



## Premature Birth

An effort to prevent a first time and every time

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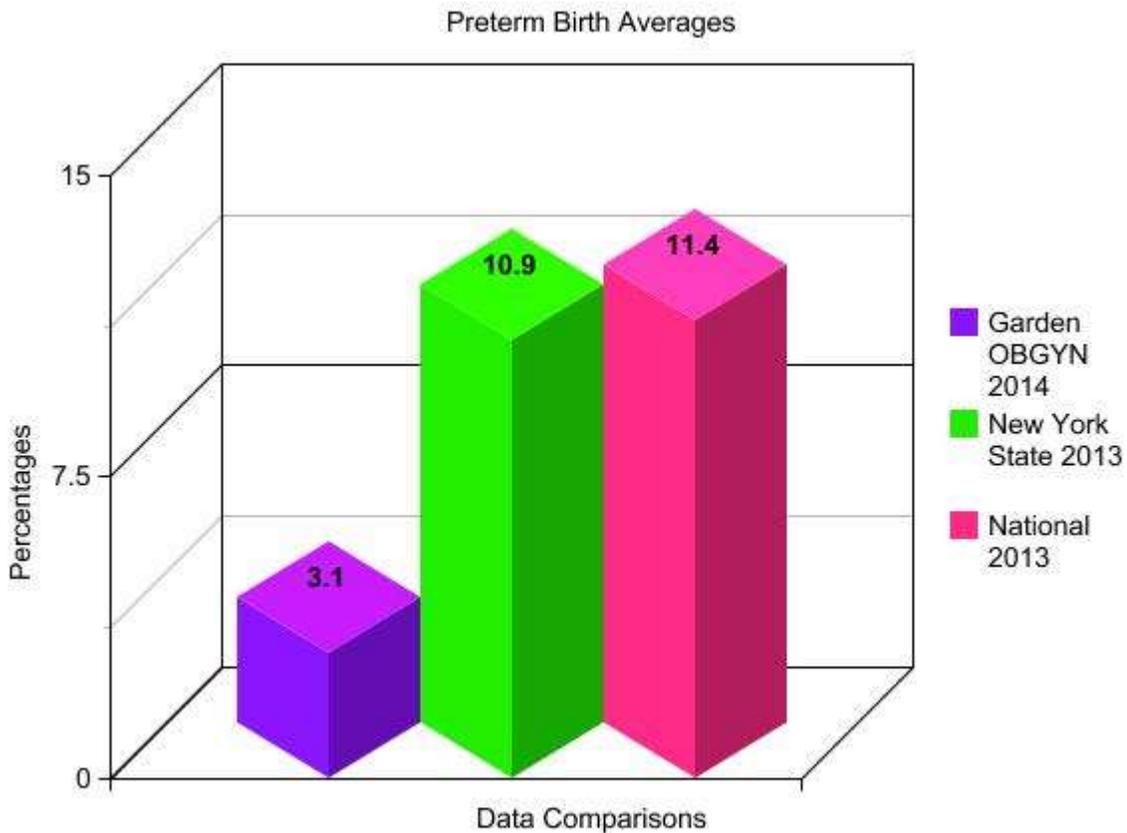
# Introduction

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At Garden OB/GYN, we believe that the key to a favorable pregnancy outcome is routine monitoring for fetal and maternal well being. This is why it is vital that we are diligent in our practices to ensure a baby stay in the womb for as long as possible. Preterm birth is one of our nation’s leading problems. According to the *CDC*, in 2012 , 1:9 babies were born prematurely .

Prematurity is defined as a fetus that is born before the 37 weeks of gestation. There are many risk factors that are known or suspected to contribute to what is known as the leading cause of neonatal death. According to *Child Health USA*, preterm birth is leading cause of infant death in the United States, accounting for over a third of all infant deaths.

At our practice we deliver over 1,200 babies annually. In 2014 we delivered 1,309. Of these, only 41 patients delivered prematurely giving us a preterm delivery rate of 3.10% which is significantly lower than the national average at 11.4%. New York State, although slightly better than the National Average at 10.9%, is still more than double the percentage of Garden OB/GYN (Graph 1).



Graph 1: National vs. NY State vs. Garden OBGYN

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## Ultrasound Aiding in Detection of Preterm Birth

Our hypothesis suggests that routine transvaginal ultrasound is the reason Garden OB/GYN has a lower preterm birth rate than the National average & average for New York State.



Garden OB/GYN has created strict guidelines in the management of our obstetrical patients. Patients are closely monitored in early pregnancy up to delivery with state of the art ultrasound technology. Doing so, we are able to ensure our patients are being evaluated thoroughly at every office visit. With routine ultrasound imaging, we can help reduce the occurrence of premature delivery with measurement of cervical length (Image 1). Cervical assessment and measurement is most useful to help predict pregnancies which are at a higher risk of preterm delivery. The most accurate measurements are obtained through transvaginal ultrasound (Image 2).

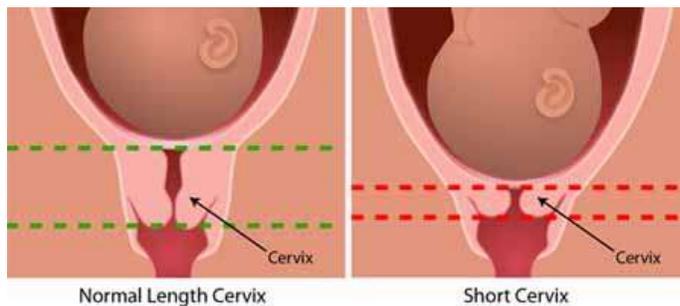


Image 1

**Image 1:** Normal cervical length vs. Short cervix

**Image 2:** Transvaginal ultrasound transducer.

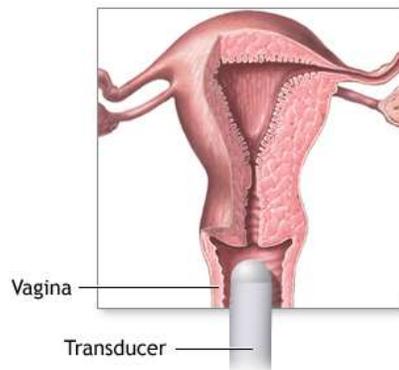


Image 2

ADAM.

Knowing the risk factors contributing to potential preterm birth (Chart 1), at Garden OBGYN, patients are assessed thoroughly, whether there are known risk factors or not. Our goal is to ensure all pregnancies whether it be a patients' first or several later, are carried to term. Transvaginal ultrasound provides us the imaging needed to detect uterine and cervical changes suggestive for preterm labor. When cervical shortening is detected, cerclage placement and/or progesterone therapy is initiated. Close observation of patients along with Perinatal examination, allows us to ensure all patients are evaluated equally. These factors set us apart from the other OB/GYN practices.



### Risk Factors Contributing to Potential Preterm birth

- Women, who have experienced preterm labor or delivery in the past, are considered to be at high risk for preterm labor and birth.<sup>1</sup>
- Multiple gestational pregnancies or the women who have turned to assisted reproductive technology are associated with a higher risk of preterm labor and birth. One study showed that more than 50% of twin births occurred preterm, compared with only 10% of births of single infants.<sup>2</sup>
- Female reproductive organ abnormalities such short cervix predispose women for preterm delivery.
- Hypertension
- Vaginal bleeding
- Shortened intervals between pregnancies (less than 6 months from birth to start of new pregnancy)
- IVF pregnancies
- Placenta previa
- Women with history of uterine surgery (i.e. myomectomy - surgical removal of uterine fibroid, or prior cesarean delivery)
- Blood clotting disorders
- Diabetes (preexisting and gestational)
- Age of mother – teenage pregnancy (under 18 years of age) or advanced maternal age (over age 35)
- Ethnicity. Preterm labor and birth occur more often among certain racial and ethnic groups. Infants of African American mothers are 50% more likely to be born preterm than are infants of white mothers.<sup>4</sup>
- Certain lifestyle and environmental factors, including: smoking, drinking alcohol, illegal drug use, late or no prenatal health care, abuse, stress, exposure to environmental pollutants, long working hours with long periods of standing, etc.<sup>3</sup>

Chart 1

*Premature infants in the NICU*



## Cerclage

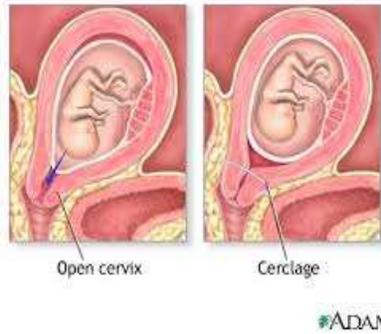
In our medical practice, we have cared for many women with incidental cervical shortening as well as women with a history of incompetent cervix. Cervical shortening can occur in any patient – whether it is a woman’s first pregnancy or is she has been pregnant before.

Preexisting conditions may lead to cervical incompetence or premature cervical shortening resulting in preterm birth. Cervical incompetence and cervical shortening may occur due the following factors:

- Uterine abnormalities
- Genetic disorders affecting collagen
- If the woman’s anatomy has a short cervix to begin with
- History of previous cervical insufficiency
- History of cervical tear from a previous labor
- History of a Conization surgery or Loop Electrosurgical Excision Procedure (LEEP) due to cervical dysplasia
- History of Dilation and Curettage
- History of several terminated pregnancies
- Maternal exposure to diethylstilbestrol (DES) before birth by her mother

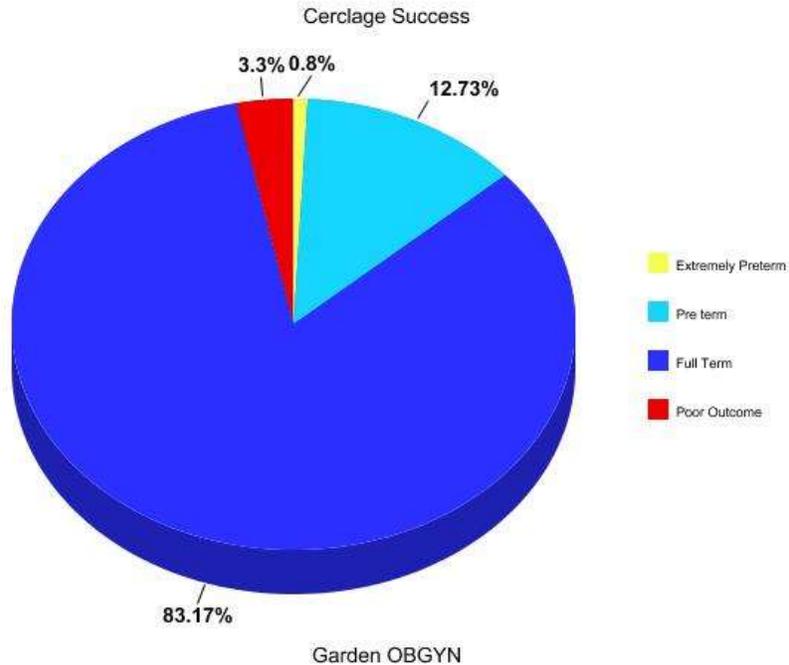
***However, patients may also experience these changes for unknown reasons.***

Cerclage success rates are measured in live births. At Garden OB/GYN, our cervical cerclage success rate over the past ten years exceeds national reported averages in both singleton and twin pregnancies.



Regardless of the above factors, all patients are approached with the same care guidelines, including transvaginal ultrasound for screening and cerclage for prevention of preterm birth. This key factor sets us apart from all other practices. When the cervix demonstrates shortening, without hesitation, cerclage is recommended.

Our success rate for singletons is at 96.61% this is inclusive of elective as well as emergent cerclages that were ultrasound indicated; compared to the national average of 80-95% for elective cerclage and 40-60% for emergent cerclage. Of those patients 85.96% were delivered after 37 weeks gestation (full term); 95.76% of the successful outcomes, were delivered after 32 weeks gestation. Although all premature babies are at risk for health issues, babies born before the 32<sup>nd</sup> week are at a much higher risk of severe lasting health issues.



Thanks to exceptional transvaginal ultrasound imaging, more babies are carried to term, healthy.

## Complications Due to Prematurity

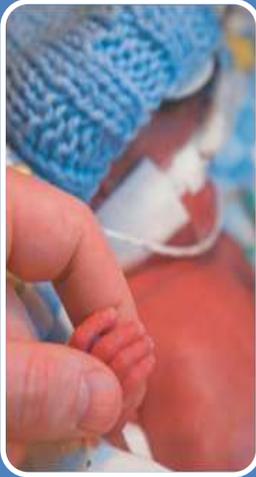
The national average of preterm birth rate in 2013 resulted in nearly half a million babies born premature.

From the very first time parents bring their premature baby home, the experience will differ tremendously compared to a baby born full term.

*Example: A 2 month old baby who was born full term will begin making a lot of cooing and gurgling sounds and start to find their voice. This early milestone of communication is very exciting for parents. When a premature baby is at 2 months, they may have only just learned how to digest milk and finally come home from the hospital. A premature baby at 2 months may only start to act like a newborn full term baby.*

Preterm birth is a serious concern in the United States which could lead to serious health complications (Chart 2).

## Potential Preterm Birth Complications



- Half of neonatal deaths are due to preterm birth
- Cerebral Palsy
- NICU admission (average 8 weeks)
- Mental retardation
- Palsies
- Impaired vision/blindness
- Impaired hearing/deafness
- Speech Impediment
- Learning and developmental delays
- Inability to experience a normal childhood along with peers
- Quality of life impaired
- Decreased lifespan
- Asthma

**Chart 2:** List of preterm birth complications.



*Children wheelchair bound due to Cerebral Palsy*

Preterm birth leads to unnecessary pain and suffering of an innocent child due to circumstances they have no control over. Not only do the children suffer, but the families do as well. Parents are unable to work enough to provide adequate care for children with health problems and developmental issues. Inadequate work leads to inadequate financial status which can also lead to families growing apart.

- 30% more marriages end in divorce due to child disabilities
- 20% of all divorces in the United States are parents of children with disabilities – more of which are due to Cerebral Palsy

### Financial Consequences of Preterm Birth

***In 2005, the national cost of preterm birth was more than \$26 billion-if divided up equally, would amount to \$51,600 per infant born in that year alone. If appropriate protocols were set in place, and for the sake of comparison the national preterm birth average was 3.1% instead, the healthcare system would save an average of \$19 billion.***

***-Garden OB/GYN***

Preterm birth complications lead to extensive financial burdens. Average daily NICU costs can average anywhere from \$4,000 up to \$13,000 in New York state. According to the March of Dimes, the average expenditures for premature/low birth weight (LBW) infants were more than 10 times as high as uncomplicated newborns<sup>5</sup>. Total costs for a premature birth can exceed \$2 million for one family, according to *TIME*. In providing prenatal care utilizing the guidelines of Garden OB/GYN, health care costs could be reduced significantly.

In the past 10 years, Garden OB/GYN has delivered over 7,700 babies. In providing our patients preventative prenatal care, we are able to not only save on initial healthcare costs associated with delivery but as well save for the future of the child and the family. The cost of a premature baby is astronomical.

- Special education costs \$30,000 a year per student

- Combined federal state and local spending on special education rose to more than \$3 billion per year and is on the rise

Not only can prematurity result in the monetary problems, but also in unexplainable heartache and tears. The toll taken on a family caring for a sick child can be devastating.

Preterm birth continues to be a serious complication for obstetrical patients, worldwide. With routine ultrasound imaging, we have a clear understanding about the pregnancy and are capable of diagnosing changes before it is too late. Although, the exact reasons for preterm birth continue to be speculated, we firmly believe a simple in office ultrasound cannot only help bring pregnancies to term but can also save lives. Our practice continues to perform ultrasound for patients and continues to excel in patient care. If all Obstetricians practice alike, preterm birth can become a rarity.



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## ***Supporting Articles***

**15-24** Iams JD, Goldenberg RL, Meis PJ, Mercer BM, Moawad A, Das A, Thom E, McNellis D, Copper RL, Johnson F, Roberts JM. "The Length of the Cervix and the Risk of Spontaneous Premature Delivery". February 29, 1996. NEJM. Retrieved March 4, 2015. <http://www.nejm.org/doi/full/10.1056/NEJM199602293340904>

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## The Length of the Cervix and the Risk of Spontaneous Premature Delivery

Jay D. Iams, M.D., Robert L. Goldenberg, M.D., Paul J. Meis, M.D., Brian M. Mercer, M.D., Atef Moawad, M.D., Anita Das, M.S., Elizabeth Thom, Ph.D., Donald McNellis, M.D., Rachel L. Copper, M.S.N., C.R.N.P., Francee Johnson, R.N., B.S.N., James M. Roberts, M.D., and the National Institute of Child Health Human Development Maternal Fetal Medicine Unit Network

N Engl J Med 1996; 334:567-573 [February 29, 1996](#) DOI: 10.1056/NEJM199602293340904

The length of the cervix may be useful in predicting the risk of premature delivery, with a shorter cervix predicting a higher risk. Traditional methods to evaluate the cervix in pregnancy are limited and unsatisfactory. Digital examination, the standard method, suffers from large variation among examiners.<sup>1</sup> In contrast, transvaginal ultrasonography is a reproducible method of examination during pregnancy.<sup>2,3</sup> In a multicenter, population-based study, we used vaginal ultrasonography to measure the length of the cervix and examined the relation of this measurement to the risk of prematurity.

### **METHODS**

#### **Study Design and Subjects**

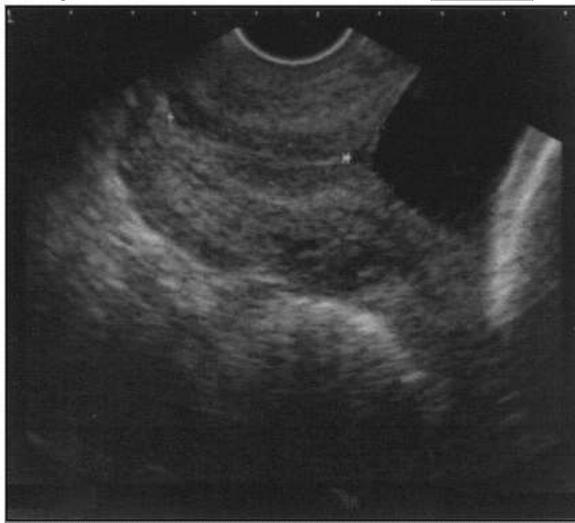
This investigation was part of a prospective study of screening tests to predict spontaneous premature delivery conducted by the Maternal Fetal Medicine Network of the National Institute of Child Health and Human Development between October 1992 and July 1994. The patient population at each center was characterized demographically before the study began. The study population was selected to reflect the parity and race of women receiving prenatal care at participating centers, without regard to medical or socioeconomic factors. No center was allowed to recruit more than 20 percent of the study population. The primary outcome was spontaneous preterm delivery, defined as delivery after premature labor or rupture of membranes less than 35 weeks from the last menstrual period (<34 6/7 weeks of gestation). This end point was chosen because neonatal morbidity and mortality occur primarily in infants born before 35 weeks' gestation. Because specific hypotheses were not proposed, sample-size calculations were based on the precision of the odds ratio. We calculated the necessary sample size, assuming that the rate of premature delivery was 3.5 percent, that at least 5 percent of the women would have positive results on any given screening test, and that the odds ratio for premature delivery was 2.0 or more for women with positive results on that screening test as compared with women with negative results. A sample of 3000 women was chosen to give a lower 95 percent confidence limit greater than 1 for this odds ratio.

Women identified before 24 weeks of gestation were recruited and enrolled if they gave informed consent. Subjects were required to have an ultrasound examination after 15 weeks, before enrollment. Gestational age was based on the date of last menses if the age based on that date and that based on the earliest ultrasound

measurement of the biparietal diameter of the fetal head agreed within 10 days. If not, ultrasound dating was used. Women whose pregnancies were complicated by multiple gestation, cerclage, placenta previa, or a major fetal anomaly were ineligible. Once the women were enrolled, the only study results available to the women's physicians for patient care concerned fetal death, prolapsed membranes, advanced cervical dilatation (>2 cm in primigravidas and >3 cm in multigravidas), hydramnios, oligohydramnios, and painful regular contractions.

### **Collection of Data and Ultrasonography**

Data collected included information about obstetrical history and sociodemographic variables, results of psychological assessment, blood assays, culture of cervical or vaginal samples (or both), measurements of pH and fetal fibronectin, and findings on digital and transvaginal ultrasonographic assessment of the cervix. The first study visit was scheduled between 22 and 24 6/7 weeks of gestation (referred to here as the 24-week visit), with subsequent visits 2, 4, and 6 weeks thereafter. Transvaginal ultrasonographic assessment of the cervix was performed at the initial visit and at the visit 4 weeks later (referred to here as the 28-week visit). The ultrasound images were analyzed to assess changes in the cervix that are associated with spontaneous prematurity and to evaluate ultrasonography as an indicator of the risk of premature delivery. The length of the cervix was measured with a transvaginal real-time ultrasound probe placed in the anterior fornix of the vagina while the woman's bladder was empty; this method has an interobserver variation of 5 to 10 percent.<sup>2</sup> Transabdominal images were not used because the size of the maternal bladder has an unpredictable effect on the measurement of cervical length.<sup>3</sup> Digital cervical examination preceded each ultrasound examination. The appropriate sagittal view was identified by the location of the triangular area of echodensity at the external os, a V-shaped notch at the internal os, and a faint line of echodensity or echolucency between the two. Undue pressure on the cervix that might artificially increase its apparent length was avoided by first obtaining an apparently satisfactory image, then withdrawing the probe until the image blurred, and finally reapplying only enough pressure to restore the image. The cervix was measured in this fashion three times along the line made by the interface of the mucosal surfaces, with calipers placed at the notches made by the internal os and external os (Figure 1)



**FIGURE 1**

Transvaginal Ultrasound Image of a Normal Cervix.

The cervical length we recorded was the shortest measurement that clearly displayed the criteria described above. This measurement was chosen because first measurements are often 3 to 5 mm longer than subsequent measurements, apparently because of the pressure of the probe required to identify the cervix. Each examination was performed during a minimum of three minutes to allow time for development of a “funnel,” defined as a protrusion of the amniotic membranes 3 mm or more into the internal cervical os as measured along the lateral border of the funnel (Figure 2)



**FIGURE 2** Transvaginal Ultrasound Image of a Cervix Characterized by both a Short Length and a Funnel of Amniotic Membrane Protruding into the Internal Os..

The presence or absence of a funnel and its length were recorded.

Cervical measurement was standardized by means of operator-training and quality-control programs. A teaching videotape and guide were developed and distributed to each center. Each sonographer submitted for review by an investigator a videotape of 10 cervical sonographic examinations performed in patients who were not study subjects; study subjects were examined only after the sonographer was certified by this process. Sonographers submitted a videotape of five consecutive examinations of study subjects at a time randomly chosen by the data-coordinating center for purposes of quality control. All sonographic images for every study subject were reviewed by a single investigator who was unaware of the outcome of pregnancy, to ensure that measurements were made appropriately and consistently.

### **Statistical Analysis**

Cervical length (a continuous variable) and the presence or absence of funneling (a dichotomous variable) were the principal variables used to predict preterm delivery (defined as spontaneous premature delivery before 35 weeks of gestation). Percentiles for cervical length and the presence or absence of funneling were analyzed with the use of chi-square tests. We calculated relative risks and 95 percent confidence intervals by

comparing subjects at or below each percentile for cervical length with those above the 75th percentile. Cervical length was analyzed with the use of logistic regression, survival analysis, and receiver-operating-characteristic curves. Correlation of cervical length and the Bishop score (a composite measure of cervical length, dilatation, position, consistency, and degree of descent [station] of the presenting part) was tested by the Jonckheere–Terpstra test.<sup>4</sup>

## **RESULTS**

### **Study Population**

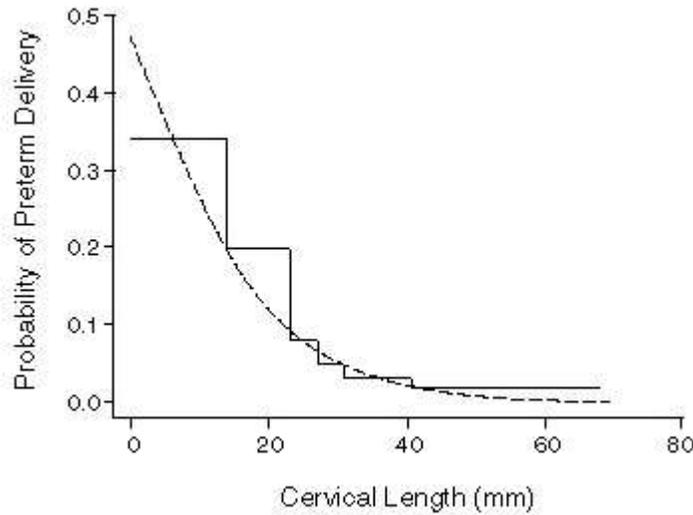
A total of 3073 subjects were enrolled at 10 sites; 73 of this group consented to participate but were excluded from the analysis because the length of gestation was greater than the specified limit for the first visit. Of the 3000 subjects examined at the 24-week visit, 71 were lost to follow-up and 14 did not undergo cervical sonography. There remained 2915 subjects (72 actually seen at 22 weeks of gestation, 1523 at 23 weeks, and 1320 at 24 weeks) whose cervixes were measured ultrasonographically at the 24-week visit. Of these women, 384 were not examined again at 28 weeks: 35 of them gave birth before the 28-week visit, 168 withdrew from the study, and 171 did not come to the clinic for the 28-week visit during the specified period (26 to 29 weeks). Another 10 declined to undergo cervical sonography. There were therefore 2531 subjects examined at the 28-week visit (52 actually seen at 26 weeks, 1058 at 27 weeks, 1193 at 28 weeks, and 228 at 29 weeks). Of the 2915 subjects examined at 24 weeks, 42 percent were nulliparous, 28 percent were married, 63 percent were black, 72 percent had not completed high school, and 54 percent had an income below \$800 per month. Sixteen percent (n = 458) of the women had previously had one or more preterm deliveries (403 spontaneous and 55 with medical intervention) before 37 weeks of gestation. The frequency of preterm delivery before 35 weeks was 4.3 percent (n = 126) among the 2915 subjects examined at 24 weeks. This figure includes the 3.3 percent (n = 83) of the 2531 subjects examined at 28 weeks who delivered spontaneously before 35 weeks. The rate of spontaneous preterm delivery ranged from 1.5 percent to 5.1 percent among the centers. Ninety-one subjects (3.1 percent) were treated with parenteral tocolysis, 65 of whom delivered after 35 weeks.

### **Length of the Cervix in Relation to Preterm Delivery**

The mean ( $\pm$ SD) cervical length at 24 weeks was 34.0 $\pm$ 7.8 mm for nulliparous women and 36.1 $\pm$ 8.4 mm for parous women; the comparable measurements at 28 weeks were 32.6 $\pm$ 8.1 for nulliparous women and 34.5 $\pm$ 8.7 for parous women. The differences between nulliparous and parous women, although statistically significant, were clinically unimportant. Among parous women, the number of previous deliveries had no effect on the length of the cervix. Data on cervical length in parous and nulliparous women were therefore combined for analysis.

The cervical length was normally distributed at both examinations and decreased slightly from 24 to 28 weeks (mean, 35.2 $\pm$ 8.3 mm at 24 weeks and 33.7 $\pm$ 8.5 mm at 28 weeks). The mean cervical length was similar among the centers, except for one center that reported significantly longer measurements. Data analysis was performed both with and without the inclusion of the women enrolled at this center, and also for this center alone. Since the exclusion of the center did not change our results or conclusions and since the results were the same for the data from this center alone, combined data are presented here.

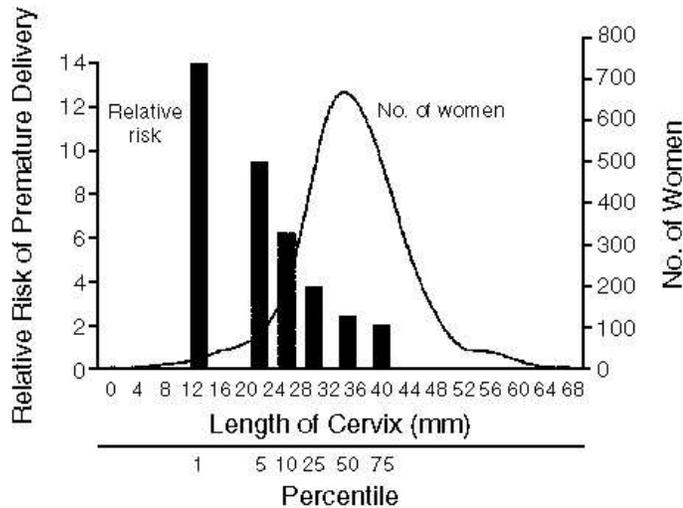
The estimated probability of preterm delivery from the logistic-regression analysis and the observed frequency of preterm delivery according to cervical length at 24 weeks are shown in [Figure 3](#)



**FIGURE 3** Estimated Probability of Spontaneous Preterm Delivery before 35 Weeks of Gestation from the Logistic-Regression Analysis (Dashed Line) and Observed Frequency of Spontaneous Preterm Delivery (Solid Line) According to Cervical Length Measured by Transvaginal Ultrasonography at 24 Weeks.

Logistic-regression analysis of data collected at the 28-week visit produced similar results (data not shown). When women with values at or below a particular percentile for cervical length at 24 weeks were compared with those who had cervical-length values above the 75th percentile, the relative risk of preterm delivery was 1.98 (95 percent confidence interval, 1.20 to 3.27) for women at or below the 75th percentile (cervical length, 40 mm), 2.35 (95 percent confidence interval, 1.42 to 3.89) at or below the 50th percentile (35 mm), 3.79 (95 percent confidence interval, 2.32 to 6.19) at or below the 25th percentile (30 mm), 6.19 (95 percent confidence interval, 3.84 to 9.97) at or below the 10th percentile (26 mm), 9.49 (95 percent confidence interval, 5.95 to 15.15) at or below the 5th percentile (22 mm), and 13.99 (95 percent confidence interval, 7.89 to 24.78) at or below the 1st percentile (13 mm) ( $P < 0.001$  for the comparisons involving values at or below the 50th percentile, and  $P = 0.008$  for values at or below the 75th percentile).

At 28 weeks, the corresponding relative risks for preterm delivery were 2.80 (95 percent confidence interval, 1.41 to 5.56), 3.52 (95 percent confidence interval, 1.79 to 6.92), 5.39 (95 percent confidence interval, 2.82 to 10.28), 9.57 (95 percent confidence interval, 5.24 to 17.48), 13.88 (95 percent confidence interval, 7.68 to 25.10), and 24.94 (95 percent confidence interval, 13.81 to 45.04) ( $P < 0.001$  for values at or below the 50th percentile, and  $P = 0.003$  for values at or below the 75th percentile).

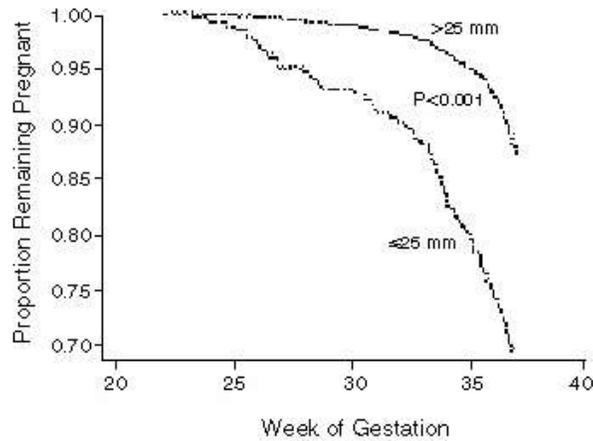


**FIGURE 4** Distribution of Subjects among Percentiles for Cervical Length Measured by Transvaginal Ultrasonography at 24 Weeks of Gestation (Solid Line) and Relative Risk of Spontaneous Preterm Delivery before 35 Weeks of Gestation According to Percentiles for Cervical Length (Bars).

Figure 4 shows the relative risks according to the distribution of cervical-length values at 24 weeks. The association between cervical length and the risk of preterm delivery was evident across the entire range of cervical lengths. Even among women whose cervical length was above the 10th percentile, the risk of preterm delivery increased as cervical length decreased. The logistic-regression analysis indicated that for each increase of 1 mm in cervical length, the odds ratio for preterm delivery was 0.91 (95 percent confidence interval, 0.89 to 0.93).

A change in cervical length between the 24-week and 28-week visits had a small but significant association with the risk of preterm delivery that was independent of the initial cervical length. Among the 56.3 percent of subjects whose cervixes decreased in length between 24 and 28 weeks, the rate of preterm delivery was 4.2 percent, as compared with 2.1 percent among those whose cervixes did not decrease (relative risk, 2.03; 95 percent confidence interval, 1.28 to 3.22). The magnitude of the decrease also had an effect on risk of preterm delivery; the relative risk was 2.80 (95 percent confidence interval, 1.87 to 4.20) for women whose cervixes shortened by 6 mm or more as compared with those whose cervixes changed by less than 6 mm.

The duration of pregnancy according to whether the cervical length was <25 mm or >25 mm at the 24-week visit is shown in terms of survival curves in [Figure 5](#)



**FIGURE 5** Survival Curves Showing the Duration of Pregnancy among Women Examined at 24 Weeks of Gestation, According to Cervical Length ( $\leq 25$  mm or  $> 25$  mm)..

The difference in the duration of pregnancy between women whose cervixes measured 25 mm or less and those whose cervical length was more than 25 mm was significant and continued to widen as gestation progressed. The survival curves for data collected at 28 weeks are similar.

**Cervical Ultrasonography to Predict Preterm Delivery**

Receiver-operating-characteristic curves suggested 30 mm, 25 mm, and 20 mm as potential threshold values for clinical use, corresponding approximately to the 25th, 10th, and 5th percentiles for cervical length in this study. The sensitivity, specificity, and predictive values of these percentiles are shown in [Table 1](#)

**TABLE 1**

Table 1. Sensitivity, Specificity, and Predictive Value of Cervical Length, Funneling, and Bishop Score for Preterm Delivery before 35 Weeks of Gestation.\*

VARIABLE	CERVIX AT 24 WK						CERVIX AT 28 WK					
			PRESENCE OF FUNNEL		BISHOP SCORE $\geq 6$				PRESENCE OF FUNNEL		BISHOP SCORE $\geq 6$	
	$\leq 20$ mm	$\leq 25$ mm	$\leq 30$ mm				$\leq 20$ mm	$\leq 25$ mm	$\leq 30$ mm			
	<i>percent</i>											
Sensitivity	23.0	37.3	54.0	25.4	7.9	27.6	31.3	49.4	69.9	32.5	15.8	42.5
Specificity	97.0	92.2	76.3	94.5	99.4	90.9	94.7	86.8	68.5	91.6	97.9	82.5
Positive predictive value	25.7	17.8	9.3	17.3	38.5	12.1	16.7	11.3	7.0	11.6	25.6	9.9
Negative predictive value	96.5	97.0	97.4	96.6	96.0	96.5	97.6	98.0	98.5	97.6	96.3	96.9

\*The rate of spontaneous delivery before 35 weeks was 4.3 percent among the women examined at 24 weeks and 3.3 percent among those examined at 28 weeks.

**Sensitivity, Specificity, and Predictive Value of Cervical Length, Funneling, and Bishop Score for Preterm Delivery before 35 Weeks of Gestation.\***

There were 185 subjects at 24 weeks (6.3 percent) and 232 subjects at 28 weeks (9.2 percent) whose cervixes had a funnel at the internal cervical os on ultrasound examination, a finding reported to indicate an increased risk of premature delivery.<sup>5</sup> Among these women, the mean length of the funnel was  $16.0 \pm 9.1$  mm at 24 weeks and  $14.3 \pm 8.0$  mm at 28 weeks. Parity had no effect on the frequency of funneling. Funneling correlated with an increased risk of preterm delivery both at 24 weeks (relative risk, 5.02; 95 percent confidence interval, 3.53 to 7.15) and at 28 weeks (relative risk, 4.78; 95 percent confidence interval, 3.18 to 7.19).

The clinical value of funneling as a predictor of preterm delivery was similar to that of the cervical length ([Table 1](#)), but the data on funneling are confounded by substantial variation among centers. Funneling was observed at 24 weeks in no women at one center and in 12.7 percent at another; at these same two centers the values at 28 weeks were 1.3 percent and 21.4 percent. Most centers reported funneling in 3 to 7 percent of subjects at both visits. Variation in the frequency of funneling among centers persisted throughout the study, despite the quality-control measures described earlier. Ultrasound images from centers with the highest and lowest rates of funneling differed in two ways: sonographers at the center with the highest rate appeared to apply less pressure and used a 7-MHz transducer; sonographers at the center with the lowest rate appeared to apply greater pressure and used a 5-MHz transducer. Nevertheless, funneling remained a significant predictor of premature delivery after we controlled for study center and cervical length.

#### **Relation of Cervical Ultrasonography to Digital Examination**

Cervical length at both visits correlated significantly ( $P < 0.001$  by the Jonckheere–Terpstra test<sup>4</sup>) with the Bishop score, a composite measure that assigns a score of 0 to 3 points to each of five features of the cervix: length, dilatation, position, consistency, and station of the presenting part.<sup>6</sup> Subjects with Bishop scores of 6 or more at 24 weeks ( $n = 26$ ) and 28 weeks ( $n = 78$ ) had mean cervical lengths of  $23.1 \pm 13.3$  mm and  $25.4 \pm 11.2$  mm, respectively. The clinical value of the Bishop score is indicated in [Table 1](#).

#### **DISCUSSION**

Our findings confirm those of previous studies that have found an inverse relation between the length of the cervix, as measured by ultrasonography during pregnancy, and the frequency of preterm delivery.<sup>3,5,7</sup> The most intriguing finding of our study is that this relation persisted for cervical lengths above the 10th percentile. Women with cervical lengths at or below the 25th, 50th, and 75th percentiles had a significantly greater risk of preterm delivery than those whose cervical lengths were above the 75th percentile. This observation challenges the traditional understanding of the cervix as being either “competent” or “incompetent” and requires reconsideration of the role of the cervix in the pathogenesis of spontaneous premature delivery. In 1961, Parikh and Mehta used digital examination of the cervix to investigate the hypothesis that cervical competence is a continuum; they concluded that degrees of competence did not exist.<sup>8</sup> Our data suggest that these authors were correct in their hypothesis that there was a continuum of cervical competence but that their method of cervical examination led them to the erroneous conclusion, now firmly stated in obstetrical textbooks,<sup>9</sup> that the cervix is either fully functional or nonfunctional (i.e., incompetent).

Our data suggest that the length of the cervix is an indirect indicator of its competence and should be seen as a continuous rather than a dichotomous variable. The length of the cervix is directly correlated with the duration of pregnancy: the shorter the cervix, the greater the likelihood of preterm delivery. Some might argue that this association is tautological — that is, that uterine contractions, whether perceived by the woman or not, shorten the cervix. We offer four observations in response to this proposition. First, the women in this study were outpatients without symptoms of preterm labor at the time of examination. Second, the relation between the length of the cervix and risk of prematurity extended to values well above the 25th percentile for cervical length. Third, survival-curve analysis ([Figure 5](#)) shows increasing divergence of the two curves, rather than a difference established in the days immediately after examination, as might be expected if women with shorter

cervixes had occult early labor. Finally, the relation between the length of the cervix and the duration of pregnancy has been observed in successive pregnancies. In a study of 323 women who had previously had a premature delivery,<sup>10</sup> the length of gestation at the time of the earlier preterm delivery was correlated with cervical length in a subsequent pregnancy, suggesting that cervical length operates as a continuous variable in serial gestations. We interpret these observations to mean that there is a continuum of cervical performance that is reflected functionally by the gestational age of the infant delivered prematurely and anatomically by the length of the cervix.

Theories of premature labor based on an understanding of the cervix as uniformly competent may underestimate the importance of the cervix, and overestimate the role of uterine activity, in the pathogenesis of prematurity. Reassessment of the cervix as a structure with variable performance along a continuum supports a theory of spontaneous prematurity as a multifactorial phenomenon in which the causal importance of decreased cervical resistance increases as the length of gestation at the time of the preterm delivery decreases. Uterine activity is known to vary widely among normal pregnancies<sup>11</sup> and could also affect the risk of prematurity in a continuous manner. Just as contraction-based theories of premature labor have led to trials of prophylactic tocolytic agents, our findings raise but do not resolve the question of the appropriate role of cervical cerclage in women with a history of early preterm delivery.<sup>12-14</sup> Perhaps cervical ultrasonography will prove useful in selecting candidates for cerclage.

Obstetricians should be comfortable using the percentile of cervical length as an estimate of the risk of prematurity, since many obstetrical tests are based on percentiles. Although funneling was predictive of prematurity, the ability to identify this phenomenon was not consistent among our 10 study centers. Cervical length was more consistently measured than funneling and performed as well as or better than funneling in terms of sensitivity and predictive value. Transabdominal ultrasonography is unsatisfactory for measurement of the cervix because of technical drawbacks that produce inaccurate or poor-quality images.<sup>5,7</sup> Vaginal ultrasonography produced good images in our study and was well accepted by patients. There were no apparent risks associated with the examination. Although the predictive value of ultrasonography was low in this low-risk population, it will rise with the risk of prematurity in the population studied. Ultimately, we expect that cervical ultrasonography will be used to evaluate women with a historical or current risk factor, such as a previous preterm delivery or a Bishop score of 6 or above, and to select candidates for clinical trials to evaluate cerclage.

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#### **SOURCE INFORMATION**

From the Departments of Obstetrics and Gynecology at Ohio State University, Columbus (J.D.I., F.J.), the University of Alabama, Birmingham (R.L.G., R.L.C.), Bowman Gray School of Medicine, Winston-Salem, N.C. (P.J.M.), the University of Tennessee, Memphis (B.M.M.), and the University of Chicago, Chicago (A.M.); the Biostatistics Center, George Washington University, Washington, D.C. (A.D., E.T.); the National Institute of Child Health and Human Development (NICHD), Bethesda, Md. (D.M.); and the University of Pittsburgh, Pittsburgh (J.M.R.). Other contributing authors were Menachem Miodovnik, M.D. (University of Cincinnati, Cincinnati), J. Peter Van Dorsten, M.D. (Medical University of South Carolina, Charleston), Steve N. Caritis, M.D. (University of Pittsburgh, Pittsburgh), Gary R. Thurnau, M.D. (University of Oklahoma, Oklahoma City), and Sidney F. Bottoms, M.D. (Wayne State University, Detroit).

Address reprint requests to Dr. Iams at the Department of Obstetrics and Gynecology, Ohio State University, 1654 Upham Dr., Columbus, OH 43210.

The members of the network are listed in the Appendix.

Members

## **APPENDIX**

In addition to the authors, the participants in the National Institute of Child Health and Human Development (NICHD) Maternal Fetal Medicine Network were as follows: *University of Alabama, Birmingham* — J.C. Hauth, A. Northern, and C. Neely; *Bowman Gray School of Medicine* — E. Mueller-Heubach, M. Swain, and A. Frye; *University of Chicago* — M. Lindheimer, P. Jones, and M.E. Lewis Brown; *University of Cincinnati* — T.A. Siddiqi, N. Elder, T. Coombs, and J. VanHorn; *George Washington University Biostatistics Center* — R. Bain, L. Leuchtenburg, and M. Fischer; *Magee–Women's Hospital* — J.H. Harger, M. Cotroneo, and C. Stallings; *NICHD* — S. Yaffe, C. Catz, and M. Klebanoff; *Ohio State University* — M.B. Landon, J. Schneider, and C. Mueller; *University of Oklahoma, Oklahoma City* — J.C. Carey, A. Meier, and E. Liles; *Medical University of South Carolina* — R.B. Newman, B.A. Collins, T. Metcalf, and V. Odell; *University of Tennessee, Memphis* — B. Sibai, R. Ramsey, and J.L. Fricke; and *Wayne State University* — M. Treadwell and G.S. Norman.



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## 503: Implementation of a universal cervical length surveillance program for prediction of preterm birth

Kelly Orzechowski, Sara Nicholas, Stuart Weiner, Jason Baxter, Vincenzo Berghella

### Article Outline

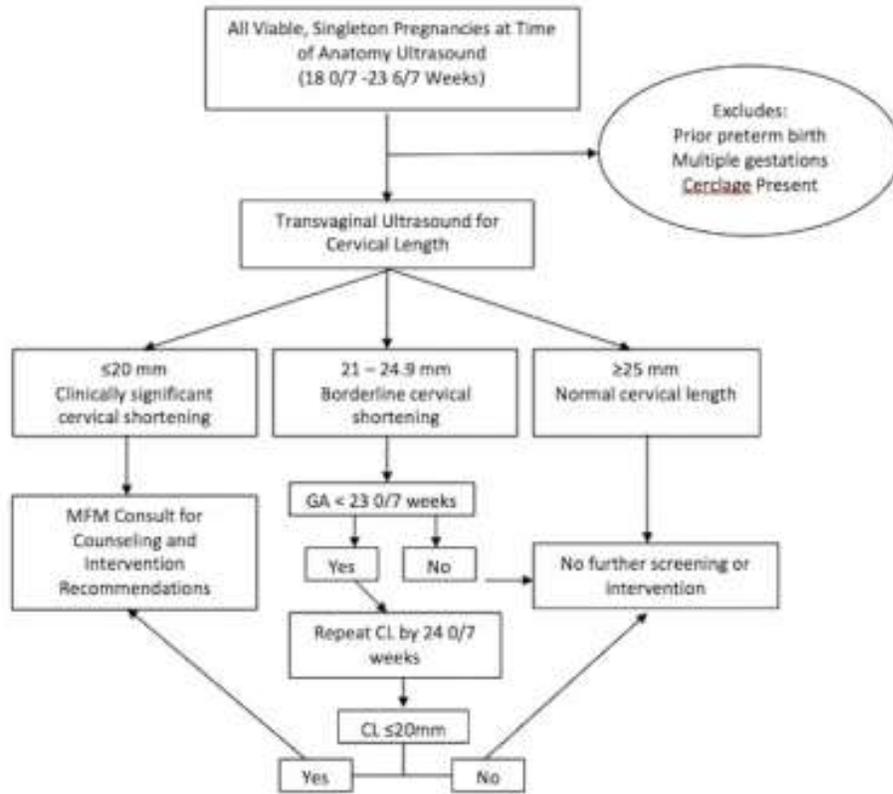
- I. Objective
- II. Study Design
- III. Results
- IV. Conclusion

### Objective

To evaluate factors associated with successful implementation of a universal cervical length (CL) screening program for prediction of preterm birth.

### Study Design

We performed a retrospective cohort study to evaluate the acceptability of universal CL screening program for the prediction of preterm birth (PTB) between January 1, 2012 and June 30, 2012. Women with singleton gestations undergoing obstetric ultrasounds between 18 0/7-23 6/7 weeks were eligible for CL screening. Patients with prior spontaneous PTB were excluded. CL measurements were always performed in a uniform fashion with transvaginal ultrasound and the results were interpreted according to a standard protocol ([Figure](#)). Sonographers and medical staff received education prior to implementation and appointment times were extended by 10 minutes. Patients received educational handouts at check-in. On June 1, 2012, our program was modified from “opt-in” to “opt-out” in attempt to improve patient acceptance rates. Independent samples Mann-Whitney U, Chi-square, and independent samples t-tests were performed using SPSS 20.0.



Universal CL screening algorithm

## Results

During the study period, 733 (82%) of 898 eligible patients were offered CL screening. Women were more likely to accept CL screening if they were nulliparous and if the sonographer was female. Implementation of an “opt-out” CL screening program significantly increased the percentage of women screened ([Table](#)). Among 561 women who accepted CL screening, 9 (1.6%) had a CL  $\leq$ 5mm and 6 (1%) had a CL  $\leq$ 0mm and were offered vaginal progesterone.

## Conclusion

Universal CL screening is acceptable to most women and is feasible to implement on a large scale. Patient education is necessary to achieve optimal rates of acceptance. An “Opt-out” screening approach increases acceptance rates.

# Debating cervical length measurement to predict and prevent preterm birth

## Should cervical length risk assessment be universal?

May 01, 2013

By Sonia S. Hassan MD, Patrick S. Ramsey MD MSPH

### PRO: Patients deserve information about cervical length

By Sonia S. Hassan, MD

Dr. Hassan is Associate Dean for Maternal, Perinatal, and Child Health and Professor, Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology at Wayne State University School of Medicine, Detroit, Michigan.

In 1960, the United States ranked twelfth in the world in infant mortality; this ranking has fallen steadily to forty-third.<sup>1</sup> Preterm birth (PTB)-related deaths are one of the leading causes of this infant mortality rate.<sup>2,3</sup> In 2005, 12.9 million births worldwide were preterm.<sup>4</sup> In 2011, the rate of PTB in the United States was 11.7% (463,361 babies per year).<sup>5,6</sup>

The challenge for providers and researchers has been, first, to predict who will deliver prematurely, and second, to implement an intervention that will prevent PTB. A *sonographic short cervix diagnosed by transvaginal ultrasound (TVUS) is the most powerful predictor of PTB*. Fifty percent of women with a cervical length  $\leq 15$  mm will deliver  $<32$

weeks.<sup>6,7</sup> TVUS provides the most accurate and reproducible cervical length measurement with no associated risks; it is widely accepted by patients. Yet implementation of a program in which all pregnant women undergo cervical length measurement requires the availability of an intervention that can prevent PTB.

### ***Vaginal progesterone for prevention of PTB and neonatal complications***

*Two randomized clinical trials have demonstrated that vaginal progesterone reduces the rate of PTB in women with a sonographic short cervix.*<sup>8,9</sup> A randomized clinical trial investigating the use of vaginal progesterone to prevent PTD (<34 weeks) in women with a short cervix ( $\leq 15$  mm) reported a 44% reduction in risk of PTB (19.2% vs 34.4%; relative risk [RR], 0.56; 95% confidence interval [CI], 0.36-0.86).<sup>8</sup> In 2011, a randomized clinical trial<sup>9</sup> demonstrated that administration of vaginal progesterone to women with a short cervix (10 mm-20 mm) was associated with:

- a 45% decrease in the rate of PTB at <33 weeks (primary endpoint), a 38% decrease in the rate of PTB at < 35 weeks, and a 50% decrease in the rate of PTB at <28 weeks' gestation;
  
- a 61% decrease in the rate of respiratory distress syndrome (RDS); and
  
- a decrease in the rate of composite neonatal morbidity.

A meta-analysis of individual patient data from 5 randomized clinical trials revealed that in addition to reducing the rate of PTB and respiratory distress syndrome, administration of vaginal progesterone to women with a short cervix was associated with a reduction in the rate of mechanical ventilation, admission to neonatal intensive care units (NICUs), and composite neonatal morbidity/mortality.<sup>10</sup>

### ***Impact and implications for the healthcare system***

The potential impact of the use of vaginal progesterone in women with a short cervix can be surmised from the estimate that 11 patients need to be treated to prevent 1 PTB <35 weeks, and that 9 patients need to be treated to prevent 1 PTB before 34 weeks'

gestation. Furthermore, 15 patients need to be treated to prevent 1 episode of respiratory distress syndrome.<sup>10</sup>

Estimates indicate that 141 pregnant women from the general population need to be screened with TVUS (treating those with a cervical length  $\leq 25$  mm with vaginal progesterone) to prevent 1 case of PTB <33 weeks.<sup>9,10</sup>

*Cost-effectiveness analysis studies have demonstrated that the preterm prevention strategy of implementing universal cervical length risk assessment with TVUS and using vaginal progesterone is cost-effective.*<sup>11-13</sup> Werner and colleagues<sup>12</sup> have estimated that for every 100,000 women screened, there is a cost savings of more than \$19 million annually. In the United States, the total annual cost savings is estimated to be \$500 million, based on the 2011 population.

Numerous institutions now employ universal TVUS cervical length risk assessment. Delaying implementation at other centers will result in patients missing the opportunity for treatment. This is similar to what happened with antenatal steroids, for which efficacy was demonstrated in 1972.<sup>14</sup> Not until 1994, however, were they widely adopted for use in women at risk of PTB.<sup>15</sup>

Delaying universal sonographic cervical length risk assessment would result in the ethical problem of having an intervention for a diagnosis that we are not seeking in all patients. Vaginal progesterone's efficacy has been demonstrated in women with and without a prior PTB; hence, all patients need to be assessed for cervical length. As obstetricians, we are becoming obligated to provide pregnant women with the knowledge about the length of their cervixes. Therefore, this critical question must be considered: When there is a treatment available to prevent PTB for those with a sonographic short cervix, doesn't every woman have a right to know her cervical length? The answer is yes.

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# Universal cervical-length screening to prevent preterm birth: a cost-effectiveness analysis

Authors

E. F. Werner, C. S. Han, C. M. Pettker, C. S. Buhimschi, J. A. Copel, E. F. Funai, S. F. Thung

## Abstract

### Objective

To determine whether routine measurement of second-trimester transvaginal cervical length by ultrasound in low-risk singleton pregnancies is a cost-effective strategy.

### Methods

We developed a decision analysis model to compare the cost-effectiveness of two strategies for identifying pregnancies at risk for preterm birth: (1) no routine cervical length screening and (2) a single routine transvaginal cervical length measurement at 18–24 weeks' gestation. In our model, women identified as being at increased risk (cervical length < 1.5 cm) for preterm birth would be offered daily vaginal progesterone supplementation. We assumed that vaginal progesterone reduces preterm birth at < 34 weeks' gestation by 45%. We also assumed that a decreased cervical length could result in additional costs (ultrasound scans, inpatient admission) without significantly improved neonatal outcomes. The main outcome measure was incremental cost-effectiveness ratio.

### Results

Our model predicts that routine cervical-length screening is a dominant strategy when compared to routine care. For every 100 000 women screened, \$ 12 119 947 can be potentially saved (in 2010 US dollars) and 423.9 quality-adjusted life-years could be gained. Additionally, we estimate that 22 cases of neonatal death or long-term neurologic deficits could be prevented per 100 000 women screened. Screening remained cost-effective but was no longer the dominant strategy when cervical-length ultrasound measurement costs exceeded \$ 187 or when vaginal progesterone reduced delivery risk at < 34 weeks by less than 20%.

## Conclusion

In low-risk pregnancies, universal transvaginal cervical length ultrasound screening appears to be a cost-effective strategy under a wide range of clinical circumstances (varied preterm birth rates, predictive values of a shortened cervix and costs).

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## Introduction

Preterm birth is a major cause of neonatal morbidity and mortality in the USA. According to the National Vital Statistics Reports, 11–12% of the 4 million neonates born each year are delivered before 37 weeks' gestation and 3.6% are delivered before 34 weeks. Early preterm birth (before 34 weeks) is particularly associated with high rates of mortality and morbidity, including intraventricular hemorrhage, necrotizing enterocolitis, respiratory distress syndrome and neurological deficits<sup>1</sup>. The relevance of preterm birth as a major public health problem is emphasized by the more than \$ 26 billion spent annually in the USA to treat these preterm infants<sup>2</sup>. Additionally, over 50% of neonates born before 28 weeks are rehospitalized within 24 months of birth and almost one third are diagnosed with asthma or reactive airway disease by their fifth birthday<sup>3</sup>. 9.1% of surviving infants born between 23 and 28 weeks' gestation are diagnosed with cerebral palsy, 4.4% with mental retardation and 2.5% with behavioral or emotional disorders<sup>4</sup>.

Traditionally, physicians assessed a woman's risk for preterm birth using clinical factors including multiple gestations, history of preterm birth or prior cervical surgery. Yet, more than half of all preterm births occur to women without historical risk factors<sup>5–7</sup>. Compelling data suggest that the length of the cervix as assessed by transvaginal ultrasonography is inversely related to the risk of preterm birth, and may be a stronger predictor than the previously used clinical risk factors<sup>8–10</sup>. For example, Goldenberg *et al.*<sup>6</sup> demonstrated that a cervical length of < 2.5 cm had a relative risk of 3.5 (95% confidence interval (CI), 2.7–4.6) for preterm birth, while previous preterm birth had a relative risk of 2.7 (95% CI, 2.1–3.4).

Although valuable, this information had limited clinical utility until more recent studies demonstrated interventions that could potentially reduce the frequency of preterm birth<sup>11, 12</sup>. In a randomized trial, Fonseca *et al.*<sup>11</sup> demonstrated that daily vaginal progesterone reduced the risk of preterm birth by 45% in low-risk women identified with a cervical length of  $\leq 1.5$  cm. Given this finding, we sought to investigate the cost-effectiveness of routine cervical-length screening in the low-risk population. To this end, we constructed a decision-analysis model, which provided evidence that universal cervical-length screening would be cost-effective.

## Methods

We used a decision-tree model to compare two clinical strategic approaches to preterm birth prevention in low-risk pregnancies. The population targeted included singleton pregnancies in women without a history of prior preterm birth. The first strategy was consistent with the current clinical recommendations advocated by the American College of Obstetricians and Gynecologists: no screening for preterm birth in asymptomatic low-risk pregnant women with a singleton gestation<sup>13</sup>. The second strategy included performance of a single routine transvaginal ultrasound cervical-length measurement on all asymptomatic, low-risk singleton pregnant individuals at between 18 and 24 weeks' gestation. In the second strategy the cervical length was considered short (< 1.5 cm), mid length (1.5–2.49 cm), or normal length ( $\geq 2.5$  cm).

Our model proposed that women with a cervical length of < 1.5 cm be offered vaginal progesterone<sup>11, 14</sup>. This strategy was based on the data presented by Fonseca *et al.*<sup>11</sup> This trial enrolled 24 620 asymptomatic women, including 24 189 singletons, for cervical-length measurement. Cervical length was ≤ 1.5 cm in 413 women, 250 of whom were randomized to receive vaginal progesterone or placebo. The primary outcome was delivery before 34 weeks' gestation. Thirty-six of 112 women (32.1%) with singletons in the placebo group went on to deliver prior to 34 weeks compared to 20 of 114 (17.5%) in the progesterone group. Thus, we assumed that there would be a 45% reduction in deliveries before 34 weeks with progesterone administration. An adherence rate of 92% was also assumed based on the data of Fonseca *et al.*<sup>11</sup>.

The baseline probability and outcomes for each strategy were obtained based on a comprehensive bibliographic survey of the English literature in PubMed, using the following search terms: vaginal progesterone, Prometrium, preterm birth, preterm delivery, preterm prevention and cervical length, as well as combinations of these terms. Point estimates were determined from published randomized controlled trials and prospective cohorts when possible. Retrospective cohorts or review studies were used when no other sources of information were available. The decision tree was developed and the analysis performed with TreeAge Pro 2007 (TreeAge Software, Williamstown, MA, USA). The probability estimates and the references used in support of our model are reported in Table 1.

Table 1 Probability and utility estimates in support of the model

Variable	Base case (range) (%) <sup>a</sup>
Preterm birth (< 34 weeks) <sup>1,11,15</sup>	2.1 (2.0–3.6)
If birth at < 34 weeks, probability of birth at < 28 weeks <sup>11</sup>	20.6
If birth at ≥ 34 weeks, probability of birth at < 37 weeks <sup>11</sup>	8.4
Prevalence of cervical length	
< 1.5 cm <sup>9,11,17</sup>	1.7 (0.9–1.88)
1.5–2.49 cm <sup>11</sup>	8.3 (7.9–8.7)
≥ 2.5 cm <sup>11</sup>	90 (89.5–91.8)
Prevalence of inpatient admission if cervical length < 1.5 cm	0.0 (0.0–100.0)
Delivery at < 34 weeks if cervical length < 1.5 cm <sup>8,11</sup>	34.1 (9.7–58.7)
Delivery at < 34 weeks if cervical length 1.5–2.49 cm <sup>9,11</sup>	5.1 (4.2–14.0)
Delivery at < 34 weeks if cervical length ≥ 2.5 cm <sup>10,11</sup>	1.2 (1.1–3.0)
Adherence to progesterone therapy <sup>11</sup>	92.8 (86.0–97.0)
Reduction in deliveries prior to 34 weeks with progesterone <sup>11</sup>	45 (12.0–66.0)
Probability of severe disability if delivery at <sup>4</sup> :	
< 28 weeks	10.6 (9.1–17.1)
≥ 28 weeks, < 34 weeks	5 (3.3–9.7)
≥ 34 weeks, < 37 weeks	2.4 (2.1–2.6)
≥ 37 weeks	1.7 (1.5–1.8)
Probability of death if delivery at <sup>16</sup> :	
< 28 weeks	17.9 (8.0–49.3)
≥ 28 weeks, < 34 weeks	0.9 (0.2–8.6)
≥ 34 weeks, < 37 weeks	0.2 (0.1–0.4)
≥ 37 weeks	0.07 (0.05–0.09)
Utility of neonatal outcome <sup>18</sup>	
Death	0
Severe neurologic disability	0.61 (0.5–0.8)
Health	1.0

<sup>a</sup>All data except utility of neonatal outcome given as %.

The overall incidence of preterm birth at < 34 weeks' gestation was estimated at 2.1% based upon data provided by Fonseca *et al.*<sup>11</sup>. A preterm birth rate as high as 3.6% for birth at < 34 weeks' gestation was based upon data from the 2006 United States National Vital Statistics data<sup>1</sup> and as low as 2% from UK data<sup>15</sup>. Given the differences in neonatal morbidity and mortality between early preterm birth at < 28 weeks' gestation compared with those delivering at  $\geq 28$  weeks, we utilized data from United States National Vital Statistics summaries to estimate the proportion of deliveries at < 28 weeks, 28–34 weeks, 34–37 weeks and  $\geq 37$  weeks<sup>4, 16</sup>. Of the deliveries that occurred at < 34 weeks, we assumed that 20% would occur prior to 28 weeks while the remaining 80% would deliver at 28–34 weeks<sup>1</sup>. Of the deliveries that occurred after 34 weeks' gestation, 8% were assumed to occur at between 34 and 37 weeks while the remaining 92% were full-term births<sup>1</sup>.

The prevalence of cervical length of < 1.5 cm and of 1.5–2.49 cm is fairly consistent in the literature (0.9–1.88% and 7.9–8.7%, respectively)<sup>9, 11, 17</sup>; we used these ranges in our sensitivity analysis. However, we also explored implausible prevalences to establish the threshold at which cervical-length ultrasound measurement was no longer cost-effective. The preterm birth rates used in the model were inversely related to cervical length based on previously published data<sup>8–11</sup>.

Only the study of Fonseca *et al.*<sup>11</sup> examined the effect of vaginal progesterone therapy on neonatal morbidity. It showed a reduction in morbidity but the results were not statistically significant, as the study was not specifically powered for this purpose. Thus we used large pediatric cohort studies to estimate the mortality and short- and long-term morbidities based on gestational age at birth<sup>4, 16</sup>.

Based upon the literature, utilities were given to the offspring studied in this model<sup>18</sup>. Utilities are a means of evaluating the relative quality of life as compared to health. We determined three health states that would be relevant for our analysis: normal health (utility = 1), severe disability (utility = 0.61) and death (utility = 0). Severe disability was defined as serious medical conditions that significantly limit working capacity and included cerebral palsy, mental retardation, blindness, deafness and epilepsy<sup>4</sup>. Severe disability was assigned a value of 0.61 based on the decision analysis of Odibo *et al.*<sup>19</sup> for the use of 17-alpha-hydroxyprogesterone caproate for the prevention of preterm birth. A range of 0.5–0.8 was used in our sensitivity analysis based on Tengs and Wallace's quality of life data<sup>18</sup>. This range encompasses several severe disabilities and all moderate disabilities. We ran our model using many different life expectancies for the premature infants. In the final analysis, we assigned an average life expectancy of 76 years for the purpose of calculating the quality-adjusted life-years (QALYs) for all surviving offspring<sup>17</sup>. We chose to assume that the life span of premature infants who survive the neonatal period is not significantly shortened in an effort to bias our model against screening, thus further validating the efficiency of screening if the model was cost-effective, even assuming this best case scenario.

Cost data were derived from the published literature (Table 2). Screening consisted of transvaginal ultrasono-graphic measurement of cervical length at between 18 and 24 weeks' gestation. The costs associated with this ultrasound scan were determined from *Medicare* data using the current procedural terminology (CPT) code 76817<sup>20</sup>. In the base-case analysis, only practice expenses were included (1.95 relative value units (RVUs), using an average RVU cost of \$ 36.07). In the sensitivity analysis, the total cost of a transvaginal ultrasound scan was adjusted to as low as \$ 50/scan given geographic discounting and as high as \$ 300/scan to include physician fees, malpractice fees, geographic increases and charges associated with repeating fetal growth assessment (CPT code 76816).

**Table 2** Cost estimates of the model

Variable	<i>Base case (range*) in 2010 (\$)</i>
Cervical-length ultrasound scan (cost per scan) <sup>20</sup>	70 (50–300)
Vaginal progesterone supplementation (total cost for gestation) <sup>21</sup>	206 (100–400)
Admission cost for short cervix, including corticosteroids <sup>22</sup>	0 (0–10 000)
Cost of maternal care if delivery at <sup>23</sup> :	
< 28 weeks	10 953 (5477–21 907)
≥ 28 weeks, < 34 weeks	8153 (4077–16 307)
≥ 34 weeks, < 37 weeks	4627 (2314–9254)
≥ 37 weeks	3577 (1789–7155)
Cost of neonatal care if delivery at <sup>23,25</sup> :	
< 28 weeks	207 927 (85 251–415 922)
≥ 28 weeks, < 34 weeks	37 159 (15 235–74 329)
≥ 34 weeks, < 37 weeks	5460 (2239–10 922)
≥ 37 weeks	1806 (741–3613)
Cost of early intervention (0–3 years) if delivery at <sup>16</sup> :	
< 28 weeks	8847 (4427–17 699)
≥ 28 weeks, < 34 weeks	4201 (2102–8406)
≥ 34 weeks, < 37 weeks	1632 (816–3264)
≥ 37 weeks	862 (431–1725)
Cost of severe disability <sup>24</sup>	262 667 (131 333–525 335)
Income and domestic productivity losses due to bed rest <sup>30</sup>	0 (0–11 310)

\*Range of values used in sensitivity analysis and Monte Carlo Simulation.

If the cervix was short (< 1.5 cm), maternal costs included nightly progesterone administration until delivery or 36 weeks' gestation<sup>21</sup>. These women also received two follow-up cervical-length ultrasound scans. In the sensitivity analysis we varied the number of follow-up scans from none to four. In the base-case analysis, we did not account for any hospital admissions purely for a short cervix. However, in the sensitivity analysis we varied admission rates from 0 to 100% for a cervical length of < 1.5 cm and 0 to 50% for a cervical length of 1.5–2.49 cm. As we adjusted the admission rates we also varied admission costs from 0 to \$ 10 000, with a median cost of \$ 3000. This median was selected as it is consistent with a 48-h stay to facilitate steroid administration<sup>22</sup>. We included a maximum of \$ 10 000 to include up to 1 week of inpatient care. Within the sensitivity analysis, we performed a similar evaluation of potential hospital admissions and treatment without clinical benefits in women with mid cervical length (1.5–2.49 cm).

Delivery costs were based upon the gestational age at delivery, as the length of stay and the percentage of Cesarean deliveries are known to be inversely related to the timing of delivery<sup>23</sup>. Offspring costs were broken down into: neonatal care costs, costs of care in the first 3 years, and long-term costs associated with severe neurologic disability<sup>4, 16, 23–25</sup>. The cost of care in the first 3 years was included in an attempt to account for the early intervention and special education that many of these children receive. Long-term care costs included only direct medical costs, thus productivity losses, both to the affected individual and their family members, are not included. We based long-term disability costs on cerebral palsy data as that was the most prevalent disability noted in this population<sup>4</sup>.

All costs are presented in 2010 US dollars and were adjusted based on the use of the medical care component of the Consumer Price Index. Costs and utilities were discounted at a baseline rate of 3% based on average inflation, although the range was varied from 1–5% in the sensitivity analysis. All analyses were from a societal perspective.

For a cohort of 100 000 women, we calculated the cost of care for each strategy. The primary outcome of the study was cost-effectiveness, measured as the incremental cost-effectiveness ratio (ICER). Cost-effectiveness was defined as an ICER of \$ 100 000. We performed univariate sensitivity analyses by varying the values of the variables in the model to their plausible extremes. Other parameters we estimated included: total cost of each strategy, total QALYs per strategy, incidence of preterm birth and incidence of adverse neonatal outcomes such as fetal death or disability.

## Results

The results for the base-case model are presented in Table 3. Our model predicts that the current standard of care costs \$ 1 314 520 247 per 100 000 low-risk women, while the care model involving routine screening would cost \$ 1 302 400 300 per 100 000 low-risk women. We estimate that screening would prevent 248 births before 34 weeks' gestation and 22 neonatal deaths or neonates with long-term neurologic deficits per 100 000 deliveries. Thus, screening is the dominant strategy, saving cost with improved outcomes.

**Table 3** Summary of results (per 100 000 women) for the base-case model

<i>Variable</i>	<i>Standard procedure</i>	<i>With screening</i>
Neonatal death ( <i>n</i> )	170	159
Severe neurologic deficits ( <i>n</i> )	1827	1816
Neurologic deficit/death averted ( <i>n</i> )	—	22
Births < 34 weeks' gestation ( <i>n</i> )	2106	1858
Births < 34 weeks' gestation averted ( <i>n</i> )	—	248
Total QALY	2 954 795	2 955 218
Marginal QALY gained	—	423.9
Total cost (\$)	1 314 520 247	1 302 400 300
Marginal cost savings (\$)	—	12 119 947
Marginal cost (\$)/QALY gained	—	28 592

QALY, quality-adjusted life-years. \$, 2010 US dollars.

We performed a univariate sensitivity analysis to evaluate the impact of changing the probability and cost variables on the ICER of screening with transvaginal cervical-length ultrasonography (Table 4). In this study, a negative value (denoted by parentheses) equates to a cost saving. The model was robust for all parameters at the ranges that we examined. As expected, the model was sensitive to changes in the cost of cervical-length ultrasound scans, the effectiveness of progesterone in preventing preterm delivery, the predictive value of a shortened cervix and the prevalence of a shortened cervix.

**Table 4** Sensitivity analysis evaluating impact of changing probability and cost variables: incremental cost-effectiveness ratio (ICER)\*

<i>Variable</i>	<i>ICER at:</i>	
	<i>Variable minimum</i>	<i>Variable maximum</i>
Preterm birth (at < 34 weeks' gestation)	(26 814)	(38 175)
Prevalence of cervical length < 1.5 cm	(14 100)	(29 667)
Prevalence of inpatient admission if delivery at ≥ 34 weeks	(28 652)	(584)
Delivery at < 34 weeks if cervical length < 1.5 cm	33 275	(38 237)
Adherence to progesterone therapy	(26 327)	(28 965)
Reduction in deliveries prior to 34 weeks with progesterone	35 264	(34 801)
Probability of severe disability	(28 058)	(29 004)
Probability of death	(35 404)	(23 133)
Utility of disability	(26 069)	(32 175)
Cost of cervical-length ultrasound scan	(33 519)	27 461
Cost of progesterone	(28 951)	(27 794)
Cost of maternal care	(26 578)	(30 919)
Cost of admission for short cervix	(28 652)	(10 632)
Cost of neonatal care	(4307)	(68 236)
Cost of early intervention	(26 919)	(30 258)
Cost of severe disability	(25 080)	(33 933)

\*Negative ICER is denoted by parentheses and indicates screening is the dominant strategy in all cases.

While the variables listed above cause screening to shift from a cost-saving to a cost-effective strategy, there was no plausible situation in which the no-screening strategy was dominant. For example, when the cost of a single transvaginal ultrasound scan passes \$ 187, cervical-length screening is no longer cost saving, but it remains cost-effective. Even at an extreme cost of \$ 300 per transvaginal scan, screening costs \$ 27 461 per QALY gained. When administration of vaginal progesterone reduces preterm birth by less than 20% instead of the previously predicted 45%, screening ceases to be a cost-saving strategy but remains cost-effective. Likewise, if the probability of delivery before 34 weeks with a shortened cervix is only 9.7%, not the estimated 34%, screening costs \$ 33 276 per QALY gained.

We varied the prevalence of cervical length < 1.5 cm from 0.9 to 1.88% based upon values found in the literature<sup>9, 11, 17</sup>. In this range, cervical-length screening is cost saving. In order to identify transition values, we also ran the model with a prevalence as low as zero. When the prevalence of a cervical length < 1.5 cm falls below 0.8%, screening is no longer cost saving, but it remains cost-effective. Below the implausible prevalence of 0.35%, the no-screening strategy becomes dominant. Monte Carlo Simulation (a computational algorithm that relies on repeated random sampling) was also used to simultaneously vary all variables across the extreme ranges listed in Tables 1 and 226. With 100 000 simulations, the screening strategy was cost-effective 99.4% of the time. In most of these instances (68%) screening was also cost saving.

## Discussion

Although only approximately one sixth of preterm births occur before 34 weeks' gestation, these neonates account for the majority of morbidity, mortality and cost<sup>1, 4, 16, 23, 27</sup>. Assessment of maternal history alone misses significantly more than half of women at risk for preterm birth<sup>5</sup>. Cervical-length measurement by transvaginal ultrasound provides a necessary screening tool to better predict which women are at risk for preterm birth<sup>7–9</sup>. Moreover, a combination of cervical-length measurement and vaginal progesterone supplementation has been shown to reduce the risk of preterm birth in a low-risk population<sup>11</sup>. Given this information, one could argue that expanding cervical-length screening to include the low-risk population would be reasonable. However, before any major screening initiatives are adopted, an understanding of the costs (intended and unintended) associated with screening is needed. We undertook this decision analysis to estimate the implications to the health of the offspring as well as the additional costs to the healthcare system associated with a comprehensive program using transvaginal ultrasound screening and progesterone intervention. Our analysis demonstrates that a screening program with appropriate interventions to reduce preterm birth would be cost-effective and in many cases cost saving.

Our findings are consistent with the only other study to examine cervical-length screening in low-risk patients, that of Cahill *et al.*<sup>28</sup>. While this prior study was thorough in its analysis, it did not account for many of the subsequent and unintended costs that a screening strategy would elicit. Thus, its conclusion that cervical-length screening is cost-effective needed to be verified in a study that included these unintended expenditures and consequences. The costs for serial cervical-length ultrasound scans, inpatient hospitalizations and progesterone administration for the mid-length (1.5–2.49 cm) cervix were included in our cost analysis despite the lack of evidence that any of these interventions improve neonatal outcome.

The model of Cahill *et al.* also used a significantly lower cost per transvaginal scan—\$ 52, with a range of \$ 43 to \$ 74. These rates are consistent with *Medicaid* reimbursement for non-facility charges only at inexpensive locales. This range does not include technical fees, which are a significant portion of the cost of ultrasound services, or additional ultrasound fees from repeat cervical assessments. It also does not account for many sites, including many cities, where higher *Medicaid* rates are charged using an adjustment factor, the Geographic Practice Cost Indices. As the model is from a societal perspective, it is important that the range of costs includes geographic price differences and physician fees. This was particularly important as the cost per transvaginal ultrasound scan was one of the few variables to which the model was sensitive.

While our model is somewhat biased against screening compared to the Cahill *et al.*<sup>28</sup> model (higher costs for ultrasound screening and more accountability for false-positives), we reached the same conclusion: a strategy of universal cervical-length screening would be cost-effective. This strengthens the growing evidence in favor of routine assessment of cervical length by ultrasonography. As with any decision analysis, the accuracy of our outcomes depends on the quality of the data used within our model. Although we were fortunate to have a randomized trial that demonstrated the effects of progesterone supplementation at reducing the risk of preterm birth in low-risk women with a short cervix, this could also be considered a weakness, and it certainly would be ideal (and a luxury) to have multiple randomized controlled trials that demonstrate this finding. Based on our sensitivity analysis, if progesterone is found to be significantly less effective at preventing preterm birth before 34 weeks, then cervical-length screening may not be cost saving. Therefore, our study highlights the importance of verifying the efficacy of progesterone at reducing the risk of preterm birth with future randomized controlled trials.

Our analysis was from the perspective of society. Direct costs were ascertained and accounted for and we did not use indirect costs in our model. However, most of these costs are likely to favor screening, such as the psychological and financial impact of caring for a premature neonate. However, we did examine the potential effects of productivity losses from prescribed bed rest due to a short cervix. While bed rest has never been shown to decrease preterm birth rates in women with shortened cervixes, a recent survey of members of the American College of Obstetricians and Gynecologists demonstrated that 34% of obstetricians prescribed bed rest for a cervical length of < 2.5 cm<sup>29</sup>. Thus, we explored the impact of bed rest on the cost-effectiveness of universal cervical-length screening in women with short and mid-length cervixes (< 1.5 cm and 1.5–2.49 cm, respectively). The losses in work productivity and domestic productivity are based on data from Goldenberg *et al.*<sup>30</sup> and adjusted to 2010 dollars. Even if all women with cervical length < 1.5 cm were placed on bed rest, cervical-length screening would remain cost saving. However if all women with a cervical length of < 2.5 cm were placed on bed rest, screening would shift from a cost-saving practice to a strictly cost-effective strategy, with each QALY costing \$ 82 000. This highlights the large cost to society of prescribed bed rest despite its unclear efficacy. We believe that this study provides a comprehensive analysis of the intended and unintended costs of transvaginal cervical-length screening in women at low risk for preterm birth. When this screening protocol is combined with vaginal progesterone treatment, screening is cost-effective for the healthcare system and should be investigated further.

## Addendum

We reanalyzed our model incorporating the recently published data of Hassan *et al.*<sup>31</sup>. We added an additional assumption to the base case that vaginal progesterone treatment reduced preterm birth rates in women with mid-pregnancy cervical lengths between 1.5 cm and 2.5 cm. With these adjustments, universal cervical length ultrasound screening continued to be the dominant strategy. For every 100 000 women screened we predict a net health improvement of 735 QALYs and net savings to the healthcare system of \$ 19 603 380 with universal cervical length screening. The results by Hassan *et al.* strengthen the evidence that universal cervical length screening could both improve quality of life and be cost-saving under a wide range of circumstances.

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## Use of transvaginal ultrasonography to predict preterm birth in women with a history of preterm birth

J. M. G. Crane\* and D. Hutchens

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### Abstract

#### Objective

To investigate whether cervical length measured by transvaginal ultrasonography predicts spontaneous preterm birth at < 35 weeks' gestation in women with a history of spontaneous preterm birth, stratified by spontaneous preterm birth history subtype (preterm premature rupture of membranes (PPROM) or preterm labor with intact membranes at onset of labor).

#### Methods

This retrospective cohort study included women with a history of spontaneous preterm birth that were subsequently pregnant with singleton gestations, compared with a low-risk control group. Transvaginal ultrasonographic cervical lengths were measured at 24 to 30 weeks of gestation. The primary outcome was spontaneous preterm birth at < 35 weeks. Secondary outcomes included spontaneous preterm birth at < 37 weeks and < 34 weeks, low birth weight, Cesarean delivery and perinatal morbidity and mortality. Multiple logistic regression analysis was used to control for potential confounders and calculate odds ratios and 95% confidence intervals. Receiver–operating characteristics (ROC) curves were used to determine the best cut-off for transvaginal ultrasound cervical length in predicting spontaneous preterm birth at < 35 weeks.

#### Results

Women with a history of spontaneous preterm birth with intact membranes at onset of labor ( $n=42$ ) had a shorter cervical length (3.28 cm) than women with a history of spontaneous preterm birth with PPRM at onset of labor ( $n=48$ , cervical length 3.77 cm;  $P=0.019$ ), and both subgroups had shorter cervical lengths than the low-risk control group ( $n=103$ , cervical length 4.30 cm;  $P<0.0001$ ). Both subgroups were associated with spontaneous preterm birth at < 35 weeks, < 37 weeks, < 34 weeks and birth weight < 2500 g. ROC curves determined that the best

cut-off for cervical length to predict spontaneous preterm birth at < 35 weeks was 3.0 cm. By multiple logistic regression analysis, the only independent predictors of spontaneous preterm birth at < 35 weeks were cervical length < 3.0 cm, a history of spontaneous preterm birth and antepartum bleeding in the current pregnancy. In women with a history of spontaneous preterm birth, a cervical length as measured by transvaginal ultrasonography of < 3.0 cm had a sensitivity of 63.6%, specificity of 77.2%, positive predictive value of 28.0% and negative predictive value of 93.8%, for preterm birth at < 35 weeks.

## Conclusion

Women with a history of spontaneous preterm birth with preterm labor and intact membranes at the onset of labor have shorter cervixes than women with a history of spontaneous preterm birth and PPRM at the onset of labor, and both groups have shorter cervixes than a low-risk control group. Both groups of women with a history of spontaneous preterm birth have an increased risk of recurrent spontaneous preterm birth at < 35 weeks, and this is predicted by a transvaginal ultrasound cervical length of < 3.0 cm.

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## Introduction

Preterm birth is a major cause of perinatal morbidity and mortality<sup>1–5</sup>, and may be classified by its clinical presentation—including preterm premature rupture of membranes (PPROM), spontaneous preterm labor or indicated preterm delivery for maternal or fetal reasons<sup>6, 7</sup>. One of the most important risk factors for preterm birth is a history of spontaneous preterm birth<sup>8–14</sup>. Cervical length measured by transvaginal ultrasonography has been shown to predict preterm birth in asymptomatic low-risk women as well as in those presenting with threatened preterm labor<sup>15–18</sup>. We recently performed a meta-analysis to estimate the accuracy of cervical length measured by transvaginal ultrasonography in asymptomatic high-risk women in predicting spontaneous preterm birth<sup>19</sup>. We found that cervical length measured by transvaginal ultrasonography in asymptomatic high-risk women predicted spontaneous preterm birth. However the studies did not distinguish between the specific subtypes of spontaneous preterm birth history (PPROM prior to the onset of labor compared with spontaneous onset of labor with intact membranes) in the same study. In addition, only one study evaluated the use of transvaginal ultrasonography after 24 weeks' gestation in women specifically with a history of spontaneous preterm birth<sup>20</sup>.

The objective of the current study was to evaluate the efficacy of transvaginal ultrasonography at 24–30 weeks' gestation in women with a history of spontaneous preterm birth, stratified by spontaneous preterm birth history subtype, in predicting spontaneous preterm birth at < 35 weeks' gestation.

## Patients and Methods

This retrospective cohort study included women with singleton pregnancies delivering between June 2000 and July 2006 at the Women's Health Centre of Eastern Health, St John's, Newfoundland, Canada, who had previously had a spontaneous preterm birth at between 16 + 0 weeks and 36 + 6 weeks, and who had undergone measurement of cervical length by transvaginal ultrasonography at between 24 and 30 weeks' gestation in the current pregnancy. This group of women was divided into two subgroups: Group 1 comprised women with a history of PPRM prior to preterm labor leading to delivery, and Group 2 comprised women with a history of intact membranes at the onset of preterm labor resulting in preterm birth. Women were excluded if they had undergone cervical cerclage placement. None of the women received progesterone in the current pregnancy, as this was not the practice at the center at the time of the study. A comparison group of low-risk women with singleton gestations without a history of spontaneous preterm birth, who had also undergone cervical-length measurement by transvaginal ultrasonography at between 24 and 30 weeks, was also included. The study was approved by the Human Investigation Committee of Memorial University and the Ethics Committee of the hospital.

Methods of transvaginal ultrasonography have been previously described<sup>21</sup>. Some of the low-risk women have been described in a previous publication evaluating transvaginal ultrasonography in women who had treatment for cervical intraepithelial neoplasia compared with low-risk women who had not had such treatment<sup>21</sup>. Transvaginal ultrasonography was performed by one of three maternal–fetal medicine specialists, with the ATL HDI 5000 Ultrasound System (Philips Medical Systems, Markham, Ontario, Canada) or Voluson 730 Ultrasound System (GE Medical Systems, Milwaukee, WI, USA) using a 5–9-MHz transvaginal probe. With the maternal bladder empty, the cervical length was measured in the sagittal plane after visualizing simultaneously the internal and external cervical os. Three measurements were obtained. Next suprapubic pressure was applied, displacing the presenting fetal part to determine whether funneling had occurred, defined as a ‘V’ or ‘U’ shaped indentation of the internal os by the amniotic membranes. The shortest of these measurements was considered the cervical length. If the cervical length was measured on more than one occasion between 24 and 30 weeks' gestation, the shortest measurement was used. The women and attending physicians were not blinded to the cervical length measurements. Gestational age was deduced from known last menstrual period or dating ultrasound at less than 20 weeks' gestation. Complications of each pregnancy were recorded, including antepartum bleeding after 20 weeks, the use of tocolytics, polyhydramnios, diabetes (both gestational and pregestational), and maternal smoking. Demographics including gravidity, parity, maternal age and ethnicity were recorded. The primary outcome of the study was spontaneous preterm birth at less than 35 weeks' gestation, with cervical length as determined by transvaginal ultrasound being the primary exposure variable of interest. Spontaneous preterm birth included preterm birth related to the spontaneous onset of labor with intact membranes or with PPRM. Secondary outcomes included the occurrence of spontaneous preterm birth at less than 37 and at less than 34 weeks' gestation, with the presence of funneling on transvaginal ultrasonography being a secondary exposure variable of interest. Neonatal outcomes included gestational age at delivery, birth weight, Apgar score, admission to the neonatal intensive care unit (NICU) and perinatal

morbidity and mortality. Perinatal morbidity was defined as at least one of the following: 5 min Apgar score less than 7; cord arterial pH less than 7.10; bacterial infection within 72 h of delivery; NICU admission for more than 24 h; seizure; ventilation after initial resuscitation; and evidence of end-organ dysfunction within 72 h of delivery (e.g. hepatic, cardiac, renal, coagulation or hypotension).

Sample size was based on detecting a 5-mm difference in cervical length with a standard deviation of 8 mm<sup>18</sup> (based on a previous study), which required 42 women per group, and detecting a difference in the occurrence of spontaneous preterm birth from 2%<sup>21</sup> (based on the control group in a previous study) to 20% (based on the estimated risk of spontaneous preterm birth if there was a history of spontaneous preterm birth in a previous pregnancy)<sup>8, 9</sup>. In order to achieve this, a minimum of 39 women in each study group and 78 in the control group were needed, using a ratio of 1 : 2 subjects to controls.

Statistical analysis was performed with SPSS 15.0 (SPSS Inc., Chicago, IL, USA) and PEPI 3.01, 2000 (Computer Programs for Epidemiologists, Stone Mountain, GA, USA). Continuous variables that were normally distributed were described and compared with Student's *t*-test and analysis of variance (ANOVA). If the null hypothesis was rejected in ANOVA, pair-wise comparisons were performed using the Tukey HSD test. Categorical variables were compared with the  $\chi^2$  or Fisher's exact test, where appropriate. Ordinal variables and continuous variables that were not normally distributed were described as medians and compared with the Wilcoxon Rank Sum or Kruskal–Wallis test, and a *P* of less than 0.05 was considered statistically significant. Multiple logistic regression analysis was used to control for potential confounders and determine which variables significantly predicted the primary outcome of spontaneous preterm birth at less than 35 weeks. Variables in the initial models were maternal age, parity, smoking, antepartum bleeding after 20 weeks, diabetes, polyhydramnios, previous spontaneous preterm birth, and cervical length. Variables were retained in the final models if they had a *P* less than 0.10. Receiver–operating characteristics (ROC) curves were used to determine the best cut-off point for cervical length for the prediction of spontaneous preterm birth at less than 35 weeks' gestation.

## Results

One hundred ninety-three women were included in the study—48 women with a history of spontaneous preterm birth with prior PPRM (Group 1), 42 with a history of spontaneous preterm birth with preterm labor with intact membranes at the onset of labor (Group 2), and 103 low-risk controls. Maternal characteristics of the three groups are shown in Table 1. All the women except one were Caucasian. Both the preterm study groups had greater median gravidity and parity than the low-risk control group. Women in Group 2 had a higher rate of diabetes and polyhydramnios than those in the control group. Women in Group 1 had a higher incidence of antepartum bleeding in the current pregnancy than the women in Group 2.

**Table 1** Maternal characteristics of the study population

<i>Parameter</i>	<i>Group 1</i> (n = 48)	<i>Group 2</i> (n = 42)	<i>Controls</i> (n = 103)	<i>P</i>
Maternal age (years)	29.9 ± 5.3	29.4 ± 4.1	29.4 ± 5.1	0.83*
Gravidity	3 [2,4]	3 [3,4]	2 [1,3]	<0.0001†
Parity	1 [1,2]	1 [1,2]	1 [0,1]	<0.0001†
Parous	45 (93.8)	38 (90.5)	55 (53.4)	<0.0001*
Smoker	11 (22.9)	6 (14.3)	16 (15.5)	0.46‡
Gestational age at TVUS (days)	184 ± 14	187 ± 14	186 ± 18	0.73*
<b>Antepartum complications</b>				
Bleeding	6 (12.5)	0 (0)	12 (11.7)	0.035§
Diabetes	7 (14.6)	9 (21.4)	8 (7.8)	0.068‡
Polyhydramnios	1 (2.1)	3 (7.1)	0 (0)	0.015§

Data expressed as mean ± SD, median [quartiles] or n (%). P-values are for comparison of all three groups. Group 1, women with previous spontaneous preterm birth with preterm premature rupture of membranes; Group 2, women with previous spontaneous preterm birth with intact membranes at onset of labor. \*ANOVA. †Kruskall–Wallis test. ‡ $\chi^2$  test. §Fisher's exact test. TVUS, transvaginal ultrasonography.

Table 2 shows the transvaginal ultrasound findings of the study groups and the control group. Women in Group 2 had a significantly shorter cervix than women in Group 1. Both groups had shorter cervixes than the control group (ANOVA,  $p = 0.0001$ ; Tukey HSD: Group 2 vs. Group 1,  $p = 0.019$ ; Group 2 vs. control group,  $p < 0.0001$ ; Group 1 vs. control group,  $p = 0.001$ ). Funneling was found more commonly in women in Group 2 than in those in the control group. A cervical length of less than 3.0 cm was found more frequently in both Group 1 and Group 2 than in the control group.

**Table 2** Transvaginal ultrasound findings

<i>Parameter</i>	<i>Group 1</i> (n = 48)	<i>Group 2</i> (n = 42)	<i>Controls</i> (n = 103)	<i>P</i>
Shortest cervical length (cm)	3.77 ± 0.96	3.28 ± 1.01	4.30 ± 0.71	<0.0001*
Funneling	3 (6.3)	7 (16.7)	1 (1.0)	0.0008†
Cervical length < 3.0 cm	10 (20.8)	15 (35.7)	2 (1.9)	<0.0001‡

Data expressed as mean ± SD or n (%). Group 1, women with previous spontaneous preterm birth with preterm premature rupture of membranes; Group 2, women with previous spontaneous preterm birth with intact membranes at onset of labor. \*ANOVA. †Fisher's exact test. ‡ $\chi^2$  test.

Maternal outcomes are shown in Table 3. Both the study groups were more likely to have spontaneous preterm birth at less than 35 weeks' gestation in the current pregnancy, as well as spontaneous preterm birth at less than 37 weeks and at less than 34 weeks, compared with the control group. The study groups were also more likely to have episodes of threatened preterm labor. The lengths of the first and second stages of labor, excluding Cesarean deliveries, were shorter in women in Group 2 than in those in the control group. There was no difference in Cesarean delivery rates. Women in Group 1 were more likely to have recurrent PPROM than those in Group 2.

Table 3 Maternal outcomes of the study population

<i>Outcome</i>	<i>Group 1</i> (n = 48)	<i>Group 2</i> (n = 42)	<i>Controls</i> (n = 103)	<i>P</i>
Spontaneous PTB at < 35 weeks	6 (12.5)	5 (11.9)	1 (1.0)	0.002*
Spontaneous PTB at < 37 weeks	13 (27.1)	8 (19.0)	4 (3.9)	<0.0001†
Spontaneous PTB at < 34 weeks	4 (8.3)	4 (9.5)	1 (1.0)	0.016*
Gestational age at delivery (days)	262 ± 19	264 ± 15	274 ± 14	<0.0001‡
Cesarean delivery	11 (22.9)	10 (23.8)	26 (25.2)	0.95†
Threatened preterm labor	17 (35.4)	18 (42.9)	12 (11.7)	<0.0001†
Tocolysis	2 (4.2)	1 (2.4)	2 (1.9)	0.83*
PPROM in current pregnancy	10 (20.8)	2 (4.8)	5 (4.9)	0.003†
Length of first stage of labor (min)§	322 ± 239	248 ± 158	362 ± 205	0.036‡
Length of second stage of labor (min)§	39 ± 62	33 ± 44	62 ± 72	0.055‡

Data expressed as *n* (%) or mean ± SD. Group 1, women with previous spontaneous preterm birth with preterm premature rupture of membranes (PPROM); Group 2, women with previous spontaneous preterm birth with intact membranes at onset of labor. \*Fisher's exact test. † $\chi^2$  test. ‡ANOVA. §Excluding Cesarean delivery. PTB, preterm birth.

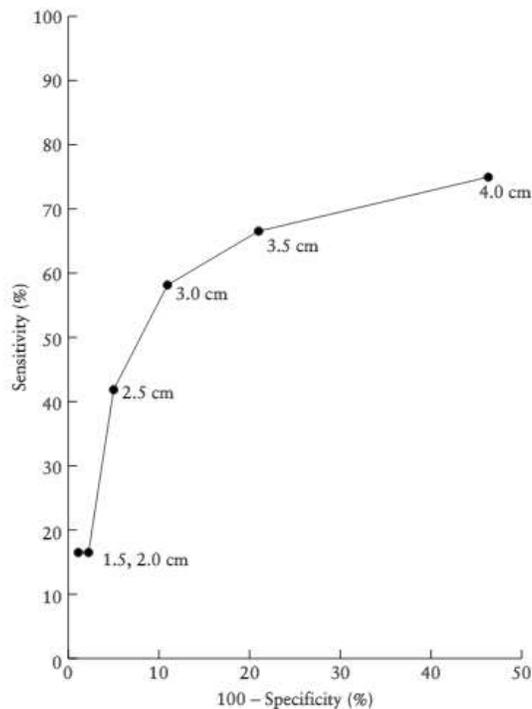
Table 4 shows the neonatal outcomes of the three groups. Birth weight was significantly lower in both the study groups and there was a higher incidence of birth weight less than 2500 g in these groups compared with the control group. There were no differences in other neonatal outcomes including Apgar score, NICU admission, and perinatal morbidity. There was one perinatal death in this study. The mother was in the control group and had a Cesarean delivery for transverse lie at term; a major congenital heart defect was diagnosed in the baby in the neonatal period. This child had palliative care and died at 32 days of age.

**Table 4 Neonatal outcomes of the study population**

<i>Outcome</i>	<i>Group 1</i> (n = 48)	<i>Group 2</i> (n = 42)	<i>Controls</i> (n = 102)*	<i>P</i>
Birth weight (g)	3115 ± 665	3159 ± 652	3441 ± 625	0.005†
Birth weight < 2500 g	8 (16.7)	7 (16.7)	6 (5.9)	0.058‡
Apgar score < 7 at 1 min	6 (12.5)	2 (4.8)	9/101 (8.9)	0.47§
Apgar score < 7 at 5 min	1/47 (2.1)	0 (0)	3/101 (3.0)	0.81§
NICU admission	8 (16.7)	6 (14.3)	8/101 (7.9)	0.24‡
Perinatal morbidity	8 (16.7)	6 (14.3)	9 (8.9)	0.34‡

Data expressed as *n* (%) or mean ± SD. Group 1, women with previous spontaneous preterm birth with preterm premature rupture of membranes; Group 2, women with previous spontaneous preterm birth with intact membranes at onset of labor. \*Neonatal data (apart from gestational age at delivery) missing for one patient. †ANOVA. ‡ $\chi^2$  test. §Fisher's exact test. NICU, neonatal intensive care unit.

ROC curves were developed to predict spontaneous preterm birth at less than 35 weeks' gestation, revealing the best cut-off for cervical length to be less than 3.0 cm (Figure 1). Sensitivity, specificity, positive and negative predictive values and likelihood ratios for this cut-off for women with a history of spontaneous preterm birth are shown in Table 5.



**Figure 1** Receiver–operating characteristics curve for transvaginal ultrasonographic measurement of cervical length to predict spontaneous preterm birth at < 35 weeks' gestation.

Receiver–operating characteristics curve for transvaginal ultrasonographic measurement of cervical length to predict spontaneous preterm birth at < 35 weeks' gestation.

**Table 5** Screening test accuracy for transvaginal ultrasonographic cervical length < 3.0 cm to predict spontaneous preterm birth at < 35 weeks' gestation in women with a history of spontaneous preterm birth

<i>Parameter</i>	<i>Value</i>
Sensitivity	63.6% (7/11; 95% CI, 33.6–87.2%)
Specificity	77.2% (61/79; 95% CI, 67.0–85.5%)
Positive predictive value	28.0% (7/25; 95% CI, 13.2–47.7%)
Negative predictive value	93.8% (61/65; 95% CI, 85.5–98.0%)
Positive likelihood ratio	2.79 (95% CI, 1.53–5.11)
Negative likelihood ratio	0.47 (95% CI, 0.21–1.04)

Multiple logistic regression analysis was performed to control for potential confounders to identify predictors of spontaneous preterm birth at less than 35 weeks' gestation, revealing that the only independent predictors were a history of spontaneous preterm birth (odds ratio (OR) 13.64; 95% CI, 1.34–138.81), cervical length less than 3.0 cm (OR 5.00; 95% CI, 1.28–19.49) and antepartum bleeding (OR 11.37; 95% CI, 2.01–64.16). Multiple logistic regression analysis was also performed for birth weight less than 2500 g, finding that smoking (OR 3.85; 95% CI, 1.34–11.08) and cervical length < 3.0 cm (OR 6.81; 95% CI, 2.40–19.31) were the independent predictors.

## Discussion

Our results confirm that cervical length as measured by transvaginal ultrasonography predicts spontaneous preterm birth in women with a history of spontaneous preterm birth, a finding common to both subgroups of spontaneous preterm birth history. It is important that both groups of women be evaluated separately, as the pathogenic process may be different for these two etiological categories of preterm birth<sup>14</sup>. Similarly to previous studies<sup>14, 22–24</sup>, we also found that women with a history of preterm birth preceded by PPRM were at increased risk of recurrent PPRM (20.8%) compared with low-risk women (4.9%). Unlike other investigators<sup>24</sup>, we found that women with a history of preterm birth with intact membranes at onset of labor did not have a higher risk for PPRM in the current pregnancy (4.8%) compared with low-risk women (4.9%). These findings of different rates of PPRM in the current pregnancy, based on the type of previous preterm birth, support the hypothesis that different mechanisms are responsible for preterm birth in these two groups of women<sup>14</sup>.

Interestingly, unlike most other studies of women with a history of spontaneous preterm birth<sup>20, 25–28</sup>, we noted the best cut-off for cervical length to predict spontaneous preterm birth to be < 3.0 cm, rather than < 2.5 cm. This may be owing to the later gestational age at which transvaginal ultrasonography was carried out in our study, as most other studies evaluated cervical length prior to 24 weeks<sup>20, 25–28</sup>, with only one study evaluating cervical length after 24 weeks, in 42 women<sup>20</sup>. It is important that cervical length measured by transvaginal ultrasonography at this later gestational age be evaluated as many centers currently offer

transvaginal ultrasound beyond 24 weeks of gestation to women with a history of spontaneous preterm birth<sup>29</sup>. Although no randomized clinical trials have shown that the use of transvaginal ultrasonography at this gestational age reduces perinatal morbidity and mortality, this information may be useful in counseling and managing women (such as the use of corticosteroids for fetal lung maturation) and may identify a group of high-risk women for future trials of interventions to reduce the incidence of preterm birth. A recent study found that the use of progesterone in women found to have a short cervix by transvaginal ultrasonography at 20–25 weeks reduced the rate of spontaneous preterm birth at less than 34 weeks' gestation<sup>30</sup>; however this study did not evaluate transvaginal ultrasonography at later gestational ages. Also, this study was not powered to detect a reduction in perinatal morbidity and mortality. It is important that the shortcomings of this study be addressed. We did not have adequate power to evaluate perinatal morbidity and mortality. Although we were able to control for many potential confounders (including maternal age, parity, antepartum bleeding, smoking, polyhydramnios and diabetes) we were not able to control for socioeconomic status as this information was not available to us. Also as we only evaluated cervical length between 24 and 30 weeks, we were not able to comment on the outcomes of extreme prematurity or the use of cervical cerclage (as women undergoing cervical cerclage were excluded). We do not know the number of women undergoing cervical cerclage during the study period. In addition, this study evaluated the shortest cervical length between 24 and 30 weeks, and did not evaluate changes in cervical length if serial assessments were performed. Finally, we did not evaluate other potential predictors of preterm birth in this group, such as fetal fibronectin.

In summary, women with a history of spontaneous preterm birth with preterm labor and intact membranes at the onset of labor had shorter cervixes than women with a history of spontaneous preterm birth and PPROM, and both groups had shorter cervixes than the low-risk control group. Both groups of women with a history of spontaneous preterm birth had an increased risk of recurrent spontaneous preterm birth at less than 35 weeks' gestation. This is predicted by a transvaginal ultrasound cervical length of < 3.0 cm.

## Acknowledgements

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# Cost-effectiveness of transvaginal ultrasound cervical length screening in singletons without prior preterm birth: an update

Maureen Hamel, Kelly Orzechowski, Vincenzo Berghella, Stephen Thung, Erika Werner

## Article Outline

- I. Objective
- II. Study Design
- III. Results
- IV. Conclusion

## Objective

To evaluate the cost effectiveness of universal transvaginal ultrasound (TVU) cervical length (CL) screening in singleton pregnancies without prior spontaneous preterm birth (PTB).

## Study Design

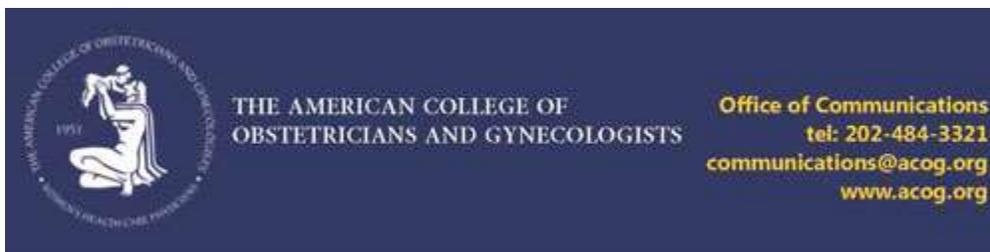
We developed a decision model to assess costs and effects of universal TVU CL screening at 18-24 weeks gestation compared to routine care for singletons pregnancies without prior PTB. Based on recent data, the model contains the following updates: 1) reduced prevalence of  $CL \leq 20\text{mm}$  at initial screening ultrasound (0.82%), 2) vaginal progesterone supplementation for women with  $CL \leq 20\text{ mm}$ , 3) one additional ultrasound for women with  $CL 21-24.9\text{mm}$ , and 4) the assumption that vaginal progesterone reduces the rate of  $PTB < 34$  weeks gestation by 39% if a short CL is diagnosed. The primary outcome was Incremental Cost-Effectiveness Ratio (ICER). We assumed a willingness to pay of \$100,000 per quality adjusted life year (QALY) gained. Additional outcomes included offspring incidence with long-term neurological deficits and neonatal death. Sensitivity analyses were performed to assess the robustness of the results.

## Results

For every 100,000 women screened, universal TVU CL screening saves \$2,325,457 compared to routine care. Screening results in 240 QALYS gained and 11 fewer neonatal deaths or neonates with long-term neurologic deficits per 100,000 women screened. Cervical length screening is the dominant strategy (cost saving with improved outcomes). Sensitivity analyses reveal that when prevalence of TVU CL  $\leq$  20mm is  $<0.33\%$ , universal TVU CL screening is no longer cost-effective. Additionally, when TVU CL costs  $>\$122$ , prometrium reduces delivery risk before 34 weeks  $<34\%$ , or the prevalence of a TVU CL  $\leq$  20 mm is  $<0.7\%$ , CL screening is cost-effective but not cost saving.

## Conclusion

Despite the reduced prevalence and efficacy used in this model, universal TVU CL continues to be a dominant strategy when compared to routine care in singletons without prior PTB.



## 17P Plus Cerclage Decreases Preterm Labor Risk

May 6, 2013

**New Orleans, LA** -- Pregnant women at risk of preterm labor who have their cervix stitched closed may increase their chances of carrying a fetus to term by also receiving injections of 17P, according to research presented today at the Annual Clinical Meeting of The American College of Obstetricians and Gynecologists.

The cervix is stitched closed in a minor surgery known as “cerclage.” 17P (17 alpha-hydroxyprogesterone) is a progesterone-based hormone given to pregnant women at high risk for preterm birth. It is available as a gel or an injectable.

A small study, lead by Lorene Temming, MD, at Carolinas Medical Center in Charlotte, NC, looked at 123 women from 2009 to 2011. It found that pregnant women receiving cerclage alone were 22 times more likely to experience preterm birth before 34 weeks’ gestation than those given cerclage plus 17P.

Cerclage is often performed on pregnant women with a history of multiple second-trimester losses who have painless cervical dilation and deliver early, a condition called cervical insufficiency. Other studies have shown 17P prevents recurrent preterm birth in women with a history of preterm birth.

“Preterm birth is a spectrum of disease, and preterm labor as well as cervical insufficiency, are both on this spectrum,” said Dr. Temming. “Preterm labor is typically treated with weekly injections of 17P, and cervical insufficiency is typically treated with cerclage. I wanted to see if the addition of 17P to people treated with cerclage showed improved outcomes,” Dr. Temming added.

According to Dr. Temming, the results are surprising because other studies have not shown a statistically significant benefit of adding 17P treatment to cerclage, though

some showed a trend toward decreased rates of preterm labor with the addition of 17P.

Women in Dr. Temming's study had cerclage for various reasons, but a large percentage were emergency cerclage. Dr. Temming said this could account for some of the differences between her study and others because this group may reflect a population with more significant risk.

*\*Monday Poster #78: Cerclage Alone vs. Cerclage and 17P for the Prevention of Preterm Birth*

*The American College of Obstetricians and Gynecologists (The College), a 501(c)(3) organization, is the nation's leading group of physicians providing health care for women. As a private, voluntary, nonprofit membership organization of more than 57,000 members, The College strongly advocates for quality health care for women, maintains the highest standards of clinical practice and continuing education of its members, promotes patient education, and increases awareness among its members and the public of the changing issues facing women's health care. The American Congress of Obstetricians and Gynecologists (ACOG), a 501(c)(6) organization, is its companion organization. [www.acog.org](http://www.acog.org)*

## **Management of Pregnancies With Cervical Shortening: A Very Short Cervix Is a Very Big Problem**

Hee Joong Lee, MD, PhD,\* Tae Chul Park, MD, PhD,\* and Errol R Norwitz, MD, PhD†

### **Abstract**

Preterm birth, Cervical length measurement, Cervicovaginal fetal fibronectin Preterm birth (PTB), defined as birth before 37 weeks of gestation, complicates more than 12% of deliveries and is the leading cause of perinatal morbidity and mortality.<sup>1–5</sup> Of all neonatal deaths, 75% to 95% occur as a result of preterm delivery.<sup>6</sup> The prognosis for individual preterm infants depends primarily on gestational age at birth. Mortality rises from about 2% for infants born at or after 32 weeks to more than 90% for those born at 23 weeks.<sup>7</sup> The risk of severe handicap in survivors is more than 60% for those born at 23 weeks and less than 5% by 32 weeks.<sup>8–10</sup> PTB is also a major cause of long-term health problems in neonates, including respiratory distress syndrome, chronic lung disease (bronchopulmonary dysplasia), infection, intraventricular hemorrhage, and severe neurologic deficit.<sup>11,12</sup> Unfortunately, despite intensive research efforts, we cannot effectively stop preterm labor and there has been no decrease in the overall incidence of PTB over the past 30 years.<sup>13–16</sup>

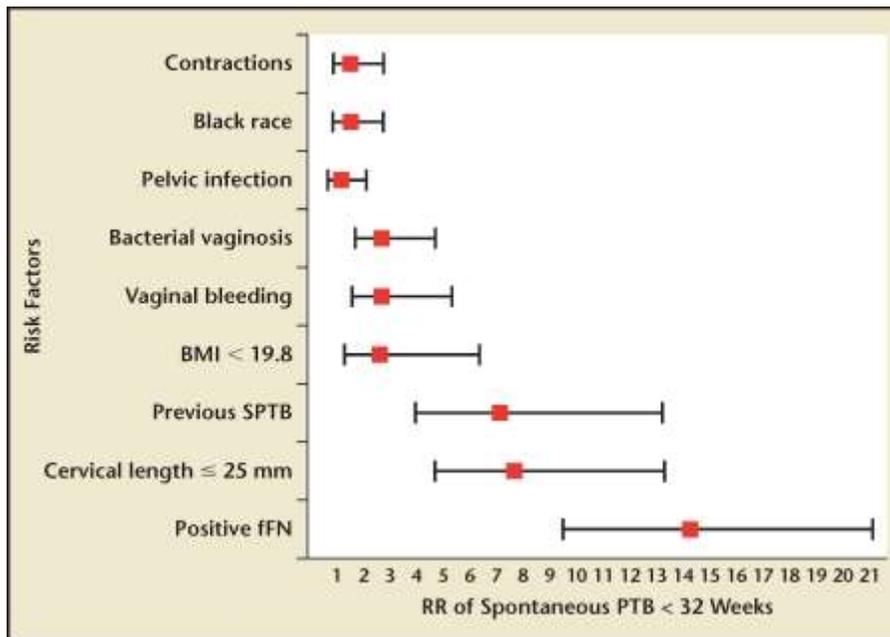
### **Can We Accurately Predict Preterm Delivery?**

#### **Clinical Features Are Not Reliable**

A history of a prior spontaneous PTB is the best demographic predictor for a recurrent PTB, but it is not useful for nullipara. There are 4 major groups of tests that have been developed to identify women at high risk for PTB: home uterine activity monitoring (HUAM), risk factor scoring, cervical length measurements, and biochemical/endocrine markers. Unfortunately, measurement of the frequency of uterine contractions is not clinically useful for predicting PTB,<sup>17</sup> and HUAM has been largely abandoned. A number of epidemiologic, demographic, and historic risk factors for PTB have been identified including, among others, multiple pregnancy, black race, reduced prepregnancy maternal body mass index (< 19.8 kg/m<sup>2</sup>), bacterial vaginosis, vaginal bleeding, smoking, and illicit drug use (cocaine).<sup>18,19</sup> However, risk factor scoring has proven to be of limited benefit in identifying women at risk of PTB, and reliance on risk factor scoring alone will fail to identify more than 50% of women who deliver preterm.<sup>20</sup> Most importantly, perhaps, premonitory symptoms and signs—including reported uterine contractions (regular or irregular), pelvic pressure, backache, increased vaginal discharge, or vaginal bleeding—that have traditionally been the cornerstone of clinical assessment for PTB—have been shown to be nonspecific and poorly predictive of a subsequent PTB.<sup>17,21</sup>

Direct digital examination of the cervix is subjective and may be misleading, especially in multipara. For this reason, serial digital examination of the cervix throughout pregnancy has not been shown to significantly improve pregnancy outcome.<sup>22</sup> However, sonographic measurement of residual cervical length (CL) does appear to accurately identify women at risk for PTB.<sup>23</sup> A number of biochemical/ endocrine markers have been studied as potential predictors of PTB.<sup>24</sup> The most widely used and consistently supported of these markers is cervicovaginal fetal fibronectin (fFN).<sup>25,26</sup> In the absence of reliable clinical predictors of PTB, obstetric care providers should be focusing their attention on the 2 best and most widely accepted methods of identifying women at high risk of PTB in both nullipara and multipara: fFN and CL measurements ([Figure 1](#)).

[Figure 1](#)



Risk of spontaneous preterm birth (SPTB) before 32 weeks of gestation according to various risk factors. BMI, body mass index; fFN, fetal fibronectin; RR, relative risk. Data from Goldenberg RL et al.<sup>19</sup>

## fFN

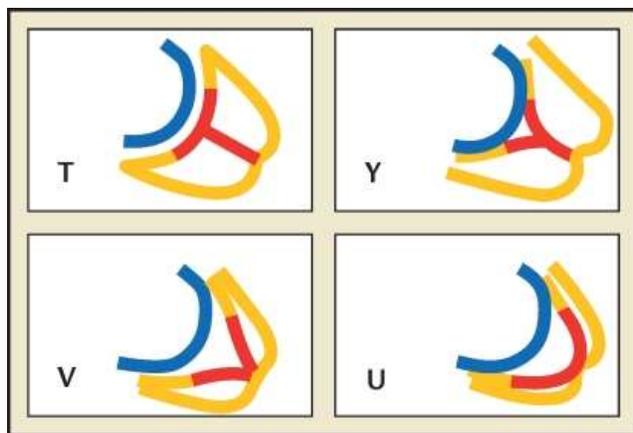
Fetal fibronectin is a fetal glycoprotein found at the interface between the maternal decidua and fetal amniochorion. It serves as the glue that holds the fetal membranes down to the underlying uterine tissues. fFN is normally present in the cervicovaginal secretions of pregnant women before 20 weeks of gestation and again at term, but should be absent between 22 and 37 weeks.<sup>26,27</sup> Elevated levels of fFN in the cervicovaginal discharge (defined as > 50 ng/mL) has been shown to be a reliable predictor of subsequent PTB in the setting of intact membranes, and likely represents premature separation of the fetal membranes from the underlying maternal decidua.<sup>27</sup> It is approved by the US Food and Drug Administration (FDA) and recommended by The American College of Obstetricians and Gynecologists (ACOG) for this indication. Interestingly, markedly elevated levels of cervicovaginal fFN from 13 to 22 weeks of gestation have also been associated with an increased risk of spontaneous PTB,<sup>26,27</sup> but the test is not FDA approved nor ACOG recommended at this gestational age. The detection of fFN in the

cervicovaginal discharge at 22 to 24 weeks of gestation is associated with a delivery rate of only 13% by 28 weeks of gestation and 36% by 37 weeks.<sup>28</sup> The major value of the fFN test lies in its high negative predictive value. At least 99% of symptomatic patients with a negative fFN will not deliver within 7 days.<sup>29</sup>

## Cervical Length Measurements

The gold standard for the measurement of CL in pregnancy is transvaginal ultrasonography (TVS) using sterile technique, which has many advantages when compared with digital examination. TVS is objective, reproducible, and acceptable to patients.<sup>30</sup> Cervical changes such as dilatation of the internal cervical os with funneling (beaking) of the membranes can be easily appreciated by TVS, but not by digital examination.<sup>31</sup> Moreover, TVS appears to be safe and does not increase the risk of ascending infection even in patients with preterm premature rupture of membranes (PROM).<sup>32,33</sup>

A number of sonographic features of the cervix on TVS have been correlated with PTB, including funneling of the membranes and the presence of debris within the adjacent amniotic fluid,<sup>34</sup> but the most consistent association is with the so-called residual CL, which refers to the measurement of closed cervix (canal length) between the internal os and external os. The CL measurement should be acquired in the sagittal view using TVS while the bladder is empty and without excessive pressure applied by the transvaginal probe. This measurement has an interobserver variation of 5% to 10%.<sup>35</sup> It has been suggested that the process of cervical shortening begins with dilatation of the internal os leading to funneling and progressive shortening of the CL.<sup>36</sup> Dr. Jay Iams has described the appearance of the cervix on TVS over time as a progression of the letters T, Y, V, and U (Trust Your Vaginal Ultrasound) representing the progressive increasing funneling and decreasing CL (Figure 2).<sup>37</sup> Although some degree of cervical shortening may be explained by normal biologic variance, it is likely that most cases of cervical shortening result from pathologic processes such as inflammation, hemorrhage, premature uterine contraction, or uterine overdistension.<sup>19,38</sup>



**Figure 2** Sonographic appearance of the cervix on transvaginal sonography with progressive effacement and shortening: Trust Your Vaginal Ultrasound. Reproduced with permission from Iams JD.<sup>37</sup>

In unselected or low-risk pregnancies, the CL does not change significantly between 20 and 30 weeks of gestation with a median CL of 35 mm (10th–90th percentile, 25 mm and 45 mm,

respectively) at 22 weeks of gestation and 33.7 mm at 28 weeks.<sup>39</sup> In women at high risk for spontaneous PTB, average CL measurements are 36.7 mm at 15 weeks, 35.7 mm at 20 weeks, and 33.8 mm at 25 weeks.<sup>40</sup> After 28 weeks, however, even women who deliver at term begin to have cervical shortening.<sup>40</sup> For these reasons, CL measurements prior to 16 weeks and after 32 weeks are of little use in predicting women at risk of PTB. Transvaginal CL measurements between 16 and 24 weeks of gestation, however, have been shown to be very useful for predicting PTB in high-risk pregnancies.<sup>41</sup>

Shortened CL is a risk factor for PTB in both low- and high-risk pregnancies. As discussed above, a strong inverse correlation exists between CL and PTB. The risk of spontaneous PTB increases as CL decreases. In low-risk pregnancies, women with a cervix that is shorter than 25 mm (10th percentile) at 24 weeks have a 6-fold increase in the risk of spontaneous PTB before 35 weeks of gestation compared with women with values above 40 mm (75th percentile).<sup>39</sup> Only 2% of low-risk pregnancies at 22 to 24 weeks of gestation will have a CL shorter than 15 mm, but 60% of these women will deliver before 28 weeks of gestation and 90% will deliver before 32 weeks.<sup>42</sup> In a prospective study of 705 high-risk women, the risk of spontaneous PTB before 35 weeks decreased by approximately 6% for each additional millimeter of CL ( $P = .001$ ) and by approximately 5% for each additional week of pregnancy during which the CL was measured ( $P = .004$ ).<sup>40</sup> Although it is controversial, most authorities use a cutoff of shorter than 25 mm to define a short CL at 22 to 24 weeks of gestation in both low- and high-risk pregnancies.<sup>39,43</sup> Routine measurement of CL to identify women at risk for spontaneous PTB is not currently recommended in otherwise low-risk pregnancies because of the low positive predictive value and absence of proven effective interventions.<sup>43-48</sup> However, serial measurements of CL should be performed in high-risk women to better identify those pregnancies at risk for spontaneous PTB prior to 35 weeks of gestation ([Table 1](#)).<sup>39,43-48</sup>

**Table 1**

Observational Studies Comparing Cervical Length Measured by Transvaginal Ultrasound With the Risk of Spontaneous Preterm Birth

Author (Year)	Gestational Age at Evaluation (wk)	No.	Population	Gestational Age End Point (wk)	Preterm Birth Rate (%)	Cervical Length Cutoff (mm)	Sensitivity	Specificity	Positive Predictive Value
Tongsong et al (1995) <sup>44</sup>	28-30	730	Unselected	<37	12.5	≤30	0.31	0.87	0.26
Iams et al (1996) <sup>39</sup>	24	2915	Unselected	<35	4.3	≤25	0.37	0.92	0.18
Taipale and Hiilesmaa (1998) <sup>45</sup>	18-22	3695	Unselected	<35	0.8	≤31	0.19	0.91	0.018
Berghella et al (1997) <sup>46</sup>	14-22	96	High-risk	<35	18	<25	0.59	0.85	0.45
Andrews et al (2000) <sup>47</sup>	15-20	53	High-risk	<35	30	≤22	0.86	1.0	1.0
Owen et al (2001) <sup>48</sup>	16-24	183	High-risk	<35	26	<25	0.69	0.80	0.55

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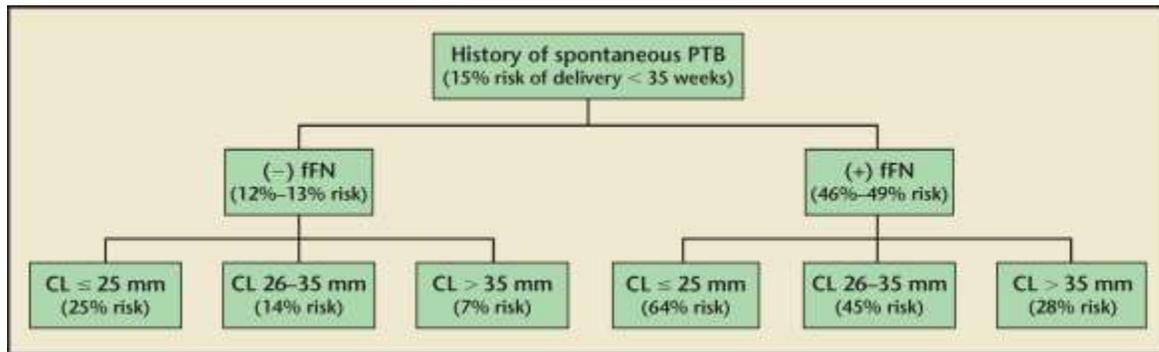
[Table 1](#)

Observational Studies Comparing Cervical Length Measured by Transvaginal Ultrasound With the Risk of Spontaneous Preterm Birth

## CL Measurements Combined With fFN

Cervical length measurements and fFN measurements are independent risk factors for PTB. The risk of spontaneous PTB is higher if both tests are abnormal than if only 1 is abnormal. For example, in a prospective, observational study of 3076 asymptomatic high- and low-risk pregnancies, women with a positive fFN and a CL shorter than 25 mm had a 33.3% risk of spontaneous PTB prior to 30 weeks of gestation compared with a 6.2% risk if they had only 1 of these findings and a 1.3% risk if both markers were absent.<sup>38</sup>

Similarly, the risk of recurrent PTB in asymptomatic women with a prior spontaneous PTB is different depending on the fFN and CL measurements. In this setting, a positive fFN at 22 to 24 weeks of gestation is associated with a 2- to 4-fold increased risk of recurrent PTB prior to 35 weeks, and the recurrence risk increases exponentially with decreasing CL irrespective of the fFN.<sup>49</sup> In this cohort, the tests were also additive. The recurrence risk in women with a positive fFN was 65% if the CL at 22 to 24 weeks of gestation was less than 25 mm, but only 25% if the CL was more than 35 mm. In women with a negative fFN, the recurrence risk was 25% if the CL was less than 25 mm and 7% if the CL was more than 35 mm ([Figure 3](#)).<sup>49</sup>



[Figure 3](#)

Risk of preterm birth (PTB) before 35 weeks of gestation in women with a history of a prior spontaneous PTB with or without cervicovaginal fetal fibronectin (fFN) and/or sonographic cervical length (CL) at 22 to 24 weeks of gestation. Data from Iams JD ...

Even in women with symptoms of preterm labor, PTB is highly unlikely if the CL is longer than 30 mm or if the fFN is negative.<sup>43</sup> In such women, selective use of fFN after CL measurement is more specific than CL alone for predicting PTB (81% vs 63%, respectively).<sup>50</sup> In light of these and other data showing conclusively that combined use of the CL measurement by TVS and cervicovaginal fFN is more effective for predicting PTB than any of these methods alone, 2-step testing should be performed in all women with symptoms of preterm labor to better identify those women at risk of PTB. To demonstrate the utility of such an approach, Hincz and colleagues<sup>51</sup> performed sonographic measurement of CL in 82 women with symptoms of preterm labor. A CL of less than 20 mm was regarded as a positive (abnormal) result for the prediction of PTB and a CL of greater than 31 mm was interpreted as a negative (normal) test. Cervicovaginal fFN was performed only in patients with a CL of 21 to 31 mm. In this cohort, the 2-step approach had an overall sensitivity of 86%, specificity of 90%, positive predictive value of 63%, and negative predictive value of 97% for predicting delivery within 28 days.<sup>51</sup>

## Treatments for Women With a Short Cervix

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A number of interventions have been proposed in an attempt to prevent PTB in women at high risk.

### Bed Rest, Tocolytics, and Cervical Cerclage

Bed rest and hydration are often recommended in an attempt to prevent PTB in women at high risk, but there is no consistent evidence that they are able to delay delivery.<sup>52</sup> Similarly, tocolytic medications are often prescribed with a view to preventing PTB. Again, there are no reliable and consistent data to suggest that any tocolytic agent can delay delivery for longer than 24 to 48 hours.<sup>53</sup> Although it is not unreasonable to use tocolytics in the acute setting to delay delivery for 24 to 48 hours to administer the first course of antenatal corticosteroids and to transfer the patient to a tertiary care center, if indicated, there is no place for routine administration of long-term maintenance tocolysis.<sup>54,55</sup> If maintenance tocolysis is offered, it should be clear to the patient that it is being done to make her more comfortable, to minimize her anxiety, and to decrease phone calls and visits to hospital at 3:00 AM, but that it will not prevent PTB.

Cervical cerclage has been widely used as a surgical method to prevent recurrent midtrimester pregnancy loss in women at risk. Elective (prophylactic) cerclage placement at 13 to 15 weeks of gestation may benefit some women with proven cervical insufficiency. Although highly contentious, more recent data suggest that cervical cerclage may reduce the risk of PTB in that subgroup of asymptomatic singleton pregnancies with both cervical shortening on TVS and a history of a prior spontaneous PTB.<sup>56-61</sup> Of note, the only randomized, controlled clinical trial on the use of cervical cerclage to prevent PTB in women with cervical shortening showed no benefit.<sup>61</sup> Cervical cerclage placement does not appear to prevent PTB in women with multiple pregnancies.<sup>56,57</sup>

### Progesterone

Progesterone supplementation (not treatment) is being increasingly accepted as an effective intervention to prevent PTB in select women, although it has not yet received FDA approval for this indication. Although not all studies have shown a benefit,<sup>62</sup> there is increasing evidence to suggest that progesterone supplementation from 16 to 20 weeks of gestation through 34 to 36 weeks of gestation may prevent preterm birth in some women at high risk by virtue of a prior spontaneous PTB<sup>63,64</sup> or cervical shortening.<sup>65</sup>

In a randomized clinical trial, weekly intramuscular injections of 17 alpha-hydroxyprogesterone caproate (17P) (250 mg) from 16 to 20 weeks of gestation through 36 weeks of gestation significantly reduced the risk of spontaneous PTB prior to 37 weeks by 33% in 459 women at high risk by virtue of a prior spontaneous PTB.<sup>63</sup> This translated into a significant reduction in the rates of complications of prematurity, including necrotizing enterocolitis, intraventricular hemorrhage, and need for supplemental oxygen.<sup>63</sup> In another randomized clinical trial, the daily use of progesterone (100 mg) by vaginal suppository between 24 and 34 weeks of gestation in a similar high-risk population of 142 women significantly reduced the frequency of preterm uterine contractions (by 56%) and the risk of spontaneous delivery before 37 weeks (by 51%).<sup>64</sup> More recently, 413 low-risk women with asymptomatic cervical shortening (< 15 mm) at 20 to 24 weeks of gestation were randomized to vaginal progesterone (200 mg daily) or

matching placebo from 24 weeks through 34 weeks of gestation. Those women randomized to progesterone had a significantly lower rate of spontaneous PTB prior to 34 weeks compared with those who received placebo (19.2% vs 34.4%, respectively; a reduction of 44.2%).<sup>65</sup> The study was not adequately powered to demonstrate a significant reduction in perinatal mortality or neonatal morbidity.

Several recent studies have investigated the utility of progesterone supplementation to preterm PTB in twin pregnancies and found it to be ineffective.<sup>66-68</sup> Whether this is due to inadequate dosing of progesterone in these studies as has been suggested by some investigators or whether it speaks to a different mechanism of PTB in twins as compared with singletons is not known.

To date, studies looking at the safety of 17P and vaginal progesterone have found no increase in the rate of congenital anomalies in infants exposed to these agents starting in the second trimester of pregnancy.<sup>63,64</sup> However, the ideal progesterone formulation, the most appropriate route of administration, and the long-term safety of these medications still remain unclear. At this time, therefore, progesterone supplementation should be used only in women at high risk of a PTB by virtue of a prior spontaneous preterm delivery or cervical shortening.<sup>5</sup> Until these outstanding issues have been resolved, progesterone supplementation should not be recommended to all pregnant women.

### **Indomethacin, Vaginal Pessary, Folic Acid, and Omega-3 Fatty Acids**

A number of other management strategies have been recommended to prevent PTB, although the data in this regard are limited and additional clinical trials with larger numbers are needed. Indomethacin, for example, may confer some benefit in preventing PTB in some high-risk women. In a clinical trial, indomethacin treatment of asymptomatic women with cervical shortening in the second trimester who declined cervical cerclage significantly reduced the rate of spontaneous PTB before 24 weeks, although it did not change the overall rate of spontaneous PTB before 35 weeks.<sup>69</sup> Insertion of a vaginal pessary may be effective in preventing spontaneous PTB in singleton pregnancies before 36 weeks and in twins before 32 weeks.<sup>70</sup> Dietary manipulation has also been proposed as a way of preventing preterm birth in both low- and high-risk populations, including prepregnancy supplementation with folic acid<sup>71</sup> and omega-3 fatty acid supplementation throughout pregnancy.<sup>72</sup>

### **A Management Algorithm for Women With Cervical Shortening**

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Existing data suggest that waiting for patients to present with symptoms of preterm labor (such as regular uterine contractions and pelvic pressure) is a highly inaccurate and unreliable method of identifying women at risk of PTB. Obstetric care providers should be focusing instead on objective tests to identify women at risk, including CL by TVS and cervicovaginal fFN. To assist in this initiative, we have included 2 clinical algorithms: one for symptomatic women ([Figure 4](#)) and the other for high-risk asymptomatic women such as women with a prior spontaneous PTB prior to 35 weeks or a multiple pregnancy ([Figure 5](#)).

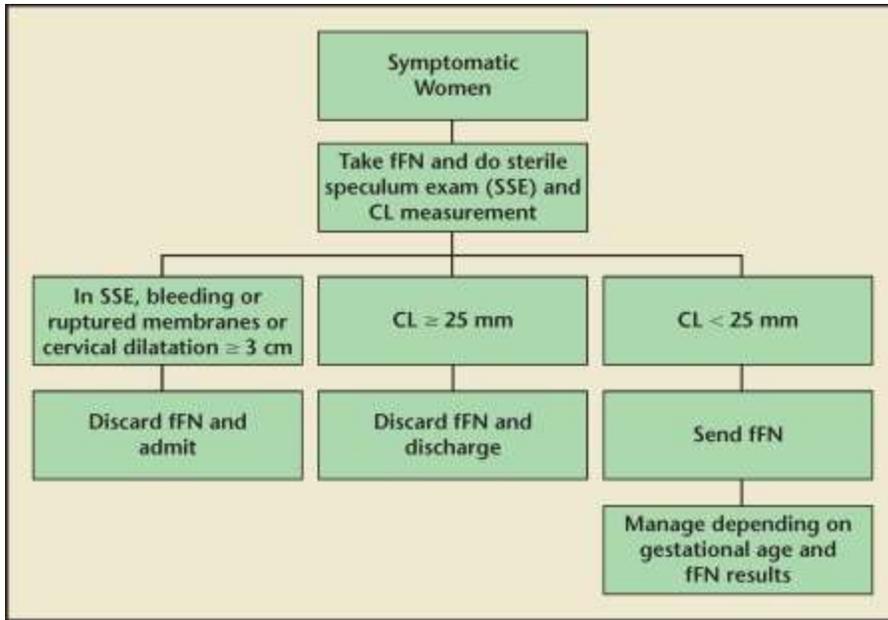


Figure 4

Proposed clinical algorithm for the management of women with symptoms suggestive of preterm labor. CL, cervical length; fFN, fetal fibronectin.

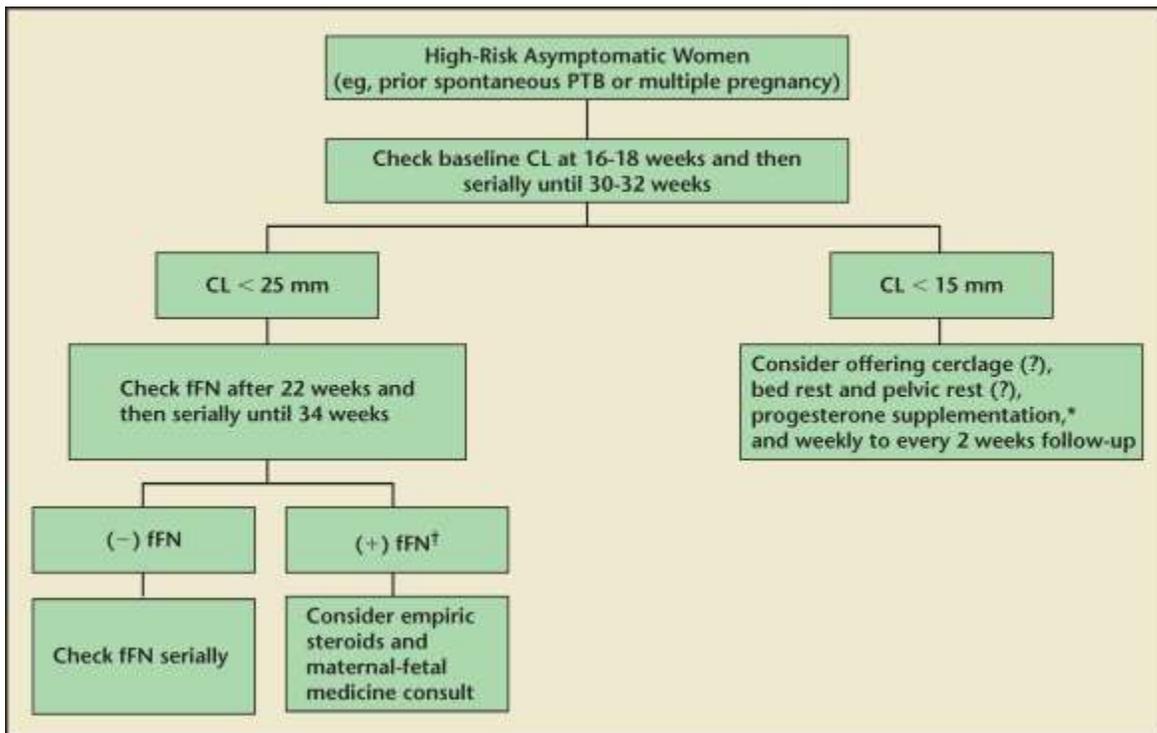


Figure 5

Proposed clinical algorithm for the management of asymptomatic women at high risk for spontaneous preterm birth. \*Progesterone administration by intramuscular injection of 17 alpha-hydroxyprogesterone caproate or vaginal suppository between 16 to 24 weeks ...

## Conclusions

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Both CL measurements and cervicovaginal fFN are objective and reliable screening tests to identify women at risk of spontaneous PTB. Serial CL measurements on TVS from 16 weeks of gestation to 30 to 32 weeks of gestation with or without fFN testing from 22 through 35 weeks in women at high risk will help to individualize management, prevent unnecessary hospitalization and obstetric intervention, and improve perinatal outcome by optimizing the timing of antenatal steroid therapy and transfer to a tertiary care center. The combined use of CL and fFN is more effective than reliance on any single test alone. In addition to optimizing perinatal outcome in pregnancies destined to deliver preterm, recent data suggest that progesterone supplementation in women with cervical shortening may be able to significantly delay delivery and prevent PTB in some women.

### Main Points

- Elevated levels of fetal fibronectin (fFN) in the cervicovaginal discharge have been shown to be a reliable predictor of subsequent preterm birth (PTB) in the setting of intact membranes.
- The gold standard for the measurement of cervical length (CL) in pregnancy is transvaginal ultrasonography (TVS) using sterile technique; it is objective, reproducible, and acceptable to patients.
- Cervical length measurements and fFN measurements are independent risk factors for PTB, and the risk of spontaneous PTB is higher if both fFN and CL tests are abnormal than if only 1 is abnormal.
- Bed rest and hydration are often recommended in an attempt to prevent PTB in women at high risk, but there is no consistent evidence that they are able to delay delivery.
- There is increasing evidence to suggest that progesterone supplementation from 16 to 20 weeks of gestation through 34 to 36 weeks of gestation may prevent preterm birth in some women at high risk due to prior spontaneous PTB or cervical shortening.
- Obstetric care providers should focus on objective tests to identify women at risk of PTB, including CL by TVS and cervicovaginal fFN.

## Footnotes

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Dr. Norwitz is a member of the Speakers Bureau for Hologic, Inc.

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# Outcomes of Mid-Trimester Emergency Cerclage in Twin Pregnancies

Levin I. · Salzer L. · Maslovitz S. · Avni A. · Lessing J.B. · Groutz A. · Almog B.

Department of Gynecology, Lis Maternity Hospital, Tel Aviv Sourasky Medical Center, Affiliated to the Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

## Abstract

*Introduction:* Placement of emergency cerclage at mid-trimester is controversial. At present, clinical trials comparing outcomes of mid-trimester cerclage to bed rest in twin pregnancies are lacking. Our aim was to examine the efficacy, safety and outcomes of mid-trimester cerclage in patients carrying twin gestations. *Material and Methods:* We retrospectively studied the outcomes of 14 patients carrying twin gestations with significant cervical dynamics who underwent cerclage. Outcomes of patients with cervical effacement only and patients with bulging membranes through the external os were examined. The interval between cerclage and delivery and the complication rates were calculated. *Results:* The average time interval between cerclage placement and delivery was 71.1 days overall. Patients with cervical shortening or effacement only (n = 10) gave birth an average of 80.2 days after the procedure, while 4 patients with bulging membranes gave birth an average of 48.5 days after cerclage placement. The overall procedure failure rate, defined as delivery before 28 completed weeks, was 14.2%. *Discussion:* Patients carrying twin gestations with advanced cervical changes might benefit from therapeutic cerclage. Further studies are required to demonstrate whether there is a difference compared to bed rest alone.

## Introduction

The role of second-trimester placement of cerclage is still controversial. Originally indicated for patients with an obstetrical history of mid-trimester painless dilatation, its use has now been extended to patients presenting with cervical effacement and dilatation (emergency cerclage). A significant amount of clinical research has dealt with the pros and cons of late emergency cerclage, given its high rates of complications. Some researchers were able to demonstrate benefits of cerclage placement even in cases of significant dilatation and membranes protruding through the external os [1,2]. The dilemma of cerclage placement is compounded by the heterogeneous characteristics of patients needing this intervention, such as singleton versus multiple gestations. As an example, Newman et al. [3] were not able to demonstrate a reduction in the risks of prematurity associated with cerclage placement in twin gestations with a shortened cervical length of <25 mm measured by ultrasound. In another study, Roman et al. [4] were unable to demonstrate a lower incidence of spontaneous preterm delivery with cerclage as compared to conservative treatment in twin and triplet pregnancies. A study comparing the outcomes of late cerclage in twins with the twin-to-twin transfusion syndrome and treated with fetoscopic selective laser coagulation demonstrated improved outcomes after cerclage compared with bed rest [5].

As clinicians, we are sometimes faced with situations where there is limited evidenced-based data and the patients expect decisive action that is lacking. A patient with twin gestations presenting at mid-trimester with painless dilatation and bulging membranes is a clinical dilemma with a prognosis that seems dire, and as yet we still do not know if cerclage is the best solution. Our fear in such cases is primarily of causing a delivery at an extremely premature gestational week – after 23 weeks and 6 days and before 28 weeks. Survival before 24 weeks is anecdotal, and so most neonates do not survive. Neonates after 28 weeks usually have a good prognosis. Neonates between 23 weeks and 6 days and 28 weeks usually suffer severe long-term morbidity. It is these deliveries that we want to avoid.

In this case series, our primary aim was to report our results with emergency cerclage placement in patients with twin gestations presenting with significant effacement and dilatation at mid-trimester. This study is by no means a comparative study between cerclage and bed rest as our patients opted for intervention. As such we present the outcomes of late emergency cerclage in twin gestations for patients with cervical effacement and dilatation as well as results of the extreme condition of membranes protruding vaginally. Promising results would encourage us to conduct further studies comparing cerclage to bed rest, the current treatment of choice. Also, we would feel safer suggesting this type of operative intervention to patients presenting with such a clinical condition.

## Material and Methods

Institutional ethics committee approval was given for this retrospective study. We retrospectively studied charts of patients with twin pregnancies admitted for cervical dynamics in mid-trimester. Data collection was carried out for patients admitted between October 1998 and September 2009. We collected demographic as well as gynecological and obstetrical data. Clinical examination of the cervix as well as cervical length measurements by ultrasound were recorded. Clinically evident cervical dynamics was defined as 50% effacement and over or estimation of cervical

length below 2 cm. On transvaginal ultrasound measurement, cervical shortening was defined as cervical length below 25 mm. Due to the retrospective nature of this study, we could not record Bishop scores as these were not used or entered in the patients' charts.

Patients included in the study were patients with twin pregnancies of a minimum of 14 weeks + 0 days. Patients were referred to the gynecological department by their treating physicians for clinically apparent cervical dynamics or because of symptoms such as abdominal pain or vaginal bleeding. All patients were examined, and cervical shortening was also verified by transvaginal ultrasound measurement. Before cerclage placement, all patients were hospitalized with bed rest for at least 24 h. Infectious process was ruled out when no uterine activity was recorded, when there was no fever and when the patient was asymptomatic. Routine blood tests were taken to rule out leukocytosis as a marker of infection. For data recording purposes, we defined patients with clinical cervical dynamics as group 1 and patients with membranes bulging through the external os as group 2.

All patients were started on oral amoxicillin and clavulanic acid (Augmentin) on admission and up to 7 days after cerclage. Cervical cerclage was placed under general anesthesia using the McDonald technique. After bladder drainage and cleansing with povidone-iodine 10% solution, the anterior and posterior lips of the cervix were grasped and a Mersilon cervical cerclage tape (Cervix-Set, Braun) was inserted at 4 points (upper and lower right and upper and lower left). The knot was fixed at the lower right point with long tails for easy removal. In cases of bulging membranes, we used the same technique but the membranes were gently pushed beyond the internal os with a Foley catheter inflated balloon. After cerclage, the balloon was deflated and gently removed. Tocolytic agents were not administered. Intraoperative techniques and complications were reviewed. We studied the complications of the procedures carried out as well as the time interval between the operative procedure and delivery and additional events following surgery. Pregnancy outcomes such as birth week, birth weights and Apgar scores were recorded. Because of the severe consequences of delivery of an extremely premature neonate, our definition of failure was delivery between 24 and 27 completed weeks (27 weeks + 6 days), while success was defined as delivery beyond 28 completed weeks of gestation.

We analyzed the data for normal distribution using the Shapiro-Wilk test. As the data were normally distributed, we compared continuous variables using a t test and Fisher's exact test as appropriate. Logistic regression analysis was performed in order to identify predictors associated with cerclage success. Variables included in the regression analysis were the following: age, number of previous pregnancies, number of previous abortions, cervical length by ultrasound, bulging of membranes, clinical cervical length and gestational week. A p value of less than 0.05 was required to reject the null hypothesis.

## Results

Between October 1998 and September 2009, we identified 14 patients with twin gestations who were treated with late emergency cerclage using the McDonald procedure. Ten patients had cervical shortening and dilatation or effacement as defined above (group 1), and 4 patients had cervical dilatation with membranes protruding through the external os to the vagina (group 2). Demographic as well as obstetrical data for the two groups of patients are summarized in table [1](#). Among the group 1 patients, 2 were parents to one child each, but the women in the second group did not have children. All previous deliveries were spontaneous, without previous cesarean

section. Among the patients in the first group, 2 patients had had a single previous late abortion at 22 and 23 weeks, respectively, and among the patients with bulging membranes (group 2), 1 patient had had a previous late abortion at 22 weeks. Twelve out of 14 patients in the two groups conceived after controlled ovarian stimulation or IVF for various indications.

	All patients (n = 14)	Group 1 (n = 10)	Group 2 (n = 4)
Age, years	31.1 ± 6.5	32.7 ± 6.2	27.6 ± 6.1
Nulligravida	12 (85.7)	9 (90)	3 (75)
Previous early abortions	5 patients had 1 2 patients had 2 1 patient had 3	3 patients had 1	2 patients had 1 2 patients had 2 1 patient had 3
Previous preterm birth	3 (21.4)	2 (20)	1 (25)

Figures in parentheses represent percentages.

Table 1. Demographic and obstetrical data

Pregnancy and neonatal outcomes for the two groups combined and separately are summarized in table 2.

	All patients (n = 14)	Group 1 (n = 10)	Group 2 (n = 4)
Symptoms at presentation: pain/bleeding, n	6/14	4/10	2/4
Gestation week at cerclage	20.1 ± 2.5	19.6 ± 2.8	21.5 ± 1.3
Cervical length, mm <sup>1</sup>	18.6 ± 6.9	19.4 ± 4.4	16.5 ± 11.9
Time interval until delivery, days	71.1 ± 44.6	80.2 ± 45.3	48.5 ± 43.9
Delivery week	30.7 ± 6.5	31.4 ± 6.5	29.0 ± 7.2
Weight of 1st twin, g	1,664.3 ± 846.9	1,692.4 ± 798.7	1,580.0 ± 1,174.3
Weight of 2nd twin, g	1,546.7 ± 764.7	1,650.3 ± 777.1	1,235.7 ± 778.9
Chorioamnionitis, n	3 (21.4)	2 (20)	1 (25)
PPROM, n	2 (14.3)	1 (10)	1 (25)
Mortality, n	7/28 (25)	4/20 (20)	3/8 (37.5)
Preterm delivery <24 weeks, n	2 (14.3)	1 (10)	1 (25)
Preterm delivery <28 weeks, n	2 (14.3)	1 (10)	1 (25)

Figures in parentheses represent percentages. PPROM = Preterm premature rupture of membranes. <sup>1</sup> On ultrasound measurement.

Table 2. Symptoms and outcomes

Of the patients with cervical shortening (group 1), 1 patient had chorioamnionitis and delivered at 21 weeks of gestation, 14 days after cerclage placement, and 1 patient had preterm premature rupture of membranes with chorioamnionitis and delivered 64 days after cerclage placement at 19 weeks. One delivery in this group occurred at 27 weeks of a pair of twins weighing 759 and 872 g.

Of the patients with bulging membranes (group 2), 1 patient had chorioamnionitis and delivered at 24 weeks (1 neonate survived), 19 days after cerclage placement, and 1 patient had chorioamnionitis and consequentially a late abortion at 22 weeks, 4 days after cerclage. Logistic

regression analysis did not single out factors associated with cerclage success. In summary, 9 patients (64.3%) delivered healthy babies after 28 weeks weighing 1,244–2,830 and 1,044–2,700 g for the 1st and 2nd twin, respectively, all with Apgar scores of 9 or above. Average delivery week in this group was  $34.8 \pm 3.8$ . Three patients (21.4%) had late abortions at 22–23 weeks, and 2 patients (14.3%) delivered extremely premature neonates of 24 and 27 weeks. The overall mortality rate was 25% (7/28 neonates; table 2).

## Discussion

In this study, we evaluated the efficacy and outcomes of mid-trimester cerclage placement in twin gestations. We evaluated outcomes for cerclage when cervical effacement is clinically apparent, and even in worse conditions, when dilatation and bulging of membranes occur. We found that patients can benefit from cerclage placement as the complication rate is low and the prognosis is good with only a 14.2% chance of delivery of an extremely premature neonate of below 28 weeks' gestation.

The benefits of mid-trimester cerclage placement in a singleton gestation have been the subject of wide research. In a large multicenter randomized study, Owen et al. [6] demonstrated benefits of mid-trimester cerclage placement for patients with singleton pregnancies and a shortened cervix of less than 25 mm. In this study, women with a prior preterm birth and shortened cervix were less likely to have preivable births. The perinatal mortality was also reduced, but preterm births of less than 35 weeks were not reduced, unless the cervical length was less than 15 mm. In this large and well-designed study, the benefits of mid-trimester cerclage were apparent for singleton pregnancies with a shortened but not dilated cervix.

Placement of cerclage in worse scenarios of dilatation of the cervix and bulging membranes has also been examined [7]. Lipitz et al. [7] found a total mortality rate of 48.4% in a group of 32 patients carrying singleton pregnancies at mid-trimester with emergency cerclage. Perinatal mortality was significantly higher for patients with protruding membranes on admission. The mean interval from procedure to delivery was 7 weeks. In a similar study, Nelson et al. [8] demonstrated worse outcomes for mid-trimester cerclage placement in emergent cerclage (clinically indicated) as opposed to urgent (ultrasound-indicated) or elective (history-indicated) cerclage. In a retrospective cohort study of 99 patients who underwent mid-trimester cerclage, Debby et al. [2] demonstrated an overall neonatal survival of 82%. Results were not significantly different when cerclage was placed with shortening or even with dilatation and bulging membranes. The time interval between procedure and delivery was statistically increased for patients without bulging membranes as opposed to patients with shortening of the cervix only, being 14.3 versus 9.3 weeks, respectively. In fact, factors associated with successful mid-trimester placement of cerclage have also been studied [9]. Nulliparity, the presence of membranes protruding beyond the external os and gestational age of less than 22 weeks at the procedure were associated with a decreased chance of delivery at or beyond 28 gestational weeks.

The dilemma of mid-trimester placement of cerclage in twin gestations has also been examined. Roman et al. [4] found that sonographically indicated (closed cervix of length below 25 mm) cerclage did not reduce the rate of spontaneous preterm birth as compared to no treatment in 414 sets of twins. Similar conclusions were found by Newman et al. [3], namely that mid-trimester cerclage in twins does not alter the risks of prematurity. However, both studies compared the results of cerclage placement to bed rest when the cervix was deemed short on ultrasound examination but not when patients presented with clinically apparent effacement. Moreover, Parilla et al. [10] found that patients with twin gestations and mid-trimester cerclage placement who did not have a history of preterm delivery were more likely to deliver earlier than patients with no cerclage. These authors concluded that expectant management starting at 16–18 weeks seems more prudent. In their study, 17 patients with twins who needed emergent cerclage (cervical length of less than 15 mm with >50% funneling) were identified, but no cases of cervical dilatation or membranes protruding through the external os were included [10].

This, in fact, was the aim of our study. The two studies cited above were conclusive in the respect that emergency cerclage is not beneficial when a short cervical length is demonstrated on ultrasound scan. Currently, most patients will be advised to remain in bed and rest throughout pregnancy in accordance with the papers cited above. Our aim was to examine whether mid-trimester emergency cerclage in extreme situations of cervical dynamics and twin gestations is in fact worthwhile. To date, this is the largest series of patients carrying twin gestations treated with emergency cerclage at mid-term due to clinically evident and significant cervical dynamics. Only a few reports in the literature exist to that effect. Benifla et al. [11] had 3 sets of twins in their study of emergency cerclage placement in extreme cervical conditions of dilatation or bulging membranes, but their outcomes for these twins were poor, with a delivery at 24 weeks in one set of twins.

The paucity of clinical data regarding emergency cerclage in twin gestations is also compounded by the fact that some twin pregnancies are dichorionic while others are monochorionic. Our study was underpowered to evaluate whether there is a difference in dichorionic compared to monochorionic twin pregnancies. Monochorionic twins are known to experience a substantially higher rate of complications, and it is possible that the use of cerclage could be of particular benefit in such cases [12].

As no guidelines exist regarding placement of cerclage for twins, and no comparative studies of cerclage versus bed rest exist, we aimed to determine whether this procedure was safe when performed in our patients and to estimate its success rate. As stated above, promising results would encourage us to conduct comparative studies of cerclage versus bed rest in such patients.

In essence, the main dilemma troubling the clinician is whether this procedure prolongs pregnancy into the viable neonatal range or whether complications will bring about delivery of an extremely premature neonate of between 24 and 27 completed weeks of gestation. Although pregnancy loss before 24 weeks is always a tragedy, we are rarely faced with neonates that survive. As such, the long-term neonatal morbidity is nonexistent. Also, neonates born after 28

weeks usually have good prognoses. The greatest tragedy in our belief is delivery at extreme neonatal prematurity, between 24 and 27 completed weeks, with severe long-term sequelae. Accordingly, it is of utmost importance to determine if cerclage placement in twin pregnancies under extreme cervical conditions and neonatal viability is beneficial to patients and neonates such that the time interval until delivery will be sufficient to prolong pregnancy to the viable and good prognosis range.

Our two groups of patients were similar with regard to demographic data, gynecological and obstetrical history and gestational age when the procedure was performed. Whereas patients with a shortened cervix had a mean interval of 80.2 days between procedure and delivery, patients with bulging membranes had a mean interval of 48.5 days until delivery.

In order to assess the true benefit of such a procedure, a prospective randomized study comparing treatment to bed rest should be undertaken, although obtaining the patients' approval for 'no intervention' would be difficult. Faced with an urgent situation of trying to rescue a pregnancy for which the prognosis seems poor, our patients will in all probability opt for treatment and not observation.

As stated above, the benefits in respect to observation are difficult to conclude, but we have demonstrated that clinically at least, emergency cerclage for this population is an option that may have a success rate of 64.4% for delivery beyond 28 weeks and a 14.2% chance of delivery of an extremely premature neonate. This information may help the clinician when consulting such patients.

We conclude that patients carrying twin gestations with advanced cervical changes might benefit from therapeutic cerclage. Further studies are required to demonstrate whether there is a difference compared to bed rest alone. Our encouraging results should act as the incentive to conduct a prospective comparative study of bed rest compared to mid-trimester emergency cerclage in twin gestations.

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Hindawi

Clinical Study

# Outcome of Late Second Trimester Emergency Cerclage in Patients with Advanced Cervical Dilatation with Bulging Amniotic Membranes: A Report of Six Cases Managed at the Douala General Hospital, Cameroon

Thomas Obinchemti Egbe, Theophile Nana Njamen, Gregory Halle Ekane, Jacques Kamgaing Tsingaing, Charlotte Nguefack Tchente, Gerard Beyiha, Esther Barla, and Ernest Nyemb

Faculty of Health Sciences, University of Buea, P.O. Box 63, Buea, Cameroon

Douala General Hospital, P.O. Box 4856, Douala, Cameroon

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## *Abstract*

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*Purpose.* To show the feasibility of emergency late second trimester cerclage with advanced cervical dilatation and bulging of amniotic membranes. *Setting.* Department of Obstetrics and Gynecology of the Douala General Hospital. *Method.* This is a retrospective study of case files of patients who underwent emergency late second trimester cerclage with advanced cervical dilatation, some with bulging of fetal membranes between June 2003 and June 2010. The modified Shirodkar technique was employed in all the cases. *Results.* Altogether, six patients (100%) underwent late second trimester cervical cerclage between 24 and 26 weeks of gestational age. Four cases (66.7%) carried on their pregnancies to term that resulted in healthy live-born babies all delivered vaginally. The other two cases (33.3%) presented with preterm premature rupture of fetal membranes (PPROM) which led us to undo the stitch with eventual delivery of live-born premature fetuses which died in the neonatal intensive care unit because of complications of prematurity and neonatal infection. *Conclusion.* In experienced hands and in the absence of other risk factors like infection, the success rates of this procedure are encouraging with improved prognosis. Finally, the modified Shirodkar technique yielded excellent results in our series.

Cervical insufficiency is a well-known cause of second trimester pregnancy loss. This is usually accompanied by painless uterine contractions effecting cervical effacement and dilatation [1]. There may also be bulging of the fetal amniotic membranes through the uterine cervix and vagina [2]. In severe cases the fetal membranes could be seen protruding through the external genitalia [3]. In such cases rupture of the fetal membranes could occur resulting in painless preterm labour and delivery of a live-born fetus [4].

However, this condition usually leads to the empiric use of tocolytic agents and cerclage. Furthermore, some studies have advocated early transvaginal sonographic follow-up with or without application of fundal pressure with the aim of detecting cases with occult cervical insufficiency, thereby indicating early cerclage.

Cervical incompetence can occur after operations (e.g., conisation for cervical intraepithelial neoplasia and forceful cervical dilatation for advanced abortions) or as a result of congenital weakness (e.g., after intrauterine exposure to diethylstilboestrol). Uterine malformations may also give rise to preterm labour, but common ones such as a bicornuate shape are often compatible with term labour, while those such as a thin uterine septum that renders implantation insecure are rare [4]. The equivocal results of trials of cervical cerclage, however, indicate that genuine cervical insufficiency is rare, being implicated in less than 5% of cases.

Since the introduction of the cervical stitch procedure in clinical practice over 50 years ago, the efficacy of the operation has not been established by evidence-based standards for many indications. At present, five randomized clinical trials have offered significant information about elective cerclage performed for clinical indications, and the expected neonatal survival rate with properly selected elective cerclage is about 87% [5].

The 3–12% incidence of preterm labor and preterm delivery varies widely with different populations, including risk factors such as low maternal prepregnancy weight, socioeconomic status, racial and ethnic factors, maternal education, maternal work patterns, physical effort during pregnancy and especially during the third trimester, maternal sexual activity, tobacco use, interval between pregnancies, bacterial vaginosis, and other types of bacterial colonization, uterine abnormalities, number of fetuses, and more.

Finally, other studies have not found any benefits with cerclage compared with expectant management [5]. The purpose of this report is to show the feasibility of emergency late second trimester cerclage in cases with advanced cervical dilatation and bulging of fetal membranes.

## *2. Materials and Methods*

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### 2.1. Setting

This is an observational study carried out at the Department of Obstetrics and Gynecology of the Douala General Hospital, Cameroon, between the periods June 2002 and June 2010. It is noteworthy that the Douala General Hospital is a tertiary care centre in Cameroon covering the Central African subregion with patients coming for treatment from neighbouring countries (Chad, Gabon, Congo Republic, Equatorial Guinea, and Central African Republic) including those coming from other towns in Cameroon.

### 2.2. Methods

Case files of patients treated during the study period were analyzed. The patients sociodemographic data were collected including age, occupation, marital status, gravidity and gestational age based on last normal menstrual period and/or ultrasound scanning [6]. Furthermore, data regarding the current pregnancy follow-up and any other medical conditions including smoking habits were recorded. The diagnosis of cervical incompetence was by physical examination because all the patients were referred to our department from other centres already with advanced cervical effacement and dilatation, some with bulging of fetal membranes. During hospitalization, blood samples were taken for full blood count, coagulation studies, HIV, syphilis, toxoplasma, and rubella serum titres. Furthermore, thick and thin film for malaria, C-reactive protein, urinalysis and culture, electrolytes, fasting blood glucose levels.

High vaginal swaps and cultures for gonococcal, chlamydiae, mycoplasma, beta-haemolytic streptococcus, and bacterial vaginosis were taken and transabdominal ultrasound scans were done for estimating gestational age, fetal weight, position, amniotic fluid volume, placenta, fetal viability, and morphologic studies. Furthermore, all our patients who underwent cerclage did not present with signs of uterine contractions, chorioamnionitis or bleeding, and preterm premature rupture of membranes (PPROM) [7].

On admission to hospital, the patients were put to bed rest preferably in the lateral recumbent position and hydration with IV fluids 2000 mL ringers lactate per day was commenced. Furthermore, they received prophylactic tocolysis with terbutaline (Bricanyl LP) 5 mg orally twice daily and betamethazone 12 mg in two doses 12 hours apart for enhancement of fetal lung maturity. The fetal wellbeing was monitored with a hand held Huntleigh Sonicaid FD2 (Fetal dopplex II) containing a 2 MHz probe until 28-week gestation when we switched to twice daily external cardiotocographic monitoring. Maternal vital signs (blood pressure, pulse, temperature, etc.) were also monitored and finally the patients were programmed for emergency late second trimester cerclage.

During the procedure patients were placed in the trendelenberg position under general anesthesia, bladder emptied, and antibiotic prophylaxis begun intraoperatively with ceftriaxone 2 gm intravenous bolus. Using vaginal retractors for exposure, the bulging membranes were pushed into the uterus using a gauze mounted to a sponge holding forceps (Figure 1). The cervix was then grasped using an atraumatic ring forceps. The modified Shirodkar procedure was used in all the cases. The bladder was mobilized cephalad with submucosal placement of a Mersilene Band (Ethicon France) anterior to posterior bilaterally at the level of the internal os, tying posteriorly and burying the anterior knot at 6 o'clock.

Finally, all our patients were hospitalized for 48 hours after the modified Shirodkar procedure. During this period they received tocolysis (salbutamol 5 mg in 500 mL 5% Dextrose solution) and antibiotic prophylaxis with ceftriaxone 1 gm every 12 hours for 24 hours. Furthermore, they continued with tocolysis and bed rest at home for two weeks. No chronic use of tocolysis was advised.

Follow-up was with bed rest and routine consultations every two weeks. We usually removed the cervical stitch at 36-week gestation or when indicated because of complications (rupture of membranes, chorioamnionitis, or uterine contractions).

Ethical clearance to carry out this study was obtained from the ethical board of the Douala General Hospital, Cameroon.

### 3. Results

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Altogether, six patients were analyzed during the study period and their average age was 27.6 years (range 22–35 years) while their gestational ages on admission ranged between 24 and 26 weeks. There were a total of 17 (100%) pregnancies recorded during this period. Among these pregnancies, the global number of deliveries and miscarriages in the study group between the period 2002 and 2010 was 5 (29.4%) and 12 (70%), respectively. Furthermore, most of the pregnancies 12 (70%) and abortions 8 (66.7%) were from the older (30–35 years) age group. Four deliveries were also recorded from this age group

Their mean gravidity was 2.83 (17/6) pregnancies with a mean parity of 0.29 (5/17). There were no differences in the socioeconomic status of these patients. Among the six patients who underwent cerclage in our department, 4 (66.7%) carried their pregnancy to term and had normal vaginal deliveries while, in two patients (33.3%), we had to undo the stitch at 24-week, 2-day, and 26-week gestation because of preterm premature rupture of membranes (PPROM) and chorioamnionitis, respectively. These two patients were also positive for chlamydiae and *Mobiluncus species* infection, respectively, and also had bulging of fetal membranes for over 4 days prior to admission into our

department. All the other patients who took their pregnancy to term had bulging of fetal membranes into the vagina for a period no more than one day before the cerclage procedure.

The two babies from the spontaneous abortions succumbed in the neonatal intensive care unit two and six days later, respectively. On discharge from hospital, the two patients were prescribed roxithromycin 300 mg orally per day to be taken for three consecutive weeks and metronidazole 1500 mg per day for 10 days, respectively.

#### *4. Discussion*

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Late second trimester cervical stitch is not a common procedure in current gynecologic practice in Cameroon. The diagnosis of cervical insufficiency is usually clinical in our country where ultrasonography is not accessible to all the regions. Cameroon being one of the low income economies, our neonatal intensive care units may not be as equipped as in the developed economies. This could explain why the two babies delivered at 24 wks 2 days and 26 weeks succumbed a few days later. On the contrary, according to literature reports from the United States, about 50% of infants born as early as 22–25 weeks of gestation may survive, and half of the survivors were without moderate to profound impairment at 18–22 months of age.

Furthermore, it has been estimated that 9.6% of all births worldwide were preterm in 2005. Approximately, 85% of this burden was concentrated in Africa and Asia, where 10.9 million births were preterm. About 0.5 million preterm births occurred in Europe and the same number in North America, while 0.9 million occurred in Latin America and the Caribbean.

The incidence of cervical insufficiency is very difficult to determine in Cameroon because there are no studies made towards that direction and the diagnostic criteria are (facility based) not homogeneous. The limitations of this study are that the study population is too small to draw meaning conclusions of statistical significance. Therefore, a multicentric study becomes imperative in Cameroon.

A meta-analysis of trials regarding cerclage for short cervix diagnosed by ultrasonography identified four properly conducted trials. In the total population, preterm birth at less than 35 weeks of gestation occurred in 29.2% (89/305) of the cerclage group, compared with 34.8% (105/302) of the no-cerclage groups (relative risk [RR] 0.84, 95% confidence interval [CI] 0.67–1.06). It was concluded that cerclage does not prevent preterm birth in all women with short cervical length on transvaginal ultrasonography. In the subgroup analysis of singleton gestations with short cervical length, especially those with a prior preterm birth, cerclage may reduce preterm birth, and a well-powered trial should be carried out in this group of patients. In contrast, in twins, cerclage was associated with a significantly higher incidence of preterm birth [8].

In other literature reports 225 women were studied, 152 underwent a physical examination with indicated cerclage, and 73 were managed expectantly without cerclage. Cervical dilatation, gestational age at presentation, and antenatal steroid use differed between groups. In the adjusted analyses, cerclage was associated with longer interval from presentation until delivery, improved neonatal survival, birthweight greater than 1500 g, and preterm birth less than 28 weeks, compared with expectant management. Similar results were obtained in the analyses of women with cervical dilatation between 2 and 4 cm () [9].

Song et al. 2010 evaluated repeat cerclage in women with prolapsed membranes. Twenty-two women with bulging membranes after primary cerclage were offered repeat cerclage; 11 chose a repeat cerclage and 11 chose bed rest. The median gestational age at delivery, birthweight and survival rates were significantly higher in the repeat cerclage group compared to the bed rest group (mean 26.8 weeks versus 21.7 weeks, , mean birthweight 1180 g versus 491 g, odds ratio for survival 22.0, 95% CI, 2.1–236). They concluded that early repeat cerclage under antibiotic cover may be beneficial in women with bulging membranes after a prior failing cerclage attempt [10]. In our series we had to undo the cerclage in two patients 33% because of complications leading to late second trimester abortions [11].

Other authors have reported laparoscopic abdominal cerclage with good results compared with patients put on expectant management [12]. Furthermore, there are recent reports of Da Vinci robotic assisted abdominal cerclage [13]. Nevertheless, these techniques are not well known in developing nations.

If silent membrane prolapse to or past the external os occurs at 22 weeks or before, the incidence of intrauterine bacterial colonization is 20% to 50% as reported by Romero et al. 1992 [14]. This is in conformity with our study where two patients were diagnosed to have vaginal infection with *C. trachomatis* and *Mobiluncus species*.

The above-mentioned studies elucidate the fact that late second trimester cerclage could be beneficial in some selected cases with true cervical insufficiency. The use of prophylactic antibiotics, tocolysis, and corticosteroids for fetal lung maturity is mandatory in such cases.

## 5. Conclusion

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We recommend that salvage cervical cerclage should be considered in patients with advanced cervical dilatation and bulging membranes in the second trimester. Despite overall poor prognosis in such cases successful outcomes may be obtained in selected cases especially when bulging of membranes has occurred no later than 24 hours and in the absence of maternal vaginal infection.

We would recommend facility based introduction of ultrasound scanning for the diagnosis of the short cervix and clinical risk factors for cervical insufficiency in order to fight against the poor morbidity/mortality related to this condition.

Follow-up of these patients after the cervical stitch with sonography could be an adjunctive modality to predict the outcomes of these pregnancies. Finally, the development of strategies for improving access to effective care in developing countries must remain a top research and operational priority.

### *Conflict of Interests*

The authors declare that there is no conflict of interests pertaining the publication of this paper.

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