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# Sonographic measurement of cervical length and fetal fibronectin testing in threatened preterm labor

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**KEYWORDS:** cervical length; fetal fibronectin; preterm labor; sonography

## ABSTRACT

***Objective*** *In women presenting with threatened preterm labor, both fetal fibronectin and sonographic measurement of cervical length have been shown to distinguish between true and false labor. The aim of this study was to determine whether the combination of both tests provides a better prediction than the individual tests alone.*

***Methods*** *We examined 195 women with singleton pregnancies presenting at 24–36 (median 31) weeks of gestation with regular and painful uterine contractions, intact membranes and cervical dilatation of less than 3 cm. On admission to the hospital fetal fibronectin positivity in cervicovaginal secretions was determined and transvaginal sonographic measurement of cervical length was carried out. The results were not made available to the attending obstetrician. The primary outcome measure was delivery within 7 days of presentation.*

***Results*** *Delivery within 7 days occurred in 51.4% (18 of 35) of those with cervical length below 15 mm and 0.6% (1 of 160) of those with cervical length of 15 mm or more, in 21.2% (18 of 85) of the fibronectin positive group and in 0.9% (1 of 110) of the fibronectin negative group. There was a significant association between cervical length and the incidence of fibronectin positivity* ($r = -0.921$, $P = 0.003$)*. Logistic regression analysis demonstrated that the only significant contributor to the prediction of delivery within 7 days was cervical length, with no significant contribution from fibronectin positivity, ethnic origin, maternal age, gestational age, body mass index, parity, previous history of preterm delivery, cigarette smoking, or use of tocolytics.*

***Conclusions*** *In women with threatened preterm labor assessment of fetal fibronectin in cervicovaginal secretions does not improve the prediction of delivery within 7 days provided by the sonographic measurement of cervical length.* 

## INTRODUCTION

Preterm delivery is the leading cause of neonatal mortality and morbidity. Consequently, women presenting with threatened preterm labor are often treated with hospitalization and the administration of tocolytics to avoid preterm delivery. Randomized studies on the use of tocolytics in threatened preterm labor have demonstrated a significant prolongation of pregnancy by about 7 days but no significant reduction in the incidence of preterm delivery, perinatal mortality or morbidity[1,2]. Furthermore, these studies have shown that more than 70% of women presenting with threatened preterm labor are not in true labor and do not deliver within 7 days[2]. The primary aim of tocolysis is to achieve prolongation of pregnancy for a couple of days for effective treatment with steroids for fetal lung maturity, rather than prevention of preterm delivery as such.

Recent studies have demonstrated that sonographically measured cervical length and fetal fibronectin assessment in cervicovaginal secretions can distinguish between those that will and those that will not deliver within 7 days[3–17]. In three sonographic studies on a combined total of 532 singleton pregnancies presenting with threatened preterm labor, delivery within 7 days occurred in 48.6% (53 of 109) of those with cervical length less than 15 mm and in 1.2% (5 of 423) of those with cervical length of 15 mm or more[3–5]. Similarly, in the combined data from 11 studies on a total of 1941 pregnancies, including some twins, presenting with threatened preterm labor, delivery within 7–10 days occurred in 23.5% (97 of 412) of those with a positive fetal fibronectin result and in 2.0% (31 of 1529) of those with a negative result (Table 1)[6–16].

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The aim of this study was to determine whether, in singleton pregnancies with threatened preterm labor, the combination of short cervix and fetal fibronectin positivity provides a better prediction of delivery within 7 days than that provided by each test alone.

## PATIENTS AND METHODS

This was a prospective observational study of sonographic measurement of cervical length and determination of fetal fibronectin positivity in cervicovaginal secretions in women with singleton pregnancies presenting to the labor ward with painful and regular uterine contractions at 24–36 weeks of gestation. In all cases gestation was calculated from the menstrual history and by an ultrasound scan in early pregnancy. Women in active labor, defined by the presence of cervical dilatation of 3 cm or more, and those with ruptured membranes, were excluded. The study was carried out at four hospitals in the UK and two hospitals in South Africa. Written informed consent was obtained from those agreeing to take part in the study, which was approved by the research ethics committee of each hospital.

At presentation to the hospital a sterile speculum examination was performed, a specimen of cervicovaginal secretions was collected from the posterior fornix or endocervix and qualitative detection of fetal fibronectin was performed (Adeza Biomedical Fetal Fibronectin Membrane Immunoassay, Sunnyvale, California, USA). The test was performed at the bedside as described by the manufacturer and a positive or negative result was recorded. Subsequently, a digital examination was performed by the attending clinicians, and patients with a cervical dilatation of 3 cm or more were excluded from further analysis. Transvaginal sonography was carried out and the cervical length was measured by appropriately trained sonographers as previously described[17]. The management of the women, including hospitalization and administration of tocolytics, was determined by the attending obstetricians, who were not aware of the ultrasound or fetal fibronectin findings. The primary outcome measure was delivery within 7 days of presentation.

### Statistical analysis

Univariate regression analysis was used to investigate the effect on delivery within 7 days of presentation of: maternal age in years; ethnic origin (Caucasian, Afro-Caribbean, Asian); hospital where examined (1 to 6); parity (parous, nulliparous); gestational age at presentation in weeks; cigarette smoking (yes or no); body mass index (kg/m$^2$); history of previous preterm delivery or second-trimester miscarriage (yes or no); use of tocolytics (yes or no); fetal fibronectin (positive or negative); and cervical length in mm. Multiple logistic regression analysis was subsequently performed to determine the significant independent contribution of those variables yielding a $P < 0.05$ in the univariate analysis. This showed that the only significant independent contributor was cervical length.

We then used multiple regression analysis to develop a model to predict delivery within 7 days on the basis of demographic characteristics, obstetric history and the results of the fetal fibronectin test, without inclusion of cervical length. Receiver–operating characteristics (ROC) curves were constructed and the c-index or area under the curve was used to compare the performance of the two approaches (with or without cervical length) for prediction of delivery within the subsequent 7 days. The data were analyzed using the statistical software SPSS 13.0 (Chicago, Illinois, USA).

## RESULTS

During the study period (February 2002 to June 2003) we recruited 195 women presenting with threatened

**Table 1** Prospective studies examining the value of fetal fibronectin positivity in cervicovaginal secretions in women with threatened preterm labor in the prediction of delivery within 7 days of presentation. Under *n* is the total number of women, and in some studies twin pregnancies are included and the number is given (T). There are only two studies with a definite statement that the pregnancies were singleton and in the combined total of 602 fetal fibronectin negative cases there were only 2 (0.3%) deliveries within 7 days[9,11]

| | | | | *Delivery within 7 days* | | |
|---|---|---|---|---|---|---|
| *Authors* | n | *Gestation (weeks)* | *Fibronectin* +ve *(%)* | *Total* n *(%)* | *Fibronectin* +ve n *(%)* | *Fibronectin* −ve n *(%)* |
| Iams *et al.* 1995[6] | 192 (T?) | 24–34 | 23.4 | 14 (7.3) | 13/45 (28.9) | 1/147 (0.7) |
| Bartnicki *et al.* 1996[7] | 112 (T6) | 22–35 | 30.4 | 2 (1.8) | 2/34 (5.9) | 0/78 (0) |
| Malak *et al.* 1996[8] | 112 (T?) | 24–34 | 16.1 | 10 (8.9) | 8/18 (44.4) | 2/94 (2.1) |
| Senden & Owen 1996[9] | 25 (T0) | 25–35 | 24.0 | 3 (12.0) | 3/6 (50.0) | 0/19 (0) |
| Benattar *et al.* 1997[10] | 124 (T14) | 24–36 | 15.3 | 9 (7.3) | 8/19 (42.1) | 1/105 (1.0) |
| Peaceman *et al.* 1997[11] | 725 (T0) | 24–35 | 19.6 | 21 (2.9) | 19/142 (13.4) | 2/583 (0.3) |
| Coleman *et al.* 1998[12]* | 121 (T15) | 24–34 | 22.3 | 17 (14.0) | 11/27 (40.7) | 6/94 (6.4) |
| McKenna *et al.* 1999[13] | 50 (T?) | 22–34 | 32.0 | 4 (8.0) | 4/16 (25.0) | 0/34 (0) |
| Giles *et al.* 2000[14] | 141 (T?) | 24–34 | 27.0 | 7 (5.0) | 5/38 (13.2) | 2/103 (1.9) |
| Coleman *et al.* 2001[15] | 104 (T13) | 24–34 | 18.3 | 13 (12.5) | 8/19 (42.1) | 5/85 (5.9) |
| Rinehart *et al.* 2001[16] | 235 (T9) | 24–34 | 20.4 | 28 (11.9) | 16/48 (33.3) | 12/187 (6.4) |
| Total | 1941 | 22–36 | 21.2 | 128 (6.6) | 97/412 (23.5) | 31/1529 (2.0) |

*Reports delivery within 10 rather than 7 days.

preterm labor at a median gestation of 31 (range, 24–36) weeks. Delivery within 7 days of presentation occurred in 19 (9.7%) cases. The characteristics of the population examined and the results of the univariate analysis on the associations with the incidence of delivery within 7 days are shown in Table 2. Delivery within 7 days occurred in 51.4% (18 of 35) of those with cervical length below 15 mm and 0.6% (1 of 160) of those with cervical length of 15 mm or more, in 21.2% (18 of 85) of the fibronectin positive group and in 0.9% (1 of 110) of the fibronectin negative group. The positive and negative likelihood ratios for delivery within 7 days for the finding of cervical length < 15 mm were 9.8 and 0.05. The corresponding values for fibronectin positivity were 2.6 and 0.08. Delivery within 7 days increased exponentially with decreasing cervical length from 0%, to 5.0%, 6.7%, 46.2% and 91.7% for respective cervical lengths of > 20 mm, 16–20 mm, 11–15 mm, 6–10 mm and 1–5 mm (Figure 1). There was a significant association between cervical length and the incidence of fibronectin positivity ($r = -0.921$, $P = 0.003$; Figure 2).

For the prediction of delivery within 7 days, multiple logistic regression analysis demonstrated that the only significant independent contributor was cervical length. Multiple logistic regression analysis (without inclusion of cervical length) demonstrated that significant independent contribution to the prediction of delivery within 7 days was provided by fibronectin positivity (odds ratio (OR), 25.88; 95% confidence interval (CI), 3.29–204, $P = 0.002$), Afro-Caribbean ethnic origin (OR, 5.73; 95% CI, 1.79–18.39, $P = 0.003$) and gestational age at presentation (OR, 1.21; 95% CI, 1.03–1.42, $P = 0.019$). The probability (%) of delivery within 7 days is:

$(1/[1 + e^{y}]) \times 100$, where $y = 11.431 - 3.254 \times$ (fibronectin positive = 1, negative = 0) $- 0.192 \times$ gestation in weeks $- 1.746 \times$ (Afro-Caribbean yes = 1, no = 0).

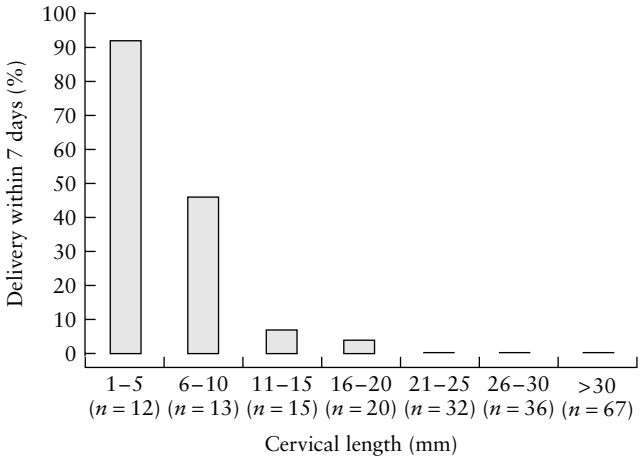


**Figure 1** Relationship between cervical length and incidence of delivery within 7 days.

**Table 2** Characteristics of the population examined ($n = 195$) and the results of the univariate analysis on the associations with the incidence of delivery within 7 days

| *Variable* | n *(%) or median (range)* | *Odds ratio (95% CI)* | P |
|---|---|---|---|
| Cervical length (mm) | 26 (1–50) | 0.660 (0.55–0.80) | < 0.001 |
| Fibronectin | | | 0.001 |
| Negative | 110 (56.4) | 1.00 | |
| Positive | 85 (43.6) | 29.28 (3.82–224.4) | |
| Hospital where examined | | | 0.001 |
| UK 1 | 57 (29.2) | 1 | |
| UK 2 | 52 (26.7) | 1.08 (0.15–7.95) | |
| UK 3 | 14 (7.2) | 4.91 (0.62–38.7) | |
| UK 4 | 32 (16.4) | 1.86 (0.25–13.9) | |
| SA 1 | 14 (7.2) | 2.08 (0.17–24.7) | |
| SA 2 | 26 (13.3) | 16.9 (3.34–85.0) | |
| Maternal age (years) | 27 (16–41) | 0.97 (0.90–1.05) | 0.441 |
| Gestational age (weeks) | 31 (24–36) | 1.17 (1.00–1.36) | 0.049 |
| Body mass index (kg/m$^2$) | 24 (14–45) | 0.93 (0.82–1.06) | 0.284 |
| Ethnic origin | | | 0.001 |
| Caucasian | 111 (56.9) | 1.00 | |
| Afro-Caribbean | 63 (32.3) | 7.64 (2.39–24.4) | |
| Asian | 21 (10.8) | 1.34 (0.14–12.6) | |
| Cigarette smoking | | | 0.163 |
| No | 148 (75.9) | 1.00 | |
| Yes | 47 (24.1) | 0.34 (0.08–1.54) | |
| Parity | | | 0.171 |
| Nulliparae | 74 (37.9) | 1.00 | |
| Parae | 121 (62.1) | 0.51 (0.20–1.33) | |
| Use of tocolytics | | | < 0.001 |
| No | 153 (78.5) | 1.00 | |
| Yes | 42 (21.5) | 6.43 (2.39–17.3) | |
| Previous preterm delivery | | | 0.344 |
| No | 171 (87.7) | 1.00 | |
| Yes | 24 (12.3) | 0.37 (0.05–2.9) | |

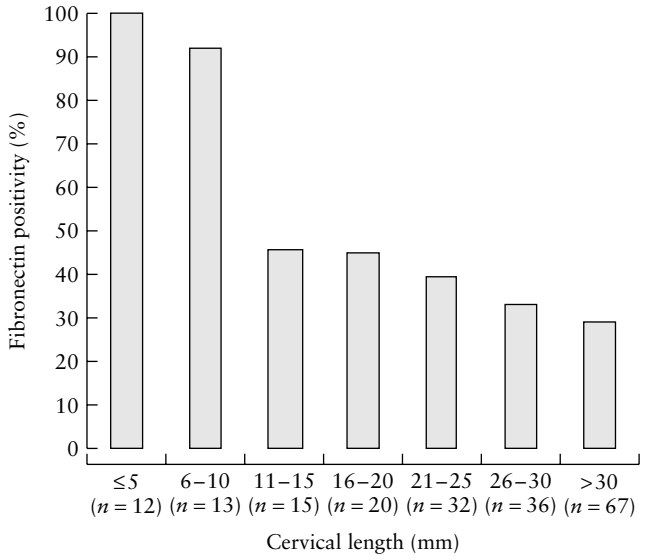


**Figure 2** Relationship between cervical length and incidence of fetal fibronectin positivity.

The ROC curves demonstrated that the prediction provided by cervical length appeared to be better than that provided by the fibronectin model (Figure 3). The area under the curve for the prediction provided by cervical length was 98.4% (95% CI, 96.6–100%) while for the model that incorporates fibronectin and maternal characteristics the area was 90.4% (95% CI, 84.0–96.7%).

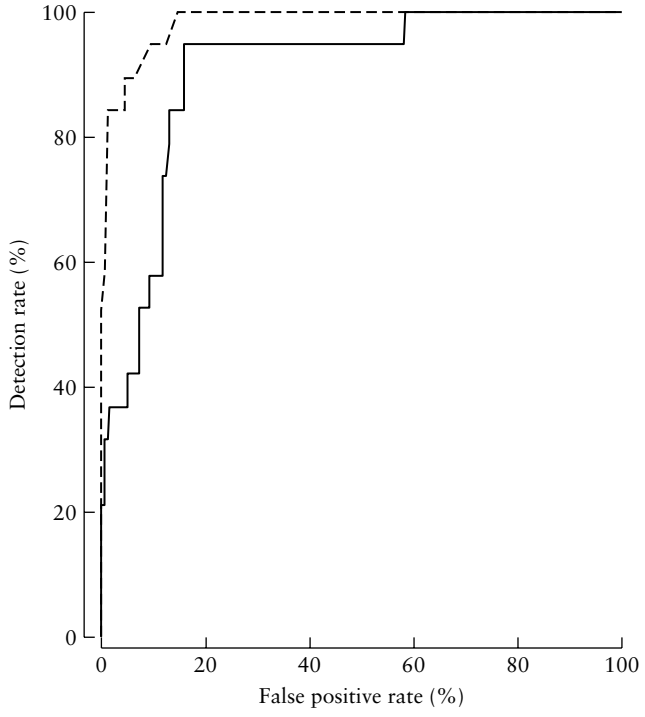


**Figure 3** Receiver–operating characteristics (ROC) curves comparing the performance of the two methods: cervical length (– – – –) and a model combining fibronectin with maternal characteristics (———).

## DISCUSSION

The findings of this study confirm that first, only about 10% of women presenting with threatened preterm labor deliver in the subsequent week; second, if at presentation the cervical length is longer than 15 mm or the fetal fibronectin test is negative the risk of such delivery is less than 1%; and third, short cervical length or fetal fibronectin positivity identifies pregnancies at high risk of early delivery[3–16]. Furthermore, the data demonstrate that first, a short cervix is better than fetal fibronectin positivity in identifying the high-risk group for early delivery; second, the incidence of fetal fibronectin positivity is inversely related to cervical length; and third, the prediction of the likelihood of delivery within 7 days provided by cervical length is not improved by the addition of fetal fibronectin testing.

Two previous studies have investigated the effect of combining cervical length and fetal fibronectin in 108[18] and 76[19] singleton pregnancies, respectively, presenting with threatened preterm labor in the prediction of preterm delivery, but they did not provide data on delivery within 7 days of presentation. In both studies the performance of the two tests was similar, with a screen positive rate for fetal fibronectin positivity and short cervix of about 40% and detection rates for preterm delivery of about 70–75%[18,19]. In the study of Rozenberg *et al.*, 70% of the patients with a short cervix were also fetal fibronectin positive, and combining the two tests did not provide a substantial improvement in the prediction of preterm delivery[19]. In contrast, Rizzo *et al.* reported that combining the two tests provided a significant improvement in the prediction of preterm delivery[18].

There are also two screening studies in asymptomatic women with singleton pregnancies examining the value of short cervix and fetal fibronectin positivity at 22–24 weeks' gestation in the prediction of spontaneous delivery before 32 and 33 weeks, respectively[20,21]. Goldenberg *et al.*[20] examined 2915 pregnancies at 24–26 weeks' gestation and Heath *et al.*[21] examined 5146 women at 22–24 weeks. Fetal fibronectin positivity was reported in 6.6%[20] and 3.5%[21] of patients, respectively, and cervical length of 25 mm or less in 9.1%[20] and 8.4%[21]. Heath *et al.* reported that fetal fibronectin positivity increased exponentially with decreasing cervical length from 3% to 19% and 57% for respective cervical lengths of 31–40 mm, 11–15 mm and 0–5 mm[21]. Similarly, Goldenberg *et al.* found that the incidence of fetal fibronectin positivity was 6% in those with cervical length of more than 25 mm and 16% for cervical length of 25 mm or less[20]. In both studies, short cervix and fetal fibronectin positivity provided significant independent contributions for the prediction of early delivery with similar odds ratios (12.5 vs. 12.2[21], and 8.7 vs. 9.8 in nulliparous women and 10.0 vs. 4.6 for parous women[20]).

In pregnancies presenting with threatened preterm labor the outcome measure of relevance to clinical management is delivery within the subsequent 7 days, rather than preterm delivery as such. The clinical

dilemma revolves around the issue of whether the patient is truly in labor and therefore in need of, first, hospitalization in a unit with facilities for neonatal intensive care and second, administration of tocolytics with the potentially achievable objective of short-term prolongation of pregnancy for the effective administration of corticosteroids to improve fetal lung maturity. It could be argued that, in the absence of reliable ways to distinguish between true and false labor, the high mortality and handicap rates associated with early preterm delivery justify treatment of all patients with threatened preterm labor, because such risks outweigh the economic cost of hospitalization, the maternal risks associated with tocolytics[1,2] and the potential fetal risks associated with corticosteroids[22,23]. However, the findings of this and previous studies that fewer than 1% of singleton pregnancies with a negative fetal fibronectin test or cervical length longer than 15 mm deliver within 7 days of threatened preterm labor, present a challenge to the concept of 'treatment for all'.

Hospitalization and the administration of tocolytics and steroids should be reserved for women that are truly in labor. These women can be identified by sonographic measurement of cervical length at presentation. In centers with no facilities for such assessment prediction of the high-risk group can be provided by a model that combines data on the fetal fibronectin test, ethnic origin and gestation at presentation.

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