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AMNIOTIC FLUID PROSTAGLANDIN F2 INCREASE EVEN IN STERILE AMNIOTIC FLUID AND IS AN INDEPENDENT PREDICTOR OF IMPENDING DELIVERY IN PRETERM PROM

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Abstract

Objective—To determine whether amniotic fluid concentration of prostaglandins (PGs) increases in patients with intra-amniotic inflammation and/or proven amniotic fluid infection in preterm PROM, and whether the amniotic fluid PG concentration can predict impending delivery.

Methods—Amniotic fluid PGF2a concentrations were determined by ELISA in 140 singleton pregnancies with preterm PROM (< 35 weeks). Amniotic fluid was cultured for aerobic and anaerobic bacteria, as well as genital mycoplasmas. Intra-amniotic inflammation was defined as an elevated amniotic fluid MMP-8 concentration (>23 ng/mL). Non-parametric tests and survival techniques were used for the statistics.

Results—1) Patients with intra-amniotic inflammation and a negative amniotic fluid culture had a significantly higher median amniotic fluid PGF2a concentration than those without intra-amniotic inflammation and a negative amniotic fluid culture (median, 206 vs. 64 pg/mL; $p<0.001$); 2) however, there was no difference in the median amniotic fluid PGF2a concentration between patients with intra-amniotic inflammation with a negative culture and those with culture-proven amniotic fluid infection (median, 206 vs. 314 pg/mL, $p=0.4$); 3) amniotic fluid PGF2a > 170 pg/mL had a sensitivity of 63% and a specificity of 89% in the identification of intra-amniotic inflammation and/or amniotic fluid infection; 4) patients with an elevated amniotic fluid PGF2a (> 170 pg/mL) had a significantly shorter interval-to-delivery than those with low amniotic fluid PGF2a (median, 72 vs. 155 hours; $p<0.001$); and 5) an elevated amniotic fluid PGF2a concentration was a significant predictor of the duration of pregnancy after adjusting for gestational age and amniotic fluid inflammation/infection (OR, 2.3; 95% CI, 1.4–4.0; $p<0.005$).

Conclusions—The amniotic fluid PGF2a concentration increased in patients with intra-amniotic inflammation regardless of amniotic fluid culture results. Moreover, an elevated AF PGF2a concentration was an independent predictor of impending delivery in preterm PROM.

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Keywords

Amniotic fluid infection; intra-amniotic inflammation; prostaglandin; preterm PROM; parturition

Introduction

Prostaglandins (PGs) are the central mediators in human parturition [5, 6, 9, 22, 25]. There is substantial evidence that PGs are involved in the mechanisms of human parturition associated with culture-proven intra-amniotic infection [11, 13, 19, 26, 27]. These infections are present in one third of patients with preterm PROM [28]. Microbial invasion of the amniotic cavity can be recognized by the innate immune system in gestational tissue and can lead to an inflammatory response which includes PG production and induction of labor [1, 7, 8, 10].

Intra-amniotic inflammation is found in approximately 40% of patients with preterm premature rupture of membranes (PROM) and is a risk factor for impending preterm delivery, adverse pregnancy and neonatal outcome, regardless of the presence or absence of culture-proven amniotic fluid (AF) infection [31].

There is a paucity of information regarding the concentration of PGs in the AF of patients exposed to intra-amniotic inflammation in the absence of culture-proven AF infection. The purpose of this study was to examine if AF PGs change in patients with intra-amniotic inflammation without culture-proven AF infection and if AF PG concentrations are a risk factor for impending delivery in preterm PROM.

Materials and Methods

Study design

The concentrations of PGF2a were examined in AF obtained from 140 pregnant women admitted to the participating institution with the diagnosis of preterm PROM and who met the following criteria: (1) singleton pregnancy; (2) preterm pregnancy (gestational age \leq 35 weeks); and (3) AF obtained by transabdominal amniocentesis or collected at the time of cesarean delivery. Patients were divided into 3 groups according to the presence or absence of intra-amniotic inflammation and AF culture results; Group 1: patients without intra-amniotic inflammation and a negative AF culture (N=81); Group 2: women with intra-amniotic inflammation and a negative AF culture (N=31); Group 3: patients with a positive AF culture (N=28).

Retrieval of AF was performed after obtaining written informed consent. The Institutional Review Board of the participating institution approved the collection and use of these samples and clinical information for research purposes.

Amniotic fluid studies

AF was cultured for aerobic and anaerobic bacteria, as well as for genital mycoplasmas (*Mycoplasma hominis* and *Ureaplasma urealyticum*). An aliquot of AF was transported to the laboratory and processed for white blood cell (WBC) count and matrix

metalloproteinase-8 (MMP-8) determinations. AF MMP-8 concentration was measured with a commercially available enzyme-linked immunosorbent assay (Amersham Pharmacia Biotech, Inc, Bucks, UK). The sensitivity of the test was 0.3 ng/mL. Intra- and inter-assay coefficients of variation were 3.1% and 9.5%, respectively. MMP-8 was used to assess the presence of intra-amniotic inflammation because previous studies indicated that it is a sensitive and specific index of inflammation [3, 23, 31]. Intra-amniotic inflammation was defined as an elevated AF MMP-8 concentration (>23 ng/mL), as previously reported [23, 31]. Intra-amniotic infection/inflammation was defined as a positive AF culture and/or elevated AF MMP-8 concentration (>23ng/ml).

Amniotic fluid prostaglandins

AF was centrifuged and supernatants were stored at -70° until assayed. PGF_{2a} concentrations at 12,000 rpm for 10 minutes and the supernatant was collected and frozen. PGF_{2a} was measured with a commercially available enzyme-linked immunoassay (Assay Design, Inc, Ann Arbor, MI, USA). AF was assayed in duplicate samples. All assays were conducted by the same individual, blinded to the clinical information. The sensitivity of the assay was 7.7 pg/mL. Intra- and inter-assay coefficients of variation were 1.2% and 8.8%. High AF PGF_{2a} concentration was defined when AF PGF_{2a} concentration was ≥ 170 pg/mL. This was based upon our previous report [18] that AF PGF_{2a} concentration of 170 pg/mL corresponds to the value of 95 percentile of AF PGF_{2a} concentration among pregnant women who were at 15–36 weeks of gestation and not in labor.

Statistical analysis

AF PGs concentrations were compared among groups with Kruskal-Wallis and Mann-Whitney U tests. The amniocentesis-to-delivery interval was compared using the generalized Wilcoxon test for survival analysis. The interval-to-delivery of patients delivered for maternal or fetal indications was treated as a censored observation, with a censoring time equal to the amniocentesis-to-delivery interval. A p-value <0.05 was considered statistically significant.

Results

Table 1 describes the clinical characteristics and pregnancy outcomes of the study population according to the results of AF culture and MMP-8 concentrations. Patients with intra-amniotic inflammation but with a negative AF culture (group 2) had a significantly lower median gestational age at amniocentesis as well as at delivery, a higher median WBC count and AF MMP-8 concentration, and a shorter interval-to-delivery than those with a negative AF culture without intra-amniotic inflammation (group 1). However, there were no significant differences in the clinical characteristics and pregnancy outcomes between cases with intra-amniotic inflammation and a negative AF culture (group 2) and those with proven AF infection (group 3).

Figure 1 shows that patients with a negative AF culture but with intra-amniotic inflammation (group 2) had a significantly higher median AF PGF_{2a} concentration than those with a negative AF culture, without intra-amniotic inflammation (group 1) (median, 206.2 pg/mL

[range, 26.1–38715.2 pg/mL] vs. median, 64.0 pg/mL [range, 7.7–2776.2 pg/mL], $p < 0.001$). However, there was no significant difference in the median AF PGF2a concentration between patients with intra-amniotic inflammation but a negative AF culture (group 2) and those with culture-proven AF infection (group 3) (median, 206.2 pg/mL [range, 26.1–38715.2 pg/mL] vs. median, 313.7 pg/mL [range, 40.5–8492.3 pg/mL], $p = 0.4$).

Table 2 describes the clinical characteristics and pregnancy outcomes of the patients according to the AF PGF2a concentrations. There was no significant difference in the gestational age at amniocentesis between groups. However, patients with a high AF PGF2a concentration (≥ 170 pg/mL) had a significantly lower median gestational age at delivery, a shorter interval-to-delivery, and a higher frequency of preterm delivery within 36 weeks than those patients with a low AF PGF2a concentration (< 170 pg/mL). Patients with a high AF PGF2a concentration had a higher median WBC count and AF MMP-8 concentration, a higher rate of a positive AF culture, intra-amniotic infection/inflammation and funisitis compared with those with a low AF PGF2a concentration.

Table 3 describes the relationship between AF PGF2a concentrations and the presence or absence of intra-amniotic infection/inflammation. Forty-two percent (59/140) of patients had intra-amniotic infection/inflammation defined as a positive AF culture and/or elevated AF MMP-8 concentration (> 23 ng/mL). Sixty-three percent (37/59) of patients with intra-amniotic infection/inflammation had an elevated AF PGF2a concentration (≥ 170 pg/mL), whereas those without intra-amniotic infection/inflammation had only 11% (9/81) ($p < 0.001$). An AF PGF2a concentration of ≥ 170 pg/mL had a sensitivity of 63% and a specificity of 89% in the identification of intra-amniotic infection/inflammation.

Figure 2 illustrates interval-to-delivery according to the concentration of AF PGF2a among patients with and without intra-amniotic infection/inflammation, respectively. Among patients with intra-amniotic infection/inflammation, those with a high AF PGF2a had a significantly shorter amniocentesis-to-delivery interval than those with a low AF PGF2a (median, 137 hours [range, 1–1587 hours] vs. median, 75 hours [range, 0–1849 hours], $p < 0.05$). Moreover, among patients without intra-amniotic infection/inflammation, those with a high AF PGF2a had a significantly shorter amniocentesis-to-delivery interval than those with a low AF PGF2a (median, 159 hours [range, 0–3545 hours] vs. median, 66 hours [range, 2–141 hours], $p < 0.001$). A high AF PGF2a concentration (≥ 170 pg/mL) was associated with a shorter amniocentesis-to-delivery than those with lower AF PGF2a concentrations after adjusting for gestational age and the presence of AF inflammation/infection (OR, 2.3; 95% CI, 1.4–4.0; $p < 0.005$).

Comment

Principal findings of this study

- 1) Intra-amniotic inflammation in preterm PROM was associated with an increased AF PGF2a concentration, regardless of the presence or absence of culture-proven AF infection;
- 2) an elevated AF PGF2a concentration (≥ 170 pg/mL) was present in 63% of cases with intra-amniotic infection/inflammation and in 11% of those without intra-amniotic infection/inflammation;
- 3) a high AF PGF2a concentration (≥ 170 pg/mL) was an independent risk

factor for impending delivery, not only among patients with intra-amniotic infection/inflammation, but also among cases without intra-amniotic infection/inflammation in preterm PROM.

Amniotic fluid prostaglandin, intra-amniotic infection and preterm birth

Substantial evidence indicates that PGs play a role in preterm birth associated with intra-amniotic infection [11, 13, 19, 26, 27, 29, 30]. Microbial products such as endotoxin or microorganisms can induce an immune response in fetal membranes [7, 16, 21, 24] and decidua [1, 21], and stimulate PG production. Indeed, there is evidence that patients with AF infection had significantly higher concentrations of AF PG compared with those with sterile AF [26, 27, 29, 30]. Our data, obtained from a larger cohort, is consistent with the previous study and extends the observations by exploring the relationship between intra-amniotic inflammation with negative AF cultures. Such study has not been reported before.

An increase of amniotic fluid PG in the absence of culture-proven amniotic fluid infection

A novel finding of this study is that patients with intra-amniotic inflammation, even in the absence of proven AF infection, had a higher concentration of AF PGF2a than those without intra-amniotic infection/inflammation. Previous studies in vitro demonstrated that PG production was induced by pro-inflammatory cytokines (e.g., interleukin-1 beta, tumor necrosis factor-alpha) [7, 21]. Previous studies showed that the intensity of the intra-amniotic inflammatory process (measured by AF WBC count and AF MMP-8 concentration) was not different between patients with intra-amniotic inflammation and a negative culture and patients with culture-proven AF infection [17, 31]. Therefore, an increase of AF PG concentration in preterm PROM with intra-amniotic inflammation, even in the absence of a positive AF culture, is not an unexpected finding. Our data is the first evidence of an increase in PG AF concentrations in sterile AF in humans.

Why are amniotic fluid prostaglandin concentrations elevated in patients with intra-amniotic inflammation without culture-proven amniotic fluid infection?

One possibility is that infection is present but microorganisms escaped detection by traditional microbiological methods. Studies using molecular microbiology techniques indicate that culture methodology underestimates the frequency of infection of the amniotic cavity [20, 34]. Some cases with intra-amniotic inflammation and a negative AF culture may have an extra-amniotic intrauterine infection. Decidual colonization of microorganisms can induce an immune reaction and PG production from decidual cells [1, 2, 21].

Non-infection related causes of amniotic fluid prostaglandin production

The possibility that AF PG concentrations can be elevated by non-infection-related mechanisms must also be considered. Activation of the hypothalamic pituitary-adrenal (HPA) axis of the fetus leads to an increase in fetal cortisol secretion and ultimately an increase in PGF2a production [5, 9, 14, 22, 33]. The fetus would activate the HPA axis in response to stress caused by inflammation or other pathologic processes [5, 33]. Moreover, CRH, produced in the placenta in response to maternal [12] and fetal [5, 33] stress, stimulates PG production from the fetal membranes. Even in normal term parturition, an

abrupt increase of AF PGF2a concentrations (25 fold) occurs before the onset of spontaneous labor [18].

Our study indicates that 11% of patients without intra-amniotic infection/inflammation, had a high level of AF PGF2a concentration (Table 3), and these patients had a shorter interval-to-delivery than those who had a lower concentration of AF PGF2a (Figure 2). These findings suggest that AF PGF2a can be elevated in cases with neither infection nor inflammation.

Interval to delivery

PGs can induce increased uterine contractility and cervical ripening in animals and humans. Therefore, PGs have been proposed to be part of the common pathway of parturition, regardless of the cause (physiologic parturition or pathologic parturition). Our data indicates that a high AF PGF2a concentration is a risk factor for impending delivery in patients without intra-amniotic infection/inflammation as well as in those with intra-amniotic infection/inflammation in preterm PROM. Moreover, a high AF PGF2a was a significant predictor of the duration of pregnancy after adjusting for gestational age. We propose that once AF PGF2a increased, regardless of cause or gestational age, the ruptured fetal membranes should be easy to allow PGF2a to reach the decidua and myometrium and to initiate a preterm labor. Further studies are required to determine if the interval-to-delivery in patients with intact membranes is longer than that in patients with ruptured membranes among cases with increased AF PG concentration. Such studies are now in progress to examine this question.

Clinical implication

The major implication of our study is that the assessment of AF PGF2a concentration has prognostic value in preterm PROM. Currently, studies of AF in preterm PROM have been limited to the determination of AF inflammatory markers, infection and fetal lung maturity [4, 15, 32]. We propose that the determination of AF PGF2a concentration could have prognostic value in patients presenting with preterm PROM.

Acknowledgments

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AF PGF2a concentration (pg/mL)

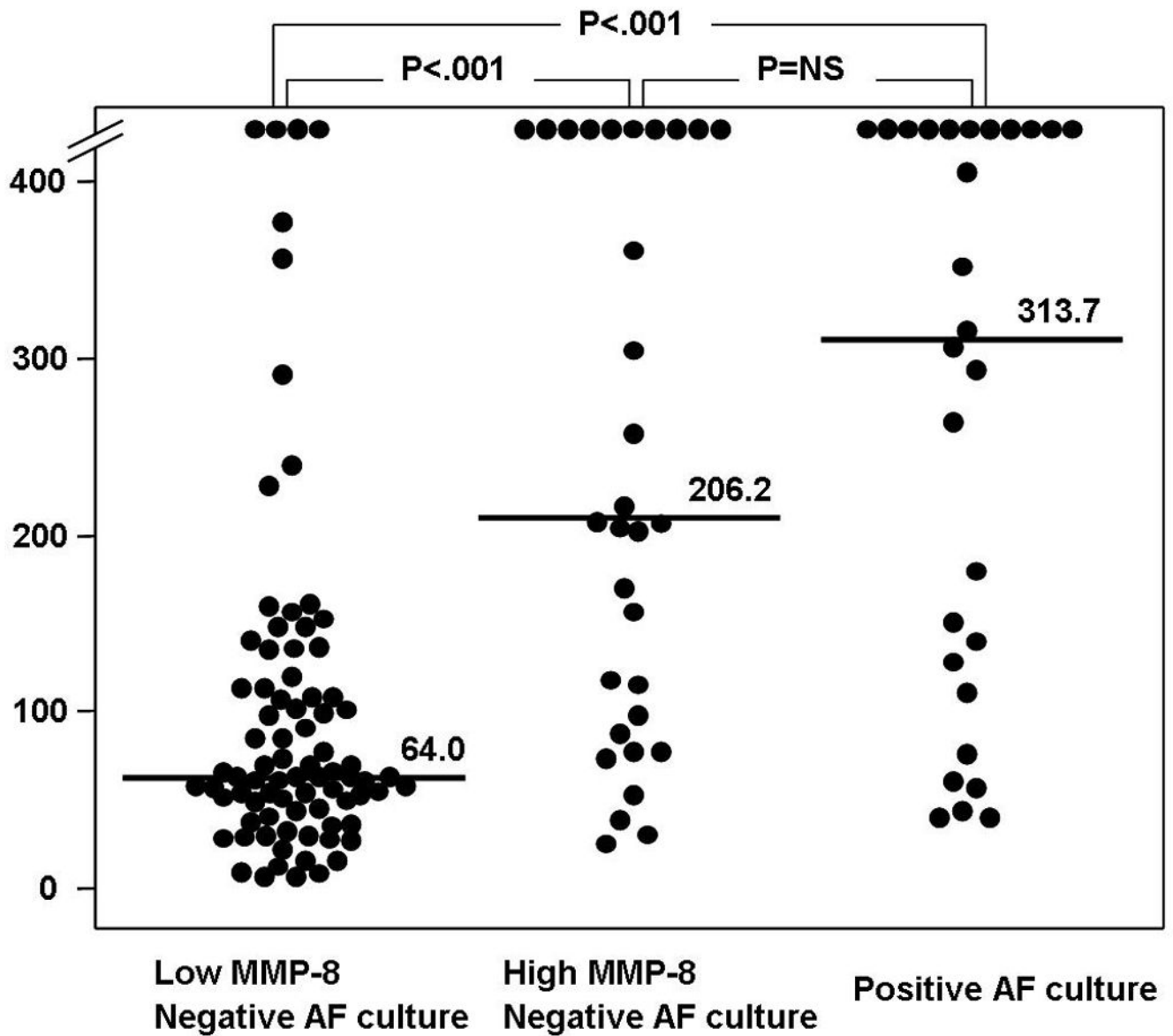


Figure 1. Amniotic fluid (AF) prostaglandin F2a (PGF2a) concentrations according to the results of AF culture and AF MMP-8 concentrations (group 1: median, 64.0 pg/mL [range, 7.7–2776.2 pg/mL]; group 2: median, 206.2 pg/mL [range, 26.1–38715.2 pg/mL]; group 3: median, 313.7 pg/mL [range, 40.5–8492.3 pg/mL]; p<0.001, by Kruskal-Wallis ANOVA test).

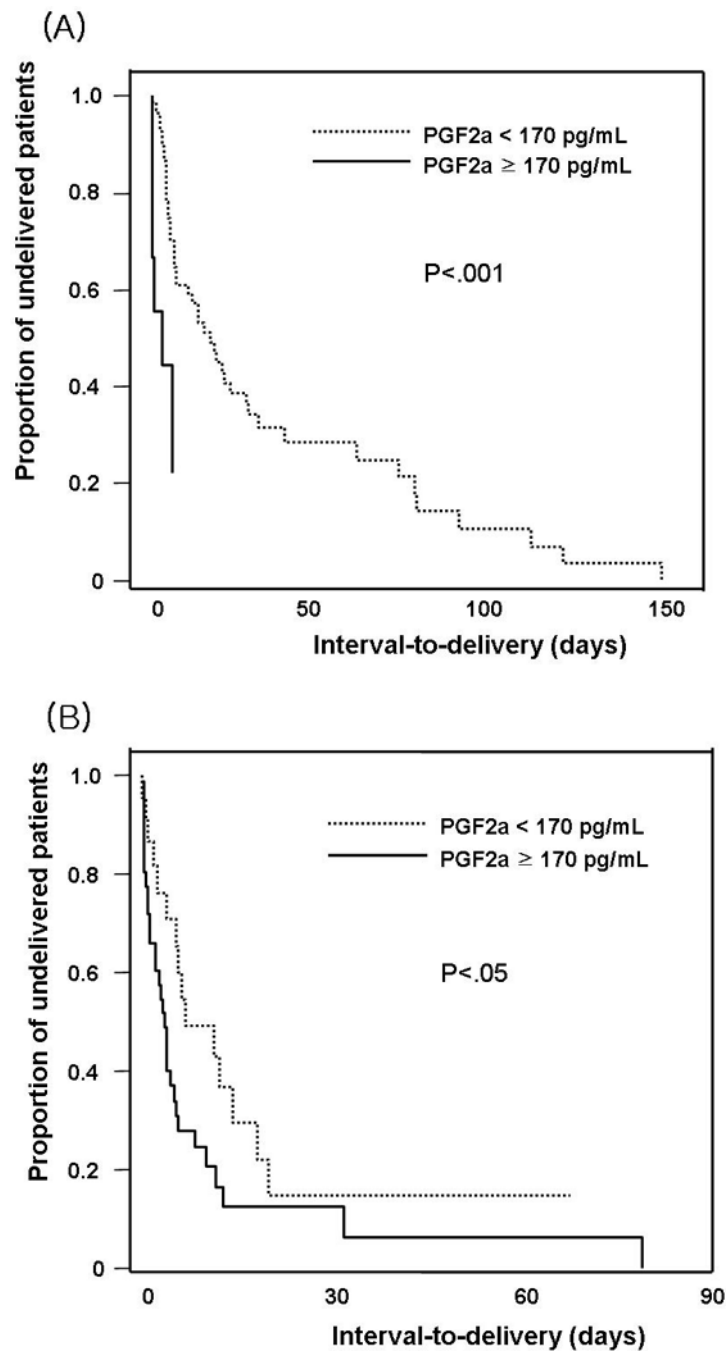


Figure 2. Survival analysis of the interval-to-delivery according to the concentration of AF PGF2a; (A) among patients without intra-amniotic infection/inflammation: median, 159 hours [range, 0–3545 hours] vs. median, 66 hours [range, 2–141 hours], $p < 0.001$; (B) among patients with intra-amniotic infection/inflammation: median, 137 hours [range, 1–1587 hours] vs. median, 75 hours [range, 0–1849 hours], $p < 0.05$.

Clinical characteristics and pregnancy outcomes of the study population according to the results of AF culture and MMP-8 concentrations

Table 1

	(-) AF culture Low MMP-8 (group 1; n=81)	P*	(-) AF culture High MMP-8 (group 2; n=31)	P [†]	(+) AF culture (group 3; n=28)	P [‡]
Maternal age (y)	30 (21–45)	NS	31 (23–39)	NS	29 (24–37)	NS
Nulliparity (n)	40 (49%)	NS	9 (29%)	NS	9 (32%)	NS
GA at amniocentesis (week) [#]	33.3 (20.4–35.0)	<001	29.7 (21.3–34.7)	NS	29.6 (21.6–34.3)	<001
GA at delivery (week) [#]	34.7 (23.7–41.6)	<001	30.9 (22.3–35.7)	NS	30.0 (21.9–34.7)	<001
Amniocentesis-to-delivery interval (hour) [§]	141 (0–3545)	<005	46 (0–1849)	NS	116 (2–748)	<005
AF WBC (cells/mm ³) [#]	1 (0–250)	<001	153 (0–>1000)	NS	270 (0–>1000)	<001
AF MMP-8 (ng/mL) [#]	1.1 (0.3–22.3)	<001	211.8 (35.0–2874.5)	NS	119.3 (1.6–5019.5)	<001

Values are medians and ranges.

AF, amniotic fluid; MMP-8, matrix metalloproteinase-8; Low MMP-8, matrix metalloproteinase-8 <23 ng/mL; High MMP-8, matrix metalloproteinase-8 >23 ng/mL; GA, gestational age; NS, not significant; WBC, white blood cell

* Comparison between groups 1 and 2.

[†] Comparison between groups 2 and 3.

[‡] Comparison between groups 3 and 1.

[#] P<.05, by Kruskal-Wallis ANOVA test

[§] Compared by generalized Wilcoxon test for survival analysis.

Table 2

Clinical characteristics and pregnancy outcomes of the patients according to the concentration of AF PGF2a

	Low PGF2a (n=94)	High PGF2a (n=46)	P
Maternal age (y)	30 (23–45)	30 (21–38)	NS
Nulliparity (n)	42 (45%)	16 (35%)	NS
GA at amniocentesis (week) [*]	32.6 (20.4–35.0)	30.5 (21.6–34.7)	NS
GA at delivery (week) [*]	34.3 (23.7–41.6)	31.5 (21.9–35.7)	<.001
Amniocentesis-to-delivery interval (hour) [†]	155 (0–3545)	72 (0–1849)	<.001
within 48 hours	14 (15%)	20 (44%)	<.001
within 7 days	52 (55%)	37 (80%)	<.005
Preterm delivery <36 weeks	80 (85%)	46 (100%)	<.005
Positive AF culture	10 (11%)	18 (39%)	<.001
Intraamniotic infection/inflammation [‡]	22 (23%)	37 (80%)	<.001
AF WBC (cells/mm ³) [*]	1 (0–621)	397 (0– >1000)	<.001
AF MMP-8 (ng/mL) [*]	1.8 (0.3–260.5)	267.0 (0.3–5019.5)	<.001
Clinical chorioamnionitis	4 (4%)	4 (9%)	NS
Histologic chorioamnionitis (n/N)	39/72 (54%)	24/36 (67%)	NS
Funisitis (n/N)	21/74 (28%)	20/36 (56%)	<.01

Values are medians and ranges.

AF, amniotic fluid; MMP-8, matrix metalloproteinase-8; Low PGF2a, PGF2a <170 pg/mL; High PGF2a, PGF2a ≥ 170 pg/mL; GA, gestational age; NS, not significant; WBC, white blood cell

^{*} P<.05, by Kruskal-Wallis ANOVA test

[†] Compared by generalized Wilcoxon test for survival analysis.

[‡] Intraamniotic infection/inflammation was defined as a positive AF culture and/or elevated AF MMP-8 concentration (>23ng/ml).

Table 3

AF PGF2a concentrations according to the presence or absence of intraamniotic infection/inflammation

	Intraamniotic infection/inflammation (-)	Intraamniotic infection/inflammation (+)	Total
Low PGF2a	72 (89%)	22 (37%)	94
High PGF2a	9 (11%)	37 (63%)	46
Total	81	59	140

P<.001, by Chi-square test; Intraamniotic infection/inflammation was defined as a positive AF culture and/or elevated AF MMP-8 concentration (>23ng/ml).

AF, amniotic fluid; Low PGF2a, PGF2a <170 pg/mL; High PGF2a, PGF2a ≥ 170 pg/mL

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