# Economic evaluations and clinical decision making in obstetrical care

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# CHAPTER 3

## Predictive value of cervical length measurement and fibronectin testing in threatened preterm labor

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## ABSTRACT

OBJECTIVE: To estimate the performance of combining cervical length measurement with fetal fibronectin testing in predicting delivery in women with symptoms of preterm labor.

METHODS: We conducted a prospective nationwide cohort study in all 10 perinatal centers in the Netherlands. Women with symptoms of preterm labor between 24 and 34 weeks of gestation with intact membranes were included. In all women, qualitative fibronectin testing (0.050-microgram/mL cutoff) and cervical length measurement were performed. Logistic regression was used to predict spontaneous preterm delivery within 7 days after testing. A risk less than 5%, corresponding to the risk for women with a cervical length of at least 25 mm, was considered as low risk.

RESULTS: Between December 2009 and August 2012, 714 women were enrolled. Fibronectin results and cervical length were available for 665 women, of whom 80 (12%) delivered within 7 days. Women with a cervical length of at least 30 mm or with a cervical length between 15 and 30 mm with a negative fibronectin result were at low risk (less than 5%) of spontaneous delivery within 7 days. Fibronectin testing in case of a cervical length between 15 and 30 mm additionally classified 103 women (15% of the cohort) as low risk and 36 women (5% of the cohort) as high risk.

CONCLUSION: Cervical length measurement, combined with fetal fibronectin testing in case of a cervical length between 15 and 30 mm, improves identification of women with a low risk to deliver spontaneously within 7 days.

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## BACKGROUND

Spontaneous preterm delivery remains one of the most challenging problems in obstetrics. It occurs in 5–13% of deliveries and is a major cause of perinatal mortality and neonatal morbidity.[1] In the developed world, women presenting with symptoms of preterm labor before 32 weeks of gestation are often transferred to a perinatal center and receive treatment with tocolysis and corticosteroids. However, 75–95% of these women will not deliver within 7 days after presentation, and half of these women will continue pregnancy until term.[2-5] Consequently, many women are transferred and exposed to interventions without benefit. If we could improve identification of women who will not deliver in the short term—say within 7 days—we would be able to avoid side effects from unnecessary treatments, reduce health care costs, and lower stress for pregnant women and their families.[6-8]

Cervical length measurement and fetal fibronectin testing are often used in the clinical evaluation of women with symptoms of preterm labor. Either a cervical length of at least 25 mm or a negative fibronectin test (less than 0.050 micrograms/mL) signifies that the risk of preterm delivery within 7 days is less than 5%, giving a sound argument to withhold treatment.[3,5,9] However, a cervical length below 25 mm and a positive fibronectin test both have a poor positive predictive value for preterm birth. Treating all symptomatic women with a short cervix or a positive fibronectin test would lead to overtreatment.[3,5]

A recently published meta-analysis concluded that combining fibronectin results with cervical length may result in more accurate identification of women who will not deliver preterm, thereby reducing the number of hospital referrals, admissions, treatments, and costs. In these studies, preterm delivery before either 35 or 37 weeks of gestation was the most frequently used outcome measure, yet these outcome measures do not give an answer to the most acute clinical question, namely, whether a woman with symptoms of preterm labor needs immediate treatment and referral to a perinatal center to optimize circumstances if preterm delivery occurs. Two studies, which included only 192 women, reported on the outcome of preterm delivery within 7 days, which is a more relevant clinical outcome. The predictive value of combining cervical length and fibronectin results seems to be promising for the outcome preterm delivery within 7 days and more accurate compared with long-term outcomes.[10]

We analyzed data from a nationwide cohort study to evaluate whether the combination of fibronectin testing and cervical length measurement leads to more accurate identification of women who will not deliver within 7 days compared with either cervical length measurement or fibronectin testing in isolation.

## METHODS

We collected data in a prospective cohort study between December 2009 and August 2012 in all 10 Dutch perinatal centers that serve as tertiary referral centers for high-risk obstetrics. In the Netherlands, symptomatic women with a high risk of preterm delivery before 34 weeks of gestation are referred to one of these 10 perinatal centers and managed according to national guidelines.[11] The study protocol was approved by the ethics committee of the Amsterdam Medical Center (MEC 08/363) and was published thereafter.[12]

Women with symptoms consistent with preterm labor such as contractions (more than 3/30 min), vaginal bleeding, or abdominal or back pain, who were between 24 and 34 weeks of gestation, and who had intact membranes were eligible for the study. Women either presented directly to one of the participating perinatal centers or were referred by their primary gynecologist in a general hospital (secondary care) or by a general practitioner or midwife (primary care). Women who had received tocolysis within the previous 7 days were excluded with the exception of women who had received a single dose of tocolytic treatment for transport to the referral center. Women with contraindications for tocolysis such as a lethal congenital abnormality, suspected intrauterine infection, or non-reassuring fetal status were excluded as were women in whom the cervix was more than 3 cm dilated. Women who had iatrogenic delivery within 7 days after study enrollment for hypertensive disorders, non-reassuring fetal status, or other reasons for immediate delivery also were excluded. Eligible women were identified by study personnel and invited to participate in the study. They participated if they had given written informed consent. We intended to include 660 women.[12]

At the time the study started, cervical length measurement, but not fibronectin testing, was standard care in the Netherlands for risk stratification in women with symptoms of preterm labor. In the Netherlands clinically active physicians are trained in transvaginal ultrasonography and perform cervical length measurements themselves. To standardize these measurements, all participating physicians were given a set of instructions and a pocket card with illustrated examples of accurate cervical length measurements. Before this study, fibronectin tests were not performed as part of routine care. Before the study started, physicians and midwives were trained on how to collect a fetal fibronectin specimen from the posterior fornix of the vagina. Preferably, a specimen had to be collected before vaginal examination or cervical length measurement. In four participating centers, the fibronectin test was done at the hospital's central laboratory and in six within the obstetric departments. The involved personnel were trained to perform the fibronectin test. We used the qualitative rapid fibronectin $TLI_{IQ}$ analyzer with a 0.050-microgram/mL positivity cutoff. All centers guaranteed the results of the fibronectin tests to be available within 1 hour.[12]

No strict protocol was available for treatment decisions, but recommendations were provided. We recommended to start tocolysis in women with cervical length below 10 mm and in women with a cervical length between 10 and 30 mm with a positive fibronectin result and

to withhold tocolysis in women with a cervical length above 30 mm. For women with a cervical length between 10 and 30 mm in combination and a negative fibronectin test, the clinician on call decided whether to start tocolysis in these women. Clinicians could prescribe nifedipine, indomethacin, atosiban, ritodrine, or all of these. Corticosteroids were given to women at the discretion of the clinician on call.[12]

The primary outcomes were spontaneous preterm delivery within 7 days after enrollment and stratification into a low-risk and a high-risk group using a 5% risk threshold. This threshold has been derived from the interpretation of cervical length because it is currently applied in women with signs of preterm labor. A cervical length between 20 and 30 mm decreases the risk of delivery within 7 days from a prior of 11% to a posttest probability of 4–5%.[3] The Dutch guideline, for example, uses 25 mm as a cutoff for cervical length, which corresponds to a risk of 5% to deliver within 7 days.[11]

To assess whether the combination of both tests could better identify women who will not deliver within 7 days as compared with current practice, four logistic regression models were developed: a model with only cervical length as predictor, a model with only fibronectin as predictor, a model with both fibronectin and cervical length as predictors, and a combined model in which the increase of the risk associated with cervical length could differ for women with a positive fibronectin test result and for those with a negative result (an interaction model).[13,14] Cervical length was analyzed as a continuous variable. Linearity of the association between cervical length and the risk of preterm delivery was assessed using cubic spline analyses. Bootstrapping techniques were used for internal validation of the four models to avoid overfitting. Two hundred samples, of a size equaling that of the original data set, were drawn from the original data set with replacement. A shrinkage factor calculated from these additional analyses was used to adjust regression coefficients.[13,15]

A test was considered positive when the predicted risk was equal to or greater than 5%. Positive and negative predictive values were calculated for the prediction model. The model with the best overall performance in term of overall fit, discrimination, calibration, and reclassification (with further details provided in Supplement 1) was used to create a risk graph and decision rule for clinical use.[16] To facilitate the use of the prediction model in clinical practice, where cervical length cutoffs are frequently defined in 5-mm steps, we defined the cutoff accordingly. The performance of this decision rule was compared with that of other widely applied other decision rules: cervical length only, with a 25-mm cutoff, and fibronectin testing only, with a 0.050-microgram/mL cutoff.[3,11,17] Data analyses were performed in R 2.10.0 and SPSS 20.0.

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## RESULTS

Between December 2009 and August 2012, 758 potentially eligible women were identified. Five women did not meet the inclusion criteria, 23 had one or more exclusion criteria, and 16 did not consent to the study. In the remaining 714 participating women, we performed cervical length measurement and fibronectin testing. Fibronectin results were invalid in 21 women, whereas fibronectin and cervical length were not recorded in nine and 13 women (n=43), respectively. We excluded six women who underwent labor induction or had an elective caesarean delivery within 7 days after study entrance, leaving 708 women in the study group (Figure 1).

Two hundred forty-three women (37%) presented directly to one of the perinatal centers, 210 women (32%) were referred to a perinatal center from secondary care centers, and 208 women (31%) were referred from primary care midwifery practices (Table 1). The mean gestational age at study entrance was 29 weeks (interquartile range 27–31). There were 103 women (16%) with a multiple pregnancy, 143 (22%) with a previous preterm delivery before 37 weeks of gestation, and 107 (16%) with a previous preterm delivery before 34 weeks of gestation. The median cervical length was 25 mm (interquartile range 18–35 mm) and the fibronectin result was negative in 364 women (55%). Eighty women (12%) delivered within 7 days. The median time to delivery in these 80 women was 2.2 days (interquartile range 0.6–3.6).
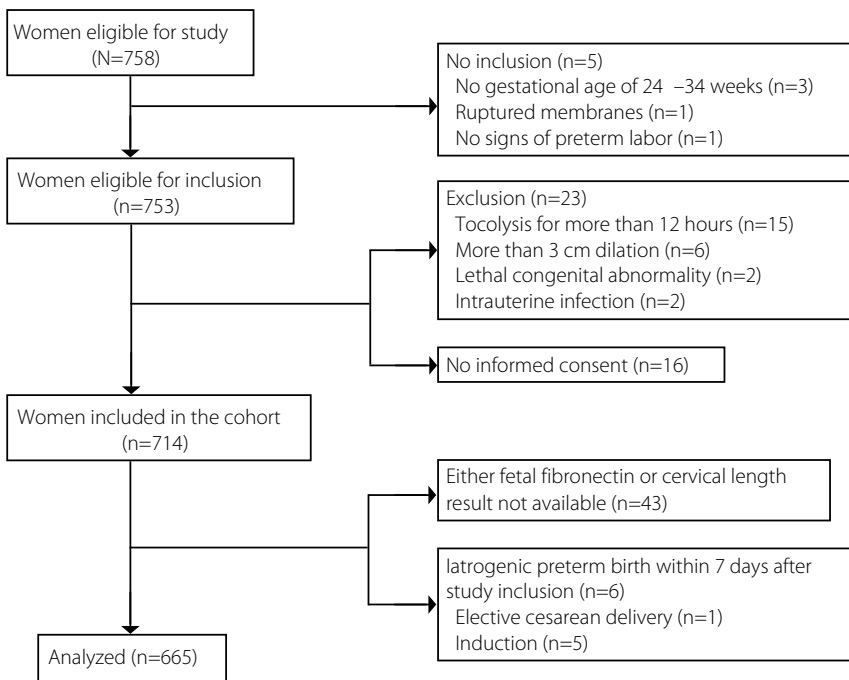


**FIGURE 1** - *Participant flow diagram*

**TABLE 1** - *Demographic and Clinical Characteristics (n=665)*

| | |
|---|---|
| **Delivery within 7 days after study entrance** | 80 (12%) |
| **Maternal age, (SD), years** | 29.7 (+/- 5.3) |
| **Body-mass index* (IQR), kg/m²** | 22.5 (20.4 - 25.3) |
| **Caucasian** | 454 (68%) |
| **Maternal smoking* (n = 619)** | 90 (15%) |
| **Education†** | |
| Primary school | 6 (0.9%) |
| Secondary school | 29 (4.4%) |
| Lower professional school | 17 (2.6%) |
| Medium professional school | 164 (25%) |
| Higher professional school | 117 (18%) |
| University | 68 (10%) |
| Unknown | 263 (40%) |
| **Nulliparous** | 343 (52%) |
| **Previous preterm delivery, < 34 wks** | 107 (16%) |
| **Previous preterm delivery, <37 wks** | 143 (22%) |
| **Previous term delivery, >37 wks** | 206 (31%) |
| **Twin gestation** | 100 (15%) |
| **Triplet gestation** | 3 (0.5%) |
| **Symptoms** | |
| Objectified contractions (CTG/manual) | 529 (80%) |
| **Last prenatal visit in** | |
| Perinatal center | 243 (37%) |
| Peripheral hospital | 210 (32%) |
| Midwifery practice | 208 (31%) |
| Unknown | 3 (0.5%) |
| **Cervical length (IQR), mm** | 25 (18-35) |
| **Fetal fibronectin** | |
| Positive | 301 (45%) |
| Negative | 364 (55%) |
| **Digital examination* (n = 510)** | |
| Cervical dilation, 1 cm | 152 (30%) |
| Cervical dilation, 2 cm | 39 (7.6%) |
| Cervical dilation, 3 cm | 18 (3.6%) |

*IQR, interquartile range; SD, standard deviation; CTG, cardiotocogram. *, data are missing; †, lower, medium, and higher professional schools denote preparatory, intermediate, and higher vocational education, respectively*

The models for spontaneous preterm delivery within 7 days based on cervical length and fibronectin are shown in Table 2. A positive fibronectin test was associated with an increased risk of preterm delivery within 7 days regardless of whether it was considered on its own (odds ratio [OR] 10.7, 95% confidence interval [CI] 5.4–21.2) or conditionally on cervical length (OR 4.2, 95% CI 2.0–9.0). Adding fibronectin to a model with cervical length increased the positive predictive value from 0.23 (95% CI 0.19–0.29) to 0.27 (95% CI 0.22–0.33). It also significantly increased model fit ($x^2$ test statistic 23; p 0,001) and improved calibration. Overall discrimination did not improve (area under the curve 0.89, 95% CI 0.86–0.93). Adding the interaction term to the model including cervical length and fibronectin did not lead to a significant improvement in model fit and caused the positive predictive value and calibration to deteriorate. After these analyses, the model including cervical length and fibronectin (without interaction term) was selected as the best model. Further performance characteristics of these models, including a receiver operating characteristic curve and a calibration plot of the best performing model, can be found in Supplement 1.

The risk graph based on the model including cervical length and fibronectin (without interaction term) is shown in Figure 2. When the fibronectin result is taken into account, we found that fibronectin-negative women with a cervical length of 17 mm and fibronectin positive women with a cervical length of 27 mm have a 5% or higher risk of preterm delivery within 7 days. To facilitate its use in clinical practice, we redefined this interval to be from 15 to 30 mm. The corresponding decision rule translates into women with a cervical length of 30 mm or higher being classified as at low risk of preterm delivery and women with a cervical length of 15 mm or lower being classified as at high risk of preterm delivery. For women with a cervical length between 15 and 30 mm, classification is contingent on the fibronectin result: those with a positive fibronectin test result are classified as high risk, whereas those with a negative fibronectin test result as low risk.

**TABLE 2** - *Risk of preterm delivery within 7 days as predicted with cervical length and fetal fibronectin results (n = 665)*

|  | Cervical length model | Fetal fibronectin model | Fetal fibronectin and cervical length model | Fetal fibronectin and cervical length model (interaction) |
|---|---|---|---|---|
| Cervical length (mm)* | 0.84 (0.81 to 0.86) | - | 0.86 (0.83 to 0.89) | 0.81 (0.74 to 0.88) |
| Positive fibronectin test* | - | 10.7 (5.4 to 21.2) | 4.2 (2.0 to 8.9) | 1.4 (0.27 to 6.7) |
| Interaction term* | - | - | - | 1.1 (0.98 to 1.2) |
| Positive predictive value† | 0.23 (0.19 to 0.29) | 0.23 (0.19 to 0.29) | 0.27 (0.22 to 0.33) | 0.26 (0.21 to 0.32) |
| Negative predictive value† | 0.97 ( 0.95 to 0.99) | 0.97 ( 0.95 to 0.99) | 0.98 (0.96 to 0.99) | 0.98 (0.96 to 0.99) |

*, values express odds ratios (95% confidence interval) estimated with logistic regression modelling, shrunk with a bootstrap technique; †, values express percentages based on a 5% risk threshold (95% confidence interval) ; - , not included in the model
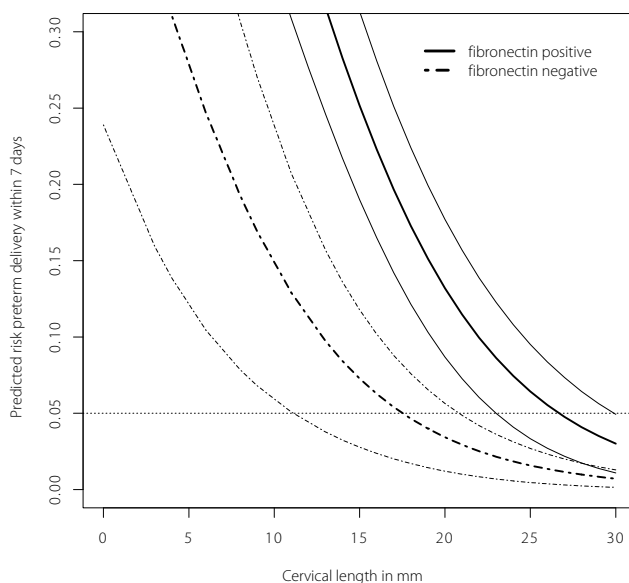
**FIGURE 2 -** *Risk graph for clinical use, based on the model including fetal fibronectin and cervical length as predictors. Horizontal dashed black line indicates whether the predicted risk to deliver within 7 days is above or below the threshold of 5%. Above this threshold women are classified as high risk to deliver within 7 days. The thin lines represent 95% confidence intervals.*

Table 3 illustrates the reclassification of participants according to the contingent decision rule. Compared with cervical length with a 25-mm cutoff, the contingent test resulted in 139 women (21%) being reclassified: 103 women (15%) were reclassified as low risk, of whom three (3%) delivered within 7 days. Conversely, 36 women (5%) were reclassified as high risk, of whom four (11%) delivered within 7 days. Summing these results shows that 67 low-risk women (10% of the cohort) and one woman with spontaneous preterm delivery within 7 days were additionally identified by using the contingent (on the fibronectin results) decision rule. Compared with fibronectin testing only, the contingent decision rule reclassified 84 women (13%): 62 (9%) were reclassified as low risk, of whom two (3%) delivered within 7 days. In addition, 22 women (3%) were reclassified as high risk, of whom six (27%) delivered within 7 days.

The risk of delivering within 1 week in case of a "low-risk" outcome of the decision rule is 6 of 404 (1.5%; 95% CI 0.7–3%); in case of "high risk" it is 74 of 261 (28%; 95% CI 23–34%). Reclassification rates were similar regardless of whether participants were from midwife practices, from general hospitals, or directly from home (Supplement 2).

**TABLE 3** - *Risk of preterm delivery within 7 days, reclassification with the fetal fibronectin test of women with different cervical lengths*

| | Fetal fibronectin Negative | | Fetal fibronectin Positive | | Total | |
|---|---|---|---|---|---|---|
| | n | PTD (%) | n | PTD % | n | PTD (%) |
| Cervical length < 15 mm | 22 | 6 (27%)* | 91 | 47 (52%)* | 113 | 53 (47%) |
| Cervical length 15 - 20 mm | 41 | 0 (0%)† | 54 | 9 (17%)* | 95 | 9 (9.5%) |
| Cervical length 20 - 25 mm | 62 | 3 (4.8%)† | 58 | 8 (4%)* | 120 | 11 (9.2%) |
| Cervical length 25 - 30 mm | 46 | 1 (2.2%)† | 36 | 4 (11%)* | 82 | 5 (6.1%) |
| Cervical length => 30 mm | 193 | 0 (0%)† | 62 | 2 (3.2%)† | 255 | 2 (0.7%) |
| | 364 | 10 (2.7%) | 301 | 70 (23%) | 665 | 80 (12%) |

*n, number of women in this stratum; PTD, preterm delivery within 7 days; \*, risk equal to or greater than 5% to deliver within 7 days; †, risk less than 5% to deliver within 7 days*

## DISCUSSION

This study assessed the value of fibronectin testing when used as an adjunct to cervical length measurement in women with symptoms of preterm labor between 24 and 34 weeks of gestation. Our analyses showed that fetal fibronectin testing in women with a cervical length between 15 and 30 mm was helpful in stratifying women as low risk (ie, risk of delivery within 7 days less than 5%) or high risk. We found that the combination of cervical length and fibronectin results could reduce the number of referrals and admissions to perinatal centers in 10% of all women compared with cervical length as the sole predictor regardless of whether women initially presented to a primary, secondary, or tertiary care setting. Such a reduction would also result in fewer medication side effects, less maternal stress, and lower health care costs.[18]

The strengths of this study include the use of a well-described, large, nationwide and clinically diverse cohort of women, in which the occurrence of preterm delivery within 7 days was high (12.0%). All Dutch perinatal centers that serve as a referral center for high-risk obstetrics participated, which is, besides the strict inclusion criteria, an explanation for the high delivery rate within 7 days. Because of the high density of midwifery practices and general hospitals in the Netherlands, two-thirds of our study population were from these centers. This composition gave the opportunity to estimate the potential reduction of false-positive results by combining cervical length and fibronectin in each clinical setting. To enhance the general applicability of the model, we focused on cervical length and fibronectin, both of which can be collected by any clinician on call. We used delivery within 7 days as the primary outcome, because the probability to deliver within 7 days has consequences for clinical decision-making; women who have a low risk of preterm delivery within 7 days can be sent home or stay in secondary care for monitoring and therefore avoid transport and prescription of unnecessary medications.

An important question is whether this model also applies to twin pregnancies, because the tests may behave differently in multiple pregnancies. It would be preferable to repeat all analyses in multiple pregnancies, yet the sample included too few women with preterm delivery to

develop a separate prediction model for this group (in our cohort, 20/103 [19.4%]). As a solution we created reclassification tables for singleton and multiple pregnancies (Supplements 3a and 3b). According to these results, the contingent rule enhances prediction for both groups. The question of whether other factors, such as ethnicity, body mass index (calculated as weight (kg)/ [height (m)]$^2$) or age, affect the accuracy of fibronectin levels also has not been resolved. To answer these questions we need larger sample sizes.

A final issue is whether tocolysis reduces the number of women who had preterm delivery within 7days, and consequently, whether it affects the reported decision rule. There is no good evidence that tocolytics can delay delivery by this amount of time, because double-blind placebo-controlled trials are scarce and only include betamimetics and indomethacin as tocolytic agents. Aggregated data suggest that these tocolytics might have an effect on the outcome delivery within 7 days.[19] However, if tocolysis had an effect on the outcome measure preterm delivery within 7 days, it would mainly have affected the high-risk fibronectin-positive women in our study, because these women disproportionately received tocolysis, which would have decreased our estimate of the potential predictive capacity of fibronectin and attenuated the contrast in outcomes between low and high-risk women. That is, the positive predictive value that we report is a conservative estimate.

The outcome measure of preterm delivery within 7 days has been used in three prior studies that combined cervical length and fibronectin results.[4,20,21] The first prospective cohort study (n=51) concluded that additional fibronectin testing in cases of cervical length below 25 mm improved accuracy compared with cervical length measurement only.[19] The second prospective cohort study (n=215) concluded that additional fibronectin measurement improved diagnostic accuracy significantly in cases of cervical length below 30 mm.[4] The a priori risks of preterm delivery and the results of both studies correspond in general with our study, but these studies did not assess whether there was a cervical length cutoff below which the fibronectin test is redundant because the risk of preterm delivery is already high based on cervical length only. Furthermore, the potential effect of implementing the additional fibronectin test was not studied. A third study (n=141), in which a retrospective cohort was analyzed, concluded that implementation of a strict protocol using cervical length and fibronectin could reduce costs.[20] Unfortunately, comparing their results with the present findings is difficult, because the a priori risks of preterm delivery within 7 days was so different (3.6% compared with 12.0% in our study).

Future analyses need to focus on further individualized risk assessment using additional biomarkers such as vaginal examination, laboratory findings, and patient characteristics, eg, age, socioeconomic status, and previous preterm delivery. The quantitative fibronectin test and other point-of-care tests also may improve prediction of preterm delivery. We also need to externally validate prediction models and evaluate the cost-effectiveness of implementing these models and corresponding treatment strategies in clinical practice. To increase external validity and enhance sample size, this requires individual patient data meta-analysis.

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## SUPPLEMENTAL MATERIAL

**SUPPLEMENT 1** - *Performance of logistic regression models: preterm delivery within 7 days predicted with cervical length and fetal fibronectin results*

The performance of the 3 prediction models including cervical length as a predictor was compared in terms of overall fit, discrimination, calibration and reclassification. Overall fit of the models was expressed with Nagelkerke $R^2$, Brier and *scaled* Brier score. Improvement in fit by adding fibronectintest results was tested with the $X^2$ test. The ability of the models to discriminate between women who delivered within 7 days and those who delivered at least 7 days after testing was expressed as the area under the receiver operating characteristics curve (AUC) and as discrimination slopes. Agreement between predicted and observed proportions of women with spontaneous preterm delivery within 7 days after enrollment, also known as calibration, was visualized in a calibration plot and miscalibration was tested for significance with the Hosmer-Lemeshow test statistic.[1]

Improvement in reclassification between the model based on cervical length only and the model including fibronectin results was expressed as Net Reclassification Improvement (NRI) and integrated discrimination improvement (IDI). One needs to define a decision threshold, indicating high and low risk, before calculating the NRI. The NRI is the sum of the difference in proportion of individuals with the outcome moving up (above the 5% risk) minus the proportion of those moving down (beneath the 5% risk), and the proportion of individuals without the outcome moving down minus the proportion in those moving up. The IDI integrates the NRI over all possible cut-offs, and is the equivalent to difference in discrimination slopes.[1]

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**TABLE** - *Performance of logistic regression models: preterm delivery within 7 days predicted with cervical length and fetal fibronectin results*

| Performance measure | Cervical length | Fetal fibronectin and cervical length | Fetal fibronectin and cervical length with interaction |
|---|---|---|---|
| **Overall fit** | | | |
| Brier | 0.070 | 0.069 | 0.069 |
| Brier scaled | 33.1% | 34.9% | 34.6% |
| $R^2$ (Nagelkerke) | 41.2% | 45.2% | 44.9% |
| **Discrimination** | | | |
| C-stat (95%CI) | 0.87 (0.83 to 0.91) | 0.89 (0.86 to 0.93) | 0.89 (0.86 to 0.93) |
| Discrimination slope | 0.3331 | 0.3621 | 0.3483 |
| **Calibration** | | | |
| Calibration in the large | 0.0043 | 0.0088 | -0.0281 |
| Calibration slope | 0.9918 | 0.9977 | 0.9717 |
| Hosmer-Lemeshow test | $X^2$= 10.668  p= 0.055 | $X^2$= 6.653   p=0.354 | $X^2$=12.143  p= 0.059 |
| **Reclassification** | | | |
| IDI | x | 1.8% | 1.5% |
| NRI | x | 0.099 | 0.091 |
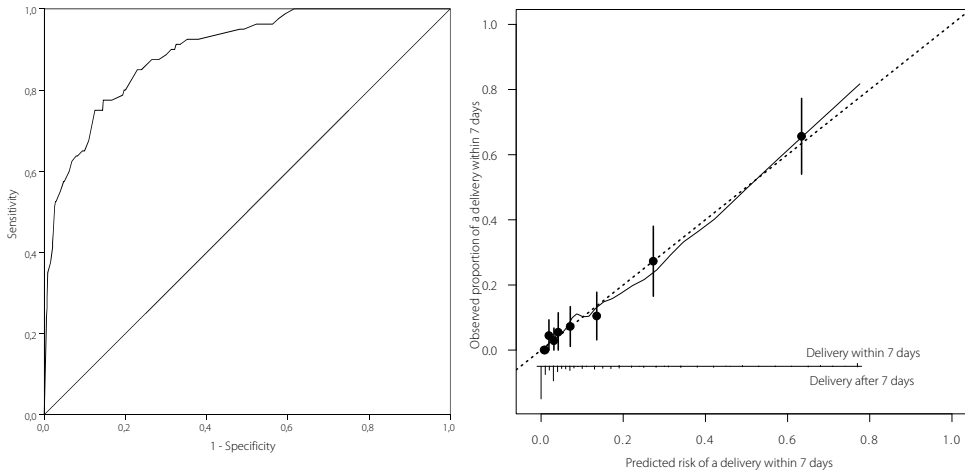


**FIGURES** - *Receiver operating curve and calibration plot of the model including cervical length and fetal fibronectin results (without interaction term); the model with the best performances as been shown in the table above.*

**SUPPLEMENT 2** - *Additional fetal fibronectin test in case of cervical length between 15 and 30 mm in women referred from primary, secondary and tertiary care*

| First presentation | n | Risk of preterm delivery | | | Reclassification[†] | | |
|---|---|---|---|---|---|---|---|
| | | A priori | Negative test[*] | Positive test[*] | Nr treated | Down reclassification | Upward reclassification |
| Midwifery practice (prim. care) | 208 | 0.09 | 0.00 | 0.29 | 63 | 23 | 11 |
| General hospital (sec. care) | 211 | 0.18 | 0.02 | 0.34 | 103 | 34 | 8 |
| Perinatal center (tert. care) | 243 | 0.10 | 0.03 | 0.21 | 95 | 43 (3 PTD) | 17 (4 PTD) |

*Data are missing for 3 participants. Preterm delivery, preterm delivery within 7 days; *, test is considered positive in case cervical length of 15 mm or below, or in case of a positive fetal fibronectin test and a cervical length between 15 and 30 mm.†, compared with cervical length measurement with a decision threshold of 25 mm*

**SUPPLEMENT 3a** - *Risk on preterm delivery within 7 days: women assigned to their cervical length group and fetal fibronectin result (singletons)*

| | Fetal fibronectin Negative | | Fetal fibronectin Positive | | Total | |
|---|---|---|---|---|---|---|
| | n | PTD (%) | n | PTD (%) | n | PTD (%) |
| Cervical length < 15 mm | 14 | 2 (14%)* | 71 | 39 (55%)* | 85 | 41 (48%) |
| Cervical length 15 - 20 mm | 35 | 0 (0%)† | 42 | 6 (14%)* | 77 | 6 (7.8%) |
| Cervical length 20 - 25 mm | 51 | 3 (5.8%)† | 48 | 7 (15%)* | 99 | 10 (10%) |
| Cervical length 25 - 30 mm | 37 | 0 (0%)† | 30 | 2 (6.6%)* | 67 | 2 (3.0%) |
| Cervical length => 30 mm | 177 | 0 (0%)† | 57 | 1 (1.7%)† | 234 | 1 (0.4%) |
| | 314 | 5 (1.6%) | 248 | 55 (22%) | 562 | 60 (11%) |

*n, number of women in this stratum; PTD, preterm delivery within 7 days; *, risk equal to or greater than 5% to deliver within 7 days; †, risk less than 5% to deliver within 7 days*

**SUPPLEMENT 3b** - *Risk on preterm delivery within 7 days: women assigned to their cervical length group and fetal fibronectin result (multiple gestation)*

| | Fetal fibronectin Negative | | Fetal fibronectin Positive | | Total | |
|---|---|---|---|---|---|---|
| | n | PTD (%) | n | PTD (%) | n | PTD (%) |
| Cervical length < 15 mm | 8 | 4 (50%)* | 20 | 8 (40%)* | 28 | 12 (43%) |
| Cervical length 15 - 20 mm | 6 | 0 (0%)† | 12 | 3 (25%)* | 18 | 3 (17%) |
| Cervical length 20 - 25 mm | 11 | 0 (0%)† | 10 | 1 (10%)* | 21 | 1 (4.7%) |
| Cervical length 25 - 30 mm | 9 | 1 (11%)† | 6 | 2 (33%)* | 15 | 3 (20%) |
| Cervical length => 30 mm | 16 | 0 (0%)† | 5 | 1 (20%)* | 21 | 1 (4,7%) |
| | 50 | 5 (10%) | 153 | 12 (28%) | 103 | 20 (19%) |

*n, number of women in this stratum; PTD, preterm delivery within 7 days; *, risk equal to or greater than 5% to deliver within 7 days; †, risk less than 5% to deliver within 7 days*

3 Chapter