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The amniotic fluid prostaglandin $F_{2\alpha}$ concentration in patients with preterm labor

조기진통 환자에서 양수 내 프로스타글란딘 $F_{2\alpha}$의 농도

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The amniotic fluid prostaglandin $F_{2\alpha}$ concentration in patients with preterm labor

by

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Abstract

Objective: To determine if 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.

Methods: A retrospective cohort study was performed including 132 singleton pregnancies with preterm labor and intact membranes (<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 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 for amniotic fluid $PGF_{2\alpha}$ concentrations 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% (53/132) in patients with preterm labor and intact membranes; (2) patients with an elevated amniotic fluid $PGF_{2\alpha}$ concentration

had significantly higher rates of a 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 as well as funisitis, higher median amniotic fluid MMP-8 concentration and amniotic fluid white blood cell count, and shorter amniocentesis-to-delivery interval than those without an elevated amniotic fluid $PGF_{2\alpha}$ ($p<0.05$ for each); and (3) an elevated amniotic fluid $PGF_{2\alpha}$ 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].

Conclusions: The concentration of $PGF_{2\alpha}$ was elevated in the amniotic fluid of 40% 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: Preterm labor, prostaglandin, intra-amniotic inflammation, intra-amniotic infection, preterm birth, histologic chorioamnionitis, funisitis

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CONTENTS

LIST OF TABLES

LIST OF FIGURES

Introduction

Preterm birth is the leading cause of perinatal morbidity and mortality worldwide and remains a major obstetrical challenge [1-5]. Two-thirds of all preterm births result from spontaneous preterm labor [6] which is a syndrome [7-9] characterized by the combination of increased uterine contractility [10], cervical remodeling [11-15] and/or activation of the chorioamniotic membranes and decidua [16-19].

The diagnosis, treatment and prevention of spontaneous preterm birth have been a major focus of attention in contemporary obstetrics and perinatal medicine [20-21]. Biomarkers for the diagnosis of preterm labor and impending preterm delivery are desirable because they would allow rational allocation of resources and can influence management (e.g. admission to the hospital, administration of steroids, transfer to a tertiary care center, etc.). This has been the basis for the use of cervical length [22-24], fetal fibronectin [25-29], alpha-macroglobulin-1 [30-32], insulin-like growth factor binding protein-1 [33-36], and the concentrations of inflammatory mediators in amniotic fluid [37-50]/cervicovaginal fluid [51-60] in patients presenting with increased uterine contractility or suspected preterm labor.

Prostaglandins are considered the mediators of parturition [61-79] and they can stimulate myometrial contractility [80-92] in the first, second and third trimester (unlike oxytocin), induce cervical remodeling [93-102] and participate in extracellular matrix degradation leading to rupture of

membranes [103-111]. The main prostaglandins found in amniotic fluid are prostaglandin E_2 (PGE_2) and prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) [112-113]. The concentrations of these eicosanoids increase prior to the onset of labor at term [70, 74, 76], during labor [113] and rupture of membranes [66], as well as in spontaneous preterm labor [particularly in the setting of microbial invasion of the amniotic cavity (MIAC)] [63-65, 71, 107]. 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 [63-65, 71, 107].

We have previously reported that the amniotic fluid concentrations of $PGF_{2\alpha}$ in women with preterm prelabor rupture of membranes (PROM) was associated with intra-amniotic inflammation and short latency period [107]. Specifically, an amniotic fluid concentration of $PGF_{2\alpha}$ $\geq$170 pg/mL was a predictor of pregnancy duration after adjusting for gestational age and the presence of amniotic fluid inflammation/infection [107]. Thus the objective of this study was to determine whether amniotic fluid concentrations of $PGF_{2\alpha}$ have diagnostic and prognostic value in patients with preterm labor and intact membranes.

Methods

1. Study design

This was a retrospective cohort study which included patients with singleton gestations admitted to the Seoul National University Hospital with the diagnosis of preterm labor and intact membranes. The diagnosis of this condition was made if the following criteria were met: 1) gestational age between 20 weeks and 35 weeks; 2) regular uterine contractions – eight or more in 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 a written informed consent was obtained. The Institutional Review Board of the Seoul National University Hospital approved the collection and use of these samples and clinical information for research purposes.

2. 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 for white blood cell count determination. Amniotic fluid not used for studies was centrifuged and stored in polypropylene tubes at -70°C until assayed. $PGF_{2\alpha}$ concentrations were measured with a commercially available enzyme-linked 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 intra- and inter-assay coefficients of variation were <10%.

3. Intra-amniotic inflammation and an elevated amniotic fluid $PGF_{2\alpha}$

The presence of intra-amniotic inflammation was defined as an elevation of amniotic fluid MMP-8 concentration (>23 ng/mL), as previously reported [114]. An elevated amniotic fluid $PGF_{2\alpha}$ concentration was defined as ≥170 pg/mL. This is based on our previous study which reported that amniotic fluid $PGF_{2\alpha}$ concentration of 170 pg/mL corresponded to the value at the 95^{th} percentile for amniotic fluid $PGF_{2\alpha}$ concentrations among pregnant women with intact membranes not in labor between 15-36 weeks of gestation [76].

4. Diagnosis of funisitis, histologic and clinical chorioamnionitis

Placental tissue samples were obtained for histopathologic evaluation and were fixed in 10% neutral buffered formalin followed by embedding in paraffin. Sections of blocks were stained with Hematoxylin and Eosin. Pathologists were blinded to the clinical information. Funisitis was diagnosed in the presence of neutrophil infiltration into the umbilical vessel walls or

Wharton's jelly [114-115]. Acute histologic chorioamnionitis was diagnosed in the presence of acute inflammatory changes on any of tissue samples including amnion, chorion-decidua, umbilical cord, and chorionic plate [115]. Clinical chorioamnionitis was diagnosed by the presence of maternal fever (temperature >37.8°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/mm^3) [116-117].

5. Statistical analysis

The Continuous variables were compared between two groups that were divided according to the concentration of amniotic $PGF_{2\alpha}$ with the Mann-Whitney U test. Proportions were compared with 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 for maternal or fetal indications rather than spontaneous progression of labor was treated as censored data and censoring time was considered equal to the amniocentesis-to-delivery interval. Cox proportional hazard model was used to determine hazard ratio of amniocentesis-to-delivery interval according to amniotic fluid $PGF_{2\alpha}$ concentrations with adjustment of confounding factors. A p-value <0.05 was considered statistically significant. Analysis was performed by SPSS, version 21 (SPSS Inc., Chicago, IL, USA).

Results

1. Clinical characteristics and pregnancy outcomes of the study population

The prevalence of an elevated $PGF_{2\alpha}$ in amniotic fluid was 40.2% (53/132). Table 1 describes the clinical characteristics and pregnancy outcomes according to $PGF_{2\alpha}$ concentration in 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 $PGF_{2\alpha}$ had significantly lower median gestational age at delivery, higher rates of a positive amniotic fluid culture, intra-amniotic inflammation, clinical and histologic chorioamnionitis, funisitis as well as preterm delivery. A significantly higher median amniotic fluid MMP-8 concentration and white blood cell count were observed in patient with elevated amniotic fluid $PGF_{2\alpha}$ concentration when compared to those without an elevated concentration of amniotic fluid $PGF_{2\alpha}$ (p-value <0.05 for all) (see Table 1).

2. The amniocentesis-to-delivery interval according to the concentration of amniotic fluid $PGF_{2\alpha}$

Figure 1 demonstrates amniocentesis-to-delivery interval according to the concentration of amniotic fluid $PGF_{2\alpha}$. Patients with an elevated amniotic

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

3. Diagnostic indices and likelihood ratios of concentration of amniotic fluid $PGF_{2\alpha}$ for spontaneous preterm delivery

The diagnostic indices and likelihood ratios for spontaneous preterm delivery within 48 hours and 7 days of amniocentesis as well as spontaneous preterm delivery before 36 weeks 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 amniotic fluid $PGF_{2\alpha}$ concentration would have 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

1. Principal findings of this study

The principal findings of this study are: (1) The prevalence of an elevated $PGF_{2\alpha}$ concentration in amniotic fluid was 40% in patients with preterm labor and intact membranes; (2) an elevated amniotic fluid $PGF_{2\alpha}$ concentration is associated with intra-amniotic inflammation/infection, acute histologic chorioamnionitis and funisitis; and (3) patients with an elevated $PGF_{2\alpha}$ concentration ($\geq$170 pg/mL) have a shorter amniocentesis-to-delivery interval than those with a normal amniotic fluid $PGF_{2\alpha}$ concentration after adjustment for the presence of intra-amniotic inflammation/infection.

2. Prostaglandins in term and preterm labor

Prostaglandins, bioactive lipid mediators of arachidonic acid metabolism via the cyclooxygenase (COX) pathway, are known to play an important role in reproductive physiology [62, 68-60, 76, 77]. Increased expression of the inducible forms of cyclooxygenase and cyclooxygenase-2, in human amnion and other tissues are responsible for the increased biosynthesis of prostaglandins with the onset of labor [70, 74, 76, 113]. Previous studies have documented increased concentrations of the primary prostaglandins and their metabolites in labor at term [66, 67, 70, 71, 76, 82, 83], as well as in spontaneous preterm labor [63-65, 76, 107].

The premise for this study was that an elevated concentration of amniotic fluid prostaglandins is associated with the progression of the parturitional process and particularly in the context of intra-amniotic inflammation/infection. We found that an elevated amniotic fluid $PGF_{2\alpha}$ concentration was observed in 40% of patients with preterm labor and intact membranes and those patients with an elevated amniotic fluid $PGF_{2\alpha}$ 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 $PGF_{2\alpha}$ concentration.

What are the mechanisms responsible for an elevated $PGF_{2\alpha}$ concentration in amniotic fluid? Microbial invasion of the amniotic cavity results in the production of pro-inflammatory cytokines such as interleukin-1β and tumor necrosis factor-α, which can stimulate prostaglandin production by gestational tissues (amnion, chorion and decidua) [63-65, 103].

3. Clinical implications

A major challenge in clinical obstetrics is to identify 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 $PGF_{2\alpha}$ is related to the amniocentesis-to-delivery interval (see Figure 1B). However, the diagnostic indices for the identification of patients who delivered within 48 hours, 7 days or before 36 weeks of

gestation were not optimal (see Table 2). It is possible that $PGF_{2\alpha}$ can be a part of a multimarker panel to assess the likelihood of preterm delivery in such patients. Further research is required to identify additional biomarkers in patients with preterm labor without intra-amniotic inflammation/infection.

4. Strengths and limitations

The major strength of this study is its design (i.e. cohort study) and the inclusion of patients with preterm labor in whom the amniotic fluid status was assessed by measuring a marker of inflammation (MMP-8), performing culture for amniotic fluid microorganisms and systematic histopathologic examination of the placenta to determine the presence of acute histologic chorioamnionitis and funisitis. This study is unique in that such a multidimensional evaluation has not been performed before when assessing the potential value of eicosanoids. A limitation of this study is that we have used an immunoassay rather than a chemical assay for the determination of $PGF_{2\alpha}$. New developments in lipidomics have now made it possible to assess metabolites of multiple pathways of arachidonic acid (i.e. cyclooxygenase, lipoxygenase and epoxygenase) [78]. Further research could use lipidomics to identify biomarkers for intra-amniotic inflammation, intra-amniotic infection, sterile intra-amniotic inflammation and impending preterm delivery in patients with preterm labor.

Conclusion

An elevated amniotic fluid $PGF_{2\alpha}$ 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 adjustment for the presence of intra-amniotic inflammation/infection.

References

1. Beck S, Wojdyla D, Say L, Betran AP, Merialdi M, Requejo JH, et al. The worldwide incidence of preterm birth: a systematic review of maternal mortality and morbidity. Bulletin of the World Health Organization. 2010;88(1):31-8.

2. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet. 2012;379(9832):2162-72.

3. Guinsburg R, de Almeida MF, de Castro JS, Silveira RC, Caldas JP, Fiori HH, et al. Death or survival with major morbidity in VLBW infants born at Brazilian neonatal research network centers. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2015:1-5.

4. Esteves JS, de Sa RA, de Carvalho PR, Coca Velarde LG. Neonatal outcome in women with preterm premature rupture of membranes (PPROM) between 18 and 26 weeks. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2015:1-5.

5. Pugni L, Pietrasanta C, Acaia B, Merlo D, Ronchi A, Ossola MW, et al. Chorioamnionitis and neonatal outcome in preterm infants: a clinical

overview. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2015:1-5.

6. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet. 2008;371(9606):75-84.

7. Romero R, Dey SK, Fisher SJ. Preterm labor: one syndrome, many causes. Science. 2014;345(6198):760-5.

8. Romero R, Espinoza J, Kusanovic JP, Gotsch F, Hassan S, Erez O, et al. The preterm parturition syndrome. BJOG : an international journal of obstetrics and gynaecology. 2006;113 Suppl 3:17-42.

9. Romero R. Prenatal medicine: the child is the father of the man. 1996. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2009;22(8):636-9.

10. Renthal NE, Williams KC, Mendelson CR. MicroRNAs--mediators of myometrial contractility during pregnancy and labour. Nature reviews Endocrinology. 2013;9(7):391-401.

11. Maul H, Mackay L, Garfield RE. Cervical ripening: biochemical, molecular, and clinical considerations. Clin Obstet Gynecol. 2006;49(3):551-63.

12. Word RA, Li XH, Hnat M, Carrick K. Dynamics of cervical

remodeling during pregnancy and parturition: mechanisms and current concepts. Seminars in reproductive medicine. 2007;25(1):69-79.

13. House M, Kaplan DL, Socrate S. Relationships between mechanical properties and extracellular matrix constituents of the cervical stroma during pregnancy. Seminars in perinatology. 2009;33(5):300-7.

14. Timmons B, Akins M, Mahendroo M. Cervical remodeling during pregnancy and parturition. Trends in endocrinology and metabolism: TEM. 2010;21(6):353-61.

15. Gonzalez JM, Dong Z, Romero R, Girardi G. Cervical remodeling/ripening at term and preterm delivery: the same mechanism initiated by different mediators and different effector cells. PloS one. 2011;6(11):e26877.

16. Menon R, Fortunato SJ. Fetal membrane inflammatory cytokines: a switching mechanism between the preterm premature rupture of the membranes and preterm labor pathways. Journal of perinatal medicine. 2004;32(5):391-9.

17. Moore RM, Mansour JM, Redline RW, Mercer BM, Moore JJ. The physiology of fetal membrane rupture: insight gained from the determination of physical properties. Placenta. 2006;27(11-12):1037-51.

18. Menon R, Fortunato SJ. Infection and the role of inflammation in preterm premature rupture of the membranes. Best practice & research Clinical obstetrics & gynaecology. 2007;21(3):467-78.

19. Lannon SM, Vanderhoeven JP, Eschenbach DA, Gravett MG, Adams

Waldorf KM. Synergy and interactions among biological pathways leading to preterm premature rupture of membranes. Reprod Sci. 2014;21(10):1215-27.

20. Iams JD. Clinical practice. Prevention of preterm parturition. The New England journal of medicine. 2014;370(3):254-61.

21. Dudenhausen JW. Primary prevention of preterm birth. Journal of perinatal medicine. 2014;42(4):431-3.

22. Hassan SS, Romero R, Vidyadhari D, Fusey S, Baxter JK, Khandelwal M, et al. Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicenter, randomized, double-blind, placebo-controlled trial. Ultrasound in obstetrics & gynecology. 2011;38(1):18-31.

23. Romero R, Yeo L, Chaemsaithong P, Chaiworapongsa T, Hassan SS. Progesterone to prevent spontaneous preterm birth. Seminars in fetal & neonatal medicine. 2014;19(1):15-26.

24. Hiersch L, Yogev Y, Domniz N, Meizner I, Bardin R, Melamed N. The role of cervical length in women with threatened preterm labor: is it a valid predictor at any gestational age? American journal of obstetrics and gynecology. 2014;211(5):532 e1-9.

25. Lockwood CJ, Senyei AE, Dische MR, Casal D, Shah KD, Thung SN, et al. Fetal fibronectin in cervical and vaginal secretions as a predictor of preterm delivery. New England journal of medicine. 1991;325(10):669-74.

26. Chandiramani M, Di Renzo GC, Gottschalk E, Helmer H, Henrich W, Hoesli I, et al. Fetal fibronectin as a predictor of spontaneous preterm birth: a

European perspective. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2011;24(2):330-6.

27. Abbott DS, Radford SK, Seed PT, Tribe RM, Shennan AH. Evaluation of a quantitative fetal fibronectin test for spontaneous preterm birth in symptomatic women. American journal of obstetrics and gynecology. 2013;208(2):122 e1-6.

28. DeFranco EA, Lewis DF, Odibo AO. Improving the screening accuracy for preterm labor: is the combination of fetal fibronectin and cervical length in symptomatic patients a useful predictor of preterm birth? A systematic review. American journal of obstetrics and gynecology. 2013;208(3):233 e1-6.

29. Boots AB, Sanchez-Ramos L, Bowers DM, Kaunitz AM, Zamora J, Schlattmann P. The short-term prediction of preterm birth: a systematic review and diagnostic metaanalysis. American journal of obstetrics and gynecology. 2014;210(1):54 e1- e10.

30. Lee SM, Romero R, Park JW, Kim SM, Park CW, Korzeniewski SJ, et al. The clinical significance of a positive Amnisure test in women with preterm labor and intact membranes. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2012;25(9):1690-8.

31. Sukchaya K, Phupong V. A comparative study of positive rate of placental alpha-microglobulin-1 test in pre-term pregnant women with and without uterine contraction. Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology. 2013;33(6):566-8.

32. Nikolova T, Bayev O, Nikolova N, Di Renzo GC. Evaluation of a novel placental alpha microglobulin-1 (PAMG-1) test to predict spontaneous preterm delivery. Journal of perinatal medicine. 2014;42(4):473-7.

33. Kekki M, Kurki T, Karkkainen T, Hiilesmaa V, Paavonen J, Rutanen EM. Insulin-like growth factor-binding protein-1 in cervical secretion as a predictor of preterm delivery. Acta obstetricia et gynecologica Scandinavica. 2001;80(6):546-51.

34. Elizur SE, Yinon Y, Epstein GS, Seidman DS, Schiff E, Sivan E. Insulin-like growth factor binding protein-1 detection in preterm labor: evaluation of a bedside test. Am J Perinatol. 2005;22(6):305-9.

35. Hadzi-Lega M, Markova AD, Stefanovic M, Tanturovski M. Correlation of cervical length, fetal fibronectin, phIGFBP-1, and cytokines in spontaneous preterm birth up to 14 days from sampling. Journal of perinatal medicine. 2014.

36. Conde-Agudelo A, Romero R. Cervical phosphorylated insulin-like growth factor binding protein-1 test for the prediction of preterm birth: a systematic review and metaanalysis. American journal of obstetrics and gynecology. 2015.

37. Maymon E, Romero R, Pacora P, Gomez R, Athayde N, Edwin S, et

al. Human neutrophil collagenase (matrix metalloproteinase 8) in parturition, premature rupture of the membranes, and intrauterine infection. American journal of obstetrics and gynecology. 2000;183(1):94-9.

38. Athayde N, Romero R, Maymon E, Gomez R, Pacora P, Yoon BH, et al. Interleukin 16 in pregnancy, parturition, rupture of fetal membranes, and microbial invasion of the amniotic cavity. American journal of obstetrics and gynecology. 2000;182(1 Pt 1):135-41.

39. Esplin MS, Romero R, Chaiworapongsa T, Kim YM, Edwin S, Gomez R, et al. Monocyte chemotactic protein-1 is increased in the amniotic fluid of women who deliver preterm in the presence or absence of intra-amniotic infection. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2005;17(6):365-73.

40. Figueroa R, Garry D, Elimian A, Patel K, Sehgal PB, Tejani N. Evaluation of amniotic fluid cytokines in preterm labor and intact membranes. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2005;18(4):241-7.

41. Nien JK, Yoon BH, Espinoza J, Kusanovic JP, Erez O, Soto E, et al. A rapid MMP-8 bedside test for the detection of intra-amniotic inflammation identifies patients at risk for imminent preterm delivery. American journal of

obstetrics and gynecology. 2006;195(4):1025-30.

42. Holst RM, Hagberg H, Wennerholm UB, Skogstrand K, Thorsen P, Jacobsson B. Prediction of spontaneous preterm delivery in women with preterm labor: analysis of multiple proteins in amniotic and cervical fluids. Obstetrics and gynecology. 2009;114(2 Pt 1):268-77.

43. Cobo T, Palacio M, Navarro-Sastre A, Ribes A, Bosch J, Filella X, et al. Predictive value of combined amniotic fluid proteomic biomarkers and interleukin-6 in preterm labor with intact membranes. American journal of obstetrics and gynecology. 2009;200(5):499 e1-6.

44. Yoneda S, Shiozaki A, Yoneda N, Shima T, Ito M, Yamanaka M, et al. Prediction of exact delivery time in patients with preterm labor and intact membranes at admission by amniotic fluid interleukin-8 level and preterm labor index. The journal of obstetrics and gynaecology research. 2011;37(7):861-6.

45. Park CW, Yoon BH, Park JS, Jun JK. An elevated maternal serum C-reactive protein in the context of intra-amniotic inflammation is an indicator that the development of amnionitis, an intense fetal and AF inflammatory response are likely in patients with preterm labor: clinical implications. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2013;26(9):847-53.

46. Hsu TY, Lin H, Lan KC, Ou CY, Tsai CC, Cheng BH, et al. High

interleukin-16 concentrations in the early second trimester amniotic fluid: an independent predictive marker for preterm birth. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2013;26(3):285-9.

47. Cift T, Uludag S, Aydin Y, Benian A. Effects of amniotic and maternal CD-146, TGF-beta1, IL-12, IL-18 and IFN-gamma, on adverse pregnancy outcome. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2013;26(1):21-5.

48. Chaemsaithong P, Romero R, Korzeniewski SJ, Dong Z, Yeo L, Hassan SS, et al. A point of care test for the determination of amniotic fluid interleukin-6 and the chemokine CXCL-10/IP-10. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2014:1-10.

49. Stampalija T, Chaiworapongsa T, Romero R, Tarca AL, Bhatti G, Chiang PJ, et al. Soluble ST2, a modulator of the inflammatory response, in preterm and term labor. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2014;27(2):111-21.

50. Jia X. Value of amniotic fluid IL-8 and Annexin A2 in prediction of preterm delivery in preterm labor and preterm premature rupture of membranes. The Journal of reproductive medicine. 2014;59(3-4):154-60.

51. Coleman MA, Keelan JA, McCowan LM, Townend KM, Mitchell MD. Predicting preterm delivery: comparison of cervicovaginal interleukin (IL)-1beta, IL-6 and IL-8 with fetal fibronectin and cervical dilatation. European journal of obstetrics, gynecology, and reproductive biology. 2001;95(2):154-8.

52. Lange M, Chen FK, Wessel J, Buscher U, Dudenhausen JW. Elevation of interleukin-6 levels in cervical secretions as a predictor of preterm delivery. Acta obstetricia et gynecologica Scandinavica. 2003;82(4):326-9.

53. Torbe A, Czajka R. Proinflammatory cytokines and other indications of inflammation in cervico-vaginal secretions and preterm delivery. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2004;87(2):125-30.

54. Jacobsson B, Mattsby-Baltzer I, Hagberg H. Interleukin-6 and interleukin-8 in cervical and amniotic fluid: relationship to microbial invasion of the chorioamniotic membranes. BJOG : an international journal of obstetrics and gynaecology. 2005;112(6):719-24.

55. Holst RM, Mattsby-Baltzer I, Wennerholm UB, Hagberg H, Jacobsson B. Interleukin-6 and interleukin-8 in cervical fluid in a population of Swedish women in preterm labor: relationship to microbial invasion of the

amniotic fluid, intra-amniotic inflammation, and preterm delivery. Acta obstetricia et gynecologica Scandinavica. 2005;84(6):551-7.

56. Yoneda S, Sakai M, Sasaki Y, Shiozaki A, Hidaka T, Saito S. Interleukin-8 and glucose in amniotic fluid, fetal fibronectin in vaginal secretions and preterm labor index based on clinical variables are optimal predictive markers for preterm delivery in patients with intact membranes. The journal of obstetrics and gynaecology research. 2007;33(1):38-44.

57. Brik M, Antonio P, Perales-Puchalt A, Diago V, Perales A. Cervical interleukin-6 as a predictive test for preterm delivery in symptomatic women: preliminary results. European journal of obstetrics, gynecology, and reproductive biology. 2011;155(1):14-8.

58. Perales-Puchalt A, Brik M, Diago VJ, Perales A. The negative predictive value of cervical interleukin-6 for the risk assessment of preterm birth. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2013;26(13):1278-81.

59. Brik M, Aguar M, Valiente A, Perales A. Cervical IL-6 and pIGFBP-1 and the prediction of neonatal outcome in symptomatic preterm labour. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2014;27(12):1241-7.

60. Combs CA, Garite TJ, Lapidus JA, Lapointe JP, Gravett M, Rael J, et al. Detection of microbial invasion of the amniotic cavity by analysis of cervicovaginal proteins in women with preterm labor and intact membranes. American journal of obstetrics and gynecology. 2015;212(4):482 e1- e12.

61. Karim SM. The role of prostaglandins in human parturition. Proc R Soc Med. 1971;64(1):10-2.

62. Mitchell MD. Prostaglandins during pregnancy and the perinatal period. J Reprod Fertil. 1981;62(1):305-15.

63. Romero R, Emamian M, Wan M, Quintero R, Hobbins JC, Mitchell MD. Prostaglandin concentrations in amniotic fluid of women with intra-amniotic infection and preterm labor. American journal of obstetrics and gynecology. 1987;157(6):1461-7.

64. Romero R, Wu YK, Mazor M, Hobbins JC, Mitchell MD. Amniotic fluid prostaglandin E2 in preterm labor. Prostaglandins Leukot Essent Fatty Acids. 1988;34(3):141-5.

65. Romero R, Wu YK, Sintori M, Oyarzun E, Mazor M, Hobbins JC, et al. Amniotic fluid concentrations of prostaglandin F2 alpha, 13,14-dihydro-15-keto-prostaglandin F2 alpha (PGFM) and 11-deoxy-13,14-dihydro-15-keto-11, 16-cyclo-prostaglandin E2 (PGEM-LL) in preterm labor. Prostaglandins. 1989;37(1):149-61.

66. Romero R, Baumann P, Gomez R, Salafia C, Rittenhouse L, Barberio D, et al. The relationship between spontaneous rupture of membranes, labor, and microbial invasion of the amniotic cavity and amniotic fluid

concentrations of prostaglandins and thromboxane B2 in term pregnancy. American journal of obstetrics and gynecology. 1993;168(6 Pt 1):1654-64; discussion 64-8.

67. Romero R, Baumann P, Gonzalez R, Gomez R, Rittenhouse L, Behnke E, et al. Amniotic fluid prostanoid concentrations increase early during the course of spontaneous labor at term. American journal of obstetrics and gynecology. 1994;171(6):1613-20.

68. Romero R, Gonzalez R, Baumann P, Behnke E, Rittenhouse L, Barberio D, et al. Topographic differences in amniotic fluid concentrations of prostanoids in women in spontaneous labor at term. Prostaglandins Leukot Essent Fatty Acids. 1994;50(2):97-104.

69. Mitchell MD, Romero RJ, Edwin SS, Trautman MS. Prostaglandins and parturition. Reproduction, fertility, and development. 1995;7(3):623-32.

70. Romero R, Munoz H, Gomez R, Parra M, Polanco M, Valverde V, et al. Increase in prostaglandin bioavailability precedes the onset of human parturition. Prostaglandins Leukot Essent Fatty Acids. 1996;54(3):187-91.

71. Gibb W. The role of prostaglandins in human parturition. Annals of medicine. 1998;30(3):235-41.

72. Challis JR, Sloboda DM, Alfaidy N, Lye SJ, Gibb W, Patel FA, et al. Prostaglandins and mechanisms of preterm birth. Reproduction. 2002;124(1):1-17.

73. Olson DM. The role of prostaglandins in the initiation of parturition. Best practice & research Clinical obstetrics & gynaecology. 2003;17(5):717-

30.

74. Mitchell MD, Chang MC, Chaiworapongsa T, Lan HY, Helliwell RJ, Romero R, et al. Identification of 9alpha,11beta-prostaglandin F2 in human amniotic fluid and characterization of its production by human gestational tissues. The Journal of clinical endocrinology and metabolism. 2005;90(7):4244-8.

75. Challis JR, Bloomfield FH, Bocking AD, Casciani V, Chisaka H, Connor K, et al. Fetal signals and parturition. The journal of obstetrics and gynaecology research. 2005;31(6):492-9.

76. Lee SE, Romero R, Park IS, Seong HS, Park CW, Yoon BH. Amniotic fluid prostaglandin concentrations increase before the onset of spontaneous labor at term. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2008;21(2):89-94.

77. Vidaeff AC, Ramin SM. Potential biochemical events associated with initiation of labor. Curr Med Chem. 2008;15(6):614-9.

78. Maddipati KR, Romero R, Chaiworapongsa T, Zhou SL, Xu Z, Tarca AL, et al. Eicosanomic profiling reveals dominance of the epoxygenase pathway in human amniotic fluid at term in spontaneous labor. FASEB journal : official publication of the Federation of American Societies for Experimental Biology. 2014;28(11):4835-46.

79. Sykes L, MacIntyre DA, Teoh TG, Bennett PR. Anti-inflammatory

prostaglandins for the prevention of preterm labour. Reproduction. 2014;148(2):R29-40.

80. Kirton KT, Wyngarden LJ, Bergstrom KK. Prostaglandins and myometrial contractility. Adv Biosci. 1973;9:651-5.

81. Novy MJ, Thomas CL, Lees MH. Uterine contractility and regional blood flow responses to oxytocin and prostaglandin E2 in pregnant rhesus monkeys. American journal of obstetrics and gynecology. 1975;122(4):419-33.

82. Wikland M, Lindblom B, Wilhelmsson L, Wiqvist N. Oxytocin, prostaglandins, and contractility of the human uterus at term pregnancy. Acta obstetricia et gynecologica Scandinavica. 1982;61(5):467-72.

83. Rydnert J, Joelsson I. Effect of the naturally occurring prostaglandins E2 and F2 alpha on the human myometrium in vivo during pregnancy. Acta obstetricia et gynecologica Scandinavica. 1985;64(7):577-82.

84. Wiqvist N, Bryman I, Lindblom B, Norstrom A, Wikland M. The role of prostaglandins for the coordination of myometrial forces during labour. Acta Physiol Hung. 1985;65(3):313-22.

85. Astle S, Thornton S, Slater DM. Identification and localization of prostaglandin E2 receptors in upper and lower segment human myometrium during pregnancy. Mol Hum Reprod. 2005;11(4):279-87.

86. Woodcock NA, Taylor CW, Thornton S. Prostaglandin F2alpha increases the sensitivity of the contractile proteins to Ca2+ in human myometrium. American journal of obstetrics and gynecology. 2006;195(5):1404-6.

87. Olson DM, Ammann C. Role of the prostaglandins in labour and prostaglandin receptor inhibitors in the prevention of preterm labour. Front Biosci. 2007;12:1329-43.

88. Hurd WW, Gibbs SG, Rudinsky KA. Differential regulation of myometrial prostaglandin production by changes in length. American journal of obstetrics and gynecology. 2008;198(2):225 e1-4.

89. Durn JH, Marshall KM, Farrar D, O'Donovan P, Scally AJ, Woodward DF, et al. Lipidomic analysis reveals prostanoid profiles in human term pregnant myometrium. Prostaglandins Leukot Essent Fatty Acids. 2010;82(1):21-6.

90. Arulkumaran S, Kandola MK, Hoffman B, Hanyaloglu AC, Johnson MR, Bennett PR. The roles of prostaglandin EP 1 and 3 receptors in the control of human myometrial contractility. The Journal of clinical endocrinology and metabolism. 2012;97(2):489-98.

91. Chiossi G, Costantine MM, Bytautiene E, Kechichian T, Hankins GD, Sbrana E, et al. The effects of prostaglandin E1 and prostaglandin E2 on in vitro myometrial contractility and uterine structure. Am J Perinatol. 2012;29(8):615-22.

92. Conde-Agudelo A, Nieto A, Rosas-Bermudez A, Romero R. Misoprostol to reduce intraoperative and postoperative hemorrhage during cesarean delivery: a systematic review and metaanalysis. American journal of obstetrics and gynecology. 2013;209(1):40 e1- e17.

93. Keirse MJ, Thiery M, Parewijck W, Mitchell MD. Chronic

stimulation of uterine prostaglandin synthesis during cervical ripening before the onset of labor. Prostaglandins. 1983;25(5):671-82.

94. Norman M, Ekman G, Malmstrom A. Prostaglandin E2-induced ripening of the human cervix involves changes in proteoglycan metabolism. Obstetrics and gynecology. 1993;82(6):1013-20.

95. Wing DA, Ham D, Paul RH. A comparison of orally administered misoprostol with vaginally administered misoprostol for cervical ripening and labor induction. American journal of obstetrics and gynecology. 1999;180(5):1155-60.

96. Ben-Aroya Z, Hallak M, Segal D, Friger M, Katz M, Mazor M. Ripening of the uterine cervix in a post-cesarean parturient: prostaglandin E2 versus Foley catheter. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2002;12(1):42-5.

97. Fujimoto T, Savani RC, Watari M, Day AJ, Strauss JF, 3rd. Induction of the hyaluronic acid-binding protein, tumor necrosis factor-stimulated gene-6, in cervical smooth muscle cells by tumor necrosis factor-alpha and prostaglandin E(2). Am J Pathol. 2002;160(4):1495-502.

98. Hertelendy F, Zakar T. Prostaglandins and the myometrium and cervix. Prostaglandins Leukot Essent Fatty Acids. 2004;70(2):207-22.

99. Tornblom SA, Patel FA, Bystrom B, Giannoulias D, Malmstrom A, Sennstrom M, et al. 15-hydroxyprostaglandin dehydrogenase and

cyclooxygenase 2 messenger ribonucleic acid expression and immunohistochemical localization in human cervical tissue during term and preterm labor. The Journal of clinical endocrinology and metabolism. 2004;89(6):2909-15.

100. Ji H, Dailey TL, Long V, Chien EK. Prostaglandin E2-regulated cervical ripening: analysis of proteoglycan expression in the rat cervix. American journal of obstetrics and gynecology. 2008;198(5):536 e1-7.

101. Kishore AH, Owens D, Word RA. Prostaglandin E2 regulates its own inactivating enzyme, 15-PGDH, by EP2 receptor-mediated cervical cell-specific mechanisms. The Journal of clinical endocrinology and metabolism. 2014;99(3):1006-18.

102. Timmons BC, Reese J, Socrate S, Ehinger N, Paria BC, Milne GL, et al. Prostaglandins are essential for cervical ripening in LPS-mediated preterm birth but not term or antiprogestin-driven preterm ripening. Endocrinology. 2014;155(1):287-98.

103. McLaren J, Taylor DJ, Bell SC. Prostaglandin E(2)-dependent production of latent matrix metalloproteinase-9 in cultures of human fetal membranes. Mol Hum Reprod. 2000;6(11):1033-40.

104. Ulug U, Goldman S, Ben-Shlomo I, Shalev E. Matrix metalloproteinase (MMP)-2 and MMP-9 and their inhibitor, TIMP-1, in human term decidua and fetal membranes: the effect of prostaglandin F(2alpha) and indomethacin. Mol Hum Reprod. 2001;7(12):1187-93.

105. Oger S, Mehats C, Dallot E, Cabrol D, Leroy MJ. Evidence for a role

of phosphodiesterase 4 in lipopolysaccharide-stimulated prostaglandin E2 production and matrix metalloproteinase-9 activity in human amniochorionic membranes. J Immunol. 2005;174(12):8082-9.

106. Makino S, Zaragoza DB, Mitchell BF, Robertson S, Olson DM. Prostaglandin F2alpha and its receptor as activators of human decidua. Seminars in reproductive medicine. 2007;25(1):60-8.

107. Lee SE, Park IS, Romero R, Yoon BH. Amniotic fluid prostaglandin F2 increases even in sterile amniotic fluid and is an independent predictor of impending delivery in preterm premature rupture of membranes. J Matern Fetal Neona. 2009;22(10):880-6.

108. Lee DC, Romero R, Kim JS, Yoo W, Lee J, Mittal P, et al. Evidence for a spatial and temporal regulation of prostaglandin-endoperoxide synthase 2 expression in human amnion in term and preterm parturition. The Journal of clinical endocrinology and metabolism. 2010;95(9):E86-91.

109. Rossi D, Pianta S, Magatti M, Sedlmayr P, Parolini O. Characterization of the conditioned medium from amniotic membrane cells: prostaglandins as key effectors of its immunomodulatory activity. PloS one. 2012;7(10):e46956.

110. Alzamil HA, Pawade J, Fortier MA, Bernal AL. Expression of the prostaglandin F synthase AKR1B1 and the prostaglandin transporter SLCO2A1 in human fetal membranes in relation to spontaneous term and preterm labor. Frontiers in physiology. 2014;5:272.

111. Phillips RJ, Fortier MA, Lopez Bernal A. Prostaglandin pathway

gene expression in human placenta, amnion and choriodecidua is differentially affected by preterm and term labour and by uterine inflammation. BMC pregnancy and childbirth. 2014;14:241..

112. Dray F, Frydman R. Primary prostaglandins in amniotic fluid in pregnancy and spontaneous labor. American journal of obstetrics and gynecology. 1976;126(1):13-9.

113. Nieder J, Augustin W. Increase of prostaglandin E and F equivalents in amniotic fluid during late pregnancy and rapid PG F elevation after cervical dilatation. Prostaglandins Leukot Med. 1983;12(3):289-97. Epub 1983/11/01.

114. Park JS, Romero R, Yoon BH, Moon JB, Oh SY, Han SY, et al. The relationship between amniotic fluid matrix metalloproteinase-8 and funisitis. American journal of obstetrics and gynecology. 2001;185(5):1156-61.

115. Yoon BH, Romero R, Kim CJ, Jun JK, Gomez R, Choi JH, et al. Amniotic fluid interleukin-6: a sensitive test for antenatal diagnosis of acute inflammatory lesions of preterm placenta and prediction of perinatal morbidity. American journal of obstetrics and gynecology. 1995;172(3):960-70.

116. Romero R, Chaemsaithong P, Korzeniewski SJ, Kusanovic JP, Docheva N, Martinez-Varea A, et al. Clinical chorioamnionitis at term III: how well do clinical criteria perform in the identification of proven intra-amniotic infection? Journal of perinatal medicine. 2015.

117. Gibbs RS. Diagnosis of intra-amniotic infection. Seminars in perinatology. 1977;1(1):71-7.

Table I. Clinical characteristics and pregnancy outcomes of the patients according to the $PGF_{2\alpha}$ concentration in amniotic fluid

	Low $PGF_{2\alpha}$ (n=79)	Elevated $PGF_{2\alpha}$ (n=53)	p-value
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 (cells/mm^3)★	0 (0-711)	3 (0->1000)	<0.001
Amniotic fluid MMP-8 (ng/mL)★	0.9 (0-829.9)	17.0 (0.1-3,929.0)	<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 (0-2,683.2)	37.0 (0.1-2,112.0)	<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 MMP-8=matrix metalloproteinase-8 ≤23 ng/mL; Elevated MMP-8=matrix metalloproteinase-8 >23 ng/mL; NS=not significant; $PGF_{2\alpha}$=Prostaglandin $F_{2\alpha}$; WBC=white blood cells.

Values are medians and ranges.

★ $p < 0.05$, by Mann-Whitney U test

† Compared by 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)

Table II. Diagnostic indices and likelihood ratios for spontaneous preterm delivery within 48 hours and 7 days of amniocentesis, and before 36 weeks of gestation

	Prevalence	Sensitivity % (n)	Specificity % (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)	2.60	0.44
sPTD within 7 days of amniocentesis	37.1% (49/132)	63.3% (31/49)	76.6% (49/64)	2.71	0.48
sPTD before 36 weeks	43.2% (57/132)	59.6% (34/57)	78.6% (44/56)	2.79	0.36

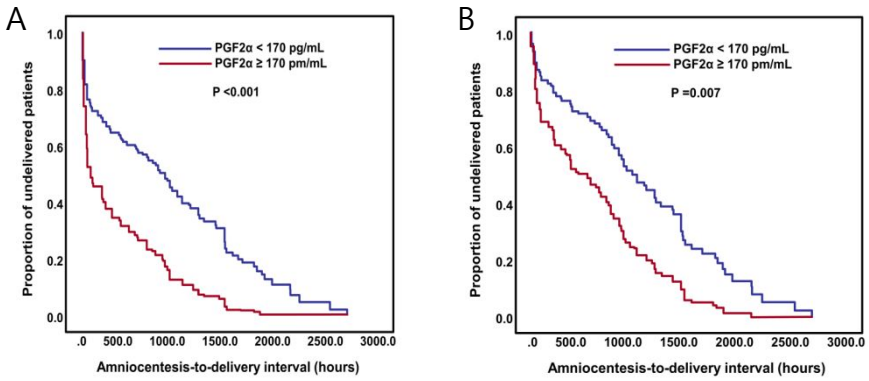
sPTD=spontaneous preterm delivery

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

	Prevalence	Sensitivity % (n)	Specificity % (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)	2.67	0.48
sPTD within 7 days of amniocentesis	17.8% (16/90)	56.3% (9/16)	77.6% (45/58)	2.51	0.56
sPTD before 36 weeks	23.3% (21/90)	52.4% (11/21)	79.2% (42/53)	2.52	0.60

sPTD=spontaneous preterm delivery

Figure 1. Survival analysis of the amniocentesis-to-delivery interval according to the concentration of amniotic fluid $PGF_{2\alpha}$



(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) only in patients without intra-amniotic inflammation/infection: median, 208.4 hours (range, 0.3-2112.0 hours) vs. median, 905.5 hours (range, 3.6-2683.2 hours), p=0.007

초 록

목적: 양막이 파열되지 않은 조기진통 환자에서 양수 내 프로스타글란딘 $F_{2\alpha}$ (Prostaglandin $F_{2\alpha}$, 이하 $PGF_{2\alpha}$)의 농도가 양수 내 염증/감염 및 부정적인 임신 결과와 어떠한 관련이 있는지 알아보고자 하였다.

방법: 양막이 파열되지 않은 조기진통으로 서울대학교 병원에 35주 이전에 입원한 단태아 임신 132례을 대상으로 후향적 코호트 연구를 시행하였다. 양수는 생식기 마이코플라즈마를 포함하여 세균 배양을 실시하였다. 양수 내 염증은 상승된 양수 내 metalloproteinase-8 (MMP-8) 농도로 정의하였다 (>23 ng/mL). $PGF_{2\alpha}$는 면역분석법으로 측정하였고, 15에서 36주 사이의 진통이 없는 산모의 양수 내 농도를 기준으로 95백분위보다 높은 경우 상승되어 있는 것으로 생각하였다 (≥170 pg/mL).

결과: 1) 조기진통 환자들에서 상승된 양수 내 $PGF_{2\alpha}$ 농도의 빈도는 40% (53/132) 였다. 2) 양수 내 $PGF_{2\alpha}$ 농도가 상승되어 있는 환자들의 경우 양수 배양검사가 양성인 비율[19% (10/53) vs. 5% (4/79); p=0.019], 양수 내 염증/감염이 있는 비율[49% (26/53) vs. 20% (16/79); p=0.001], 자연조산의 빈도, 임상적 그리고 병리학적 융모양막염과 태반 제대염의 빈도가 유의하게 높았다. 또한 양수 내 $PGF_{2\alpha}$ 농도가 상승되어 있는 환자들의 양수 내 MMP-8 농도의 중위값과 양수 내 백혈구의 숫자 중위값이 유의하게 높았고, 양수검사로부터 분만까지의 시간도 유의하게 짧았다 (모두 p<0.05). 3) 양수 내 $PGF_{2\alpha}$ 농도가 상승되어 있는 경우 양수 내

염증/감염의 유무로 보정을 한 뒤에도 더 짧은 양수검사로부터 분만까지의 시간과 관련이 있었다 [hazard ratio 2.1, 95% confidence interval (CI) 1.4-3.1; p=0.001].

결론: 양막 파열이 되지 않은 조기진통 환자들의 40%에서 양수 내 $PGF_{2\alpha}$의 농도가 증가되어 있었고, 이는 양수 내 염증/감염, 임박한 조산, 융모양막염과 태반 제대염의 독립적인 위험인자이다.

주요어: 조기진통, 프로스타글란딘, 양수 내 염증, 양수 내 감염, 조산, 융모양막염, 태반 제대염

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