I, Emily A DeFranco, hereby submit this original work as part of the requirements for the degree of:
Master of Science
in Clinical and Translational Research
It is entitled:
Placental pathologic aberrations in cases of familial idiopathic spontaneous preterm birth

Student Signature: Emily A DeFranco

This work and its defense approved by:

Committee Chair: Erin Nicole Haynes, DrPH
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Louis Muglia, PhD
Louis Muglia, PhD
David Lewis, MD, MBA
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Placental pathologic aberrations in cases of familial idiopathic spontaneous preterm birth

A thesis submitted to the
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Master of Science

Clinical and Translational Research
in the Department of Environmental Health,
Division of Epidemiology and Biostatistics
of the College of Medicine

by

Emily DeFranco

D.O. University of Medicine and Biosciences
Kansas City, Missouri, May 1998
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Joplin, Missouri, May 1992

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ABSTRACT

OBJECTIVE: To test the hypothesis that placental histologic characteristics in pregnancies complicated by familial spontaneous preterm birth (sPTB) will differ by gestational age (GA) and reflect possible mechanisms of pathogenesis.

METHODS: We conducted a prospective cohort study in women who had both an idiopathic sPTB <35 weeks and a first degree family member affected by PTB. Parturients with clinical chorioamnionitis in labor or medically indicated PTB were excluded. Placental specimens were reviewed by a single pathologist blind to GA at birth. Results were categorized with respect to the presence of maternal and/or fetal inflammatory response (MIR, FIR). The placental findings were compared to three categories of preterm GAs: 32–35 (referent), 28–32, and <28 weeks, adjusting for statistically influential factors.

RESULTS: Placental specimens were evaluated from 79 spontaneous PTBs. Inflammatory responses were found frequently: 41 (51.9%) had MIR and 28 (35.4%) had FIR. Placental inflammatory changes of maternal origin were most frequent at the earliest GAs, 85% with PTB <28 weeks [adjOR 77.5 (95% CI 5, 1213.1)], and 57% at 32-35 weeks [adjOR 6.1 (0.8, 48.5)] compared to later PTBs occurring at 32–35 weeks (22%). Inflammatory changes of fetal origin (FIR) also occurred more frequently in cases of extreme PTB, adjOR 38.4 (95% CI 2.9, 514.2).

CONCLUSION: Placental inflammatory responses are common in women with familial sPTB. Maternal and fetal inflammatory responses occur most frequently in the earliest cases of PTB. This data suggests that inflammation plays an
important role in the onset of parturition in cases otherwise classified as idiopathic or spontaneous in nature, especially at the earliest GAs when neonatal outcomes are the poorest.
ACKNOWLEDGEMENTS:

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INTRODUCTION

Preterm birth is a prevalent disease that poses a significant public health burden. Despite extensive efforts to elucidate the complex pathophysiologic mechanisms which contribute to the onset of parturition at an abnormally early time in gestation, the process remains poorly understood.

Preterm onset of labor is a complex process influenced by a variety of environmental, genetic, infectious, and other factors. The interplay among contributing etiologic factors logically differs between various preterm birth phenotypes. The underlying pathologic mechanisms leading to the onset of labor in cases of idiopathic spontaneous preterm birth likely differ significantly from cases complicated by placental abruption, multifetal gestation, or even those involving a major fetal malformation.

There is a growing appreciation for a potential genetic contribution to the determination of birth timing.(1-3) A previously published segregation analysis performed from the cohort of families affected by preterm birth reported in this study suggests that maternal genes play an important, complex role in determining the timing of birth.(4) Due to the complex nature of this disease, it has aptly been referred to as the “preterm parturition syndrome”.(5) Other than local uterine, environmental, hormonal, and genetic factors, intrauterine inflammation is felt to be an important contributing factor to the onset of preterm parturition. This study was performed to provide new insights into the relative
contribution of inflammation to spontaneous preterm birth in women with a strong familial component to their birth timing mechanism.
MATERIALS AND METHODS

We conducted a prospective cohort study aimed to identify genetic factors influencing spontaneous preterm birth. Women with an idiopathic spontaneous preterm birth at less than 35 0/7 weeks from an otherwise uncomplicated singleton gestation who also had a 1st degree family member affected by preterm birth were considered for inclusion. Delivery logs from an academic medical center (Washington University in St. Louis, Barnes-Jewish Hospital) were reviewed over a 3 year period (January 2004 - March 2008) to identify preterm deliveries. To minimize misclassification bias from variations in gestational age estimates, only preterm deliveries occurring at <35 0/7 weeks of gestation were considered for inclusion. We did not offer enrollment if the current (index) preterm birth was medically indicated, involved a pregnancy complicated by multifetal gestation, polyhydramnios, significant vaginal bleeding or suspected placental abruption, cocaine use, documented history of uterine malformation, abdominal/uterine trauma within one week of delivery, or maternal infection with HIV or Hepatitis C. Any delivery complicated by a clinical suspicion of chorioamnionitis was also excluded from enrollment. The clinical criteria suggesting intra-amniotic infection could include maternal temperature > 38.0 degrees Celsius, uterine tenderness, fetal tachycardia, or any documentation of the diagnosis of “chorioamnionitis” in the medical record during the antepartum or intrapartum course.

Postpartum women with preterm deliveries <35 weeks considered to be idiopathic and spontaneous in nature were queried regarding their family history
of preterm birth. If a first degree family member of the patient (child, sibling, parent) was also affected by preterm birth, the mother/infant pair and other pertinent family members were offered enrollment into the study. A reference cohort of mother-infant pairs with delivery at 37-41 weeks, no family history of preterm birth, and similar exclusion criteria was also enrolled. Study participants consented to use of commonly collected biologic samples such as placenta and blood for research purposes, and provided mouthwash and/or oral swabs if biologic samples were unavailable. Participants also provided detailed obstetric, medical and family history information. Obstetric and medical records were reviewed at the time of enrollment. The study was approved by the Human Studies Committee of Washington University in Saint Louis and exempt from IRB review at the University of Cincinnati.

To investigate placental histologic characteristics in this cohort of women with familial idiopathic spontaneous preterm birth, pathology reports from the index preterm birth cases were obtained. Due to variations in classification of placental histology over the enrollment period, and to minimize interobserver variability, placental specimens were rereviewed. Microscope slides from samples of each case placenta were reviewed by a single pathologist blind to clinical history, prior pathologic diagnoses, and gestational age at birth. Histopathologic diagnoses were classified according to standard nosologic criteria. Placental inflammatory changes were classified by grade (1-2) and stage (1-3) of maternal and fetal inflammatory responses. Data regarding other placental histologic abnormalities were also recorded.
To describe the relationship between preterm birth and placental inflammation, their association was compared by several approaches. First, the dichotomous variables of any maternal or fetal inflammatory response were compared to a three stratum categorical variable of preterm GAs: 32–35, 28–32, and <28 weeks. The later gestational age category of 32-35 weeks was used as the reference category for comparisons in this study. The presence and rate of MIR or FIR were then calculated for each grade and stage of inflammatory response within each stratum of preterm birth. Chi square was used for categorical comparisons and t-test for comparisons involving continuous variables. Multinomial logistic regression analyses estimated the association between placental inflammation and PTB categories after adjustment for statistically influential covariates. Results were reported as crude and adjusted odds ratios with 95% confidence intervals. Differences and outcome estimates were considered statistically significant if the 95% confidence interval did not include 1.0 or p-value for comparison was < 0.05. Data were analyzed using Stata SE 9.2 for Windows (College Station, TX).
RESULTS

During the study period, 85 enrolled study participants had placenta specimens collected at delivery. Two cases were excluded from this analysis due to identification of erroneous inclusion to the study with a documented indication for delivery of pre-eclampsia. Slides from four other cases were not available for rereview. A total of 79 placental specimens were included in this analysis.

The study population consisted of 16 (20.25%) white mothers and 63 (79.75%) black mothers with spontaneous preterm birth <35 0/7 weeks. The mean gestational age of the index preterm birth was 29.97 ± 3.88 weeks. Of the 20 (25.32%) participants with a prior preterm birth, the mean gestational age of the antecedant preterm birth was 30.72 ± 4.0 weeks. All participating mothers were confirmed to have a 1st degree family member with preterm birth. The majority of the study population was multiparous (80%) with a mean parity of 2.72 ± 1.51. The rate of coexisting medical conditions was low (<10%), see Table 1.

Of the 79 women with spontaneous onset of preterm birth, 33 (41.8%) had preterm premature rupture of membranes (PPROM) prior to delivery. Despite a mean duration of membrane rupture of 65.3 hours in the PPROM group, no study participant had clinical chorioamnionitis in labor, maternal temperature >38.0 degrees Celsius, nor endomyometritis during the postpartum course (Table 1).

Despite no clinical evidence of intra-amniotic infection, maternal and fetal inflammatory responses occurred frequently at all gestational ages of preterm birth. The overall rate of placental inflammatory changes of maternal origin (MIR)
in the study population of preterm birth <35 weeks was 51.9%. The rate of MIR increased as the gestational age decreased, 22% at 32-35 weeks, 57% at 28-32 weeks, and 85% at 20-28 weeks (p=0.001), Table II. Fetal inflammatory responses are considered a more severe and later finding than maternal responses, and as expected the overall rate of FIR was lower (35.4%) than that of MIR (51.9%). Despite the absence of clinical evidence of intra-amniotic infection in this study cohort, the presence of fetal inflammatory response was surprisingly high, 57.7%, at the earliest gestational ages of birth (Table III, Figure 1).

The presence any maternal inflammatory response was significantly increased in cases of extreme preterm birth (<28 wks), crude OR 19.6 (95% CI 5.1, 76.2) and adjOR 77.5 (95% CI 5, 1213), compared to later preterm births from 32 – 35 weeks. Likewise, any fetal inflammatory response (grade or stage) was more common in cases of extreme preterm birth, crude OR 7.4 (2.1, 25.2) and adjOR 38.4 (95% CI 2.9, 514), Figure 2.

Histologic evidence of other placental patterns of injury and maladaptation was also examined and categorized in a previously described fashion.(8) The presence of non-inflammatory placental changes was uncommon in this study population, and did not differ significantly among the three stratum of preterm gestational ages (data not shown).
DISCUSSION

This study demonstrates that intrauterine inflammation plays an important role in the cascade of events leading to spontaneous preterm birth, despite a lack of clinical evidence of intra-amniotic infection. The presence of placental inflammation and infection of the amniotic cavity has been reported in high rates in cases of spontaneous preterm birth. Additionally, the frequency of inflammation and infection are higher at earlier gestational ages of birth. (9, 10) Placental histologic findings of chorioamnionitis, specifically maternal and/or fetal inflammatory responses, are both sensitive and specific for intra-amniotic infection and have historically been considered the “gold standard” for its diagnosis. (5, 7, 11-14). Despite this, placental histologic findings of an inflammatory response do not ensure the certain identification of a definitive infectious source. Several studies have reported that greater than 30% of cases with confirmed placental chorioamnionitis lack the presence of identifiable microorganisms. (11, 15) Difficulty in confirming microorganisms from cases with placental inflammation may be explained by limitations inherent to the techniques required to cultivate microorganisms in the laboratory. (5) On the other hand, it is plausible that placental inflammation does not correlate directly to the presence of intra-amniotic infection.

Inconsistencies among previously reported rates of placental inflammation in cases of preterm birth are largely attributed to differences in study populations, definition of chorioamnionitis, and methodologic approach. (16-21) Despite these differences, our results confirm prior studies demonstrating a high rate of
placental inflammatory/ infectious processes in cases of spontaneous preterm birth, especially at the earliest gestational ages. Uniquely, we report this finding in a cohort of idiopathic preterm births selected specifically to be without any preceding clinical evidence of intra-amniotic infection, and with no subsequent postpartum infectious sequelae.

The prospective design of this study is one of its significant strengths and distinguishes it from many other studies reporting placental inflammation and prematurity.(17-19, 21) We collected detailed medical, obstetric and family history data as well as labor and delivery characteristics in a systematic prospective fashion, thus limiting ascertainment, measurement, classification, and other information biases inherent to those of a retrospective nature. The careful method in which cases were chosen, with the aim to enhance for a population of truly “unexplained” genetic-associated preterm birth, also enhanced the capacity to identify specific risk factors that cluster in families affected by multiple episodes of prematurity. To further strengthen internal validity, all placenta pathologic specimens in this study were reviewed by a single pathologist blind to patient characteristics, and categorized in a detailed fashion according to standard nosologic criteria.(6, 7)

The selection of a late preterm birth group (32-35 weeks of gestation) as a referent category in this study may have limited our ability to quantify the magnitude of effect of gestational age on inflammatory changes. Despite this limitation, we considered it the optimal reference category for comparison for this study’s purposes. Other potential control groups were considered but thought
more likely to introduce bias. For example, term gestation placentas were considered to be a suboptimal reference group due to selection bias as those selected for pathologic evaluation would be more likely to have suspected abnormalities. Placentas from preterm births due to other causes (medically indicated) would also not be an optimal referent as they would have a preponderance of pathologic abnormalities indicative of their underlying pathophysiologic processes. Furthermore, choosing an internal reference group from the same population has desirable advantages over the use of an external reference group that may differ significantly from the at-risk group in many ways other than the factor being examined (in this case, gestational age).(22) Choice of an internal reference group therefore limits selection bias.(23) Because a late preterm birth category was utilized as reference for comparisons, the estimates of risk for the earlier gestational age categories reported in this study are likely shifted toward the null, underestimating the true risk.

This study included a unique population of patients, those with a strong familial component to their preterm birth, likely reflecting genetics. We have demonstrated through segregation analyses of this patient population that genetic factors of maternal origin are largely responsible for determining the timing of birth.(4) Our finding of higher rates of inflammatory responses at early gestational ages at birth suggest mechanistic differences between preterm births occurring at early versus late preterm gestational ages. Future studies aimed to evaluated genetic influences to parturition may benefit from analyzing early and late preterm gestational age groups separately.
The frequency with which maternal and inflammatory changes occur in cases of spontaneous familial preterm birth demonstrates the important role that intrauterine inflammation plays in the onset of otherwise unexplained spontaneous preterm parturition. The normal processes of parturition may contribute to the presence of inflammatory changes to a degree, but can not be entirely explanatory as they are much less frequently found in the later cases of preterm birth, 15-22% at 32-25 weeks of gestational age compared 58-85% of extreme preterm births <28 weeks. Likewise, while inflammation appears to be an important contributor it is not an essential component to spontaneous familial preterm birth as approximately half of cases were without evidence of placental inflammatory changes.

Through our pathologic analysis of cases likely to have a genetic predisposition but with otherwise clinically unexplained preterm birth, we feel that we provide new insight into the relative contribution of inflammation to the onset of spontaneous familial preterm birth. Rather than infection being a common component of genetic-associated preterm birth, we suggest that a genetic aberration in the inflammatory pathways leading to premature labor may cluster in families with recurrent episodes of preterm birth. Although our findings are observational, they can be considered further evidence to describe the complex interplay of factors in the “preterm parturition syndrome”(5) and reflect possible mechanisms of pathogenesis of familial preterm birth.
REFERENCES


Table I. Baseline characteristics of women with familial idiopathic spontaneous preterm birth <35 weeks of gestation (n = 79)

<table>
<thead>
<tr>
<th>Etiology of preterm birth</th>
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<tr>
<td>Idiopathic spontaneous preterm labor</td>
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</tr>
<tr>
<td>Maternal age (years)</td>
<td>25.00 ± 5.61</td>
</tr>
<tr>
<td>Maternal race/ ethnicity</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>16 (20.25)</td>
</tr>
<tr>
<td>Black</td>
<td>63 (79.75)</td>
</tr>
<tr>
<td>First degree family members with preterm birth</td>
<td>79 (100)</td>
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<tr>
<td>Primiparous</td>
<td>16 (20.25)</td>
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<tr>
<td>Parity</td>
<td>2.72 ± 1.51</td>
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<td>Mean gestational age of index PTB</td>
<td>29.97 ± 3.88</td>
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<td>Mean gestational age of prior PTB &lt; 37 gestational weeks (n=20)</td>
<td>30.72 ± 4.00</td>
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<td>Medicaid</td>
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<td>Body mass index at delivery</td>
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<td>Gestational diabetes</td>
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<tr>
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<td>Cigarette use</td>
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<td>PPROM (cases with labor induction are excluded)</td>
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<td>Mean maternal temperature at delivery (degrees Celsius)</td>
<td>36.66 ± 1.20</td>
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<td>Duration of ruptured membranes (hours) in patients diagnosed with PPROM , n=33</td>
<td>65.30 ± 69.61</td>
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<td>Duration of ruptured membranes (hours) in patients with spontaneous PTL (excluding PPROM cases), n= 46</td>
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<td>Clinical chorioamnionitis in labor</td>
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<td>Treated with antibiotics for endomyometritis postpartum</td>
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Categorical variables are expressed as n(%) and continuous variables as mean ± SD
TABLE II: Association of maternal inflammatory response (MIR) with idiopathic familial spontaneous preterm birth

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<th>None</th>
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<th>MIR Stage 1</th>
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<tr>
<td>&lt;35 weeks</td>
<td>38 (48.1%)</td>
<td>41 (51.9%)</td>
<td>12 (15.2%)</td>
<td>12 (15.2%)</td>
<td>17 (21.5%)</td>
<td>14 (17.7%)</td>
<td>27 (34.2%)</td>
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<tr>
<td>n=79</td>
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<td></td>
<td></td>
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<tr>
<td>PTB 32-35 weeks</td>
<td>25 (78)</td>
<td>7 (22)</td>
<td>4 (12.5%)</td>
<td>1 (3)</td>
<td>2 (6)</td>
<td>4 (12.5%)</td>
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<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTB 28-32 weeks</td>
<td>9 (43)</td>
<td>12 (57)</td>
<td>4 (19)</td>
<td>4 (19)</td>
<td>4 (19)</td>
<td>4 (19.1)</td>
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<td>(95% CI)</td>
<td>(0.8, 48.5)</td>
<td>(0.5, 108.5)</td>
<td>**</td>
<td>(0.5, 83.9)</td>
<td>(0.3, 45.9)</td>
<td>(0.7, 130.9)</td>
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<td>PTB &lt;28 weeks</td>
<td>4 (15)</td>
<td>22 (85)</td>
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<td>7 (27)</td>
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<td>(95% CI)</td>
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<td>(6.3, 3584.2)</td>
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* Adjusted for prior preterm birth, history of miscarriage, cigarette use.
** unable to calculate
TABLE III: Association of fetal inflammatory response (FIR) with idiopathic familial spontaneous preterm birth

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</tr>
<tr>
<td>n=21 (26.6%)</td>
<td>13 (61.9%)</td>
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<td>4 (19.1%)</td>
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<td>5 (23.8%)</td>
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<tr>
<td>n=26 (32.9%)</td>
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<td>7 (26.9%)</td>
<td>6 (23.1%)</td>
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<td>2.94</td>
<td>**</td>
<td>13.5</td>
<td>3.3</td>
</tr>
<tr>
<td>Adjusted OR* (95% CI)</td>
<td>1.0</td>
<td>38.4</td>
<td>**</td>
<td>19.8</td>
<td>**</td>
<td>**</td>
<td>4.5</td>
</tr>
</tbody>
</table>

* Adjusted for prior preterm birth, history of miscarriage, cigarette use.
** unable to calculate
Figure I: Rate of maternal and fetal inflammatory response (MIR and FIR) by gestational age

Rate of preterm birth, %

- MIR Grade 2
- MIR Grade 1
- MIR Stage 3
- MIR Stage 2
- MIR Stage 1
- MIR - any
- No MIR
- FIR grade 2
- FIR grade 1
- FIR stage 3
- FIR stage 2
- FIR stage 1
- FIR - any
- No FIR

Legend:
- <28 wks
- 28-32 wks
- 32-35 wks (referent)
Figure II: Association between maternal and fetal inflammatory responses and familial idiopathic spontaneous preterm birth