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The Combination of the Fetal Fibronectin Bedside Test and Cervical Length in Preterm Labor Is Useful for Prediction of Preterm Birth

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Abstract

Objective: To determine the value of fetal fibronectin (FFN), cervical length (CL) measurement and their combination as binary predictors for preterm birth (PB) in women with preterm labour (PTL) between 24 + 0 and 34 + 0 weeks. Methods: One hundred fifty-nine patients with signs of PTL (singleton pregnancies (SP) = 125, twin pregnancies (TP) = 34) were evaluated in a retrospective study. Inclusion criteria were contractions > 4/20 min, intact membranes, no bleeding. The cut-off was ≥50 ng/ml for FFN and ≤20 mm for CL measured by transvaginal ultrasound. The primary outcome variable was delivery within 7 days from admission. Results: We evaluated 125 SPs and 34 TPs. In SPs, both methods had a sensitivity of 80%; the specificity was 82% for FFN, and 50% for CL. For the combination of both tests sensitivity was 80% and specificity 88%. In TPs, the sensitivity of both tests was lower (FFN 33%, CL 67%) but the combination of both tests represented the highest result for specificity (77% compared to 68% for FFN alone and 32% for CL alone). Conclusion: The combination of FFN and CL in PTL results in a significant higher specificity in SPs. In TPs the performance of the tests is less accurate.

Keywords

Preterm Labor, Fetal Fibronectin, Cervical Length, Preterm Birth

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#First and second authors contributed equally to the study.

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1. Introduction

Preterm birth (PTB) is the leading cause of neonatal mortality and morbidity. Therefore, women presenting with signs of preterm labour (PTL) but intact membranes are often hospitalised and receive tocolytics and corticosteroids for lung maturation. The clinical diagnosis of PTL that precedes PTB has been characterised by its inaccuracy, with about two thirds of women presenting with PTL ultimately delivering at term. Correct identification of a mother at risk for a PTB allows risk specific treatment, stabilisation, and referral to a perinatal centre for achieving optimal neonatal outcome. It avoids otherwise unnecessary transport of the patient, potential harmful interventions and costly hospitalisations.

Several predictive markers have been proposed detecting women at risk for PTB. The biophysical sonographic measurement of cervical length (CL) and the biochemical assays for fetal fibronectin (FFN) appear to be the most promising and have been assessed in multiple studies [1] [2].

FFN is a normal constituent of the extracellular matrix of the maternal-fetal interface. This high molecular weight glycoprotein seems to play an essential role in maintaining the integrity of the chorionic-decidual interface. It is accepted that the disruption of the maternal-fetal interface often precedes the onset of PTL and results in the release of FFN into the cervicovaginal fluid [2] [3].

CL measurement is well established as a predictor for PTB at 20 weeks of gestation in asymptomatic women at increased risk [4] but less evaluated in symptomatic women with PTL using mostly thresholds below 15 mm or above 30 mm cervical length [5]. Short cervix reportedly predicts PTD with a sensitivity of 69% - 83%, a specificity of 69% - 88%, and a relatively low positive predictive value (PPV) of 22% - 54% in symptomatic women.

The usefulness of both tests has been shown by improving the accuracy of diagnosis and in reducing unnecessary maternal interventions and transferral of patients to a tertiary center. Furthermore, they are easily to apply after minimal training, safe, well accepted by pregnant women and cost effective [6]-[9].

There are, however, conflicting results from retrospective and observational studies, as well as from meta-analysis. Two Cochrane reviews have found no significant association between knowledge of CL results and a lower incidence of PTB, but for FFN an association between knowledge of FFN results and a lower incidence of PTB before 37 weeks was mentioned [10] [11]. Some authors found the combination not superior to either test alone, especially compared to CL measurement [3] [12] [13] and a recent meta-analysis found the cervicovaginal FFN assay to have limited accuracy in predicting PTB within 7 days of sampling in symptomatic pregnant women [14].

The discordant results of these studies illustrate the predicament for the clinical routine situation. Furthermore, the studies use different cut-off values and different ranges of examined weeks of gestation, which makes them even more difficult to compare and interpret.

Our objective was to determine whether the combination of the two tests was superior to each test alone as a prediction of preterm birth within seven days in symptomatic women with singleton and twin pregnancies.

2. Methods

This was a retrospective study with reviewed case notes conducted at two Swiss tertiary centres (center A 2000 deliveries/year and center B 1300 deliveries/year) from 2005-2008. Included were patients with PTL (at least 4 contractions within 20 minutes), between 24 + 0 and 33 + 6 weeks of gestation with a twin or singleton pregnancy and who had a documented assessment of FFN and CL. Gestational age was confirmed by first trimester ultrasound. Exclusion criteria were preterm premature rupture of membranes, cervical dilation > 3 cm, cerclage, vaginal bleeding, vaginal examination or intercourse within 24 h before FFN measurement, intrauterine fetal demise, fetal malformation, intrauterine growth restriction < 5th percentile, preeclampsia, and uterine malformation. At presentation to the hospital FFN was collected during speculum examination from the posterior fornix and the qualitative detection of FFN (Quikcheck FFN, Hologic, Marlborough, MA, USA) was performed as a rapid qualitative bedside test, described by the manufacturer (http://www.ffntest.com/hcp/testing/quikcheck.html). Subsequently transvaginal ultrasound (using a 4 - 8 MHz vaginal probe, Logiq or Voluson, GE healthcare or Alpha 5, Aloka) was carried out by the attending physician and CL was measured with an empty bladder as described in earlier publications and the shortest functional CL was used [15].

The cut off values used were FFN $\geq$ 50 ng/ml and CL $\leq$ 20 mm on transvaginal ultrasound. The CL cut-off value of 20 mm was chosen, since it is commonly used in both singleton pregnancies (SP) and twin pregnancies

(TP).

Results of the FFN tests were available to the attending clinicians who were free to use this information at their discretion for clinical management. However only CL was part of the local clinical management protocols, which physicians followed also with regard to the administration of tocolysis and corticosteroids for fetal lung maturation.

The primary outcome was the occurrence of PTB within 7 days (≤7 days) from admission. The two tests were evaluated separately as well as in combination, considering the combined test positive if both tests were positive ("AND" combination). As the management of preterm labor was not changed during the study period it was described as part of the assessment of the institutional quality of the service and therefore ethical approval was not obtained.

Patients with SP and with TP were analysed separately. Sensitivity, specificity and likelihood ratios, as well as positive and negative predictive values were computed, together with 95% confidence intervals (CI) according to Blaker 2000 and were tested with the McNemar-Test at a significance level of 0.05. The data were analysed using the statistical software R.

3. Results

A total of 159 patients were included, of which 125 were SPs and 34 TPs. They presented with PTL at a median age of gestation of 29 + 5 weeks and 29 + 1 weeks in SP and TP, respectively. Demographic characteristics of the women, which were comparable between singleton and twin pregnancies and the main pregnancy outcomes, are displayed in **Table 1**.

Table 1. Baseline characteristics.

		N	Singleton N = 125	Twins N = 34
Age	years	159	25 30 33	30 33 35
BMI	kg/m^2	159	23 26 29	24 27 29
History of preterm birth		159	11.2% (14)	5.9% (2)
Prity		159		
0			52.0% (65)	64.7% (22)
1			28.8% (36)	17.6% (6)
>1			19.2% (24)	17.6% (6)
Gravidity		159		
1			48.0% (60)	61.8% (21)
2			20.0% (25)	14.7% (5)
>2			32.0% (40)	23.5% (8)
Gestation age at hospitalization	day	159	28 + 1 29 + 5 31 + 6	27 + 0 29 + 1 30 + 4
Cervical length	mm	159	14.0 20.0 30.0	13.0 18.0 22.8
Lung maturation		159	65.6% (82)	91.2% (31)
Gestation age at birth	day	159	36 + 3 38 + 1 39 + 3	33 + 1 35 + 1 36 + 2
Fetal weight at birth	g	157	2770 3050 3400	1962 2202 2551
Days of hospitalization	day	132	2.00 4.00 8.00	4.75 7.50 13.25
Preterm birth before 37 + 0 weeks		159	31.2% (39)	85.3% (29)
Preterm birth before 34 + 0 weeks		159	8.8% (11)	32.4% (11)
Tocolysis		159	84.8% (106)	91.2% (31)
Vaginal bacterial or yeast colonization		159	37.6% (47)	26.5% (9)

a b c represent the lower quartile a, the median b, and the upper quartile c for continuous variables. N is the number of non-missing values. Numbers after percents are frequencies.

PTB within 7 days occurred in 5/125 of SP and in 3/34 of TP. In SP and TP CL ≤ 20 mm occurred in 64/125 and 23/34, respectively. FFN was positive in 26/125 of SP and in 11/34 of TP. Tocolytics were administered in 106/125 (84.8%) of SP and in 31/34 (91.2%) of TP in PTL. The PTB rate < 37 weeks in women with symptoms of labor was 31.2% for SP and 85.3% for TP. **Table 2** and **Table 3** present the baseline characteristics according to the results of FFN and cervical length measurement.

In SP both methods had a sensitivity of 80% with 95%-CI: [34.3%; 99%] for the given time period of 7 days. The specificity of the CL test alone was 50% with 95%-CI: [40.8%; 59.2%] which was significantly smaller than the specificity of the combination of CL and FFN-test of 88.3% with 95%-CI: [81.5; 93.2] (McNemar-Test, $p < 0.001$). Also, the specificity of the FFN test alone (81.7% [73.9%; 87.8%]) was significantly smaller than the specificity of the combination of cervix and FFN-test (McNemar-Test, $p = 0.013$).

The Positive Predictive Value for CL was 6.2% [2.2%; 15.1%], for FFN 15.4 [5.4; 34.1] and for the combination 22.2 [8%; 47.1%].

The Negative Predictive Value for CL was 98.4% [91.6%; 99.9%] and for FFN 99.0% [94.8%; 99.9%], for the combination 99.1% [95.2%; 99.9%]. In **Figure 1**, the estimates are shown together with the corresponding 95% confidence interval.

In TP, the sensitivity of both tests was less (FFN 33% and CL 67%) compared to SPs, but again the combination of the two tests showed the highest result for specificity (77% compared to 68% for FFN alone and 32% for CL alone).

Table 2. Baseline characteristics separated by the test out comes for singletons.

		N	fFN+, CL+ N = 18	fFN+, CL− N = 8	fFN−, CL+ N = 46	fFN−, CL− N = 53
Age	years	125	29 32 34	25 30 33	24 29 35	25 30 32
BMI	kg/m^2	125	25 28 31	24 26 28	23 25 30	24 25 28
History of preterm birth		125	5.6% (1)	50.0% (4)	8.7% (4)	9.4% (5)
Parity		125				
0			61% (11)	50% (4)	48% (22)	53% (28)
1			22% (4)	12% (1)	35% (16)	28% (15)
>1			17% (3)	38% (3)	17% (8)	19% (10)
Gravidity		125				
1			61% (11)	50% (4)	44% (20)	47% (25)
2			17% (3)	12% (1)	17% (8)	24% (13)
>2			22% (4)	38% (3)	39% (18)	28% (15)
Gestation age at hospitalization	day	125	29 + 1 30 + 3 32 + 0	28 + 0 28 + 2 29 + 3	28 + 0 29 + 0 31 + 4	27 + 5 30 + 2 32 + 2
Cervical length	mm	125	7.8 12.0 16.0	27.0 31.5 34.8	11.2 14.0 17.0	25.0 30.0 34.0
Lung maturation		125	94.4% (17)	87.5% (7)	84.8% (39)	35.8% (19)
Gestation age at birth	day	125	34 + 0 35 + 3 37 + 5	35 + 4 37 + 1 38 + 2	36 + 6 38 + 2 39 + 4	37 + 3 38 + 4 40 + 0
Fetal weight at birth	g	125	2195 2840 2998	2569 2735 2995	2869 3170 3400	2870 3130 3500
Days of hospitalization	day	108	0.00 0.00 0.75	0.00 0.00 4.00	5.00 8.00 20.25	1.00 3.00 4.00
Preterm birth before 37 + 0 weeks		125	67% (12)	50% (4)	26% (12)	21% (11)
Preterm birth before 34 + 0 weeks		125	27.8% (5)	12.5% (1)	8.7% (4)	1.9% (1)
Tocolysis		125	100.0% (18)	87.5% (7)	93.5% (43)	71.7% (38)
Vaginal bacterial or yeast colonization		125	44% (8)	25% (2)	30% (14)	43% (23)

a b c represent the lower quartile a, the median b, and the upper quartile c for continuous variables. N is the number of non-missing values. Numbers after percents are frequencies.

Table 3. Baseline characteristics separated by the test out comes for twins.

		N	fFN+, CL+ N = 7	fFN+, CL− N = 4	fFN−, CL+ N = 16	fFN−, CL− N = 7
Age	years	34	32 34 37	28 32 36	30 34 34	30 33 34
BMI	kg/m^2	34	24 24 31	27 27 28	24 26 30	23 27 28
History of preterm birth		34	14% (1)	25% (1)	0% (0)	0% (0)
Parity		34				
0			71.4% (5)	50.0% (2)	68.8% (11)	57.1% (4)
1			0.0% (0)	25.0% (1)	25.0% (4)	14.3% (1)
>1			28.6% (2)	25.0% (1)	6.2% (1)	28.6% (2)
Gravidity		34				
1			71% (5)	50% (2)	69% (11)	43% (3)
2			0% (0)	25% (1)	12% (2)	29% (2)
>2			29% (2)	25% (1)	19% (3)	29% (2)
Gestation age at hospitalization	day	34	27 + 1 29 + 1 30 + 1	30 + 2 31 + 1 31 + 6	26 + 0 28 + 4 30 + 2	27 + 0 28 + 6 29 + 1
Cervical length	mm	34	10 13 14	25 25 26	12 16 19	22 30 33
Lung maturation		34	100% (7)	100% (4)	100% (16)	57% (4)
Gestation age at birth	day	34	31 + 6 35 + 3 36 + 2	33 + 0 34 + 0 35 + 3	34 + 2 35 + 3 36 + 2	32 + 4 35 + 0 35 + 5
Fetal weight at birth	g	32	1738 2365 2844	2133 2230 2506	2071 2194 2551	1874 2031 2406
Days of hospitalization	day	24	9.0 9.0 9.0		4.8 7.0 15.2	4.0 8.0 8.0
Preterm birth before 37 + 0 weeks		34	71% (5)	100% (4)	88% (14)	86% (6)
Preterm birth before 34 + 0 weeks		34	43% (3)	50% (2)	19% (3)	43% (3)
Tocolysis		34	100.0% (7)	100.0% (4)	93.8% (15)	71.4% (5)
Vaginal bacterial or yeast colonization		34	43% (3)	50% (2)	12% (2)	29% (2)

a b c represent the lower quartile a, the median b, and the upper quartile c for continuous variables. N is the number of non-missing values. Numbers after percents are frequencies.

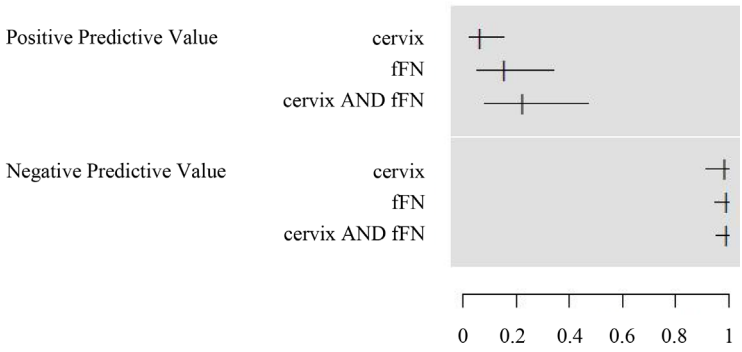

Figure 1. Singleton pregnancies, positive and negative predictive values.

The Positive Predictive Value for CL was 8.7% [1.60%; 27.4%], for FFN 9.1% [0.50%; 40.1%] and for the combination 0% [0%; 37.7%]. The Negative Predictive Value for CL was 90.9% [59.9%; 99.5%], for FFN 91.3% [72.6%; 98.4%] and for combination 88.9% [71.1%; 96.9%] (**Figure 2**).

The NPV was similar for both tests alone and the combination of the two.

Likelihood ratios are demonstrated in **Figure 3** and **Figure 4** (in all figures the estimates are shown together with the corresponding 95% confidence interval).

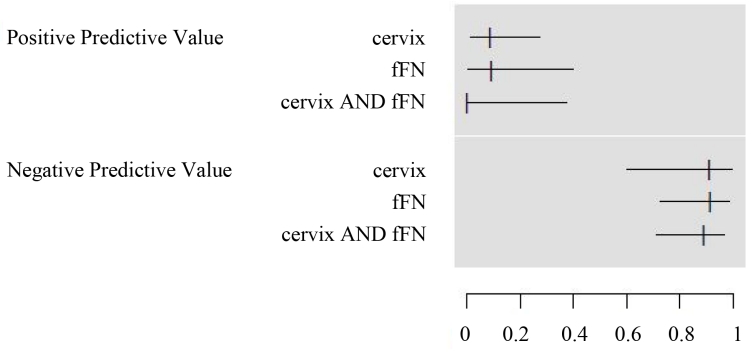

Figure 2. Twin pregnancies, positive and negative predictive values.

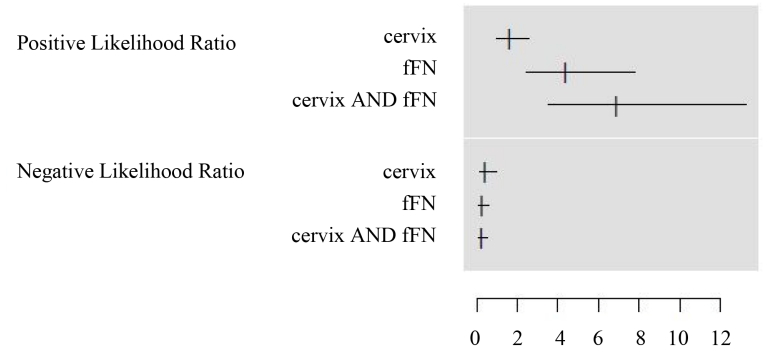

Figure 3. Singleton pregnancies, positive and negative likelihood ratios.

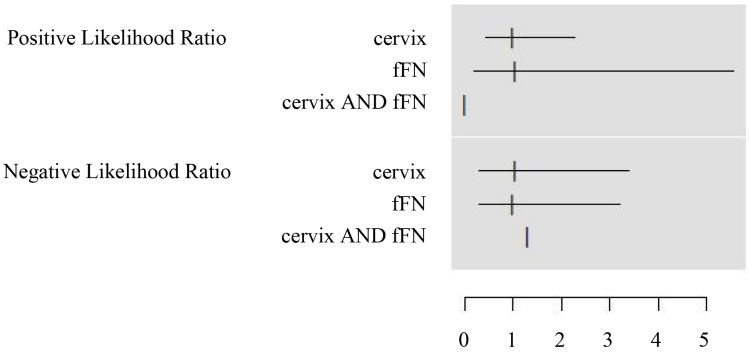

Figure 4. Twin pregnancies, positive and negative likelihood ratios.

For the combined test women with a positive result received tocolytics in 100% compared to those with two negative tests (7.41%). Not only the rate for preterm birth within seven days was higher in this group but also the rate for PTB < 34 and <37 weeks.

4. Discussion

The findings of this study clearly demonstrate the advantage of the combined test of a positive FFN and a short CL for the identification of patients with true preterm labour. A very small part of women with SP and clinical symptoms of labor delivered within 7 days. Compared to the clinical assessment we had a modest but higher positive predictive value with the combination of FFN and CL and a high negative predictive value. For SPs the combination of both tests provides a better estimate of the risk of PTB within seven days and therefore could be integrated into the decision to hospitalize high risk women, use acute tocolysis and antenatal lung maturation or identify safely women at low risk and avoid overtreatment.

For TPs the combination also seems to be superior, but in the sense that if either test is positive hospitalisation should occur. This underlines furthermore the high-risk situation for PTB in twin pregnancies, but should be interpreted with caution due to the small numbers of TP.

In contrast to many other countries cervical ultrasound assessment is mostly always available 24 h in Swiss obstetric departments. The combination of both tests might be more expensive than one test alone, but the higher specificity and negative predictive value allows reducing costs from unnecessary interventions.

Because the etiology of preterm labor is multifactorial, using multiple biomarkers from distinct biologic pathways will better predict the risk of preterm labor. Furthermore, combining non-invasive tools such as a physical or ultrasound finding may improve the ability of specific biomarker in predicting outcome [16].

Our findings concerning the properties of FFN and sonographic CL are in agreement with the previous reports considering the two tests in isolation [4] [8] [17] [18]. The results are in contrast to the study of Tsoi *et al*., where CL was the only significant contributor to the prediction of delivery within 7 days. FFN did not improve the prediction [12]. This prospective observational study, however, included women up to 36 weeks of gestation and 32% of the patients were of Afrocaribbean ethnicity. A limitation of our study is its retrospective non-randomized design. In this context, a potential source of bias is represented by the fact that test results were available to clinicians and may have influenced clinical decision making. A possible indication in that direction is that patients with negative tests appear to have received tocolytics significantly less frequently. Although relatively small, our sample is one of the largest among published studies on this topic.

5. Conclusion

In singleton and twin pregnancies with PTL, both tests are significantly associated with a prediction of preterm birth within seven days. However, the combination of the FFN and sonographic CL in PTL outperforms either test. Our data suggest that a combination of FFN-testing and CL measurement is recommendable for singleton and twin pregnancies, but large prospective studies are needed too. There are a number of research projects and clinical trials currently underway in Europe evaluating the properties of these tests [19].

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