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Pentraxin 3 in amniotic fluid: a novel association with intra-amniotic infection and inflammation

Laura Cruciani[1], Roberto Romero[1–3,*], Edi Vaisbuch[1,2], Juan Pedro Kusanovic[1,2], Tinnakorn Chaiworapongsa[1,2], Shali Mazaki-Tovi[1,2], Pooja Mittal[1,2], Giovanna Ogge[1], Francesca Gotsch[1], Offer Erez[1,2], Sun Kwon Kim[1], Zhong Dong[1], Percy Pacora[1], Ronald F. Lamont[1,2], Lami Yeo[1,2], Sonia S. Hassan[1,2] and Gian Carlo Di Renzo[4]

[1] Perinatology Research Branch, NICHD/NIH/DHHS, Bethesda, Maryland and Detroit, Michigan, USA
[2] Department of Obstetrics and Gynecology, Wayne State University School of Medicine, Detroit, Michigan, USA
[3] Center for Molecular Medicine and Genetics, Wayne State University, Detroit, Michigan, USA
[4] Santa Maria della Misericordia University Hospital, Perugia, Italy

Abstract

Objective: Pentraxin 3 (PTX3) is a soluble pattern recognition receptor (PRR) that has an important role in immunoregulation and vascular integrity. The aim of this study was to determine if PTX3 is present in amniotic fluid (AF) and whether its concentration changes with gestational age (GA), in the presence of preterm or term labor, and in cases of intra-amniotic infection/inflammation (IAI) associated with spontaneous preterm labor (PTL) or preterm prelabor rupture of membranes (PROM).

Study design: This cross-sectional study included the following groups: 1) mid-trimester (n = 45); 2) uncomplicated pregnancies at term with (n = 48) and without (n = 40) spontaneous labor; 3) women with PTL and intact membranes who: a) delivered at term (n = 44); b) delivered preterm without IAI (n = 40); or c) delivered preterm with IAI (n = 62); 4) women with preterm PROM with (n = 63) and without (n = 36) IAI. PTX3 concentration in AF was determined by ELISA. Non-parametric statistics were used for analyses.

Results: 1) Among women with PTL and intact membranes, the median AF PTX3 concentration was significantly higher in women with IAI than in those without IAI (7.95 ng/mL vs. 0.38 ng/mL; $P < 0.001$) and than in those who delivered at term (0.55 ng/mL; $P < 0.001$); 2) women with preterm PROM and IAI had a higher median AF PTX3 concentration than those without IAI (9.12 ng/mL vs. 0.76 ng/mL; $P < 0.001$); 3) the median AF PTX3 concentration did not change with GA (mid-trimester: 0.79 ng/mL vs. term not in labor: 0.58 ng/mL; $P = 0.09$); and 4) labor at term was not associated with a significant change of AF PTX 3 concentration (in labor: 0.54 ng/mL vs. not in labor: 0.58 ng/mL, $P = 0.9$).

Conclusions: PTX3 is a physiologic constituent of the AF, and its median concentration is elevated in the presence of IAI, suggesting that PTX3 may play a role in the innate immune response against IAI.

Keywords: Amniocentesis; cytokines; microbial invasion of the amniotic cavity (MIAC); pattern recognition receptors (PRRs); pregnancy; preterm delivery; preterm labor (PTL); preterm prelabor rupture of membranes (PROM).

*Corresponding author:
Roberto Romero, MD
Perinatology Research Branch, NICHD, NIH, DHHS
Wayne State University/Hutzel Women's Hospital
3990 John R, Box 4
Detroit
MI 48201
USA
Tel.: +1 (313) 993-2700
Fax: +1 (313) 993-2694
E-mail: prbchiefstaff@med.wayne.edu

Introduction

Preterm labor (PTL) is a syndrome [107], and one of the most important mechanism of disease is intrauterine infection, the only pathological process for which a causal link with prematurity has been established [27, 29, 35, 36, 38, 45, 48, 58, 61, 70, 71, 73, 77, 99, 104, 106]. Intra-amniotic infection/inflammation (IAI) is present in about one-third of women with spontaneous PTL with intact membranes [100, 130] and is associated with the development of the fetal inflammatory response syndrome (FIRS) [37, 84, 102], and severe neonatal morbidity [7, 16, 17, 64, 74, 85, 125–129].

Several investigators [5, 30, 72, 117, 120] have reported on the antimicrobial activity of components of the amniotic fluid (AF), which are involved in the innate and adaptative immune response against microorganisms. The innate component of the immune system represents the first line of defense against infection and includes a wide range of nonspecific mechanisms [23, 26, 47, 56, 101, 105, 116, 118]. One of the mechanisms by which the innate immune system recognizes microorganisms is mediated through pattern recognition receptors (PRRs) [53], which bind to surface markers on microorganisms [46, 83].

Pentraxins are essential components of the humoral arm of the innate immune response and act as soluble PRRs [11, 32] in response to pro-inflammatory signals and Toll-like receptors (TLRs) activation [4, 8, 132]. Pentraxin 3 (PTX3) is produced and released by a variety of cell types, such as

mononuclear cells, phagocytes, dendritic cells, fibroblasts, and endothelial cells [3, 13, 21, 40, 51, 57, 62, 89]. PTX3 recognizes microbial products, opsonizes fungi, selected Gram-positive and Gram-negative bacteria, viruses, and activates complement [11]. It is considered as an acute phase response protein because its concentrations increase considerably and rapidly in plasma of patients with systemic inflammatory response syndrome, sepsis, or septic shock [75]. Thus, the objective of this study was to determine if PTX3 is present in AF, if its concentration changes with gestational age (GA), spontaneous labor at term, and in the presence of IAI in women with spontaneous PTL with intact membranes and in those with preterm prelabor rupture of the membranes (PROM).

Materials and methods

Study design and population

A cross-sectional study was carried out by searching our clinical database and bank of biological samples, and included 378 pregnant women in the following groups: 1) women at 14–18 weeks gestation whose amniocentesis was conducted for genetic indications (n = 45) and who subsequently had an uncomplicated pregnancy; 2) uncomplicated term pregnancies with (n = 48) and without (n = 40) spontaneous labor; 3) women with PTL and intact membranes without IAI who delivered at term (n = 44); without IAI who delivered preterm (n = 40); and with IAI (n = 62); and 4) women with preterm PROM with (n = 63) and without IAI (n = 36). All women provided written informed consent prior to the collection of AF. The collection and utilization of AF for research purposes was approved by the Institutional Review Boards of the participating institutions and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, NIH, DHHS. Many of these samples have been used previously to study the biology of inflammation, hemostasis, and growth factor concentrations in uncomplicated pregnancies and those with adverse pregnancy outcomes.

Definitions

Women were considered to have an uncomplicated pregnancy if they did not have any medical, obstetrical, or surgical complication, and delivered a normal neonate at term appropriately grown for GA [2, 39]. Spontaneous PTL was defined as the presence of regular uterine contractions occurring at a frequency of at least two every 10 min associated with cervical change that required hospitalization before 37 completed weeks of gestation. Preterm PROM was diagnosed by sterile speculum examination which confirmed pooling of AF in the vagina in association with a positive nitrazine and ferning tests when necessary, before 37 weeks of gestation and prior to labor. Intra-amniotic infection was defined as a positive AF culture for micro-organisms. Intra-amniotic inflammation was diagnosed by an AF interleukin (IL)-6 concentration $\geq$2.6 ng/mL [130]. The AF IL-6 concentrations were used only for research purposes. Histologic chorioamnionitis was diagnosed on the basis of inflammatory cells in the chorionic plate and/or chorioamniotic membranes [92]. Acute funisitis was diagnosed by the presence of neutrophils in the wall of the umbilical vessels and/or Wharton's jelly using criteria previously described [82].

Sample collection

The AF samples were obtained by transabdominal amniocentesis. The details for collection and processing of AF have been described elsewhere [59]. Among women with spontaneous PTL with intact membranes who delivered within 72 h of amniocentesis, placenta, umbilical cord, and chorioamniotic membranes were collected, and the presence or absence of histologic chorioamnionitis and/or funisitis was assessed. The 72 h interval was chosen to preserve a meaningful temporal relationship between AF PTX3 concentration and placental histopathologic findings.

Determination of human PTX3 concentration in AF

Specific and sensitive enzyme-linked immunoassays (Linco Research, St. Charles, MO, USA) were used to determine concentrations of PTX3 in human AF. The PTX3 assays were validated for use in human AF in our laboratory prior to their use in this study. The concentrations of PTX3 in AF samples were determined by extrapolation from individual standard curves. The calculated inter-assay and intra-assay coefficients of variation for PTX3 in our laboratory were 2.7% and 3.9%, respectively. The sensitivity was 0.12 ng/mL.

Statistical analysis

The normality of the data was tested using the Shapiro-Wilk and Kolmogorov-Smirnov tests. Since AF PTX3 concentrations were not normally distributed, non-parametric tests were used for analyses. Kruskal-Wallis with post-hoc analysis and Mann-Whitney *U*-tests were used for continuous variables. Adjustment for multiple comparisons was performed using the Bonferroni method [9]. Comparisons between proportions were performed with the χ^2-test. Analysis of covariance (ANCOVA) was used to examine the difference of AF PTX3 concentration between the PTL and preterm PROM subgroup while adjust for storage time. Spearman's rank correlation was utilized to assess correlations between AF concentrations of PTX3, IL-6, glucose and WBC count. A $P < 0.05$ was considered statistically significant. The statistical package used was SPSS v.15.0 (SPSS Inc., Chicago, IL, USA).

Results

Demographic and clinical characteristics of the study population

Table 1 presents the demographic and clinical characteristics of women in the mid-trimester, term not in labor and term in labor groups. Predictably, women in the genetic amniocentesis group had a higher median maternal age and lower median GA at amniocentesis than women at term not in labor. Tables 2 and 3 display the demographic and clinical characteristics of women with spontaneous PTL and intact membranes and those with preterm PROM, respectively. Among women with PTL and intact membranes, those with IAI had a lower median GA at amniocentesis than those without IAI who delivered preterm, as well as a lower GA at delivery compared to women without IAI who delivered preterm and at term. In women with preterm PROM, the birth weight and GA were lower in women with IAI than in those without IAI.

Table 1 Demographic and clinical characteristics of women in the mid-trimester and those at term with and without spontaneous labor.

	Mid-trimester (n = 45)	P[a]	Term no labor (n = 40)	Term in labor (n = 48)	P[b]
Maternal age (years)	36 (35–38)	< 0.001	27 (21–32)	23 (19–30)	NS
GA at amniocentesis (weeks)	16 (16–17)	< 0.001	39 (38–40)	39 (37.8–40)	NS
GA at delivery (weeks)	40 (38–40)	NS	39 (38–40)	39 (37.8–40)	NS
Birthweight (g)	3320 (3064–3570)	NS	3260 (3055–3595)	3250 (3060–3620)	NS

Values are expressed as median (interquartile range).
P[a]: Comparison between women in the mid-trimester and those at term not in labor, P[b]: Comparison between women at term not in labor and those at term in labor. GA = gestational age; NS = not significant.

AF PTX3 concentrations did not change with advancing GA or in the presence of labor at term

PTX3 was detected in 95.2% (360/378) of AF samples. There were no differences in the median AF PTX3 concentration between women in the mid-trimester and those at term not in labor (0.79 ng/mL vs. 0.58 ng/mL, respectively; P = 0.09) (Figure 1). Similarly, no differences were observed in the median AF PTX3 concentration between women at term in labor and those not in labor (0.54 ng/mL vs. 0.58 ng/mL, respectively; P = 0.9) (Figure 1).

AF PTX3 concentrations are increased in the presence of IAI in women with spontaneous PTL and intact membranes as well as in those with preterm PROM

Among women with PTL, those with IAI had a significantly higher median AF concentration of PTX3 compared to those without IAI who delivered preterm (7.95 ng/mL vs. 0.38 ng/mL, respectively; P < 0.001) and than those without IAI who delivered at term (0.55 ng/mL; P < 0.001) (Figure 2). There were no differences in the median AF PTX3 concentration between women with PTL without IAI who delivered preterm and those who delivered at term (P = 0.6) (Figure 2). These results did not change after adjusting for GA at amniocentesis, and storage time.

Among patients with preterm PROM, those with IAI had a significantly higher median AF PTX3 concentration than those without IAI (9.12 ng/mL vs. 0.76 ng/mL, respectively; P < 0.001) (Figure 3). These results did not change after adjusting for GA at amniocentesis, and storage time.

Correlation of AF PTX3 concentration and other indirect markers of IAI

A significant correlation was observed between AF PTX3 concentrations and IL-6, WBC count and glucose concentration in women with spontaneous PTL and those with preterm PROM (Spearman's rho: IL-6 0.74, P < 0.001; WBC count 0.49; P < 0.001; and glucose –0.3, P < 0.001).

AF PTX3 concentrations and histological chorioamnionitis

Fifty-two women with spontaneous PTL delivered within 72 h, and histologic chorioamnionitis was present in 62% (23/37) of the cases with available placental pathologic examination. The median AF PTX3 concentration was significantly higher in women with histologic chorioamnionitis compared to those without placental inflammation (28.5 ng/mL vs. 1.32 ng/mL, respectively; P = 0.002) (Figure 4).

Discussion

Principal findings of the study

1) Pentraxin 3 is a physiologic constituent of the AF; 2) in women with spontaneous PTL and intact membranes, as well

Table 2 Demographic and clinical characteristics of women presenting with spontaneous preterm labor with intact membranes.

	PTL without IAI term delivery (n = 44)	P	PTL without IAI preterm delivery (n = 40)	P[a]	PTL with IAI preterm delivery (n = 62)	P[b]
Maternal age (years)	23 (20–27)	NS	21.5 (20–28.8)	NS	22 (20–26.8)	NS
Smoking	28.6 (6/21)	< 0.05	3.6 (1/28)	< 0.05	24.2 (8/33)	NS
GA at amniocentesis (weeks)	30.5 (27.7–33.2)	NS	31.9 (28.1–33.3)	< 0.05	28.9 (26.5–32.7)	NS
GA at delivery (weeks)	39.1 (38.1–40)	< 0.001	34.6 (33.2–35.8)	< 0.001	30.6 (27.0–32.9)	< 0.001
Birthweight (g)	3154 (2910–3505)	< 0.001	2455 (1973–2693)	< 0.001	1515 (930–2112)	< 0.001

Values are expressed as percentage (number) or median (interquartile range).
P: Comparison between PTL who delivered at term and PTL without IAI, P[a]: Comparison between PTL who delivered preterm without IAI and PTL with IAI, P[b]: Comparison between PTL who delivered at term and PTL with IAI. PTL = preterm labor; GA = gestational age; IAI = intra-amniotic infection/inflammation; NS = not significant.

Table 3 Demographic and clinical characteristics of women presenting with preterm prelabor rupture of membranes.

	Preterm PROM without IAI (n = 36)	Preterm PROM with IAI (n = 63)	P
Maternal age (years)	24.5 (20–31)	26 (22–32)	NS
Smoking	28.6 (4/14)	29 (9/31)	NS
GA at amniocentesis (weeks)	31.5 (28.1–32.6)	30 (27–32)	NS
GA at delivery (weeks)	32.7 (30.9–33.8)	30.7 (28.4–32.6)	<0.05
Birthweight (g)	1837 (1455–2190)	1660 (1304–1895)	<0.05

Values expressed as percentage (number) or median (interquartile range). Preterm PROM = preterm prelabor rupture of membranes; GA = gestational age; IAI = intra-amniotic infection/inflammation; NS = not significant.

as in those with preterm PROM, the median AF PTX3 concentration was significantly elevated in the presence of IAI; 3) advancing GA and spontaneous labor at term were not associated with significant changes in the median AF PTX3 concentrations; and 4) AF PTX3 concentrations correlated significantly with indirect AF markers of IAI, such as IL-6.

What is PTX3?

Pentraxins are a group of evolutionarily conserved soluble PRRs and essential components of the humoral arm of the innate immune response, together with other soluble PRRs such as mannose-binding lectin, ficolins and the complement cascade [32]. Pentraxins are characterized by a distinctive cyclic pentameric structure [32, 34] and can be divided into short and long pentraxins, since they share a C-terminal pentraxin-like domain but the long pentraxins hold a unique and unrelated long N-terminal domain [13, 25, 34, 62, 68]. C-reactive protein (CRP) and serum amyloid P-component (SAP) are short pentraxins. CRP was the first described fluid-phase pattern recognition molecule and named after its ability to bind in a calcium-dependent manner the C-polysaccharide of *Streptococcus pneumoniae* [11]. CRP and SAP are acute-phase proteins that regulate innate resistence to microbes and scavenging of cellular debris [86].

PTX3, also called TNF stimulated gene 14 (TSG14) [62], is a 381 amino acids protein with a molecular weight of 40 kDa, and its gene is located on chromosome 3 [13]. PTX3

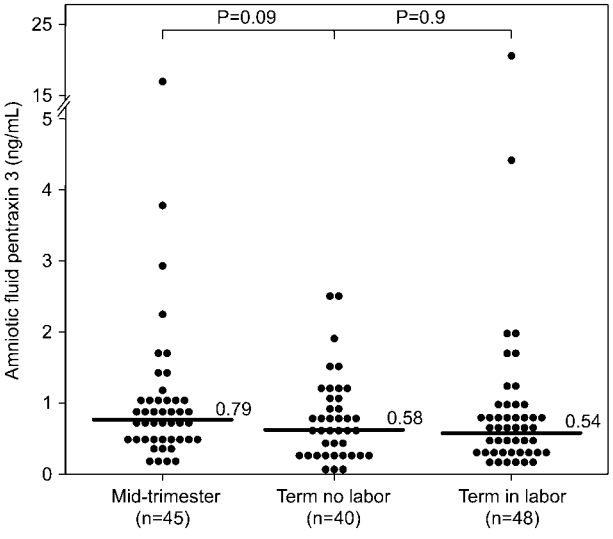

Figure 1 Amniotic fluid (AF) concentrations of pentraxin 3 (PTX3) in normal pregnancies at mid-trimester and in those at term with and without labor. There were no differences in the median AF PTX3 concentration between women in the mid-trimester and those with a normal pregnancy at term not in labor (0.79 ng/mL, IQR 0.57–1.08 vs. 0.58 ng/mL, IQR 0.27–1.05, respectively; P = 0.09); no significant differences were observed in the median AF PTX3 concentration between women with spontaneous labor at term and those at term not in labor (0.58 ng/mL, IQR 0.27–1.05 vs. 0.54 ng/mL, IQR 0.34–0.82, respectively; P = 0.9).

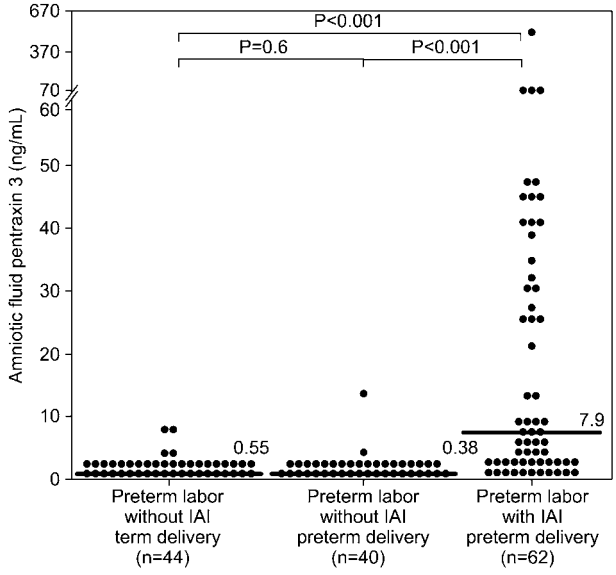

Figure 2 Amniotic fluid (AF) concentrations of pentraxin 3 (PTX3) among women with spontaneous preterm labor (PTL) and intact membranes. The median AF concentration of PTX3 was significantly higher in women with intra-amniotic infection/inflammation (IAI) than in women who delivered preterm without IAI (7.9 ng/mL, IQR 1.7–35.3 vs. 0.38 ng/mL, IQR 0.22–0.82; P < 0.001) and in those who delivered at term (0.55 ng/mL, IQR 0.24–1.19; P < 0.001). Among women without IAI, there was no significant difference in the median AF concentration of PTX3 between those who delivered preterm and those who delivered at term. (0.38 ng/mL, IQR 0.22–0.82 vs. 0.55 ng/mL, IQR 0.24–1.19; P = 0.6).

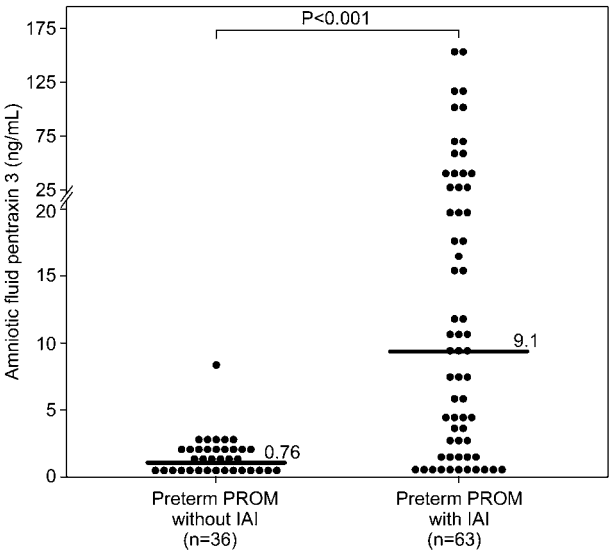

Figure 3 Amniotic fluid (AF) concentrations of pentraxin 3 (PTX3) in women with preterm prelabor rupture of the membranes (Preterm PROM). The median AF concentration of PTX3 was significantly higher in women with intra-amniotic infection/inflammation (IAI) than in those without IAI (9.1 ng/mL, IQR 1.85–29.6 vs. 0.76 ng/mL, IQR 0.34–1.53; $P < 0.001$).

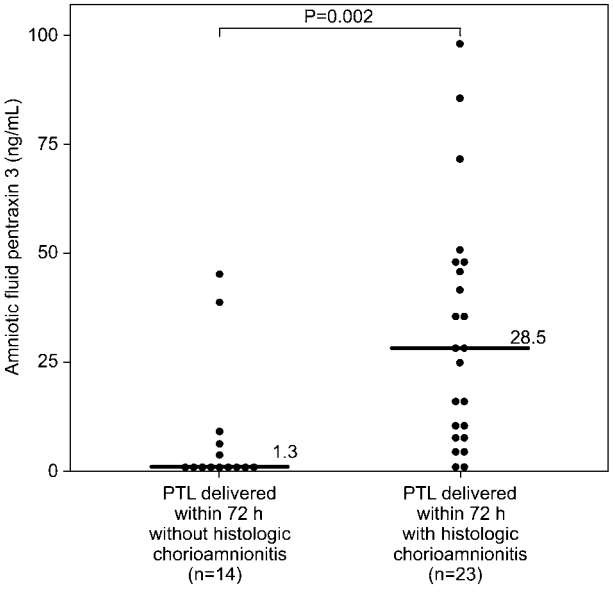

Figure 4 Amniotic fluid (AF) concentrations of pentraxin 3 (PTX3) in women with spontaneous preterm labor (PTL) with and without histologic chorioamnionitis who delivered within 72 h from amniocentesis. Women with histologic chorioamnionitis and/or funisitis had a significantly higher median PTX3 concentration in AF than those without histologic inflammation (28.5 ng/mL, IQR 9.25–48.68 vs. 1.32 ng/mL, IQR 0.63–7.36; $P = 0.002$).

was the first long pentraxin identified [13, 62, 63] and other members of this family subsequently discovered are neuronal pentraxin 1 [112], neuronal pentraxin 2 [50], neuronal pentraxin receptor [20], and guinea pig apexin [80]. Similarly to CRP, PTX3 performs as an acute phase response protein in plasma: its physiologic concentration is low (≤ 2 ng/mL) but increases rapidly (peak at 6–8 h) and dramatically (200–800 ng/mL) during inflammatory conditions, such as autoimmune disease, endotoxic shock, infections, degenerative disorders and sepsis [69, 75, 87].

PTX3 is expressed by human peripheral blood monocytes in response to IL-1β and tumor necrosis factor-α (TNF-α) or after stimulation with microbial components, such as lypopolysaccharide (LPS) [10, 32, 54], while IL-6, monocyte chemotactic protein 1 (MCP-1/CCL2), macrophage colony-stimulating factor (M-CSF), granulocyte–macrophage colony-stimulating factor (GM-CSF), or interferon-γ (IFN-γ), are not strong inducers of PTX3 [3, 11]. Interestingly, IL-10 is a mild inducer of PTX3 in monocytes and dendritic cells [88], and can amplify PTX3 production induced by LPS [11, 32].

PTX3 is also present in neuthrophil granules [52], acting as a reservoir for a rapid release after microbial recognition [11]. Dendritic cells [21, 22] produce high concentrations of PTX3 in response to LPS or TLR agonists, such as peptidoglycan (TLR2), double-stranded DNA (TLR3), *Candida* (TLR4), and flagellin (TLR5) [21]. In contrast to neutrophils, dendritic cells and macrophages produce PTX3 *de novo* in response to inflammatory signals [11]. Other cell types that produce PTX3 *in vitro* are endothelial cells [13, 62, 90], smooth muscle cells [57], epithelial cells [79], adipocytes [1], fibroblasts [113], synovial cells [66] and chondrocytes [124].

PTX3 and normal pregnancy

Only few studies have investigated PTX3 during pregnancy. It has been demonstrated that the maternal blood PTX3 concentration is significantly higher during normal pregnancy compared to non-pregnant women [14, 109], supporting the view that normal pregnancy is a pro-inflammatory state [49, 67, 76, 94, 110]. However, conflicting results have been reported regarding the changes in maternal circulating PTX3 concentration throughout gestation. While Rovere-Querini et al. [109] reported an increase in the maternal serum PTX3 concentrations with advancing GA and the highest concentration during labor, Cetin et al. [14] found no change in maternal plasma PTX3 concentrations during pregnancy.

PTX3 in pregnancy complications

Women with preeclampsia have a significantly higher (6–10-fold) median serum/plasma PTX3 concentration than women with uncomplicated pregnancies [14, 109]. Moreover, it has been reported that serum PTX3 concentrations correlate with the severity of preeclampsia [109]. Since PTX3 is expressed in endothelial cells [13, 90], it was proposed [14] that elevated circulating concentrations of PTX3 in women with preeclampsia may represent a state of endothelial dysfunction that characterizes this obstetrical syndrome [15, 33, 93, 95, 96, 119]. Indeed, PTX3 has been recently considered to be a marker of vascular bed injury in conditions, such as myo-

cardial infarction [60, 87, 111] and disorders associated with autoimmunity, such as small-vessel vasculitis [28, 123]. Vascular endothelial cells and smooth muscle cells produce high concentrations of PTX3 in response to inflammatory signals, suggesting a role as a regulator of endothelium during thrombogenesis and ischemic vasculature disease [57, 90, 97].

A single study reported on maternal circulating PTX3 concentrations in women with preterm delivery. Assi et al. [6] reported that, regardless of the clinical presentation (PTL or preterm PROM), women with a preterm delivery (<34 weeks) had a significantly higher maternal plasma PTX3 concentration (but not in vaginal fluid) than normal pregnant women. Moreover, women with placental vasculopathy had significantly higher plasma PTX3 concentrations than those without these placental lesions. In contrast, no differences were found in the peak plasma or peak vaginal concentration of PTX3 between women with and without clinical and/or histologic chorioamnionitis. The authors suggested that elevated PTX3 concentrations in maternal plasma of women with PTL or preterm PROM may be associated to mechanisms other than intra-uterine infection, such as insults related to placental underperfusion [6].

PTX3 in AF in normal pregnancy and term parturition

There is a paucity of information regarding PTX3 concentration in AF. In this study, PTX3 was detected in 95% of AF samples, suggesting that this molecule is a physiologic constituent of the AF. In addition, we observed that AF PTX3 concentrations did not change significantly with advancing GA. This finding is in agreement with a report by Greco et al. [43] who compared PTX3 concentrations in AF obtained in mid-trimester amniocenteses and during elective cesarean sections from uncomplicated pregnancies [43].

Spontaneous labor at term is regarded as an inflammatory process [44, 55, 65, 81, 98, 103, 121]. In the study reported herein, labor at term was not associated with a significant change in the AF concentration of PTX3, whereas Rovere-Querini et al. [109] reported that the maternal serum PTX3 concentrations peaked during labor. These results suggest that PTX3 in AF may have a limited role in the physiologic process of parturition at term.

PTX3 in AF and intra-amniotic infection/inflammation

The findings that IAI is associated with an elevated median AF concentration of PTX3 in women with PTL and in those with preterm PROM, as well as in women with histologic chorioamnionitis, are novel. Among women with PTL or preterm PROM, the presence of IAI was associated with a 16-fold and a 12-fold increase in AF PTX3 concentrations, respectively. Similarly, women with histologic chorioamnionitis had a dramatically higher AF PTX3 concentration (22-fold) than those without placental inflammation. Furthermore, a significant correlation was observed between AF PTX3 concentrations and indirect markers of intra-amniotic infection, such as IL-6. Recently, Greco et al. [43] reported an increased concentration of PTX3 in AF collected from the vaginal fornix from women with preterm PROM, and the AF concentration of PTX3 correlated with the presence of histologic chorioamnionitis.

Compelling evidence supports the notion that PTX3 plays an important role against bacterial infection caused by *Staphylococcus aureus*, *Pseudomonas aeroginosa*, *Salmonella typhimurium*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Neisseria meningitides* [31, 54], fungal infection caused by *Aspergillus fumigatus* and *Paracoccidioides brasiliensis* [19, 31], and viral infections, such as cytomegalovirus (CMV) and H3N2 influenza virus [12, 91]. In addition, the binding of PTX3 with C1q, which was the first described ligand for PTX3, activates the classical pathway of the complement system and facilitates pathogen recognition by phagocytes [78, 108]. PTX3 also modulates factor H, which is considered the main soluble regulator of the alternative pathway, preventing an exaggerated activation of the complement system [18]. Thus, it has been proposed that PTX3 participates in the crosstalk between the cellular and humoral arms of the innate immunity in response to microbial invasion by facilitating the activity of the cellular arm of the innate immune response and modulating complement activation [11]. This supports the concept of activation of the innate immune system and the complement cascade as part of the inflammatory response to microbial invasion of the amniotic cavity [24, 114, 115, 122].

What is the origin of PTX3 in AF?

The origin of PTX3 in the AF and the main compartment contributing to the higher concentrations in cases with IAI is still unknown. Several potential sources can be suggested: 1) PTX3 was shown to be physiologically expressed in fetal membranes (amniotic epithelium, chorionic mesoderm) from uncomplicated pregnancies [42, 109]. Furthermore, its expression increased in membranes from pregnancies complicated by preterm PROM and/or with histologic chorioamnionitis [42]. This suggests that the fetal membranes may contribute to the higher AF concentration of PTX3 observed in cases with IAI and histologic chorioamnionitis; 2) the fetus is capable of mounting an inflammatory response to the presence of microbial invasion of the amniotic cavity [37, 41, 102] characterized by systemic activation of the innate immune system. Indeed, it has been reported that CRP, one of the short pentraxins, is significantly higher in preterm neonates from mothers with a positive AF culture than in those with negative culture, as well as in neonates with funisitis than in those without funisitis [131]. Although there are no data regarding PTX3 in cord blood, it is possible that AF PTX3 may represent, in part, a fetal inflammatory response to intra-amniotic infection; and 3) in maternal circulation, PTX3 concentrations were shown to increase with advancing gestation and to peak during term labor [109]. However, the lack of significant change in AF PTX3 concentrations throughout gestation and during term parturition suggests that maternal blood and AF are two independent compartments.

In conclusion, this study demonstrates that PTX3 is a physiologic constituent of the AF, and its concentration is significantly elevated in the presence of IAI, suggesting that PTX3 may play a role in the innate immune response against intra-amniotic infection.

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