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An elevated amniotic fluid prostaglandin $F_{2\alpha}$ concentration is associated with intra-amniotic inflammation/infection, and clinical and histologic chorioamnionitis, as well as impending preterm delivery in patients with preterm labor and intact membranes

Jee Yoon Park¹, Roberto Romero^{2,3,4,5}, JoonHo Lee¹, Piya Chaemsaihong^{2,6}, Noppadol Chaiyasit^{2,6}, and Bo Hyun Yoon¹

¹Department of Obstetrics and Gynecology, Seoul National University College of Medicine, Seoul, Republic of Korea

²Perinatology Research Branch, Program for Perinatal Research and Obstetrics, Division of Intramural Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH/DHHS, Bethesda, MD and Detroit, MI, USA

³Department of Obstetrics and Gynecology, University of Michigan, Ann Arbor, MI, USA

⁴Department of Epidemiology and Biostatistics, Michigan State University, East Lansing, MI, USA

⁵Center for Molecular Medicine and Genetics, Wayne State University, Detroit, MI, USA

⁶Department of Obstetrics and Gynecology, Wayne State University School of Medicine, Detroit, MI, USA

Abstract

Objective—To determine whether an elevated amniotic fluid concentration of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) is associated with intra-amniotic inflammation/infection and adverse pregnancy outcomes in patients with preterm labor and intact membranes.

Materials and Methods—The retrospective cohort study included 132 patients who had a singleton pregnancy with preterm labor (<35 weeks of gestation) and intact membranes. Amniotic fluid was cultured for aerobic and anaerobic bacteria as well as genital mycoplasmas. Intra-amniotic inflammation was defined by an elevated amniotic fluid matrix metalloproteinase-8 (MMP-8) concentration (>23 ng/mL). $PGF_{2\alpha}$ was measured with a sensitive and specific immunoassay. The amniotic fluid $PGF_{2\alpha}$ concentration was considered elevated when it was above the 95th percentile among pregnant women at 15–36 weeks of gestation who were not in labor (170 pg/mL).

Results—(1) The prevalence of an elevated amniotic fluid $PGF_{2\alpha}$ concentration was 40.2% (53/132) in patients with preterm labor and intact membranes; (2) patients with an elevated amniotic fluid $PGF_{2\alpha}$ concentration had a significantly higher rate of positive amniotic fluid

culture [19% (10/53) vs. 5% (4/79); $p = 0.019$], intra-amniotic inflammation/infection [49% (26/53) vs. 20% (16/79); $p = 0.001$], spontaneous preterm delivery, clinical and histologic chorioamnionitis, and funisitis, as well as a higher median amniotic fluid MMP-8 concentration and amniotic fluid white blood cell count and a shorter amniocentesis-to-delivery interval than those without an elevated concentration of amniotic fluid $\text{PGF}_{2\alpha}$ ($p < 0.05$ for each); and (3) an elevated amniotic fluid $\text{PGF}_{2\alpha}$ concentration was associated with a shorter amniocentesis-to-delivery interval after adjustment for the presence of intra-amniotic inflammation/infection [hazard ratio 2.1, 95% confidence interval (CI) 1.4–3.1; $p = 0.001$].

Conclusion—The concentration of $\text{PGF}_{2\alpha}$ was elevated in the amniotic fluid of 40.2% of patients with preterm labor and intact membranes and is an independent risk factor for intra-amniotic inflammation/infection, impending preterm delivery, chorioamnionitis, and funisitis.

Keywords

acute inflammatory lesions of the placenta; amniocentesis; amniotic fluid infection; funisitis; MMP-8; mycoplasma; prematurity; prostanoids

Introduction

Preterm birth is the leading cause of perinatal morbidity and mortality worldwide and remains an important obstetrical challenge [1–11]. Two-thirds of all preterm births result from spontaneous preterm labor [12], a syndrome [13–17] characterized by the combination of increased uterine contractility [18–20], cervical remodeling [21–28], and/or activation of the chorioamniotic membranes and decidua [29–32].

The major focus of attention in contemporary obstetrics and perinatal medicine is the diagnosis, treatment, and prevention of spontaneous preterm birth [33–41]. Biomarkers for the diagnosis of preterm labor and impending preterm delivery are desirable because they would allow the rational allocation of resources and influence clinical management (e.g. admission to the hospital, administration of steroids, transfer to a tertiary care center, etc.). This has been the basis for the evaluation of cervical length [42–56], fetal fibronectin [57–75], alpha-macroglobulin-1 [76–79], insulin-like growth factor binding protein-1 [80–89], and the concentration of inflammatory mediators in the amniotic fluid [90–116] and cervicovaginal fluid [88, 108, 117–126] in patients presenting with increased uterine contractility or suspected preterm labor.

Prostaglandins are considered the mediators of parturition [127–145], and they (unlike oxytocin) can stimulate myometrial contractility [146–158] during the first, second, and third trimesters, induce cervical remodeling [22, 24, 27, 159–168], and participate in extracellular matrix degradation leading to rupture of the membranes [30, 132, 169–177]. The main prostaglandins found in amniotic fluid are prostaglandin E_2 (PGE_2) and prostaglandin $\text{F}_{2\alpha}$ ($\text{PGF}_{2\alpha}$) [142, 178, 179]. The concentration of these eicosanoids increases prior to the onset of labor at term [136, 140, 142], during labor [133, 179] and rupture of the membranes [132], and in spontaneous preterm labor [particularly in the setting of microbial invasion of the amniotic cavity (MIAC)] [129–131, 137, 173, 180–187]. Despite the physiologic and pharmacologic importance of prostaglandins in spontaneous

term and preterm labor, there is a paucity of literature examining the potential role of prostaglandin concentrations in the assessment of patients with preterm labor [129–131, 142, 173, 180–184, 187].

We previously reported that the amniotic fluid concentration of $\text{PGF}_{2\alpha}$ in women with preterm prelabor rupture of the membranes (PROM) was associated with intra-amniotic inflammation and a short latency period [173]. Specifically, an amniotic fluid concentration of $\text{PGF}_{2\alpha}$ 170 pg/mL was a predictor of pregnancy duration after adjusting for gestational age and the presence of amniotic fluid inflammation/infection [173]. Thus, the objective of this study was to determine whether the amniotic fluid concentration of $\text{PGF}_{2\alpha}$ has diagnostic and prognostic value for patients with preterm labor and intact membranes.

Materials and Methods

Study design

This retrospective cohort study included patients with a singleton pregnancy admitted to the Seoul National University Hospital with the diagnosis of preterm labor and intact membranes. The diagnosis of this condition was made when the following criteria were met: 1) gestational age of 20–35 weeks; 2) regular uterine contractions – eight or more within 60 minutes; and 3) amniotic fluid obtained by transabdominal amniocentesis or collected at the time of cesarean delivery. Retrieval of amniotic fluid was performed after written informed consent was obtained from each patient. The Institutional Review Board of the Seoul National University Hospital approved the collection and use of the samples and clinical information for research purposes. The Seoul National University has a Federalwide Assurance with the Office for Human Research Protections (OHRP) of the U. S. Department of Health and Human Services (DHHS).

Amniotic fluid

Amniotic fluid was cultured for aerobic and anaerobic bacteria as well as genital mycoplasmas. An aliquot of amniotic fluid was examined in a hemocytometer chamber to determine the white blood cell count. Amniotic fluid not used for this study was centrifuged and stored in polypropylene tubes at -70°C until assay. $\text{PGF}_{2\alpha}$ concentrations were measured with a commercially available enzyme immunoassay (Assay Design, Ann Arbor, MI, USA). The sensitivity of the assay was 7.7 pg/mL. Intra- and inter-assay coefficients of variation were $< 10\%$. Matrix metalloproteinase-8 (MMP-8) concentrations were measured with a commercially available enzyme-linked immunosorbent assay (ELISA) (Amersham Pharmacia Biotech, Inc, Little ChalfontBucks, UK). The sensitivity of the test was 0.3 ng/mL, and the intra- and inter-assay coefficients of variation were $< 10\%$.

Intra-amniotic inflammation and an elevated amniotic fluid $\text{PGF}_{2\alpha}$

The presence of intra-amniotic inflammation was defined as an elevation of the amniotic fluid MMP-8 concentration (>23 ng/mL), as previously reported [188–191]. An elevated amniotic fluid $\text{PGF}_{2\alpha}$ concentration was defined as 170 pg/mL. This is based on our previous study which reported that an amniotic fluid $\text{PGF}_{2\alpha}$ concentration of 170 pg/mL

corresponded to the value at the 95th percentile for pregnant women with intact membranes at 15–36 weeks of gestation who were not in labor [142].

Diagnosis of funisitis and histologic and clinical chorioamnionitis

Placental tissue samples were obtained for histopathologic evaluation, fixed in 10% neutral buffered formalin, and embedded in paraffin. Sections of the blocks were stained with Hematoxylin and Eosin. Pathologists were blinded to the clinical information. Funisitis was diagnosed by the presence of neutrophil infiltration into the umbilical vessel walls or Wharton's jelly [188, 192–200]. Acute histologic chorioamnionitis was diagnosed by the presence of acute inflammatory changes observed in the tissue samples collected from the amnion, chorion-decidua, umbilical cord, and chorionic plate [192, 196, 197, 200–202]. Clinical chorioamnionitis was diagnosed by the presence of maternal fever (temperature $>37.8^{\circ}\text{C}$) accompanied by two or more of the following criteria: 1) maternal tachycardia (heart rate >100 beats/min); 2) uterine tenderness; 3) foul-smelling amniotic fluid; 4) fetal tachycardia (heart rate >160 beats/min); and 5) maternal leukocytosis (leukocyte count $>15,000$ cells/mm³) [203–211].

Statistical analysis

Continuous variables were compared between the two groups according to the concentration of amniotic PGF_{2 α} using the Mann-Whitney U test; proportions were compared using the Fisher's exact test. The generalized Wilcoxon test for survival analysis was applied to examine the interval from amniocentesis to delivery. The amniocentesis-to-delivery interval of patients delivered with maternal or fetal indicators, rather than by the spontaneous progression of labor, was treated as censored data, and the censoring time was considered equal to the amniocentesis-to-delivery interval. The Cox proportional hazard model determined the hazard ratio of the amniocentesis-to-delivery interval according to the concentration of amniotic fluid PGF_{2 α} with an adjustment for confounding factors. A p -value < 0.05 was considered statistically significant. Analysis was performed by SPSS, version 21 (SPSS Inc., Chicago, IL, USA).

Results

The prevalence of an elevated concentration of PGF_{2 α} in the amniotic fluid was 40.2% (53/132). Table 1 describes the clinical characteristics and pregnancy outcomes of the study population according to the concentration of PGF_{2 α} in the amniotic fluid. There were no significant differences in the median degree of cervical dilatation and gestational age at amniocentesis between the two groups of patients ($p > 0.05$). However, patients with an elevated concentration of amniotic fluid PGF_{2 α} had a significantly lower median gestational age at delivery and a higher rate of positive amniotic fluid culture, intra-amniotic inflammation, clinical and histologic chorioamnionitis, and funisitis as well as preterm delivery. A significantly higher median amniotic fluid MMP-8 concentration and white blood cell count were observed in patients with an elevated concentration of amniotic fluid PGF_{2 α} when compared to those without an elevated concentration of amniotic fluid PGF_{2 α} (p values < 0.05 for all) (Table 1).

Figure 1 illustrates the amniocentesis-to-delivery interval according to the concentration of amniotic fluid $\text{PGF}_{2\alpha}$. Patients with an elevated concentration of amniotic fluid $\text{PGF}_{2\alpha}$ had a significantly shorter amniocentesis-to-delivery interval than those without an elevated concentration of amniotic fluid $\text{PGF}_{2\alpha}$ ($p < 0.001$, Figure 1A). Moreover, among patients without intra-amniotic inflammation/infection, those with an elevated concentration of amniotic fluid $\text{PGF}_{2\alpha}$ had a significantly shorter amniocentesis-to-delivery interval than those without an elevated amniotic fluid $\text{PGF}_{2\alpha}$ concentration ($p = 0.007$, Figure 1B). This association was still observed after an adjustment for the presence of amniotic fluid inflammation/infection [hazard ratio 2.1, 95% confidence interval (CI) 1.4–3.1; $p = 0.001$].

The diagnostic indices, predictive values, and likelihood ratios for spontaneous preterm delivery within 48 hours to 7 days of an amniocentesis as well as spontaneous preterm delivery before 36 weeks of gestation are presented in Table 2. A subgroup analysis was performed focusing on patients without intra-amniotic inflammation/infection. Such results are presented in Table 3. This analysis was undertaken to explore whether the amniotic fluid $\text{PGF}_{2\alpha}$ concentration would have a different diagnostic performance in patients with and without intra-amniotic inflammation/infection. However, the observations reported in Table 2 suggest that the performance is similar in patients with and without intra-amniotic inflammation/infection.

Discussion

Principal findings of the study

(1) The prevalence of an elevated $\text{PGF}_{2\alpha}$ concentration in the amniotic fluid was 40.2% in patients with preterm labor and intact membranes; (2) an elevated amniotic fluid $\text{PGF}_{2\alpha}$ concentration is associated with intra-amniotic inflammation/infection, acute histologic chorioamnionitis, and funisitis; and (3) patients with an elevated $\text{PGF}_{2\alpha}$ concentration (> 170 pg/mL) have a shorter amniocentesis-to-delivery interval than those with a normal amniotic fluid $\text{PGF}_{2\alpha}$ concentration after adjustment for the presence of intra-amniotic inflammation/infection.

Prostaglandins in term and preterm labor

Prostaglandins, the bioactive lipid mediators of arachidonic acid metabolism via the cyclooxygenase (COX) pathway, are known to play an important role in reproductive physiology [128, 134–136, 142, 143]. Increased expression of the inducible forms of cyclooxygenase and cyclooxygenase-2 in the human amnion and other reproductive tissues is responsible for the increased biosynthesis of prostaglandins with the onset of labor [136, 140, 142, 179]. Previous studies documented increased concentrations of the primary prostaglandins and their metabolites for patients in labor at term [132, 133, 136, 137, 142, 178, 179, 212–214] as well as for those in spontaneous preterm labor [129–131, 142, 173, 180–184, 187].

The premise for this study proposed that an elevated concentration of amniotic fluid prostaglandins is associated with the progression of the parturition process, particularly in the context of intra-amniotic inflammation/infection. We found that an elevated amniotic

fluid $\text{PGF}_{2\alpha}$ concentration was observed in 40.2% of patients with preterm labor and intact membranes and that those patients were more likely to have intra-amniotic infection, histologic chorioamnionitis, funisitis, and a shorter amniocentesis-to-delivery interval than those without an elevated amniotic fluid $\text{PGF}_{2\alpha}$ concentration.

Which mechanisms are responsible for an elevated $\text{PGF}_{2\alpha}$ concentration in the amniotic fluid? MIAC results in the production of pro-inflammatory cytokines, such as interleukin- 1β and tumor necrosis factor- α , which can stimulate prostaglandin production in the gestational tissues (amnion, chorion, and decidua) [129–131, 169, 180, 181, 213].

Clinical implications

An important challenge in clinical obstetrics is the identification of biomarkers that would have prognostic significance in patients with preterm labor without intra-amniotic inflammation/infection. The results reported herein suggest that, in the absence of intra-amniotic inflammation/infection, the amniotic fluid concentration of $\text{PGF}_{2\alpha}$ is related to the amniocentesis-to-delivery interval (Figure 1B). However, the diagnostic indices for the identification of patients who delivered within 48 hours to 7 days, or before 36 weeks of gestation, were not optimal (Table 2). It is possible that $\text{PGF}_{2\alpha}$ could be included in a multi-marker panel to assess the likelihood of preterm delivery in such patients. Further research is required to identify additional biomarkers in patients with preterm labor but without intra-amniotic inflammation/infection.

Strengths and limitations

The major strengths of this study are its design (i.e. a cohort study), the inclusion of patients with preterm labor, and the assessment of amniotic fluid status by measuring a marker of inflammation (MMP-8), performing a culture for microorganisms in the amniotic fluid, and conducting a systematic histopathologic examination of the placenta to determine the presence of acute histologic chorioamnionitis and funisitis. This study is unique in that such a multi-dimensional evaluation has not been performed before when assessing the potential value of eicosanoids. A limitation of this study is that we utilized an immunoassay rather than a chemical assay for the determination of $\text{PGF}_{2\alpha}$. New developments in lipidomics have now made it possible to assess the metabolites of multiple pathways of arachidonic acid (i.e. cyclooxygenase, lipoxygenase, and epoxygenase) [144, 214–217]. Further research could make use of lipidomics to identify biomarkers for intra-amniotic inflammation/infection, sterile intra-amniotic inflammation, and impending preterm delivery in patients with preterm labor.

Conclusion

An elevated concentration of amniotic fluid $\text{PGF}_{2\alpha}$ in patients with preterm labor and intact membranes is associated with intra-amniotic inflammation/infection, clinical chorioamnionitis, acute histologic chorioamnionitis, funisitis, and a short amniocentesis-to-delivery interval after an adjustment for the presence of intra-amniotic inflammation/infection.

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Figure 1.

Survival analysis of the amniocentesis-to-delivery interval according to the concentration of amniotic fluid PGF_{2α}: (A) median, 37.0 hours (range, 0.1–2112.0 hours) vs. median, 671.0 hours (range, 0–2683.2 hours), $p < 0.001$; (B) median, 208.4 hours (range, 0.3–2112.0 hours) vs. median, 905.5 hours (range, 3.6–2683.2 hours), $p = 0.007$.

Table 1

Clinical characteristics and pregnancy outcomes of the study population according to the PGF_{2α} concentration in the amniotic fluid

	Low PGF _{2α} (n=79)	Elevated PGF _{2α} (n=53)	p-values
GA at amniocentesis (weeks)	31.7 (16.1–35.1)	32.4 (23.6–35.1)	NS
GA at delivery (weeks) *	37.3 (16.4–42.0)	34.1 (23.6–41.1)	<0.001
Positive amniotic fluid culture (n)	4 (5.1%)	10 (18.9%)	0.019
Intra-amniotic inflammation (n/N)	14/77 (18.2%)	26/53 (49.1%)	<0.001
Intra-amniotic inflammation/infection (n/N) [‡]	16/79 (20.3%)	26/53 (49.1%)	0.001
Amniotic fluid WBC count (cells/mm ³) *	0 (0–711)	3 (0–>1000)	<0.001
Amniotic fluid MMP-8 (ng/mL) *	0.9 (0–829.9)	17.0 (0.1–3929.0)	<0.001
Cervical dilatation (cm)	1.0 (0–10.0)	1.5 (0–8.0)	NS
Clinical chorioamnionitis (n)	1 (1.3%)	8 (15.1%)	0.003
Amniocentesis-to-delivery interval (hours) [‡]	671.0 (0–2683.2)	37.0 (0.1–2112.0)	<0.001
Within 48 hours (n)	18 (22.8%)	29 (54.7%)	<0.001
Within 7 days (n)	25 (31.6%)	36 (67.9%)	<0.001
Preterm delivery <36 weeks (n)	35 (44.3%)	41 (77.4%)	<0.001
Acute histologic chorioamnionitis (n/N)	17/45 (37.8%)	24/38 (63.2%)	0.028
Funisitis (n/N)	4/43 (9.3%)	11/36 (30.6%)	0.022

GA: gestational age; MMP-8: matrix metalloproteinase-8; low PGF_{2α} amniotic fluid PGF_{2α} concentrations < 170 pg/mL; elevated PGF_{2α} amniotic fluid PGF_{2α} concentrations ≥ 170 pg/mL; NS: not significant; PGF_{2α} prostaglandin F_{2α}; WBC: white blood cell. Values are presented as medians and ranges.

* p < 0.05, by the Mann-Whitney U test.

[‡] Compared with the generalized Wilcoxon test for survival analysis.

[‡] Intra-amniotic inflammation/infection was defined as a positive amniotic fluid culture and/or an elevated amniotic fluid MMP-8 concentration (>23 ng/mL).

Diagnostic indices, predictive values, and likelihood ratios for spontaneous preterm delivery within 48 hours to 7 days of amniocentesis and before 36 weeks of gestation

Table 2

	Prevalence % (n)	Sensitivity % (n)	Specificity % (n)	PPV % (n)	NPV % (n)	Positive likelihood ratio	Negative likelihood ratio
sPTD within 48 hours of amniocentesis	30.3% (40/132)	67.5% (27/40)	74.0% (54/73)	58.7% (27/46)	80.6% (54/67)	2.60	0.44
sPTD within 7 days of amniocentesis	37.1% (49/132)	63.3% (31/49)	76.6% (49/64)	67.4% (31/46)	73.1% (49/67)	2.71	0.48
sPTD < 36 weeks of gestation	43.2% (57/132)	59.6% (34/57)	78.6% (44/56)	73.9% (34/46)	65.7% (44/67)	2.79	0.36

NPV: negative predictive value; PPV: positive predictive value; sPTD: spontaneous preterm delivery.

Diagnostic indices, predictive values, and likelihood ratios for spontaneous preterm delivery within 48 hours to 7 days of an amniocentesis and before 36 weeks of gestation in patients without intra-amniotic inflammation/infection

Table 3

	Prevalence % (n)	Sensitivity % (n)	Specificity % (n)	PPV % (n)	NPV % (n)	Positive likelihood ratio	Negative likelihood ratio
sPTD within 48 hours of amniocentesis	12.2% (11/90)	63.6% (7/11)	76.2% (48/63)	31.8% (7/22)	92.3% (48/52)	2.67	0.48
sPTD within 7 days of amniocentesis	17.8% (16/90)	56.3% (9/16)	77.6% (45/58)	40.9% (9/22)	86.5% (45/52)	2.51	0.56
sPTD < 36 weeks of gestation	23.3% (21/90)	52.4% (11/21)	79.2% (42/53)	50.0% (11/22)	80.8% (42/52)	2.52	0.60

NPV: negative predictive value; PPV: positive predictive value; sPTD: spontaneous preterm delivery.