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Comparison of the Actim Partus test and the fetal fibronectin test in the prediction of spontaneous preterm birth in symptomatic women undergoing cervical length measurement

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ABSTRACT

Objective: To compare the accuracy of the Actim Partus test and fetal fibronectin (fFN) test in the prediction of spontaneous preterm delivery within seven days in symptomatic women undergoing cervical length measurement.

Study design: We performed a post-hoc analysis on frozen samples of a nationwide cohort study in all 10 perinatal centres in the Netherlands. We selected samples from women with signs of preterm labour between 24 and 34 weeks of gestational age and a cervical length below 30 mm. Delivery within seven days after initial assessment was the primary endpoint. We calculated sensitivity, specificity, and positive and negative predictive values for the combination of both the Actim Partus test and fFN test with cervical length. A test was considered positive in case of a cervical length between 15 and 30 mm with a positive Actim Partus or fFN test, and a cervical length below 15 mm regardless the test result.

Results: In total, samples of 350 women were tested, of whom 69 (20%) delivered within seven days. Eighty-four women had a positive Actim Partus test and 162 women a positive fFN test, of whom 54 (64%) and 63 (39%) delivered within seven days, respectively. Ninety-seven women had a cervical length below 15 mm, of whom 50 (52%) delivered within seven days. Sensitivity, specificity, positive and negative predictive values of combining cervical length with the Actim Partus test or the fFN test were 91%, 75%, 47% and 97%, and 96%, 58%, 36% and 98%, respectively.

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Conclusion: According to this post-hoc study, in combination with cervical length, the Actim Partus test could be used as an alternative for the fFN test to identify women who will not deliver within seven days after presentation. Further evidence should be collected in a prospective comparative study.

Introduction

Preterm birth, defined as delivery before 37 weeks of gestation, occurs in 11% of all live births worldwide, resulting in a total of 15 million babies born preterm per year [1]. In 2013, preterm birth was the leading cause of both neonatal mortality (35% of 2.8 million deaths) and morbidity worldwide [2]. The majority of preterm births follows spontaneous onset of labour or premature rupture of the membranes [3]. Establishing a diagnosis of preterm labour remains a long-standing challenge. Accurate identification of women who will actually deliver on a short term could allow targeted interventions and referrals.

The most commonly used biochemical test to predict preterm birth in symptomatic women is the fetal fibronectin (fFN) test. Fetal fibronectin is a glycoprotein found at the interface between the chorion and decidua parietalis [4]. Another test is the Actim Partus test, which detects the presence of phosphorylated insulin-like growth factor binding protein-1 (phIGFBP-1), synthesized by maternal decidual cells, in cervical secretions [5]. As a result of mechanical or inflammatory-mediated detachment of the fetal membrane from the decidua, both fFN and phIGFBP-1 leak into cervical secretions, indicating the early stages of labour. The detection of both biochemical markers in cervical secretions, indicated by a positive test result, has been shown to be associated with an increased risk of preterm birth [6–11]. The Actim Partus test has several advantages, such as faster testing without the need of an analyser and therefore lower costs and the test is unaffected by vaginal bleeding, urine or seminal plasma [5,12].

A recently published meta-analysis reported that the overall predictive ability of the Actim Partus test for the identification of symptomatic women at risk for preterm birth was limited, with a pooled sensitivity and specificity for preterm delivery within seven days of testing of 67% and 77% respectively [13]. Comparing these results with those obtained in recent systematic reviews on fetal fibronectin, they concluded that the qualitative fetal fibronectin test is more accurate to predict preterm birth within seven days (sensitivity of 75–77% and specificity of 79–83%). However, direct comparisons between the Actim Partus test and the qualitative fFN test with adequate sample sizes are currently lacking.

Previous studies have shown that combining fFN with cervical length measurement improves the prediction of preterm birth within seven days in symptomatic women [14,15]. An improved identification of women in labour with the combination of the Actim Partus test and cervical length was suggested in previous research, but sample sizes were small [16,17]. The aim of this study was to compare the predictive value of the Actim Partus test and the qualitative fFN test, both in combination with cervical length measurement, for spontaneous preterm birth in symptomatic women.

Materials and methods

We performed a secondary analysis on frozen samples obtained during the Apostel-1 study. The Apostel-1 study was a nationwide cohort study conducted in all ten perinatal centres in the Netherlands between December 2009 and August 2012. The objective of the study was to evaluate the predictive value of the qualitative fetal fibronectin (fFN) test in combination with cervical length measurement. Further description of the design and results of the study have been reported elsewhere [15,18]. The study was approved by the ethical board of the Academic Medical Centre and written informed consent was obtained from all participants.

In short, women with signs of preterm labour between 24 and 34 weeks of gestational age with intact membranes were included. Signs of preterm labour were contractions ($\geq$3/30 min), vaginal bleeding and abdominal or back pain. Exclusion criteria were cervical dilatation of more than three centimetres, previous treatment with tocolysis within seven days before inclusion and contra-indications for tocolysis, such as suspected intra-uterine infections, fetal distress or lethal congenital abnormalities. The primary outcome was spontaneous preterm birth within seven days after inclusion. Therefore, women who had iatrogenic delivery within seven days after inclusion were excluded. At inclusion, all women underwent cervical length measurement using a transvaginal ultrasound. Besides that a qualitative fFN test was performed, using the qualitative Rapid fFN TLI_{IQ} analyser (Hologic) with a 50 ng/mL threshold for a positive result. Physicians and midwives were trained on how to collect a fFN specimen from the posterior fornix of the vagina according to manufacturer's instructions. We stored the fFN samples after test performance at a temperature of $-80\,^{\circ}C$.

There was no strict protocol for treatment decisions; however, we recommended treating women with a short cervix ($<$10 mm) or a cervical length between 10 and 30 mm with a positive fFN result. Clinicians could prescribe treatment including tocolysis (nifedipine, atosiban, indomethacin or ritodrine) and corticosteroids

For this secondary analysis, we only selected women with a cervical length below 30 mm, as women with a cervical length above 30 mm were known to be at low risk of preterm birth (1% delivered within seven days) [15]. We excluded women without a frozen fFN sample available or with more than one frozen sample and an unknown reason for repetition of the test. After thawing of the selected samples, we first performed the Actim Partus test (Medix Biochemica, Finland) using the one-step dipstick provided in the bedside test kit. The test was interpreted as being positive or negative, respectively, when two or one blue line appeared in the result area. Two individuals independently evaluated the results to assess the inter-observer agreement. Afterwards, the fFN testing was performed using the recently developed Rapid fFN 10Q analyser (Hologic®). An fFN concentration of more than 50 ng/mL was considered as a positive result. As the interpretation of the Actim Partus test requires a subjective judgement, whereas the result of the fFN test is generated by an analyser, we performed the Actim Partus test before the fFN test.

Analysis

Descriptive characteristics were obtained for baseline demographics. For risk stratification, cervical length was divided into groups of 5 mm. The risk of preterm birth within seven days was calculated for a positive and a negative test result in the different cervical length groups, for both the fFN test and the Actim Partus test. We assessed the predictive accuracy of both tests by calculating the sensitivity, specificity, positive and negative

predictive values. In the Apostel-1 study, we found that additional fFN could best be tested in women with a cervical length between 15 and 30 mm. Therefore, we compared this strategy to the use of the Actim Partus test in women with a cervical length between 15 and 30 mm. To assess the predictive accuracy in terms of sensitivity and specificity as well as positive and negative predictive values of both the fFN test and the Actim Partus test in combination with cervical length, we considered a test positive in case of a cervical length below 15 mm (regardless the fFN/Actim Partus result) and a cervical length between 15 and 30 mm with a positive fFN/Actim Partus test result. We considered a test negative in case of a cervical length between 15 and 30 mm with a negative fFN/Actim Partus test result. The McNemar test was used to determine whether the sensitivity and specificity were statistically different. A P-value of <0.05 was considered to indicate statistically significance. Statistical analyses were performed in SPSS version 20.0 (Chicago, IL, USA).

Results

We performed cervical length measurement and fFN testing in 714 women participating in the Apostel-1 study. Six women were excluded because they underwent induction of labour or had an elective caesarean section within seven days after inclusion. Samples of 121 women were missing, while 20 women had more than one frozen samples and were therefore also excluded. Eleven women were excluded because cervical length measurement was missing. Another 201 women were excluded because they had a cervical length above 30 mm, of whom 2 (1%) delivered within seven days. In total, 355 samples were available for testing. Five samples did not contain enough fluid for testing. Therefore, a total of 350 fFN samples from symptomatic women were eligible for this post-hoc analysis (Fig. 1). Baseline characteristics of the study population are shown in Table 1. The complete demographics of the overall study population are presented elsewhere [15].

In total, 69 of these 350 women (20%) delivered within seven days after presentation. Table 2 shows the risk stratification of preterm birth within seven days. The inter-observer agreement for evaluation of the Actim Partus test results was found to be 99.4%. Two samples that were assessed differently were considered positive for further analyses. Ninety-seven women (28%) had a cervical length below 15 mm, of whom 50 (52%) delivered within seven days. Eighty-four women (24%) had a positive Actim Partus test, of whom 54 (64%) delivered within seven days. Of 162 women (46%) with a positive fFN test, 63 (38%) delivered within seven days.

Combining the fFN test with cervical length measurement resulted in 185 women (53%) with a positive test, of whom 66 (36%) delivered within seven days, and 165 women (47%) with a negative test, of whom 3 (2%) delivered within seven days. Combining the Actim Partus test with cervical length measurement resulted in 134 women (38%) with a positive test, of whom 63

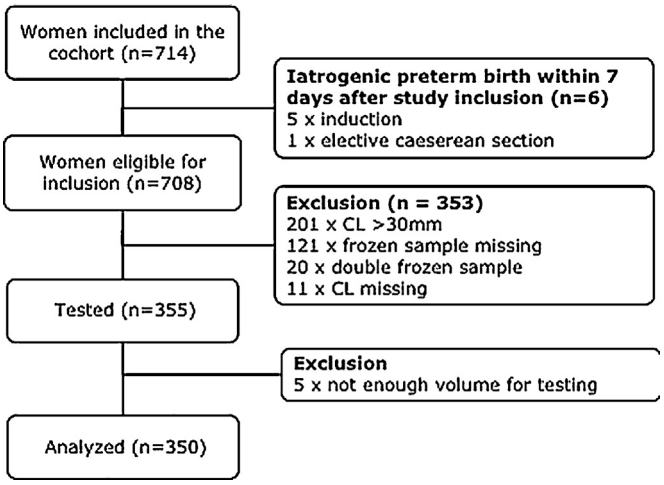

Fig. 1. Participant flow diagram.

Table 1
Baseline characteristics of the study population (n = 350).

Nulliparous (n (%))	207 (59%)
Age—years (mean ± SD)	29.9 ± 5.4
Gestational age—weeks (mean ± SD)	29.0 ± 2.7
Multifetal gestation (n (%))	71 (20%)
Previous preterm delivery (n (%))	79 (23%)
Caucasian race (n (%))	202 (58%)
Body-mass index kg/m^2 (mean ± SD)	23.1 ± 4.3
Cervical length—mm (median (IQR))	19 (13–24)
Positive post-hoc fibronectin result (n (%))	162 (46%)
Positive post-hoc Actim Partus result (n (%))	85 (24%)

Data are presented as number of patients (%) of the total study population for categorical and dichotomous variables and mean ± standard deviation (SD) or median (IQR) for continuous variables.

Table 2
Risk stratification of preterm delivery within 7 days for the fetal fibronectin test and the Actim Partus test in combination with cervical length measurement.

	Fetal fibronectin				Total	
	Negative		Positive			
Cervical length <15 mm	23	(3 PTB—13%)	74	(47 PTB—64%)	97	(50 PTB—52%)
Cervical length 15–19 mm	41	(0 PTB—0%)	39	(7 PTB—18%)	80	(7 PTB—9%)
Cervical length 20–24 mm	60	(3 PTB—5%)	29	(5 PTB—17%)	89	(8 PTB—9%)
Cervical length 25–30 mm	64	(0 PTB—0%)	20	(4 PTB—20%)	84	(4 PTB—5%)
Total	188	(6 PTB—3%)	162	(63 PTB—39%)	350	(69 PTB—20%)
	Actim Partus				Total	
	Negative		Positive			
Cervical length <15 mm	50	(9 PTB—18%)	47	(41 PTB—87%)	97	(50 PTB—52%)
Cervical length 15–19 mm	64	(1 PTB—2%)	16	(6 PTB—38%)	80	(7 PTB—9%)
Cervical length 20–24 mm	79	(5 PTB—6%)	10	(3 PTB—30%)	89	(8 PTB—9%)
Cervical length 25–30 mm	73	(0 PTB—0%)	11	(4 PTB—36%)	84	(4 PTB—5%)
Total	266	(15 PTB—6%)	84	(54 PTB—64%)	350	(69 PTB—20%)

PTB = Preterm birth within 7 days.

Table 3
The predictive value of the fFN test, the Actim Partus test and the combination of both tests with cervical length measurement.

	fFN	AP	fFN + cervical length[a]	AP + cervical length[a]
Sensitivity (%)	90.0	78.3	95.7	91.3
Specificity (%)	64.8	89.3	57.7	74.7
PPV (%)	38.9	64.3	35.7	47.0
NPV (%)	96.8	94.4	98.2	97.2

fFN = fetal fibronectin, AP = Actim Partus, PPV = positive predictive value, NPV = negative predictive value.
[a] A cervical length below 15 mm (regardless the fFN or AP result) and a cervical length between 15–30 mm with a positive fFN or AP result was considered as a positive test result. A cervical length between 15 and 30 mm with a negative fFN or AP result was considered as a negative result.

(47%) delivered within seven days, and 216 women (62%) with a negative test, of whom 6 (3%) delivered within seven days. Sensitivity, specificity, and positive and negative predictive values for the fFN test, the Actim Partus test and both tests in combination with cervical length measurement are shown in Table 3. The sensitivity and specificity of the fFN and Actim Partus test alone both significantly differed from each other ($P < 0.001$), as did the specificity of both tests in combination with cervical length ($P < 0.001$). The sensitivity of both tests in combination with cervical length did not differ significantly ($P = 0.25$).

Comment

In this study, we compared the accuracy of the fFN test and the Actim Partus test, both in combination with cervical length measurement, in the prediction of spontaneous preterm birth within seven days in symptomatic women. We demonstrated that, in combination with cervical length, the Actim Partus test could be used as an alternative for the fFN test to identify more women with a low risk to deliver within seven days, reducing unnecessary referrals and treatment.

To our knowledge, this is the first study making a direct comparison between the fFN and Actim Partus test in combination with cervical length with a reasonable sample size. The data were derived from a well-described, large, nationwide cohort of women, in which qualitative fFN was collected according to protocol.

It is arguable that tocolysis has influenced our results. However, as tocolytics have a short half-life and are in general only given for the first 48 h after admission in order to delay delivery long enough to administer antenatal corticosteroids causing improved neonatal outcomes [19,20]. Moreover, good evidence that tocolysis, given during the first 48 h after admission, delays delivery after seven additional days have passed, is lacking [21]. Therefore, we think that it is unlikely that tocolysis have influenced the results of this study.

The sampling methodology is an important issue of the present study. The frozen samples used for this post-hoc analysis were obtained during the Apostel-1 study to evaluate the predictive value of the fFN test in combination with cervical length measurement [15]. These samples were collected by applying a sterile dacron swab to the posterior fornix of the vagina for 10–15 s, according to manufacturer's instructions for the fFN test. The sample for the Actim Partus test, however, is advised to be taken from the external cervical os. Rahkonen et al. examined the different sampling methodologies of the Actim Partus test in unselected pregnant women during the first and second trimester [12]. They demonstrated that phIGFBP-1 concentrations were significantly higher in cervical than in vaginal samples, indicating that the site of sampling might have an effect on the data. For our study, this means that in fact more Actim Partus results may have been positive, abolishing the improved identification of low-risk women, but this would not affect the sensitivity of the test in a negative way.

Despite this potential limitation, we found the Actim Partus test, in combination with cervical length, to be equivalent, if not slightly better than qualitative fFN to predict spontaneous preterm birth on short term. Although Conde-Agudelo and Romero suggested a lower accuracy of the Actim Partus test by comparing their pooled results with pooled results obtained in recent systematic reviews on fFN, our results are in line with previous studies making a direct comparison between the two tests [13]. Ting et al. showed somewhat higher positive and negative predictive values of the Actim Partus test compared to the fFN test for predicting preterm birth within seven days (39% versus 32% and 92% versus 89%, respectively), and Riboni et al. showed equal values of 97.7% versus 97.6% and 10.8% versus 9.1%, respectively [22,23]. Eroglu et al. demonstrated that combining either of the two tests with cervical length measurement (threshold of 25 mm) led to an improved prediction of preterm birth [17]. However, with 51 women the sample size was very small. Danti et al. evaluated the combined use of the Actim Partus test with cervical length measurement and confirmed that a cervical length above 30 mm identifies a low-risk subgroup, as none of these 42 women delivered within seven days. Moreover, they reported that the test may be useful to further stratify risk in women with a cervical length between 20 and 30 mm [16].

Several studies have recently reported that the novel quantitative fFN bedside test has added value over the currently used qualitative fFN test, as increasing fFN concentrations are associated with an increasing risk of preterm birth [24,25]. In our study, we demonstrated that the Actim Partus test could be an alternative for the qualitative fFN test, but it is unknown how the test relates to the quantitative fFN test. However, our results are particularly important for settings where the fFN test is not available at all, for example because of the costs of the test. In that case, the Actim Partus test could be considered, as it is the cheaper option.

Future research should focus on further improvement of personalized risk assessment to overcome the problem over overtreatment, unnecessary referrals and subsequent health costs. Prediction models including diagnostic tests such as the fFN test, the Actim Partus test and cervical length measurement, combined with other laboratory finding and patient characteristics should be developed and externally validated. Finally, cost-effectiveness analyses should determine the best strategies in clinical practice.

In summary, according to this post-hoc study, the Actim Partus test could be used as an alternative for the fFN test in combination with cervical length measurement to identify women who will not deliver within seven days after presentation. This information is particularly useful for settings where an infrastructure for measuring fFN is not present.

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