Cervical length (CL) measured by transvaginal ultrasound is an effective screening test for the prevention of preterm birth (PTB). The criteria for an effective screening test are all met by CL. It studies an important condition (PTB); it is safe and acceptable by >99% of women; it recognises an early asymptomatic phase that precedes PTB by many weeks; it has a well-described technique, is reproducible, is predictive of PTB in all populations studies so far; and, perhaps most importantly, it has been shown that ‘early’ treatment is effective in prevention. These two interventions, effective only in specific populations, are ultrasound-indicated cerclage and vaginal progesterone.

Keywords: Cerclage, cervical length, preterm birth, progesterone, ultrasound.

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Introduction

Cervical length (CL) measured by transvaginal ultrasound (TVU) is a screening approach for the prediction of preterm birth (PTB). The aims were to review recent level A evidence, based on randomised trials and meta-analyses, on the effectiveness of this screening test as part of a strategy for preventing, not just predicting, PTB in both asymptomatic and symptomatic women and to summarise this recent literature and offer easy guidelines for everyday clinical care recommendations.

As any screening test, certain criteria must be met to make this screening effective (Table 1). Interventions to stop the progress to PTB once a short CL has been identified have been devised, making CL the first effective biophysical screening test for the prevention of PTB. Interventions that may be effective in certain specific populations include cerclage and progesterone. These two interventions were discovered more than 50 years ago, and finally, we have the evidence of their usefulness.

CL as a screening test

CL is not a diagnostic test because the finding of a short cervix does not equate to cervical insufficiency or preterm labour per se. CL must therefore be evaluated as a screening test. To have clinical utility, desirable characteristics of a screening test include those listed in Table 1.1

CL screening by TVU meets the criteria of screening for an important condition. PTB is the main cause of perinatal mortality, and its incidence has increased to 12.8% in the USA in 2006.

CL screening by TVU has not been shown to associate with complications, even in women with preterm prelabour rupture of membranes,2 as it is not associated with an increase in infection or higher inoculation of bacteria.3 It has been shown to be acceptable by more than 99% of pregnant women, as <2% experience pain or severe discomfort.4

TVU CL recognises an early asymptomatic phase of the process leading to PTB. TVU CL is the only screening test that identifies early the opening of the internal cervical os, the first physical change of cervical ripening that precedes labour and birth. Regardless of the underlying cause, the most likely pathophysiological sequence leading to spontaneous PTB involves cervical effacement and dilatation; these changes first occur at the internal os, which cannot be assessed by a manual vaginal examination. This advantage over physical manual examination has been recognised in many studies and makes TVU CL screening a test associated with superior predictive accuracy for PTB than digital physical examinations.5

The technique of TVU CL screening has been well described6 and is summarised in Table 2.7 As for any screening
test, it should be performed by qualified staff, with continuing quality assurance. Transabdominal screening is not precise, inferior to TVU screening, \(^5\) and should not be used for prediction of PTB.

When performed with appropriate technique by quality sonographers, TVU CL is a test with high reproducibility. Its inter- and intra-observer variability have been reported to be <10%. \(^5\) This reliability can probably be achieved only after about 50 supervised TVU CL scans.

TVU CL has been associated with accurate prediction in all populations in which it has been studied for prediction of PTB (Table 3).

The CL is the best measurement to obtain on TVU as it is the most reproducible and the most predictive. After dynamic changes (spontaneous and elicited by transfundal pressure) have been evaluated over at least 5 minutes, and at least three measurements taken before and again at least three after pressure, only one measurement should be reported for clinical use. This measurement is the best short-

### Table 1. Criteria for an effective screening test

- Important condition
- Safe and acceptable
- Recognisable early asymptomatic phase
- Technique well described
- Reliable (reproducible)
- Valid (accuracy of prediction)
- ‘Early’ treatment is effective (prevention)

Modified from Grimes. \(^1\)

### Table 2. Technique of TVU CL

- Empty bladder
- Condom-covered probe
- Let patient insert probe
- Guide probe into anterior fornix
- Obtain sagittal sonographic view of cervix with echogenic endocervical mucosa along the length of the canal
- Withdraw probe until blurred, then reinsert making sure to avoid excessive pressure
- Enlarge image (at least 2/3 of screen)
- Obtain symmetric image of entire endocervical canal, with internal os at flat or isosceles angle, and symmetric view of external os (anterior lip diameter should be equal to posterior lip diameter)
- Measure from internal os to external os along entire cervical canal
- Obtain three measurements, use shortest best
- Apply transfundal pressure for at least 15 seconds
- Total examination duration: at least 5 minutes

Modified from Berghella et al. \(^7\)

### Table 3. Populations in which TVU CL is predictive of PTB

**Asymptomatic**
- Singleton
- Low risk
- ‘High-risk’
- Prior PTB
- Cone biopsy
- Mullerian anomaly
- ≥2 dilatation and evacuation procedures
- Multiple
- Twins
- Triplets

**Symptomatic**
- Preterm labour
- Preterm prelabour rupture of membranes

### Table 4. Key points for interpretation of TVU CL for prediction of PTB

- Best gestational age for screening is 16–24 weeks
- Normal CL: 15–50 mm
- CL <25 mm is below the 10th percentile at 16–24 weeks
- CL <15 mm is below the second percentile at 21–25 weeks
- Not very helpful before 14 weeks (CL usually normal even if later PTB)
- Not very helpful after 28 weeks (CL may be physiologically short)
- The shorter the CL, the higher the risk of PTB
- The earlier the short CL is detected, the higher the risk of PTB
- Sensitivity, specificity, and positive and negative predictive values vary widely depending on population
- Best (blinded) studies have mostly used TVU CL screening at 16–24 weeks, with a cutoff of <25 mm and outcome of PTB <35 weeks

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after about 28 weeks in women destined to deliver at term. Several studies have shown that, when scanning the cervix between 14 and 30 weeks, the mean gestational age when shortening occurs is 18–22 weeks.5,8 So, if one were to look just once at the cervix of low-risk women, perhaps, just one TVU CL screening at the routine anatomy scan may be sufficient,11 but this deserves further research. Serial TVU screening is clearly associated with better predictive accuracy than a single scan9 and may be best for higher-risk women.

TVU CL screening has highest sensitivity and positive predictive value (both >60%) in women with a prior PTB and a singleton pregnancy,8 making this population the clear favourite to potentially be associated with an effective intervention based on this screening test. Its sensitivity is lower (about 30–40%) in either low-risk singleton or multiple pregnancies, as these women may have PTBs that are not as related to an abnormal CL.6,12

First do no harm

A great benefit of ultrasound screening is that it can easily identify high-risk women who do not need any intervention. In fact, more than 60% of high-risk women, such as those with a prior PTB, maintain a normal CL up to 24 weeks and need no intervention. In particular, routine history-indicated cerclage can be spared to women with such histories. Only women with three or more second-trimester losses and/or PTBs may benefit from this procedure.13 Women with one or two of these events can be safely followed with TVU CL, as shown by a randomised trial14 and at least three case–control studies.15–17

Effectiveness of interventions to prevent PTB based on a short CL

Perhaps, the most important criterion to estimate the value of any screening test is to assess that there is an early treatment that effectively prevents the outcome predicted, in this case PTB. Interventions have been based on hypotheses on the reason why the cervix shortening occurs.

Asymptomatic women (no symptoms of preterm labour)

Cerclage

Cervical cerclage has been the intervention most commonly studied and used in clinical practice to prevent PTB once a short TVU CL has been detected. To evaluate its efficacy, one must evaluate this intervention separately for different indications. In the literature, indications for cerclage have varied but can be summarised as in Table 5. Terms such as salvage, urgent, emergent, or rescue should be avoided, as they are vague in terms of the true indication.18 It is for this reason that meta-analyses that include all randomised trials on all types of cerclage together may not be clinically helpful.19

Four randomised trials have assessed the effectiveness of ultrasound-indicated cerclage performed for a short CL on TVU.20–23 They have been summarised in a patient-level meta-analysis.24 These data were analysed by patient population, accounting not only for the different characteristics that TVU CL screening has in different populations but also for possible different effect on cerclage in different populations. In the 208 women with a prior PTB and a short TVU CL <25 mm, the incidence of PTB <35 weeks was 23% in the cerclage group versus 39% in no cerclage group [relative risk (RR) 0.61, 95% CI 0.40–0.92]. PTB <32 weeks was also significantly decreased (RR 0.58, 95% CI 0.34–0.98). All four studies contributing to this meta-analysis had a trend towards benefit, and there was no significant heterogeneity. The 107 cerclages may have saved five neonatal lives (about 1:21 number needed to treat).24 A multicentred National Institutes of Health-sponsored trial enrolled more than 300 women with one or more prior PTBs at 16–34 weeks and TVU CL <25 mm at 16–23 weeks. If its results, due in 2009, confirm that ultrasound-indicated cerclage is beneficial in this specific population, then cerclage would have been proven to be beneficial in women with previous PTB.

Only about 10–15% of women who deliver preterm have a prior PTB. Nevertheless, this is the only population in which, if TVU shows a short CL, cerclage has been shown to prevent PTB. In women with a singleton gestation with other risk factors such as a history of cone biopsy or ≥2 dilatation and evacuation procedures, ultrasound-indicated cerclage has been insufficiently studied.24

The most common population encountered in clinical practice is those women with a singleton gestation and none of these risk factors for PTB. In 235 such women randomised so far, the incidence of PTB <35 weeks was 26% in the cerclage group and 33% in the no cerclage group (RR 0.76, 95% CI 0.52–1.15).24 Further research is necessary to evaluate if this is a result associated truly with no effect or with insufficient sample size.

| Table 5. Main indications proposed in the literature for cerclage and cerclage nomenclature |
|---------------------------------|---------------------------------|-------------------|
| Proposed indication for cerclage | Nomenclature for cerclage |
| Poor prior obstetric history (e.g. three or more prior PTBs or second-trimester losses) | History indicated |
| Short TVU CL | Ultrasound indicated |
| Cervical dilatation on manual examination of the cervix | Physical examination indicated |
In the 49 sets of twins and TVU CL <25 mm reported so far in randomised trials, cerclage was associated with a much higher (75 versus 36%) incidence of PTB <35 weeks compared with controls (RR 2.15, 95% CI 1.15–4.01) and eight more neonates died in the cerclage compared with the no cerclage group.24 Therefore, cerclage should not be used in twin pregnancy for short TVU CL.

Other aspects related to cerclage may affect its efficacy, such as performing an amniocenteses pre-cerclage, type, technique, suture material, height, physical activity, additional use of tocolytics, progesterone, or antibiotics. There are no specific trials assessing these variables, but some data are available. For example, performing Shirodkar versus McDonald cerclage does not seem to affect outcomes.25 Ultrasound-indicated cerclage should be placed as ‘high’ as safely possible, as a distance of >17 mm above the external os is associated with lower rates of PTB.26 Indomethacin, used in one of the trials together with ultrasound-indicated cerclage with success,21 was not associated with benefit in a retrospective cohort study.27 Screening for interleukins, collagenases, sialidases, fibronectins, or other cervicovaginal molecules may better define best candidates for cerclage.28

**Progesterone**

Different forms of progesterone have been used for PTB prevention in different patient populations, and these differences in trials make it difficult to assess the efficacy of this intervention. The most common forms tested in trials are intramuscular 17-hydroxy-progesterone-caproate and vaginal natural progesterone. The patient populations tested are women with prior PTB and singleton gestation, a short TVU CL, preterm labour, and multiple gestation. The focus of this manuscript is on women with a short TVU CL.

In women with a short CL, two trials have reported outcomes. A non-prespecified secondary analysis of a larger trial evaluated 46 women with singleton gestation, prior spontaneous PTB 20–35 weeks, and a short CL (less than 28 mm) at 18–22+6 weeks. In this trial, treatment with vaginal progesterone (90 mg) until 37 weeks was associated with prevention of PTB ≤32 weeks compared with controls (0 versus 29.6%, P = 0.014).29 Treatment with progesterone in this group was associated with a significant reduction in the number of admissions to the neonatal intensive care unit (NICU) (15.8 versus 31.9%, P = 0.016) and the length of NICU stay (1.1 versus 16.5 days, P = 0.013). There were decreasing rates of PTB for <37, ≤35, and ≤28 weeks; however, these differences did not reach statistical significance in this secondary analysis, which can only be used as pilot data for a properly powered randomised trial.

In a much larger trial, 24 620 asymptomatic women were screened at 22 (20–25) weeks by TVU. Of these, 250 (24 with twins) were identified to have a CL ≤15 mm and randomised to 200 mg vaginal progesterone or placebo every night from 24 to 34 weeks.31 Progesterone was associated with a reduction in the risk of spontaneous delivery before 34 weeks of 44.2% (hazard ratio for progesterone, 0.57; 95% CI 0.35–0.92; P = 0.02). Neonatal outcomes were not reported. Based on this trial, vaginal progesterone seems effective in preventing PTB in women with CL ≤15 mm, no matter what their history. Progesterone for prevention of PTB is currently being investigated by several trials, including some on women with a short TVU CL.

**Indomethacin**

The efficacy of indomethacin therapy for prevention of PTB in women with a TVU CL <25 mm has not been evaluated in any randomised trials. In one retrospective cohort of 139 women with CL <25 mm, the incidence of PTB <35 weeks was 29.3% with ultrasound-indicated cerclage and 42.5% without cerclage (RR 0.69, 95% CI 0.44–1.13).30 This is insufficient to make a clinical recommendation but should stimulate further research.

**Antibiotic therapy**

The efficacy of antibiotic therapy for prevention of PTB in women with a TVU CL <25 mm has not been evaluated in any randomised trials. In one retrospective cohort of 276 women with CL <25 mm, the incidence of PTB <35 weeks was 29% with antibiotics and 33% without antibiotics (adjusted RR 0.80, 95% CI 0.40–1.59).31 As for most PTB prevention literature, antibiotics seem to have no apparent role for prevention of PTB in women with a short CL, but further research is necessary.

**Omega-3 fatty acids, pessary, and other interventions**

The efficacy of omega-3 fatty acid therapy, pessary, or any other intervention for prevention of PTB in women with a short CL on TVU has not been evaluated in any randomised or nonrandomised trials.

**Women with symptoms of preterm labour**

**Preterm labour**

As shown in Table 3, TVU CL is also predictive of PTB in symptomatic women, including those with preterm labour. A study has evaluated the efficacy of TVU CL in this population as part of a strategy for prevention of PTB.32 One hundred women with singleton gestations being evaluated for preterm labour at 24–33+6 weeks had fetal fibronectin (FFN) and TVU CL performed. In 50%, knowledge of TVU CL and FFN results was made available to managing obstetricians, while in 50%, they were blinded to TVU CL and FFN results. The ‘knowledge’ group was advised to follow a protocol for management of preterm labour based mainly on the TVU CL.
results, with FFN results suggesting management in women with a CL of 20–29 mm. Knowledge of TVU CL and FFN results was associated with a 13% incidence of PTB <37 weeks compared with 36% in the blinded group (RR 0.35, 95% CI 0.15–0.78). It was speculated that knowledge of CL and FFN may be beneficial to avoid intervention in women not at risk, such as those with a TVU CL ≥30 mm (or CL 20–29 mm and negative FFN), and that interventions such as admission and/or tocolysis may be more effective in women truly at risk for PTB, such as those with CL <20 mm (or CL 20–29 mm and positive FFN).32 This trial needs to be repeated before TVU CL can be recommended for routine evaluation of women with threatened preterm labour.

17-hydroxy-progesterone-caproate has been evaluated in a randomised trial for PTB prevention in women who remained undelivered after tocolysis for preterm labour.33 Compared with no such treatment, 341 mg of 17-hydroxy-progesterone-caproate twice weekly was associated with prevention of both cervical shortening and PTB (OR 0.15, 95% CI 0.04–0.58).33

Conclusions

CL by TVU has been shown to meet all the criteria of an effective screening test (Table 1). When performed with adequate technique (Table 2), it has been shown to be predictive of PTB in all populations studied so far (Table 3).

TVU CL is beneficial as it helps avoid interventions in more than 60% of women with risk factors for PTB (e.g. a prior PTB) who maintain a TVU CL ≥25 mm by 24 weeks and deliver at term without intervention (Figure 1).

When evaluating interventions aimed at stopping the continuum that is detected early with TVU CL and eventually ends in PTB, it is important to evaluate populations separately as the test has different predictive accuracy in pregnant women with differing risk factors. A meta-analysis of randomised trials has shown that cerclage may be efficacious in preventing PTB in women with both a prior PTB and a short CL <25 mm before 24 weeks.24 These women may be those in whom the cervix is truly ‘insufficient’.

A recent large randomised trial has shown that progesterone may prevent PTB in 1.6% of pregnant women in the whole population (mostly nulliparous women with singleton gestations) who are found to have a short CL ≤15 mm at 20–25 weeks. It could be postulated that in this study cervical insufficiency and inflammatory processes are stopped in certain cases.

Lastly, in women with symptoms of preterm labour, knowledge of TVU CL (and FFN) has been associated with prevention of PTB in a randomised trial,32 so that this screening test holds potential for benefiting women and their babies also in this population.

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References