

# Comparison between fetal fibronectin and cervical index in early detection of preterm labor

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## ABSTRACT

*The present study compared two methods of diagnosis of preterm labor which included transvaginal ultrasonography (for cervical index) and fetal fibronectin in cervicovaginal secretions and evaluated their roles in early detection of preterm labor.*

*This was a prospective study carried out at Obstetrics & Gynecology Department, Suez Canal University Hospital, Ismailia Governorate (2001-2002), Egypt.*

*Patients attending the Department of Obstetrics & Gynecology who were pregnant  $\geq 24$  - < 37 weeks of gestation and at risk of preterm labor were included in this study.*

*There were 50 cases divided into two groups according to strict inclusion criteria. Each case was subjected to thorough questionnaire obstetric examination, determination of fibronectin level in cervico-vaginal secretions and estimation of the cervical index.*

*The results of this study showed the superiority of the fibronectin estimation for the earlier detection of cases with impending preterm delivery compared to cervical index. The conclusion of the study was that the combined use of cervical index and fibronectin assay provided better prediction of impending preterm delivery.*

## INTRODUCTION

The WHO has recommended that 'preterm' be defined as gestational age less than 37 completed weeks of pregnancy or less than 259 days from the

first day of the last menstrual period.

Within the last 20 years, the incidence of preterm birth with spontaneous onset in singletons varied between 4% in 1989 in France<sup>1</sup> and 9.3% in North Carolina in 1986-87.<sup>2</sup> The estimated number of preterm birth worldwide is nearly 13,000,000. It is estimated that nearly 5.5 million women in preterm labor, world wide, are potentially treatable.<sup>3</sup>

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weight babies range from \$6000 per survivor for babies weighting 1000-1500 gm in the United Kingdom, to \$159000 per survivor for babies weighing less than 750 gm in the U.S. Special education costs alone for all infants of birth weight less than 2500 gm would be approximately 150,000,000 Sterling annually.<sup>4</sup> Methods used to predict preterm labor include:

- 1- Weekly cervical assessment<sup>5</sup>
- 2- Transvaginal ultrasonography<sup>6</sup>
- 3- Detection of fetal fibronectin<sup>7</sup>
- 4- Home uterine activity monitoring<sup>8</sup>

It appears from data described above that preterm labor is the most challenging problem in the modern obstetrics, and detection of preterm labor is an important area of scientific investigation.

The presence of fetal fibronectin in the posterior vaginal fornix of women with preterm uterine contractions has been shown repeatedly to be associated with subsequent preterm delivery. The predictive capability of the fetal fibronectin test, however, is in fact, greatest when the test is negative. In the large cohort documented by Peaceman et al,<sup>1</sup> for example, women with a positive test result had a 13% chance of being delivered within 1 week, and women with a negative test result had a >99% chance that they would not be delivered within 1 week. Thus, the high negative predictive value of fetal fibronectin sampling supports less intervention for patients with this result.

The question remains, however, whether fetal fibronectin use in clinical practice actually will lead to decreased interventions. Three studies have attempted to elucidate the relationship between the use of the test and consequent physician behavior. Giles et al<sup>10</sup> New Zealand found that women with preterm contractions who had a negative fetal fibronectin test result were less likely to be transferred to a tertiary care center than women with a positive test result. However, there was no formal cost analysis or control group of women who had not received the fetal fibronectin test; therefore, it was difficult to know the attributable impact of the test itself. Joffe et al<sup>11</sup> did compare a cohort of women who had the fetal fibronectin test with women who did not and found that the use of the test resulted in lower hospital costs, but this control group was historic, and the biases that are generated by this type of control impair the validity of the conclusions. Plaut et al<sup>12</sup> randomly assigned women with preterm contractions to have fetal fibronectin results either available or not available. Their study showed no significant differences between the

2 groups, although there was not sufficient power to evaluate the primary end point, namely, transport to a tertiary care facility.

The present study compared two methods of diagnosis of preterm labor, which were, transvaginal ultrasonography (for cervical index) and fetal fibronectin in cervicovaginal secretions and to evaluate their roles in early detection of preterm labor.

### Patients and methods

This prospective study was conducted at the Department of Obstetrics & Gynecology, Suez Canal University Hospital, Ismailia Governorate during the period 2001- 2002 from patients attending the clinics. The pregnant women were  $\geq 24$  - < 37 weeks of gestation and at risk of preterm labor.

Inclusion criteria:

Any woman at risk of spontaneous preterm labor

Exclusion criteria:

- 1- Preterm Rupture Of Membrane.
- 2- Multifetal gestation.
- 3- Medical disorders: Cardiac, diabetic, etc.
- 4- Cervical cerclage.
- 5- Congenital malformations of the fetus.
- 6- Uterine congenital anomalies.

Patients were subjected to:

- Full medical history.
- Complete physical examination:
  - A: General examination.
  - B: Obstetric examination:
    - Abdominal examination
    - P.V. examination (for Bishop score)
- Bishop score  $\leq 6$  mean that the cervix is unripe<sup>13</sup>
- investigations
  - 1- cardiotocography (CTG) for documentation of uterine contraction
  - 2- Transvaginal ultrasonography for cervical index.
  - 3- Estimation of fetal fibronectin in cervicovaginal secretions.
- Investigations and examination were carried out at the beginning of the study, and repeated every 2 weeks till 37 weeks of gestation or till spontaneous delivery in patients delivered preterm, or till diagnosis of preterm labor.

### Cervical index:

Cervical index was considered to be  $=(\text{funnel length} + 1) / (\text{endocervical length})$ .<sup>14</sup>

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Cervical length was measured with a transvaginal ultrasonography probe placed into the anterior fornix of the vagina with an empty maternal bladder.<sup>15</sup>

The cervical length measurement recorded was the shortest measurement that most clearly displayed the criteria described.<sup>16</sup> Funneling means dilatation of the upper part of cervical canal, which is not taken in the measurement of cervical length.<sup>17</sup>

### Fetal fibronectin

Using monoclonal antibodies or enzyme-linked immunosorbent assays, fibronectin from fetal sources such as the placenta can be specifically identified in vaginal and cervical secretions.<sup>18</sup>

The basis for vaginal screening of fetal fibronectin is to detect an increase in fetal fibronectin levels in vaginal secretions.<sup>19</sup>

In this study quantitative specimen is obtained (20  $\mu$  of cervicovaginal secretions) from the posterior fornix by Eppendorf micropipettes and it is recommended to use samples collected as early as possible.<sup>20</sup>

The level of fetal fibronectin in cervicovaginal secretions if greater than 50 ng / ml is considered positive.<sup>19,20</sup>

Data were collected, revised and analyzed by using computer software.

Levels of fetal fibronectin in the cervicovaginal secretions were compared with transvaginal ultrasound finding to assess sensitivity and specificity of each test in the early detection of preterm delivery.

### RESULTS

Fifty women who were pregnant  $\leq 24 - < 37$  weeks of gestation, and at risk of preterm labor were studied. They were followed every two weeks for investigations by transvaginal ultrasonography for estimation of cervical index and fetal fibronectin, measurements in cervicovaginal secretions till diagnosis of preterm labor or till spontaneous delivery either preterm or full term.

Twenty per cent of the study population ( 10 patients) delivered preterm  $< 37$  weeks (preterm group) while 80% of the study population (40 patients) delivered at full term  $> 37$  weeks (full term group)

**Table I: Age of the patients in preterm and full term groups**

Gestational age at delivery	Maternal Age			
	N	Mean	S.D	N
Preterm	10	33.5000	4.5277	0.164
Full term	40	31.0375	5.7159	

There was no statistically significant difference between the mean ages in women delivered preterm and women delivered full term ( $P=0.164$ ).

**Table 2: Patients occupation in the preterm and full term groups of women.**

Work outside the home (p= 0.140)	Gestation at delivery				Total	
	Preterm		Full term			
	N	%	N	%	N	%
Housewives	4	40.0%	26	65.0%	30	60.0%
Working women	6	60.0%	14	35.0%	20	40.0%
<b>Total</b>	10	100.0%	40	100.0%	50	100.0%

There was statistically no significant difference between the mean ages in women delivered preterm and women delivered full term (P=0.164).

**Table 3: The mean & standard deviation (SD) of gravidity and parity in preterm and full term groups.**

Parameters	Preterm	Full term	p
	Mean ± S.D	Mean ± S.D	
Gravidity	4.5000 ± 1.6499	2.6750 ± 1.2687	0.007**
Parity	2.3000 ± 1.1595	1.8333 ± 0.7915	0.259

\*\* Highly significant at the 0.01 level.

**Table 4: Correlation between history of preterm labor and preterm delivery**

History of preterm labor (p=0.001**)	Gestation at delivery				Total	
	Preterm		Full term			
	N	%	N	%	N	%
Yes	8	80.0%	8	20.0%	16	32.0%
No	2	20.0%	32	80.0%	34	68.0%
<b>Total</b>	10	100.0%	40	100.0%	50	100.0%

There was statistically no significant difference between the two groups (P<0.001).

**Table 5: Correlation between history of abortion and preterm delivery**

History of abortion ( $p=0.012^*$ )	Gestation at delivery				Total	
	Preterm		Full term			
	N	%	N	%	N	%
<b>Yes</b>	7	70.0%	10	25.0%	17	34.0%
<b>No</b>	3	30.0%	30	75.0%	33	66.0%
<b>Total</b>	10	100.0%	40	100.0%	50	100.0%

There is significant correlation between history of abortion and preterm delivery  
There was statistically significant difference between the two groups ( $P=0.012$ ).

**Table 6: Correlation between uterine contraction and preterm labor**

Presence of uterine contraction in current pregnancy ( $p<0.001$ )	Gestation at delivery				Total	
	Preterm		Full term			
	N	%	N	%	N	%
<b>Yes</b>	9	90.0%	5	12.5%	14	28.0%
<b>No</b>	1	10.0%	35	87.5%	36	72.0%
<b>Total</b>	10	100.0%	40	100.0%	50	100.0%

There is significant correlation between presence of uterine contraction and preterm labor ( $P<0.001$ ).

**Table 7: Significance of Bishop Score in diagnosis of preterm labor**

Bishop Score on examination ( $p<0.001$ )	Gestation at delivery				Total	
	Preterm		Full term			
	N	%	N	%	N	%
<b>≤ 6</b>	2	20.0%	33	82.5%	35	70%
<b>&gt; 6</b>	8	80.0%	7	17.5%	15	30%
<b>Total</b>	10	100%	40	100%	50	100%

Statistically significant difference existed between the two groups ( $p<0.001$ ).

**Table 8: Correlation between cervical length and preterm labor**

Short cervix $\leq$ 26mm ( $p < 0.001$ )	Gestation at delivery				Total	
	Preterm		Full term			
	N	%	N	%	N	%
Yes	5	50.0%	1	2.5%	6	34.0%
No	5	50.0%	39	97.5%	44	66.0%
Total	10	100.0%	40	100.0%	50	100.0%

There is significant difference between the two groups, between short cervix and preterm labor ( $P = 0.0001$ ).

**Table 9: Significance of cervical index in early detection of preterm labor**

High cervical index ( $p < 0.001$ )	Gestation at delivery				Total	
	Preterm		Full term			
	N	%	N	%	N	%
Yes ( $> 0.31$ )	5	50.0%	1	2.5%	6	12.0%
No ( $< 0.31$ )	5	50.0%	39	97.5%	44	88.0%
Total	10	100.0%	40	100.0%	50	100.0%

Normal level of cervical index is 0.31 while above that level is considered as high cervical index. There is statistically significant difference between the two groups ( $P = 0.0001$ ).

**Table 10: Significance of fetal fibronectin in early detection of preterm labor**

High fetal fibronectin ( $p < 0.001$ )	Gestation at delivery				Total	
	Preterm		Full term			
	N	%	N	%	N	%
Yes ( $> 50$ ng/ml)	8	80.0%	0	0%	8	16.0%
No ( $< 50$ ng/ml)	2	20.0%	40	100%	42	84.0%
Total	10	100.0%	40	100.0%	50	100.0%

Significant high fetal fibronectin discovered in preterm group usually about 2 weeks before spontaneous preterm labor, while transvaginal ultrasound finding (short cervix and high cervical index) can predict preterm labor 3-5 days before delivery.

There was significant difference between the two groups with regard to the high fetal fibronectin ( $P = 0.001$ ).

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**Table11: Comparison between cervical index and fetal fibronectin in early detection of preterm labor**

High cervical index ( $p < 0.001$ )	G. A. at delivery				Total	
	Preterm		Full term			
	N	%	N	%	N	%
<b>Yes</b>	5	62.5%	1	2.4%	6	12.0%
<b>No</b>	3	37.5%	41	97.6%	44	88.0%
<b>Total</b>	8	100.0%	42	100.0%	50	100.0%

Fifty percent of patients delivered preterm had high cervical index and 80% of cases delivered preterm had fetal fibronectin level in cervicovaginal secretions  $> 50\text{ng/ml}$ , which is a significant level.

The total study group is divided into two subgroups:

1. Group I: include 8 patients with high fetal fibronectin. 5 patients (62.5%) of this group have high cervical index and 3 patients (37.5%) have normal cervical index.
2. Group II: 42 patients of normal fetal fibronectin level, 2.4% of them (only one patient) has high cervical index, while 97.6% (41 patient) have normal cervical index. So high fetal fibronectin in cervicovaginal secretion is more sensitive than cervical index in detection of preterm labor ( $P < 0.001$ )

**Table12: Sensitivity, specificity, positive and negative predictive values of different parameters**

Parameter	SENSITIVITY	SPECIFICITY	PPV	NPV
<b>Fetal fibronectin</b>	50%	97%	87%	83%
<b>Cervical index</b>	42%	100%	100%	81%
<b>Combined tests</b>	71%	97%	90%	89%
<b>Uterine contractions</b>	90%	87%	64%	97%
<b>Bishop score</b>	57%	83%	57%	83%

PPV = positive predictive value

NPV = negative predictive value

**Table 13: Modes of delivery in total study population**

Parameter	N	%
NVD	40	80.0
CS	10	20.0
<b>Total</b>	50	100.0

NVD = Normal Vaginal Delivery

CS = Cesarean Section.

Preterm birth which affects 7-11 % of all newborn infants<sup>21</sup> remains the major cause of perinatal morbidity and mortality and is probably the most challenging problem in the modern obstetrics. This makes the early identification of women at risk of preterm delivery an urgent need and an important area of scientific investigation<sup>22</sup>

Fifty women who were pregnant between 24 - ≤37 weeks gestation and at risk of preterm labor were studied.

Ten patients (20% of cases) delivered preterm ≤37 weeks (spontaneous preterm labor) while 40 patients (80% of cases) delivered at term >37 weeks gestation.

The reported incidence of preterm delivery ranges from 14.4% to 59.4%<sup>16,23,24</sup>

Preterm delivery therefore accounts for about 75% to 85% of neonatal deaths in euploid infants without congenital anomalies<sup>25,26</sup>

Although a number of different pathogenic mechanisms (infection, hemorrhage, stress) may initiate preterm labor, they all appear to involve the disruption of the chorionicdecidual interface, Several biochemical markers that are released by this disruption have been proposed as predictors of spontaneous preterm birth, but, to date, only fetal fibronectin has proved clinically useful in screening for preterm delivery.

Fetal fibronectin is an extracellular matrix protein found at the interface between the chorion and decidua parietalis. It is normally absent, however, from the cervix and vagina after 20 weeks of gestation. Many studies have evaluated the use fetal fibronectin testing in both highrisk (history of preterm delivery multiple gestations) and low-risk populations that were

either symptomatic and symptom free.<sup>27-31</sup> The results of these studies have demonstrated that the main clinical benefit of fetal fibronectin is its specificity (up to 93%) and negative predictive value (up to 99%). Several of these studies have included women with cervical cerclage as part of their "high risk" group,<sup>27,32</sup> but no study has extracted data from this population alone to determine whether fetal fibronectin is a valid test for the prediction of spontaneous preterm delivery. In fact, there is concern that cerclage placement and the resulting inflammatory response may increase the false-positive rate and decrease the predictive value of this test. Furthermore the exposed suture material in the vagina may cause chronic vaginal irritation and microhemorrhage that theoretically could increase the false-positive rate.

The maternal age as a risk factor for preterm labor was considered to be < 18 years or > 40 years.<sup>33</sup> The frequency of preterm birth when maternal age >30 years was 14.7%.<sup>24</sup> In this study no statistically significant difference between preterm and full term group was observed with regard to maternal age. (Table 1).

In this study 60% of the preterm group were workers while 40% were non-workers. This categorizes working status as a risk factor for preterm delivery (Table 2) and this is supported by some workers<sup>38,41</sup> but not others.<sup>33</sup>

As seen in Table 3 nulliparity was present in 40% of cases who delivered prematurely so it is considered as a risk factor for premature delivery in this study. The is supported by the results of some researchers but not others.<sup>34</sup>

Sixteen patients (32%) in this study have prior history of preterm labor, 50% of them delivered preterm. So patients who have history of one or more preterm labor carry 50% risk of preterm delivery than in current



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pregnancy (Table 4). This coincides with the findings of Mercer and other investigators.<sup>15,35,36</sup>

As seen in table 5 the prior history of abortion is a risk factor for preterm delivery in the current pregnancy observed in this study. This is in accordance with the findings of most previous studies.<sup>21,37,38</sup>

In this study the risk of preterm labor increase to 64.2 % in patients with documented uterine contractions. (table 6) this agrees with the findings of Meis and associates.<sup>24</sup>

The results seen in Table 7 agree to the findings of Rozenberg and associates in 2000<sup>23</sup> but not Vincenzo and colleagues.<sup>39</sup>

The cervical length measurements seen in Table 8 and their relation to the occurrence of preterm labor coincide with the findings of some workers in the field<sup>40,41</sup> but not others.<sup>42</sup>

Twelve percent of our study population had cervical indices > 0.31, Eighty-three percent of them delivered preterm. 50% of the preterm group had cervical indices > 0.31 while 50% of them had normal cervical indices. (Table 9)

Eight patients (16% of cases) had fetal fibronectin level > 50 ng/ml, all of them delivered preterm. Eighty percent of the preterm group had high fetal fibronectin, while 100% of the full term group had fetal fibronectin < 50 ng/ml (Table 10)

It was reported that the incidence of preterm delivery was 64% when fibronectin level was positive<sup>16</sup> and 84.6% when it was positive with short cervix.<sup>40</sup> In a review of 13 studies, the sensitivity and specificity rates PPV, NPV of fetal fibronectin levels in cervicovaginal secretions for the outcome of delivery at < 34weeks gestation ranged from 23% to 92% and 59% to 97% respectively, in women without uterine contractions.<sup>41</sup> In women with symptoms of preterm labor, however, sensitivity and specificity rates were between 86% to 100% and 46% to 81%,<sup>43</sup> which are consistent with findings obtained in our study.

Therefore, results obtained from this study indicate that fetal fibronectin is more sensitive and less specific than cervical index

and has lower PPV and higher NPV than cervical index which are consistent with results obtained by Piotr and coworkers.<sup>44</sup> However Nicholson and colleagues reported different results as he found that fetal fibronectin less sensitive and more specific than cervical index<sup>45</sup> but the same finding on PPV and NPV was obtained by him.

The economic impact of preterm labor on society is substantial.<sup>46</sup> The most obvious economic burden comes from the intensive medical care that is required by preterm neonates. Another significant component, however, comes from the over treatment of women who are not actually in preterm labor. This over treatment is prevalent because the signs and symptoms of women in actual preterm labor are far from unique and overlap considerably with those of women with preterm contractions only. Thus, the development of a test that can help to identify those women who are not likely to deliver preterm has been desired widely.

Fetal fibronectin holds the promise of being such a test. In several studies, it has been shown repeatedly to have a high negative predictive value for delivery within 1 week of testing.<sup>9,47,48</sup> Because women with a negative fetal fibronectin test result are at low risk for imminent delivery, physicians correspondingly should be less likely to prescribe unnecessary treatment (eg, tocolytic medications) and interventions that have long been used but have never been shown to be beneficial (eg. bed rest).<sup>49</sup> The reduction of these needless strategies could help reduce medical costs and social disruption.

In this study the combined use of fetal fibronectin and cervical index have sensitivity 71 %, specificity 97%, PPV 90%, and NPV 89%. (Table 11). So combined use of two tests is more sensitive than single test and also has higher NPV. Even better results of combining the cervical index and fibronectin levels in the early diagnosis of cases at risk of preterm delivery were reported by many other workers.<sup>50,51</sup>

### Conclusions

The combined use of transvaginal ultrasonography and cervicovaginal fetal fibronectin increased the accuracy and predictive ability for the early detection of preterm labor.

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