

# Prediction of spontaneous preterm delivery from endocervical length at 11 to 13 weeks

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**Objective** To define the potential value of endocervical length at 11 to 13 weeks' gestation in the prediction of spontaneous early delivery.

**Method** The lengths of the endocervix and cervico-isthmic complex were measured by transvaginal ultrasound at 11 to 13 weeks in singleton pregnancies, including 1492 that subsequently delivered after 34 weeks and 16 (1.1%) who had spontaneous delivery before 34 weeks. In 1320 of the cases, the measurements were repeated at 20 to 24 weeks.

**Results** There were significant associations in the length of the endocervix and cervico-isthmic complex between 11 to 13 and 20 to 24 weeks ( $r = 0.548$ ,  $p < 0.0001$  and  $r = 0.194$ ,  $p < 0.0001$ ), and the respective median lengths were 32.4 and 32.2 mm for the endocervix and 45.3 and 40.4 mm for the cervico-isthmic complex. At 11 to 13 weeks in the early delivery group, compared to unaffected pregnancies, the median endocervical length was shorter (27.5 vs 32.5 mm,  $p < 0.0001$ ), but there was no significant difference in the length of the cervico-isthmic complex (41.4 vs 45.4 mm,  $p = 0.054$ ).

**Conclusion** In the measurement of cervical length, the endocervix should be distinguished from the isthmus. The endocervical length at 11 to 13 weeks is shorter in pregnancies resulting in spontaneous delivery before 34 weeks than in those delivering after 34 weeks. Copyright © 2010 John Wiley & Sons, Ltd.

KEY WORDS: first-trimester screening; preterm delivery; cervical length; endocervix; isthmus; transvaginal ultrasound

## INTRODUCTION

Preterm birth is responsible for 75% of all neonatal deaths and over half the neurological handicap in children [McCormick, 1985; Centre for Maternal and Child Enquiries (CMACE), 2010]. Although all births before 37 weeks' gestation are defined as preterm, the vast majority of mortality and morbidity relates to early delivery before 34 weeks. Although improvements in neonatal care have led to higher survival of very premature infants, a major impact on the associated mortality and morbidity will only be achieved through the development of a sensitive method to identify women at high risk of preterm delivery and an effective strategy for the prevention of this complication.

The risk of spontaneous preterm birth is inversely related to cervical length measured by transvaginal sonography at 20 to 24 weeks' gestation (Iams *et al.*, 1996; Heath *et al.*, 1998; Kagan *et al.*, 2006; To *et al.*, 2006; Celik *et al.*, 2008). In women with a short cervix, administration of progesterone reduces the risk of spontaneous early preterm delivery by about 40% (Fonseca *et al.*, 2007). However, progesterone is not as effective in women with cervical length below 12 mm as in those with a length of 12 to 15 mm. An alternative treatment for women with a short cervix is cervical

cerclage. This reduces the risk of spontaneous early preterm delivery by about 40% in women who had a previous preterm birth or second-trimester loss but not in those without such history (To *et al.*, 2004; Berghella *et al.*, 2005).

The disadvantages of measuring cervical length at 20 to 24 weeks are first, inevitable failure to identify cervical incompetence leading to miscarriage before this gestation and second, the effectiveness of prophylactic administration of progesterone or cervical cerclage may be inversely related to the gestation at which treatment is initiated. Certainly in women who had a previous preterm birth or second-trimester loss, cervical cerclage is either carried out electively in the first trimester or it is reserved for those where serial scans, starting from the first-trimester, demonstrate cervical shortening (Althuisius *et al.*, 2000).

Several studies reported that the measurement of cervical length in the first trimester is not predictive of preterm delivery (Zorzoli *et al.*, 1994; Hasegawa *et al.*, 1996; Carvalho *et al.*, 2003; Conoscenti *et al.*, 2003; Ozdemir *et al.*, 2007). The mean or median cervical length in these studies (40–44 mm) was considerably longer than in the second trimester. It is possible that cervical shortening in cases of preterm delivery is not apparent in the first trimester because it occurs after 16 weeks (Berghella *et al.*, 2003). Alternatively, preterm delivery is associated with short cervix in the first trimester but this has not been recognised because

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in the measurement of cervical length sonographers inadvertently include the uterine isthmus.

The aim of this study was to define and standardise the technique for the measurement of cervical length at 11 to 13 weeks and to determine the potential value of this measurement in the prediction of spontaneous early preterm birth.

## METHODS

The data for this study were derived from prospective screening for fetal abnormalities and pregnancy complications in women attending for their routine first hospital visit in pregnancy at University College Hospital, London, UK. In this visit, which is held at 11<sup>+0</sup> to 13<sup>+6</sup> weeks of gestation, we record maternal characteristics and medical history and perform transabdominal and transvaginal sonography to (1) determine gestational age from the measurement of the fetal crown-rump length, (2) diagnose any major fetal abnormalities and (3) measure fetal nuchal translucency thickness as part of screening for chromosomal abnormalities (Robinson and Fleming, 1975; Snijders *et al.*, 1998). The transvaginal scan includes the measurement of cervical length and if this is less than 15 mm the women who are at high risk for preterm delivery are referred to a specialist clinic. However, in this study, none of the patients had such a short cervix. In our hospital, all women at 20 to 24 weeks of gestation are offered another ultrasound scan for the diagnosis of fetal abnormalities, assessment of fetal growth and transvaginal measurement of cervical length.

The inclusion criteria for this study were singleton pregnancies with the measurement of cervical length at 11 to 13 weeks and delivery at or after 24 weeks' gestation. We excluded pregnancies ending in termination, miscarriage or fetal death before 24 weeks and those with iatrogenic delivery before 34 weeks.

### Measurement of endocervical and isthmic length

We have observed that in the majority of women undergoing cervical assessment before the development of the lower uterine segment, there is a persistent myometrial thickening between the endocervix and the gestational sac (Figure 1). This thickening is likely to represent the isthmus rather than a contraction. Consequently, in the measurement of cervical length, which for the purpose of clarity we define as endocervical length, we undertake the following steps. First, the women are asked to empty their bladder and are placed in the dorsal lithotomy position. Second, the vaginal transducer (2.7–9.3 MHz) is introduced in the anterior fornix of the vagina and adjusted to obtain a sagittal view of the entire length of the cervical canal, which may be either translucent or echodense. The canal is bordered by the endocervical mucosa, which is usually of decreased but occasionally of increased echogenicity compared to the surrounding tissues. Third, the probe is withdrawn until the image

is blurred and then advanced gently until the image is restored without exerting undue pressure on the cervix. Fourth, the settings of the ultrasound machine are altered to obtain the widest viewing angle and the magnification is increased so that most of the screen is occupied by the tissues between the external cervical os at one end of the picture and gestational sac at the other end. Fifth, callipers are used to measure in sequence the linear distance between the two ends of the glandular area around the endocervical canal and the shortest distance between the glandular area and the gestational sac (isthmus).

All the operators performing the scans had received extensive training and had all passed a practical examination administered by an expert to demonstrate their competence in the technique. In addition, all ultrasound 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.

### Diagnosis of spontaneous early preterm delivery

Data on pregnancy outcome were obtained from the maternity computerised records or the general medical practitioners of the women and were also recorded in our database. The obstetric records of all patients delivering before 34 weeks were examined to determine whether the preterm delivery was medically indicated or spontaneous. The latter included those with spontaneous onset of labour and those with preterm pre-labour rupture of membranes.

### Statistical analysis

Comparison between the outcome groups was by Mann–Whitney *U*-test for continuous variables and  $\chi^2$ -test or Fisher's exact test for categorical variables. The significance of difference in endocervical length and cervico–isthmic complex length (endocervical plus isthmic length) in the spontaneous early delivery and unaffected groups was determined. Regression analysis was used to examine the association in the measurements between 11 to 13 weeks and those at 20 to 24 weeks for the length of both the endocervix and the cervico–isthmic complex.

The statistical software package SPSS 16.0 (SPSS Inc., Chicago, IL, USA) was used for data analyses.

## RESULTS

During the study period (July 2009 to February 2010), we measured the cervical length at 11 to 13 weeks in 1548 singleton pregnancies. We excluded 40 cases because the pregnancies resulted in miscarriage or termination ( $n = 34$ ) or there was iatrogenic delivery at 24 to 33 weeks ( $n = 6$ ), for preeclampsia in 4, maternal cerebral haemorrhage in 1 and bleeding from a placenta previa in 1. In the 1508 cases included in the study, 16 (1.1%) had spontaneous delivery before 34 weeks and

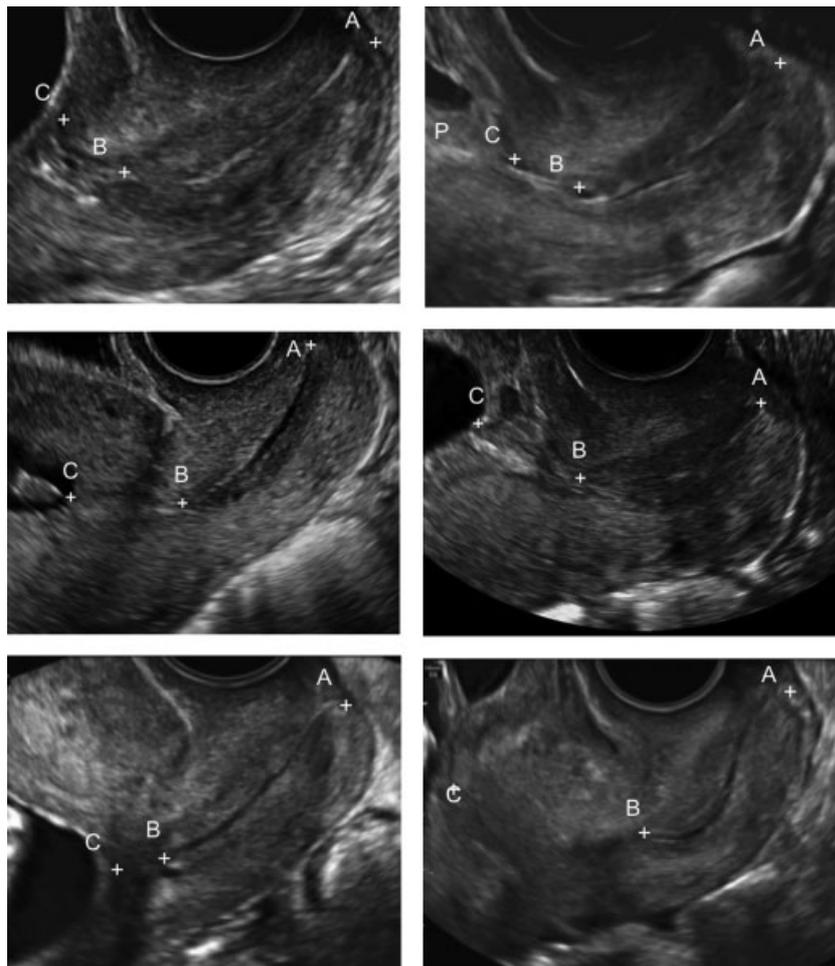


Figure 1—Ultrasound pictures illustrating the measurement of the length of the endocervix (A to B) and the isthmus (B to C). In one picture, the placenta (P) overlies the opening of the isthmus into the uterine cavity

1492 delivered after 34 weeks. The cervical length was also measured at 20 to 24 weeks in 1320 of the cases, including 12 of those with subsequent spontaneous delivery before 34 weeks.

The maternal characteristics and obstetric history in the screened population are summarised in Table 1. In the group with spontaneous early delivery, there was a higher prevalence of women of African racial origin and women with a previous miscarriage at 16 to 23 weeks or spontaneous delivery at 24 to 33 weeks.

### Findings at 11 to 13 weeks

The maternal and pregnancy characteristics are presented in Table 1.

The median endocervical length at 11 to 13 weeks was 32.4 mm (5th centile 25.6 mm, 95th centile 40.2 mm) and median length of the cervico-isthmic complex was 45.3 mm (5th centile 30.9 mm, 95th centile 65.3 mm) (Figures 2 and 3). The median length of the isthmus was 13.8 (range 0–49.4) mm and it was above 5 mm in 1287 (85.3%) of the 1508 cases.

In the spontaneous early delivery group, compared to unaffected pregnancies, the median endocervical length

was significantly shorter, but there was no significant difference in the length of the cervico-isthmic complex (Figure 3 and Table 2).

The endocervical length was below the median in all 16 cases with spontaneous early delivery. The endocervical length was below 25 mm in 6 (37.5%) of the early preterm delivery group and 42 (2.8%) of the unaffected pregnancies. The respective values for endocervical length 25 to 29.9 mm and  $\geq 30$  mm were 9 (56.3%) versus 367 (24.6%) and 1 (6.3%) versus 1083 (72.6%). Therefore, the rate of spontaneous early delivery decreased with endocervical length from 12.5% (6 of 48) for length below 25 mm to 2.4% (9 of 376) for length of 25 to 29.9 mm and 0.1% (1 of 1084) for length of  $\geq 30$  mm ( $\chi^2$ -test,  $p < 0.0001$ ).

### Relation of findings at 11 to 13 weeks and 20 to 24 weeks

In the 1320 cases examined at 20 to 24 weeks, the median endocervical length was 32.2 mm (5th centile 24.6 mm, 95th centile 40.2 mm) and median length of the cervico-isthmic complex was 40.4 mm (5th centile 26.1 mm, 95th centile 60.6 mm). The median length

Table 1—Maternal characteristics and obstetric history in the screened population

Characteristics	Delivery $\geq 34$ weeks ( $n = 1492$ )	Early preterm ( $n = 16$ )
Maternal age in years, median (IQR)	32.5 (29.3–35.6)	33.2 (29.7–35.9)
Maternal weight, median (IQR)	63.0 (57.2–70.7)	61.8 (55.5–81.0)
Maternal height in cm, median (IQR)	165 (160–170)	163 (156–167)
Racial origin		
Caucasian, $n$ (%)	1096 (73.5)	10 (62.5)
African, $n$ (%)	126 (8.4)	4 (25.0)*
South Asian, $n$ (%)	149 (10.0)	1 (6.3)
East Asian, $n$ (%)	91 (6.1)	0
Mixed, $n$ (%)	30 (2.0)	1 (6.3)
Cigarette smoker, $n$ (%)	32 (2.1)	0
Conception		
Spontaneous, $n$ (%)	1,402 (94.0)	16.0 (100)
Ovulation drugs, $n$ (%)	90 (6.0)	0
Obstetric history		
Nulliparous—no pregnancy at $>16$ weeks, $n$ (%)	937 (62.8)	9 (56.3)
Nulliparous—miscarriage at 16 to 23 weeks, $n$ (%)	22 (15)	2 (12.5)*
Parous—preterm delivery 24 to 33 weeks, $n$ (%)	14 (0.9)	2 (12.5)*
Parous—delivery $>34$ weeks, $n$ (%)	519 (34.8)	3 (18.8)

Comparisons between groups ( $\chi^2$ -test and Fisher's exact test for categorical variables and Mann-Whitney  $U$ -test for continuous variables).

\* $p < 0.05$ .

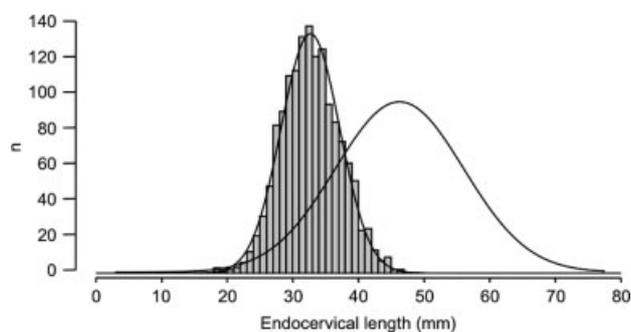


Figure 2—Distribution of endocervical length at 11 to 13 weeks (histograms and overlying curve). The curve on the right is the distribution of length of the cervico-isthmic complex

of the isthmus was 7.8 (range 0–51.0) mm and it was above 5 mm in 862 (65.3%) cases.

There was a significant association in the measurements between 11 and 13 weeks and those at 20 to 24 weeks for the length of the endocervix ( $r = 0.548$ ,  $p < 0.0001$ ; Figure 4), isthmus ( $r = 0.089$ ,  $p = 0.001$ ) and the cervico-isthmic complex ( $r = 0.194$ ,  $p < 0.0001$ ).

In the spontaneous early delivery group, compared to unaffected pregnancies, the length of both the endocervix and the cervico-isthmic complex was significantly shorter (Table 2).

## DISCUSSION

This study has demonstrated that (1) in the measurement of cervical length it is important to distinguish between the endocervix and the isthmus and (2) the endocervical length at 11 to 13 weeks is shorter in pregnancies resulting in spontaneous delivery before 34 weeks than in those delivering after 34 weeks.

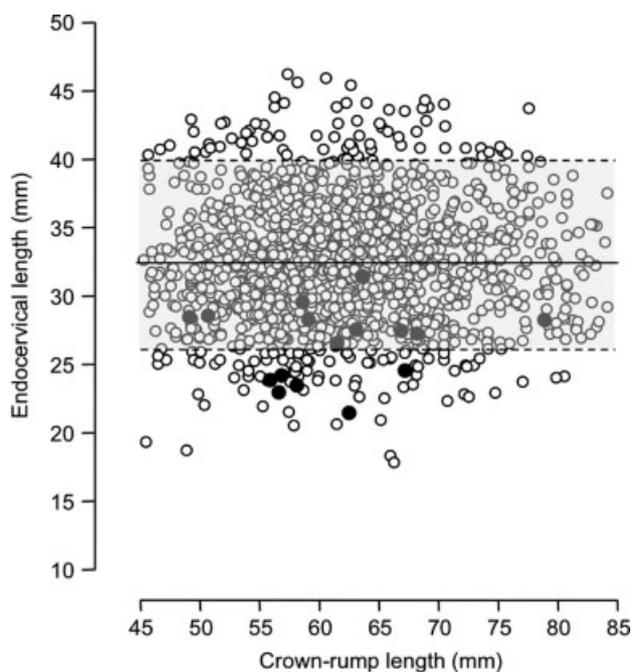


Figure 3—Reference range (50th, 5th and 95th centiles) and individual measurements in women with subsequent spontaneous delivery before 34 weeks (closed circles) and those delivering at or after 34 weeks (open circles)

In the measurement of cervical length, we adhered to the criteria suggested by Sonek and Shellhaas (1998). These authors highlighted the importance of including in the measurement only the portion of the cervix where the canal is bordered by the endocervical mucosa. Anatomical studies have demonstrated that during the early stages of pregnancy there is marked hypertrophy of the isthmic muscle (Danforth, 1947). In the second and third trimesters, the isthmus undergoes a gradual

Table 2—Comparison of the length of the endocervix and cervico–isthmic complex at 11 to 13 weeks and 20 to 24 weeks in women with spontaneous delivery before 34 weeks' gestation and those delivering at or after 34 weeks

Variables	Delivery $\geq 34$ weeks	Delivery $< 34$ weeks	<i>p</i>
11 to 13 weeks			
Endocervical length, median (IQR)	32.5 (29.5–35.6)	27.5 (24.0–28.6)	$< 0.0001$
Cervico–isthmic length, median (IQR)	45.4 (39.0–53.1)	41.4 (34.8–45.8)	0.054
20 to 24 weeks			
Endocervical length, median (IQR)	32.2 (29.3–35.3)	20.6 (17.0–27.7)	$< 0.0001$
Cervico–isthmic length, median (IQR)	40.7 (33.9–47.7)	27.0 (17.0–33.8)	$< 0.0001$

IQR, interquartile range.

Comparisons between the outcome groups were by Mann–Whitney *U*-test.

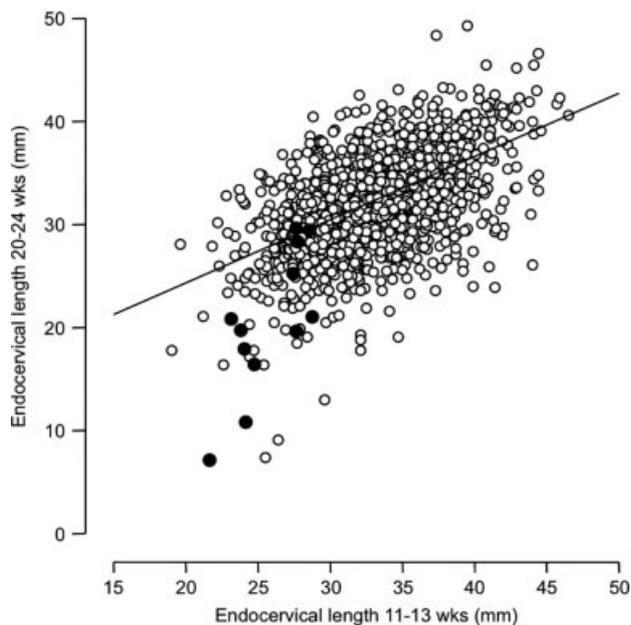


Figure 4—Relationship of endocervical length at 11 to 13 weeks with 20 to 24 weeks in women with subsequent spontaneous delivery before 34 weeks (closed circles) and those delivering at or after 34 weeks (open circles)

unfolding, thinning and ‘taking up’ into the body of the uterus but this process leading to the formation of the lower uterine segment is completed only during labour (Wendell-Smith, 1954). Ultrasound studies in the 1990s investigating changes in cervical length throughout gestation reported that the median or mean length in the first trimester was 42 to 52 mm and this remained stable throughout the second trimester with shortening only after 30 weeks (Zorzoli *et al.*, 1994; Tongsong *et al.*, 1997; Ayers *et al.*, 1998). It is likely that in these studies the cervico–isthmic complex rather than the cervix was measured and the reported shortening in the third trimester was the consequence of formation of the lower segment with eventual obliteration of the isthmus.

At 11 to 13 weeks, the median length of the endocervix and of the cervico–isthmic complex was 32 and 45 mm, respectively. The median endocervical length at 20 to 24 weeks was the same as at 11 to 13 weeks, and there was a significant association in the measurements between the first and the second trimesters. In contrast, between 11 to 13 weeks and 20 to 24 weeks there was

shortening of the isthmus resulting in a decrease in the median length of the cervico–isthmic complex.

Previous studies investigating the potential value of first-trimester cervical length in the prediction of preterm delivery did not distinguish between the endocervix and isthmus and reported that the mean or median cervical length was 40 to 44 mm (Zorzoli *et al.*, 1994; Hasegawa *et al.*, 1996; Carvalho *et al.*, 2003; Conoscenti *et al.*, 2003; Ozdemir *et al.*, 2007). It is therefore likely that in these studies the measurement was not confined to the endocervix but included the whole cervico–isthmic complex.

The endocervical length was below the median in all 16 cases with spontaneous early delivery. The endocervical length was below 25 mm in 6 (37.5%) of the early preterm delivery group and 42 (2.8%) of the unaffected pregnancies. The respective values for endocervical length 25 to 29.9 mm and  $\geq 30$  mm were 9 (56.3%) versus 367 (24.6%) and 1 (6.3%) versus 1083 (72.6%). Therefore, the rate of spontaneous early delivery decreased with endocervical length from 12.5% (6 of 48) for length below 25 mm to 2.4% (9 of 376) for length of 25 to 29.9 mm and 0.1% (1 of 1084) for length of  $\geq 30$  mm ( $\chi^2$ -test,  $p < 0.0001$ ).

At 11 to 13 weeks, the endocervical length in pregnancies complicated by subsequent spontaneous delivery before 34 weeks was shorter than in those delivering after 34 weeks and the risk of early delivery was inversely related to cervical length. This apparent contradiction between our results and those of previous first-trimester studies may be explained by the possibility that in the previous studies the cervico–isthmic complex rather than the endocervix was measured (Zorzoli *et al.*, 1994; Hasegawa *et al.*, 1996; Carvalho *et al.*, 2003; Conoscenti *et al.*, 2003; Ozdemir *et al.*, 2007). We also found no significant differences in the length of the cervico–isthmic complex between the two outcome groups.

Larger studies involving several thousands of pregnancies will define the exact relation between cervical length at 11 to 13 weeks and spontaneous early delivery and the performance of such early screening either by cervical length alone or in combination with maternal characteristics and serum biomarkers (Beta *et al.*, 2010). Similarly, the extent to which early identification of the group at high risk of subsequent early delivery would improve pregnancy outcome through earlier intervention

with such measures as prophylactic use of progesterone or cervical cerclage remains to be determined.

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