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

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Published In/Presented At

Rust, O., Kiefer, D. G., Keeler, S. M., Demishev, M., Muscat, J. C., Bornstein, E., & Hanna, N. (2010). Is Fetal Fibronectin (fFN) a Markerof Intra-Amniotic Inflammation in Patients with Midtrimester Short Cervix?. *LVHN Scholarly Works*. Retrieved from https://scholarlyworks.lvhn.org/obstetrics-gynecology/14

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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 shown 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 of <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 2). There was also no difference in the inflammatory score between fFN groups.

CONCLUSION: Although they are likely correlated, fFN does not appear to be a strong marker for intra-amniotic inflammation in patients with midtrimester short cervix. This finding may be a reflection of our limited sample size. Alternatively, it may reflect different pathways in the preterm partution 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.

Background

- Fetal fibronectin (fFN) has been proven clinically useful in identifying patients at risk for preterm delivery.
- The mechanism by which fFN is released from the chorio-decidual interface and found in vaginal secretions, yielding a positive fFN, is unclear.
- Inflammation has been shown to be present in a large proportion of patients with preterm labor and in some patients with mid-trimester short cervix.

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Objective

- To determine the relationship between fFN and amniotic fluid (AF) cytokines in patients presenting with midtrimester short cervix.

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 of ≤25mm
  - Underwent amniocentesis with an aliquot of unspun AF stored at -70°C
- fFN Sampling:
  - fFN testing was performed using speculum-directed sampling of the cervico-vaginal secretions in the posterior vaginal fornix using a polyester swab.
  - Tests were reported as positive or negative, with greater than or equal to 50ng/dl signifying a positive test.
  - fFN sample was obtained 24 hours after the last vaginal exam or transvaginal ultrasound.
- Cytokine Analysis:
  - AF samples were simultaneously analyzed for 25 inflammatory mediators using the Bio-Plex™ array system (Bio-Rad 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-utero 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 1).
- While there was a trend for some cytokines to be higher in fFN+ patients, none of the 25 cytokines evaluated reached significance (Table 2).
- There was no difference in the AF cytokine inflammatory score between fFN- and fFN+ patients (4 vs 6.5, respectively, P=0.10)
- 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

Variable	fFN Negative (N=56)	fFN Positive (N=30)	P Value *
Demographic Characteristics †			
Maternal Age (yrs)	25 (16-41)	29 (16-41)	0.10
Gestational Age at Admission (weeks)	20 (16-24)	20 (17-23)	0.40
Clinical Characteristics†			
Cervical Length (mm)	15 (1-25)	13 (0-25)	0.50
AF Glucose	35 (20-75)	41 (10-60)	0.19
AF WBC Count	24 (1-950)	21 (0-1150)	0.56

* Wilcoxon Rank-Sum
† Data are presented as median (range)

Table 2. Comparison of Cytokine Levels by fFN Status

Cytokine	FFN Negative N=56		FFN Positive N=30		P Value *
	Median	Range	Median	Range	
IL-1β	0.8	0.8-13.2	1.0	0.8 – 780.1	0.029
Il-1ra	4050.2	1.4- 9691.8	4726.0	1.4 – 29929.7	0.103
IL-2	1.1	1.1 – 45.5	1.1	1.1 – 19.4	0.196
IL-4	0.5	0.5 – 2.5	0.6	0.5 – 4	0.764
IL-5	0.8	0.8 – 0.8	0.8	0.8 – 2	0.006
IL-6	351.5	1.1 – 4131.9	417.3	1.1 – 25903	0.052
IL-7	3.1	0. – 13.9	4.1	0.5 – 11	0.082
IL-8	267.9	0.5 – 6797.0	468.7	0.5 – 25022.3	0.065
IL-9	14.1	0.7 – 46.2	17.0	0.7 – 76	0.342
IL-10	0.9	0.9 – 521.4	0.9	0.9 – 869.4	0.297
IL-12	0.5	0.5 – 10.1	0.8	0.5 – 21.3	0.005
IL-13	2.1	2.1 – 4.7	2.1	2.1 – 4.3	0.634
IL-15	5.8	4.2 – 30.2	6.7	4.2 – 29.9	0.577
IL-17	0.2	0.2 – 60.7	0.2	0.2 – 79.8	0.286
Eoxatin	14.6	14.6 – 178.1	15.2	14.6 – 142.2	0.258
G-CSF	170.6	1.1 – 8216	215.0	1.1 – 15059.2	0.590
IFN-γ	67.5	19.3 – 1188.1	105.0	19.3 – 690.9	0.054
IP-10	11074.5	6.5 – 118257.5	34868.8	58.9 – 148778.1	0.006
MCP-1	336.5	6.7 – 5327.9	570.2	6.7 – 3955.3	0.025
MIP-1α	2.4	2.4 – 301.0	2.4	2.4 – 362.9	0.050
MIP-1β	36.6	1.1 – 1634.6	69.4	1.1 – 1721	0.007
PDGF-bb	237.7	1.0 – 5554.8	275.9	57.0 – 1617.5	0.379
RANTES	17.3	1.2 – 7072.1	22	1.5 - 8743.0	0.475
TNF-α	3.0	3.0 – 69.0	3.0	3.0 – 143.2	0.216
VEGF	1.6	0.5 – 56.2	7.0	0.5 – 114	0.131

*Bonferroni correction; P<0.002 required for significance

Key: Interleukin (IL), granulocyte colony stimulating factor (G-CSF), interferon gamma (IFN-γ), inducible protein-10 (IP-10), monocyte chemotactic protein-1 (MCP-1), macrophage inflammatory protein (MIP), platelet derived growth factor (PDGF), tumor necorsis factor alpha (TNF-α), regulated on activation normal T cell expressed and secreted (RANTES), and vascular endothelial growth factor (VEGF)