Diagnostic Accuracy of Cervicovaginal Interleukin-6 and Interleukin-6:Albumin Ratio as Markers of Preterm Delivery

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Background: Absence of fetal fibronectin (fFN) in the cervicovaginal fluid (CVF) of women with symptoms of preterm labor is an excellent predictor of women who will not deliver within 2 weeks of testing. Preliminary studies suggest interleukin (IL)-6 performs similarly to fFN. The positive predictive values of both these assays are poor. Inconsistent specimen collection may explain this poor performance. The objective of this study was to validate the clinical utility of cervicovaginal IL-6 and investigate the utility of the IL-6:albumin ratio to predict delivery within 14 days.

Methods: We quantified albumin and IL-6 with the DPC Immulite® in 660 CVF specimens collected for physician-ordered fFN analysis. The clinical utility of IL-6 and IL-6:albumin to predict delivery within 14 days of collection was determined.

Results: The sensitivity, specificity, and positive and negative likelihood ratios for delivery within 14 days were 65%, 87%, 4.8, and 0.4, respectively, for fFN and 35%, 91%, 3.8, and 0.7 for IL-6, with a 250 ng/L cutoff. With a preterm delivery prevalence of 4.7%, positive and negative predictive values were 19%, and 98%, respectively for fFN and 16% and 97% for IL-6. The areas under the ROC curves were 0.71 and 0.51 for IL-6 and IL-6:albumin, respectively. Odds ratios for delivery within 14 days of collection were 11.8 (P <0.0001), 5.5 (P = 0.0001), and 2.4 (P = 0.06) for fFN, IL-6, and IL-6:albumin, respectively.

Conclusions: Cervicovaginal IL-6 may have utility for predicting preterm labor while offering the potential for substantial cost-savings. Assay performance characteristics are not improved by normalizing IL-6 to albumin.

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Nonstandard abbreviations: fFN, fetal fibronectin; IL, interleukin; NPV, negative predictive value; CVF, cervicovaginal fluid; PPV, positive predictive value.
because a negative test result enables physicians to avoid unnecessary interventions in women who are unlikely to deliver early. fFN is a costly test to perform (>$100 US per test), however, and therefore a test that performs similarly to fFN at a lower cost would be an attractive alternative.

Cytokines have been investigated as biomarkers of impending preterm delivery and may be involved in the etiology of preterm birth through their stimulation of prostaglandin synthesis (6). Increased serum and amniotic fluid concentrations of several cytokines, including interleukin (IL)-6, have been reported in women with preterm labor (7–11). The use of cervicovaginal fluid (CVF) is a less invasive alternative to amniotic fluid testing for monitoring markers of preterm delivery.

A few studies have examined IL-6 in CVF and demonstrated that IL-6 is associated with preterm delivery (12–14). These studies were small, however, and used different IL-6 cutoffs. Our group has recently performed a study examining the measurement of several cytokines in CVF as predictive markers for preterm delivery (15). We determined that IL-6 was the only cytokine among 3 measured (IL-6, tumor necrosis factor α, and IL-2R) that was significantly associated with preterm delivery (n = 165), and as in previous studies we observed no statistically significant correlation between gestational age and IL-6 concentrations. When an IL-6 cutoff of 250 ng/L was used, the clinical sensitivity, specificity, and positive predictive values (PPV) and NPV were virtually identical to those of fFN, with a PPV of 14% and NPV of 96%. This same study provided preliminary evidence that cervicovaginal IL-6, for which reagent costs are $7/test compared to >$100/fFN assay, can be used as a less expensive marker of delivery within 14 days in women with symptoms of preterm labor.

Our previous study was limited by its small size, however, with only 9 patients delivering within 14 days of testing. The study we describe here is the largest to date (n = 660) that examines the diagnostic accuracy of CVF IL-6 for predicting delivery within 14 days. In addition, we examined cervicovaginal IL-6 concentration as a ratio to CVF albumin to determine if this ratio improves diagnostic utility. We hypothesized that discrepancies among other studies may have been a result of inconsistent specimen collection techniques leading to variable amounts of CVF fluid in each sample, and we investigated whether normalization of IL-6 to albumin could increase the clinical utility of CVF-based tests.

**Materials and Methods**

**PATIENT SAMPLES**

In this retrospective cohort study, we used 1145 physician-ordered cervicovaginal fFN samples received by the Barnes-Jewish Hospital or University of North Carolina Hospitals laboratories between May 2002 and September 2005. Samples were included in the study if they were from women with singleton pregnancies between 240/7 and 340/7 weeks of gestation and if patient medical records were available for review. The following specimens were excluded (n = 485): those from women whose labor was induced or who had a cesarean section without natural progression into labor within 2 weeks of fFN collection (n = 15); or within 3 weeks when analyzed for prediction within 21 days; from women for whom the patient chart was not available (n = 252); from women with multiple gestation (n = 132), cervical dilatation ≥3 cm (n = 13), cervical cerclage (n = 26), moderate or gross vaginal bleeding (n = 1), or placenta previa (n = 3); from women whose fFN results were not available because of sample handling error or test order cancellation (n = 11); and from women with no delivery information (n = 48), whose sample was collected before 24 weeks or after 35 weeks gestation (n = 31), or who had sexual intercourse within 24 h before cervicovaginal sampling (n = 1). Included in the study were 660 samples from 552 patients. None of these samples have been used in any previous study; 61 samples were from patients without symptoms of preterm labor at the time of fFN collection. Preliminary analysis of the IL-6:albumin ratio data indicated that the ratio was not useful as a predictor of delivery within 7 or 14 days (16). Therefore, that portion of the study was terminated early, and albumin analysis was performed on only 487 of the 660 samples.

Cervicovaginal specimens were collected according to the assay manufacturer’s (Adeza Biomedical) instructions using a Dacron® swab that was placed in the posterior fornix of the vagina for 10 s during a sterile speculum examination. The swab was inserted into a tube containing 1 mL of fFN extraction buffer containing proprietary concentrations of BSA, Tween 20, EDTA, phenylmethane sulfonylfluoride, and sodium azide (Adeza Biomedical), incubated for 10 min at 37 °C, and then filtered through a plunger filter (Adeza Biomedical). fFN testing was performed within 30 min of specimen arrival in the laboratory. Immediately after fFN testing, specimens were frozen at −70 °C until IL-6 and albumin testing (3 months to 3 years). Before analysis, samples were thawed to 25 °C and centrifuged at 1700g for 5 min. Institutional review board approval at both institutions was obtained for this study.

**fFN ASSAY**

fFN was measured with the Rapid fFN TLi™ Analyzer (Adeza Biomedical), a qualitative membrane immunosay that uses a monoclonal anti-fFN antibody coupled to a blue microsphere and an immobilized polyclonal goat antifibronectin antibody. The intensities of the test and control lines on the device were interpreted with the TLi analyzer. Specimens with fFN concentrations >50 µg/L were interpreted as positive. fFN testing was performed in a CLIA-approved laboratory.

**IL-6 AND ALBUMIN ASSAYS**

We quantified cervicovaginal IL-6 and albumin with the DPC Immulite® (Diagnostic Products Corporation) se-
quential, 2-site, solid-phase, chemiluminescent serum IL-6 and urine-albumin enzyme immunometric assays. We have previously validated the serum IL-6 assay for quantitative measurements of IL-6 in fFN collection buffer (15). IL-6 and albumin assays were performed at a single site by a single medical technologist who was blinded to the patient outcomes and fFN results.

VALIDATION OF URINE-ALBUMIN ASSAY FOR USE WITH SAMPLES IN fFN COLLECTION BUFFER

Human serum with known amounts of albumin (measured on the IMMULITE by diluting serum into saline) was added (<20% serum by volume) to sample collection buffer provided in the fFN collection reagent set (Adeza Biomedical). Samples with mean albumin concentrations of 33.4, 8.4, and 3.3 mg/L were analyzed 10 times each for both recovery and intraassay imprecision studies and 7 times each for interassay imprecision. Samples for analytical sensitivity and linearity studies were analyzed in duplicate. The minimum detection limit was determined by measuring albumin in unaltered fFN sample collection buffer 10 times and adding 2 SDs to the mean.

STABILITY STUDY OF IL-6 AND ALBUMIN IN fFN COLLECTION BUFFER

Human serum with a known amount of IL-6 or albumin was added (<20% serum by volume) to fFN sample buffer. One aliquot was used to measure albumin and IL-6 and the remainder were stored at −70 °C, −20 °C, 4 °C, or room temperature for 4, 24, or 72 h until albumin and IL-6 measurement. Three separate aliquots were measured per time point.

STATISTICS

Using GraphPad StatMate (GraphPad Software, version 2.00), the sample size for this study was determined from an estimate that 5% of patients would give birth within 14 days of testing. We calculated that 600 specimens would be needed to be 95% confident that a difference of 0.0548 between the 2 proportions was detected and 700 specimens needed to be 95% confident that a difference of 0.0501 was detected. Therefore, a number between 600 and 700 was targeted. Differences between groups were assessed with the Student t-test for continuous variables or Fisher exact test for discrete variables. We performed ROC curve analysis with GraphPad Prism (GraphPad Software, version 4.00).

Results

The DPC Immulite urine-albumin immunoassay was validated for use with samples in fFN collection buffer. Recovery studies with 3 different concentrations of albumin (33.4, 8.4, and 3.3 mg/L) demonstrated that the albumin measurement was linear (observed = 1.3x + 1.9; $r^2 = 0.999$; see Fig. 1 in the Data Supplement that accompanies the online version of this article at http://www.clinchem.org/content/vol53/issue8). The minimum detection limit was 1.5 mg/L. Analytical sensitivity and linearity studies demonstrated that the dynamic range of the assay was 2.5–60 mg/L (data not shown). These data were consistent with the analytical sensitivity (1.0 mg/L) and calibration range (2.5–60 mg/L) given by the manufacturer for the assay in urine (17). Intraassay imprecision was <6%, and interassay imprecision was ≤10.2% at all concentrations measured (see Table 1 in the online Data Supplement).

To assess the stability of IL-6 and albumin in fFN sample buffer, human serum with known amounts of IL-6 or albumin was added to Adeza Biomedical fFN buffer (containing protease inhibitors, see Materials and Methods), and stored at room temperature, 4 °C, or −20 °C for 0, 4, 24, and 72 h, or samples were subjected to up to 2 freeze/thaw cycles (Fig. 1). Concentrations of IL-6 and albumin were measured in triplicate at select time points and temperatures. Both IL-6 and albumin were shown to be stable in fFN sample buffer for up to 72 h at room temperature with repeat freeze/thaw cycles.

To assess the clinical utility of cervicovaginal IL-6 and the IL-6:albumin ratio, albumin and/or IL-6 were measured in the 660 patient samples included in this study. Among these, 14 patients (2.1%) gave birth within 7 days of fFN testing, 31 (4.7%) within 14 days, and 49 (7.4%) within 21 days of testing. The mean (SD) gestational ages at the time of sampling in women who delivered within 14 days [30.1 (2.8) weeks] or longer [30.2 (3.1) weeks] after testing were not significantly different ($P = 0.4$). The mean (SD) gestational age at the time of sampling in women with cervicovaginal IL-6 concentrations <250 ng/mL [30.0 (2.8) weeks] or ≥250 ng/mL [30.0 (2.8) weeks] was 31.1 (4.7) weeks.

To assess the stability of IL-6 and albumin in fFN sample buffer.

Serum samples with known amounts of albumin and IL-6 were added to fFN sample buffer at final concentrations of ~60 mg/L and 33 ng/L, respectively. The stability of each analyte was assessed at select time points after 1 or 2 freeze/thaw cycles, storage at room temperature for up to 72 h, and storage at 4 °C for up to 24 h by measuring concentrations of albumin and IL-6 in triplicate after storage at different conditions. Each data point is represented as percent of original sample. Error bars represent the SD.
were also not significantly different \( (P = 0.76; \text{Table 1}) \). The mean gestational age at delivery and the interval between sampling and delivery were statistically different between patients with cervicovaginal IL-6 concentrations <250 ng/L or ≥250 ng/L (Table 1). There was no change in CVF IL-6 or albumin concentrations with gestational age (see Fig. 2 in online Data Supplement). There was no difference in the proportions of African American, white, or other patients with IL-6 values above cutoff (≥250) compared to the total population (Table 1). In addition, there was not a significant difference in the proportion of patients whose IL-6 was above cutoff when patients with symptoms of preterm labor, evidence of infection, or positive group B streptococcus test were compared with patients with no symptoms, no infection, or negative group B streptococcus, respectively. There were however, a significantly higher proportion of samples with an IL-6 ≥ 250 that were also fFN positive or who delivered preterm (<37 weeks gestational age; Table 1).

The IL-6:albumin ratio value with optimal specificity and sensitivity according to ROC curve analysis was selected as the decision threshold concentration (5.35; Fig. 2 and Table 2). The IL-6 cutoff was previously measured to be 250 ng/L (15). The decision threshold concentration for IL-6 from that study population was chosen to match the sensitivity of fFN and provided virtually identical specificity and predictive values. The optimal cutoff for IL-6 as determined by ROC curve analysis in this study was 295 ng/L (Fig. 2). Because the performance characteristics at this cutoff were nearly identical to the previously determined cutoff of 250 ng/L (15), we chose to maintain the 250 ng/L cutoff to better compare the results of this study to our previous study (the complete data set is provided in Table 2 of the online Data Supplement if the reader wants to adjust the cutoff and calculate clinical utility). The area under the curve for IL-6 and the IL-6:

### Table 1. Demographic and clinical characteristics of patients according to concentration of cervicovaginal IL-6.

<table>
<thead>
<tr>
<th>Demographic or clinical variable</th>
<th>Cervicovaginal IL-6 concentration</th>
<th>Significance*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;250 ng/L</td>
<td>≥250 ng/L</td>
</tr>
<tr>
<td>Total samples; ( n = 660 ) (% total sample)</td>
<td>592 (90%)</td>
<td>68 (10%)</td>
</tr>
<tr>
<td>Patients with symptoms of preterm labor; ( n = 600 ) (91%)</td>
<td>534 (89%)</td>
<td>66 (11%)</td>
</tr>
<tr>
<td>Average gestational age at sampling; mean week (SD)</td>
<td>30.0 (2.76)</td>
<td>30.0 (2.83)</td>
</tr>
<tr>
<td>Average gestational age at delivery; mean week (SD)</td>
<td>37.9 (2.07)</td>
<td>36.4 (3.55)</td>
</tr>
<tr>
<td>Interval between sampling and delivery; mean week (SD)</td>
<td>7.8 (3.3)</td>
<td>6.3 (4.2)</td>
</tr>
<tr>
<td>Race; total patients; ( n = 552 ) (% total patients)b</td>
<td>492 (89%)</td>
<td>60 (11%)</td>
</tr>
<tr>
<td>African American; ( n = 199 ) (36%)b</td>
<td>170 (85%)</td>
<td>29 (15%)</td>
</tr>
<tr>
<td>White; ( n = 223 ) (40%)b</td>
<td>198 (89%)</td>
<td>25 (11%)</td>
</tr>
<tr>
<td>Other; ( n = 15 ) (3%)b</td>
<td>14 (93%)</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Unknown; ( n = 115 ) (21%)b</td>
<td>110 (96%)</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>Evidence of infection; ( n = 281 ) (51%)b,c</td>
<td>249 (89%)</td>
<td>31 (11%)</td>
</tr>
<tr>
<td>Group B Strep positive; ( n = 107 ) (19%)b,d</td>
<td>92 (86%)</td>
<td>15 (14%)</td>
</tr>
<tr>
<td>fFN positive; ( n = 92 ) (17%)b</td>
<td>54 (59%)</td>
<td>38 (41%)</td>
</tr>
<tr>
<td>Patients delivering preterm (&lt;37 weeks GA); ( n = 109 ) (20%)b</td>
<td>87 (80%)</td>
<td>22 (20%)</td>
</tr>
<tr>
<td>Patients delivering &lt;28 weeks GA; ( n = 3 ) (0.5%)b</td>
<td>1 (33%)</td>
<td>2 (66%)</td>
</tr>
<tr>
<td>Patients delivering &lt;32 weeks GA; ( n = 11 ) (2.0%)b</td>
<td>4 (36%)</td>
<td>7 (64%)</td>
</tr>
</tbody>
</table>

* P values were determined by Fisher exact test.

b If more than 1 sample was available for a patient, the one collected closest to delivery was chosen for statistical analysis in rows indicated.

c Evidence of infection includes: fever, urinary tract infection, pathology with chorioamnionitis, or positive Group B Strep culture.

d Group B Strep status was determined by culture during pregnancy in which fFN was measured, GA, Gestation.
albumin ratio to predict delivery within 14 days was 0.71 (95% CI 0.62–0.79; P = 0.0001) and 0.51 (95% CI 0.38–0.65; P = 0.81), respectively. The area under the curve for IL-6 to predict delivery within 7 days was 0.83 (P <0.0001), a value similar to previously published data for fFN (0.87) (18). The qualitative results of the fFN test used here do not allow ROC curve analysis in our study population, but data points corresponding to the sensitivity/specificity pairs at days 7 and 14 have been plotted for fFN in Fig. 2. Because repeated measures of cervicovaginal IL-6 were made for some patients, for statistical rigor data analysis was also performed with only the single sample closest to delivery. The sensitivity, specificity, PPV, NPV, odds ratio, and area under the curve gave virtually identical results.

Dot plots indicating the number of women with cervicovaginal IL-6, IL-6:albumin ratio, and fFN valued above (positive) and below (negative) their respective cutoffs are shown in Fig. 3. Among women who delivered in ≤14 days and >14 days after testing, there were similar numbers of fFN and IL-6 positive results (Fig. 3).

The performance characteristics of fFN, IL-6, and IL-6: albumin ratio to predict delivery in this study population are shown in Table 2. Each analyte had a high NPV that was increased further with diminished time between sample collection and delivery (Table 2). These results were similar when symptomatic patients were analyzed separately (data not shown). None of the asymptomatic patients delivered within 14 days. Only a positive fFN (odds ratio 11.8; 95% CI 5.5–25.5; P <0.0001) and an IL-6

<table>
<thead>
<tr>
<th>Analyte (cutoff)</th>
<th>Delivery ≤7 days</th>
<th>Sensitivity, % (95% CI)</th>
<th>Specificity, % (95% CI)</th>
<th>PPV, % (95% CI)</th>
<th>NPV, % (95% CI)</th>
<th>LR +</th>
<th>LR−</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Sensitivity, % (95% CI)</td>
<td>Specificity, % (95% CI)</td>
<td>PPV, % (95% CI)</td>
<td>NPV, % (95% CI)</td>
<td>LR +</td>
<td>LR−</td>
</tr>
<tr>
<td>≤7 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fFN (50 µg/L)</td>
<td></td>
<td>93 (66–100)</td>
<td>86 (83–89)</td>
<td>13 (7–20)</td>
<td>100 (99–100)</td>
<td>6.59</td>
<td>0.08</td>
</tr>
<tr>
<td>IL-6 (250 ng/L)</td>
<td></td>
<td>57 (29–82)</td>
<td>91 (88–93)</td>
<td>12 (5–22)</td>
<td>99 (98–100)</td>
<td>6.05</td>
<td>0.47</td>
</tr>
<tr>
<td>IL-6:albumin (5.35)</td>
<td></td>
<td>40 (12–74)</td>
<td>83 (80–86)</td>
<td>5 (1–12)</td>
<td>99 (97–99)</td>
<td>2.39</td>
<td>0.72</td>
</tr>
<tr>
<td>≤14 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fFN (50 µg/L)</td>
<td></td>
<td>65 (45–89)</td>
<td>87 (84–89)</td>
<td>19 (12–28)</td>
<td>98 (96–99)</td>
<td>4.83</td>
<td>0.41</td>
</tr>
<tr>
<td>IL-6 (250 ng/L)</td>
<td></td>
<td>35 (19–55)</td>
<td>91 (88–93)</td>
<td>16 (8–27)</td>
<td>97 (95–98)</td>
<td>3.85</td>
<td>0.71</td>
</tr>
<tr>
<td>IL-6:albumin (5.35)</td>
<td></td>
<td>32 (25–54)</td>
<td>84 (80–87)</td>
<td>10 (4–18)</td>
<td>96 (93–98)</td>
<td>1.95</td>
<td>0.81</td>
</tr>
<tr>
<td>≤21 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>fFN (50 µg/L)</td>
<td></td>
<td>55 (40–69)</td>
<td>88 (85–90)</td>
<td>26 (18–36)</td>
<td>96 (94–98)</td>
<td>4.45</td>
<td>0.51</td>
</tr>
<tr>
<td>IL-6 (250 ng/L)</td>
<td></td>
<td>29 (17–43)</td>
<td>91 (89–93)</td>
<td>21 (12–33)</td>
<td>94 (92–96)</td>
<td>3.27</td>
<td>0.78</td>
</tr>
<tr>
<td>IL-6:albumin (5.35)</td>
<td></td>
<td>34 (19–51)</td>
<td>84 (81–88)</td>
<td>16 (9–25)</td>
<td>94 (91–96)</td>
<td>2.18</td>
<td>0.78</td>
</tr>
</tbody>
</table>

a Prevalence = 14/660 (2.1%).
b Prevalence = 31/660 (4.7%).
c Prevalence = 49/655 (7.4%). LR, Loss rate.

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concentration ≥250 ng/L, (odds ratio 5.5; 95% CI 2.5–11.9; P = 0.0001) were significantly associated with delivery within 14 days.

**Discussion**

The DPC Immulite urine-albumin assay was validated for use in Adeza Biomedical fFN collection buffer. We found albumin measurement in this matrix to be linear (see Fig. 1 in the online Data Supplement), although not parallel, as to be expected, with acceptable precision (see Table 1 in the online Data Supplement) and dynamic range. The stability of both albumin and IL-6 in fFN collection buffer was also confirmed (Fig. 1). Although the stability of albumin in fFN collection buffer has not previously been examined, the stability of IL-6 in fFN collection buffer is consistent with that reported by Lockwood et al. (12).

We measured IL-6 concentrations in 660 CVF samples and albumin in 487 CVF samples. We did not identify any correlation between gestational age (between 240/7 and 340/7 weeks of gestation) and the concentrations of either CVF IL-6 or albumin in this population (see Fig. 2 in the online Data Supplement), a finding that is consistent with our previous study (15). Inglis et al. (19) also reported no correlation between gestational age and CVF concentrations of IL-6 collected at <37 weeks of gestation in their prospective cohort study of 111 pregnant women. Coleman et al. (20) reported similar findings with IL-6 in symptomatic women at 240/7 to 336/7 weeks of gestation.

The decision threshold for CVF IL-6 was determined previously to be 250 ng/L (15). ROC analysis was used to determine the optimal cutoff of 5.35 for the IL-6:albumin ratio (Fig. 2). The area under the curve was 0.51 (not statistically different from 0.50, the value that would be obtained for a worthless test). The sensitivity, specificity, PPV, and NPV were 32%, 84%, 10%, and 96% respectively. These data clearly indicate that expressing CVF IL-6 concentrations as a ratio to albumin does not improve clinical utility.

The high NPV of fFN for delivery within 14 days (98%, 95% CI, 96%–99%, prevalence 4.7%) is consistent with other studies (4, 5). The results from this study confirm our previous findings that CVF IL-6 has similar utility to CVF fFN for predicting premature birth (15). The utility of both markers is in their high NPV (97%–98%) and specificity (87%–91%). Positive CVF fFN and CVF IL-6 values were both associated with a statistically significant increased risk of delivery within 14 days, with an 11.8-fold increased risk associated with positive fFN and a 5.5-fold increased risk for positive IL-6.

Despite the fact that both CVF fFN and CVF IL-6 achieved high NPVs in this study, assuming a prevalence rate of 4.7% for preterm delivery, it is important to note that achieving a high NPV does not mean either test is an excellent rule-out test. Confirmation is still needed that a test with no diagnostic value (sensitivity = 50% and specificity = 50%) will yield an NPV of 95% assuming a 5% prevalence rate. Likelihood ratios provide an alternative criterion for evaluation of test diagnostic value. Negative likelihood ratios <0.2 are needed to provide strong diagnostic evidence in rule-out situations (21). By this criterion, given the negative likelihood ratios of 0.4 for CVF fFN and 0.7 for CVF IL-6, neither test can be rated strongly for ruling out preterm delivery.

This study is the largest to date that examines cervicovaginal IL-6. Our data provide evidence that cervicovaginal IL-6 demonstrates accuracy only slightly less than that of fFN for predicting delivery within 14 days. Cervicovaginal IL-6, therefore, may have utility in the prediction of preterm labor while offering the potential for substantial cost reductions.

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