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GUIDELINES

ISUOG Practice Guidelines: role of ultrasound in the prediction of spontaneous preterm birth

Clinical Standards Committee

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INTRODUCTION

Epidemiology and definitions

According to the World Health Organization, a preterm birth (PTB) or delivery is defined as occurring between 20 + 0 and 36 + 6 gestational weeks[1]. In 75–80% of cases, it occurs spontaneously, following either preterm labor (PTL) or preterm prelabor rupture of membranes (PPROM), while, in the remaining 20–25% of cases, it results from the health provider's intervention (iatrogenic or medically indicated)[2,3]. The estimated global PTB rate increased from 9.8% to 10.6% between 2000 and 2014, accounting for almost 15 million live PTBs in 2014[4] and over one million deaths in 2010[5]; PTB is the leading cause of neonatal mortality worldwide and in survivors may be responsible for lifelong morbidities[5].

In addition to neonatal death, there are several short-term consequences of prematurity, including respiratory distress syndrome (RDS), bronchopulmonary dysplasia, intraventricular hemorrhage, periventricular leukomalacia, necrotizing enterocolitis, retinopathy of prematurity and sepsis, while the long-term sequelae include cerebral palsy, cognitive impairment and behavioral/social deficits[6]. Apart from the health consequences for the individual and the family, the burden of prematurity on society and the economic impact of long-term stay in a neonatal intensive care unit (NICU), recurrent hospital admissions and specialized follow-up needs can also be devastating. The annual societal economic burden of PTB in the USA was estimated by the Institute of Medicine to be at least $26.2 billion in 2007[7]. In 2014, the annual expenditure for the Canadian population was reported, corresponding to the gestational-age distribution, to be: $123.3 million for early preterm infants, $255.6 million for moderately preterm infants, $208.2 million for late preterm infants and $587.1 million for all infants[8].

In contrast to PTB, defining PTL is not straightforward. Different criteria have been reported in different publications, contributing to a lack of consistency in the response to symptomatic patients presenting at maternity units. The physiologic pathways involved in spontaneous term labor are fundamentally different from the pathological ones involved in PTL. Spontaneous PTL is considered to be a syndrome rather than a single condition, in part because it may be induced by one or more of several distinct mechanisms[9]. Infection and inflammation were among the first mechanisms to be studied as potential causes of PTB, possibly because the detection of pathogens in the amniotic cavity can be achieved relatively easily. Other important causal factors were described subsequently; these included cervical insufficiency, a decline in progesterone action, uterine overdistention and malformations, vascular disorders, breakdown of maternal–fetal tolerance and allergy-induced mechanisms[10]. The heterogeneity of causality explains the difficulty in developing universally effective diagnostic, preventive and therapeutic measures for PTB. Nevertheless, cervical effacement (shortening) is one of the common pathways to PTB, preceding delivery by weeks or even months, and it is possible to assess and quantify this phenomenon by transvaginal sonographic (TVS) examination[11]. Sonographic cervical-length (CL) measurement has been shown consistently to be an

efficient and cost-effective strategy in the prediction of PTB in asymptomatic women[12–14] and also a helpful tool in the diagnosis and decision process regarding the management of PTL-symptomatic patients[15].

Screening for spontaneous PTB in asymptomatic women is important, since there are preventive strategies that can be offered to patients at high risk of delivery[12,16]. The preventive modalities that have been tested include progesterone supplementation (vaginal or intramuscular), cervical cerclage and silicon pessaries. The particular indications and potential benefits with regard to neonatal outcome should be discussed thoroughly with patients, and this is also considered throughout the Guideline. Routine CL measurement during pregnancy has been implemented in some populations, with subsequent reductions in spontaneous PTB rate[17,18], and the practice is supported by many national and international bodies[6,19,20].

In a different clinical scenario, the sonographic measurement of CL has been assessed in the setting of threatened PTL to detect the women at highest risk for PTB in order to direct their care[15].

The difficulty in determining the optimal outcome measure for PTB prevention strategies should not be underestimated. First, there is profound heterogeneity among studies regarding the cut-offs used for clinically relevant prematurity (commonly < 37 weeks, < 34 weeks or < 32 weeks). Second, gestational age at birth alone is not an optimal marker for determining the effectiveness of preventive or therapeutic measures against PTB, because it could be harmful to prolong a pregnancy in suboptimal conditions, such as in the presence of disseminated infection or non-reassuring maternal and fetal conditions, although such circumstances are uncommon. So far, there has been no formal consensus on the ideal set of outcomes, which would probably involve long-term health and developmental parameters, that should be used uniformly in future studies on PTB.

The scope of this Guideline is to evaluate the role of ultrasound in the prediction of PTB in asymptomatic women and women with symptoms of PTL, with the goal of preventing prematurity and improving the perinatal and long-term outcome of the infant.

Identification and assessment of the evidence

A literature search was conducted for relevant publications in the following databases: PubMed, The Cochrane Library and Cochrane Register of Controlled Trials, The National Library for Health and The National Guideline Clearing House, and on the websites of international obstetrics and imaging Societies. Keywords used in the search were: 'ultrasound', 'preterm birth', 'preterm labor', 'prediction' and 'prevention'. The search was filtered for the period 1990–2022 and the last search was conducted on 20 May 2022. When possible, recommendations are based on the evidence that supports them. We specify 'Good practice points' for areas in which evidence is still lacking. Details of the grades of recommendation and levels of evidence used in ISUOG Guidelines are given in Appendix 1.

ULTRASOUND-BASED SCREENING STRATEGIES FOR SPONTANEOUS PTB IN ASYMPTOMATIC WOMEN WITH SINGLETON PREGNANCY

Although a history of spontaneous PTB is the most important epidemiological risk factor for PTB, it is present in only 10% of women who deliver before 34 weeks of gestation[21,22]. Numerous risk scoring systems using exclusively clinical history have been developed with the purpose of identifying patients at risk for PTB. However, they suffer from variations in their accuracy and limited reproducibility across different populations[23]. Vaginal digital examination has always been the most common method for evaluating the uterine cervix in the context of labor. Though this simple and inexpensive assessment provides information about both the cervix and the fetal presentation, when compared to no intervention or to recent imaging methods, routine digital evaluation does not improve the detection of PTB[24]. Its potential weaknesses include the subjectivity of the evaluation and the inability to detect early-stage cervical remodeling, which starts with dilation of the internal os and is, therefore, inaccessible to the examiner's fingers. The same limitations seem to apply to use of a cervicometer, another low-cost alternative to identify short cervix, which was advocated recently as a tool to select which patients would not benefit from TVS[25]. Application of these suboptimal screening strategies might be best limited to settings without access to ultrasound.

The sonographic measurement of CL has been established as an indispensable part of screening for PTB. The inverse relationship between CL measured by TVS and the incidence of spontaneous PTB was first described more than 30 years ago, challenging the previous dichotomous theory of competent *vs* incompetent cervix and establishing this measurement as a continuous variable[11,26].

Measurement of cervical length

Reproducibility is essential for any predictive method to perform well, and CL measurement should always be performed following a sequential and standardized protocol. Inter- and intraobserver variability for CL measurement have been reported to be more favorable than those for digital examination[27]. Among the numerous training methods for CL measurement, The Fetal Medicine Foundation's Certificate of Competence in cervical assessment[28] and the Cervical Length Education and Review (CLEAR) program[29] are the two high-standard internet-based educational courses that award certification for professionals who complete the theoretical course and submit scan images for audit. Providers should perform sonographic CL measurement only if they are familiar with the recommended technique[30] (Table 1), which is based on these two recognized courses.

Table 1 Technique for assessment of cervical length by transvaginal ultrasound

Stage of exam	*Recommendation*
Pre-exam	Maternal bladder empty
Maternal position	Semi-recumbent position with abducted legs
Transducer selection	High-frequency transvaginal transducer covered with disposable sheath and lubricated with gel on both sides (caution: remove air bubbles)
Introduction	Place probe at anterior fornix with longitudinal axis orientation for sagittal imaging. Gentle pressure may be necessary for better identification of structures
Required structures	Inferior bladder border, external os, endocervical canal and mucosa, internal os (limited by edge of mucosa)
Minimize pressure	Certify that both cervical lips have same width, keeping all required structures in image
Magnification	Cervix should occupy 50–75% of screen
Measurement	Place calipers between functional internal os and external os, obtaining a straight line between them
Repetition	Obtain three distinct measurements and choose the shortest technically correct one
Duration	Allow sufficient time to obtain three technically correct measurements to allow for observation of dynamic changes over time
Describe additional findings	Funneling, amniotic fluid debris, sludge, membrane separation, vasa previa, low-lying placenta, abnormally invasive placenta
Avoid pitfalls	Full bladder or excessive transducer pressure may elongate artificially cervical length Thickened lower segment or uterine contractions may mimic funneling: identify cervical mucosa properly Avoid confounding cervical mucus with funnel by delineating course of membranes at level of internal os

Briefly, sonographic CL measurement should be performed with the maternal bladder empty. It requires a sagittal view of the cervix, with the cervix occupying 50–75% of the screen and the cervical canal, internal os and external os visible. Pressure on the cervix should be minimized. To allow for dynamic changes, at least three straight-line measurements should be obtained, between the internal os and the external os, with the shortest technically correct measurement being recorded. Figure 1 presents a schematic representation of the structures that can be observed on TVS cervical assessment and additional aspects with regard to the correct technique are illustrated in Figures 2–7.

Technically, the sonographic assessment of CL can be performed using a transabdominal, transperineal or transvaginal approach. Although the transabdominal approach may be associated with reduced scan time, use of resources and discomfort for the patient, the transvaginal approach is recommended, as it is more precise and reproducible and less prone to technical issues[31,32]. The greater distance on transabdominal ultrasound between the probe and the cervix, the artificial elongation of the cervix produced by a full bladder or by the pressure applied on the probe, acoustic attenuation observed in patients with high body mass index and shadowing from fetal or maternal structures are possible explanations for the lower accuracy of this approach[32] (Figure 4b). A prospective study has shown that higher CL cut-offs would be needed for assessment by transabdominal sonography ($\leq$ 36 mm) compared with TVS ($\leq$ 25 mm), and TVS would still be necessary in more than 60% of cases[33]. Additionally, all randomized controlled trials (RCTs) that have demonstrated benefits of intervention in patients with a short cervix used the transvaginal approach and there are no society guidelines supporting the routine use of transabdominal ultrasound for CL screening[12,19,20,34]. Excluding cultural factors, patient acceptance of TVS can be extremely high if effective counseling is provided, as demonstrated by the 99.9% acceptance rate described in a population-based study of 17 609 patients[18,35].

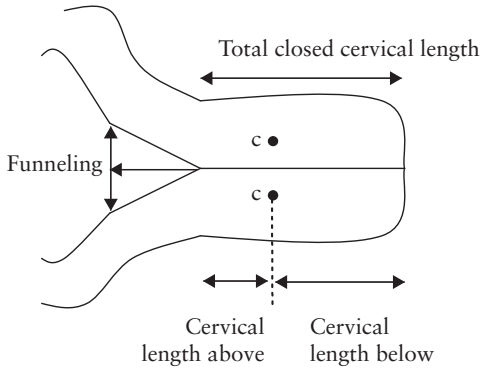

Figure 1 Schematic representation of transvaginal ultrasonographic cervical assessment (adapted from Hughes *et al.*[191]). c, cerclage.

Curvature of the cervix is present in 51% of cases when CL is > 25 mm, in 25% of cases when CL is between 16 and 25 mm and in no cases when CL is < 16 mm[36]. Thus, in cases with significant cervical curvature, the CL measurement may be longer if it is performed using two segments or tracing the cervical curvatures, compared with placing a straight line between two calipers. However, as a short cervix always appears to be straight, it is our opinion that universal use of a straight-line measurement can be adopted without affecting management of the pregnancy.

Recommendations

- CL measurement for the prediction of PTB should be performed using TVS (**GRADE OF RECOMMENDATION: B**).

- The shortest technically correct measurement of at least three CL measurements should be used for reporting and clinical management (**GOOD PRACTICE POINT**).
- TVS CL measurements should be performed in a standardized way, preferably by operators who have been certified by a scientific body, such as The Fetal Medicine Foundation[28] or the Perinatal Quality Foundation (CLEAR)[29] (**GOOD PRACTICE POINT**).

Changes in cervical length during pregnancy

The CL is generally stable between 14 and 28 weeks of gestation, and tends to shorten gradually afterwards[11], its median length decreasing from ~43 mm at 16 weeks to ~31 mm at 36 weeks' gestation[37]. The cervix in the second trimester is shorter, on average, in women of African or Asian origin, in young women (< 20 years old) and in those with a lower body mass index[38,39].

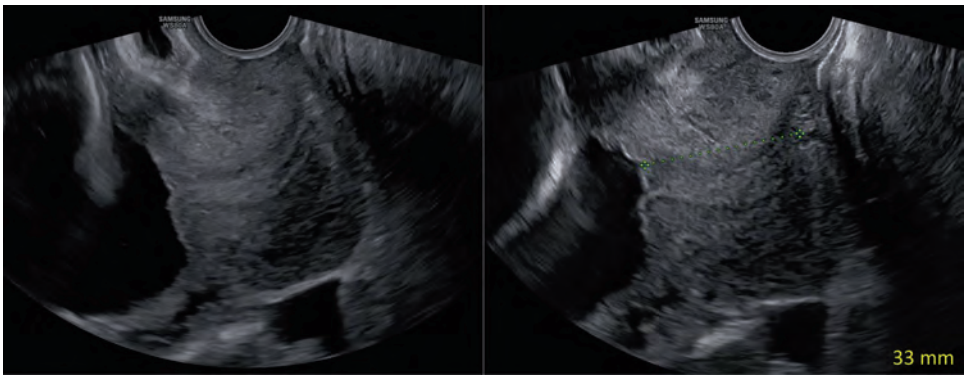

Figure 2 Transvaginal ultrasound images of a normal cervix with slightly hyperechoic cervical mucosa.

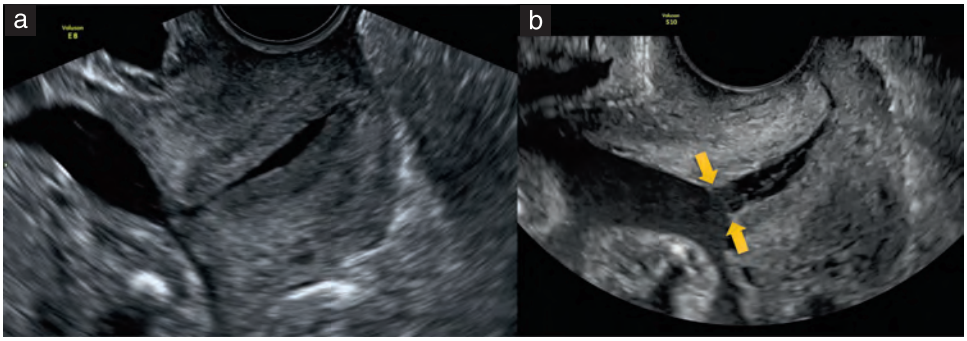

Figure 3 Transvaginal ultrasound images of normal cervices with hypoechoic content within the endocervical canal. (a) Mucus is visible inside the canal. (b) Amniotic membranes are demonstrated (arrows), indicating that funneling is not present.

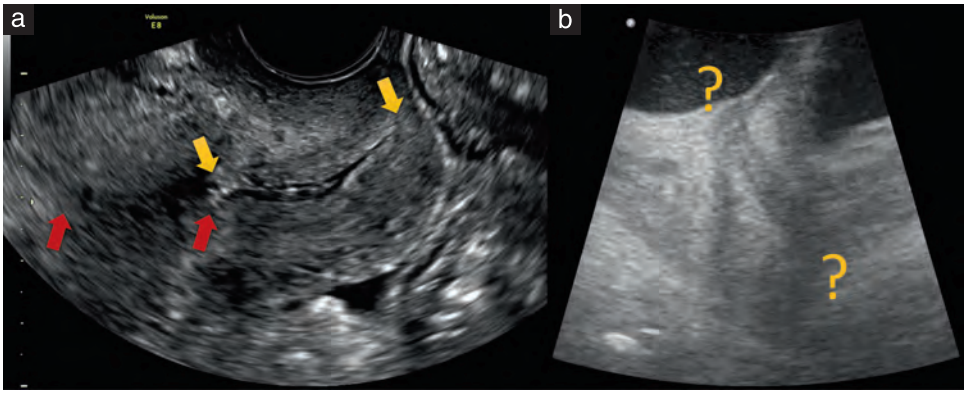

Figure 4 Non-recommended strategies for cervical-length (CL) assessment. (a) Transvaginal CL assessment during the first trimester. Note the internal and external cervical ora (yellow arrows) that are limited by the edges of the cervical mucosa and the thickened underdeveloped lower uterine segment (red arrows). (b) Transabdominal CL assessment, with bladder half empty. Note the difficulty in identifying the internal and external cervical ora (question marks).

Screening in asymptomatic singleton pregnancy without prior risk factors for spontaneous PTB

The ultrasound finding of a short cervix increases the risk for PTB in singleton pregnancies without additional risk factors or symptoms. In general, the shorter the CL measurement and the earlier the gestational age at shortening, the higher the rate of spontaneous PTB[40,41]. However, the accuracy of CL measurement to predict PTB depends on various factors, such as the population studied, its baseline PTB prevalence, the cut-off values for defining short cervix and PTB, the gestational age at

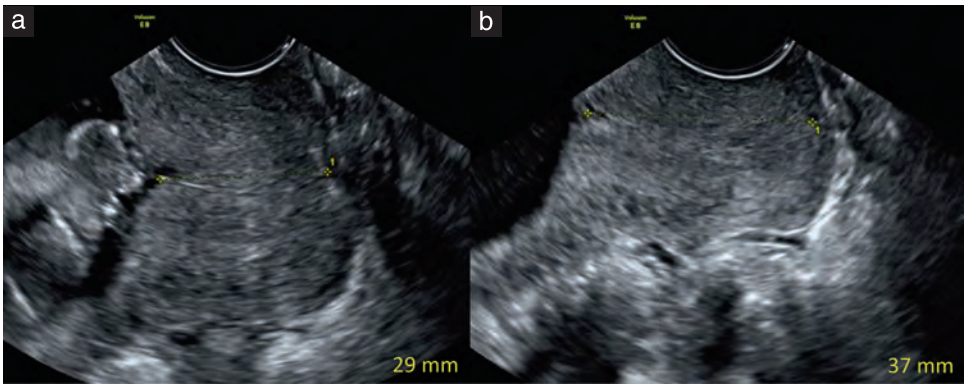

Figure 5 Transvaginal ultrasound measurements of cervical length in the same patient, illustrating the effect on the measurement of pressure exerted by the probe: (a) avoiding pressure (correct); (b) with excessive probe pressure (incorrect), which elongates the cervix and creates a difference in width between the cervical lips.

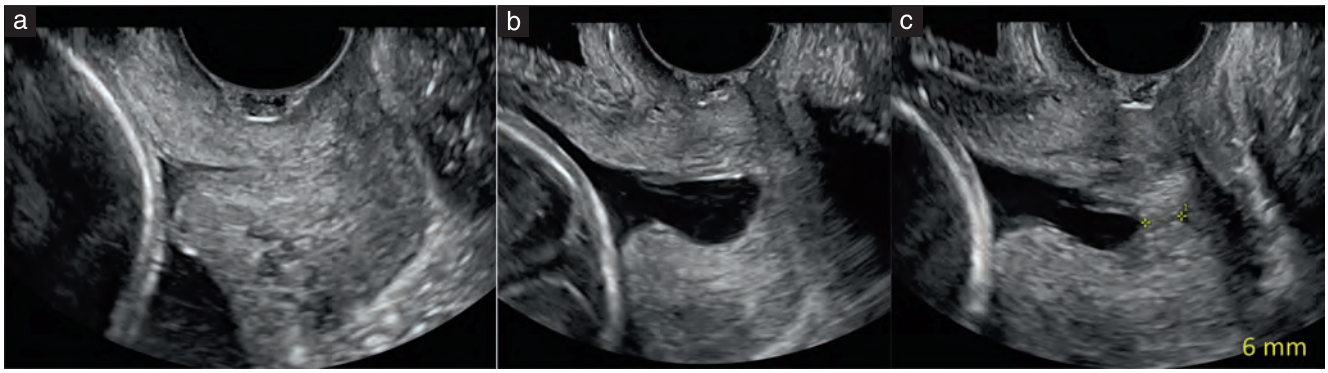

Figure 6 Transvaginal ultrasound measurements of cervical length in the same patient, illustrating the potential effect on the identification of dynamic changes of the cervix of different degrees of pressure exerted by the probe. (a) Excessive pressure (incorrect) elongates the cervix, producing a difference in the widths of the cervical lips. (b,c) Gentle probe pressure (correct) allows identification of funneling and the short cervical length, with dynamic changes during the course of the examination.

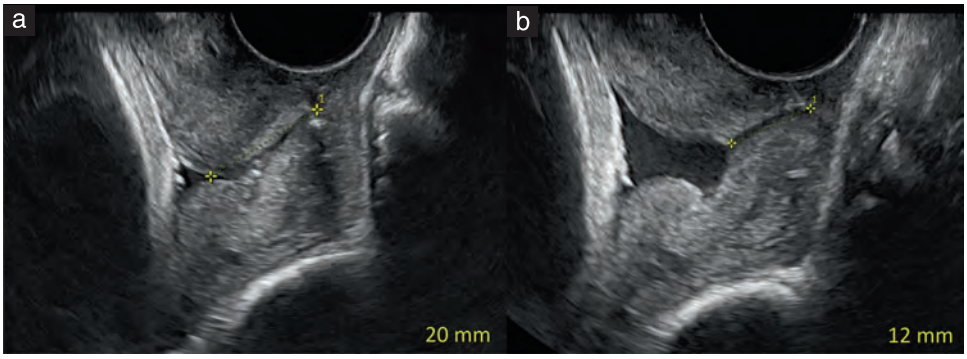

Figure 7 Transvaginal ultrasound measurements of cervical length in the same patient, taken 1 min apart, showing the relevance of taking a minimum of three technically correct measurements to allow observation of dynamic changes over time. Note that both cervical lips have approximately the same width in (a) and (b).

which the screening test is performed, and the compliance of healthcare providers and patients with the preventive strategy that is applied after a high-risk result.

For logistical reasons, it is advisable to screen asymptomatic women by CL measurement between 18 and 24 weeks of gestation[19,20], as part of the second-trimester anomaly scan. Measurements taken prior to this gestational age tend to overestimate CL, due to the difficulty in identifying the internal os and incorporation of the underdeveloped lower uterine segment (Figure 4a). A gestational age of 24 weeks is usually the upper limit for screening strategies, because this is a common deadline for preventive measures, such as progesterone administration and cerclage placement, as well as a starting point for therapeutic interventions, such as tocolysis, administration of antenatal corticosteroids and magnesium sulfate use for neuroprotection[19,42]. Prepregnancy measurements of CL are not useful for predicting PTB in a subsequent pregnancy[43].

The first large general-population studies showed that, in the second trimester, the 10th centile for CL was 26 mm[11], the 5th centile was 22 mm[11] to 23 mm[38] and the 1st centile was 11 mm[38] to 13 mm[11]. At a cut-off of $\leq$ 15 mm, the rate of PTB < 35 weeks was 50% and that at a cut-off of $\leq$ 25 mm was 18%[11]. Later, a large cross-sectional study that included more than 6600 CL assessments reported that CL does not have a normal distribution during pregnancy, and suggested new reference values, based on centiles and *Z*-scores between 16 and 36 gestational weeks[37].

Cut-off to define short cervix

As with any screening test, the selection of a cut-off value is a trade-off between sensitivity and screen-positive rate. A meta-analysis showed that a CL cut-off of 20 mm had a sensitivity of 22.1% for PTB < 35 weeks, for a screen-positive rate of 1.8%; increasing the cut-off to 25 mm increased the sensitivity to 33.1%, at the cost of increasing the screen-positive rate to 4.1%[44]. The selection of an optimal cut-off is further hampered by the fact that CL can be part of a combined screening strategy, in which other factors may affect the estimation of risk. In practice, for more than 10 years, a cut-off of 25 mm has been used in the majority of interventional trials as the best option to predict PTB prior to 24 weeks' gestation[6,12,20,40].

Recommendation

- CL $\leq$ 25 mm can be used as a cut-off for the initiation of measures to prevent PTB in asymptomatic singleton pregnancies, irrespective of risk factors (**GOOD PRACTICE POINT**).

Other ultrasound findings as predictors of spontaneous PTB

Funneling is the protrusion of the amniotic sac into the upper cervical canal (Figures 1 and 6–10). Its sonographic presentation is variable, according to the severity of cervical shortening. The mnemonic, 'Trust Your Vaginal Ultrasound' represents the progression in terms of severity, starting from a normal T-shaped appearance, with subsequent Y-, V- and eventually U-shaped appearance of the internal cervical os and upper cervix (Figure 8). None of the possible measurements of funneling has been proved to serve as an accurate independent risk factor for PTB[45,46]. Thus, if funneling is present, its length should not be included in the CL measurement (Figure 1).

Amniotic sludge or debris is observed as hyperechoic matter concentrated near the internal os or dispersed in the amniotic cavity (Figures 8 and 9). Sludge may contain pus, microbes and/or other solid particles, such as blood clots, vernix or meconium, and has been associated with intra-amniotic infection and increased risk for PTB, especially in the context of a short cervix and previous spontaneous second-trimester loss[47–49]. However, there is no consensus regarding the need for additional diagnostic tests or treatment.

Although separation of the amniotic membranes from the decidua was initially associated with increased

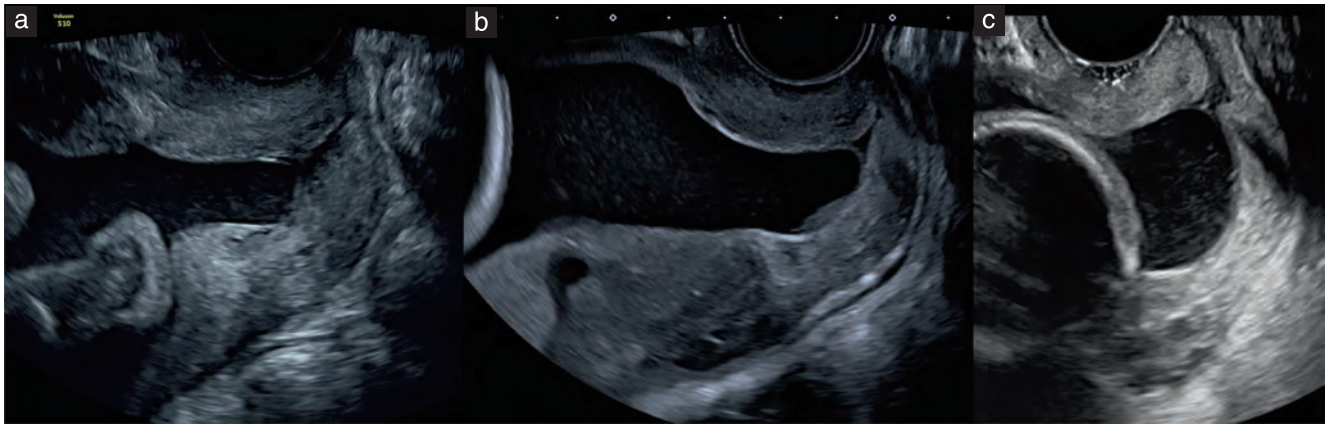

Figure 8 Transvaginal ultrasound images in three pregnant women, illustrating progression of funneling of the internal cervical os and upper cervix in line with worsening prognosis: (a) Y-shaped funneling; (b) V-shaped funneling, with separation of the amniotic membranes and amniotic debris; (c) U-shaped funneling, with dilation of the external cervical os.

rates of PTB, statistical significance was not confirmed after controlling for CL (Figures 8 and 9)[50]. Neither cervical tissue density measured by elastography nor measurements of the cervical axis in relation to the uterine longitudinal axis is considered to be a significant predictor of PTB when added to CL measurement[50].

Management options after identifying short cervix in asymptomatic singleton pregnancy

The main objective of measuring CL in low-risk pregnant women is to make a targeted selection of the patients with a short cervix and therefore a higher risk of PTB, in order to initiate preventive intervention in a timely fashion (secondary prevention). Different preventive strategies have been proposed; some of them have demonstrated a high level of effectiveness, whereas the evidence is mixed, or even unfavorable, for others.

Conservative measures

Although usually deemed safe by clinicians, prolonged bed-rest and hospitalization in women with a short cervix have been associated with increased risk of thromboembolic events[51] and negative psychological effects[52], and even with higher rates of PTB[53]. In fact, in asymptomatic women with singleton pregnancy and a short cervix, exercising ≥ 2 days per week for ≥ 20 min per day has been associated with a 32% reduction in deliveries < 37 weeks, rather than an increase in the risk for PTB[54]. Therefore, patients should be advised to maintain their usual baseline activity.

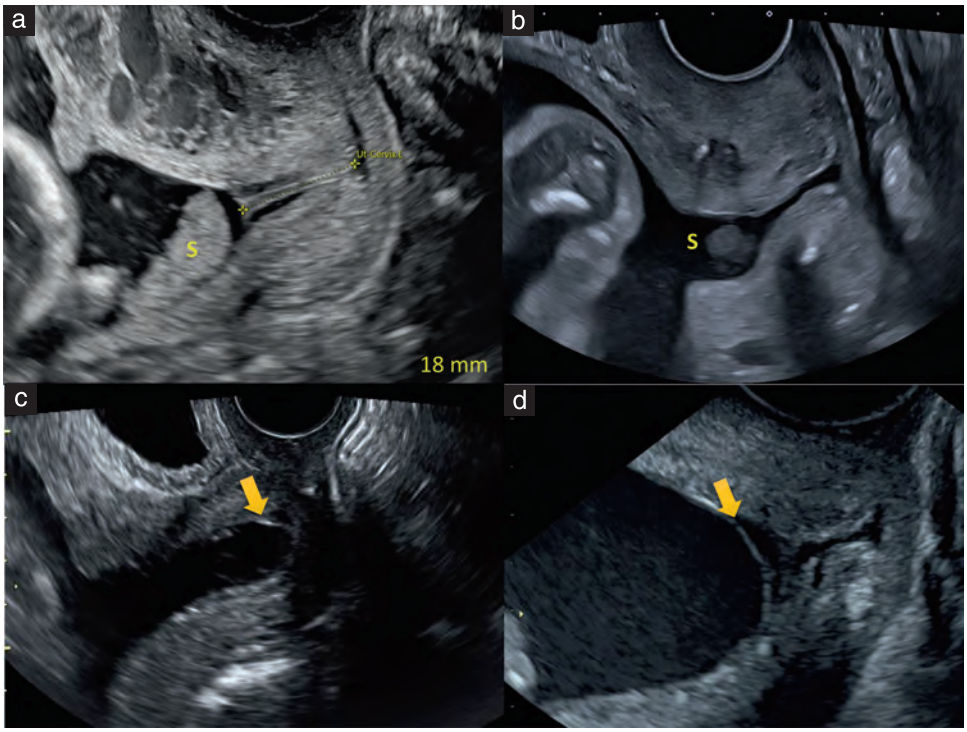

Figure 9 Transvaginal ultrasound images showing findings additional to short cervical length. (a) Short cervix in a patient with placenta accreta spectrum and amniotic debris (S). (b) Funneling, amniotic debris (S) and short cervix in a patient treated with cerclage (echogenic dots on upper and lower cervical lips). (c,d) Amniotic membrane separation (arrows) in patients with funneling and short cervix.

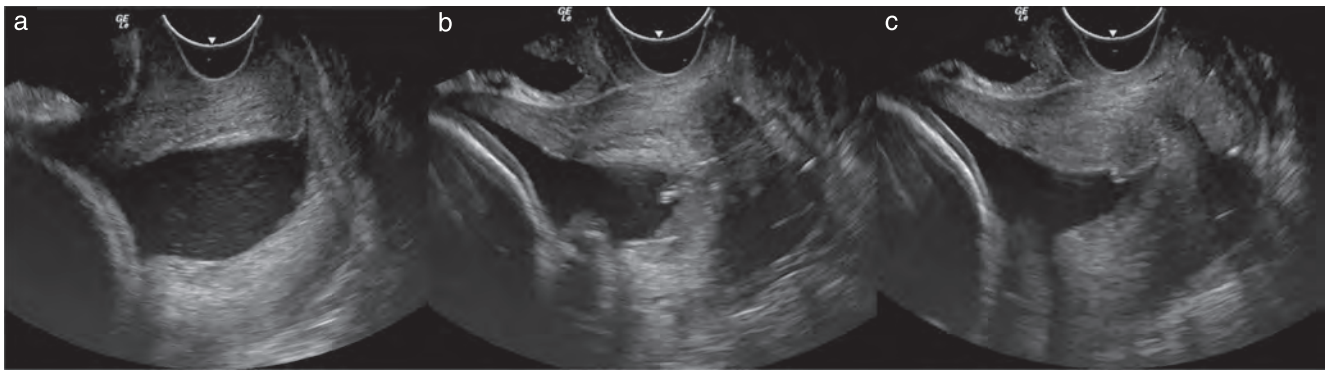

Figure 10 Sequential transvaginal ultrasound images obtained during the course of a physical-exam-indicated cerclage: (a) pre-cerclage U-shaped funneling; (b) Y-shaped funneling after placement of the first stitch; (c) post-cerclage image after placement of two stitches.

Recommendation

- Restriction of baseline physical activity is not recommended in asymptomatic women at risk of PTB (**GRADE OF RECOMMENDATION: C**).

Progesterone

The beneficial effect of supplemental progestogens in the prevention of PTB is thought to be related to the promotion of myometrial quiescence and inhibition of cervical ripening by downregulation of the production of cytokines and by its anti-inflammatory effect on the chorioamniotic membranes[55,56]. Two RCTs published in 2003 raised the interest of the scientific community in the use of two progestogens for prevention of PTB, namely the weekly intramuscular application of 17α-hydroxyprogesterone caproate (17-OHPC)[57] and daily use of natural vaginal progesterone[58]. Since then, especially in the USA, 17-OHPC has been recommended for the prevention of PTB in patients with previous spontaneous preterm delivery. However, after almost two decades, a subsequent international RCT reported that, when compared with placebo (578 women), 17-OHPC (1130 women) did not decrease recurrent PTB < 35 weeks (11% *vs* 11.5%) or neonatal morbidity rates (5.6% *vs* 5.0%) in a population with a history of singleton spontaneous PTB[59]. In contrast, the application of natural vaginal progesterone, in the form of suppositories or gel, was found to decrease PTB and neonatal morbidity and has now been established as the cornerstone of PTB prevention in asymptomatic patients with singleton pregnancy and a short cervix[60]. In 2012, the first meta-analysis of individual patient data (IPD) demonstrated a significant reduction in the prevalence of PTB < 28 to < 35 weeks and in composite neonatal morbidity associated with the use of vaginal progesterone[61]. Following some concern after the publication of the 'dOes Progesterone Prophylaxis To prevent preterm labour IMprove oUtcoMe' (OPPTIMUM) trial, which reported neither significant benefits nor harm associated with the use of progesterone in a heterogeneous group of patients at risk for PTB, including low-risk women with short CL[62], an updated IPD meta-analysis was published[12] including data from the OPPTIMUM trial. This reaffirmed the reduction in the risk of PTB < 28 to < 36 weeks (PTB < 33 weeks; 974 women; relative risk (RR), 0.62; 95% CI, 0.47–0.81), as well as reductions in the rates of composite neonatal morbidity and mortality, in singleton gestations with a second-trimester sonographic short cervix treated with progesterone, without any deleterious effects on childhood neurodevelopment[12]. In 2021, the Evaluating Progestogens for Preventing Preterm birth International Collaborative (EPPPIC) group published an IPD meta-analysis including 11 644 women at risk for PTB, mostly women with previous spontaneous PTB or a short cervix[63]. Its results again reaffirmed that vaginal progesterone decreases the risk of PTB < 34 weeks in singleton gestations (3769 women; RR, 0.78; 95% CI, 0.68–0.90) and reduces the risk of some adverse neonatal outcomes, including low and very low birth weight, NICU admission, RDS and need for respiratory support. The use of 17-OHPC was also associated with a tendency towards reduction of PTB < 34 weeks, without, however, achieving significance (3053 women; RR, 0.83; 95% CI, 0.68–1.01). The EPPPIC group considered that there were insufficient data to evaluate adequately the safety and efficacy of oral progesterone (181 women; RR, 0.60; 95% CI, 0.41–0.90)[63]. In 2022, another meta-analysis[64] reported that, among many interventions, vaginal progesterone should be considered the best choice for asymptomatic singleton pregnancies at risk of PTB because of short CL or a history of previous spontaneous PTB. When compared with placebo or no treatment, there was high certainty of evidence for a reduction in PTB < 34 weeks (odds ratio (OR), 0.50; 95% CI, 0.34–0.70) and moderate certainty for prevention of perinatal death (OR, 0.66; 95% CI, 0.44–0.97)[64]. Therefore, administration of natural vaginal progesterone (e.g. 200 mg micronized progesterone every night) is recommended for asymptomatic women with singleton pregnancy with no prior spontaneous PTB and a TVS CL ≤ 25 mm before 24 weeks, from detection of the short cervix until 36 gestational weeks.

Recommendation

- For asymptomatic women with singleton pregnancy without prior spontaneous PTB and with TVS CL ≤ 25 mm before 24 weeks, administration of natural vaginal progesterone is recommended, from the time of detection of the short cervix until 36 weeks (**GRADE OF RECOMMENDATION: A**).

Cerclage

Cervical cerclage involves placing one or two stitches as close as possible to the internal os, as a mechanical means to support the cervix and prevent PTB. The cerclage techniques reported most frequently in RCTs are the McDonald and Shirodkar procedures, performed with permanent monofilament or braided tape sutures, but there are no data to indicate superiority of one technique over the other. An IPD meta-analysis comparing insertion of cerclage with expectant management reported no significant reduction in PTB < 35 weeks in asymptomatic women with singleton pregnancy and a short second-trimester CL (< 25 mm) and absence of historical risk factors, such as recurrent loss consistent with cervical insufficiency or previous spontaneous PTB[65]. Nonetheless, a planned subgroup analysis of 126 patients from this same study showed a significant reduction in PTB < 35 weeks for patients with CL < 10 mm treated with cerclage. This is also supported by the finding, in retrospective studies, of patients with extremely shortened cervix despite progesterone treatment, in whom the placement of a cerclage doubled pregnancy latency and decreased neonatal morbidity and mortality overall[66,67]. For pregnant women with incidental CL between 10 and 25 mm, these studies recommend initiation of vaginal progesterone and CL measurements every 1–2 weeks

until 24 weeks. If the CL shortens progressively to < 10 mm, cervical cerclage can be considered. After placement of a cerclage for short CL, further CL measurements are not recommended, as no further therapy has been shown to change outcome.

Recommendations

- After initiating progesterone treatment, follow-up every 1–2 weeks up to 24 weeks can detect further shortening of the cervix (**GOOD PRACTICE POINT**).
- Cervical cerclage can be considered in women whose cervix shortens to < 10 mm despite being on progesterone (**GRADE OF RECOMMENDATION: C**).

Pessary

Cervical pessaries are mostly silicone-based cups inserted transvaginally and positioned around the cervix. They act as mechanical support, promoting both cervical elongation and sacralization of the cervix[68,69]. Two major RCTs have been published, with conflicting results. The Pesario Cervical para Evitar Prematuridad (PECEP) trial studied 385 patients with CL < 25 mm and reported a significant reduction in PTB < 34 weeks in the group of patients treated with a pessary (6% *vs* 27%)[70], while the largest multicenter pessary trial, of 932 patients with a short cervix, did not report a significant difference in the incidence of PTB between treatment and control groups (12% *vs* 11%)[71]. A systematic review and meta-analysis of six RCTs (1982 women) comparing cervical pessary with standard care or alternative interventions in asymptomatic women at high risk for PTB also failed to show differences in the rates of PTB < 37, < 34, < 32 and < 28 weeks and the rates of adverse perinatal outcome[72]. The Pessary Plus Progesterone to Prevent Preterm Birth (P5) RCT (936 women) also failed to demonstrate effectiveness of cervical pessary in addition to vaginal progesterone in decreasing rates of neonatal morbidity or mortality in asymptomatic pregnant women with incidental short cervix[73]. Thus, the evidence does not support the use of cervical pessaries to prevent PTB in asymptomatic patients with CL < 25 mm outside research protocols.

Recommendation

- Current evidence does not support the use of cervical pessaries to prevent PTB in asymptomatic patients with CL < 25 mm outside research protocols (**GRADE OF RECOMMENDATION: B**).

Contingent *vs* universal cervical-length screening

Whether implementation of contingent or universal CL screening should be recommended generally remains a matter of debate. Although a (probably overestimated) increment of $175 million in healthcare expenditure per year has been calculated for the introduction of universal CL screening in the USA[74], several publications attest the cost-effectiveness of this strategy, especially because, after the identification of a short cervix in asymptomatic patients, the timely prescription of vaginal progesterone results in a reduction of PTB along with its individual-, family- and healthcare-related costs[13,14,75–79]. Furthermore, contingent CL screening, limited to patients with at least one risk factor for PTB, would miss nearly 40% of women with a short cervix, who are potentially at high risk for PTB[80].

Two retrospective cohort studies assessed the effectiveness of universal CL screening in reducing PTB. Son *et al.*[18] focused on women with singleton gestation and without previous PTB and enrolled 46 598 participants before and 17 609 after initiation of this screening program in 2011. It was demonstrated that TVS measurement of the CL was accepted by 99.9% of patients, with a rate of short cervix of 0.9%, and a significant reduction in the frequency of spontaneous PTB < 37 weeks (6.7% *vs* 6.0%), < 34 weeks (1.9% *vs* 1.7%) and < 32 weeks (1.1% *vs* 1.0%)[18]. In the other retrospective cohort study, encompassing 1751 singleton pregnancies with no history of previous PTB, the introduction of universal CL screening was associated with a decrease in the frequency of threatened PTL (from 11.1% to 6.7%) and in the subsequent hospital admission of these patients (from 2.3% to 1.4%)[81]. A prospective population-based cohort study in the state of Western Australia assessed a comprehensive PTB prevention program which included universal ultrasound CL assessment for pregnant women between 18 and 20 weeks of gestation[82]. One year after its full implementation, there was a 7.6% reduction in the rate of singleton PTB, especially for the 28–31, 32–36 and < 37-week gestational-age groups[17], and this reduction was sustained particularly in tertiary centers, in centers caring for patients initially classified as being at low risk for PTB and in centers in which vaginal progesterone was provided free-of-charge[83].

It should be acknowledged that there has been no RCT comparing contingent *vs* universal CL screening. Also, the accuracy and cost-effectiveness of implementation of universal CL screening might be impacted by population-specific factors, such as the local baseline prevalence of PTB, prevalence and definition of short cervix, gestational age at screening, availability of preventive strategies and compliance by patients and healthcare providers. Screening could also promote potential untoward effects, such as anxiety and the use of treatments that it is recommended not to use, which might be attenuated by strict adherence to protocols.

Therefore, in accordance with the 2022 updated ISUOG Practice Guidelines on the performance of the routine mid-trimester fetal ultrasound scan[84], when a comprehensive local feasibility analysis coupled with availability of preventive measures indicate that there are sufficient funding, skills and equipment, we recommend universal CL screening for PTB using TVS for asymptomatic singleton pregnancies between 18 and 24 weeks, and prescription of natural vaginal progesterone for patients identified

as having CL ≤ 25 mm (Figure 11). The benefit/risk ratio favors a CL cut-off of ≤ 25 mm rather than ≤ 20 mm or ≤ 15 mm, since a missed opportunity to intervene carries a greater risk of poor outcome than does overtreating with natural vaginal progesterone, which carries only minimal, if any, risk.

Recommendation

- When feasible, TVS CL measurement should be performed at the second-trimester scan to screen for PTB (**GRADE OF RECOMMENDATION: C**).

Asymptomatic singleton pregnancy with additional risk factors for spontaneous PTB

Several conditions are associated with PTB and will lead to the woman being classified as high-risk for PTB. Risk factors can be modifiable or non-modifiable. Examples of modifiable risk factors include urinary and/or genital tract infections, smoking, substance use, poor access to medical care and physical abuse. Pre-conceptional or early-pregnancy screening and interventions for prevention or limitation of these modifiable infectious or environmental risk factors are beyond the scope of this Guideline; suffice to say that interventions such as treatment of asymptomatic bacteriuria[85], quitting smoking[86] and illicit drug cessation programs[87] are associated with general health benefits to pregnant women, which might include reduction in PTB rates.

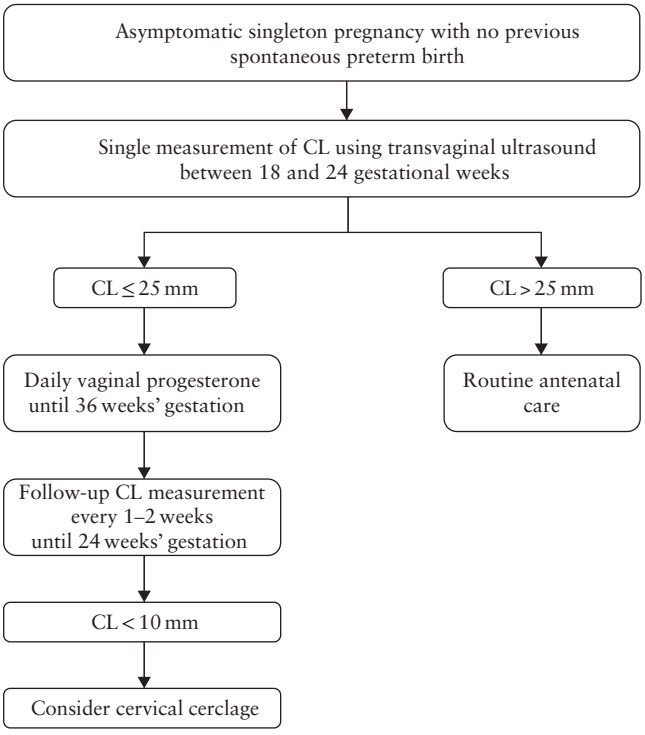

Figure 11 Flowchart illustrating universal cervical-length (CL) screening program using transvaginal ultrasound.

Previous spontaneous PTB

The most significant pre-existing non-modifiable risk factor for PTB in an ongoing pregnancy is a history of spontaneous PTB. A cross-country individual participant analysis in five high-income countries reported ORs for PTB ranging from 4.6 to 6.0 in women with previous spontaneous PTB compared with women who had only term deliveries previously[88]. Multiple previous spontaneous PTB, no previous term birth and interpregnancy interval < 12 months have also been described as independent risk factors for recurrent PTB[89].

Progesterone has been used for the prevention of PTB in high-risk asymptomatic pregnant women for decades. The first Cochrane Database systematic review dates from 2006[90], but only in the 2013 update was the subgroup of singleton pregnancies with a previous spontaneous PTB addressed specifically[91]. Since then, progesterone use compared with placebo has been associated with prevention of perinatal mortality and many short- and long-term morbidities, as well as pregnancy prolongation, and its prescription has been supported widely[92–97]. More recently, the debate has focused on the type and route of administration of progesterone. A 2022 RCT comparing vaginal progesterone with intramuscular 17-OHPC reported a trend towards increased latency to delivery with the former, but, while there was a trend towards reduced risk of PTB in association with vaginal progesterone use, the reduction was < 50% compared with 17-OHPC[98]. A subsequent meta-analysis including this RCT also concluded that vaginal progesterone was superior to 17-OHPC in preventing PTB < 34 weeks, but acknowledged that, although a sensitive subanalysis for high-fidelity studies showed the same trend, statistical significance was no longer demonstrated[99].

The EPPPIC IPD meta-analysis, which included mostly women with previous spontaneous PTB or a short cervix, demonstrated a statistically significant 22% reduction in PTB < 34 weeks in women who used vaginal progesterone[63]. While subpopulation analysis supported these findings for patients with CL < 30 mm, irrespective of obstetric history, the reverse was not supported: for patients with previous spontaneous PTB and CL > 30 mm, there was no apparent benefit, but the 95% CI was wide, demanding further investigation[63]. In 2022, a Bayesian network meta-analysis including 61 RCTs and 17 273 pregnant women at risk for spontaneous PTB because of a history of spontaneous PTB or short CL also indicated that vaginal progesterone should be considered the preventive intervention of choice for this population[64]. However, a smaller meta-analysis of three studies focusing on women with a history of PTB and a normal CL in the index pregnancy failed to show a beneficial effect of progesterone[100], and a subsequent meta-analysis of 10 trials focusing specifically on singleton pregnancies with a history of spontaneous PTB concluded that there is no convincing evidence to support the use of vaginal progesterone for prevention of PTB. Although the primary evaluation demonstrated a decreased risk of PTB < 37 and < 34 weeks and of NICU admission, these results

became non-significant after sensitivity analyses adjusted for small-study effects and restricted inclusion of RCTs to those with low risk of bias[101].

The effectiveness of using vaginal progesterone prophylactically in unselected asymptomatic pregnant women with a history of spontaneous PTB, or women with a history but normal CL, is, therefore, still under debate. The logical approach would be to perform follow-up CL measurements (discussed below).

To prevent PTB in unselected asymptomatic pregnant women with a history of spontaneous PTB, it seems reasonable to consider using vaginal natural progesterone (gel or pessary, 90–200 mg/day) until 36 weeks, irrespective of CL measurement, bearing in mind the following three points. First, taking into consideration the pool of publications reporting on asymptomatic pregnant women with a history of spontaneous PTB, its use is associated with a reduction in PTB and a potential reduction in serious neonatal complications and low birth weight across a heterogeneous high-risk group. Second, there appears to be a low risk of adverse events associated with its use. Third, the benefit for patients with a previous spontaneous PTB and normal CL has been under debate recently, given that few trials at low risk of bias have included this group of pregnant women. Although published trials[99] studied the efficacy of progesterone supplementation starting between 16 and 28 gestational weeks, there was a tendency for earlier initiation to be associated with lower rates of recurrent PTB in a retrospective cohort study[102]. Alternatively, progesterone could be prescribed only for patients whose CL reduces to ≤ 25 mm, but there is no consensus regarding recommendations for the frequency of CL measurement and indications for cerclage.

Recommendation

- Although evidence is still conflicting, in women with singleton gestation and prior spontaneous PTB, treatment with vaginal progesterone every night from 16 to 36 weeks, or surveillance and treatment in those with CL ≤ 25 mm, should be considered (**GOOD PRACTICE POINT**).

Previous spontaneous PTB with cervical insufficiency

Historical clues suggestive of cervical insufficiency, such as painless advanced cervical dilation[103] or early-second-trimester pregnancy loss with spontaneous onset of labor, are significant risk factors for recurrent pregnancy loss or severe PTB (< 28 weeks)[104]. History-indicated (or prophylactic) cerclage placement at 12–14 weeks for women with previous PTB suggestive of cervical insufficiency was associated with a significant reduction in the rate of PTB < 33 weeks compared to withholding the procedure (13% *vs* 17%, $P = 0.03$) in a multicenter RCT[105]. This finding is supported by the 2017 Cochrane Database systematic review on cerclage for preventing PTB in singleton pregnancies, which reported a decrease in PTB < 37 weeks (with some heterogeneity noted; average RR, 0.80; 95% CI, 0.69–0.95; nine studies; 2898 women; $I^2 = 39\%$), < 34 weeks (average RR, 0.77; 95% CI, 0.66–0.89; nine studies; 2415 women; high-quality evidence) and probably < 28 weeks, although this result was marginal, with the 95% CI meeting the line of no effect (average RR, 0.80; 95% CI, 0.64–1.00; eight studies; 2392 women)[106]. However, most patients with previous spontaneous PTB do not meet clinical criteria for cervical insufficiency.

Previous spontaneous PTB with short cervix

A 2011 IPD meta-analysis showed that, for pregnant women with singleton gestation and previous spontaneous PTB, with CL < 25 mm detected < 24 weeks, ultrasound-indicated cerclage decreases significantly both PTB < 35 weeks, from 41% to 28% (RR, 0.70; 95% CI, 0.55–0.89), and composite perinatal morbidity and mortality, from 24.8% to 15.6% (RR, 0.64; 95% CI, 0.45–0.91), compared with no cerclage[107]. The introduction of prophylactic progesterone offered an alternative to cerclage, and an updated indirect comparison meta-analysis[108], as well as a subgroup analysis of an IPD meta-analysis[12], concluded that vaginal progesterone and cerclage have similar efficacy in preventing PTB and perinatal morbidity and mortality in patients with previous spontaneous PTB and CL ≤ 25 mm detected before 24 weeks.

Role of cervical-length follow-up after initiation of preventive measures

Studies on serial CL measurement showed that cervical shortening is significantly associated with spontaneous PTB, regardless of the initial CL measurement[11,109]. Once the decision regarding whether to initiate vaginal progesterone has been taken, a follow-up strategy is important, both for patients at high risk for recurrent spontaneous PTB and for those without an obstetric history suggestive of cervical insufficiency. A policy of sonographic CL screening and ultrasound-indicated cerclage compared with history-indicated cerclage has been proved similarly effective and resulted in comparable pregnancy outcomes[107,110]. Ultrasound follow-up can prevent cerclage in 58% of cases when CL measurements remain stable, thus preventing potential surgical complications[110]. Ultrasound-indicated cerclage can provide a safety net for women with a shortening CL despite being on progesterone. Indeed, a retrospective cohort study indicated that, in patients using vaginal progesterone with progressive CL shortening to < 10 mm, the placement of a cerclage reduced the rate of spontaneous PTB at < 37, < 35, < 32, < 28 and < 24 weeks, with a reduction in rate of 48% for PTB < 37 weeks and of 70% for PTB < 24 weeks, doubled pregnancy latency and decreased the overall rate of adverse perinatal outcome, compared with vaginal progesterone alone[66]. Therefore, serial CL measurements are recommended for patients on progesterone with previous spontaneous PTB, starting from the early second trimester (14–16 weeks) and continuing until 24 weeks, as cerclage

is usually not performed after this gestational age. According to two prospective studies, first-trimester TVS screening is unreliable even for high-risk patients, as CL is rarely short at this gestational age[40,111]. During the period of TVS CL surveillance, measurements should be repeated every 2 weeks if the CL measurement remains ≥ 30 mm and, potentially, weekly when the CL is 26–29 mm. For patients with CL ≤ 25 mm before 24 weeks, the risks and benefits of cervical cerclage should be discussed and cerclage may be recommended[107]. A suggested monitoring protocol with serial TVS CL measurements is presented in Figure 12. There have been descriptions of TVS parameters to predict PTB after placement of a cerclage, such as CL[112], location of the stitch within the cervix, curvature of the cervical canal and presence of funneling or amniotic debris[113]; however, further TVS evaluation has not been proven beneficial, as no further therapy has been shown to change outcome[114].

Recommendations

- In women with singleton gestation and prior spontaneous PTB, TVS CL screening every 2 weeks between 14–16 and 24 weeks if CL is ≥ 30 mm should be considered. If TVS CL is 26–29 mm, TVS CL could be repeated weekly (**GOOD PRACTICE POINT**).
- In women with singleton gestation and prior spontaneous PTB who are on progesterone and have TVS CL ≤ 25 mm on CL screening before 24 weeks, ultrasound-indicated cerclage may be recommended (**GRADE OF RECOMMENDATION: A**).
- Follow-up CL measurements should be considered after initiation of progesterone, as women with shortening cervix despite progesterone treatment may benefit from cervical cerclage (**GRADE OF RECOMMENDATION: C**).
- There is a lack of evidence regarding CL follow-up after cerclage placement, so this practice cannot be recommended at this time (**GOOD PRACTICE POINT**).

Role of cervical pessary in women with previous spontaneous PTB and short cervix

According to a 2020 systematic review and meta-analysis, current evidence does not support use of cervical pessary to prevent PTB in women with singleton gestation and TVS CL ≤ 25 mm before 24 weeks, irrespective of previous obstetric history ($P = 0.24$), concomitant use of vaginal progesterone ($P = 0.70$) or severity of CL shortness ($P = 0.68$)[72].

Additional non-modifiable risk factors associated with spontaneous PTB

Women with previous cervical surgery, such as loop electrosurgical excision procedures (LEEP) and cold knife conization, are at increased risk for PTB. A depth of cervical resection greater than 10–12 mm is associated with increased risk of PTB[115]. Nonetheless, underlying risk factors other than the procedure itself may be present in women with cervical dysplasia and could act as confounders[115–117]. Prophylactic cerclage failed to reduce the risk of PTB in women following excisional surgery[118]. The role of serial second-trimester CL monitoring by TVS is also questionable, since no significant difference in the proportion of women with CL ≤ 25 mm before 24 weeks

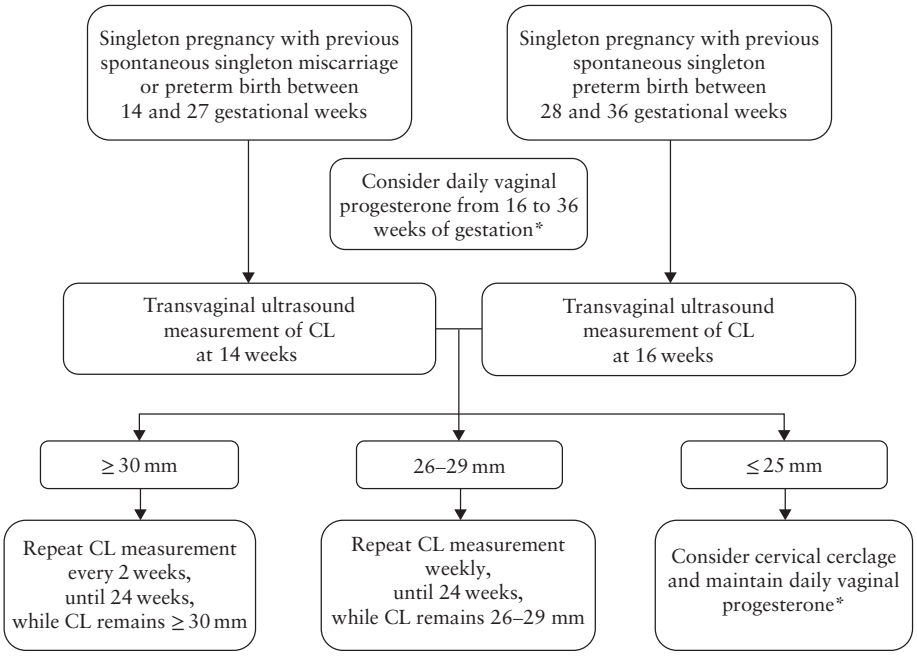

Figure 12 Transvaginal ultrasound cervical-length (CL) screening program for singleton pregnancy with previous spontaneous singleton second-trimester miscarriage or preterm birth. *Alternatively, progesterone could be prescribed only for patients whose CL had reduced to ≤ 25 mm at surveillance, but there is less consensus regarding recommendations for the frequency of CL scans and cerclage indication.

was observed when comparing women undergoing conization/LEEP to a control group[119]. Consequently, it seems reasonable to manage pregnant women with a history of conization/LEEP similarly to those without such history, i.e. either with one second-trimester TVS CL examination or by prescribing progesterone and performing serial TVS CL measurements in case of previous history of spontaneous PTB.

Women with a congenital uterine anomaly, fibroids or pre-existing medical condition that could affect the cervical connective structure are at increased risk of spontaneous PTB, particularly women with unicornuate uterus or uterus didelphys, these being related more to late than to early PTB[120–122]. However, screening for short cervix by second-trimester TVS CL surveillance is only moderately predictive of PTB at 24 weeks in patients with a septate uterus[120]. Therefore, this group of women should also benefit from the same predictive and preventive strategies as pregnant women with a history of conization/LEEP.

Observational data have associated a previous term Cesarean section at full cervical dilation with a 3-fold higher rate of subsequent recurrent spontaneous late miscarriage or PTB[123]. One possible explanation is structural damage to the cervix or superior vagina by the uterine incision, incorporated into the lower segment in the second stage of labor. Although serial second-trimester CL monitoring by TVS in patients with previous term Cesarean section at full cervical dilation would seem reasonable, both history- and ultrasound-indicated TVS cerclage were less efficacious in preventing PTB in the subgroup of patients who had a subsequent previous spontaneous PTB[124]. The ongoing 'Cerclage after full dilatation caesarean section' (CRAFT) RCT is currently investigating diagnostic and therapeutic options for the optimal management of this group of women[125].

Role of specialized antenatal clinics for pregnant women at high risk for spontaneous PTB

Although dedicated antenatal clinics for pregnant women with risk factors for PTB have been advocated as an intervention to improve outcomes for these women and their infants, two systematic reviews failed to show the efficacy of these clinics in reducing the rate of PTB[126,127]. This failure was probably due to: (i) the limited number of studies on this topic, (ii) recent changes in practice that were not assessed sufficiently in previous publications and (iii) differences in referral criteria, types of investigation performed, preventive/therapeutic interventions offered and the timing and frequency of review among different settings. The fact that specialized antenatal clinics are usually accepted as part of care in many settings makes it unlikely that further RCTs will be carried out in the future[128]. Therefore, implementation of PTB prevention programs based on current evidence-based strategies and global consistency in practice are indispensable for evaluating the performance of specialized antenatal services.

ULTRASOUND IN THE MANAGEMENT OF SINGLETON PREGNANCY WITH SYMPTOMS OF PRETERM LABOR

A significant proportion of spontaneous PTBs are preceded by spontaneous PTL[129]. Women with singleton pregnancy presenting with symptoms of PTL, a condition also known as threatened PTB, are seen frequently in clinical practice, accounting for > 15% of cases attending the obstetric triage units of tertiary hospitals[130]. The definition of PTL is problematic and usually takes into consideration serial cervical digital examinations for the assessment of dilation and effacement, and manual or tocographic recording of uterine contractions. Furthermore, in 25–45% of patients with threatened PTL and minimal cervical dilation, there is spontaneous resolution[131] and 76% of these patients deliver at term[130]. This discrepancy has an obvious impact on management decisions, the cost of treatment and, ultimately, the outcome of pregnancy. Therefore, in recent years, ultrasound assessment of CL and point-of-care biochemical markers have been evaluated as tools to help in predicting which symptomatic patients are at increased risk for PTB and rationalize their care.

Several observational studies have analyzed the performance of TVS CL measurement in the prediction of PTB in symptomatic singleton pregnancy[132–134]. One study, encompassing more than 1000 singleton pregnancies with threatened PTL and cervical dilation < 3 cm, reported that TVS CL measurement was associated independently with the risk of PTB in both patients with closed and those with dilated cervix[133].

An IPD meta-analysis published in 2017 investigated the impact of knowledge of CL measured at TVS in preventing PTB in 287 symptomatic singleton pregnancies. Women randomized to the group with known CL had a significant 36% reduction in the rate of PTB < 37 weeks (22.1% *vs* 34.5%; RR, 0.64; 95% CI, 0.44–0.94) and an increased latency to delivery of approximately 4.5 days (95% CI, 1.18–9.98 days) compared with the control group[15]. A Cochrane review, 2 years later, addressing the effect of knowing the TVS CL on prevention of PTB in 242 singleton symptomatic patients, could not confirm a clear effect on reduction of delivery < 37 weeks (RR, 0.59; 95% CI, 0.26–1.32), but reported that limited evidence suggests that use of CL to inform the management of these women appears to prolong pregnancy by about 4 days, compared to women with unknown CL[129].

Cervical-length cut-off for clinical decision-making in symptomatic women

Although CL measurement seems to help in the rationalization of PTL care, different cut-offs and protocols for management have been used across studies. Management options may involve a decision between hospital discharge or admission, and the use of antibiotics for Group-B streptococcus colonization, antenatal corticosteroids, tocolysis and neuroprotection

with magnesium sulfate, but these are beyond the scope of this Guideline.

Ness *et al.*[135] used TVS CL cut-offs of < 20 mm for treatment and > 30 mm for discharge from hospital, adding fetal fibronectin (FFN) as a support tool in cases with CL between 20 and 29 mm. Alfirevic *et al.*[136] used a cut-off of 15 mm to guide the decision between active and conservative management, while Palacio *et al.*[137] opted to use CL ≥ 25 mm as the limit above which a patient could be discharged safely. A meta-analysis of 25 studies[138] reported that, for birth within 7 days from presentation, using TVS CL cut-offs of < 15 mm *vs* < 20 mm, the sensitivity was 59.9% (95% CI, 52.7–66.8%) *vs* 75.4% (95% CI, 66.6–82.9%), specificity was 90.5% (95% CI, 89.0–91.9%) *vs* 79.6% (95% CI, 77.1–81.9%), positive likelihood ratio (LR) was 5.71 (95% CI, 3.77–8.65) *vs* 3.74 (95% CI, 2.77–5.05) and negative LR was 0.51 (95% CI, 0.33–0.80) *vs* 0.33 (95% CI, 0.15–0.73).

In contrast to the commonly used fixed cut-off policy, a retrospective analysis of 1077 women who presented with PTL proposed that the optimal cut-off of CL for the purpose of clinical decision-making should be adjusted for the gestational age at presentation[139]. According to this study, the optimal thresholds to maximize the negative predictive value (NPV) for delivery within 14 days would be 36 mm for women presenting at 32 + 0 to 33 + 6 weeks, 32.5 mm for those presenting at 30 + 0 to 31 + 6 weeks, 24 mm for those presenting at 27 + 0 to 29 + 6 weeks and 20.5 mm for those presenting at 24 + 0 to 26 + 6 weeks[139].

Therefore, although the heterogeneity across studies makes it difficult to achieve consensus regarding CL cut-offs for the management of symptomatic women, fixed values of < 15 mm or < 20 mm and ≥ 30 mm may be used as predictors for higher and lower risk of PTB within 7 days, respectively.

Point-of-care biochemical markers in management of symptomatic women

Point-of-care biochemical markers have also been proposed for the prediction of PTB in symptomatic patients, in isolation or, most commonly, combined with CL measurement.

FFN is the most well-studied of these tests. It is an extracellular matrix glycoprotein found in the decidua and amniotic membranes. The qualitative detection of FFN in the cervical or vaginal tissues at concentrations of > 50 ng/mL after 22 weeks has been associated with increased rates of spontaneous PTL[140]. More recently, a quantitative FFN test was developed and, although it aggregates the information of a progressively increased risk of PTB < 7 days across the reference risk range compared with the qualitative test, it does not seem to improve the predictive efficacy of FFN associated with CL measurement[141,142]. Recent systematic reviews and cost-effectiveness analyses[143,144], as well as a clinical implementation study[145], failed to demonstrate a benefit of using FFN compared with usual care in the prediction of PTB. A RCT that assessed the use of FFN in association with CL measurement failed to show improvement in predictive values for PTB in patients with CL < 20 mm[135]. Moreover, there are known limitations to its clinical use, as its performance is suboptimal after manipulation of the cervix by digital examination, after sexual intercourse and in the presence of amniotic fluid, blood, lubricants, soaps and disinfectants[141]. Two additional point-of-care biochemical markers have been evaluated for the prediction of PTB in symptomatic singleton patients: phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1) and placental alpha microglobulin-1 (PAMG-1). A multicenter prospective study of 403 patients concluded that both tests have comparable sensitivity to predict spontaneous PTB within 7 days in women symptomatic for PTL, but PAMG-1 was significantly more specific[146]. Furthermore, for patients with a CL between 15 and 30 mm, PAMG-1 also had higher positive predictive value (PPV) and specificity compared with phIGFBP-1[146]. A systematic review and meta-analysis comparing the accuracy of PAMG-1, FFN and phIGFBP-1 in predicting spontaneous PTB within 7 days of testing in symptomatic women concluded that the PPV of PAMG-1 was significantly higher than those of the other two tests, with no difference in the other diagnostic accuracy measures[147].

There is not yet definitive high-quality evidence to support the use of point-of-care biochemical tests, mainly FFN, in addition to TVS CL measurement. However, some medical societies validate this strategy. The 2019 National Institute for Health and Care Excellence (NICE) 'Preterm labour and birth overview' supports the use of CL measurement by TVS, performed by trained and experienced providers, for women with PTL suspected at > 30 weeks' gestation[94]. According to this guideline, a CL cut-off of 15 mm should be used to counsel patients about active *vs* expectant management, and FFN with a cut-off of < 50 mg/dL should be used as an alternative when TVS is not available or accepted. The Society for Maternal-Fetal Medicine guideline also acknowledges the value of a negative FFN test as an adjunct to CL measurement in the 'gray zone' for symptomatic patients, i.e. CL between 20 and 30 mm[19].

Based on the fact that more than 50% of symptomatic patients present with TVS CL > 30 mm and that their rate of delivery within 7 days is less than 2%, ultrasound can provide reassurance to discharge these patients, with instructions to return in case of worsening symptoms[135,148]. In contrast, the cut-off value for defining active management in RCTs is reported to be between 15 and 20 mm, and addition of point-of-care biochemical tests does not seem to improve the performance of CL measurement[135,148]. Consequently, the use of biochemical markers could be considered for selected symptomatic patients with a CL between 15 or 20 mm and 29 mm, if available. It is important to emphasize that swab collection should be done before digital or ultrasound examination, to guarantee an ultrasound-based selective approach and the best performance of the test (Figure 13).

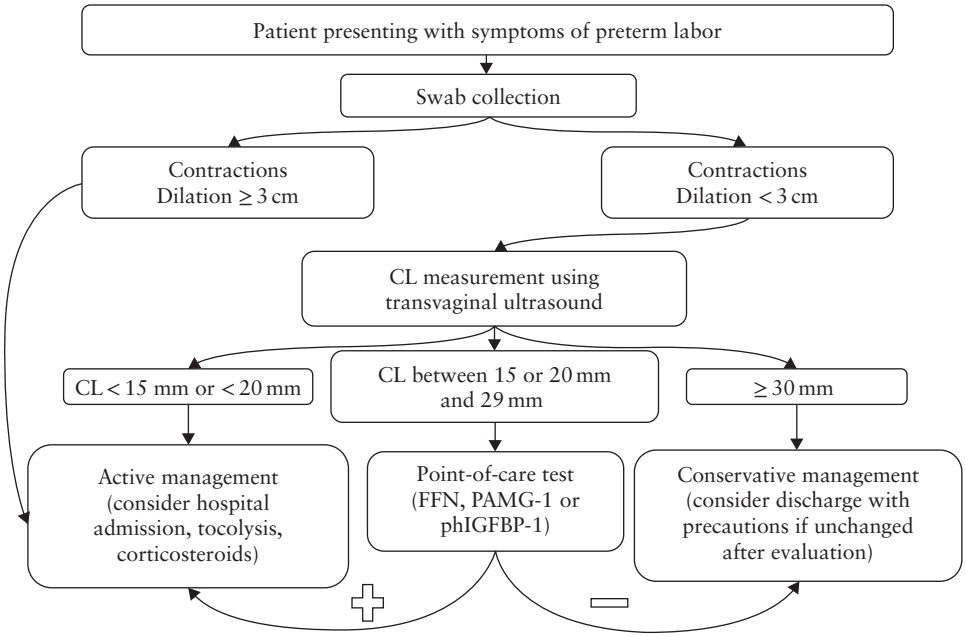

Figure 13 Decision flowchart for use of transvaginal ultrasound for cervical-length (CL) measurement and a laboratory test for prediction of preterm birth in patients presenting with symptoms of preterm labor. FFN, fetal fibronectin; PAMG-1, placental alpha microglobulin-1; phIGFBP-1, insulin-like growth factor binding protein-1.

Recommendations

- In women with singleton gestation and threatened PTL between 22 + 0 and 33 + 6 weeks, TVS CL measurement is recommended to assess the risk of PTB (**GRADE OF RECOMMENDATION: C**).
- If TVS CL is ≥ 30 mm, the woman can usually be discharged with precautions (**GRADE OF RECOMMENDATION: C**).
- If TVS CL is < 15 mm or < 20 mm, admission, administration of steroids for fetal maturity, and tocolysis (if necessary) can be considered, according to local protocols (**GOOD PRACTICE POINT**).
- If TVS CL is between 15 or 20 mm and 29 mm, a laboratory test can be considered for triage, if available. Management decisions should be based on these lab tests as follows: if result is positive, manage as for CL < 15 mm or < 20 mm; if result is negative, manage as for CL ≥ 30 mm (**GOOD PRACTICE POINT**).

ULTRASOUND IN THE MANAGEMENT OF MULTIPLE PREGNANCY

Screening for spontaneous PTB in multiple pregnancy asymptomatic for preterm labor

Screening for PTB in twin pregnancy was addressed in the 2016 ISUOG Practice Guidelines on the role of ultrasound in twin pregnancy[149], and its recommendations are still effective. Multiple pregnancy is a known risk factor for PTB. The majority of multiple pregnancies deliver preterm, and the higher the number of fetuses, the lower the expected gestational age at delivery, which leads to increased morbidity and mortality[150]. The approximate rates of preterm delivery < 34 weeks in the USA in 2018 were 2% for singletons, 20% for twins, 63% for triplets and 83% for quadruplets[150]. These rates are also dependent on chorionicity; the overall rate of delivery < 37 weeks for monochorionic monoamniotic twin pregnancy is 100%, that for monochorionic diamniotic twin pregnancy is 88.5% and that for dichorionic diamniotic twin pregnancy is 48.6%, and the corresponding rates for PTB < 32 weeks are 26.8%, 14.2% and 7.4%, respectively[151].

Role of cervical-length screening in asymptomatic twin pregnancy

As with singleton pregnancy, the TVS measurement of CL has been studied as a screening tool for PTB in twin pregnancy. Since the initial population studies, it has been known that the CL distribution in twins is skewed towards shorter lengths. While the median CL is 38 mm, similar to that for singleton pregnancy, 11% of twin pregnancies have CL < 25 mm and 4% have CL < 15 mm[152]. Furthermore, in contrast to singleton pregnancies, the CL is not affected by maternal demographics, history or chorionicity[152]. Since the initial observations, multiple studies have shown that a short cervix in asymptomatic women with multiple pregnancy is a risk factor for PTB[152–157]. A 2010 meta-analysis of asymptomatic twin pregnancies reported that a CL < 25 mm at 20–24 weeks was associated with a 25% risk of PTB < 28 weeks, while a CL < 20 mm was associated with a risk of 42% for PTB < 32 weeks and 62% for PTB < 34 weeks[155].

Cervical-length cut-off in asymptomatic twin pregnancy

In pragmatic terms, most publications tend to use the empirical fixed cut-off of 25 mm between 18 and 24 gestational weeks. However, an IPD meta-analysis published in 2016 further highlighted the significance of the timing of screening. For example, if the target is PTB < 28 weeks, screening should commence before 18 weeks, regardless of the CL used. For PTB between 28 and 32 weeks, the earlier the screening, the lower the CL cut-off to ensure better prediction. In the common gestational window of 20–22 weeks, the optimal cut-off for PTB between 28 and 32 weeks is ~15 mm, and that for PTB between 32 and 36 weeks is ~35 mm[157].

Recommendation

- CL measurement is the preferred method for screening for PTB in twins; 25 mm is a pragmatic cut-off between 18 and 24 gestational weeks (**GOOD PRACTICE POINT**).

Prevention of spontaneous PTB in multiple pregnancy asymptomatic for preterm labor

A 2017 Cochrane Database systematic review assessing strict or partial bed-rest in hospital or at home for multiple pregnancy did not report any benefit with respect to the risks of PTB < 37 or < 34 weeks, perinatal mortality or low birth weight[158]. Similarly, a Cochrane review addressing the use of prophylactic oral betamimetics *vs* placebo for reducing PTB in women with a twin pregnancy failed to demonstrate evidence to support its use[159].

Role of progesterone in preventing spontaneous PTB in twin pregnancy

Given that multiple pregnancy is the single most significant risk factor for PTB, several studies have tested the prophylactic administration of progesterone in all twin pregnancies (unselected twins). It became evident from early on that such a strategy not only fails to reduce the rate of prematurity, but might also increase the risk of some fetal complications, including perinatal death (OR, 1.55; 95% CI, 1.01–2.37)[160]. However, a 2015 IPD meta-analysis indicated that vaginal progesterone may improve the prenatal outcome for the subgroup of twin pregnancies with a short cervix[161], and the same was suggested by another IPD meta-analysis published in 2017 (303 women, 606 fetuses), which reported decreased rates of PTB < 30 to < 35 weeks and neonatal mortality and morbidity[162]. Yet, a single study[163] represented 74% of the total sample, and the reduction in PTB < 33 weeks and neonatal death became non-significant when the parameter of trial quality was taken into account. A 2019 Cochrane Database systematic review moved this study to the 'awaiting classification' category, and concluded that neither intramuscular nor vaginal progesterone administration in multiple pregnancy appears to be associated with a reduction in PTB or improved neonatal outcome[164]. This study[163] was later retracted.

One of the postulated reasons for the failure of progesterone to prevent PTB in twins was that the usual dose of 200 mg/day might be inadequate for multiple pregnancy. Therefore, the 'Early vaginal progesterone for the preVention of spontaneous prEterm birth iN TwinS' (EVENTS) multicenter trial tested the hypothesis that a higher dose of vaginal progesterone (600 mg per day) started earlier (between 11 and 14 weeks) in unselected multiple pregnancy would reduce the incidence of PTB < 34 weeks. Again, there were no differences between the treatment and placebo groups[165]. A *post-hoc* analysis suggested that progesterone might reduce the risk of PTB < 32 weeks for patients with CL < 30 mm, but might in fact increase the risk for those with CL ≥ 30 mm[165].

The EPPPIC IPD meta-analysis results demonstrated no evidence to support the use of vaginal progesterone or 17-OHPC in unselected multiple pregnancy[63]. Additionally, 17-OHPC increased the risk of preterm rupture of membranes compared with controls and the sample was not powered sufficiently to address the question of efficacy of progesterone in prevention of PTB in the subgroup with short cervix.

In 2022, an updated IPD meta-analysis, which excluded data from the abovementioned retracted study[163] and included information from the EVENTS trial, showed that vaginal progesterone significantly reduced PTB < 33 weeks in twin pregnancy with a second-trimester CL ≤ 25 mm (RR, 0.60; 95% CI, 0.38–0.95), but the sample size was limited to 95 participants. Composite neonatal morbidity and mortality were also reduced significantly[166]. These findings should be confirmed by adequately powered RCTs.

Recommendations

- Prophylactic use of progesterone is not recommended for the prevention of PTB in unselected twin pregnancy (**GRADE OF RECOMMENDATION: A**).
- Prophylactic use of vaginal progesterone may be considered in twin pregnancy with CL ≤ 25 mm (**GRADE OF RECOMMENDATION: C**).

Role of cervical cerclage in multiple pregnancy

Although the use of cerclage may be beneficial in elective or ultrasound-indicated procedures in singleton pregnancy, there is no adequate evidence to support the indication of this surgical procedure to reduce PTB in twins. Although studies with small sample sizes have shown that ultrasound-indicated[167], history-indicated[168] or emergency[169] cerclage could potentially reduce the rate of PTB or increase the latency, two IPD meta-analyses reported the opposite[170,171]. The first, assessing the use of cerclage in unselected twin pregnancy, showed an increased risk of PTB (RR, 2.15; 95% CI, 1.15–4.01) and a non-significant increase in perinatal mortality[170], while

the second assessed cerclage in patients with CL < 25 mm before 24 weeks and reported no reduction in rates of PTB from < 37 to < 28 weeks and no improvement in secondary outcomes[171]. Based on these Level-I data, cerclage is not recommended in twin pregnancy overall. Of note, a recent RCT investigating the efficacy of a combination of physical-examination-indicated cerclage (Figure 10), indomethacin and antibiotics, in a group of asymptomatic twin pregnancies with cervical dilation between 1 and 4 cm before 24 weeks, was interrupted prematurely due to the significant decrease in PTB at all gestational ages, a 50% decrease in PTB < 28 weeks and a 78% reduction in perinatal mortality[172].

Recommendations

- History-indicated cerclage is not recommended in unselected twin pregnancy (**GRADE OF RECOMMENDATION: C**).
- A combined strategy of physical-exam-indicated cerclage, antibiotics and tocolytics may be considered in asymptomatic twin pregnancy with dilated cervix before 24 weeks (**GRADE OF RECOMMENDATION: C**).

Role of cervical pessary in multiple pregnancy

The current status of cervical pessary for the prevention of PTB in multiple pregnancy is similar to that in singleton pregnancy. The two largest trials testing the use of pessary in unselected twins, including 1180 patients[173] and 808 patients[174], did not show any reduction in PTB < 34 or < 32 weeks associated with pessary *vs* expectant management. The evidence is conflicting for multiple pregnancy with a short cervix. Two trials showed benefit from using pessaries for CL < 38 mm[174] and CL < 25 mm[175], while others did not report differences in PTB rates for CL < 25 mm[173], CL < 30 mm[176] and CL ≤ 35 mm[177]. A 2020 meta-analysis assessing the effect of cervical pessary on the rates of PTB < 34 weeks and improvement of neonatal outcome in asymptomatic women, concluded that current evidence supports its use neither in unselected twin pregnancy nor in singleton or twin gestation with short cervix (either < 38 mm or ≤ 25 mm)[72]. Similarly, a meta-analysis including data from the 'Study for the Prevention of Preterm labour In Twins 2' (STOPPIT-2) RCT failed to show the target 40% reduction in PTB < 34 weeks for twin pregnancy with CL ≤ 35 mm treated with Arabin cervical pessary[177].

Recommendations

- Prophylactic use of cervical pessary is not recommended in unselected twin pregnancy (**GRADE OF RECOMMENDATION: B**).
- There are conflicting data on the effectiveness of cervical pessary in multiple pregnancy with a short cervix; therefore, its clinical use in these pregnancies is not endorsed (**GOOD PRACTICE POINT**).

Multiple pregnancy symptomatic for preterm labor

The role of ultrasound and laboratory tests in the prediction of PTB in twin pregnancy in women symptomatic for PTL is less clear. An observational study of 218 twin pregnancies which presented with threatened PTL[178] showed that the performance of CL measurement to predict PTB was similar to that in singleton pregnancy. The authors concluded, however, that the optimal threshold for active management in twins would be higher than that in singletons, stating that a cut-off of 28–30 mm should be used in order to achieve a NPV of 95%; this would increase the number of patients requiring additional intervention[178]. The 2019 Cochrane Database systematic review that investigated knowledge *vs* no knowledge of CL measured by TVS in patients with PTL did not include any trial involving twin pregnancy[129].

Recommendation

- There is insufficient evidence to support the benefit of CL measurement in symptomatic women with twin pregnancy and PTL, or to suggest optimal cut-offs to guide clinical management (**GOOD PRACTICE POINT**).

RECENT ADVANCES AND NEW PERSPECTIVES

In times of technological advances and widespread availability of internet content and mobile applications, algorithms have been developed and validated to ensure personalized care and treatment. Calculators for the prediction of PTB based on maternal risk factors and the measurement of CL between 20 + 0 and 24 + 6 weeks can be found on The Fetal Medicine Foundation's website[179]. For a 10% screen-positive rate, this model had sensitivities of 80.6% for predicting spontaneous PTB < 28 weeks, 58.5% for PTB at 28–30 weeks, 53.0% for PTB at 31–33 weeks and 28.6% for PTB at 34–36 weeks[180]. The algorithms devised for the QUiPP™ app v.2 for asymptomatic high-risk women provide personalized risk of PTB based on CL, quantitative FFN or both tests combined, while considering maternal risk factors[181]. A prospective development and validation study demonstrated high accuracy for prediction of PTB < 30, < 34 and < 37 weeks of gestation and within 1, 2 and 4 weeks of testing (areas under the receiver-operating-characteristics curve (AUC) ranged from 0.68 to 0.90)[182]. Similarly, the QUiPP app v.2 algorithms developed and validated for the prediction of PTB in women with symptoms of threatened PTL demonstrated good accuracy, with AUCs of 0.96 for PTB < 30 weeks, 0.85 for PTB < 34 weeks, 0.77 for PTB < 37 weeks, 0.91 for PTB < 1 week from testing and 0.92 for PTB < 2 weeks from testing[183]. Of note, there has been some discussion about risk thresholds for spontaneous PTB to be used for individualized risk assessment/shared decision-making in women with a previous PTB and the applicability of the QUiPP app for small samples from tertiary centers[184–186], which should

stimulate further studies addressing this tool's performance. The 'Evaluation of the QUiPP app for Triage and Transfer' (EQUIPTT) multicenter cluster RCT studied the use of the QUiPP app to triage women with symptoms of PTL *vs* the unit's conventional management[187]. For a cut-off risk of delivery of > 5% within 7 days, although the AUC was 0.9 (95% CI, 0.85–0.95) and there were no safety issues, there was no success in reducing unnecessary admissions and transfers; this may have been related to healthcare-provider non-compliance with national guidance for PTL management and app use[187]. Gudicha *et al.*[188] developed a customized CL standard and a percentile calculator for personalized assessment of CL that adjusted for gestational age and maternal parity, weight and height. This resulted in better recognition of asymptomatic women at risk for spontaneous PTB and improved the identification of patients who would go on to have a PTB among those showing signs of PTL.

Another development that has been explored recently in the prevention of PTB is the use of antibiotics to eradicate documented intra-amniotic infection and inflammation[10]. Recent clinical evidence indicates that the combined administration of ceftriaxone, clarithromycin and metronidazole in pregnant subjects with a laboratory-confirmed intra-amniotic inflammatory process can resolve 75% of cases and prevent up to 40% of deliveries < 34 weeks of gestation[189]. RCTs to confirm these findings are needed. Ultrasound has an important role to play in these cases, aiding in the identification of patients at risk for intra-amniotic infection, such as those with amniotic fluid sludge or debris[190] or those with suspected cervical insufficiency.

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APPENDIX 1 Grades of recommendation and levels of evidence used in ISUOG Guidelines

Classification of evidence levels

1++	High-quality meta-analyses, systematic reviews of randomized controlled trials or randomized controlled trials with very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of randomized controlled trials or randomized controlled trials with low risk of bias
1–	Meta-analyses, systematic reviews of randomized controlled trials or randomized controlled trials with high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with very low risk of confounding, bias or chance and high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with low risk of confounding, bias or chance and moderate probability that the relationship is causal
2–	Case–control or cohort studies with high risk of confounding, bias or chance and significant risk that the relationship is not causal
3	Non-analytical studies, e.g. case reports, case series
4	Expert opinion

Grades of recommendation

A	At least one meta-analysis, systematic review or randomized controlled trial rated as 1++ and applicable directly to the target population; or a systematic review of randomized controlled trials or a body of evidence consisting principally of studies rated as 1+ applicable directly to the target population and demonstrating overall consistency of results
B	Body of evidence including studies rated as 2++ applicable directly to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+
C	Body of evidence including studies rated as 2+ applicable directly to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or evidence extrapolated from studies rated as 2+
Good practice point	Recommended best practice based on the clinical experience of the guideline development group

