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# Increasing the Prediction Power of Preterm Labor using Interleukin 6 and Fetal Fibronectin as Alarming Signals in Symptomatic Patients

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## Abstract

**BACKGROUND:** Giving birth at preterm is considered as a bothering problem to both health-care systems and pregnant women around the world, causing alarming levels of mortality. To avoid this issue, certain biological markers can be employed for early detection to predict the occurrence of the preterm delivery (PTD) ahead of time for giving better medical care to the pregnant women who at risk of PTD.

**AIM:** The current study was performed to evaluate the power of using interleukin-6 (IL-6) and fetal fibronectin (fFN) present in the cervicovaginal fluid (CVF) as predictors of the symptomatic PTD patients.

**PATIENTS AND METHODS:** In this study, 91 pregnant hospital attendees (24–34 weeks; 18–45 years old) with suggested PTD symptoms, such as abdominal pain and uterine contraction and with cervical length of <25 mm, were participated. To detect IL-6 and fFN, vaginal swabs were collected for performing an ELISA test to later follow- up with the patients within 48 h, 7 days, and 14 days from the 1st day of admission to the hospital.

**RESULTS:** No significant association between PTD with patients age, parity, body mass index, and gestational age, but significant association with previous history of PTD. There was significant association between PTD and increase the level of CVF fFN and IL-6 with best cutoff value for CVF fFN is (>45 ng/ml) with (95%CI of 0.763–0.918) and accuracy of 85.2% with a sensitivity of 73.1% and specificity of 95.6% which is of high significant value ($p \leq 0.01$). While CVF of IL-6 (>231 pg/ml) with (95% CI of 0.630–0.820), with accuracy of 73.3%, sensitivity of 50%, and specificity of 96.9% which was statistically significant finding ($p \leq 0.01$). The predictive value of combined fFN and IL-6 in women at risk of preterm labor was 84.6% with sensitivity 84.6%, specificity 92.3%, positive predictive value 81.5%, negative predictive value 93.8%, and accuracy of 90.1%.

**CONCLUSIONS:** Each of fFN or IL-6 located in the CVF may provide a strong predictor of PTD; however, this prediction capability may provide an even stronger signal of detecting PTD ahead of time if both biomarkers requested at the same time.

## Introduction

Perinatal morbidity, fatality, and long-term impairment are all exacerbated by preterm delivery (PTD). PTD is defined as occurring before 37 weeks of pregnancy, with regular uterine contractions causing cervical alterations such as effacement and dilatation, allowing the baby to enter the birth canal [1]. Research and developments in neonatal care have enhanced the perinatal outcomes of preterm newborns significantly over the past decades, whereas rates of spontaneous PTD have basically stayed steady. In the industrialized countries, PTD is the largest cause of fatality and disabilities in the <5-year-old children, and the main reason of worldwide perinatal deaths and illness. PTD newborns contribute to 11.1% of all live births globally, with an estimated 15 million occurring each year [2]. Three types of prenatal screening tests are now available for the detection of PTD: Evaluation of risk factors, measurement of the cervix, and biochemical indicators [3].

Cervicovaginal fluid (CVF), contrary to amniotic fluid, is easy to reach, and sampling is mildly invasive and harmless. Cytokines may be secreted into the CVF after the rupture of the chorio-decidual adhesion or due to an inflammatory response within the same location. PTD may cause changes in cytokine levels throughout gestations. PTB may be linked to inflammation through the generation of acute phase proteins and the formation of enzymes essential for prostaglandin synthesis, which are both interleukin-6 (IL-6)-dependent biomarkers of inflammation [4]. CVF is a combination of fluids originating from the vaginal, endocervical, endometrial decidual, and amniochorionic compartments, and so acts as a significant diagnostic spot to evaluate the health of the mother and fetus while pregnant. Pregnancy-related membrane or placental destruction due to inflammation or mechanical destruction may lead to the discharge of CVF, which

has been recommended as a replacement to amniotic-fluid testing [5]. As up to 20 weeks and repeated after 36 weeks of gestation, higher concentrations than (50 ng/ml) of fetal fibronectin (fFN) may be seen in vaginal fluid. Due to the fact that the amniochorion and decidua haven't entirely fused until 20 weeks, detection is still feasible. Hence, the existence of fFN in vaginal fluids in a concentration more than 50 ng/mL between 20 and 36 weeks is considered as abnormal and may be utilized to indicate PTD. It is normal to identify fFN closer to birth as part of the typical mechanical and biochemical processes contributing to standard term delivery [6].

The current study was performed to evaluate the power of using IL-6 and fFN present in the CVF as predictors of the symptomatic PTD patients.

## Patients and Methods

This study was conducted at the Obstetrics and Gynecology Department, Maternity and Pediatric Teaching Hospital, Al-Diwaniyah City, Iraq, during February throughout December, 2019, in which 91 pregnant hospital attendees (24–34 weeks; 18–45 years old) with suggested PTD symptoms, such as abdominal pain and uterine contraction and with cervical length of <25 mm, were participated.

The present investigation protocol was approved by Iraqi Ethical Committee of Iraqi Board for Medical Specialization. All participants signed an informed consent form after being provided with an explanation of the study purpose and protocol.

### *Inclusion criteria*

The study patients were included if they had PTD symptoms, such as lower abdominal pain of intermittent type, uterine contraction, and pelvic pressure, plus speculum-based healthy amniotic membranes and cervical dilatation ≤3 cm.

### *Exclusion criteria*

Pregnant females were not included in the present work if they showed rupture of membranes, bleeding, active labor, >3 cm cervical dilatation, cervical cerclage in place, suspected inflammation of the chorioamniotic membrane, twin pregnancy, polyhydramnios, oligohydramnios, fetal congenital abnormality, uterine congenital abnormality, diabetes mellitus, hypertensive disorder with pregnancy, and maternal renal disease.

All patients who fill field the inclusion criteria were initially assessed with history and physical examination and send for investigation, performing complete blood picture, blood sugar analysis, urine analysis, renal function test, and ultrasound to assess gestational age, viability, any congenital abnormalities and liquor amount. Then by speculum vaginal examination, vaginal swabbing was done to collect samples for detecting cervicovaginal IL-6 and fFN. In the beginning, the participants emptied their urinary bladders and took a dorsal lithotomy lying position. Then, Dacron swabs were used to collect samples of CVF from the external os with the help of a sterile speculum. For better saturation, the swabs (two) were let-sat for 15 seconds in the posterior vaginal fornix. Later, each swab was contained in an extraction-buffer-preloaded sterile cryo-vial.

The IL-6 swabs were placed in tubes that contained phosphate-buffered saline, 0.1 mg/ml protinin, fetal bovine serum, NaCl, and sodium azide at 0.001%. The fFN swabs were placed in tubes that contained 1 ml of fFN extraction buffers provided with a commercial kit (Shanghai Korain Biotech Co., Ltd).

### *Laboratory analysis*

The IL-6 samples were incubated at 20–25°C for 60 min, 16000 rpm-centrifuged. Then, 500 ml of extraction buffer was used as a second wash and immediately centrifuged. After the extraction, the extracted materials for the IL-6 were −4°C-stored until using a chemiluminiscent enzyme immunometric assays via the utilization of a fully automated immunoassay analyzer, with a sensitivity power of 2 pg/ml (results within three hours). For fFN quantification, solid-phase ELISA kit (Biotech, USA), as part of this specimen was collected from the buffer tube and pipetted to a Rapid fFN analyzer (results within 1–4 h), and levels of more than 50 ng/ml are considered as positive.

All patients with the inclusion criteria were admitted to the emergency obstetrical department and treatment with tocolytics, corticosteroids and antibiotics according to the used hospital protocol, and follow up of the patients for the occurrence of PTD within 48 h, 7 days, and 14 days from the 1$^{st}$ day of admission to the hospital.

### *Statistical analysis*

SPSS software V23 and Microsoft Office Excel 2010 were employed to process and analyze the present work data. Non numerical data were presented as numbers and percentages, whereas, numerical data were used as mean minus plus standard deviation (Mean ± SD). For discovering if there is any association, Chi-square test was used. For differences between groups, t-test was conducted. If $p \leq 0.05$, the test was considered as significant. If p-value was equal or less than 0.01, the test was considered as highly significant.

## Results

The major demographic characteristic of the patients studied are presented in Table 1. The average age of participants was 31.3 ± 6.05 years old with no statistical differences between patients that had PTD and those who had no PTD ($P > 0.05$). The average gestational age of the patients enrolled in study was (30.70 ± 2.20) weeks and the average body mass index (BMI) (kg/m²) was (19.89 ± 1.72) kg/m², with no statistical differences between the patients that enrolled in the study ($p > 0.05$). From the 91 patients enrolled in the study, (28) 30.8% were nulliparous of which 34.6% had PTD and 29.2% had reached to term pregnancy which was no statistically significant. While multiparous patients account for (63) 69.2% of the patients, of which 65.4% had PTD, and 70.8% had reached to term.

**Table 1: Demographics for the study participants classified according to occurrence of preterm labor**

| Characteristic | Total n = 91 | PTD n = 26 | No PTD n = 65 | p |
|---|---|---|---|---|
| Age (years) | | | | |
| Range | 22–42 | 22–42 | 22–42 | 0.105† |
| Mean ± SD | 31.32 ± 6.05 | 29.69 ± 5.86 | 31.97 ± 6.04 | NS |
| Gestational age (weeks) | | | | |
| Range | 27–34 | 27–34 | 27–34 | 0.068† |
| Mean ± SD | 30.70 ± 2.20 | 31.42 ± 2.04 | 30.42 ± 2.21 | NS |
| BMI (kg/m$^2$) | | | | |
| Range | 18–23 | 18–23 | 18–23 | 0.580† |
| Mean ± SD | 19.89 ± 1.72 | 19.73 ± 1.69 | 19.95 ± 1.74 | NS |
| Parity | | | | |
| Median (IQR) | 2 (3) | 2 (3) | 2 (2) | 0.433€ |
| Range | 0–5 | 0–5 | 0–5 | NS |
| Nulliparous, n (%) | 28 (30.8) | 9 (34.6) | 19 (29.2) | 0.615¥ |
| Multiparous, n (%) | 63 (69.2) | 17 (65.4) | 46 (70.8) | NS |

n: number of cases, PTD: Preterm labor, SD: Standard deviation, BMI: Body mass index, IQR: inter-quartile range, †: Independent samples t-test, €: Mann– Whitney U test, ¥: Chi-square test, NS: not significant at $p > 0.05$, S: significant at $p \leq 0.05$.

Table 2 showed that from the total of 91 patients enrolled in the study, ten patients (11.0%) had previous history of PTD, and of which seven patients (26.9%) had ended with PTD in this study which was statistically significant correlation ($p \leq 0.01$), with a relative risk (RR) of 2.98 and confidence interval (95% CI of 1.98–4.53).

**Table 2: The association between previous preterm labor and present preterm labor in women enrolled in this study**

| History of previous PTD | Total n = 91 (%) | PTD n = 26 (%) | No PTD n = 65 (%) | p | RR | 95% CI |
|---|---|---|---|---|---|---|
| Positive | 10 (11.0) | 7 (26.9) | 3 (4.6) | 0.007 Y | 2.98 | 1.96–4.53 |
| Negative | 81 (89.0) | 19 (73.1) | 62 (95.4) | HS | | |

n: number of cases, PTD: Preterm labor, Y: Yates correction for continuity, HS: Highly significant at $p \leq 0.01$, RR: Relative risk, CI: Confidence interval.

**Table 3: Cervicovaginal fetal fibronectin (fFN) and interleukin-6 (IL-6) according to occurrence of preterm labor**

| Characteristic | PTD n = 26 | No PTD n = 65 | p |
|---|---|---|---|
| fFN (ng/ml) | | | |
| Mean ± SD | 60.73 ± 15.69 | 39.20 ± 8.99 | <0.001† |
| Range | 37–90 | 20–82 | HS |
| >50 ng/ml, n (%) | 19 (73.1) | 3 (4.6) | <0.001Y |
| <50 ng/ml, n (%) | 7 (26.9) | 62 (95.4) | HS |
| IL-6(pg/ml) | | | |
| Mean ± SD | 230.23 ± 71.38 | 173.63 ± 38.18 | <0.001Y |
| Range | 100–340 | 100–280 | HS |
| >250 pg/ml, n (%) | 13 (50.0) | 2 (3.1) | <0.001† |
| <250 pg/ml, n (%) | 13 (50.0) | 63 (96.9) | HS |

n: number of cases, PTD: Preterm labor, †: Independent samples t-test, Y: Yates correction for continuity, HS: Highly significant at $p \leq 0.01$.

Table 3 showed that patients with PTD had CVF fFn (ng/ml) 60.73 ± 15.69 ng/ml while patient who had term pregnancy had fFN level of 39.20 ± 8.99 ng/ml which was highly significant statistically ($p < 0.001$). Furthermore, in the PTD group, the level of IL-6 (pg/ml) was significantly higher than those who had reached to term (230.23 ± 71.38) pg/ml and (173.63 ± 38.18) pg/ml, respectively ($p \leq 0.01$).

**Table 4: Characteristics of the receiver operator characteristic curve**

| Characteristic | fFN | IL-6 |
|---|---|---|
| Cutoff | >45 | >231 |
| AUC | 0.852 | 0.733 |
| 95% CI | 0.763–0.918 | 0.630–0.820 |
| Accuracy % | 85.2 | 73.3 |
| *P* | <0.001 | <0.001 |
| | HS | HS |
| Sensitivity % | 73.1 | 50 |
| Specificity % | 95.6 | 96.9 |

AUC: Area under curve, fFN: Fetal fibronectin, IL-6: Interleukin -6, CI: Confidence interval, HS: Highly significant at $p \leq 0.01$.

Table 4 showed the characteristics of the receiver operator characteristics (ROC) curve in which it is found that the best cutoff value for the level of CVF of fFN that can predict PTD in this study was (>45 ng/ml) with (95%CI of 0.763–0.918) and accuracy of 85.2% with a sensitivity of 73.1% and specificity of 95.6% which is of high significant value ($p \leq 0.01$) as shown in Figure 1.

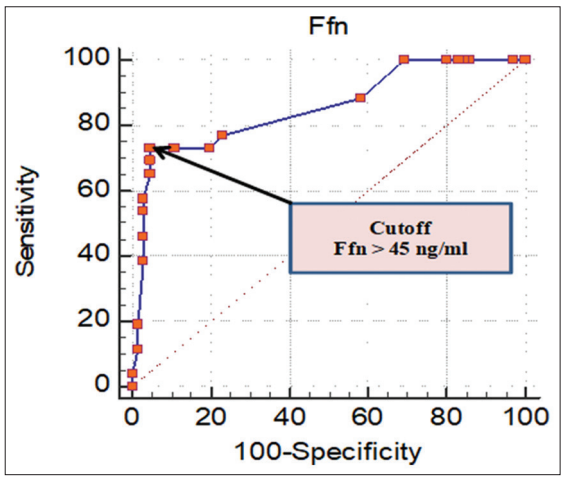


*Figure 1: Best cervicovaginal fetal fibronectin data for predicting PTD based on receiver operator characteristic curve*

Table 4 also showed the characteristics of ROC in which it is found that the best cut-off value for the level of CVF of IL-6 that can predict PTD in this study was (>231 pg/ml) with (95% CI of 0.630–0.820), with accuracy of 73.3%, with sensitivity of 50% and specificity of 96.9% which was statistically significant finding ($p \leq 0.01$) as shown in Figure 2.

Table 5 reveals the relationship between CVF fFN and IL-6 and the start of PTD as it is found that higher level of fFN (68.4 ± 13.75 ng/ml) was associated with 90% incidence of PTD within 48 h, and fFN level of (59.08 ± 15.35 ng/ml) was associated with 66.7% risk of PTD within 7 days, and level of

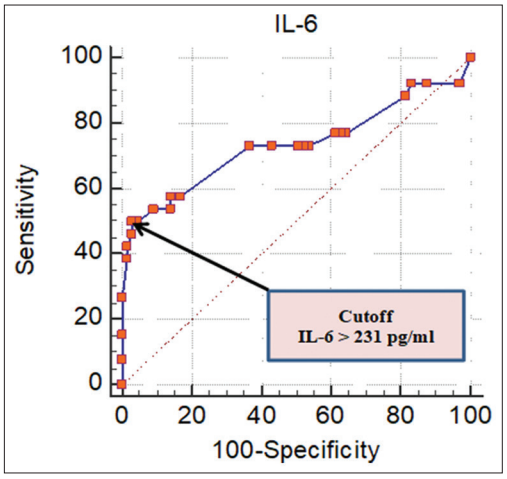


*Figure 2: Best interleukin-6 data for predicting PTD based on receiver operator characteristic curve*

46.50 ± 12.01 ng/ml was associated with 50% risk of PTD within 14 days, and these finding was highly statistically significant (p ≤ 0.01) as displayed in Figure 3.

Table 5 also showed that CVF IL-6 level was higher (226.80 ± 63.14 pg/ml) in patients with PTD within 48 h as it account for a 40.0% risk, and in patients who had PTD within 7 days from the time of admission IL-6 level was 257.33 ± 60.10 pg/ml which was associated with 66.7% risk of PTD, and in patients who had PTD within 14 days, the level of IL-6 was (157.50 ± 85.00 pg/ml) that account from 25.0% risk of PTD, and all these finding was highly statistically significant with (p ≤ 0.01) as presented in Figure 4.

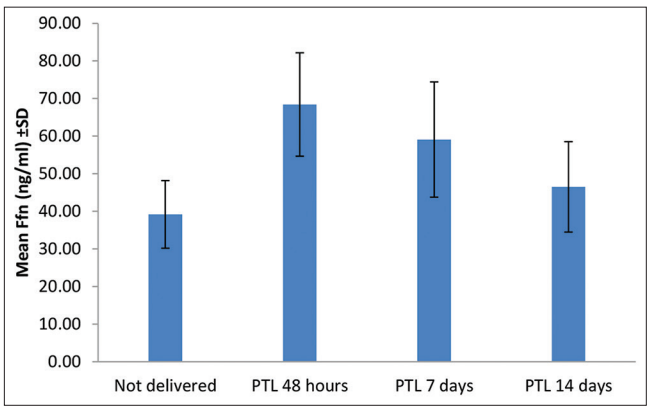


*Figure 3: Cervicovaginal fetal fibronectin according to onset occurrence of preterm labor*

Table 6 showed the predictive value of combined tests (fFN and IL-6) in the prediction of PTD. Out of 26 patients who had PTD 22 (84.6%) had both elevated cut off value of CVF fFN and IL-6 with a sensitivity of 84.6%, specificity of 92.3%, positive predictive value (PPV) of 81.5%, and negative predictive value (NPV) of 93.8% with accuracy of 90.1%.

**Table 5: Cervicovaginal fetal fibronectin (fFN) and interleukin- 6 (IL-6) according to onset occurrence of preterm labor**

| Characteristic | No PTD n = 65 (%) | PTD 48 h n = 10 (%) | PTD 7 days n = 12 (%) | PTD 14 days n = 4(%) |
|---|---|---|---|---|
| fFN (ng/ml) | | | | |
| Mean ± SD | 39.20 ± 8.99 | 68.40 ± 13.75 | 59.08 ± 15.35 | 46.50 ± 12.01 |
| Range | 20–82 | 40–90 | 37– 82 | 37–62 |
| >50 ng/ml, n (%) | 3 (4.6) | 9 (90.0) | 8 (66.7) | 2 (50.0) |
| <50 ng/ml, n (%) | 62 (95.4) | 1 (10.0) | 4 (33.3) | 2 (50.0) |
| p | Reference | <0.001[Y] | <0.001[Y] | 0.016[Y] |
| | | HS | HS | HS |
| IL-6 (pg/ml) | | | | |
| Mean ± SD | 173.63 ± 38.18 | 226.80 ± 63.14 | 257.33 ± 60.10 | 157.50 ± 85.00 |
| Range | 100–280 | 140–340 | 150–340 | 100–280 |
| >250 pg/ml, n (%) | 2 (3.1) | 4 (40.0) | 8 (66.7) | 1 (25.0) |
| <250 pg/ml, n (%) | 63 (96.9) | 6 (60.0) | 4 (33.3) | 3 (75.0) |
| p | Reference | <0.001 Y | <0.001 Y | 0.554 Y |
| | | HS | HS | HS |

n: number of cases, PTD: preterm labor, [†]: Independent samples t-test, Y: Yates correction for continuity, HS: Highly significant at p ≤ 0.01.

## Discussion

PTD remains the major factor affecting neonatal health outcomes despite the health-care development regarding such issue. The present investigation revealed non-significant alterations in the major patient demographics, such as gestational age, maternal age, and BMI. Lawlor *et al*. (2011) documented elevated links between farthest maternal age and the incidence of PTD, with the minimum PTD in the range of 24–30 years old of maternal age [7]. For BMI, while Vinturache *et al*. (2014) reported an association between BMI and PTD occurrence in nulliparous and multiparous females [8]. Smith *et al*. (2007) showed that PTD was more pronounced in obese nulliparous than that in obese multiparous [9].

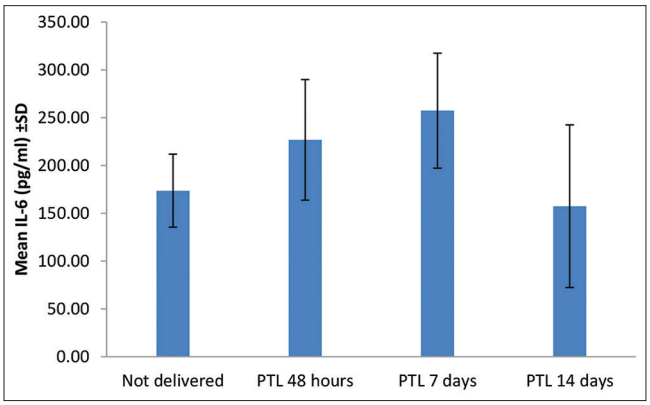


*Figure 4: Cervicovaginal interleukin-6 according to onset occurrence of preterm labor*

A study by Cnattingius *et al*. (2013) revealed an association between the risk of PTD, low weights of neonates, and increased fatality of newborns in nulliparous, especially those who were <18 years old plus if the women were at high weight, showing high rates of PTD [10]. Gibbs *et al*. (2012) revealed a parity-PTD link (a weak association at ≥3 of parity) and (no association at ≥5 of parity) [11].

**Table 6: The predictive value of combined fFN and Il-6 cutoff values in prediction of preterm labor in women at risk**

| Ffn and IL-6 | PTD n = 26 | Not delivered n = 65 | Sensitivity | Specificity | PPV | NPV | Accuracy |
|---|---|---|---|---|---|---|---|
| Positive (%) | 22 (84.6) | 5 (7.7) | 84.6 | 92.3 | 81.5 | 93.8 | 90.1 |
| Negative (%) | 4 (15.4) | 60 (92.3) | | | | | |

PPV: Positive predictive value, NPV: Negative predictive value.

Moreover, While Hendler *et al*. (2005) revealed no BMI-PTD association [12]. In addition, Smith *et al*. (2007) reported a PTD-nulliparous association in obese and mildly obese with no associations in severely and moderate obese women.

In this study from the total 91 patients, ten patients (11%) had previous history of PTD, and of which seven patients (26.9%) has ended in PTD with RR 2.98 and (95% CI of 1.96–4.53).

In a study by Laughon *et al*. (2014), PTD in women continued to place a high risk of recurrent PTD on those women in later pregnancy [13]. Simonsen *et al*. (2013) reported that gestational age of <32 weeks when PTD occurred at that time, recurrent PTD may occur during the later pregnancy more than that if PTD occurred at 32–36 weeks of gestational age [14]. These associations between early and recurrent PTD are not well understood as While Kistka *et al*. (2007) mentioned [15].

In this study, the patients that gave birth prematurely were associated with high fFN (60.73 ± 15.69) in 73.1% and high IL-6 (230.23 ± 71.38) in 50% and out of the 91 patients recruited in this study, 26 (28.57%) were delivered preterm. Our data showed that the best cutoff value for the level of CVF fFN that can predict PTD in this study was (>45 ng/ml) with (95%CI of 0.763–0.918) and accuracy of 85.2% with a sensitivity of 73.1% and specificity of 95.6% which is of high significant value ($p \leq 0.01$).

A variety of published research certainly shown the medicinal potential of fFN testing for the evaluation of individuals at risk of PTD. Peaceman *et al*. (1997) showed a beneficial use of fFN in patients at risk of PTD, involving 763 participants with a 50 ng/ml cutoff. The estimated NPV for birth within 14 days after hospitalization was 99.2% and the PPV was just 13.4%. They also revealed that the best value for fFN analysis in symptomatic PTD patients had good NPV with the power to prevent needless interventions [16].

In low-risk PTD pregnant women, a negative fFN result was shown to be associated with a lack of PTD; however, the researchers; Greenhagen *et al*. (1996) discovered that the fFN test is an important indicator of PTD in their community, which had a sensitivity of 75% and specificity of 68% [17], [18], [19].

In this study, it is found that the best cut-off reads for the level of CVF of IL-6 that can predict PTD in this study was (>231 pg/ml) with (95% CI of 0.630–0.820), with accuracy of 73.3%, with sensitivity of 50% and specificity of 96.9% which was statistically significant finding ($p \leq 0.01$). It was determined that the IL-6 test with 250 pg/ml cutoff level had a sensitivity rate of 35% and specificity of 87%. The commonly acknowledged cutoff value of IL-6 for PTD prediction is about 250 pg/mL [20], [21].

The result of this study showed the link between CVF fFN and IL-6 and the onset of PTD in participants who delivered preterm had both fFN and IL-6 positive with sensitivity of 84.6%, specificity 92.3%, PPV 81.5%, and NPV 93.8% in the prediction of PTD and conducted better performance when the tests performed together than a single test alone.

A 53% incidence of PTB before 37 weeks of pregnancy was found in women with both positive fFN and IL-6 tests, contrasted to a 10% risk in those who had both negative tests, and Bolt *et al*. (2011) advised fFN as the initial diagnostic technique [22]. Schmitz *et al*. (2006) found that good NPVs (94 and 99%) for delivery were found in women who tested positive for fFN and IL-6 over the cutoff level, both pre 35 weeks and within 7 days of hospitalization in symptomatic females [23].

The fact that this was a study of a prospective cohort imposes certain limitations. As a result, we were unable to track changes in cytokines during the course of pregnancy to pinpoint important times for the development of PTB. Another drawback was our limited sample size, which might lead to selection bias.

## Conclusions

This research demonstrates the utility of measuring fFN and IL-6 in the CVF as biochemical indicators for detecting individuals with high risk of PTD that would enable the customization of medical interventions and focused at therapeutics to enhance maternal and fetal health.

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