Is Fetal Fibronectin (fFN) a Marker of Intra-Amniotic Inflammation in Patients with Midtrimester Short Cervix?

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IS FETAL FIBRONECTIN (fFN) A MARKER OF INTRA-AMNIOTIC INFLAMMATION IN PATIENTS WITH MIDTRIMESTER SHORT CERVIX?

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Abstract

OBJECTIVE: Both fFN and amniotic fluid (AF) cytokines can predict interval to delivery in patients with midtrimester short cervix. However, no studies have examined if fFN is related to intra-amniotic inflammation. Therefore, we examined the relationship between fFN and AF cytokines in patients presenting with midtrimester short cervix.

STUDY DESIGN: Singleton gestations with a transvaginal cervical length ≤25mm at 16–24 weeks underwent amniocentesis and fFN sampling. AF was assayed for 25 mediators using the Bio-Plex™ system. Cytokine levels were stratified by fFN status and compared using the Wilcoxon rank-sum test. Using the Bonferroni correction, a P value <0.002 was required for significance. We also compared a previously described inflammatory score, which ranges from 0.20, and represents an overall summary of the inflammation status based on cytokine levels.

RESULTS: 86 paired AF/fFN samples were available for comparison; 56 fFN negative, 30 fFN positive with no differences in baseline demographics. While there was a trend for some cytokines to be higher in fFN positive patients, none of the 25 cytokines evaluated reached significance (Table 1). There was no difference in the AF inflammatory score between fFN positive and negative, 30 fFN positive with no differences in baseline demographics (Table 2).

Materials and Methods

Study Cohort: Patients presenting to Lehigh Valley Perinatal Testing between April 1998 and March 2007
- Singleton pregnancies
- Gestational age 16-24 weeks
- Transvaginal cervical length ≤25mm
- Underwent amniocentesis with an aliquot of unspun AF stored at -70°C

fFN Testing:
- fFN testing was performed using specific-directed sampling of the cervico-vaginal secretions in the posterior vaginal fornix using a polystyrene swab.
- Results were classified as negative or positive, with greater than or equal to 50ng/dl signifying a positive test.
- fFN sample was obtained 24 hours after the last vaginalexam or transvaginal ultrasound.

Cytokine Analysis:
- AF samples were simultaneously analyzed for 25 inflammatory mediators using the Bio-Plex™ array system (Bio-Red Laboratories, Hercules, CA). See Table 2 for a listing of the cytokines utilized in our analysis.

Statistical Analysis

- Patients were stratified by fFN status.
- Individual cytokine levels were compared between groups.
- We also compared a novel AF cytokine score, which gives an overall assessment of the inflammatory status of the In-vitro environment.
- Data were compared with the non-parametric rank-sum test.
- A P value <0.05 was required for statistical significance, with utilization of the Bonferroni correction where appropriate to control for simultaneous examination of 25 cytokines.
- Calculations were performed using SAS 9.2 (SAS Institute, Cary, NC).

Results

- 86 paired AF/fFN samples were available for comparison; 56 fFN negative, 30 fFN positive with no differences in baseline demographics (Table 2).
- While there was a trend for some cytokines to be higher in fFN positive patients, none of the 25 cytokines evaluated reached significance (Table 2).
- There was no difference in the AF inflammatory score between fFN positive and negative patients (4 vs 6, respectively, P=0.15).
- Four patients had an fFN sample obtained prior to 18 weeks; all were negative. Results were similar after excluding these patients.

Conclusion

- Although they are likely correlated, fFN does not appear to be a strong marker for intra-amniotic inflammation in patients with mid-trimester short cervix.
- This finding may be a reflection of our limited sample size. Alternatively, it may reflect different pathways in the preterm parturition syndrome, some of which are characterized by primary inflammation and others that initially lead to disruption of the chorio-decidual interface (and detection of fFN) and a secondary mild inflammation.

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>fFN Negative N=56</th>
<th>fFN Positive N=30</th>
<th>P Value *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational Age at Admission (d)</td>
<td>36 (32-39)</td>
<td>36 (32-39)</td>
<td>0.40</td>
</tr>
<tr>
<td>Cervical Length (mm)</td>
<td>26 (15-35)</td>
<td>17 (9-30)</td>
<td>0.50</td>
</tr>
<tr>
<td>Maternal Age (yrs)</td>
<td>31 (26-39)</td>
<td>32 (28-39)</td>
<td>0.93</td>
</tr>
<tr>
<td>Singleton Gestations</td>
<td>0.0305</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Singleton Cervicometric</td>
<td>0.0864</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Wilcoxon Rank-Sum

Table 2. Comparison of Cytokine Levels by fFN Status

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>fFN Negative N=56</th>
<th>fFN Positive N=30</th>
<th>P Value *</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1β</td>
<td>2.4</td>
<td>3.6</td>
<td>0.301</td>
</tr>
<tr>
<td>IL-2</td>
<td>2.0</td>
<td>3.0</td>
<td>0.227</td>
</tr>
<tr>
<td>IL-4</td>
<td>0.19</td>
<td>0.30</td>
<td>0.601</td>
</tr>
<tr>
<td>IL-6</td>
<td>207.7</td>
<td>208.5</td>
<td>0.770</td>
</tr>
<tr>
<td>IL-10</td>
<td>37.7</td>
<td>20.3</td>
<td>0.477</td>
</tr>
<tr>
<td>TNF-α</td>
<td>3.0</td>
<td>3.0</td>
<td>1.000</td>
</tr>
</tbody>
</table>

*Bonferroni correction; P<0.002 required for significance

Calculated corrected p-values for significance
- Interleukin (IL), granulocyte colony stimulating factor (G-CSF) interferon gamma (IFN-γ), lymphotoxin alpha (LTA), lymphotoxin beta (LTB), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1α (MIP-1α), macrophage inflammatory protein-1β (MIP-1β), monokine induced by IFN-γ (MIG), platelet derived growth factor (PDGF), tumor necrosis factor alpha (TNF-α), regulated on activation normal T cell expressed and secreted (RANTES), and vascular endothelial growth factor (VEGF)