Cervical Length and Preterm Birth

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Preterm birth is considered one of the main etiologies of neonatal death, as well as short- and long-term disability worldwide.

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1. Introduction

Preterm birth (PTB), defined as delivery that occurs between 20 and 37 weeks of gestation, is a major obstetric and global health concern with a rate of 5–18% of pregnancies worldwide[1]. It is the largest direct cause of neonatal mortality and may be associated with serious morbidity in the surviving infants[2]. PTB is the final common element for the involvement of a variety of factors. All mechanisms for PTB alignment with the final unifying process of cervical remodeling[3]. According to this rationale, a cervical assessment may potentially detect preliminary pathological changes prior to the onset of overt symptoms and signs of PTB. This may be beneficial for preventive measures of PTB.

2. The Preterm Parturition Syndrome

In 2006, Romero et al. described the preterm parturition syndrome, as a heterogeneous condition with preterm labor as the final common endpoint[3]. They proposed that spontaneous PTB (sPTB) results from mixed pathological activation of one or more of the signals that subsequently initiate spontaneous preterm labor. The pathological processes involved in preterm parturition syndrome fall into the broad categories of anatomical, physiological, biochemical, endocrinological, immunological, and clinical events that occur in the mother and/or fetus[4]. Although cervical insufficiency can result in cervical shortening and sPTB, this multifactorial model implies that shortening of the cervix may often be simply an early sign that accompanies some of the other abnormal processes which lead to a PTB.

3. The Role of Cervical Length in Predicting sPTB

One of the early changes that precede sPTB is cervical shortening, which may be detected even several weeks prior to the onset of active labor[5]. Currently, mid-trimester cervical length (CL) assessment by transvaginal ultrasound (TVUS) is one of the most commonly used tools for the prediction sPTB[6][7]. Regardless of obstetrical history, the risk of sPTB is inversely proportional to cervical length[8], while women with both a history of a PTB and a short cervix being at the highest risk[9]. However, as research addressing this topic is heterogenic with regards to the population that was studied[7] (e.g., women with prior preterm birth, women with prior cervical surgery, multiple gestations) and the clinical scenarios in which CL was used for predicting PTB (e.g., various gestational age at testing, symptomatic vs. asymptomatic women), it is important to address those aspects to optimize the use of this important tool.

4. The Preferred Approach of Cervical Length Measurement

There are three common methods for sonographic cervical assessment: TVUS, transabdominal (TAUS), and transperineal (TPUS, also called translabial). CL measured by TVUS is associated with better prediction of a PTB than other approaches, and it is, therefore considered the gold standard[10][11][12] for CL measurement. In contrast to the transabdominal method, transvaginal cervical ultrasonography is less influenced by maternal obesity, cervix position, and shadowing from the fetal presenting part [13][14].

Previous studies reported that the sensitivity of TAUS to identify a TVUS-confirmed short cervix (i.e., <25 mm) ranges from 44.7% (using a TAUS cutoff of 25 mm) to 96.1% (using a TAUS cutoff of 36 mm)[15][16]. It is also worth noting that all randomized trials suggesting the effectiveness of treatment of women with a short cervix have been used by TVUS to assess cervical length [17][18][19].

4.1. What Cervical Length Threshold Should Be Used for Prediction of sPTL?

The predictive accuracy of a short CL for predicting sPTB is primarily related to the cutoff used. The reported sensitivity of a CL ≤ 25 mm for a PTB among high and low risk women varies from 6% to 76%[20]. One of the hallmark studies addressing the association of CL and the risk of PTB was conducted by Iams et al.[5]. This was a multicenter prospective study of 2915 women with a singleton pregnancy who underwent vaginal ultrasonography at approximately 24 and again at 28 weeks of gestation. Both women with and without a history of PTB were included. The association between cervical length and the risk of spontaneous PTB has been assessed. The main results of this study were: (1) At 24 weeks' gestation, only 10% of women had CL < 26 mm; (2) The risk of PTB was inversely related to CL; (3) a CL < 26 mm at 24 weeks had a better predictive value compared to CL < 26 mm at 28 weeks (RR 6.1 vs. 5.3) for predicting PTB < 35 weeks. However, the positive predictive value (PPV) of a short CL, was low in this unselected population: Only 18% of women with a CL < 25 mm at 22–25 weeks of gestation delivered prior to 35 weeks of gestation[5].

In a different cohort of unselected women at 22–24 weeks of gestation, only 1.7% had a CL < 15 mm, but they accounted for 86% of all PTBs at <28 weeks of gestation and 58% of PTBs prior to 32 weeks of gestation[21]. It was suggested that the specificity was 99.9% for PTBs at <34 weeks of gestation for a CL cutoff of 20 mm. However, this value decreased to 90.1% and 65.5% for a CL threshold of 30 mm and 35 mm, respectively[22]. Salomon et al.[23] modeled cervical length in normal pregnancies and offered new reference values for cervical length based on a large sample. These centiles can be used to make a decision on the policy of treatments to reduce the morbidity and mortality of PTB. Currently, most major guidelines suggest using a mid-trimester CL threshold of 25 mm for risk assessment[24][25] (Table 1).

Table 1. Summary of major guidelines regarding the different aspects of CL screening and technique.

Organization	Recommendation	Grade
Society for fetal maternal medicine (SMFM)[25]	**Routine transvaginal CL screening for women with a singleton pregnancy and history of prior spontaneous PTB at 16–24 weeks' gestation.**	**A**
	Routine transvaginal CL screening to not be performed for women with cervical cerclage, multiple gestations, PPROM, or placenta previa.	**B**
	Routine CL screening in multiple pregnancies is not currently recommended.	**B**
American College of Obstetricians and Gynecologists (ACOG)[24]	**Routine transvaginal CL screening for women with a singleton pregnancy and history of prior spontaneous PTB starting 16–24 weeks' gestation.**	**A**
	Although the ACOG does not mandate universal cervical length screening in women without a prior preterm birth, this screening strategy may be considered.	**B**
International Society of Ultrasound in Obstetrics and Gynecology (ISOUG)	**For twin pregnancies, cervical length measurement is the preferred method of screening for preterm birth in twins; 25 mm is the cutoff most commonly used in the second-trimester [26].**	**A**
	Currently, there is insufficient evidence to recommend routine cervical length measurements at the mid-trimester in an unselected population[27].	**B**
Society of Obstetricians and Gynecologists of Canada (SOGC)[28][29]	**Transvaginal ultrasonography is the preferred route for cervical assessment to identify women at increased risk of spontaneous preterm birth and may be offered to women at increased risk of preterm birth.**	**B**
	Because of poor positive predictive values and sensitivities and lack of proven effective interventions, routine transvaginal cervical length assessment is not recommended in women at low risk.	**B**
	There is no consensus on the optimal timing or frequency of serial evaluations of cervical length. If repeat measurements are performed, they should be done at suitable intervals to minimize the likelihood of observation error.	**B**
	There are insufficient data to recommend a routine preterm labor surveillance protocol in terms of frequency, timing, and optimal cervical length thresholds for twins' pregnancies.	**B**

CL—cervical length, PTB—preterm birth, PPROM—premature pre-labor rupture of membranes. Grade A—strong recommendation, high-quality evidence. Grade B—weak recommendation, moderate-quality evidence.

4.2. A Single vs. Repeated Measurements

Several studies have reported that the progressive shortening of transvaginal sonographic CL over time is associated with an increased risk of preterm birth[23][30][31][32], whereas others have not been able to demonstrate such an association[33]. In the study of Iams et al.[5], the change in CL between 24- and 28-weeks' gestation was significantly associated with the risk of sPTB independently of the initial CL value. For women with cervix reduced in length throughout 24 and 28 weeks, the PTB rate was 4.2% compared to 2.1% of those whose cervix was relatively constant in length. The severity of the decline even had an impact on the likelihood of PTB; the relative risk was 2.80 (CI 1.87–4.20) for women whose cervixes had decreased by 6 mm or more compared to those whose cervixes had changed by less than 6 mm.

In an observational study of CL surveillance in 183 women with a history of one or more sPTBs[34], the predictive value of short cervix was examined in the early second trimester (16–19 weeks) and whether serial measurements had enhanced identification and prediction of sPTB for up to 24 weeks. The women who experienced an sPTB < 35 weeks shortened their cervixes at a median rate of 2.5 mm per week compared with a rate of 1.0 mm per week in the 130 women who did not (p = 0.03). The rate of change in CL (in terms of cervical slope) throughout the surveillance period was also shown to be an independent risk factor for sPTB, with women who had delivered prematurely showing a more rapid rate of cervical shortening. A steeper cervical slope was associate with the risk of sPTB even after controlling for a short CL at baseline.

In contrast, a recent systematic review[35] demonstrated that CL changes through time have been shown to have low prediction performance for PTB at <35 and <37 weeks of gestation in women with singleton gestation and weak to intermediate prediction performance for sPTB at <34, <32, <30 and <28 weeks of gestation in women with twin pregnancy. The authors concluded that changes in CL as a function of time cannot currently be considered a clinically useful test to predict an sPTB in women with singleton or twin gestations. They also considered that a single CL measurement taken at 18–24 weeks of pregnancy appears to be a better and more accurate test for predicting sPTB than changes in CL over time, and that it seems to be more cost-effective than serial CL measurements.

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