

# Screening for Preterm Labor

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## INTRODUCTION

Preterm delivery is one of the main causes of perinatal mortality and morbidity and it accounts for 60 to 80% of deaths of infants without congenital anomalies.<sup>1</sup> Moreover, preterm neonates are at high risk of developing cerebral palsy, visual and hearing impairment and chronic lung disease, while 40 to 60% of them will need special educational support. The preterm delivery rate varies between 5 to 7% in Europe and 11 to 12% in the United States. Despite the advances in obstetric care and neonatology the rate of preterm delivery was not decreased but in fact increased.<sup>2</sup> This is mainly attributed to the increased number of preterm births among multiple gestations, the trend towards iatrogenic premature delivery in conditions such as hypertension or intrauterine growth restriction as well as the more accurate estimation and registration of gestational age. Neonatal survival improves as gestational age progresses. It increases from approximately 50% at 25 weeks' gestation to over 97% at 33 weeks' gestation.<sup>2</sup> It is therefore, logical as the major benefits from delaying delivery are seen in this period, that greater attention has been focused on early preterm labor, before 32 weeks.

Extensive research has been made so far, in methods of predicting preterm delivery in both asymptomatic and symptomatic patients. The absence of reliable criteria for the selection of at risk patients, as well as the absence of effective interventions to prevent prematurity are responsible for the controversial results reported in different studies. During the last few years a clear relationship has been established between decreased cervical length and the risk of spontaneous preterm delivery. Many studies dealing with the ultrasonographic evaluation of the cervix during the course of pregnancy have suggested that cervical changes may detect or exclude the risk of preterm delivery. Unfortunately, the heterogeneity of most of them resulted in mixed performance of this procedure as a screening test. Ultrasound examination of the cervix has been applied mainly in five categories:

1. Women with symptoms of preterm labor
2. Asymptomatic women at high risk of preterm delivery
3. Asymptomatic women at low risk of preterm delivery
4. Women with multiple gestations

5. Pregnancies complicated by preterm premature rupture of membranes (PPROM).

## TECHNIQUE FOR CERVICAL ASSESSMENT BY ULTRASOUND

The cervix can be assessed by transabdominal, transvaginal or transperineal ultrasonography. The main disadvantage of the transabdominal route is the need for a full bladder. Unfortunately this artificially lengthens the cervix. Moreover it was found that the success of the cervical visualization transabdominally depends on the cervical length. In a study by To et al,<sup>3</sup> it was found that transabdominal ultrasound evaluation of the cervix increased from 13 to 51% as the length of the cervix increased from 20 to 40 mm.

When transvaginal sonography is used the bladder is empty and the woman is placed in the dorsal lithotomy position. Then the probe is inserted in the anterior vaginal fornix and a sagittal view of the cervix is obtained. It is important not to exert undue pressure on the cervix, thus avoiding false elongation of its length. The picture should be magnified to at least 75% of the screen. When a clear image of the cervix is obtained and the endocervical mucosa is visualized along the cervical canal, the calipers are placed at the internal and the external os. Any funneling, as well as its shape is recorded. Given the substantial intra- and inter-observer variations that occur with digital examinations, it has been proved that transvaginal ultrasonography is a reproducible method of examination.<sup>3,4</sup> A curved cervix can be measured either following the curvature, or as a straight line between the inner and outer cervical os. In a study by To et al,<sup>5</sup> it was shown that at 23 weeks' gestation the prevalence of curvature was higher when the cervical length was longer, while it was not found in cases of short cervixes (< 15 mm). They concluded that cervical curvature has no implications in the screening test when such a cut-off is used.

Transperineal approach is an alternative method of cervical sonographic evaluation. In a study by Owen et al,<sup>6</sup> comparing transvaginal and transperineal sonography a poor correlation between the two methods was seen. In another study Carr et al,<sup>7</sup> managed to measure the cervical length in all cases and in 95% of cases with transvaginal and translabial sonographic

evaluation respectively. More recently Cicero et al,<sup>8</sup> showed that in the vast majority of cases cervical assessment can be performed by the transperineal approach. This method could be the method of choice in patients objecting to transvaginal sonography, or in those with preterm rupture of membranes, where transvaginal ultrasound should be better avoided for fear of infection.

Several other cervical characteristics such as the presence of funneling and the cervical index [(funnel length + 1)/cervical length] can be determined by ultrasound. The shape (Y- or U-shaped), the width, the length, and the percentage of funneling have also been evaluated. Berghella et al,<sup>9</sup> suggested that funneling was an independent predictor of preterm delivery. Guzman et al,<sup>10</sup> compared various sonographic cervical parameters and failed to show any advantage of funnel width, funnel length, percentage of funneling or cervical index calculation over a cervical length measurement of less than 25 mm for the prediction of preterm birth. It seems that a short cervix and funneling usually co-exist. Therefore, a single measurement of the cervix is enough, because funneling is not an independent variable for the prediction of preterm birth in most of cases.<sup>11</sup> Several studies proposed transfundal or suprapubic pressure in order to detect cervical shortening. They suggested that this was the earliest sign of cervical incompetence and therefore identification of high-risk cases.<sup>10,12,13</sup> Maternal postural challenge and straining have also been performed by a few groups,<sup>14,15</sup> in order to examine the cervix more reliably, but these tests have a poor reproducibility.

Recently, three-dimensional transvaginal sonography has been proposed for the evaluation of cervical morphology. Bega et al,<sup>16</sup> showed that three-dimensional ultrasound gave more accurate estimation of the cervical length compared to two-dimensional ultrasound. In a study on multiple gestations Strauss et al,<sup>17</sup> failed to show any additional benefit from the use of three-dimensional versus conventional ultrasound for the measurement of the cervical length. Similar findings were observed in a study by Hoesli et al,<sup>18</sup> who compared three-dimensional to two-dimensional ultrasound for the measurement of the cervical volume.

### **TRANSVAGINAL SONOGRAPHY IN WOMEN WITH SYMPTOMS OF PRETERM LABOR**

Several methods for predicting preterm delivery in symptomatic patients have emerged during the last decade. Among them the most frequently used are the evaluation of uterine contractions by uterine activity monitoring and digital examination of the cervix. However, neither the frequency nor the intensity of uterine contractions can distinguish true from false preterm labor.<sup>19,20</sup> It is also difficult to examine the part of the cervix, which is above the vaginal fornices, by digital examination. On

the other hand, transvaginal ultrasonography has the potential to provide objective and repeatable measurements of cervical length.

Murakawa et al,<sup>21</sup> examined by transvaginal sonography 32 women with threatened preterm labor and found that the risk of preterm delivery was high when the cervical length was less than 30 mm. Moreover all women with a cervical length of less than 20 mm delivered preterm. Two other studies compared the diagnostic performance of cervicovaginal fetal fibronectin (fFN) and transvaginal sonographic evaluation of the uterine cervix in symptomatic patients. They reported that the combined use of the cervical ultrasonography and fFN testing improves the diagnostic efficiency of any of these methods alone.<sup>22,23</sup> More recently, Rozenberg et al,<sup>24</sup> in a similar study of 76 symptomatic patients, failed to show any significant additional benefit from the performance of fFN testing over the single transvaginal ultrasonographic measurement of cervical length. Crane et al,<sup>25</sup> evaluated singleton and twin pregnancies with preterm contractions and found that transvaginal sonographic measurement of the cervix was a good predictor of preterm delivery and it had a better predictive value in singletons than in twins. Tsoi et al,<sup>26</sup> examined 216 symptomatic women with singleton pregnancies and observed that a cervical length measured by transvaginal ultrasound of less than 15 mm could distinguish those at risk of delivery within seven days. Tekesin et al,<sup>27</sup> evaluated 68 patients with threatened preterm labor and observed that the risk of preterm delivery increased in patients with a cervical length of less than 25 mm. They also found that a quantitative ultrasound tissue characterization of the cervix was the best predictor of preterm delivery.

We prospectively evaluated 172 women with singleton pregnancies and symptoms of preterm labor. Gestational age ranged between 24 and 34 weeks. All women underwent cervical assessment with transvaginal ultrasonography and were given intravenous tocolytics. The only parameter evaluated was cervical length. Using a cut-off for the cervical length of 20 mm the method had a sensitivity of 56%, a positive predictive value of 90% and a specificity of 96%. Moreover, It had an excellent negative predictive value of 79%, meaning that it can identify a group of women who are at low risk for preterm delivery, allowing a reduction in the number of tocolytic treatments.

Other investigators suggested that funneling may be a predictor of preterm delivery in symptomatic patients.<sup>28,29</sup> In contrast, Crane et al,<sup>25</sup> and Hincz et al,<sup>23</sup> reported that funneling was not an independent predictor of preterm delivery in symptomatic women. Hincz et al,<sup>23</sup> also observed that there was a higher incidence of funneling with the advance of gestational age, a finding which was first seen by Iams et al,<sup>30</sup> who reported that funneling is probably normal after 32 weeks of gestation. Moreover, Berghella et al,<sup>31</sup> found that although

funneling was a good predictor of preterm delivery in the second trimester, it was of limited value in symptomatic patients after 32 weeks.

Transvaginal ultrasound can be used as a screening test for preterm delivery in symptomatic patients. It can be used easily by physicians with the equipment and experience and it can reliably diagnose patients who are in true preterm labor when they present with preterm contractions, reducing the false-positive results. Consequently different management protocols can be used for symptomatic patients, depending on cervical length. A more aggressive tocolytic treatment in combination with fetal lung maturation should be considered for those with a short cervix. In contrast, patients with a long cervix should be managed in an outpatient basis, avoiding prolonged hospitalization and potentially dangerous tocolytic treatments.

### SONOGRAPHY OF THE CERVIX IN HIGH-RISK ASYMPTOMATIC WOMEN

The high-risk population for preterm delivery includes women with a previous history of preterm delivery or rupture of the membranes, repeated mid-trimester pregnancy losses, cervical surgery, congenital uterine anomalies, or diethylstilbestrol exposure. Many studies have reported on cervical sonography for the prediction of preterm delivery in this population. Berghella et al,<sup>32</sup> prospectively evaluated 96 high-risk women at between 14 and 30 weeks with both cervical ultrasonography and manual examination of the cervix. The relative risk of preterm delivery using a cervical length cut-off of 25 mm between 16 and 20 weeks was 4.8 (95% CI 2.1 to 11.1,  $p = 0.0004$ ). Moreover, cervical ultrasonography was a better predictor of preterm delivery, than manual examination of the cervix. Guzman et al,<sup>12</sup> examined high-risk women by serial transvaginal cervical ultrasonography with transfundal pressure. Examinations were performed until the cervical length decreased to < 10 mm. They concluded that the shortening of the cervical length, or the prolapse of the membranes into the cervix following transfundal pressure, has a significant predictive value for preterm delivery. In another study Guzman et al,<sup>33</sup> examined high risk women between 15 and 24 weeks and found that transfundal pressure was the most predictive method to detect cervical incompetence, compared to coughing and standing. Andrews et al,<sup>34</sup> studied 69 high-risk women between 16 and 30 weeks by serial transvaginal sonography. They noted that a cervical length below the 10th percentile or funneling of the internal os was associated with higher risk of preterm delivery within 2 to 4 weeks from the examination. Cook and Ellwood<sup>35</sup> examined prospectively 120 high-risk women by transvaginal ultrasound and reported that endocervical canal length less than 21 mm before 21 weeks was associated with delivery < 34 weeks in 95% of them. Additionally, if the canal length was < 33 weeks 95% of the women delivered < 37 weeks. Owen et al,<sup>6</sup>

performed cervical sonography between 16 and 19 weeks on 183 high-risk women and they found that a cervical length of less than 25 mm was associated with a relative risk of preterm delivery before 32 weeks of 3.3 (95% CI 2.1 to 5.0; sensitivity = 19%, specificity = 98%, positive predictive value = 75%). They also observed that serial cervical measurements up to 24 weeks significantly improved the prediction of spontaneous preterm birth ( $p = 0.03$ ). Using the shortest ever measured cervical length on serial evaluations, after any dynamic shortening, the relative risk of a cervical length of less than 25 mm for preterm birth increased to 4.5 (95% CI 2.7 to 7.6). Guzman et al,<sup>10</sup> compared various sonographic parameters to predict preterm birth on 469 high-risk gestations which were prospectively evaluated between 15 and 24 weeks. They examined funnel width and length, percent of funneling, cervical length and cervical index and they concluded that a cervical length of < 25 mm was equal to the other cervical parameters as a predictor of preterm delivery. The sensitivities for delivery at < 28, < 30, < 32 and < 34 weeks were 94%, 91%, 83% and 76%, with negative predictive values of 99%, 99%, 98% and 96%, respectively. They also observed that the rate of preterm delivery at < 34 weeks increased dramatically when the cervical length was < 15 mm and that the placement of a cerclage did not influence the positive and negative predictive values. Vendittelli et al,<sup>36</sup> in a prospective study on 200 high-risk women reported that a cervical length of less than 30 mm had a relative risk of preterm delivery of 2.79 (95% CI 1.7 to 4.59). The presence of funneling of > 5 mm gave a relative risk of 1.39 (95% CI 0.99 to 1.95). Obido et al,<sup>37</sup> showed that a cervical funneling of more than 75% or a cervical shortening of less than 10 mm were predictive of preterm premature rupture of membranes. In a similar study Guzman et al,<sup>38</sup> showed that a progressive cervical shortening of < 20 mm before 24 weeks suggested cervical incompetence. Incompetent cervixes had significantly greater cervical shortening compared to competent ones ( $p < 0.001$ ). MacDonald et al,<sup>13</sup> prospectively evaluated 106 high-risk women and found that the opening of the cervical os at rest or in response to transfundal pressure was the earliest ultrasound feature of cervical incompetence. Recently, Berghella et al,<sup>39</sup> performed transvaginal cervical sonography in 183 high-risk women between 10 and 14 weeks and concluded that this period was not appropriate for screening for preterm delivery, as in most cases cervical changes develop after this gestational age.

### SONOGRAPHY OF THE CERVIX IN LOW-RISK POPULATION

In comparison to women at high-risk of preterm delivery, pregnant women without risk factors have a low prevalence of preterm birth of about 4 to 8%. However, more than half of the preterm births occur in these low-risk women. It is therefore of great importance to examine the potential of cervical screening

in this population. In 1990 Andersen et al,<sup>40</sup> evaluated 178 women with singleton gestations and observed that the majority of preterm deliveries occurred in women with endovaginal ultrasonographic measurements below the median. In a similar study Tongsong et al,<sup>41</sup> reported that a cervical length of less than 35 mm between 28 and 30 weeks had a sensitivity for delivery before 37 weeks of 65.9% and a specificity of 62.4%. Iams et al,<sup>42</sup> performed vaginal ultrasonography in 2915 low-risk women at 24 to 28 weeks. They reported that the relative risk of preterm delivery increased as the length of the cervix decreased. For cervical lengths below the 50th percentile at 24 weeks the relative risk was 2.35, while at 28 weeks it was 3.52 ( $p < 0.001$ ). Heath et al,<sup>43</sup> performed ultrasonographic cervical measurements in more than 2,500 singleton low-risk pregnancies and examined the relation between cervical length and the risk of preterm delivery at  $< 32$  weeks. They found that approximately 2% of their population had a cervical length of less than 15 mm and that this group contained about 90% and 60% of the women delivering at  $> 28$  and  $> 32$  weeks, respectively. Taipale et al,<sup>44</sup> performed transabdominal and transvaginal ultrasonographic measurements of the cervix at 18 to 22 weeks in 3,694 singleton pregnancies. When the cervical length was  $< 29$  mm the relative risk for preterm delivery before 35 weeks was 8, while when the dilatation of the internal os was 5 mm, the relative risk was 28. Hassan et al,<sup>45</sup> in a retrospective cohort study, examined cervical length with transabdominal ultrasonography followed by transvaginal ultrasonography if cervical length was  $< 30$  mm. They reported that the odds ratios for delivery before 32 weeks for cervical lengths  $< 10$ ,  $< 15$ ,  $< 20$ ,  $< 25$ ,  $< 30$  mm were, respectively, 29.3, 24.3, 18.3, 13.4, and 3.2. A cervical length of  $< 15$  mm had, for preterm delivery  $< 32$  weeks, a positive predictive value of 47.65 and a negative predictive value of 96.7%, a sensitivity of 8.2%, and a specificity of 99.7%. To et al,<sup>46</sup> measured cervical length prospectively in 6,819 singleton pregnancies at 22 to 24 weeks and looked for the presence of funneling. Funneling was present in about 4% of pregnancies and its presence was strongly related to a short cervical length. A cervical length  $< 15$  mm was found in 1.6% of women. The odds ratios for preterm delivery were for a short cervix 24.9 and for funneling 1.8. They concluded that funneling did not provide a significant additional contribution to cervical length in prediction of delivery before 33 weeks. Hibbard et al,<sup>47</sup> in a prospective study of 760 women, looked at cervical length measurements at 16-23 weeks and the mean cervical length was 38.5 mm. The relative risks for delivery before 35 weeks were 4.5, 7.5 and 7.8 for the 10th, 5th, and 2.5th percentiles, respectively. Recently, Conoscenti et al,<sup>48</sup> examined the value of cervical length measurement at 13 to 15 weeks' gestation in an unselected population and found that this is not a reliable screening procedure for spontaneous preterm delivery before 37 weeks. Carvalho et al,<sup>49</sup> compared cervical length measurements

obtained at 11 to 14 weeks to those obtained at 22 to 24 weeks and correlated the measurements with time of delivery. They found that there was a spontaneous shortening of the cervix from the first to the second trimester of pregnancy, which was more rapid in those women who delivered prematurely and those who had a history of previous preterm delivery. We also evaluated 1,197 singleton low-risk pregnancies at 23 weeks, with transvaginal sonographic cervical assessment. The preterm delivery rate before 37 weeks in our population was 8.7%, confirming that this was a low-risk population. The distribution of cervical length was normal and the mean cervical length was 38 mm (range: 2 to 70 mm). Less than 20 mm length of the cervix had 17 women (1.4%). Women with a cervical length  $< 20$  mm had 3.31 times increased risk for prematurity (95% CI 10.14 to 1.08) ( $p = 0.03$ ). The presence of funneling gave a relative risk for preterm delivery of 2.07 (95% CI 0.94 to 4.54) ( $p = 0.07$ ).

### SONOGRAPHY OF THE CERVIX IN MULTIPLE PREGNANCIES

Multiple pregnancies are generally considered as high-risk for preterm delivery as the mean gestational age at birth is 35 weeks for twins and 33 weeks for triplets. Although the numbers of published trials in multiples are significantly fewer compared to singletons, sonographic assessment of the cervix appears to be of value in this population. Goldenberg et al,<sup>50</sup> prospectively screened 147 twin pregnancies at 24 and 28 weeks for more than 50 potential risk factors for spontaneous preterm birth. They found that at 24 weeks a cervical length  $< 25$  mm was consistently associated with preterm birth. The odds ratios for preterm birth at  $< 32$  weeks,  $< 35$  weeks and  $< 37$  weeks were 6.9, 3.2, and 2.8. At 28 weeks the same cut-off for the cervical length was not a strong predictor of spontaneous preterm birth. Imseis et al,<sup>51</sup> showed that a transvaginal ultrasonographic measurement of the cervix of  $> 35$  mm at 24 to 26 weeks in twin pregnancies can identify women who are at low-risk for delivery before 34 weeks' gestation. The sensitivity, specificity, positive and negative predictive values of a cervical length  $> 35$  mm for predicting delivery  $> 34$  weeks were 49%, 94%, 97%, and 31%, respectively. Guzman et al,<sup>52</sup> studied 131 twin pregnancies on 524 occasions between 15 and 28 weeks with transvaginal cervical ultrasonography and transfundal pressure. They measured funnel width and length, cervical length, percentage of funneling and the cervical index. They concluded that a cervical length of  $< 20$  mm between 15 and 28 weeks was at least as good as other ultrasonographic cervical parameters at predicting spontaneous preterm birth. Yang et al,<sup>53</sup> studied 65 twin pregnancies prospectively with transvaginal or translabial ultrasound of the cervix at 18 to 26 weeks. They suggested that both cervical length  $< 30$  mm and cervical funneling were independently and strongly associated with high risk for preterm delivery. Conversely, a cervical length  $> 35$  mm

was associated with very low-risk (4%) for preterm birth. Skentou et al,<sup>54</sup> examined 464 twin pregnancies with transvaginal sonography of the cervix and in about 8% of them found a cervical length of < 20 mm. This group of women contained about 40% of those who delivered spontaneously before 33 weeks. The usefulness of cervical length measurement before 30 weeks confirmed in a retrospective review study Shapiro et al.<sup>55</sup> Similar results reported Iams et al,<sup>56</sup> who compared maternal serum relaxin, cervical length and preterm birth in twins. They also found no correlation between relaxin and cervical length, thus suggesting that relaxin does not contribute to the higher risk for preterm birth in twin gestations. Different conclusions reported Ong et al,<sup>57</sup> who found that cervical measurements were not predictive of preterm delivery in twins. Only a cervical length of less than 20 mm was predictive of delivery within one week. Soriano et al,<sup>58</sup> examined prospectively 54 twin pregnancies conceived after infertility treatment, with transvaginal ultrasonographic assessment of the cervix. They reported that a cervical length >35 mm at 18 to 24 weeks identified pregnancies at low risk for delivery before 34 weeks. In a prospective study on 251 twin gestations, Vayssiere et al,<sup>59</sup> performed transvaginal ultrasound assessment of the cervix. They observed that cervical length and funneling both predicted the very preterm birth. For spontaneous delivery before 32 and 35 weeks the sensitivity of cervical length < 25 mm was 100% and 54%, respectively and the specificity was 84% and 87%, respectively. The sensitivity of funneling was 86% and 54%, and the specificity 78% and 82%, respectively.

Ultrasonographic cervical screening has been shown to be also useful in triplet pregnancies. Ramin et al,<sup>60</sup> performed transperineal ultrasonographic measurements of the cervix in 32 triplet pregnancies between 10 and 32 weeks and found that a short cervix and funneling could predict preterm delivery. To et al,<sup>61</sup> measured cervical length by transvaginal ultrasound at 23 weeks in 43 triplet pregnancies. The rate of preterm delivery increased with decreasing cervical length at 23 weeks from 8% at 36 to 48 mm, to 11% at 26 to 35 mm, 33% at 16 to 25 mm and 67% at 15 mm or less. Guzman et al,<sup>62</sup> evaluated 51 triplet pregnancies between 15 and 28 weeks with transvaginal cervical sonography and transfundal pressure. The cervical parameters evaluated were funnel width and length, cervical length, percentage of funneling and cervical index. They concluded that cervical lengths of < 25 mm between 15 and 24 weeks and < 20 mm between 25 and 28 weeks were at least as good as other sonographic cervical parameters for the prediction of spontaneous preterm birth. In 45 triplet pregnancies examined prospectively with transvaginal cervical assessment, Maymon et al,<sup>63</sup> found that a cervical length < 25 mm was the best predictor for delivery before 33 weeks' gestation.

## SONOGRAPHY OF THE CERVIX IN PRETERM PREMATURE RUPTURE OF MEMBRANES

One of the main causes of preterm delivery is preterm premature rupture of membranes (PPROM). Ultrasonographic cervical assessment has been used in this group of patients. Carlan et al,<sup>64</sup> studied the use of transvaginal sonography in PPRM and found no relationship between a cervical length cut-off of 30 mm and latency period. Moreover, endovaginal ultrasound in these patients did not appear to increase the incidence of maternal infection. In a similar study Rizzo et al,<sup>65</sup> examined the value of ultrasonographic assessment of the cervix for the prediction of the interval from admission to delivery in women with PPRM between 24 and 32 weeks. They found that a cervical length of less than 20 mm and/or funneling, or a cervical index of more than 0.5 were associated with a short time interval from admission to delivery. Recently, Gire et al,<sup>66</sup> evaluated the usefulness of transvaginal ultrasound in the determination of the risk of preterm delivery and chorioamnionitis in 101 singleton pregnancies affected by PPRM. They found that a cervical length of less than 20 mm at admission was associated with a significant risk of early delivery. Moreover, no relation was found between cervical length and chorioamnionitis or neonatal sepsis.

## INTERVENTIONS BASED ON ULTRASONOGRAPHIC FINDINGS

It is obvious that ultrasonographic cervical assessment is extremely useful as a screening method for preterm delivery. However, the usefulness of a screening test depends on our ability to intervene, so that to change the final result.

The placement of a cervical cerclage has been a popular intervention over the years. Guzman et al,<sup>67</sup> examined 31 high-risk women with transvaginal ultrasound and transfundal pressure. In 14 cases there was dilatation of the internal os or protruding membranes. Thirteen of them were treated by cerclage. Of the cerclage cases 9 delivered at term, 3 delivered preterm and 2 miscarried. The patient who did not undergo cerclage also miscarried. Heath et al,<sup>68</sup> used transvaginal ultrasound to measure cervical length at 23 weeks in 2702 women with singleton pregnancies. In 43 cases the cervical length was < 15 mm. In 21 cases the pregnancy was managed expectantly and in 22 a Shirodkar suture was inserted. The two groups did not differ in ethnic or obstetric characteristics. In the expectant management group the prevalence of preterm delivery before 32 weeks was 52%, whereas in the cerclage group it was only 5%. Berghella et al,<sup>69</sup> examined 168 high-risk women with transvaginal sonography between 14 and 24 weeks. The subgroup of women with either a cervical length of < 25 mm or funneling of >25% or both was offered McDonald

cerclage. No difference in the rate of preterm delivery was shown between the groups with and without cerclage. McDonald et al,<sup>13</sup> followed 106 high-risk women with serial transvaginal ultrasonographic measurements of the cervix. Eleven women who were initially found to have opening of the internal cervical os, progressed to a short cervix of less than 10 mm. Nine of them had cervical cerclage. Ten out of eleven had a live birth. Hibbard et al,<sup>70</sup> examined 85 patients with a cervical length < 30 mm. Of these 43 had cerclage and 42 had bed rest, tocolytics, or no treatment. The mean gestational age at delivery and birthweight were the same in both groups. Hassan et al,<sup>71</sup> in a retrospective study looked at 70 patients with a short cervix detected by ultrasound, of whom 25 underwent cerclage. No reduction in the rate of spontaneous preterm delivery was observed in the cerclage group. An increase in cervical length following cerclage placement was observed by O'Connell and Lindow,<sup>72</sup> in 14 patients with a history of preterm delivery. The same finding was also observed by Dijkstra et al,<sup>73</sup> who looked at 80 women with a prophylactic (n = 50), or urgent cerclage (n = 30). All had transvaginal ultrasonographic evaluation before and after cerclage. However, this increase in cervical length after cerclage was not predictive of term delivery. Novy et al,<sup>74</sup> reported on a historical cohort of patients presenting between 18 and 27 weeks with early cervical changes or with cervical effacement and dilatation. Patients were allocated to either cerclage or bed rest, while all received tocolytics, antibiotics and indomethacin. Cerclage was associated with improved perinatal outcome, but this finding could be attributed to the concurrent use of antibiotics and indomethacin. A prospective cohort study of 128 twin pregnancies who underwent transvaginal sonographic cervical length measurement, between 18 and 26 weeks was performed by Newman et al.<sup>75</sup> Cerclage was offered to women with cervical lengths < 25 mm. It was found that midtrimester cerclage did not alter the risks of prematurity associated with a shortened cervical length. Only two prospective randomized trials have been published so far. In the first of that Rust et al,<sup>76,77</sup> examined 113 patients between 16 and 24 weeks. All of them had cervical funneling >25% of the total cervical length, or a shortened distal cervix < 25 mm and were randomly assigned to McDonald cerclage or no cerclage. All women were treated identically before and after randomization. Before randomization they had amniocentesis, multiple urogenital cultures and therapy with indomethacin and clindamycin for 48 to 72 hours. Fifty-five patients were randomly assigned to the cerclage group and 58 were randomly assigned to the no cerclage group. Cerclage did not affect perinatal outcome. In another study Althuisius et al,<sup>78</sup> examined 35 patients with risk factors or symptoms of cervical incompetence. Such risk factors included previous preterm delivery before 34 weeks' gestation that met clinical criteria for the diagnosis of cervical incompetence, previous preterm premature rupture of membranes before 32 weeks,

history of cold knife conization, diethylstilbestrol exposure and uterine anomaly. When a cervical length of < 25 mm was found before 27 weeks, a randomization for cerclage and bed rest or bed rest alone was performed. Nineteen patients were randomly allocated to the cerclage group and 16 to the bed rest group. Preterm delivery before 34 weeks was significantly more frequent in the bed rest group compared to the cerclage group (7 of 16 vs none, respectively; p = 0.002). Although there was no difference in neonatal survival between the groups, the compound neonatal morbidity, defined as admission to the neonatal intensive care unit or neonatal death, was significantly higher in the bed rest group than in the cerclage group (8 of 16 vs 1 of 19, respectively; p = 0.005). In the most recent Cochrane systematic review regarding the use of a cerclage for preventing preterm delivery in women with previous second trimester pregnancy losses or other risk factors such as short cervix on digital or ultrasound examination, six trials with a total of 2175 women were analyzed. Prophylactic cerclage was compared with no cerclage in four trials. There was no overall reduction in pregnancy loss and preterm delivery rates, although a small reduction in births under 33 weeks' gestation was seen in the largest trial (relative risks 0.75, 95% confidence interval 0.58 to 0.98). Cervical cerclage was associated with mild pyrexia, increased use of tocolytic therapy and hospital admissions but no serious morbidity. Two trials examined the role of therapeutic cerclage when ultrasound examination revealed short cervix. Pooled results failed to show a reduction in total pregnancy loss, early pregnancy loss or preterm delivery before 28 and 34 weeks in women assigned to cervical cerclage. The authors concluded that the use of a cervical stitch should not be offered to women at low or medium risk of mid trimester loss, regardless of cervical length by ultrasound. The role of cervical cerclage for women who have short cervix on ultrasound remains uncertain as the numbers of randomized women are too few to draw firm conclusions.<sup>79</sup>

Almost 40 years ago the first attempt to use progesterone for the prevention of preterm birth was made<sup>80</sup>. Since then the results of individual trials and the meta-analyses of them, yielded contradictory results.<sup>81,82</sup> 17 alpha-hydroxyprogesterone caproate (17P) had the most encouraging results,<sup>81</sup> but little research on the subject was conducted for nearly a decade. Recently, interest in administration of progesterone in preventing preterm birth has been rekindled. In a randomized, double-blind, placebo-controlled study da Fonseca et al<sup>83</sup> included 142 high-risk singleton pregnancies. Progesterone (100 mg) or placebo was administered daily by vaginal suppository and all patients underwent uterine contraction monitoring with an external tocodynamometer once a week for 60 minutes, between 24 and 34 weeks of gestation. Progesterone (n = 72) and placebo (n = 70) groups were compared for epidemiologic characteristics, uterine contraction frequency, and incidence of preterm birth. The preterm birth rate was 21.1% (30/142).

Differences in uterine activity were found between the progesterone and placebo groups (23.6% vs 54.3%, respectively;  $P < .05$ ) and in preterm birth between progesterone and placebo (13.8% vs 28.5%, respectively;  $P < .05$ ). More women were delivered before 34 weeks in the placebo group (18.5%) than in the progesterone group (2.7%) ( $P < .05$ ). Meis et al<sup>84</sup> conducted a double-blind, placebo-controlled trial involving pregnant women with a documented history of spontaneous preterm delivery. Women were enrolled at 19 clinical centers at 16 to 20 weeks of gestation and randomly assigned by a central data center, in a 2:1 ratio, to receive either weekly injections of 250 mg of 17 alpha-hydroxyprogesterone caproate (17P) or weekly injections of an inert oil placebo; injections were continued until delivery or to 36 weeks of gestation. The primary outcome was preterm delivery before 37 weeks of gestation. Analysis was performed according to the intention-to-treat principle. Treatment with 17P significantly reduced the risk of delivery at less than 37 weeks of gestation (incidence, 36.3% in the progesterone group vs. 54.9% in the placebo group; relative risk, 0.66 [95% confidence interval, 0.54 to 0.81]), delivery at less than 35 weeks of gestation (incidence, 20.6% vs 30.7%; relative risk, 0.67 [95% confidence interval, 0.48 to 0.93]), and delivery at less than 32 weeks of gestation (11.4% vs 19.6%; relative risk, 0.58 [95% confidence interval, 0.37 to 0.91]). Infants of women treated with 17P had significantly lower rates of necrotizing enterocolitis, intraventricular hemorrhage, and need for supplemental oxygen. Petrini et al<sup>85</sup> using 2002 national birth certificate data, augmented by vital statistics from two US states, estimated the number of singleton births delivered to women eligible for 17P through both a history of spontaneous preterm birth and prenatal care onset within the first 4 months of pregnancy. The number and rate of recurrent spontaneous preterm births were estimated. To predict effect, the reported 33%<sup>84</sup> reduction in spontaneous preterm birth attributed to 17P therapy was applied to these estimates. In 2002, approximately 30,000 recurrent preterm births occurred to women eligible for 17P, having had a recurrent preterm birth rate of 22.5%. If 17P therapy were delivered to these women, nearly 10,000 spontaneous preterm births would have been prevented, thereby reducing the overall United States preterm birth rate by approximately 2%, from 12.1% to 11.8% ( $P < .001$ ), with higher reductions in targeted groups of eligible pregnant women. In the most recent Cochrane systematic review,<sup>86</sup> for all women administered progesterone, there was a reduction in the risk of preterm birth less than 37 weeks (six studies, 988 participants, relative risk (RR) 0.65, 95% confidence interval (CI) 0.54 to 0.79) and preterm birth less than 34 weeks (one study, 142 participants, RR 0.15, 95% CI 0.04 to 0.64). Infants born to mothers administered progesterone were less likely to have birthweight less than 2500 grams (four studies, 763 infants, RR 0.63, 95% CI 0.49 to 0.81) or intraventricular hemorrhage (one study, 458 infants, RR 0.25,

95% CI 0.08 to 0.82). There was no difference in perinatal death between women administered progesterone and those administered placebo (five studies, 921 participants, RR 0.66, 95% CI 0.37 to 1.19). There were no other differences reported for maternal or neonatal outcomes. The authors concluded that intramuscular progesterone is associated with a reduction in the risk of preterm birth less than 37 weeks' gestation, and infant birthweight less than 2500 grams. However, other important maternal and infant outcomes have been poorly reported to date, with most outcomes reported from a single trial only (Meis 2003). It is unclear if the prolongation of gestation translates into improved maternal and longer term infant health outcomes. Similarly, information regarding the potential harms of progesterone therapy to prevent preterm birth is limited. Further information is required about the use of vaginal progesterone in the prevention of preterm birth.

New trials have since been reported<sup>87-89</sup> and more are in progress.<sup>90</sup> In a prospective randomized double-blind placebo-controlled study by da Fonseca et al,<sup>87</sup> cervical length was measured by transvaginal ultrasonography at a median of 22 weeks of gestation (range, 20 to 25) in 24,620 pregnant women seen for routine prenatal care (Figs 1 and 2). Cervical length was 15 mm or less in 413 of the women (1.7%), and 250 (60.5%) of these 413 women were randomly assigned to receive vaginal progesterone (200 mg each night) or placebo from 24 to 34 weeks of gestation. The primary outcome was spontaneous delivery before 34 weeks. Spontaneous delivery before 34 weeks of gestation was less frequent in the progesterone group than in the placebo group (19.2% vs 34.4%; relative risk, 0.56; 95% confidence interval [CI], 0.36 to 0.86). Progesterone was associated with a nonsignificant reduction in neonatal morbidity (8.1% vs 13.8%; relative risk, 0.59; 95% CI, 0.26 to 1.25;  $P = 0.17$ ). There were no serious adverse events associated with the use of progesterone. Preliminary data from a smaller unpublished prospective randomized double-blind placebo-controlled study from our institution are in agreement with these findings. Cervical length was measured by transvaginal ultrasonography at a median of 22 weeks of gestation (range, 20 to 24) in 1100 pregnant women seen for routine prenatal care. Cervical length was 15 mm or less in 17 of the women (1.5%), and 15 (88%) of these 17 women were randomly assigned to receive vaginal progesterone (200 mg each night) or placebo from 24 to 34 weeks of gestation. Spontaneous delivery before 34 weeks of gestation was less frequent in the progesterone group than in the placebo group, but this reduction did not reach statistical significance perhaps due to insufficient power of the study. O'Brien et al<sup>88</sup> in a randomized, double-blind, placebo-controlled, multinational trial enrolled and randomized 659 pregnant women with a history of spontaneous preterm birth. Between 18 + 0 and 22 + 6 weeks of gestation, patients were assigned randomly to once daily treatment with either progesterone vaginal gel or placebo until either delivery,

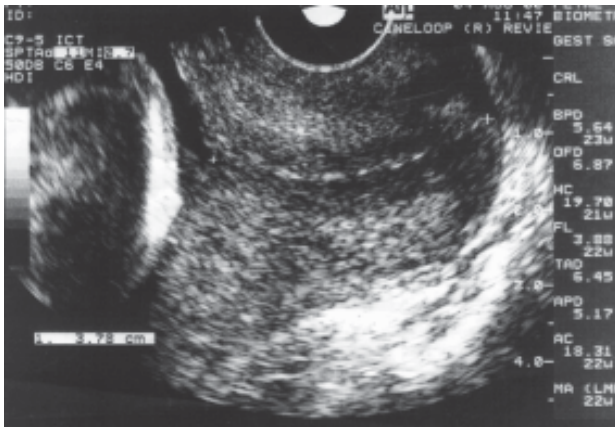


Fig. 1: Normal cervix in the second trimester (22 weeks)

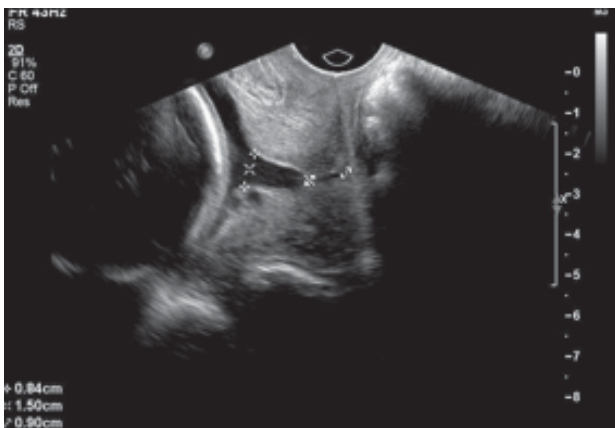


Fig. 2: Cervix with short length and funneling in the second trimester (22 weeks)

37 weeks' gestation or development of preterm rupture of membranes. The primary outcome was preterm birth at < 32 weeks of gestation. Progesterone did not decrease the frequency of preterm birth at < 32 weeks. There was no difference between the groups with respect to the mean gestational age at delivery, infant morbidity or mortality or other maternal or neonatal outcome measures. Adverse events during the course of treatment were similar for the two groups. In a secondary analysis of the same trial<sup>89</sup> women were randomized between 18 + 0 and 22 + 6 weeks of gestation to receive daily treatment with 90 mg of vaginal progesterone gel or placebo. Cervical length was measured with transvaginal ultrasound at enrollment and at 28 weeks of gestation. Treatment continued until either delivery, 37 weeks of gestation or development of preterm rupture of membranes. Maternal and neonatal outcomes were evaluated for the subset of all randomized women with cervical length < 28 mm at enrollment. The primary outcome was preterm birth at < 32 weeks. A cervical length < 28 mm was identified in 46 randomized women: 19 of 313 who received

progesterone and 27 of 307 who received the placebo. In women with a cervical length < 28 mm, the rate of preterm birth at < 32 weeks was significantly lower for those receiving progesterone than it was for those receiving the placebo (0% vs 29.6%,  $P = 0.014$ ). With progesterone, there were fewer admissions into the neonatal intensive care unit (NICU; 15.8% vs 51.9%,  $P = 0.016$ ) and shorter NICU stays (1.1 vs 16.5 days,  $P = 0.013$ ). There was also a trend toward a decreased rate of neonatal respiratory distress syndrome (5.3% vs. 29.6%,  $P = 0.060$ ).

## CONCLUSIONS

The use of cervical assessment with ultrasound has been well established. It is a widely accepted and well-standardized method which can be easily performed in both high and low-risk patients as a screening test for preterm delivery. All it requires is a well-trained operator and a few minutes to spend on the evaluation of the cervix. Although it has a high negative predictive value in a high-risk population, it has a low sensitivity and positive predictive value in a low-risk population, because of the low prevalence of preterm delivery. Therefore the cut-off value should be carefully selected in order to have an acceptable sensitivity and specificity of the test. It was shown that as the cut-off point was increased the sensitivity increased, but the specificity and the positive predictive value decreased. Unfortunately there is no cervical length below which all women deliver preterm and no cervical length above which all women deliver at term. The main issue with the cervical screening is the type of intervention following a short cervical length measurement. The identification of the patient who can benefit from a cerclage cannot be made on the basis of either history or cervical ultrasound alone. Recent evidence<sup>91</sup> suggests that there may be a subgroup of patients who have subclinical inflammation/infection in their cervixes. Cerclage can be of benefit in women with a combination of a sonographic short cervix, a history of a previous preterm delivery and the absence of such an inflammation. Prospective randomized trials evaluating cerclage must be performed in high-risk patients detected by transvaginal sonographic cervical screening, in order to confirm a potential benefit of cerclage. Such trials should be large enough and apart from the cerclage efficacy they have to examine the best surgical technique, the time of intervention, and the use of tocolytic agents and of antibiotic treatment following cerclage. Administration of progesterone is associated with a reduction in the risk of preterm birth in women with a short cervix. However, other important maternal and long-term infant outcomes have been poorly reported to date. Further prospective studies with large numbers of patients are needed to assess these important outcomes. Moreover, the combination of cervical sonographic and biochemical or endocrinological findings, may help us to better identify candidates for intervention.



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