Published in final edited form as:
J Matern Fetal Neonatal Med. 2013 September ; 26(14): 1384–1393. doi: 10.3109/14767058.2013.784258.

Soluble ST2 in the Fetal Inflammatory Response Syndrome: In-vivo Evidence of Activation of the Anti-inflammatory Limb of the Immune Response

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Abstract

Objective—Inflammation is a mechanism of host response to infection which can be harmful when inappropriately modulated. Soluble ST2 (sST2) is a decoy receptor of interleukin (IL)-33, and this complex modulates the balance in the Th1/Th2 immune response. Moreover, sST2 inhibits the production of pro-inflammatory cytokines in cooperation with an anti-inflammatory cytokine, IL-10. The objectives of this study were to: 1) determine whether umbilical cord plasma sST2 concentration differ between comparing preterm neonates with and without funisitis and between those with and without the fetal inflammatory response syndrome (FIRS); and 2) evaluate the relationship between sST2 and IL-10 among neonates with funisitis and/or FIRS.

Methods—Umbilical cord plasma was collected from neonates delivered prematurely due to preterm labor or preterm prelabor rupture of membranes with (n=36), and without funisitis (n=30). FIRS (umbilical cord IL-6 concentration ≥17.5 pg/mL) was identified in 29 neonates. Plasma sST2 and IL-10 concentrations were determined by ELISA.

Results—The median umbilical cord plasma sST2 concentration was 6.7-fold higher in neonates with FIRS than in those without FIRS (median 44.6 ng/mL, interquartile range [IQR] 13.8–80.3 ng/mL vs. median 6.7 ng/mL, IQR 5.6–20.1 ng/mL; $p<0.0001$). Similarly, the median umbilical cord plasma sST2 concentration was 2.6-fold higher in neonates with funisitis than in those without funisitis (median 19.1 ng/mL; IQR 7.1–75.0 ng/mL vs. median 7.2 ng/mL; IQR 5.9–23.1 ng/mL; $p=0.008$). There was a strong positive correlation between sST2 and IL-10 in neonates with funisitis and/or FIRS (Spearman's Rho=0.7, $p<0.0001$).

Conclusions—FIRS and funisitis are associated with an elevation of umbilical cord plasma concentrations of soluble ST2. This protein represents an important mediator of the immune

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response in neonates diagnosed with fetal inflammatory response syndrome by promoting an anti-inflammatory effect in association with IL-10.

Keywords

funisitis; IL-10; intra-amniotic infection/inflammation; inflammation; preterm labor

Introduction

Intra-amniotic infection is associated with the spontaneous onset of labor [1–9] in patients with preterm labor (PTL) and intact membranes [10–27], and patients with preterm prelabor rupture of membranes (PROM) [28–38]. Moreover, this condition has been identified in a subset of patients with a short cervix [39–42], cervical insufficiency [43,44], and other conditions which confer increased risk for preterm delivery, such as an intrauterine device in pregnancy [45], vaginal bleeding [46], and placenta previa [47].

Microbial invasion of the amniotic cavity (MIAC) can lead to fetal infection [21,48–51]. Indeed, fetal bacteremia detected in blood obtained by cordocentesis has been reported in 30% of patients who have intra-amniotic infection [51], and one-fifth of preterm neonates born before 32 weeks of gestation have evidence of bacteremia in umbilical cord blood [52,53]. Subsequently, fetal microbial invasion may lead to a systemic inflammatory response, which we have termed the fetal inflammatory response syndrome (FIRS) [21,54]. This can be detected by the presence of elevated concentrations of cytokines, such as interleukin (IL) 6, in umbilical cord blood [21,55,56] or alternatively, by the presence of inflammation in the umbilical cord (funisitis) [55–58] or chorionic vasculitis [58].

FIRS is associated with the impending onset of labor [59], as well as multi-systemic involvement and high risk of short- and long-term complications [21,54,56,60]. The fetal organ systems involved include the skin [61–63], heart [64–66], lungs [67–74], eyes [75], kidneys [76], adrenal glands [77], hematologic system [78–80], thymus [81–83] and the central nervous system [84–97]. Although FIRS is frequently found in patients with intra-amniotic infection/inflammation (IAI), it can also be observed in fetuses with congenital viral infection [98–104] or alloimmunization [105].

Inflammation is a host defense mechanism elicited by insults such as infection [106], trauma [107], ischemia-reperfusion injury [108,109], necrosis [110], and tissue injury [111,112]. The innate immune system provides the first line of defense against infection through the engagement of pattern recognition receptors (i.e. Toll-like receptors, TLRs) [113–117], which recognize microbial products [118–120] and induce an inflammatory response [121–123] through the production of both chemokines and cytokines [123–125]. The crucial balance between pro- and anti-inflammatory responses is regulated, in part, by an inhibitory system activated by the anti-inflammatory limb of the immune response [126–129]. IL-10 is considered a key player in this process, serving as a major anti-inflammatory mediator, since it is produced mainly by monocytes and inhibits the transcription of pro-inflammatory cytokines [126,130,131]. Inappropriate modulation of this process may result in immunosuppression or an exaggerated inflammatory response; both can be harmful to the

host, as shown in experimental and observational studies [56,67,132]. Indeed, a major cause of death in patients with sepsis is immunosuppression [133].

ST2 is a member of the IL-1 receptor super-family [134] and exists in four isoforms. The two best characterized isoforms are: 1) ST2L, a membrane receptor; and 2) soluble ST2 (sST2)[134,135]. The ligand for ST2L and sST2 is IL-33 [136]. Upon binding to ST2L, IL-33 is capable of stimulating the Th2 type immune response and cytokine production [137–139]. In contrast, sST2 acts as a decoy receptor for IL-33 and is thought to inhibit IL-33 function, thus favoring a shift towards the Th1 immune response [140–143]. Besides its regulatory properties on the type of the adaptive immune response, sST2 also plays a role in innate immunity [132,144–146]. Elevated sST2 production has been observed during inflammatory conditions, such as lipopolysaccharide (LPS)-induced inflammation [147,148] and ultraviolet light irradiation [149]. However, several studies have demonstrated that sST2 has anti-inflammatory properties [132,145,146]. This beneficial effect of sST2 is thought to be mediated by IL-10 [132]. During pregnancy, plasma sST2 concentrations were higher in women with preeclampsia than in those with uncomplicated pregnancies [150,151]. In contrast, among women with PTL, those with IAI had a lower median amniotic fluid sST2 concentration than those without IAI [152]. Interestingly, IL-33 expression was also found in macrophages of the chorioamniotic membranes in acute chorioamnionitis [153].

The objectives of this study were to: 1) determine whether umbilical cord plasma sST2 concentration differ between comparing preterm neonates with and without funisitis (the histologic counterpart of FIRS) and between those with and without FIRS (defined as umbilical cord IL-6 concentration ≥17.5 pg/mL); and 2) evaluate the relationship between sST2 and IL-10 in neonates with funisitis and/or FIRS.

Patients and methods

Study design and population

A retrospective cross-sectional study was conducted by searching the Detroit Medical Center/Wayne State University/Perinatology Research Branch (NICHD/NIH) clinical database and bank of biological samples. Sixty-six pregnant women with spontaneous preterm delivery (either PTL or preterm PROM) between 27 and 34 weeks of gestation with (n=36), and without (n=30) funisitis were included. Multiple gestations and pregnancies with fetal chromosomal and/or structural anomalies were excluded. Umbilical cord blood was collected immediately after birth. Placentas underwent histopathologic examination after delivery.

All women provided written informed consent before the collection of biological samples. The collection and utilization of the samples was approved by the IRB of Wayne State University and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NIH/DHHS). Many of these samples have been used in previous studies.

Clinical definitions

The diagnosis of PTL was made in the presence of regular uterine contractions (at least 3 in 30 minutes) and documented cervical change. Preterm PROM was diagnosed with sterile

speculum examination by the combination of vaginal pooling, nitrazine and/or ferning test. Funisitis was diagnosed in the presence of neutrophil infiltration into the umbilical vessel wall or Wharton's jelly, according to criteria previously described [58]. FIRS was defined as an umbilical cord blood IL-6 concentration ≥ 17.5 pg/mL [55,154].

Diagnosis of funisitis—Tissue sections for histopathologic evaluation included one chorioamniotic membrane roll, two full-thickness sections from the placental disc and one section of the umbilical cord. Tissues were fixed in 10% neutral buffered formalin, embedded in paraffin, and stained with hemotoxylin and eosin. Histopathologic examination was performed by a perinatal pathologist who was blinded to the clinical information.

Sample collection and determination of sST2 in umbilical cord plasma

Umbilical cord blood was collected immediately after birth into tubes containing EDTA. Blood was centrifuged at 1300 g for 10 minutes at 4°C. The samples were stored at −70 °C until analysis. Specific enzyme-linked immunoassays were used for the determination of umbilical cord plasma concentrations of sST2, IL-6 and IL-10 (R&D Systems, Minneapolis, MN, USA). The quantitative sandwich enzyme immunoassay was employed. The inter- and intra-assay coefficients of variation were: 1) sST2 4.6% and 3.9%, respectively; 2) IL-10 6.9% and 4.4%, respectively; and 3) IL-6 8.7% and 4.6%, respectively. The sensitivity was 17.5 pg/mL for sST2, 0.65 pg/mL for IL-10, and 0.09 pg/mL for IL-6.

Statistical analysis

The Shapiro-Wilk test was used to determine if the data were normally distributed. The Mann-Whitney U test was used to compare continuous non-parametric variables between groups. Comparison between proportions was performed using the Chi-square or Fisher's exact tests. Correlation between two continuous variables was determined using Spearman's rank correlation test. Multivariable general linear models including effect modification terms were constructed to examine whether the relationship between sST2 and IL-10 differed significantly as a function of either preterm PROM or gestational age at delivery. Plasma sST2 concentrations were log base 2 transformed to meet the assumptions of linear regression. A p value <0.05 was considered statistically significant. Analysis was performed with SPSS, version 19 (IBM Corp, Armonk, NY) and SAS version 9.3 (Cary, NC).

Results

Demographic and clinical characteristics of the study population

Demographic and clinical characteristics of the study population are presented in Table I. There were no significant differences in maternal age, gestational age at delivery, and birthweight between neonates with and without funisitis (Table I). The frequency of patients presenting with spontaneous PTL and intact membranes or preterm PROM was not significantly different between these groups (p=0.6; Table I). Similarly, when comparing neonates with and without FIRS, there were no significant differences in maternal age, gestational age at delivery, or birth weight (Table II). Neither umbilical cord plasma concentrations of sST2 nor IL-10 were correlated with gestational age at delivery

(Spearman's Rho −0.07, p=0.6 and 0.01, p=0.9, respectively). Two of 29 neonates with FIRS did not have funisitis.

Funisitis was associated with an increase in the umbilical cord plasma sST2 median concentration

Soluble ST2 was detected in all samples. The median umbilical cord plasma concentration of sST2 was 2.7-fold higher in neonates with funisitis than in those without funisitis (19.1 ng/mL; IQR 7.1–75.0 ng/mL vs. 7.2 ng/mL; IQR 5.9–23.1 ng/mL; p=0.008; Figure 1). IL-10 was below the detection limit of the assay in 16 patients; of these, three neonates had funisitis and none had FIRS. The median umbilical cord plasma concentration of IL-10 was also significantly greater in neonates with funisitis, than in those without funisitis (4.2 pg/mL; IQR 2.8–7.8 pg/mL vs. 1.9 pg/mL; IQR 0–2.7 pg/mL; p<0.0001).

Among neonates with funisitis, there was a significant positive correlation between umbilical cord plasma concentrations of sST2 and IL-10 (Spearman's Rho=0.7, p<0.0001; Figure 2). In contrast, there was no significant correlation between umbilical cord plasma concentrations of sST2 and IL-10 among neonates without funisitis (Spearman's Rho=−0.1, p=0.4; Figure 3).

FIRS was associated with an increase in the umbilical cord plasma sST2 concentration

The median plasma concentration of sST2 in the umbilical cord was 6.7-fold higher in neonates with FIRS, than in those without FIRS (44.6 ng/mL; IQR 13.8–80.3 ng/mL vs. 6.7 ng/mL; IQR 5.6–20.1 ng/mL; p<0.0001; Figure 4). The median plasma IL-10 concentration in umbilical cord of neonates with FIRS was significantly greater than in those without FIRS (5.3 pg/mL; IQR 3.5–10.9 pg/mL vs. 2.5 pg/mL; IQR 2.1–3.6 pg/mL; p<0.0001)

Among neonates with FIRS, a significant positive correlation between umbilical cord plasma concentrations of sST2 and IL-10 (Spearman's Rho=0.7, p<0.0001) was observed. In contrast, among patients without FIRS, there was no correlation between umbilical cord plasma concentrations of sST2 and IL-10 (Spearman's Rho=−0.2, p=0.1).

Use of a general linear models to examine whether the relation between IL-10 and sST2 differed as a function of preterm PROM revealed no evidence of effect modification, neither overall (p=0.27), in the presence of FIRS/funisitis (p=0.43), nor in the absence of FIRS/funisitis (p=0.32). Similarly, the relationship between FIRS/funisitis and sST2 did not vary as a function of preterm PROM (p=0.57).

DISCUSSION

Principal findings of the study

1) Preterm neonates with FIRS and/or funisitis had greater umbilical cord plasma concentrations of sST2 than neonates without FIRS and/or funisitis; 2) the median umbilical cord plasma sST2 concentration was 6.7-fold higher in FIRS and 2.7-fold higher in funisitis, compared to those without these conditions; and 3) there was a strong positive correlation between sST2 and IL-10 concentrations in the umbilical cord plasma in neonates with FIRS and/or funisitis, but not in neonates without these conditions.

The role of ST2 in infection/inflammation—ST2 has been intensively investigated to determine its involvement in the regulation of the Th1/Th2 adaptive immune response. Emerging evidence suggests that ST2 plays a role in regulating the innate limb of the immune response through inhibition of TLRs signaling [145,146,155]. TLRs are members of the Toll/IL-1R (TIR) superfamily, which also includes ST2 along with IL-1 and IL-18 [156]. TLR signaling can activate many genes identical to those induced by IL-1 [157], and, thus, are important for the initiation and development of the pro-inflammatory response. Nevertheless, a balance between activation and inhibition is required in order to avoid detrimental inflammation. Thus, negative regulators of TIR signaling are essential to achieve an immunological balance. Indeed, in contrast to other TIR family members which induce the inflammatory response through the activation of NF-κB, the TIR domain of the ST2 receptor activates mitogen-activated protein kinases [158]. Moreover, ST2 has been shown to sequester the adaptor proteins, myeloid differentiation primary response (MyD)88 and MyD88-adapter-like protein through its TIR domain, resulting in TLR4 down-regulation [146,155]. Similarly, another study has reported negative regulation of TLR2 by ST2, affecting the formation of TLR2-MyD88 and MyD88-IL-1R associated kinase immune-complexes [155].

There is also evidence that ST2 is an important selective negative regulator of the TIR domain containing receptor function [146]. Thus, it is not surprising that macrophages from ST2-deficient mice produce more pro-inflammatory cytokines in response to LPS or bacterial lipoprotein than wild-type mice. This leads to a sustained pro-inflammatory cytokine production by ST2 deficient macrophages [146]. On the other hand, sST2 has an inhibitory effect on pro-inflammatory cytokine production. Evidence in support of this is: 1) sST2 inhibits pro-inflammatory cytokine production from LPS-stimulated macrophages [145]; and 2) in animal models of sepsis and ischemia-reperfusion injury, the administration of sST2-Fc fusion protein suppresses the production of TNF-α, IL-6, and IL-12 [144,145], and increases survival [132].

ST2 is also involved in endotoxin tolerance [146]. Wild type mice remain healthy after priming with a sub-lethal dose of LPS, and subsequent challenging with a lethal dose of LPS; whereas ST2-deficient mice were unable to develop endotoxin tolerance, had an exaggerated inflammatory response, and died after the LPS challenge [146]. An increased susceptibility to polymicrobial infection with impaired bacterial clearance is associated with altered phagosome maturation and nitrogen oxide-2 derived production of reactive oxygen species in ST2-deficient mice [159].

Biology of IL-10—Traditionally, resolution of inflammation was thought to occur passively. However, it is now clear that resolution is an active process which consists mainly of a decreased production of pro-inflammatory components and removal of inflammatory cells. Both activation and resolution of the inflammatory response are of fundamental importance for survival. IL-10 is one of the most important anti-inflammatory cytokines, having a crucial role as a promoter of negative feedback in the inflammatory response [131,160,161]. IL-10 knock-out mice have an exaggerated Th1 immune activation in the presence of infection [162,163], and die quickly due to a massive and sustained inflammatory response [164,165]. The overproduction of IL-10 is associated with persistent

infection [166–170]. Moreover, mice receiving IL-10 or transgenic mice over-expressing IL-10 have decreased production of pro-inflammatory cytokines [171,172]. IL-10 production can be stimulated by administration of pro-inflammatory cytokines such as IL-6, IL-12, IL-27, and transforming growth factor-β, which stimulate T-helper cells [173–177], or by endotoxin stimulation of macrophages and dendritic cells [178].

The anti-inflammatory action of IL-10 is elicited mainly through inhibition of pro-inflammatory cytokine synthesis through the direct effect on LPS-activated macrophages and/or down-regulation of T cells [130,131,179]. However, IL-10 also prevents the release of reactive oxygen intermediates from monocytes/macrophages [180,181]. IL-10 may also lead to down-regulation of major histocompatibility complex (MHC) class II antigens [182] and cell-adhesion molecules, such as intercellular adhesion molecule (ICAM)-1 on LPS-activated macrophages [183], resulting in the reduced production of pro-inflammatory cytokines.

The link between sST2 and IL-10—In an intestinal ischemic reperfusion model, the administration of soluble ST2-Fc fusion protein (before reperfusion) resulted in a reduced local and systemic inflammatory response (reduced neutrophil influx and cytokine production) and elevation of IL-10 concentration, leading to a reduction in the mortality rate of treated mice [132]. This protective effect of sST2 did not persist in IL-10 knock-out mice, suggesting that IL-10 is essential for the beneficial effect of sST2. The mechanisms and target cells on which sST2 exerts its action and induces IL-10 production remain to be elucidated, although T-regulatory cells [184] and direct action on macrophages have been proposed [145].

Preterm neonates with FIRS and/or funisitis have a higher median concentration of sST2 in umbilical cord plasma—We found that the median umbilical cord plasma concentration of sST2 in neonates with FIRS was 6.7-fold higher than in neonates without FIRS. Similarly, but to a lesser extent, the median umbilical cord plasma concentration of sST2 was 2.7-fold higher in neonates with funisitis than in those without funisitis. FIRS is associated with an increase in pro-inflammatory cytokines (e.g. IL-1β, TNF-α)[87], chemokine (IL-8)[54], and C-reactive protein [185] in umbilical cord blood, which may lead to short- and long-term complications in preterm neonates [21,55,57,58,67,86,87,89,185–191]. On the other hand, as confirmed by the study herein, FIRS is also associated with an increased umbilical cord plasma concentration of IL-10 [192,193]. The protective anti-inflammatory effect of IL-10 in pregnancy has been confirmed by several studies [194–198]. Elevated concentration of both sST2 and IL-10 have also been described among patients with sepsis [199]. Therefore, high plasma concentrations of sST2 and IL-10 in the umbilical cord of preterm neonates with FIRS and/or funisitis most likely reflect an anti-inflammatory host response mounted to counteract pro-inflammatory cytokines. The strong positive correlation between sST2 and IL-10 in neonates with FIRS, but not in those without FIRS, is consistent with the observation that sST2 exerts its action in cooperation with IL-10 [132,199]. On the other hand, a sustained elevation of serum sST2 concentration in septic patients is correlated with disease severity and mortality [200]. One possible explanation of this observation is that after the initial

hyper-inflammatory phase, patients with sepsis can become immunosuppressed due to activation of the anti-inflammatory limb of the immune system [201–203]. Loss of delayed hypersensitivity, inability to clear infection, and predisposition to nosocomial infections can often be observed in these patients [203].

Strengths and limitations of the study

This is the first study to report the changes in umbilical cord plasma concentrations of sST2 and IL-10 in neonates with FIRS and/or funisitis. The diagnosis of FIRS was defined stringently by the IL-6 concentration in umbilical cord plasma. However, a limited sample size precluded analysis of an association between umbilical cord plasma sST2 concentration and adverse neonatal outcome. The cross-sectional nature of this study also precludes a clear determination of the temporal relationship between observed sST2 concentrations and the occurrence of FIRS and/or funisits.

Conclusions

The fetal inflammatory response syndrome is associated with an elevation of umbilical cord plasma concentrations of soluble ST2. This protein may represent an important mediator of the immune response in neonates diagnosed with this condition by promoting an anti-inflammatory response in cooperation with IL-10. Future studies examining the association between neonatal plasma sST2 concentration and adverse neonatal outcomes appear warranted.

Acknowledgments

Declaration of Interest

This project has been funded in whole or in part with Federal funds from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services, under Contract No. HHSN275201300006C.

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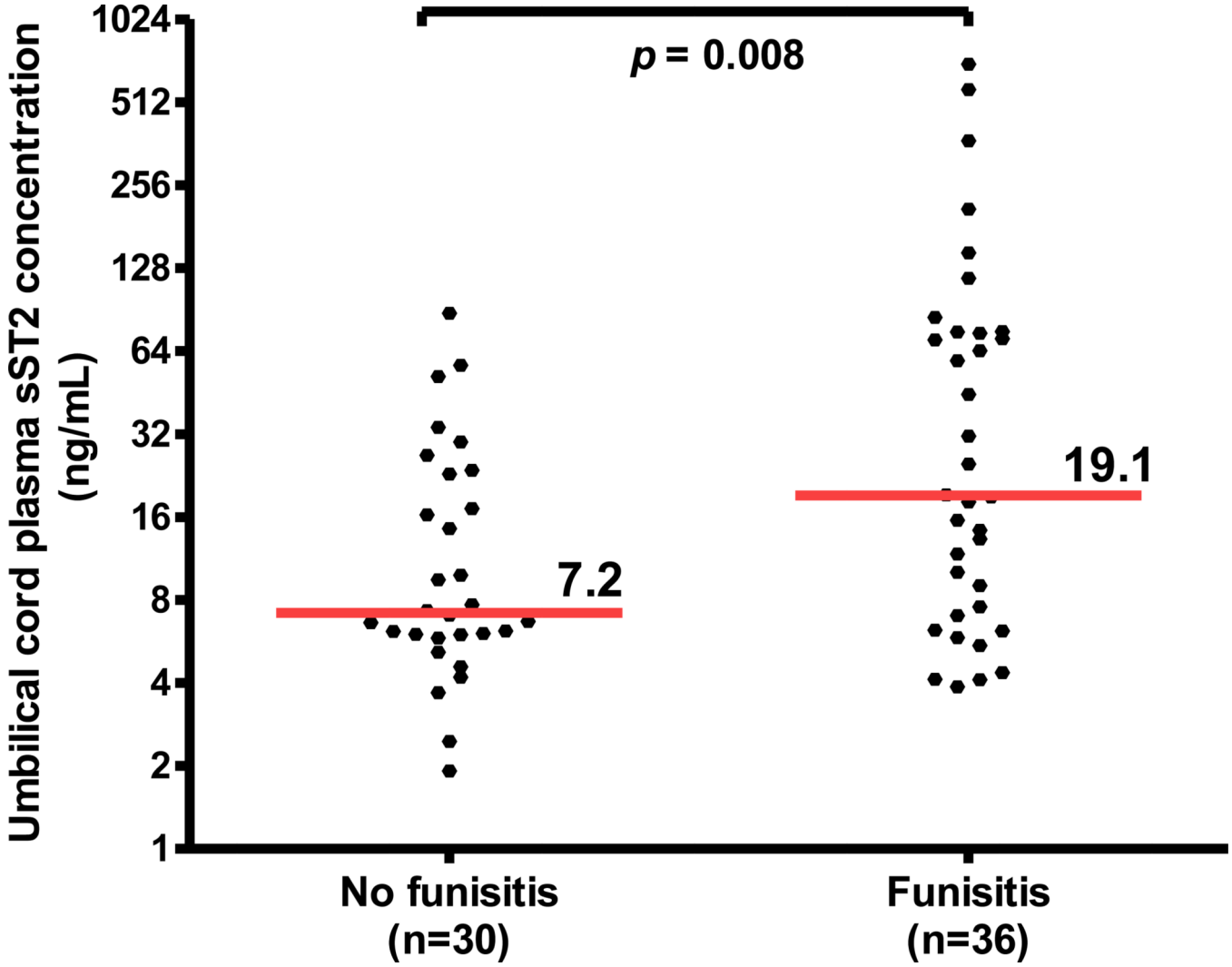

Figure 1. Umbilical cord plasma sST2 concentrations in neonates with and without funisitis

The median plasma concentration of sST2 in umbilical cord was greater in neonates with funisitis than in those without funisitis (median 19.1 ng/mL; IQR 7.1–75.0 ng/mL vs. median 7.2 ng/mL; IQR 5.9–23.1 ng/mL; p=0.008). The y axis is expressed as log2.

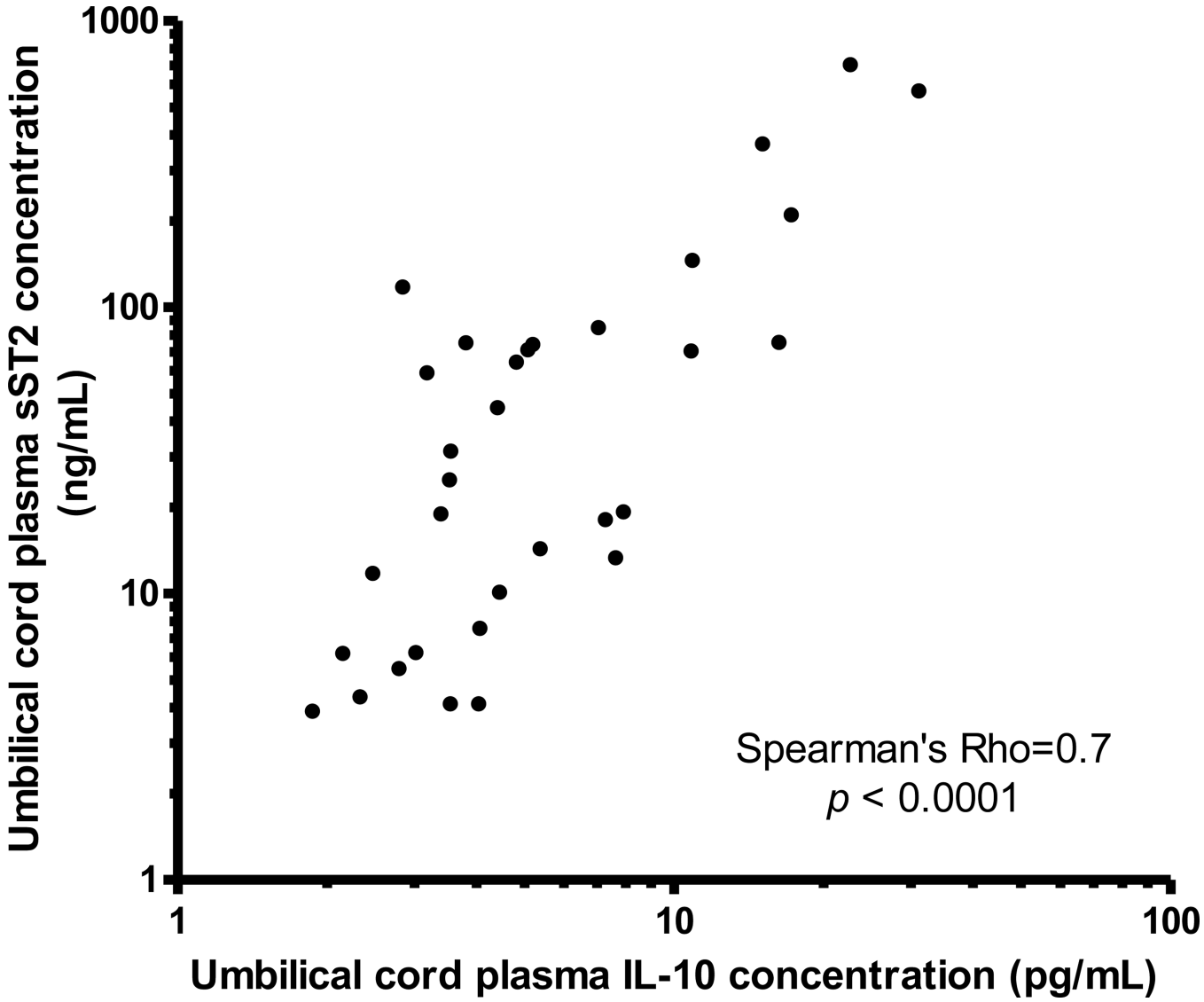

Figure 2. Correlation between umbilical cord plasma concentrations of sST2 and IL-10 in neonates with funisitis

There was a significant positive correlation between umbilical cord plasma concentrations of sST2 and IL-10 (Spearman's Rho=0.7, p<0.0001). The y and x axis are expressed as log10.

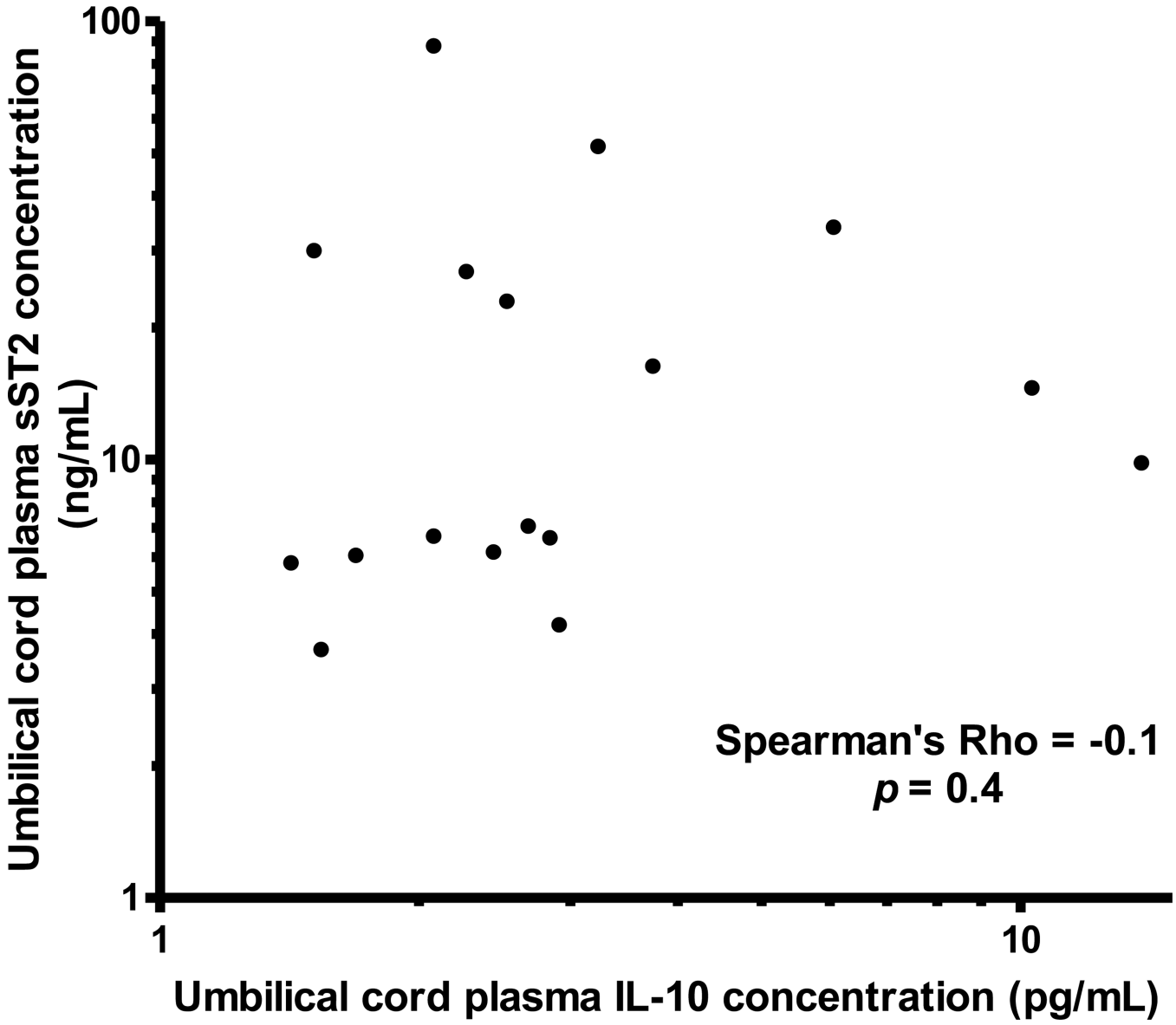

Figure 3. Correlation between umbilical cord plasma concentrations of sST2 and IL-10 in neonates without funisitis

There was no significant correlation between umbilical cord plasma concentrations of sST2 and IL-10 (Spearman's Rho=−0.1, p=0.4). The y and x axis are expressed as log10.

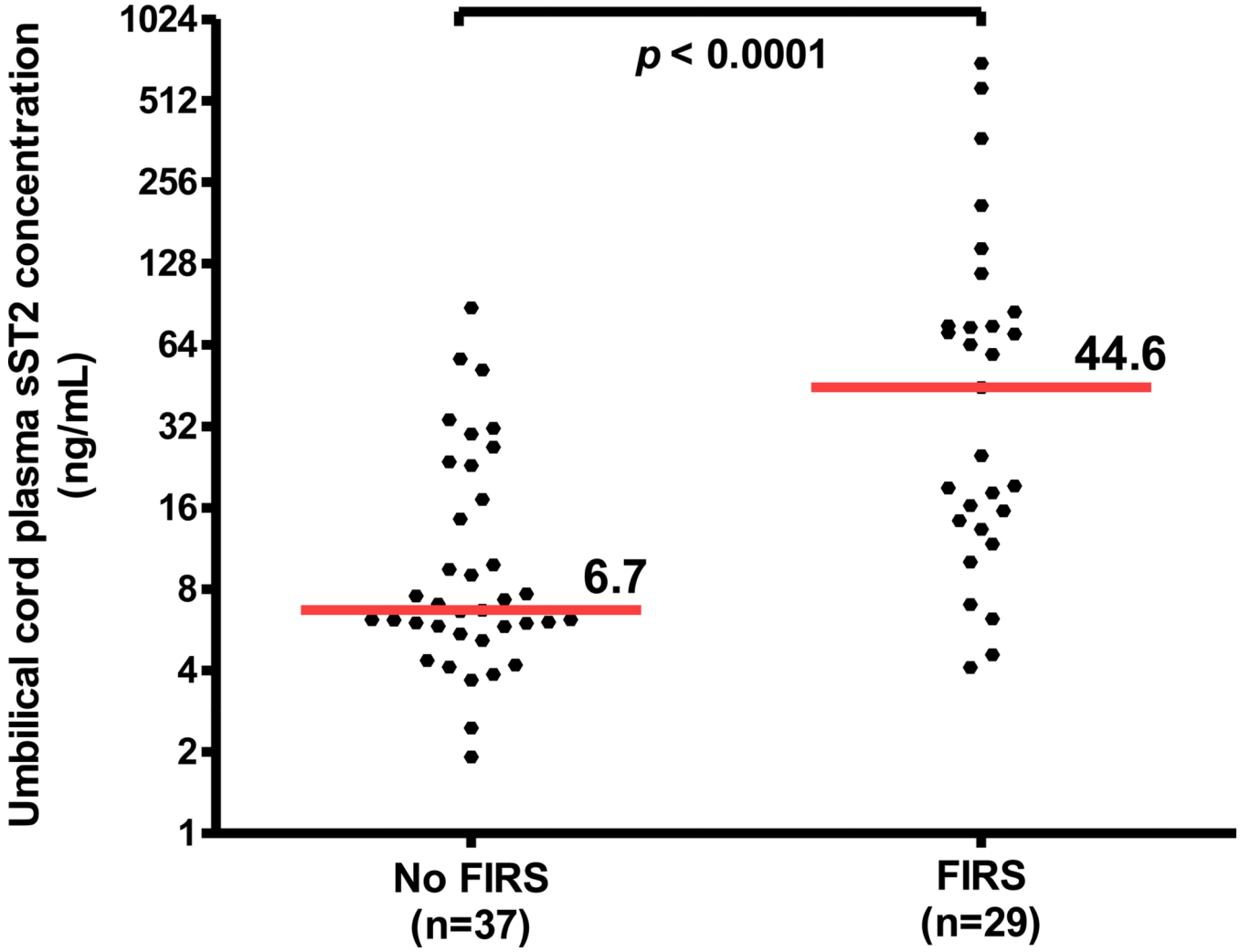

Figure 4. Umbilical cord plasma sST2 concentrations in neonates with and without the fetal inflammatory response syndrome (FIRS)

The median plasma concentration of sST2 in umbilical cord was greater in neonates with FIRS than in those without FIRS (median 44.6 ng/mL; IQR 13.8–80.3 ng/mL vs. median 6.7 ng/mL; IQR 5.6–20.1 ng/mL; p<0.0001). The y axis is expressed as log2.

Table I

Demographic and clinical characteristics of the study population with and without funisitis.

	Without funisitis (n=30)	With funisitis (n=36)	p
Maternal age (years)	24 (19–29)	24.5 (20–29)	0.8
GA at delivery (weeks)	31.9 (30.5–33.4)	31.9 (30.0–33.2)	0.6
Preterm PROM	8 (26.7%)	12 (33.3%)	0.6
PTL and intact membranes	22 (73.3%)	24 (66.7%)	0.6
FIRS	2 (6.7%)	27 (75%)	< 0.0001*
Birthweight (grams)	1660 (1499–2127)	1697 (1379–2090)	0.8

Values are expressed as number (percent) or median (IQR).

* p <0.05.

GA: gestational age; PTL: preterm labor; PROM: prelabor rupture of membranes; FIRS: fetal inflammatory response syndrome.

Table II

Demographic and clinical characteristics of the study population with and without the fetal inflammatory response syndrome (FIRS).

	Without FIRS (n=37)	With FIRS (n=29)	p
Maternal age (years)	24 (19–29)	24 (20–32)	0.8
GA at delivery (weeks)	31.7 (30–33.3)	32.1 (30–33.4)	0.3
Preterm PROM	9 (24.3%)	11 (37.9%)	0.2
PTL and intact membranes	28 (75.7%)	18 (62.1%)	0.2
Birthweight (grams)	1625 (1307–2073)	1745 (1502–2113)	0.4

Values are expressed as number (percent) or median (IQR).

* $p<0.05$.

FIRS: fetal inflammatory response syndrome; GA: gestational age; PTL: preterm labor; PROM: prelabor rupture of membranes.