Published in final edited form as:

J Matern Fetal Neonatal Med. 2016 ; 29(4): 523–531. doi:10.3109/14767058.2015.1011120.

Umbilical Cord Prostaglandins in Term and Preterm Parturition

J.-S. Hong[1,2], **R. Romero**[1,3,4,*], **D.-C. Lee**[1,5], **N. G. Than**[1,6], **L. Yeo**[1,6], **P. Chaemsaithong**[1,6], **S. Ahn**[7], **J.-S. Kim**[8], **C. J. Kim**[1,9], and **Y.M. Kim**[1,10,*]

[1]Perinatology Research Branch, NICHD/NIH/DHHS, Bethesda, Maryland, and Detroit, Michigan, 48201, USA

[2]Department of Obstetrics and Gynecology, Seoul National University Bundang Hospital, Gyeonggi-do, 463-707, Republic of Korea

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

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

[5]College of Biomedical Science, Kangwon National University, Chuncheon 200-701, Republic of Korea

[6]Department of Obstetrics and Gynecology, Wayne State University School of Medicine, Detroit, Michigan, 48201, USA

[7]Medical Research Collaborating Center, Seoul National University Bundang Hospital, Gyeonggi-do, 463-707, Republic of Korea

[8]Department of Pathology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, 440-746, Republic of Korea

[9]Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, 138-736, Republic of Korea

[10]Department of Pathology, Haeundae Paik Hospital, Inje University College of Medicine, Busan, 612-896, Republic of Korea

Abstract

Objective—Prostaglandins (PGs) are considered the universal mediators of parturition. Amniotic fluid PGE_2 and $PGF_{2\alpha}$ concentrations increase before the onset of spontaneous labor at term, as well as during labor. This study was conducted to determine if the concentrations of umbilical cord PGE_2 and $PGF_{2\alpha}$ change with advancing gestational age, spontaneous labor at term, and preterm labor (with and without funisitis).

Methods—Umbilical cord (UC) tissue samples were obtained from women (N=158) with singleton pregnancies in the following groups: 1) term deliveries without labor (TNL; n=20); 2)

*Correspondence: Roberto Romero, MD, D (Med) Sci, Perinatology Research Branch, NICHD, NIH, DHHS, Hutzel Women's Hospital, 3990 John R St, Detroit, MI 48201, USA. Tel: (313) 993 2700. Fax: (313) 993 2694. prbchiefstaff@med.wayne.edu. Yeon Mee Kim, MD, Department of Pathology, Haeundae Paik Hospital, Inje University College of Medicine, 875, Haeundae-ro, Haeundae-gu, Busan, 612-896, Korea, Tel: +82-51-797-3100. yki@med.wayne.edu.

Conflict of interest statement

The authors declare no conflicts of interest.

term deliveries with labor (TIL; n= 20); 3) spontaneous preterm deliveries (sPTD) with (n=20) and without acute funisitis (n=20); and 4) preeclampsia without labor (n=78). The concentrations of PGs were determined in different locations of the UC. PGE_2 and $PGF2_{2\alpha}$ were measured by specific immunoassays. Non-parametric statistics were used for analysis.

Results—1) In spontaneous preterm deliveries, the median UC PGE_2 concentration was higher in cases with funisitis than in those without funisitis (233.7 pg/μg vs. 87.4 pg/μg of total protein, p=0.001); 2) the median UC PGE_2 concentration in sPTD with funisitis was also higher than that obtained from samples who had undergone labor at term (233.7 pg/μg vs. 116.1 pg/μg of total protein, p=0.03); 3) the UC PGE_2 and $PGF_{2\alpha}$ concentration increased as a function of advancing gestational age before 36 weeks (PGE_2: rho = 0.59, p<0.001; $PGF_{2\alpha}$: rho=0.39, p=0.01), but not after 36 weeks (PGE_2: rho = −0.1, p=0.5; $PGF_{2\alpha}$: rho = −0.2, p=0.2); 4) the median UC concentrations of PGE_2 and $PGF_{2\alpha}$ at term was similar in samples obtained from women with and without labor (PGE_2: TNL 133.7 pg/μg vs. TIL 116.1 pg/μg of total protein, p=0.9; $PGF_{2\alpha}$: TNL 8.4 pg/μg vs. TIL 8.1 pg/μg of total protein, p=0.7); and 5) there was no correlation between UC PG concentration and gestational age at term pregnancy (PGE_2: rho = 0.01, p=0.9; $PGF_{2\alpha}$: rho = 0.07, p=0.7).

Conclusions—1) PGE_2 concentrations in the umbilical cord are higher in the presence of acute funisitis than in the absence of this lesion; 2) spontaneous labor at term was not associated with a change in the UC concentration of PGE_2 and $PGF_{2\alpha}$; and 3) the UC concentrations of PGE_2 and $PGF_{2\alpha}$ increased as a function of gestational age. We propose that UC PGs act as inflammatory mediators generated in the context of fetal systemic inflammation.

Keywords

chorioamnionitis; eicosanoids; funisitis; intra-amniotic inflammation; microbial invasion of the amniotic cavity (MIAC); PGE_2; $PGF_{2\alpha}$; preeclampsia; pregnancy

Introduction

Prostaglandins (PG) are considered key mediators of human parturition [1–19], and can induce myometrial contractility [20–34], cervical remodeling [35–58], and participate in extracellular matrix degradation leading to ruptured membranes [7,59–70]. The main PGs found in amniotic fluid are prostaglandin E_2 (PGE_2) and prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) [16,71–73], and concentrations of these eicosanoids increase prior to the onset of term labor [11,16,17], during labor [8,72], rupture of membranes at term [7], and in spontaneous preterm labor [particularly in the setting of microbial invasion of the amniotic cavity (MIAC)] [4–6,12,65,73–82].

The increased concentrations of PGs in amniotic fluid have been considered important in both normal labor at term [7,8,11,12,16,71,72,82–84], and preterm labor [4–6,16,65,73–78,81]. The amnion is an important source of PGs in the amniotic fluid [85–94]. This membrane can be anatomically divided into three distinct regions: the reflected, placental, and umbilical amnion [95–97]. Gene expression profile studies indicate that there are differences between placental and reflected amnion [97–100]. Indeed, we previously reported that the placental amnion is responsible for the tonic production of PGs with

advancing gestational age, while the reflected amnion increases the production of PGs during labor [66]. Such difference in PG production suggests that the placental amnion and the reflected amnion play different roles in the regulation of eicosanoids during pregnancy and labor [66].

The umbilical cord is a source of PGs [95,101–103]. PGE_2 and $PGF_{2\alpha}$ have been localized in the amniotic cells covering the umbilical cord and in the endothelium of the umbilical veins [103]. Furthermore, McCoshen et al. claimed that the umbilical cord is the major source of PGE_2 found in the amniotic fluid of women in labor at term [95]. However, incubation of a segment of the umbilical cord, as well as the placental and reflected amnion in a perfusion chamber, allowed demonstration of the PGE_2 output from the umbilical cord which did not change before or after labor, and the placental and reflected amnion PGE_2 output were two-fold greater in tissues collected after labor [95]. This observation suggests that the pattern of PG production by the umbilical cord is different from that of the reflected and placental amnion [95]. The current study is conducted to assess the concentrations of PGE_2 and $PGF_{2\alpha}$ in umbilical cord segments from women who had undergone labor at term, women delivered by cesarean section without labor, and a group who had preterm labor and delivery (with and without funisitis).

Materials and Methods

Tissue samples were retrieved from the Bank of Biological Specimens at the Perinatology Research Branch of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), National Institutes of Health (NIH), U.S. Department of Health and Human Services (DHHS), Detroit, Michigan. Samples were taken from the following clinical groups, all of whom had singleton gestations: 1) women at term not in labor (TNL; n=20); 2) women at term in labor (TIL; n= 20); 3) women with spontaneous preterm labor and delivery (sPTD; n=20) without acute funisitis; 4) women with sPTD with acute funisitis (n= 20); and 5) women with preeclampsia who underwent cesarean delivery without labor over a range of gestational ages (25–39 weeks; n=78). To compare the PG concentrations at different locations in a given cord, three samples from each umbilical cord (1 cm apart from umbilical cord insertion, 1 cm apart from the cord clamping, and mid-segment) were obtained from additional term delivery (n=10) cases. Samples of umbilical cord tissue were flash-frozen using liquid nitrogen, and stored at −80°C until use. All women provided written informed consent prior to the collection of samples, and the Institutional Review Boards of the NICHD and Wayne State University approved the collection and use of materials and clinical data for research purposes.

Clinical definitions

Gestational age was determined by the last menstrual period and confirmed by ultrasound examination, or by ultrasound examination alone if the sonographic determination of gestational age was not consistent with menstrual dating. Preterm labor was diagnosed by the presence of at least two regular uterine contractions every 10 minutes in association with cervical changes in patients with a gestational age between 20 and 36 6/7 weeks which led to preterm delivery (defined as birth prior to the 37th week of gestation). Spontaneous term

labor was defined as the presence of regular uterine contractions with a frequency of at least one every 10 min associated with cervical changes after 37 weeks of gestation. Funisitis was diagnosed in the presence of neutrophil infiltration into the umbilical vessel walls or Wharton's jelly, according to criteria previously published [104–109]. Preeclampsia was defined as new onset hypertension during pregnancy (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg on at least two occasions, 4 hours to 1 week apart) and proteinuria (≥300 mg in a 24-hour urine collection or one dipstick measurement ≥2+) [110].

Prostaglandins assays

Tissue samples were pulverized in liquid nitrogen using a mortar and pestle for protein isolation. Total protein lysates were obtained using T-PER® Tissue Protein Extraction Reagent with a protease inhibitor cocktail (Thermo Scientific, Rockford, IL, USA). To conduct the immunoassays for PGE_2 and $PGF_{2\alpha}$ content, 6.25 μg of total protein in 5 μl were added to 95 μl of assay buffer, and meclofenamic acid (10 μg/ml; Sigma-Aldrich Corporation, St. Louis, MO, USA) was added to all samples. The assays were performed using the Prostaglandin E_2 and Prostaglandin $F_{2\alpha}$ enzyme immunoassay kits (Assay Designs, Inc., Ann Arbor, MI, USA). The inter-assay coefficient of variation was 8.1%, and the intra-assay coefficient of variation was 6.7%.

Statistical Analyses

Pearson's chi-square test and Fisher's exact test were used to compare proportions for categorical variables, and the Mann-Whitney U test was used to compare medians for continuous variables. Spearman's correlation was used to examine the relationship between continuous variables such as gestational age at delivery and PG concentration. A repeated-measures ANOVA test was performed to compare PG concentrations in different locations within each umbilical cord. A piecewise linear regression was performed to detect a change point in PG concentrations in preeclampsia using the SiZer package in the R program (www.r-project.org). Other statistical analyses were conducted using the SPSS version 18.0 software (SPSS, Inc., Chicago, IL, USA).

Results

Prostaglandin concentration in the umbilical cord in term and preterm labor/delivery

The clinical characteristics of the study groups as well as umbilical concentrations of PGE_2 and $PGF_{2\alpha}$ are displayed in Table 1. The median umbilical cord concentrations of PGE_2 and $PGF_{2\alpha}$ were not different among women at term, according to whether the samples had been obtained in women who had undergone labor (PGE_2: TNL 133.7 pg/μg vs. TIL 116.1 pg/μg of total protein, p=0.9; $PGF_{2\alpha}$: TNL 8.4 pg/μg vs. TIL 8.1 pg/μg of total protein, p=0.7). The umbilical cord concentrations of PGE_2 and $PGF_{2\alpha}$ showed no correlation with gestational age at delivery in term pregnancies (PGE_2: rho = 0.01, p=0.9; $PGF_{2\alpha}$: rho = 0.07, p=0.7).

The median PGE_2 concentration in the umbilical cord of patients with spontaneous preterm delivery was significantly higher among patients with acute funisitis than in those without funisitis (233.7 vs. 87.4 pg/μg of total protein, p=0.001). The median $PGF_{2\alpha}$ umbilical cord

concentration was also higher in patients with funisitis than in those without funisitis (9.6 pg/μg vs. 7.1 pg/μg of total protein, p=0.051).

The umbilical cord concentration of PGE_2 (but not that of $PGF_{2\alpha}$) in cases of spontaneous preterm labor/delivery with funisitis was higher than that measured in cases who had undergone labor at term (PGE_2: 233.7 pg/μg vs. 116.1 pg/μg of total protein, p=0.03; $PGF_{2\alpha}$: 9.6 pg/μg vs. 8.1 pg/μg of total protein, p=0.3).

The concentration of prostaglandins in the umbilical cord during gestation

The evaluation of umbilical cord PG concentration is not possible in women with uncomplicated pregnancies. Therefore, we assembled a study group comprised of women with preeclampsia who underwent indicated cesarean delivery. Table 2 shows the clinical characteristics of patients with preeclampsia. All women with preeclampsia were delivered by cesarean in the absence of labor (n=78). None of the patients had acute histologic chorioamnionitis or funisitis after pathologic evaluation of the placenta. We found a positive correlation between PG concentrations in the umbilical cord and gestational age at delivery (PGE_2: rho = 0.60, P<0.001; $PGF_{2\alpha}$: rho = 0.35, P=0.002).

Since our findings showed that PG concentrations in the umbilical cord did not change with gestational age at term, we attempted to establish if there was a point of change in umbilical cord PG concentration in preeclampsia. A piecewise linear regression revealed that the slopes before 36 weeks provided an estimate of 20.1 pg/μg of total protein/week and 0.63 pg/μg of total protein/week – this difference was statistically significant for both PGE_2 and $PGF_{2\alpha}$. In both cases, the slopes after 36 weeks were estimated as −20.0 pg/μg of total protein/week and −0.53 pg/μg of total protein/week, but they were not significantly different from zero at a 5% significance level (Figure 1). These results indicate that the correlation between PG concentrations and gestational age changed significantly at about 36 weeks of gestation. Among patients with preeclampsia who were not in labor, there was an increase of PGE_2 and $PGF_{2\alpha}$ concentrations in the umbilical cord as a function of gestational age before 36 weeks (PGE_2: rho = 0.59, p<0.001; $PGF_{2\alpha}$: rho = 0.39, p=0.01) but not after 36 weeks (PGE_2: rho = −0.1, p=0.5; $PGF_{2\alpha}$: rho = −0.2, p=0.2).

A comparison of the concentrations of prostaglandins at different locations in the same umbilical cord

The concentrations of PGs at three different locations in the same umbilical cord were determined. Figure 2 illustrates concentrations of PGE_2 and $PGF_{2\alpha}$ at each umbilical cord sampling site. There was no significant difference in the concentrations of PGE_2 and $PGF_{2\alpha}$ among the three sampling sites (PGE_2 and $PGF_{2\alpha}$: p=0.7 and p=0.7, respectively).

Discussion

Principal findings of the study

1) The umbilical cord concentrations of $PGF_{2\alpha}$ and PGE_2 after spontaneous preterm labor with funisitis were significantly greater than in preterm labor without this lesion; 2) spontaneous labor at term was not associated with a change in the umbilical cord

concentrations of $PGF_{2\alpha}$ and PGE_2; and 3) among women who underwent a cesarean delivery without labor (because of preeclampsia), the umbilical cord concentrations of $PGF_{2\alpha}$ and PGE_2 increased as a function of advancing gestational age in the second and third trimesters.

Prostaglandins, different regions of the amnion, and the umbilical cord

Amniotic fluid PGs increase prior to the onset of labor [11,16,17] and further increase during labor [8,72]. The amnion is considered to be the main source of PGs (in particular, PGE_2) in the amniotic fluid [85,87–94]. The human amnion can be divided into three areas: 1) placental amnion; 2) reflected amnion; and 3) amnion covering the umbilical cord. The term “placental amnion” refers to that covering the chorionic plate of the placenta, while the reflected amnion is part of the extraplacental membranes. A small portion of amnion covers the surface of the umbilical cord [95–97]. McCoshen et al. proposed that each component of amnion contributes to the production of PGE_2, and that the umbilical cord is the major source of PG in the amniotic fluid in patients in labor at term [95]. This work was based on *in vitro* experiments in which the production of PGs by different types of amnion was studied, and calculations about the relative contribution of each type were made. The investigators reported that, before labor, the umbilical cord accounts for the greatest tissue mass (76%), compared to the placental amnion (14%) and reflected amnion (10%) [95]. They further claimed that the umbilical cord accounts for 66% of the total PGE_2 output before labor, and 44% after labor, proposing that the umbilical cord was the primary source of PGE_2 in the amniotic fluid [95].

Previously, we compared the expression of prostaglandin-endoperoxide synthase 2 (PTGS2), a key enzyme involved in PG production by amnion [111–114], in placenta vs. reflected amnion [66]. We reported that: 1) before the onset of labor, PTGS2 expression was greater in placental, rather than reflected, amnion; 2) after labor, there was a significant increase in PTGS2 expression in reflected, but not in placental, amnion; and 3) there was little expression of PTGS2 in preterm labor in the absence of acute inflammatory lesions [66].

Changes in umbilical cord prostaglandins with advancing gestational age, labor, and acute inflammatory lesions of the placenta

The results of the current study indicate that the umbilical cord concentrations of PGE_2 and $PGF_{2\alpha}$ increase with advancing gestational age. Such findings were based on studies of umbilical cord derived from patients with the diagnosis of preeclampsia who underwent cesarean delivery for obstetrical indications. It is noteworthy that the PG concentration increased until approximately 36 weeks of gestation, and there was no detectable increase thereafter. Labor at term was not associated with an increase in the PG concentration in the umbilical cord. However, in the presence of funisitis (acute inflammation of the umbilical cord), the prostaglandin concentration increased significantly in cases with spontaneous preterm labor.

Amniotic fluid prostaglandins with microbial invasion of the amniotic cavity

Amniotic fluid concentrations of eicosanoids and arachidonate lipoxygenase products are increased in the amniotic fluid of women with preterm labor and MIAC [4–6,59,74,75,82].

MIAC is frequently associated with acute histologic chorioamnionitis and funisitis [82,107,108,115–148]. Amniotic fluid PGs in cases of MIAC and/or intra-amniotic inflammation are thought to derive from amnion cells and local cells in the amniotic cavity, as well as from the human fetus. Microorganisms and their products (e.g. lipopolysaccharide endotoxin) could stimulate resident macrophages in the amniotic fluid, as well as fetal cells suspended in amniotic fluid or contained within fetal mucosa or skin to produce PGs which could be found in amniotic fluid. In a similar way, bacterial products could stimulate the amniotic epithelial cells surrounding the umbilical cord to produce PGs, which could find their way into the amniotic fluid. In the context of fetal systemic inflammatory response syndrome [104,131,149–156], PG production could be increased, as is the case for the adult systemic inflammatory response syndrome [157–162]. Prostaglandins contained within the umbilical cord may exert a local effect, such as modifying vascular reactivity of the umbilical arteries and vein [102,163–168], altering vessel permeability [169] or changing extracellular matrix metabolism in the Wharton's jelly. McCoshen et al. proposed that PGs generated in the umbilical cord could diffuse into the amniotic cavity [95]. Experimental evidence is required to prove this concept.

Conclusion

Prostaglandin concentrations in the umbilical cord are increased in the context of funisitis. We propose that PGE_2 and $PGF_{2\alpha}$ act as inflammatory mediators in the fetal inflammatory response syndrome, whose pathologic hallmark is funisitis.

Acknowledgments

The authors are grateful to the patients who agreed to provide the materials of our studies; to the nurses, laboratory staff, and clinicians who made this work possible; and to Maureen McGerty (Wayne State University) for her critical reading of the manuscript. J.-S.H., R.R., N.G.T., L.Y., P.C., C.J.K., and Y.M.K.: design of the study, data analysis, manuscript preparation; D.-C.L. and S.A.: experiments, data analysis; and J.-S.K.: histopathological analysis and manuscript preparation.

Funding

This work was supported in part by the Perinatology Research Branch, Division of Intramural Research, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, U.S. Department of Health and Human Services, Bethesda, MD, and Detroit, MI, USA.

References

1. Maddipati KR, Romero R, Chaiworapongsa T, et al. Eicosanomic profiling reveals dominance of the epoxygenase pathway in human amniotic fluid at term in spontaneous labor. FASEB J. 2014; 28:4835–4846. [PubMed: 25059230]
2. Karim SM. The role of prostaglandins in human parturition. Proc Royal Soc Med. 1971; 64:10–12.
3. Mitchell MD. Prostaglandins during pregnancy and the perinatal period. J Reprod Fertil. 1981; 62:305–315. [PubMed: 7230133]
4. Romero R, Emamian M, Wan M, et al. Prostaglandin concentrations in amniotic fluid of women with intra-amniotic infection and preterm labor. Am J Obstet Gynecol. 1987; 157:1461–1467. [PubMed: 3480691]
5. Romero R, Wu YK, Mazor M, et al. Amniotic fluid prostaglandin E_2 in preterm labor. Prostaglandins Leukot Essent Fatty Acids. 1988; 34:141–145. [PubMed: 3222272]
6. Romero R, Wu YK, Sintori M, 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; 37:149–161. [PubMed: 2717777]

7. Romero R, Baumann P, Gomez R, 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. Am J Obstet Gynecol. 1993; 168:1654–1664. discussion 1664–1668. [PubMed: 8317506]
8. Romero R, Baumann P, Gonzalez R, et al. Amniotic fluid prostanoid concentrations increase early during the course of spontaneous labor at term. Am J Obstet Gynecol. 1994; 171:1613–1620. [PubMed: 7802078]
9. Romero R, Gonzalez R, Baumann P, et al. Topographic differences in amniotic fluid concentrations of prostanoids in women in spontaneous labor at term. Prostaglandins Leukot Essent Fatty Acids. 1994; 50:97–104. [PubMed: 8171074]
10. Mitchell MD, Romero RJ, Edwin SS, et al. Prostaglandins and parturition. Reprod Fertil Dev. 1995; 7:623–632. [PubMed: 8606975]
11. Romero R, Munoz H, Gomez R, et al. Increase in prostaglandin bioavailability precedes the onset of human parturition. Prostaglandins Leukot Essent Fatty Acids. 1996; 54:187–191. [PubMed: 8860106]
12. Gibb W. The role of prostaglandins in human parturition. Ann Med. 1998; 30:235–241. [PubMed: 9677008]
13. Challis JR, Sloboda DM, Alfaidy N, et al. Prostaglandins and mechanisms of preterm birth. Reproduction. 2002; 124:1–17. [PubMed: 12090913]
14. Olson DM. The role of prostaglandins in the initiation of parturition. Best Pract Res Clin Obstet Gynaecol. 2003; 17:717–730. [PubMed: 12972010]
15. Challis JR, Bloomfield FH, Bocking AD, et al. Fetal signals and parturition. J Obstet Gynaecol Res. 2005; 31:492–499. [PubMed: 16343248]
16. Lee SE, Romero R, Park IS, et al. Amniotic fluid prostaglandin concentrations increase before the onset of spontaneous labor at term. J Matern Fetal Neonatal Med. 2008; 21:89–94. [PubMed: 18240075]
17. Mitchell MD, Chang MC, Chaiworapongsa T, et al. Identification of 9alpha,11beta-prostaglandin F2 in human amniotic fluid and characterization of its production by human gestational tissues. J Clin Endocrinol Metab. 2005; 90:4244–4248. [PubMed: 15840748]
18. Vidaeff AC, Ramin SM. Potential biochemical events associated with initiation of labor. Curr Med Chem. 2008; 15:614–619. [PubMed: 18336276]
19. Sykes L, MacIntyre DA, Teoh TG, et al. Anti-inflammatory prostaglandins for the prevention of preterm labour. Reproduction. 2014; 148:R29–40. [PubMed: 24890751]
20. Kirton KT, Wyngarden LJ, Bergstrom KK. Prostaglandins and myometrial contractility. Adv Biosci. 1973; 9:651–655. [PubMed: 4376992]
21. Novy MJ, Thomas CL, Lees MH. Uterine contractility and regional blood flow responses to oxytocin and prostaglandin E2 in pregnant rhesus monkeys. Am J Obstet Gynecol. 1975; 122:419–433. [PubMed: 1096612]
22. Wikland M, Lindblom B, Wilhelmsson L, et al. Oxytocin, prostaglandins, and contractility of the human uterus at term pregnancy. Acta Obstet Gynecol Scand. 1982; 61:467–472. [PubMed: 6961726]
23. Rydnert J, Joelsson I. Effect of the naturally occurring prostaglandins E2 and F2 alpha on the human myometrium in vivo during pregnancy. Acta Obstet Gynecol Scand. 1985; 64:577–582. [PubMed: 3866483]
24. Wiqvist N, Bryman I, Lindblom B, et al. The role of prostaglandins for the coordination of myometrial forces during labour. Acta Physiol Hung. 1985; 65:313–322. [PubMed: 3893037]
25. Asboth G, Phaneuf S, Lopez Bernal AL. Prostaglandin E receptors in myometrial cells. Acta Physiol Hung. 1997; 85:39–50. [PubMed: 9530435]
26. 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; 11:279–287. [PubMed: 15722440]

27. Woodcock NA, Taylor CW, Thornton S. Prostaglandin F2alpha increases the sensitivity of the contractile proteins to Ca2+ in human myometrium. Am J Obstet Gynecol. 2006; 195:1404–1406. [PubMed: 16769023]
28. Olson DM, Ammann C. Role of the prostaglandins in labour and prostaglandin receptor inhibitors in the prevention of preterm labour. Front Biosci. 2007; 12:1329–1343. [PubMed: 17127385]
29. Hurd WW, Gibbs SG, Rudinsky KA. Differential regulation of myometrial prostaglandin production by changes in length. Am J Obstet Gynecol. 2008; 198:225.e221–e224. [PubMed: 18226632]
30. Durn JH, Marshall KM, Farrar D, et al. Lipidomic analysis reveals prostanoid profiles in human term pregnant myometrium. Prostaglandins Leukot Essent Fatty Acids. 2010; 82:21–26. [PubMed: 19954938]
31. Mittal P, Romero R, Tarca AL, et al. A molecular signature of an arrest of descent in human parturition. Am J Obstet Gynecol. 2011; 204:177.e115–e133.
32. Chiossi G, Costantine MM, Bytautiene E, et al. The effects of prostaglandin E1 and prostaglandin E2 on in vitro myometrial contractility and uterine structure. Am J Perinatol. 2012; 29:615–622. [PubMed: 22639355]
33. Arulkumaran S, Kandola MK, Hoffman B, et al. The roles of prostaglandin EP 1 and 3 receptors in the control of human myometrial contractility. J Clin Endocrinol Metab. 2012; 97:489–498. [PubMed: 22162473]
34. Conde-Agudelo A, Nieto A, Rosas-Bermudez A, et al. Misoprostol to reduce intraoperative and postoperative hemorrhage during cesarean delivery: a systematic review and metaanalysis. Am J Obstet Gynecol. 2013; 209:40.e1–e17. [PubMed: 23507545]
35. Keirse MJ, Thiery M, Parewijck W, et al. Chronic stimulation of uterine prostaglandin synthesis during cervical ripening before the onset of labor. Prostaglandins. 1983; 25:671–682. [PubMed: 6611963]
36. Norman M, Ekman G, Malmstrom A. Prostaglandin E2-induced ripening of the human cervix involves changes in proteoglycan metabolism. Obstet Gynecol. 1993; 82:1013–1020. [PubMed: 8233252]
37. Voss DH, Cumminsky KC, Cook VD, et al. Effect of three concentrations of intracervical prostaglandin E2 gel for cervical ripening. J Matern Fetal Med. 1996; 5:186–193. [PubMed: 8796792]
38. Denison FC, Calder AA, Kelly RW. The action of prostaglandin E2 on the human cervix: stimulation of interleukin 8 and inhibition of secretory leukocyte protease inhibitor. Am J Obstet Gynecol. 1999; 180:614–620. [PubMed: 10076137]
39. Wing DA, Ham D, Paul RH. A comparison of orally administered misoprostol with vaginally administered misoprostol for cervical ripening and labor induction. Am J Obstet Gynecol. 1999; 180:1155–1160. [PubMed: 10329871]
40. Fujimoto T, Savani RC, Watari M, et al. 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; 160:1495–1502. [PubMed: 11943733]
41. Ben-Aroya Z, Hallak M, Segal D, et al. Ripening of the uterine cervix in a post-cesarean parturient: prostaglandin E2 versus Foley catheter. J Matern Fetal Neonatal Med. 2002; 12:42–45. [PubMed: 12422908]
42. Larmon JE, Magann EF, Dickerson GA, et al. Outpatient cervical ripening with prostaglandin E2 and estradiol. J Matern Fetal Neonatal Med. 2002; 11:113–117. [PubMed: 12375540]
43. D'Aniello G, Bocchi C, Florio P, et al. Cervical ripening and induction of labor by prostaglandin E2: a comparison between intracervical gel and vaginal pessary. J Matern Fetal Neonatal Med. 2003; 14:158–162. [PubMed: 14694970]
44. Chien EK, Macgregor C. Expression and regulation of the rat prostaglandin E2 receptor type 4 (EP4) in pregnant cervical tissue. Am J Obstet Gynecol. 2003; 189:1501–1510. [PubMed: 14634592]
45. Yogev Y, Ben-Haroush A, Gilboa Y, et al. Induction of labor with vaginal prostaglandin E2. J Matern Fetal Neonatal Med. 2003; 14:30–34. [PubMed: 14563089]

46. Garry D, Figueroa R, Kalish RB, et al. Randomized controlled trial of vaginal misoprostol versus dinoprostone vaginal insert for labor induction. J Matern Fetal Neonatal Med. 2003; 13:254–259. [PubMed: 12854927]
47. Hertelendy F, Zakar T. Prostaglandins and the myometrium and cervix. Prostaglandins Leukot Essent Fatty Acids. 2004; 70:207–222. [PubMed: 14683694]
48. Crane JM, Delaney T, Butt KD, et al. Predictors of successful labor induction with oral or vaginal misoprostol. J Matern Fetal Neonatal Med. 2004; 15:319–323. [PubMed: 15280123]
49. Tornblom SA, Patel FA, Bystrom B, et al. 15-hydroxyprostaglandin dehydrogenase and cyclooxygenase 2 messenger ribonucleic acid expression and immunohistochemical localization in human cervical tissue during term and preterm labor. J Clin Endocrinol Metab. 2004; 89:2909–2915. [PubMed: 15181076]
50. Word RA, Li XH, Hnat M, et al. Dynamics of cervical remodeling during pregnancy and parturition: mechanisms and current concepts. Semin Reprod Med. 2007; 25:69–79. [PubMed: 17205425]
51. Ji H, Dailey TL, Long V, et al. Prostaglandin E2-regulated cervical ripening: analysis of proteoglycan expression in the rat cervix. Am J Obstet Gynecol. 2008; 198:536.e1–e7. [PubMed: 18191800]
52. Timmons B, Akins M, Mahendroo M. Cervical remodeling during pregnancy and parturition. Trends Endocrinol Metab. 2010; 21:353–361. [PubMed: 20172738]
53. Mahendroo M. Cervical remodeling in term and preterm birth: insights from an animal model. Reproduction. 2012; 143:429–438. [PubMed: 22344465]
54. Favilli A, Acanfora MM, Bini V, et al. Single indication of labor induction with prostaglandins: is advanced maternal age a risk factor for cesarean section? A matched retrospective cohort study. J Matern Fetal Neonatal Med. 2013; 26:665–668. [PubMed: 23130593]
55. Haas J, Barzilay E, Chayen B, et al. Safety of labor induction with prostaglandin E2 in grandmultiparous women. J Matern Fetal Neonatal Med. 2013; 26:49–51. [PubMed: 22928497]
56. Melamed N, Yariv O, Hiersch L, et al. Labor induction with prostaglandin E2: characteristics of response and prediction of failure. J Matern Fetal Neonatal Med. 2013; 26:132–136. [PubMed: 22928537]
57. Timmons BC, Reese J, Socrate S, et al. Prostaglandins are essential for cervical ripening in LPS-mediated preterm birth but not term or antiprogestin-driven preterm ripening. Endocrinology. 2014; 155:287–298. [PubMed: 24189143]
58. Kishore AH, Owens D, Word RA. Prostaglandin E2 regulates its own inactivating enzyme, 15-PGDH, by EP2 receptor-mediated cervical cell-specific mechanisms. J Clin Endocrinol Metab. 2014; 99:1006–1018. [PubMed: 24471568]
59. 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; 6:1033–1040. [PubMed: 11044467]
60. Ulug U, Goldman S, Ben-Shlomo I, et al. 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; 7:1187–1193. [PubMed: 11719597]
61. Menon R, Fortunato SJ. The role of matrix degrading enzymes and apoptosis in rupture of membranes. J Soc Gynecol Investig. 2004; 11:427–437.
62. Moore RM, Mansour JM, Redline RW, et al. The physiology of fetal membrane rupture: insight gained from the determination of physical properties. Placenta. 2006; 27:1037–1051. [PubMed: 16516962]
63. Oger S, Mehats C, Dallot E, et al. 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; 174:8082–8089. [PubMed: 15944316]
64. Makino S, Zaragoza DB, Mitchell BF, et al. Prostaglandin F2alpha and its receptor as activators of human decidua. Semin Reprod Med. 2007; 25:60–68. [PubMed: 17205424]
65. Lee SE, Park IS, Romero R, et al. 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 Neonatal Med. 2009; 22:880–886. [PubMed: 19544157]

66. Lee DC, Romero R, Kim JS, et al. Evidence for a spatial and temporal regulation of prostaglandin-endoperoxide synthase 2 expression in human amnion in term and preterm parturition. J Clin Endocrinol Metab. 2010; 95:E86–91. [PubMed: 20519349]

67. Rossi D, Pianta S, Magatti M, et al. Characterization of the conditioned medium from amniotic membrane cells: prostaglandins as key effectors of its immunomodulatory activity. PLoS One. 2012; 7:e46956. [PubMed: 23071674]

68. Alzamil HA, Pawade J, Fortier MA, et 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. Front Physiol. 2014; 5:272. [PubMed: 25126080]

69. 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 Pregn Childbirth. 2014; 14:241.

70. Menon R, Fortunato SJ, Yu J, et al. Cigarette smoke induces oxidative stress and apoptosis in normal term fetal membranes. Placenta. 2011; 32:317–322. [PubMed: 21367451]

71. Dray F, Frydman R. Primary prostaglandins in amniotic fluid in pregnancy and spontaneous labor. Am J Obstet Gynecol. 1976; 126:13–19. [PubMed: 961739]

72. 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. Prostagland Leukotr Med. 1983; 12:289–297.

73. Mazor M, Wiznitzer A, Maymon E, et al. Changes in amniotic fluid concentrations of prostaglandins E2 and F2 alpha in women with preterm labor. Isr J Med Sci. 1990; 26:425–428. [PubMed: 2401604]

74. Romero R, Emamian M, Quintero R, et al. Amniotic fluid prostaglandin levels and intra-amniotic infections. Lancet. 1986; 1:1380.

75. Lopez Bernal A, Hansell DJ, Canete Soler R, et al. Prostaglandins, chorioamnionitis and preterm labour. Br J Obstet Gynaecol. 1987; 94:1156–1158. [PubMed: 2827724]

76. Bry K, Hallman M. Prostaglandins, inflammation, and preterm labor. J Perinatol. 1989; 9:60–65. [PubMed: 2496208]

77. Romero R, Wu YK, Mazor M, et al. Amniotic fluid arachidonate lipoxygenase metabolites in preterm labor. Prostaglandins Leukot Essent Fatty Acids. 1989; 36:69–75. [PubMed: 2788288]

78. Lamont RF, Anthony F, Myatt L, et al. Production of prostaglandin E2 by human amnion in vitro in response to addition of media conditioned by microorganisms associated with chorioamnionitis and preterm labor. Am J Obstet Gynecol. 1990; 162:819–825. [PubMed: 2316593]

79. Mitchell MD, Romero RJ, Avila C, et al. Prostaglandin production by amnion and decidual cells in response to bacterial products. Prostaglandins Leukot Essent Fatty Acids. 1991; 42:167–169. [PubMed: 1857723]

80. van Meir CA, Matthews SG, Keirse MJ, et al. 15-hydroxyprostaglandin dehydrogenase: implications in preterm labor with and without ascending infection. J Clin Endocrinol Metab. 1997; 82:969–976. [PubMed: 9062515]

81. Hsu CD, Meaddough E, Aversa K, et al. Dual roles of amniotic fluid nitric oxide and prostaglandin E2 in preterm labor with intra-amniotic infection. Am J Perinatol. 1998; 15:683–687. [PubMed: 10333395]

82. Romero R, Espinoza J, Goncalves LF, et al. Inflammation in preterm and term labour and delivery. Semin Fetal Neonatal Med. 2006; 11:317–326. [PubMed: 16839830]

83. Leaver HA, MacPherson HD, Hutchon DJ. Amniotic fluid prostaglandins F2 alpha and E2, measured at artificial rupture of the membranes, predict the subsequent progress of labour. Prostagland Leukotr Med. 1987; 28:237–242.

84. Menon R, Fortunato SJ, Milne GL, et al. Amniotic fluid eicosanoids in preterm and term births: effects of risk factors for spontaneous preterm labor. Obstet Gynecol. 2011; 118:121–134. [PubMed: 21691170]

85. Olson DM, Skinner K, Challis JR. Prostaglandin output in relation to parturition by cells dispersed from human intrauterine tissues. J Clin Endocrinol Metab. 1983; 57:694–699. [PubMed: 6688427]

86. Di Renzo GC, Anceschi MM, Bleasdale JE. Beta-adrenergic stimulation of prostaglandin production by human amnion tissue. Prostaglandins. 1984; 27:37–49. [PubMed: 6324289]

87. Teixeira FJ, Zakar T, Hirst JJ, et al. Prostaglandin endoperoxide-H synthase (PGHS) activity and immunoreactive PGHS-1 and PGHS-2 levels in human amnion throughout gestation, at term, and during labor. J Clin Endocrinol Metab. 1994; 78:1396–1402. [PubMed: 8200943]

88. Hirst JJ, Teixeira FJ, Zakar T, et al. Prostaglandin H synthase-2 expression increases in human gestational tissues with spontaneous labour onset. Reprod Fertil Dev. 1995; 7:633–637. [PubMed: 8606976]

89. Gibb W, Sun M. Localization of prostaglandin H synthase type 2 protein and mRNA in term human fetal membranes and decidua. J Endocrinol. 1996; 150:497–503. [PubMed: 8882169]

90. Fuentes A, Spaziani EP, O'Brien WF. The expression of cyclooxygenase-2 (COX-2) in amnion and decidua following spontaneous labor. Prostaglandins. 1996; 52:261–267. [PubMed: 8936582]

91. Brennand JE, Leask R, Kelly RW, et al. Mechanisms involved in the stimulatory effect of amniotic fluid on prostaglandin production by human fetal membranes. Prostaglandins Leukot Essent Fatty Acids. 1998; 58:369–375. [PubMed: 9690715]

92. Furuta I, Yamada H, Sagawa T, et al. Effects of inflammatory cytokines on prostaglandin E(2) production from human amnion cells cultured in serum-free condition. Gynecol Obstetr Investig. 2000; 49:93–97.

93. Challis JRG, Matthews SG, Gibb W, et al. Endocrine and paracrine regulation of birth at term and preterm. Endocr Rev. 2000; 21:514–550. [PubMed: 11041447]

94. Harirah H, Thota C, Wentz MJ, et al. Elevated expression of catechol-O-methyltransferase is associated with labor and increased prostaglandin E(2) production by human fetal membranes. Am J Obstet Gynecol. 2009; 201:496.e1–e7. [PubMed: 19664748]

95. McCoshen JA, Tulloch HV, Johnson KA. Umbilical cord is the major source of prostaglandin E2 in the gestational sac during term labor. Am J Obstet Gynecol. 1989; 160:973–978. [PubMed: 2712126]

96. Benirschke, K., Kaufmann, P., Baergen, R. Pathology of the human placenta. New York: Springer; 2006.

97. Han YM, Romero R, Kim JS, et al. Region-specific gene expression profiling: novel evidence for biological heterogeneity of the human amnion. Biol Reprod. 2008; 79:954–961. [PubMed: 18685129]

98. Marvin KW, Keelan JA, Eykholt RL, et al. Expression of angiogenic and neurotrophic factors in the human amnion and choriodecidua. Am J Obstet Gynecol. 2002; 187:728–734. [PubMed: 12237655]

99. Erez O, Romero R, Tarca AL, et al. Differential expression pattern of genes encoding for anti-microbial peptides in the fetal membranes of patients with spontaneous preterm labor and intact membranes and those with preterm prelabor rupture of the membranes. J Matern Fetal Neonatal Med. 2009; 22:1103–1115. [PubMed: 19916708]

100. Kim SY, Romero R, Tarca AL, et al. miR-143 regulation of prostaglandin-endoperoxidase synthase 2 in the amnion: implications for human parturition at term. PLoS One. 2011; 6:e24131. [PubMed: 21915288]

101. Willman EA, Collins WP. The concentrations of prostaglandin E2 and prostaglandin F2alpha in tissues within the fetoplacental unit after spontaneous or induced labour. Br J Obstet Gynaecol. 1976; 83:786–789. [PubMed: 990218]

102. Willman EA, Collins WP. Distribution of prostaglandins E2 and F2 alpha within the foetoplacental unit throughout human pregnancy. J Endocrinol. 1976; 69:413–419. [PubMed: 950532]

103. Siegel RJ, Villa LC, Fishbein MC. Immunohistochemical localization of 6-keto-prostaglandin F1 alpha and prostaglandin E2 in the human umbilical cord before and after labor. Lab Invest. 1987; 56:550–553. [PubMed: 3553739]

104. Pacora P, Chaiworapongsa T, Maymon E, et al. Funisitis and chorionic vasculitis: the histological counterpart of the fetal inflammatory response syndrome. J Matern Fetal Neonatal Med. 2002; 11:18–25. [PubMed: 12380603]

105. Redline RW, Faye-Petersen O, Heller D, et al. Amniotic infection syndrome: nosology and reproducibility of placental reaction patterns. Pediatr Dev Pathol. 2003; 6:435–448. [PubMed: 14708737]

106. Redline RW. Inflammatory responses in the placenta and umbilical cord. Semin Fetal Neonatal Med. 2006; 11:296–301. [PubMed: 16621749]

107. Mi Lee S, Romero R, Lee KA, et al. The frequency and risk factors of funisitis and histologic chorioamnionitis in pregnant women at term who delivered after the spontaneous onset of labor. J Matern Fetal Neonatal Med. 2011; 24:37–42. [PubMed: 20698737]

108. Kim SM, Romero R, Park JW, et al. The relationship between the intensity of intra-amniotic inflammation and the presence and severity of acute histologic chorioamnionitis in preterm gestation. J Matern Fetal Neonatal Med. 2015; 28:1500–1509. [PubMed: 25184305]

109. Kim YM, Chaemsaithong P, Romero R, et al. Placental lesions associated with acute atherosis. J Matern Fetal Neonatal Med. 2015; 28:1554–1562. [PubMed: 25183023]

110. Sibai BM, Ewell M, Levine RJ, et al. Risk factors associated with preeclampsia in healthy nulliparous women. The Calcium for Preeclampsia Prevention (CPEP) Study Group. Am J Obstet Gynecol. 1997; 177:1003–1010. [PubMed: 9396883]

111. Slater D, Berger L, Newton R, et al. The relative abundance of type 1 to type 2 cyclo-oxygenase mRNA in human amnion at term. Biochem Biophys Res Commun. 1994; 198:304–308. [PubMed: 8292034]

112. Slater DM, Berger LC, Newton R, et al. Expression of cyclooxygenase types 1 and 2 in human fetal membranes at term. Am J Obstet Gynecol. 1995; 172:77–82. [PubMed: 7531399]

113. Hirst JJ, Teixeira FJ, Zakar T, et al. Prostaglandin endoperoxide-H synthase-1 and -2 messenger ribonucleic acid levels in human amnion with spontaneous labor onset. J Clin Endocrinol Metab. 1995; 80:517–523. [PubMed: 7852513]

114. Slater D, Dennes W, Sawdy R, et al. Expression of cyclo-oxygenase types-1 and -2 in human fetal membranes throughout pregnancy. J Mol Endocrinol. 1999; 22:125–130. [PubMed: 10194515]

115. Hillier SL, Martius J, Krohn M, et al. A case-control study of chorioamnionic infection and histologic chorioamnionitis in prematurity. N Engl J Med. 1988; 319:972–978. [PubMed: 3262199]

116. Mueller-Heubach E, Rubinstein DN, Schwarz SS. Histologic chorioamnionitis and preterm delivery in different patient populations. Obstet Gynecol. 1990; 75:622–626. [PubMed: 2314782]

117. Romero R, Salafia CM, Athanassiadis AP, et al. The relationship between acute inflammatory lesions of the preterm placenta and amniotic fluid microbiology. Am J Obstet Gynecol. 1992; 166:1382–1388. [PubMed: 1595794]

118. Hillier SL, Witkin SS, Krohn MA, et al. The relationship of amniotic fluid cytokines and preterm delivery, amniotic fluid infection, histologic chorioamnionitis, and chorioamnion infection. Obstet Gynecol. 1993; 81:941–948. [PubMed: 8497360]

119. Greig PC, Ernest JM, Teot L, et al. Amniotic fluid interleukin-6 levels correlate with histologic chorioamnionitis and amniotic fluid cultures in patients in premature labor with intact membranes. Am J Obstet Gynecol. 1993; 169:1035–1044. [PubMed: 8238116]

120. Yoon BH, Romero R, Park JS, et al. Microbial invasion of the amniotic cavity with Ureaplasma urealyticum is associated with a robust host response in fetal, amniotic, and maternal compartments. Am J Obstet Gynecol. 1998; 179:1254–1260. [PubMed: 9822511]

121. Yoon BH, Romero R, Park JS, et al. The relationship among inflammatory lesions of the umbilical cord (funisitis), umbilical cord plasma interleukin 6 concentration, amniotic fluid infection, and neonatal sepsis. Am J Obstet Gynecol. 2000; 183:1124–1129. [PubMed: 11084553]

122. Williams MC, O'Brien WF, Nelson RN, et al. Histologic chorioamnionitis is associated with fetal growth restriction in term and preterm infants. Am J Obstet Gynecol. 2000; 183:1094–1099. [PubMed: 11084547]

123. Yoon BH, Romero R, Moon JB, et al. Clinical significance of intra-amniotic inflammation in patients with preterm labor and intact membranes. Am J Obstet Gynecol. 2001; 185:1130–1136. [PubMed: 11717646]

124. Ustun C, Kocak I, Baris S, et al. Subclinical chorioamnionitis as an etiologic factor in preterm deliveries. Int J Gynaecol Obstet. 2001; 72:109–115. [PubMed: 11166743]

125. Romero R, Espinoza J, Chaiworapongsa T, et al. Infection and prematurity and the role of preventive strategies. Semin Neonatol. 2002; 7:259–274. [PubMed: 12401296]

126. Goncalves LF, Chaiworapongsa T, Romero R. Intrauterine infection and prematurity. Ment Retard Dev Disabil Res Rev. 2002; 8:3–13. [PubMed: 11921380]
127. Shim SS, Romero R, Hong JS, et al. Clinical significance of intra-amniotic inflammation in patients with preterm premature rupture of membranes. Am J Obstet Gynecol. 2004; 191:1339–1345. [PubMed: 15507963]
128. Kim YM, Romero R, Chaiworapongsa T, et al. Toll-like receptor-2 and -4 in the chorioamniotic membranes in spontaneous labor at term and in preterm parturition that are associated with chorioamnionitis. Am J Obstet Gynecol. 2004; 191:1346–1355. [PubMed: 15507964]
129. De Paepe ME, Friedman RM, Gundogan F, et al. The histologic fetoplacental inflammatory response in fatal perinatal group B-streptococcus infection. J Perinatol. 2004; 24:441–445. [PubMed: 15141264]
130. Romero R, Espinoza J, Kusanovic JP, et al. The preterm parturition syndrome. BJOG. 2006; 113(Suppl 3):17–42.
131. Lee SE, Romero R, Kim CJ, et al. Funisitis in term pregnancy is associated with microbial invasion of the amniotic cavity and intra-amniotic inflammation. J Matern Fetal Neonatal Med. 2006; 19:693–697. [PubMed: 17127492]
132. Romero R, Gotsch F, Pineles B, et al. Inflammation in pregnancy: its roles in reproductive physiology, obstetrical complications, and fetal injury. Nutr Rev. 2007; 65:S194–202. [PubMed: 18240548]
133. Romero R, Espinoza J, Goncalves LF, et al. The role of inflammation and infection in preterm birth. Semin Reprod Med. 2007; 25:21–39. [PubMed: 17205421]
134. Holzman C, Lin X, Senagore P, et al. Histologic chorioamnionitis and preterm delivery. Am J Epidemiol. 2007; 166:786–794. [PubMed: 17625222]
135. Seong HS, Lee SE, Kang JH, et al. The frequency of microbial invasion of the amniotic cavity and histologic chorioamnionitis in women at term with intact membranes in the presence or absence of labor. Am J Obstet Gynecol. 2008; 199:375.e1–e5. [PubMed: 18928978]
136. Romero, R., Lockwood, CJ. Pathogenesis of spontaneous preterm labor. In: Creasy, RK.Resnik, R., Iams, JD., editors. Creasy and Resnik's maternal-fetal medicine: principles and practice. Philadelphia: Elsevier; 2009. p. 521-543.
137. Kim MJ, Romero R, Gervasi MT, et al. Widespread microbial invasion of the chorioamniotic membranes is a consequence and not a cause of intra-amniotic infection. Lab Invest. 2009; 89:924–936. [PubMed: 19506551]
138. DiGiulio DB, Romero R, Kusanovic JP, et al. Prevalence and diversity of microbes in the amniotic fluid, the fetal inflammatory response, and pregnancy outcome in women with preterm pre-labor rupture of membranes. Am J Reprod Immunol. 2010; 64:38–57. [PubMed: 20331587]
139. Park HS, Romero R, Lee SM, et al. Histologic chorioamnionitis is more common after spontaneous labor than after induced labor at term. Placenta. 2010; 31:792–795. [PubMed: 20655108]
140. Menon R, Taylor RN, Fortunato SJ. Chorioamnionitis--a complex pathophysiologic syndrome. Placenta. 2010; 31:113–120. [PubMed: 20031205]
141. Lee SM, Lee KA, Kim SM, et al. The risk of intra-amniotic infection, inflammation and histologic chorioamnionitis in term pregnant women with intact membranes and labor. Placenta. 2011; 32:516–521. [PubMed: 21565402]
142. Bersani I, Thomas W, Speer CP. Chorioamnionitis--the good or the evil for neonatal outcome? J Matern Fetal Neonatal Med. 2012; 25(Suppl 1):12–16. [PubMed: 22309119]
143. Martinelli P, Sarno L, Maruotti GM, et al. Chorioamnionitis and prematurity: a critical review. J Matern Fetal Neonatal Med. 2012; 25(Suppl 4):29–31. [PubMed: 22958008]
144. Romero R, Dey SK, Fisher SJ. Preterm labor: one syndrome, many causes. Science. 2014; 345:760–765. [PubMed: 25124429]
145. Vajrychova M, Kacerovsky M, Tambor V, et al. Microbial invasion and histological chorioamnionitis upregulate neutrophil-gelatinase associated lipocalin in preterm prelabor rupture of membranes. J Matern Fetal Neonatal Med. 2016; 29:12–21. [PubMed: 25424376]

146. Combs CA, Gravett M, Garite TJ, et al. Amniotic fluid infection, inflammation, and colonization in preterm labor with intact membranes. Am J Obstet Gynecol. 2014; 210:125.e1–e15. [PubMed: 24274987]

147. Kacerovsky M, Musilova I, Andrys C, et al. Prelabor rupture of membranes between 34 and 37 weeks: the intraamniotic inflammatory response and neonatal outcomes. Am J Obstet Gynecol. 2014; 210:325.e1–e10. [PubMed: 24184182]

148. Kacerovsky M, Musilova I, Hornychova H, et al. Bedside assessment of amniotic fluid interleukin-6 in preterm prelabor rupture of membranes. Am J Obstet Gynecol. 2014; 211:385.e1–e9. [PubMed: 24705131]

149. Gomez R, Romero R, Ghezzi F, et al. The fetal inflammatory response syndrome. Am J Obstet Gynecol. 1998; 179:194–202. [PubMed: 9704787]

150. Romero R, Gomez R, Ghezzi F, et al. A fetal systemic inflammatory response is followed by the spontaneous onset of preterm parturition. Am J Obstet Gynecol. 1998; 179:186–193. [PubMed: 9704786]

151. Gotsch F, Romero R, Kusanovic JP, et al. The fetal inflammatory response syndrome. Clin Obstet Gynecol. 2007; 50:652–683. [PubMed: 17762416]

152. Madsen-Bouterse SA, Romero R, Tarca AL, et al. The transcriptome of the fetal inflammatory response syndrome. Am J Reprod Immunol. 2010; 63:73–92. [PubMed: 20059468]

153. Romero R, Savasan ZA, Chaiworapongsa T, et al. Hematologic profile of the fetus with systemic inflammatory response syndrome. J Perinat Med. 2011; 40:19–32. [PubMed: 21957997]

154. Chaiworapongsa T, Romero R, Berry SM, et al. The role of granulocyte colony-stimulating factor in the neutrophilia observed in the fetal inflammatory response syndrome. J Perinat Med. 2011; 39:653–666. [PubMed: 21801092]

155. Kacerovsky M, Cobo T, Andrys C, et al. The fetal inflammatory response in subgroups of women with preterm prelabor rupture of the membranes. J Matern Fetal Neonatal Med. 2013; 26:795–801. [PubMed: 23311694]

156. Hofer N, Kothari R, Morris N, et al. The fetal inflammatory response syndrome is a risk factor for morbidity in preterm neonates. Am J Obstet Gynecol. 2013; 209:542.e1–e11. [PubMed: 23994220]

157. Baracos V, Rodemann HP, Dinarello CA, et al. Stimulation of muscle protein degradation and prostaglandin E2 release by leukocytic pyrogen (interleukin-1). A mechanism for the increased degradation of muscle proteins during fever. N Engl J Med. 1983; 308:553–558. [PubMed: 6402699]

158. Huribal M, Cunningham ME, D'Aiuto ML, et al. Endothelin-1 and prostaglandin E2 levels increase in patients with burns. J Am Coll Surg. 1995; 180:318–322. [PubMed: 7874342]

159. Haupt W, Fritzsche H, Hohenberger W, et al. Selective cytokine release induced by serum and separated plasma from septic patients. Eur J Surg. 1996; 162:769–776. [PubMed: 8934105]

160. Hahn EL, Clancy KD, Tai HH, et al. Prostaglandin E2 alterations during sepsis are partially mediated by endotoxin-induced inhibition of prostaglandin 15-hydroxydehydrogenase. J Trauma. 1998; 44:777–781. discussion 781–782. [PubMed: 9603077]

161. Brogliato AR, Antunes CA, Carvalho RS, et al. Ketoprofen impairs immunosuppression induced by severe sepsis and reveals an important role for prostaglandin E2. Shock. 2012; 38:620–629. [PubMed: 23143054]

162. Kwiatkoski M, Soriano RN, Araujo RM, et al. Hydrogen sulfide inhibits preoptic prostaglandin E2 production during endotoxemia. Exp Neurol. 2013; 240:88–95. [PubMed: 23153577]

163. Kawano M, Mori N. Prostacyclin producing activity of human umbilical, placental and uterine vessels. Prostaglandins. 1983; 26:645–662. [PubMed: 6361910]

164. Monuszko E, Halevy S, Freese KJ, et al. Umbilical vessels endothelium and vascular reactivity. Microcirc Endothelium Lymphatics. 1990; 6:183–208. [PubMed: 2247025]

165. Scalera F. Intracellular glutathione and lipid peroxide availability and the secretion of vasoactive substances by human umbilical vein endothelial cells after incubation with TNF-alpha. Eur J Clin Investig. 2003; 33:176–182. [PubMed: 12588293]

166. Daray FM, Minvielle AI, Puppo S, et al. Vasoconstrictor effects of 8-iso-prostaglandin E2 and 8-iso-prostaglandin F(2alpha) on human umbilical vein. Eur J Pharmacol. 2004; 499:189–195. [PubMed: 15363966]

167. Errasti AE, del-Rey G, Cesio CE, et al. Expression and functional evidence of the prostaglandin F2alpha receptor mediating contraction in human umbilical vein. Eur J Pharmacol. 2009; 610:68–74. [PubMed: 19289115]

168. Topal G, Foudi N, Uydes-Dogan BS, et al. Involvement of prostaglandin F2alpha in preeclamptic human umbilical vein vasospasm: a role of prostaglandin F and thromboxane A2 receptors. J Hypertens. 2010; 28:2438–2445. [PubMed: 20720498]

169. Kim SR, Bae SK, Park HJ, et al. Thromboxane A(2) increases endothelial permeability through upregulation of interleukin-8. Biochem Biophys Res Commun. 2010; 397:413–419. [PubMed: 20510674]

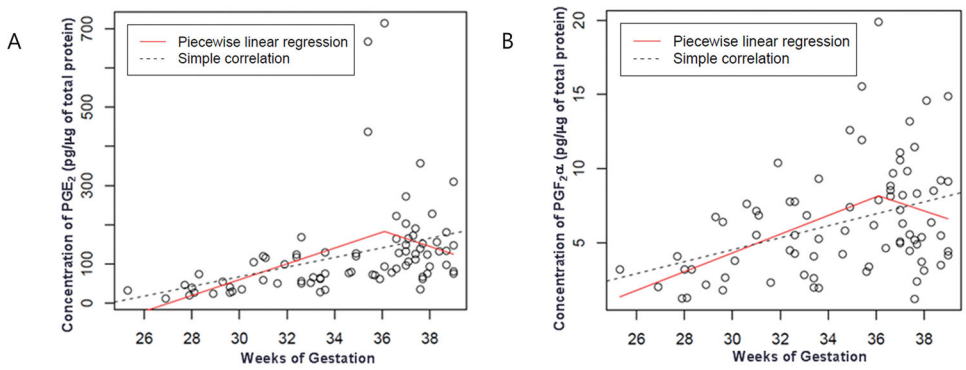

Figure 1.

PGE_2 and $PGF_{2\alpha}$ concentrations in the umbilical cord as a function of gestational age including preterm and term gestations with preeclampsia. Umbilical cord PGE_2 and $PGF_{2\alpha}$ concentrations increased with advancing gestational age until 36 weeks (PGE_2: rho = 0.59, $p<0.001$; $PGF_{2\alpha}$: rho = 0.39, p=0.01), but not after 36 weeks (PGE_2: rho = −0.1, p=0.5; $PGF_{2\alpha}$: rho = −0.2, p=0.2).

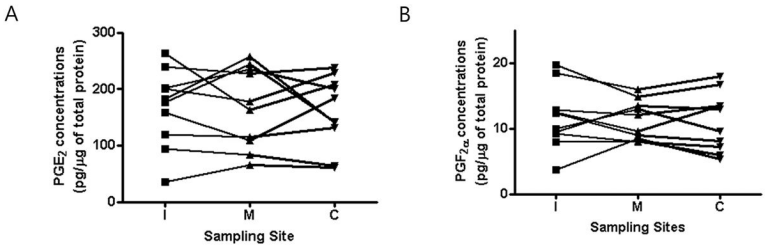

Figure 2.

PGE_2 and $PGF_{2\alpha}$ umbilical cord concentrations in different sites of the umbilical cord. There was no significant difference in the umbilical cord concentrations of PGE_2 and $PGF_{2\alpha}$ among the three different sampling sites (PGE_2; p=0.7; and $PGF_{2\alpha}$; p=0.7). (I: 1 cm apart from umbilical cord insertion. C: 1 cm apart from the cord clamping. M: mid-segment). Connected lines referred to prostaglandin concentration in a particular segment of the umbilical cord and in another segment in each patient.

Table 1

Clinical characteristics and concentrations of prostaglandins (PGE_2 and $PGF_{2\alpha}$) in the umbilical cord for each study group

	Term delivery without labor (n=20)	Term delivery with labor (n=20)	*p* value*	sPTD without funisitis (n=20)	sPTD with funisitis (n=20)	*p* value§	*p* value†
Maternal age (years)	25.5 (20–35)	26.0 (17–35)	0.8	25.5 (20–36)	23.0 (16–39)	0.7	0.4
Nulliparity	10% (2/20)	20% (4/20)	0.7	10% (2/20)	30% (6/20)	0.2	0.5
GA at delivery (weeks)	39.0 (37.1–40.1)	39.1 (37.1–40.4)	0.9	31.8 (27–34)	32.3 (28.6–34)	0.9	< 0.001
Birth weight (gm)	3323 (2545–4485)	3258 (2550–3695)	0.5	1818 (881–2690)	1665 (1010–2335)	0.6	< 0.001
Male gender	70% (14/20)	55% (11/20)	0.3	45% (9/20)	50% (10/20)	0.8	0.8
PGE_2	133.7 (44.8–252.4)	116.1 (33.5–354.9)	0.9	87.4 (6.1–258.6)	233.7 (61.3–1000)	0.001	0.03
$PGF_{2\alpha}$	8.4 (4.1–15.2)	8.1 (4.2–14.8)	0.7	7.1 (0.6–13.1)	9.6 (4.3–43.8)	0.051	0.3

Data are presented as median (interquartile range) and percentage with (n);

sPTD: spontaneous preterm delivery;

PGE_2 and $PGF_{2\alpha}$ concentrations were expressed by pg/μg of total protein.

GA: gestational age

*comparison between term delivery without labor and term delivery with labor

§comparison between sPTD without funisitis and sPTD with funisitis

†comparison between TIL and sPTD with funisitis

J Matern Fetal Neonatal Med. Author manuscript; available in PMC 2018 January 16.

Table 2

Clinical characteristics and the umbilical cord concentrations of PGE_2 and $PGF_{2\alpha}$ for term and preterm preeclampsia cases

	Preeclampsia (n=78)
Maternal age (year)	26.4 (± 6.1)
Nulliparity	45% (35/78)
Gestational age at delivery (weeks)	35.7 (25.3–39.0)
Birth weight (g)	2051 (± 859)
Male gender	58% (45/78)
PGE_2 (pg/μg of total protein) *	95.1 (11.5–714.1)
$PGF_{2\alpha}$ (pg/μg of total protein) *	5.5 (1.2–19.9)

Data are presented as mean (± SD) and percentage with (n).

*[median (range)]