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Soluble ST2, a Modulator of the Inflammatory Response, in Preterm and Term Labor

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Abstract

Objective—Intra-amniotic infection/inflammation (IAI) is causally linked with spontaneous preterm labor and delivery. The ST2L receptor and its soluble form (sST2) are capable of binding to interleukin (IL)-33, a member of the IL-1 superfamily. Members of this cytokine family have been implicated in the onset of spontaneous preterm labor in the context of infection. Soluble ST2 has anti-inflammatory properties, and plasma concentrations are elevated in systemic inflammation, such as sepsis, acute pyelonephritis in pregnancy and the fetal inflammatory response syndrome. The aims of this study were to examine: 1) whether amniotic fluid concentrations of sST2 change with IAI, preterm, and term parturition; and 2) if mRNA expression of ST2 in the chorioamniotic membranes changes with acute histologic chorioamnionitis in women who deliver preterm.

Methods—A cross-sectional study was conducted to determine amniotic fluid concentrations of sST2 in: 1) women with preterm labor (PTL) who delivered at term (n=49); 2) women with PTL who delivered preterm without IAI (n=21); 3) women with PTL who delivered preterm with IAI (n=31); 4) term pregnancies not in labor (n=13); and 5) term pregnancies in labor (n=43). The amniotic fluid concentration of sST2 was determined by ELISA. The mRNA expression of ST2 in the chorioamniotic membranes of women who delivered preterm with (n=24), and without acute histologic chorioamnionitis (n=19) was determined by qRT-PCR.

Results—1) Patients with PTL who delivered preterm with IAI had a lower median amniotic fluid concentration of sST2 compared to those with PTL who delivered preterm without IAI [median 410 ng/mL, inter-quartile range (IQR) 152-699 ng/mL vs. median 825 ng/mL, IQR

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493-1216 ng/mL; p=0.0003] and those with PTL who delivered at term [median 410 ng/mL, IQR 152-699 ng/mL vs. median 673 ng/mL, IQR 468-1045ng/mL; p=0.0003]; 2) no significant differences in the median amniotic fluid concentration of sST2 were observed between patients with PTL who delivered at term and those who delivered preterm without IAI (p=0.4), and between women at term in labor and those at term not in labor (p=0.9); 3) the mean mRNA expression of ST2 was 4-fold lower in women who delivered preterm with acute histologic chorioamnionitis than in those without this lesion (p=0.008).

Conclusions—The median sST2 amniotic fluid concentration and mRNA expression of ST2 by chorioamniotic membranes is lower in PTL associated with IAI and acute histologic chorioamnionitis than in PTL without these conditions. Changes in the median amniotic fluid sST2 concentration are not observed in preterm and term parturition without IAI. Thus, amniotic fluid sST2 in the presence of IAI behaves differently when compared to sST2 in the plasma of individuals affected by fetal inflammatory response syndrome, acute pyelonephritis in pregnancy, and adult sepsis. Decreased concentrations of sST2 in IAI are likely to promote a pro-inflammatory response, which is important for parturition in the context of infection.

Introduction

Intra-amniotic infection is associated with spontaneous preterm parturition [1-38]. The gold standard for determining the presence of microbial invasion in the amniotic fluid is a positive culture for microorganisms [20,39]. The frequency of positive amniotic fluid cultures in patients with preterm labor (PTL) and intact membranes is 12.8% [39], and 32.4% in patients with preterm premature rupture of the membranes (pPROM) [39]. The earlier the gestational age at preterm delivery, the higher the prevalence of intra-amniotic infection [40,41]. With the use of molecular microbiologic techniques, the frequency of microbial invasion of the amniotic cavity has been determined to be higher than that previously reported by culture [42-47].

The mechanisms responsible for preterm parturition in the context of infection involve the production of pro-inflammatory cytokines and chemokines [14,20,22,25,48-72]. The first cytokine to be implicated in the mechanism of parturition was interleukin (IL)-1β [17,48,51,73,74]. This cytokine is produced by the human decidua in response to microbial products, can stimulate prostaglandin production, can induce the onset of labor in pregnant mice, and administration of the IL-1 receptor antagonist can abrogate the effect of IL-1 in the induction of parturition [48,75,76]. Tumor necrosis factor-α has similar properties as IL-1β, and a role in preterm labor associated with infection has also been proposed [22,50,51,59,73,77-81]. Among chemokines, IL-8 [82-95], monocyte chemoattractant protein-1 [96-100], macrophage inflammatory protein-1α [53,101,102], and growth regulated oncogene-α [103-105] have also been shown to play a role in preterm parturition.

Acute inflammation of the chorioamniotic membranes is the maternal response to the presence of intra-amniotic infection [70,106-108]. In 72% of placentas with acute histologic chorioamnionitis, bacteria are isolated from the subchorionic plate [109-112]. Funisitis and chorionic vasculitis are the histologic hallmarks of the fetal inflammatory response syndrome (FIRS) [113-115]. Fetuses with FIRS are at increased risk for the development of

short and long-term complications [116-118] such as sepsis [54,113,119-121], intraventricular hemorrhage [122-124], periventricular leukomalacia [125-128], cerebral palsy [129-139], chronic lung disease [140-148], and retinopathy of prematurity [149-151]. In this context, the onset of preterm labor mediated by inflammation most likely represents the host defense mechanism against infection, and could be of survival value for both mother and fetus [113,152].

Toll-like receptors (TLRs), a family of pattern-recognition receptors, represent one of the mechanisms by which the innate immune system recognizes the presence of microorganisms [153-157] and triggers inflammation [158,159]. TLR-2 and TLR-4 are expressed in the dendritic cells, monocytes/macrophages [160], and in a wide range of epithelial cells [161-163]. The amniotic epithelium also expresses TLR-2 and TLR-4, and this increases in the presence of acute histologic chorioamnionitis [164]. This observation indicates that the innate immune system is part of the host defense in the presence of intra-amniotic infection [164]. Indeed, the spontaneous deletion of TLR-4 protects against lipopolysaccharide (LPS) induced preterm labor [165].

ST2 is a gene located on chromosome 2 in humans [166,167], and its two main products are a trans-membranous receptor expressed on Th2, but not Th1 immune cells (ST2L) [168-170], and a decoy receptor, soluble ST2 (sST2) [168,171]. IL-33 is the ligand for the ST2L receptor, and it stimulates the Th2 type immune response [172]. This interaction can be interrupted by sST2, which binds IL-33 and suppress its stimulating properties [171]. Soluble ST2 is involved in regulation of the Th1/Th2-associated immune response and modulation of the inflammatory response in the presence of infection [170,173-175], while it has anti-inflammatory properties through negative regulation of TLR-2 and TLR-4 [176,177]. Soluble ST2 has been implicated in several pathological conditions such as allergic asthma [178-183], lung fibrosis [184,185], chronic obstructive pulmonary disease [186], acute myocardial infarction [187,188] and preeclampsia [189,190]. Moreover, plasma concentrations of sST2 are elevated in patients with systemic inflammation (e.g. sepsis) [191,192], acute pyelonephritis in pregnancy (unpublished observation), and in the presence of FIRS [193].

The objectives of this study were to examine: 1) whether amniotic fluid concentrations of sST2 change during IAI and preterm or term parturition; and 2) whether ST2 mRNA expression in the chorioamniotic membranes changes in the presence of acute histologic chorioamnionitis in women who deliver preterm.

Material and methods

Study design and population

This is a retrospective cross-sectional study conducted by searching our clinical database and bank of biologic samples, including 157 patients who had amniotic fluid samples obtained by trans-abdominal amniocentesis. Women were included into the following groups: 1) patients with PTL who delivered at term (n=49); (2) those with PTL who delivered preterm with IAI (n=31) and without (n=21); and (3) term pregnancies in labor

(n=43) and not in labor (n=15). Women with multiple gestations, or those who had fetuses affected with chromosomal and/or sonographic abnormalities were excluded.

In a separate cohort of 43 patients with spontaneous preterm delivery, ST2 mRNA expression was determined in the chorioamniotic membranes collected from those with (n=24), and without acute histologic chorioamnionitis (n=19).

All women provided written informed consent before the collection of biological samples. The collection and utilization of the samples was approved by the Human Investigation Committee of the participating institutions and the IRB of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NIH/DHHS). Many of these samples have been used in previous studies of inflammation and growth factors in pregnancy complications.

Clinical definitions

The diagnosis of preterm labor was made in the presence of regular uterine contractions (at least 3 in 30 minutes) and a documented cervical change in patients with a gestational age of 20 to 36 6/7 weeks who required hospitalization [194]. Women at term in labor consisted of those admitted for suspected preterm labor because of uncertain dates. However, those who delivered a neonate ≥ 2500 g without neonatal complications of prematurity were considered likely to represent patients in spontaneous labor at term [195]. IAI was defined as a positive culture for microorganisms in amniotic fluid and/or an elevated amniotic fluid IL-6 concentration (≥2.6 ng/mL) [196]. Acute histologic chorioamnionitis was diagnosed in the presence of neutrophil infiltration into the chorionic plate or extra-placental membranes according to criteria previously described [114].

Amniotic fluid sample collection

Amniotic fluid samples were obtained by trans-abdominal amniocentesis under ultrasound guidance. In patients with preterm labor, amniotic fluid samples were obtained to evaluate the microbial status of the amniotic cavity. Women at term (≥ 37 weeks) not in labor underwent amniocentesis to assess fetal lung maturity prior to cesarean delivery. Women at term in labor underwent amniocentesis to assess fetal lung maturity and the presence or absence of microbial invasion of the amniotic cavity (as described in the previous paragraph).

Samples of amniotic fluid were transported to the laboratory in a sterile capped syringe and cultured for aerobic/anaerobic bacteria and genital *Mycoplasmas*. White blood cell (WBC) count [16], glucose concentration [197], and Gram stain [198] were performed shortly after collection [16,197]. The results of these tests were used for clinical management, while the amniotic fluid IL-6 concentration results were used for research purposes only. Amniotic fluid not used for clinical management was centrifuged at 1300g for 10 min at 4°C, and the supernatant was stored at -70°C.

Determination of sST2 in amniotic fluid

Concentrations of sST2 and IL-6 in amniotic fluid were determined by sensitive and specific enzyme immunoassays obtained from R&D Systems (Minneapolis, MN). The initial assay validation was performed in our laboratory prior to the conduction of this study. The quantitative sandwich enzyme immunoassay technique was utilized and concentrations were determined by interpolation from standard curves. The inter- and intra-assay coefficients of variation for sST2 in amniotic fluid were 4.5% and 3.3%, respectively, and for IL-6, these were 8.7% and 4.6%, respectively. The sensitivity of the assay for sST2 and IL-6 was 20.1 pg/mL and 0.09 pg/mL, respectively.

ST2 mRNA expression in chorioamniotic membranes in acute histologic chorioamnionitis

Total RNAs were isolated from snap-frozen chorioamniotic membrane tissue samples by using a TRIzol reagent (Invitrogen, Carlsbad, CA, USA) and Qiagen RNeasy kit (Qiagen, Valencia, CA, USA) according to the manufacturer's recommendations. Five hundred nanograms of RNA samples were reverse transcribed using the SuperScript III First-Strand Synthesis System and oligo (dT)20 primers (Invitrogen, Carlsbad, CA, USA). All qRT-PCR analyses were carried out using TaqMan Assays (ST2 / IL1RL1: Hs01073300_m1; GAPDH: Hs99999905_m1; Applied Biosystems, Foster City, CA, USA) on a BioMark™ Real-Time PCR System (Fluidigm, South San Francisco, CA, USA) according to the manufacturers' instructions.

Statistical analysis

Kolmogorov-Smirnov and Shapiro-Wilk tests were used to determine if the data were normally distributed. Kruskal-Wallis and “post-hoc” Mann-Whitney *U* test were used to compare continuous non-parametric variables among and between groups. Comparisons between proportions were performed using Chi-square or Fisher's exact tests when appropriate. Correlation between two continuous variables was determined using Spearman's rank correlation test. A p value <0.05 was considered statistically significant. Analysis was performed using SPSS, version 19 (IBM Corp, Armonk, NY).

Gene expression analysis—The fold change between groups was estimated using a linear model in which the dependent variable was the -ΔCt value of the gene, while the independent variable was the study group. All data analysis was performed using the R statistical language and environment (www.r_project.org).

Results

Demographic and clinical characteristics of the study population

Demographic and clinical characteristics of the preterm and term labor groups are displayed in Tables 1 and 2, respectively. Among women in the preterm labor group, there were no significant differences in the median maternal age, body mass index (BMI) and gestational age at amniocentesis. As expected, due to the study design, the median interval to delivery, gestational age at delivery and birthweight were significantly different among the PTL subgroups (Table 1). The median maternal age, gestational age at amniocentesis and

gestational age at delivery in women at term in labor were not significantly different from those at term not in labor (Table 2).

Intra-amniotic infection/inflammation is associated with decreased median concentrations of sST2 in amniotic fluid

Patients with PTL who delivered preterm with IAI had a lower median amniotic fluid concentration of sST2 than: 1) women with PTL who delivered preterm without IAI [median 410 ng/mL, inter-quartile range (IQR) 152-699 ng/mL vs. median 825 ng/mL, IQR 493-1216 ng/mL; p=0.0003], and 2) women with PTL who delivered at term (median 410 ng/mL, IQR 152-699 ng/mL vs. median 673 ng/mL, IQR 468-1045; p=0.0003]; Figure 1). The median sST2 concentration of women with PTL who delivered at term did not differ significantly from women with PTL who delivered preterm without IAI (median 673 ng/mL; IQR 468-1045 ng/mL vs. median 825 ng/mL; IQR 493-1216; p=0.4; Figure 1). Amniotic fluid sST2 concentrations did not correlate with amniotic fluid concentrations of IL-6, WBC count, or glucose (Spearman's Rho -0.17 [p=0.09], -0.06 [p=0.6], -0.02 [p=0.8], respectively).

Labor at term is not associated with an elevation of amniotic fluid sST2 median concentration

When comparing women at term not in labor to those at term in labor, there was no significant difference in the median amniotic fluid concentration of sST2 (median 341 ng/mL; IQR 260– 539 ng/mL vs. median 353 ng/mL; IQR 181–527 ng/mL; p=0.9) (Figure 2).

ST2 mRNA expression is down-regulated in chorioamniotic membranes in the presence of acute histologic chorioamnionitis

A case-control study was conducted to determine ST2 mRNA expression by the fetal membranes in patients with, and without acute histologic chorioamnionitis. The median gestational age at delivery was not significantly different between women with PTL and acute histologic chorioamnionitis and women with PTL without this condition (median 31.4 weeks; IQR 30.4-32.6 weeks vs. median 32 weeks; IQR 30-33.1 weeks; p=0.6). The mean ST2 mRNA expression in the chorioamniotic membranes of patients with acute histologic chorioamnionitis was 4-fold lower compared to those without the lesion (p=0.008; Figure 3).

Discussion

Principal findings of the study

1) Women with PTL who delivered preterm with IAI have a lower median amniotic fluid sST2 concentration compared to women with PTL who delivered preterm, and compared to those who delivered at term without IAI; 2) median amniotic fluid sST2 concentration did not differ between women at term not in labor and women at term in labor; and 3) ST2 mRNA expression in the chorioamniotic membranes is down-regulated in women with acute histologic chorioamnionitis who delivered preterm compared to women who delivered preterm without this lesion.

Soluble ST2 decreases in preterm labor with intra-amniotic infection/inflammation

ST2L receptor and sST2 are generated by mRNA transcript alternative splicing from a single gene [168,199]. Therefore, the expression of sST2 and ST2L can be independent of each other, and the two proteins have different roles. ST2L stimulates, while sST2 has a suppressive role on the Th2 immune response [170,173,174]. Moreover, sST2 down-regulates the inflammatory response through the modulation of TLR expression [176,177]. TLRs are of crucial importance for the recognition of microorganisms and activation of the innate immune response (inflammation) [15,153-158]. Indeed, mice with a spontaneous mutation for TLR-4 are less likely to deliver preterm after intrauterine inoculation of heat killed bacteria or LPS than wild-type mice [165].

If the initial host response fails to recognize microbial products and does not initiate an inflammatory response, overwhelming sepsis can develop with widespread infection and multiple organ damage [200]. The administration of sST2 fusion protein in ST2 knock-out mice results in the suppression of pro-inflammatory cytokine production by macrophages in response to LPS [201], and it attenuates septic shock and collagen-induced arthritis [201,202].

The finding that patients with IAI have a lower median amniotic fluid concentration of sST2 than those without IAI could indicate that the cytokine network and its receptors are organized so that a pro-inflammatory response promotes preterm delivery. The observation that the amniotic fluid concentration of sST2 are decreased in the context of infection differs from that made in other compartments, such as peripheral blood in sepsis [191,192], FIRS [193], and acute pyelonephritis in pregnancy (unpublished observation). These differences could represent distinct homeostatic mechanisms in the amniotic cavity and circulation. The increased concentration of sST2 in peripheral blood may represent the activation of the anti-inflammatory limb of the immune response to prevent the deleterious effect of an exaggerated pro-inflammatory response of a cytokine storm. Indeed, some of the molecules that have modulatory properties on the immune response have different functions, depending on the tissue localization [203]. Nevertheless, pregnant women with intra-amniotic infection represent a unique condition in which there is a potential conflict between mother and fetus. Prolonging the pregnancy by inducing an anti-inflammatory response could decrease the risk of prematurity, and thus benefit the fetus; however this exposes both the mother and fetus to risks of uncontrolled infection and sepsis. Three different host defense strategies to infection have recently been proposed: avoidance, resistance and tolerance [204]. Low concentrations of sST2 in amniotic fluid in the presence of IAI, along with other immune changes, suggest that the host (both mother and fetus) favors preterm labor by inducing an inflammatory response. Accordingly, the mechanism of preterm labor in the presence of intraamniotic infection could represent the execution of avoidance by the initiation of labor.

ST2 mRNA expression is down-regulated in the chorioamniotic membranes of women who delivered preterm and have acute histologic chorioamnionitis

The observation that ST2 mRNA expression is down-regulated in the chorioamniotic membranes of women who delivered preterm and have acute histologic chorioamnionitis

further strengthens our hypothesis. Indeed, acute histologic chorioamnionitis often results from intra-amniotic infection [53,205-209], and it is the most common placental lesion in early spontaneous preterm birth [210-212]. Moreover, *in-vitro* experiments have shown that ST2 mRNA expression is decreased in amnion mesenchymal cells, but is increased in human umbilical vein endothelial cells after treatment with IL-1β [213]. This evidence is consistent with the observed changes of sST2 concentrations in amniotic fluid (lower concentration in IAI) and in umbilical cord plasma (elevated concentration in FIRS) [193].

Amniotic fluid sST2 concentrations do not change with preterm and term parturition in the absence of intra-amniotic infection/inflammation

To determine whether changes in amniotic fluid sST2 concentration are related to labor *per se*, we examined the concentration of this soluble receptor in the amniotic fluid of women at term (with and without labor), and in those with PTL in the absence of IAI. There were no differences in the median amniotic fluid concentration of sST2 between women at term in labor and those at term not in labor. Similarly, amniotic fluid sST2 concentrations in patients without IAI who delivered preterm did not differ from those with PTL who delivered at term. These findings represent further evidence that changes in amniotic fluid concentrations of sST2 in patients with IAI are most likely due to the presence of infection/inflammation, rather than parturition.

Strengths and limitations of the study

This is the first study to examine the changes of amniotic fluid sST2 concentration in preterm labor in the presence of IAI, as well as parturition. The observations herein were supported by evaluation of ST2 mRNA expression in the chorioamniotic membranes of preterm deliveries with, and without acute histologic chorioamnionitis. We have previously studied IL-33 concentrations in amniotic fluid of patients in preterm labor, and in all patients, IL-33 was below the sensitivity of the assay (n=10) (unpublished observation).

Conclusions

The median amniotic fluid concentration of sST2 and ST2 mRNA expression by the chorioamniotic membranes is lower in patients with IAI and acute histologic chorioamnionitis than in women without infection/inflammation in the amniotic cavity or acute inflammation in the chorioamniotic membranes. Term or preterm labor without IAI is not associated with changes in the median amniotic fluid concentration of sST2. Down-regulation of ST2 in the chorioamniotic membranes and amniotic fluid in the presence of infection-induced preterm labor may have a role in enhancing pro-inflammatory response in the amniotic fluid of these patients.

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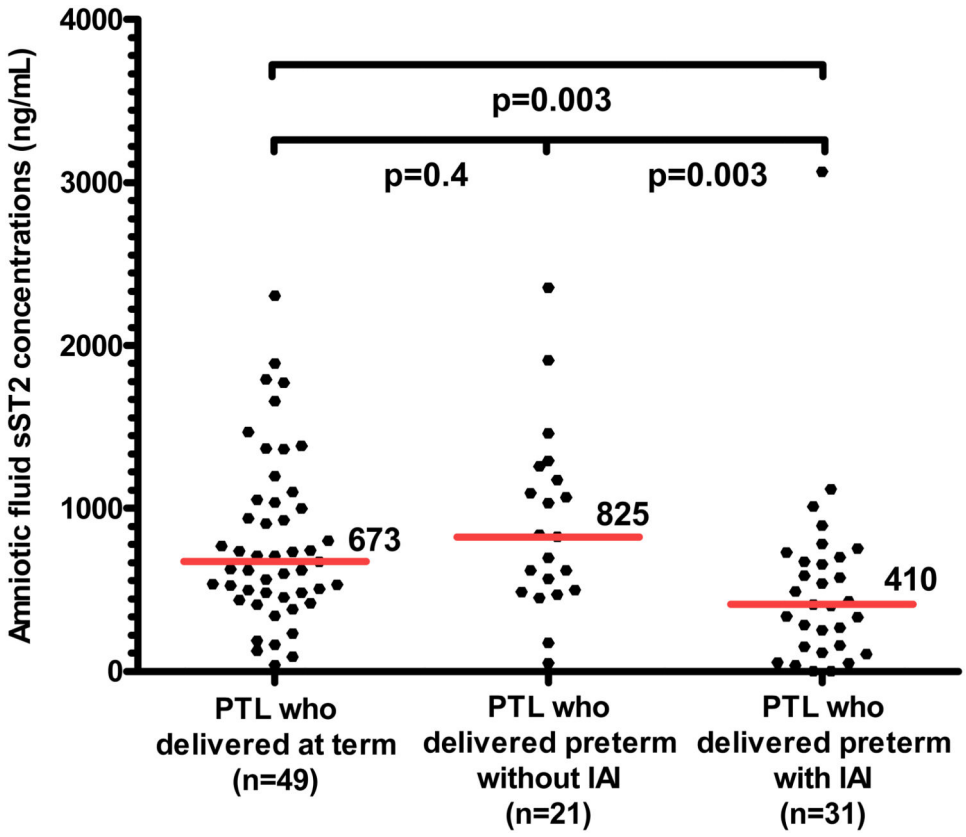

Figure 1.

Amniotic fluid concentrations of sST2 in preterm labor sub-groups.

The median amniotic fluid concentration of sST2 was significantly lower in women with PTL with intra-amniotic infection/inflammation (IAI) than in those who delivered preterm without IAI (median 410 ng/mL; IQR 152-699 vs. median 825 ng/mL; IQR 493-1216 [p=0.0003]) and those with PTL who delivered at term (median 410 ng/mL; IQR 152-699 vs. median 673 ng/mL; IQR 468-1045 [p=0.0003]). In the absence of IAI, there was no significant difference in the median amniotic fluid concentration of sST2 between women with PTL who delivered at term and those who delivered preterm without IAI (p=0.4).

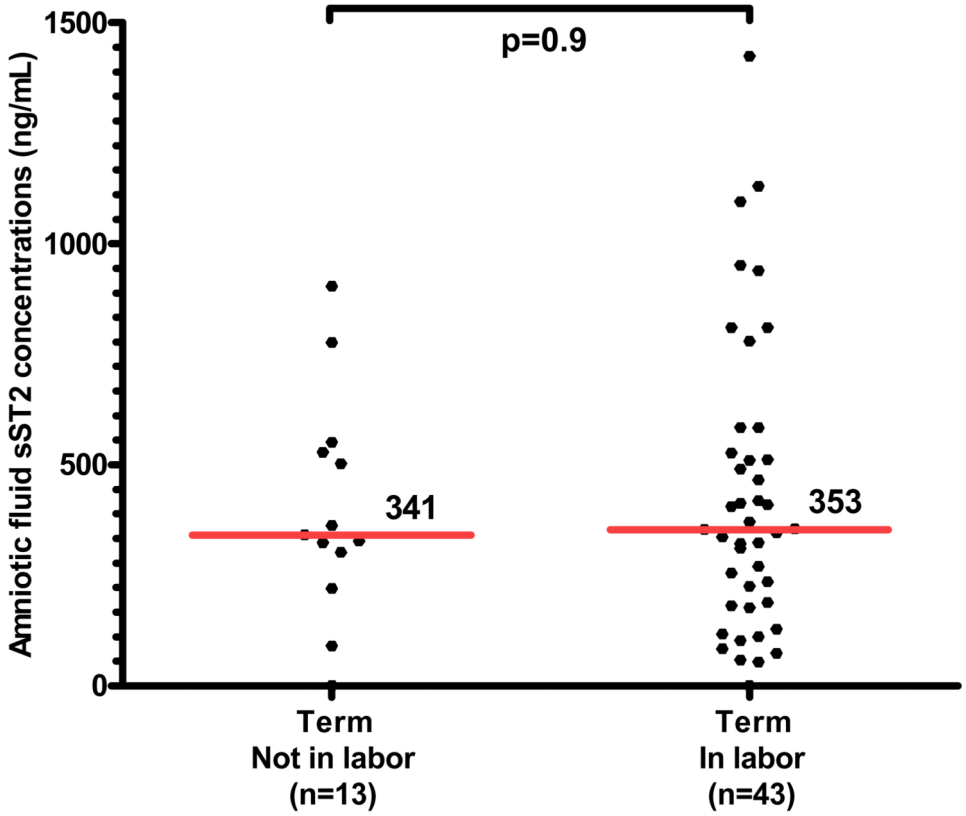

Figure 2. Amniotic fluid concentrations of sST2 in women at term

The median amniotic fluid concentration of sST2 was similar between women at term not in labor and those at term in labor (median 341 ng/mL; IQR 260–539 ng/mL vs. median 353 ng/mL; IQR 181–527 ng/mL; p=0.9).

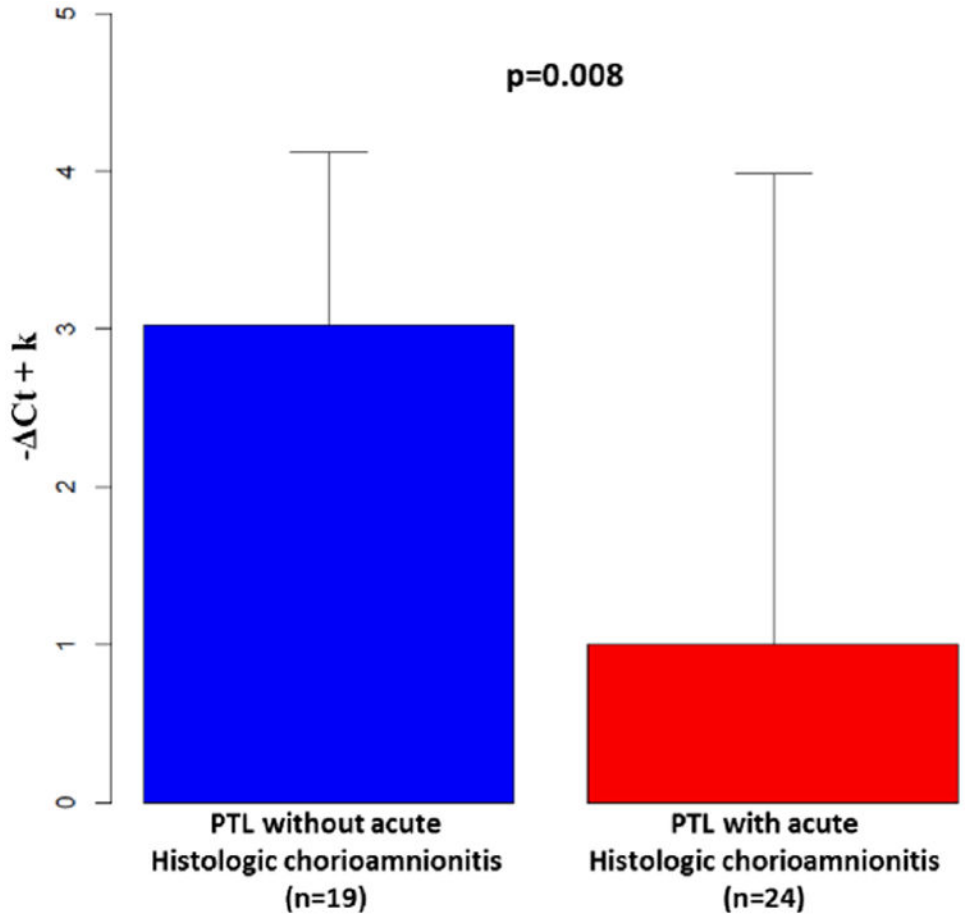

Figure 3.

ST2 mRNA expression by the chorioamniotic membranes.

The mean ST2 mRNA expression by the chorioamniotic membranes of patients who delivered preterm with acute histologic chorioamnionitis was 4-fold lower than those without this lesion (p=0.008). -ΔCt: fold change between groups estimated by a generalized linear model.

Table I

Demographic and clinical characteristics of the preterm labor sub-groups.

	Women with PTL who delivered at term (n=49)	Women with PTL who delivered preterm without IAI (n=21)	Women with PTL who delivered preterm with IAI (n=31)	*p*
Age (years)	21 (18 - 29.5)	21 (17.5 - 27.5)	24 (18 - 31)	0.43
BMI (kg/m^2)	22.2 (19.6 - 25.5)	22.6 (20.4 - 27.1)	23.3 (20.8 - 25.2)	0.38
GA at amniocentesis (weeks)	31.2 (27.5 - 33.2)	33.0 (30.9 - 33.5)	30.4 (26.4 - 33.2)	0.08
IL-6 (ng/mL)	0.43 (0.27 - 0.68)	0.53 (0.31 - 0.99)	21.5 (5.9 - 136)	<0.0001*
WBC (cells/μL)	2 (0 - 5.5)	4 (0 - 5.0)	6 (0 - 190)	0.03*
Glucose (mg/dL)	32 (23.3 - 43.5)	28.5 (20.3 - 38.8)	15 (3.0 - 34)	0.003*
Interval to delivery (days)	53.9 (37.8 - 72.1)	11.9 (3.2 - 28)	2.1 (0 - 6.3)	<0.0001*
GA at delivery (weeks)	39.0 (38.1 - 39.6)	34.4 (33.6 - 35.7)	31.6 (26.4 - 33.6)	<0.0001*
Birth weight (grams)	3320 (2985 - 3560)	2470 (2030 - 2770)	1950 (860 - 2360)	<0.0001*

Values expressed as median (inter-quartile range).

PTL: preterm labor; IAI: intra-amniotic infection/inflammation; BMI: body mass index; GA: gestational age; WBC: white blood cells.

* $p < 0.05$.

Table II

Demographic and clinical characteristics of the women at term sub-groups.

	Term not in labor (n=13)	Term in labor (n=43)	*p*
Age (years)	29 (21 – 32)	22 (20 – 28)	0.14
GA at amniocentesis (weeks)	39.5 (39 – 40.5)	39 (38 – 40)	0.4
GA at delivery (weeks)	39.5 (39 – 40.5)	39 (38 – 40)	0.4
Birth weight (grams)	3260 (3125 – 3790)	3250 (3100 – 3700)	0.6

Values expressed as median (inter-quartile range).

GA, gestational age.

* $p < 0.05$.