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Interleukin-19 in Fetal Systemic Inflammation

Zeynep Alpay Savasan, MD^{1,2}, Tinnakorn Chaiworapongsa, MD^{1,2}, Roberto Romero, MD¹, Youssef Hussein, MD¹, Juan Pedro Kusanovic, MD^{1,3}, Yi Xu, PhD¹, Zhong Dong, PhD¹, Chong Jai Kim, MD, PhD^{1,4}, and Sonia S Hassan, MD^{1,2}

¹Perinatology Research Branch, NICHD/NIH/DHHS, Detroit, Michigan, United States

²Department of Obstetrics and Gynecology, Wayne State University, Detroit, MI, United States

³Department of Obstetrics and Gynecology, Pontificia Universidad Católica de Chile, Santiago, Chile and Center for Perinatal Research, Sótero del Río Hospital, Santiago, Chile

⁴Department of Pathology, Wayne State University, Detroit, MI, United States

Abstract

Objective—The fetal Inflammatory Response Syndrome (FIRS) is considered the fetal counterpart of the Systemic Inflammatory Response Syndrome (SIRS), which can be caused by infection and non-infection-related insults. Although the initial response is mediated by pro-inflammatory signals, the control of this response is achieved by anti-inflammatory mediators which are essential for the successful outcome of the affected individual. Interleukin (IL)-19 is capable of stimulating the production of IL-10, a major anti-inflammatory cytokine, and is a potent inducer of the T-helper 2 (Th2) response. The aim of this study was to determine if there is a change in umbilical cord plasma IL-19 and IL-10 concentrations in preterm neonates with and without acute funisitis, the histologic counterpart of FIRS.

Methods—A case-control study was conducted including 80 preterm neonates born after spontaneous labor. Neonates were classified according to the presence (n=40) or absence of funisitis (n=40), which is the pathologic hallmark of FIRS. Neonates in each group were also matched for gestational age. Umbilical cord plasma IL-19 and IL-10 concentrations were determined by ELISA.

Results—1) The median umbilical cord plasma IL-19 concentration was 2.5 fold higher in neonates with funisitis than in those without funisitis (median 87 pg/mL; range 20.6–412.6 pg/mL vs. median 37 pg/mL; range 0–101.7 pg/mL; $p<0.001$); 2) newborns with funisitis had a significantly higher median umbilical cord plasma IL-10 concentration than that of those without funisitis (median 4 pg/mL; range 0–33.5 pg/mL vs. median 2 pg/mL; range 0–13.8 pg/mL; $p<0.001$); and 3) the results were similar when we included only patients with funisitis who met the definition of FIRS by umbilical cord plasma IL-6 concentrations 17.5 pg/mL ($p<0.001$).

Conclusion—IL-19 and IL-10 are parts of the immunologic response of FIRS. A subset of fetuses with FIRS had high umbilical cord plasma IL-19 concentrations. *In utero* exposure to high systemic concentrations of IL-19 may reprogram the immune response.

Address correspondence to: 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, Telephone (313) 993-2700, Fax (313) 993-2694, prbchiefstaff@med.wayne.edu.

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Keywords

fetal inflammatory response syndrome (FIRS); chorioamnionitis; funisitis; anti-inflammatory limb; IL-10; premature rupture of membranes (PROM); childhood asthma; SIDS; prematurity; preterm labor; immune programming

INTRODUCTION

The Fetal Inflammatory Response Syndrome (FIRS) [1–6] can occur in cases of the most advanced stage of microbial invasion of the amniotic cavity. The condition has been operationally defined by an elevation of fetal plasma interleukin (IL)-6 IL-6 concentration, although derangements in other cytokines (e.g. IL-10 [7,8], granulocyte-colony-stimulating factor [9], etc.) have been reported. FIRS has been diagnosed in patients with preterm labor and intact membranes, and in preterm prelabor rupture of membranes (PROM). However, FIRS can also be present in the context of congenital viral infections [10–17] and in cases of alloimmune Rh disease [18]. The significance of FIRS is that affected fetuses are at high risk for short- and long-term complications, even after adjusting for gestational age at birth [19–42]. Moreover, FIRS is associated with a short cordocentesis-to-delivery interval, suggesting that the human fetus plays a role in the onset of labor [1,19]. Evidence of multi-systemic involvement in FIRS has been characterized by the detection of high concentrations of cortisol [43], hematologic disorders (e.g. fetal neutrophilia)[44], decreased volume of amniotic fluid [33] and cardiac dysfunction [45,46], as well as fetal neuroinflammation [22–31,42,47–54]. These findings have been well-characterized in humans and animal models of intrauterine infection in a wide range of species, including mice [55–64], rabbits [65–73], sheep [74–110] and primates [111–122]. Abnormalities in the phenotype of monocytes and granulocytes as well as the production of reactive oxygen radicals in the umbilical cord blood of neonates with funisitis have been documented [123], suggesting that oxidative stress plays a role in the pathophysiology of the condition [31,124–128].

FIRS is considered to be the fetal counterpart of the systemic inflammatory response syndrome (SIRS) seen in adults [129]. SIRS is characterized by systemic inflammation after a wide range of insults, including infection-related and non-infection-related injury [130–132]. The initial response is mainly due to inflammatory mediators induced by the innate immune system [133,134]. The timing and the control of this response is crucial for the outcome of the affected individuals because an exaggerated and uncontrolled inflammatory response may be detrimental to the host; on the other hand, if the control mechanisms mediated by anti-inflammatory mediators is pronounced or prolonged, the host may be immunosuppressed and become susceptible to secondary infections [134–139]. Indeed, patients discharged after an episode of sepsis have a high mortality rate that is attributed to this immunosuppressed state [140].

Suppression of the pro-inflammatory response is accomplished by the anti-inflammatory limb of the immune system [141–143]. Interleukin (IL)-10 is considered to be a major anti-inflammatory mediator since it is mainly produced by monocytes and functions to inhibit the transcription of pro-inflammatory cytokines [141,144,145]. We have previously reported the behavior of IL-10 in the amniotic fluid of patients with preterm labor [146].

IL-19 is a newly discovered cytokine belonging to the IL-10 family. This protein can induce the production of IL-10 from human peripheral blood mononuclear cells [147,148], and is considered by some investigators to have an anti-inflammatory effect [149–152]. However, IL-19 is also capable of activating monocytes to release IL-6, tumor necrosis factor (TNF)-

α , IL-8 and reactive oxygen species [153,154] and has been implicated in the pathogenesis of sepsis-induced organ injury [154]. Since this cytokine can also up-regulate IL-4 and down-regulate interferon (IFN)- γ on T cells [155], IL-19 is a potent inducer of the T-helper 2 (Th2) response [148] and has been implicated in a wide variety of allergic (i.e. asthma and atopic dermatitis [156–158]) and non-allergic diseases (i.e. psoriasis [157,159–161], aging [162], type-1 diabetes [163], periodontal disease [164] and cardiovascular disease[151,152]).

The objective of this study was to examine the changes in umbilical cord plasma IL-19 and IL-10 concentrations – both potential members of the anti-inflammatory limb of the immune response – in newborns with and without funisitis (the histologic counterpart of FIRS) [165].

PATIENTS AND METHODS

Study population

A retrospective case-control study was conducted by searching our clinical database and bank of biological samples including 80 pregnant patients with preterm deliveries between 27 and 34 weeks of gestation with (n=40) and without funisitis (n=40) and matched for gestational age at delivery within 2 weeks. Umbilical cord blood was collected immediately after birth. Placentas were obtained after delivery and underwent histopathologic examination.

All patients provided written informed consent prior to the collection of samples. The collection and utilization of the samples for research purposes was approved by the Human Investigation Committee of Wayne State University (Detroit, MI) and the Institutional Review Board of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD/NIH/DHHS). Many of these samples have been used in previous studies.

Clinical definition

Funisitis was diagnosed in the presence of neutrophil infiltration into the umbilical vessel walls or Wharton's jelly, according to criteria previously published [165]. FIRS was diagnosed by umbilical cord blood IL-6 concentrations ≥ 17.5 pg/mL [40,54]. The diagnosis of preterm labor (PTL) 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 between 20 to 36 6/7 weeks. Preterm PROM was diagnosed with sterile speculum examination with a combination of vaginal pooling, nitrazine and ferning tests.

Sample collection and determination of IL-19, IL-10 and IL-6 in umbilical cord plasma

Umbilical cord blood was collected after birth into tubes containing EDTA. Blood was centrifuged at 1300g for 10 min at 4°C. The plasma obtained was stored at -70°C until analysis. Concentrations of IL-19, IL-10 and IL-6 in umbilical cord plasma were determined by sensitive and specific enzyme immunoassays from R&D Systems (Minneapolis, MN, USA). The initial assay validation was performed in our laboratory prior to the conduction of this study. Briefly, the immunoassay utilized the quantitative sandwich enzyme immunoassay technique and the concentrations were determined by interpolation from the standard curves. The inter- and intra-assay coefficients of variation were 4.6% and 4.3%, respectively, for IL-19; 6.9% and 4.4%, respectively, for IL-10; and 8.7% and 4.6%, respectively, for IL-6. The sensitivities of the assays for IL-19, IL-10 and IL-6 were 17.4 pg/mL, 0.65 pg/mL, and 0.09 pg/mL, respectively.

Determination 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. The tissues were fixed in 10% neutral buffered formalin, embedded in paraffin and stained with hematoxylin and eosin. Histopathologic examination was performed by a perinatal pathologist (CJK) who was blinded to the clinical information. Funisitis was diagnosed in the presence of neutrophil infiltration into the umbilical vessel walls or Wharton's jelly.

Statistical analysis

Shapiro-Wilk test was used to determine if the data was normally distributed. A two-tailed Mann-Whitney U test was used to compare continuous nonparametric variables. The Wilcoxon rank sum test was also performed for matched-case analysis. Comparisons between proportions were performed using Chi-square or Fisher's exact tests. Spearman rank correlation was utilized to assess correlations between two continuous variables. A p-value <0.05 was considered statistically significant. The analysis was performed with SPSS, version 15 (SPSS Inc., Chicago, IL, USA).

RESULTS

Demographics and clinical characteristics of the study population

Table I presents the demographic and clinical characteristics of patients included in the study. The median gestational age at delivery was not significantly different between patients with and without funisitis. Similarly, the frequency of patients presenting with spontaneous PTL and intact membranes [without funisitis: 67.5% (27/40) vs. with funisitis: 65% (26/40); $p>0.05$] or preterm PROM [without funisitis: 32.5% (13/38) vs. with funisitis: 35% (14/40); $p>0.05$] was not significantly different between the 2 groups. One patient without funisitis had umbilical cord plasma IL-19 below the detection limit of the assay. Two and five patients did not have plasma samples available for IL-6 and IL-10 determination, respectively.

Funisitis was associated with elevation of cord plasma IL-19 and IL-10 concentrations

The median umbilical cord plasma IL-19 concentration was significantly higher in neonates with funisitis than in those without funisitis (median 87 pg/mL; range 20.6–412.6 pg/mL vs. median 37 pg/mL; range 0–101.7 pg/mL; $p<0.001$; Figure 1). Newborns with funisitis had a significantly higher median umbilical cord plasma IL-10 concentration than those without funisitis (median 4 pg/mL; range 0–33.5 pg/mL vs. median 2 pg/mL; range 0–13.8 pg/mL; $p<0.001$; Figure 2). Similar results were obtained using the Wilcoxon rank sum test for both comparisons ($p<0.001$ for IL-19 and 0.001 for IL-10).

FIRS was associated with elevation of cord plasma IL-19 and IL-10 concentrations

Demographic and clinical characteristics of patients who were diagnosed with and without FIRS are displayed in Table II. Two patients did not have plasma IL-6 available. Eight newborns with funisitis had cord plasma IL-6 concentrations < 17.5 pg/mL, whereas none from the group without funisitis had cord plasma IL-6 concentrations above this cut-off. Similarly, the frequency of PTL, intact membranes and preterm PROM were not significantly different between the 2 groups (see Table II). The median gestational age at delivery was not significantly different between patients with and without FIRS.

Newborns who were diagnosed with FIRS had a significantly higher median umbilical cord plasma IL-19 concentration than those without FIRS (with FIRS median: 90 pg/mL; range 13.6–412.6 pg/mL vs. without FIRS median: 43 pg/mL; range 17.9–198 pg/mL; $p<0.001$;

Figure 3). The median umbilical cord plasma IL-10 concentration in neonates with FIRS was higher than that of those without FIRS (with FIRS median: 5 pg/mL; range 0–33.5 pg/mL vs. without FIRS median: 2 pg/mL; range 0–13.8 pg/mL; $p < 0.001$; Figure 4).

When patients were stratified according to membrane status (PTL with intact membranes or preterm PROM), neonates with FIRS still had higher median umbilical cord plasma concentrations of IL-19 and IL-10 than those without FIRS ($p < 0.05$ for each).

Umbilical cord plasma concentration of IL-19 was correlated with IL-10 in funisitis and FIRS

Among neonates with funisitis, there was a significant positive correlation between umbilical cord plasma concentrations of IL-19 and IL-10 (Spearman $Rho = 0.5$, $p = 0.003$; Figure 5a), but not between IL-19 and IL-6 ($p = 0.3$). In contrast, among patients who did not have funisitis, there were no correlations in any of the cytokines ($p > 0.05$; Figure 5b).

Similarly, among neonates who were diagnosed with FIRS, there was a significant positive correlation between umbilical cord plasma concentrations of IL-19 and IL-10 (Spearman $Rho = 0.4$, $p = 0.01$), but not between IL-19 and IL-6 ($p = 0.4$). In contrast, among neonates without FIRS, there was no significant correlation among the plasma concentration of any of the cytokines ($p > 0.05$).

DISCUSSION

Principal findings of this study

1) FIRS, diagnosed by either neonatal cord plasma IL-6 concentrations ≥ 17.5 pg/mL or the presence of funisitis, is associated with a higher concentration of umbilical cord plasma IL-19 and IL-10 than neonates without FIRS and funisitis; 2) there was a significant correlation between the umbilical cord plasma concentrations of IL-19 and IL-10 in neonates with FIRS; and 3) these observations represent the first evidence that changes in IL-19 occur during fetal life, and that this cytokine participates in the host response associated with preterm delivery and acute inflammation.

The original description of FIRS

FIRS was originally described in patients with spontaneous PTL and preterm PROM and defined by fetal plasma IL-6 concentrations ≥ 11 pg/mL obtained by cordocentesis [1]. Subsequently, umbilical cord plasma IL-6 concentrations ≥ 17.5 pg/mL [54] were shown to be associated with increased neonatal complications [1,23,26,41,42,52,54], and therefore, this definition was accepted as evidence of FIRS [166]. Indeed, funisitis is associated with an elevation of umbilical cord concentrations of IL-6 as well as short- and long-term complications in preterm neonates [1,7,19,22–30,33,35–37,41–43,45,47,49,51,54,165–184].

FIRS is frequently found in patients with intra-amniotic infection/inflammation. While several studies observed an elevation of IL-6 [19,23,37,40,41,52–54,168,174,179,183,185–191], IL-1 β [37,52,174,179,188,191–196], tumor necrosis factor- α and its receptor [37,52,53,188,196], IL-8 [188,197], matrix degrading enzymes (i.e. MMP-8, MMP-9, etc) [173,198–210] and C-reactive protein [37,173,198,211–214] in the amniotic fluid and umbilical cord blood of patients with intra-amniotic infection/inflammation, few studies examined IL-10, the anti-inflammatory limb of the immune response, in the amniotic fluid [146] and cord blood [7,8,215,216] of these patients.

Interleukin-19

IL-19 was discovered as a member of IL-10 family [147]. This protein is produced by activated monocytes and, to a lesser extent, B-cells [217], but it is also identified in non-immune cells such as keratinocytes [161], bronchial epithelial cells [158,218] and the chorioamniotic membranes [219]. The expression of IL-19 on monocytes can be induced by LPS, IL-4 and granulocyte macrophage-colony stimulating factor (GM-CSF) [147].

IL-19 exerts its biological activities through a heterodimer complex, IL-20 RI and IL-20 RII [220,221]. However, IL-19 only binds to IL-20RII and requires a conformational change before it binds to IL-20RI. The receptors are present in various tissues including skin, lung, heart, muscle, placenta, adrenal gland, small intestine, salivary gland and reproductive organs such as uterus, ovary and testis [221].

IL-19 activates monocytes in an autocrine and paracrine fashion to release IL-6, TNF- α , IL-8 and reactive oxygen species [147,154,155]. However, this cytokine can also does-dependently induce IL-10, a major anti-inflammatory cytokine, in human peripheral blood mononuclear cell cultures [148]. IL-19 can amplify its own expression during the course of the immune response [148].

IL-19 can also participate in the activation of the adaptive immune response, since this cytokine is a potent inducer of the Th2 responses [148,155]. The treatment of T cells with IL-19 up-regulates IL-4 and down-regulates IFN- γ [155]. Similarly, the treatment of maturing antigen presenting cells (eg: dendritic cells) with IL-19 induces IL-10 production, which in turn, promotes the Th2/regulatory T response [148,221]. However, IL-19 expression seems to be controlled by IL-10 since IL-10 inhibits IL-19 expression in monocyte-derived dendritic cells and the addition of anti-IL-10 monoclonal antibodies causes an increase in IL-19 transcription [148].

FIRS is associated with an elevation of IL-19

The finding that neonates with FIRS had higher plasma concentrations of IL-19 than those without FIRS is consistent with the observation in adults that IL-19 is involved in the pathophysiology of sepsis. Serum IL-19 concentrations were elevated in adult patients with sepsis [154]. In an animal model of endotoxemia, intraperitoneal administration of endotoxin up-regulated mRNA expression of IL-19 and its receptors (IL-20RI and RII) in several organs (heart, liver, lung and kidneys) [154]. Moreover, IL-19 was shown to induce the production of reactive oxygen species, TNF- α and COX-2 mRNA expression, as well as apoptosis in lung epithelial cells and hepatocytes [154]. The treatment of mice with an IL-19 blocker (soluble receptor plasmid DNA) before the administration of endotoxin reduced neutrophil infiltration in the lung and liver, as well as the serum concentrations of liver enzymes [154]. Therefore, IL-19 is a part of the immunological response in SIRS. It remains to be determined, however, if systemic elevation of IL-19 is associated with fetal injury or end-organ damage in fetuses with FIRS.

FIRS was associated with an elevation of IL-10 concentration

The observation that umbilical cord plasma IL-10 concentrations were elevated in preterm neonates with FIRS is consistent with the findings from previous studies [7,8]. Preterm infants who had funisitis in the umbilical cord had a higher gene expression of IL-10 in cord blood mononuclear cells [8]. Additionally, histologic chorioamnionitis was associated with elevated cord blood IL-10 concentrations in very preterm infants [7]. The risks of bronchopulmonary dysplasia and severity of respiratory distress in these infants were associated with elevated cord blood IL-10 concentrations [7]. One interpretation of these findings is that IL-10 is elevated in FIRS to counteract the effect of several pro-

inflammatory cytokines observed in FIRS including IL-19, since IL-10 is capable of inhibiting IL-19 expression. Consistent with the hypothesis, we observed a relationship between cord plasma concentrations of IL-19 and IL-10 in neonates with FIRS.

The protective effect of IL-10 in obstetrical diseases has been demonstrated in several studies [215,222,223]. The administration of recombinant IL-10 prevented preterm delivery and miscarriage in IL-10 knockout mice that had a high rate of pregnancy loss after exposure to endotoxin [215]. Similarly, the treatment of IL-10 significantly reduced lipopolysaccharide (LPS)-induced IL-6 production in human chorioamniotic membranes [224]. Moreover, IL-10 was shown to be protective in infection/inflammation-induced fetal brain injury [225–228].

Potential long-term consequences of IL-19 elevation in human fetuses

Asthma, a disease characterized by airway hyperreactivity, has been proposed to be a consequence of excessive production of IL-4, IL-5 and IL-13 by Th2 cells [229–232]. IL-19 is a potent inducer of the Th2 response, and the concentration of this cytokine is elevated in systemic circulation of patients with asthma [155,156,158]. Moreover, IL-19 expression has been shown to be up-regulated in the airway epithelia of these patients [156]. Accumulating evidence suggests that *in utero* exposure to immunomodulatory factors (i.e. endotoxin, allergens from farming environments, and tobacco smoke) may play a role in airway development, inflammation and remodeling, which act in concert with postnatal factors to predispose to the development of asthma later in life [233–236]. Although, in animal experiments, antenatal exposure of endotoxin to the mothers has been proposed to promote the Th1 immune environment which suppresses the development of allergic airway disease in offspring later in life [234,237], it is possible that a subset of preterm neonates with FIRS who are exposed to high systemic concentrations of IL-19 *in utero* may have an increased risk of childhood asthma. Indeed, clinical chorioamnionitis at preterm gestation, but not at term gestation, is a risk factor for childhood asthma (<8 years old) [233]. Evidence in support of this hypothesis are: 1) FIRS is more frequently observed in patients with early spontaneous preterm delivery [1,174,238] rather than in term delivery [49]; 2) amniotic fluid concentrations of IL-19 were elevated in patients with intra-amniotic infection/inflammation in preterm gestation, but not at term [239]; and 3) neonates with FIRS had systemic elevation of IL-19 concentrations as demonstrated in this study.

Strengths and limitations of the study

This is the first study to report the changes of umbilical cord plasma concentrations of IL-19 and IL-10 in neonates with FIRS. The diagnosis of FIRS was defined stringently by cord plasma IL-6 concentrations and by histopathologic examination of the umbilical cord. Patients with funisitis were matched for gestational age at delivery with those without funisitis. Moreover, umbilical cord plasma IL-10 concentrations, a major anti-inflammatory cytokine, were examined in these patients. The correlation between cord plasma IL-19 and IL-10 concentrations observed in patients with FIRS indicates a close relationship between these two cytokines. A limitation of this study is that all patients were enrolled from a single medical center and that most patients were African-American; thus, it would be desirable for this study to be replicated in other populations.

Conclusion

We conclude that IL-19 and IL-10 are part of the immunologic response of FIRS. *In utero* exposure to high systemic IL-19 concentrations may be a link between clinical chorioamnionitis in preterm gestation and the subsequent reprogramming of the immune system. This may include the development of a sustained immunosuppressive state, or a shift to a Th2 response which may predispose to the development of childhood asthma. It is

important to stress that sudden infant death syndrome (SIDS) remains unexplained in a majority of cases [240–242], and that preterm birth is a risk factor for SIDS [243]. It is possible that the activation of the anti-inflammatory limb of the immune response after *in utero* exposure to microorganisms or microbial products may predispose to SIDS [244,245], just as sepsis predisposes to death in adult patients. This hypothesis has substantial implications for the prenatal diagnosis of infection and the assessment of the immunological state of the neonate and the infant after birth. Some immune responses may be short-lived, while others may develop a chronic phase and confer different risks for the individual by reprogramming the immune system.

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Figure 1.

Umbilical cord plasma interleukin (IL)-19 concentrations in neonates with and without funisitis. The median umbilical cord plasma IL-19 concentration was significantly higher in neonates with funisitis than that of those without funisitis (median 87 pg/mL; range 20.6–412.6 pg/mL vs. median 37 pg/mL; range 0–101.7 pg/mL; $p < 0.001$). LOD = limit of detection.

Figure 2.

Umbilical cord plasma interleukin (IL)-10 concentrations in neonates with and without funisitis. Newborns with funisitis had a significantly higher median umbilical cord plasma IL-10 concentration than those without funisitis (median 4 pg/mL; range 0–33.5 pg/mL vs. median 2 pg/mL; range 0–13.8 pg/mL; $p < 0.001$). LOD = limit of detection.

Figure 3. Umbilical cord plasma interleukin (IL)-19 concentrations in neonates with and without Fetal Inflammatory Response Syndrome (FIRS). Newborns who were diagnosed with FIRS had a significantly higher median umbilical cord plasma IL-19 concentration than those who did not have FIRS (FIRS median: 90 pg/mL; range 13.6–412.6 pg/mL vs. No FIRS median: 43 pg/mL; range 17.9–198 pg/mL; $p < 0.001$).

Figure 4.

Umbilical cord plasma interleukin (IL)-10 concentrations in neonates with and without Fetal Inflammatory Response Syndrome (FIRS). The median umbilical cord plasma IL-10 concentration in neonates with FIRS was higher than that of those without FIRS (FIRS median: 5 pg/mL; range 0–33.5 pg/mL vs. No FIRS median: 2 pg/mL; range 0–13.8 pg/mL; $p < 0.001$). LOD = limit of detection.

Figure 5.

Correlation between umbilical cord plasma concentrations of interleukin (IL)-19 and IL-10 in neonates with (5a) and without funisitis (5b). Among neonates with funisitis, there was a significant positive correlation between umbilical cord plasma concentrations of IL-19 and IL-10 (Spearman Rho = 0.5, $p=0.003$; Figure 5a). In contrast, among neonates without funisitis, there was no correlation between umbilical cord plasma concentrations of IL-19 and IL-10 ($p>0.05$; Figure 5b).

Table I

Clinical characteristics of the study population with and without funisitis

	No funisitis (n=40)	Funisitis (n=40)	p
Maternal Age (years)	24 (15–39)	25 (16–44)	0.9
African American	27 (67.5%)	33 (82.5%)	0.1
GA at delivery (weeks)	31.9 (27.1–34.4)	31.9 (27.1–34.9)	0.9
Preterm PROM	13 (32.5%)	14 (35.0%)	0.8
Preterm labor and intact membranes	27 (67.5%)	26 (65.0%)	0.8
Birthweight (grams)	1612 (800–2345)	1697 (918–2530)	0.6
Birthweight Percentile (%)	31.6 (10–54.7)	33.6 (11.1–62.2)	0.3

Values were expressed as number (percent) or median (range)

GA: Gestational age; PROM: prelabor rupture of membranes

Table II

Clinical characteristics of the study population with and without FIRS

	No FIRS (n=46)	FIRS (n=32)	p
Maternal Age (years)	25 (15–39)	25 (16–44)	0.8
African American	33 (71.7%)	26 (81.3%)	0.3
GA at delivery (weeks)	31.7 (27.1–34.3)	32.3 (28.3–34.9)	0.2
Preterm PROM	14 (30.4%)	12 (37.5%)	0.5
Preterm labor and intact membranes	32 (70%)	20 (63%)	0.5
Birthweight (grams)	1612 (800–2335)	1735 (918–2530)	0.2
Birthweight Percentile (%)	32 (10–62.2)	32.2 (11.1–56.4)	0.9

Values were expressed as number (percent) or median (range)

GA: Gestational age; PROM: prelabor rupture of membranes