetent cervix: prevention of preterm delivery. *Am J Obstet Gynecol* 1986;154(3):537–546. DOI: 10.1016/0002-9378(86)90598-3.
66. Varma TR, Patel RH, Pillai U. Ultrasound assessment of the cervix in 'at risk' patients. *Acta Obstet Gynecol Scand* 1986;65(2):147–152. DOI: 10.3109/00016348609158370.
67. Bartolucci L, Hill WC, Katz M, et al. Ultrasonography in preterm labor. *Am J Obstet Gynecol* 1984;149(1):52–56. DOI: 10.1016/0002-9378(84)90291-6.
68. Berghella V, Kuhlman K, Weiner S, et al. Cervical funneling: sonographic criteria predictive of preterm delivery. *Ultrasound Obstet Gynecol* 1997;10(3):161–166. DOI: 10.1046/j.1469-0705.1997.10030161.x.
69. Sekiya T, Ishihara K, Yoshimatsu K, et al. Detection rate of the cervical gland area during pregnancy by transvaginal sonography in the assessment of cervical maturation. *Ultrasound Obstet Gynecol* 1998;12(5):328–333. DOI: 10.1046/j.1469-0705.1998.12050328.x.
70. Savitha C, Arpitha JV, Nagarathnamma R. Significance of cervical length and cervical gland area in cervical maturation. *Int J Reprod Contracept Obstet Gynecol* 2016;5(8):2634–2639.
71. Yoshimatsu K, Sekiya T, Ishihara K, et al. Detection of the cervical gland area in threatened preterm labour using transvaginal sonography in the assessment of cervical maturation and pregnancy outcome. *Gynecol Obstet Invest* 2005;53(3):149–159. DOI: 10.1159/000058366.
72. Asakura H, Fukami T, Kurashina R, et al. Significance of cervical gland area in predicting preterm delivery birth for patients with the threatened preterm delivery. Comparison CL and the fetal fibronectin. *Gynecol Obstet Invest* 2009;68(1):1–8. DOI: 10.1159/000209394.
73. Pires CR, Moron AF, Mattar R, et al. Cervical gland area as an ultrasonographic marker for preterm delivery. *Int J Gynecol Obstet* 2006;93(3):214–219. DOI: 10.1016/j.ijgo.2005.12.010.
74. Espinoza J, Gonçalves LF, Romero R, et al. The prevalence and clinical significance of amniotic fluid 'sludge' in patients with preterm labor and intact membranes. *Ultrasound Obstet Gynecol* 2005;25(4):346–352. DOI: 10.1002/uog.1871.
75. Kusanovic JP, Espinoza J, Romero R, et al. Clinical significance of the presence of amniotic fluid 'sludge' in asymptomatic high-risk patients for spontaneous preterm delivery. *Ultrasound Obstet Gynecol* 2007;30(5):706–714. DOI: 10.1002/uog.4081.
76. Goldenberg RL, Cliver SP, Bronstein J, et al. Bed rest in pregnancy. *Obstet Gynecol* 1994;84(1):131–136.
77. Sciscione AC. Maternal activity restriction and the prevention of preterm birth. *Am J Obstet Gynecol* 2010;202(3):232.e1–5. DOI: 10.1016/j.ajog.2009.07.005.
78. Sosa CG, Althabe F, Belizán JM, et al. Bed rest in singleton pregnancies for preventing preterm birth. *Cochrane Database Syst Rev* 2015(3):CD003581. DOI: 10.1002/14651858.CD003581.pub3.
79. Grobman WA, Gilbert SA, Iams JD, et al. Activity restriction among women with a short cervix. *Obstet Gynecol* 2013;121(6):1181–1186. DOI: 10.1097/AOG.0b013e3182917529.
80. Abdul Sultan A, West J, Tata LJ, et al. Risk of first venous thromboembolism in pregnant women in hospital: population based cohort study from England. *BMJ* 2013;347(nov07 15):6099. DOI: 10.1136/bmj.f6099.
81. Yost NP, Owen J, Berghella V, et al. Effect of coitus on recurrent preterm birth. *Obstet Gynecol* 2006;107(4):793–797. DOI: 10.1097/01.AOG.0000206757.92602.b5.
82. Hibbard JU, Snow J, Moawad AH. Short cervical length by ultrasound and cerclage. *J Perinatol* 2000;20(3):161–165. DOI: 10.1038/sj.jp.7200333.
83. Dijkstra K, Funai EF, O'Neill L, et al. Change in cervical length after cerclage as a predictor of preterm delivery. *Obstet Gynecol* 2000;96(2):346–350. DOI: 10.1097/00006250-200009000-00006.

84. Rust OA, Atlas RO, Reed J, et al. Revisiting the short cervix detected by transvaginal ultrasound in the second trimester: why cerclage therapy may not help. *Am J Obstet Gynecol* 2001;185(5):1098–1105. DOI: 10.1067/mob.2001.118163.
85. To MS, Alfirevic Z, Heath VCF, et al. Cervical cerclage for prevention of preterm delivery in women with short cervix: randomised controlled trial. *Lancet* 2004;363(9424):1849–1853. DOI: 10.1016/S0140-6736(04)16351-4.
86. Berghella V, Keeler SM, To MS, et al. Effectiveness of cerclage according to severity of cervical length shortening: a meta-analysis. *Ultrasound Obstet Gynecol* 2010;35(4):468–473. DOI: 10.1002/uog.7547.
87. Nott JP, Bonney EA, Pickering JD, et al. The structure and function of the cervix during pregnancy. *Translation Res Anatomy* 2016;2:1–7. DOI: 10.1016/j.tria.2016.02.001.
88. Dodd JM, Flenady V, Cincotta R, et al. Prenatal administration of progesterone for preventing preterm birth. *Cochrane Database Syst Rev* 2006(1):CD004947.
89. Romero R, Nicolaides KH, Conde-Agudelo A, et al. Vaginal progesterone decreases preterm birth $\leq$ 34 weeks of gestation in women with a singleton pregnancy and a short cervix: an updated meta-analysis including data from the OPPTIMUM study. *Ultrasound Obstet Gynecol* 2016;48(3):308–317. DOI: 10.1002/uog.15953.
90. Fonseca EB, Celik E, Parra M, et al. Progesterone and the risk of preterm birth among women with a short cervix. *N Eng J Med* 2007;357(5):462–469. DOI: 10.1056/NEJMoa067815.
91. Norwitz ER, (2017). Progesterone supplementation to reduce the risk of spontaneous preterm birth. [online] UpToDate. Available from: <https://www.uptodate.com/contents/progesterone-supplementation-to-reduce-the-risk-of-spontaneous-preterm-birth> [Accessed June 2018].
92. Meis PJ, Klebanoff M, Thom E, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. *N Engl J Med* 2003;348(24):2379–2385. DOI: 10.1056/NEJMoa035140.
93. Romero R, Yeo L, Chaemsaitong P, et al. Progesterone to prevent spontaneous preterm birth. *Semin Fetal Neonatal Med* 2014;19(1):15–26. DOI: 10.1016/j.siny.2013.10.004.
94. da Fonseca EB, Bittar RE, Carvalho MHB, et al. 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* 2003;188(2):419–424. DOI: 10.1067/mob.2003.41.
95. Northen AT, Norman GS, Anderson K, et al. Follow-up of children exposed in utero to 17 alpha-hydroxyprogesterone caproate compared with placebo. *Obstet Gynecol* 2007;110(4):865–872. DOI: 10.1097/01.AOG.0000281348.51499.bc.
96. Briery CM, Veillon EW, Klauser CK, et al. Women with preterm premature rupture of the membranes do not benefit from weekly progesterone. *Am J Obstet Gynecol* 2011;204(1):54.e1–5. DOI: 10.1016/j.ajog.2010.08.022.
97. Combs CA, Garite T, Maurel K, et al. 17-hydroxyprogesterone caproate for twin pregnancy: a double-blind, randomized clinical trial. *Am J Obstet Gynecol* 2011;204(3):221.e1–8. DOI: 10.1016/j.ajog.2010.12.042.
98. Caritis SN, Rouse DJ, Peaceman AM, et al. Prevention of preterm birth in triplets using 17 alpha-hydroxyprogesterone caproate: a randomized controlled trial. *Obstet Gynecol* 2009;113(2 Pt 1):285–292. DOI: 10.1097/AOG.0b013e318193c677.
99. US Food and Drug Administration, Center for Drug Evaluation and Research. (2006). Summary minutes of the Advisory Committee for Reproductive Health Drugs, August 29, 2006. [online]. Available from: <http://www.fda.gov/ohrms/dockets/ac/06/minutes/2006-4227M1.pdf> [accessed June 2018].
100. Silver RI, Rodriguez R, Chang TSK, et al. In vitro fertilization is associated with an increased risk of hypospadias. *J Urol* 1999;161(6):1954–1957. DOI: 10.1016/S0022-5347(05)68863-5.
101. Carmichael SL, Shaw GM, Laurent C, et al. Maternal progestin intake and risk of hypospadias. *Arch Pediatr Adolesc Med* 2005;159(10):957–962. DOI: 10.1001/archpedi.159.10.957.
102. Attardi BJ, Zeleznik A, Simhan H, et al. Comparison of progesterone and glucocorticoid receptor binding and stimulation of gene expression by progesterone, 17-alpha hydroxyprogesterone caproate, and related progestins. *Am J Obstet Gynecol* 2007;197(6):599.e1–7. DOI: 10.1016/j.ajog.2007.05.024.
103. Background Document for Meeting of Advisory Committee for Reproductive Health Drugs. January 20, 2012. NDA 22-139. (2012). Progesterone(8%). [online] FDA. Available from: <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/UCM287987.pdf> [accessed June 2018].
104. Berghella V, Rust OA, Althuisius SM. Short cervix on ultrasound: does indomethacin prevent preterm birth? *Am J Obstet Gynecol* 2006;195(3):809–813. DOI: 10.1016/j.ajog.2006.06.007.
105. King J, Flenady V. Prophylactic antibiotics for inhibiting preterm labour with intact membranes. *Cochrane Database Syst Rev* 2002(4):CD000246.
106. Bujold E, Pasquier JC, Simoneau J, et al. Intra-amniotic sludge, short cervix, and risk of preterm delivery. *J Obstet Gynaecol Can* 2006;28(3):198–202. DOI: 10.1016/S1701-2163(16)32108-9.
107. Orzechowski KM, Boelig R, Nicholas SS, et al. Is universal cervical length screening indicated in women with prior term birth? *Am J Obstet Gynecol* 2015;212(2):234.e1. DOI: 10.1016/j.ajog.2014.08.029.
108. Berghella V, (2018). Second-trimester evaluation of cervical length for prediction of spontaneous preterm birth in singleton gestations. [online] UpToDate. Available from: <https://www.uptodate.com/contents/second-trimester-evaluation-of-cervical-length-for-prediction-of-spontaneous-preterm-birth-in-singleton-gestations> [Accessed Jun 2018].
109. Berghella V, Odibo AO, To MS, et al. Cerclage for short cervix on ultrasonography: meta-analysis of trials using individual patient-level data. *Obstet Gynecol* 2005;106(1):181–189. DOI: 10.1097/01.AOG.0000168435.17200.53.
110. Conde-Agudelo A, Romero R, Nicolaides K, et al. Vaginal progesterone vs. cervical cerclage for the prevention of preterm birth in women with a sonographic short cervix, previous preterm birth, and singleton gestation: a systematic review and indirect comparison metaanalysis. *Am J Obstet Gynecol* 2013;208(1):42.e1–42.e18. DOI: 10.1016/j.ajog.2012.10.877.