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The Hematologic Profile of the Fetus with Systemic Inflammatory Response Syndrome

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Abstract

OBJECTIVE—The Fetal Inflammatory Response Syndrome (FIRS) is associated with the impending onset of preterm labor/delivery, microbial invasion of the amniotic cavity and increased perinatal morbidity. FIRS has been defined by an elevated fetal plasma interleukin-6 (IL-6), a cytokine with potent effects on the differentiation and proliferation of hematopoietic precursors. The objective of this study was to characterize the hematologic response of fetuses with FIRS.

STUDY DESIGN—Fetal blood sampling was performed in patients with preterm prelabor rupture of membranes and preterm labor with intact membranes (n=152). A fetal plasma IL-6 concentration >=11 pg/ml was used to define FIRS. Hemoglobin concentration, platelet count, total white blood cell (WBC) count, differential count and nucleated red blood cell (NRBC) count were obtained. Since blood cell count varies with gestational age, the observed values were corrected for fetal age by calculating a ratio between the observed and expected mean value for gestational age.

RESULTS—1) The prevalence of FIRS was 28.9% (44/152); 2) fetuses with FIRS had a higher median corrected WBC and corrected neutrophil count than those without FIRS (WBC median 1.4; range 0.3–5.6 vs. median 1.1; range 0.4–2.9 p=0.001; neutrophils median 3.6; range 0.1–57.5 vs. median 1.8; range 0.2–13.9 p<0.001); 3) neutrophilia (defined as a neutrophil count >95th centile of gestational age) was significantly more common in fetuses with FIRS than in those without FIRS [71% (30/42) vs. 35% (37/105); p<0 001]; 4) more than two thirds of fetuses with

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FIRS had neutrophilia, while neutropenia was present in only 4.8% (2/42); 5) FIRS was not associated with detectable changes in hemoglobin concentration, platelet, lymphocyte, monocyte, basophil or eosinophil counts and; 6) fetuses with FIRS had a median corrected NRBC count higher than those without FIRS. However, the difference did not reach statistical significance (NRBC median 0.07; range 0–1.3 vs. median 0.04; range 0–2.3 p=0.06);

CONCLUSION—The hematological response of the human fetus with FIRS is characterized by significant changes in the total white blood cell and neutrophil counts. The NRBC count in fetuses with FIRS tends to be higher than fetuses without FIRS.

Keywords

FIRS; preterm labor; preterm PROM; cordocentesis; neutrophil; nucleated red blood cells; infection; hypoxia; neutrophilia; neutropenia; white blood cell count

INTRODUCTION

The fetal inflammatory response syndrome (FIRS) was originally described in patients with spontaneous preterm labor and preterm prelabor rupture of membranes (PROM) and defined by fetal plasma interleukin (IL)-6 concentrations ≥11 pg/mL [1,2]. FIRS is also associated with an increase in fetal plasma concentrations of soluble tumor necrosis factor receptors-1 and 2, IL-1β, IL-8 and C-reactive protein [3–10]. FIRS is associated with the impending onset of preterm labor/delivery, microbial invasion of the amniotic cavity and increased perinatal morbidity after adjustment for gestational age [11–24].

A solid body of evidence supports the view that intra-amniotic infection/inflammation plays a major role in the pathophysiology of FIRS [15,25–31]. Fetuses with FIRS had a higher rate of severe neonatal morbidity (e.g. respiratory distress syndrome [1], suspected or proven neonatal sepsis [1,15], pneumonia [1], bronchopulmonary dysplasia [13,16,21,32,33], intraventricular hemorrhage [1], periventricular leukomalacia [12] and cerebral palsy [12,14,18,34–38], and necrotizing enterocolitis [1,9]. FIRS is considered the fetal counterpart of the systemic inflammatory response syndrome (SIRS) seen in adults [39,40]. Intra-amniotic infection/inflammation, which is characterized by changes in amniotic fluid concentrations of several proinflammatory cytokines [41–48], anti-inflammatory cytokines [49], chemokines [50–56], caspase-1 (a component of an inflammasome) [57], anti-microbial peptides [58–60], hemostatic factors [61,62], complement activation products [63,64], soluble pattern recognition receptor (pantraxin) [65], damage-associated molecular patterns and their receptors [66–70], protease-anti-protease [71], adipocytokines [72–75], surfactant proteins [76], angiogenic factors [77,78] and matrix degrading enzymes [25,27,28,79–87] is, therefore, a strong risk factor for short- and long-term neonatal complications [15,36,88–95].

Changes in hematologic parameters have been observed in patients with SIRS [96–101]. Indeed, either leukocytosis (white blood cell (WBC) count >12,000/μL) or leukopenia (WBC <4,000/μL) is one of the criteria for the diagnosis of SIRS. Either leukocytosis or leukopenia is associated with a poor outcome [102–104]. In adults, an increased total WBC or neutrophil count is an indicator of subclinical inflammation [103–107]. In neonates, neutrophilia is associated with respiratory distress syndrome [108–111], early-onset neonatal sepsis [112,113] and cerebral injury [95,114,115]. Similarly, an elevated nucleated red blood cell (NRBC) count has been observed in newborns with low umbilical arterial pH [116–118], intrauterine growth restriction [116,119–121], early-onset neonatal seizures [122–124], cerebral white matter injury [125–127] and infants who develop cerebral palsy [128,129]. Indeed, an abnormal NRBC count at birth is associated more strongly with short-

term neonatal outcome (requirement of mechanical ventilation, need for vasopressure agents or neonatal mortality) than birth weight or gestational age regardless of being small or appropriate for gestational age [119].

An increased NRBC count has been associated with chronic intrauterine hypoxia or stress [130–138], frequently seen in fetuses of mothers with preeclampsia [121,139–141], intrauterine growth restriction [116,119–121] or diabetes mellitus [142–144]. However, an experimental study indicates that the administration of recombinant IL-6 to animals can stimulate the erythroid progenitor cells in the bone marrow and eventually lead to the release of NRBC into circulation, suggesting that inflammation can trigger systemic elevation of NRBC count [145]. Similarly, in patients with preterm labor and preterm PROM, histologic chorioamnionitis or severe acute placental inflammation are associated with an increased neonatal NRBC count [129,146,147], suggesting that intrauterine infection may modulate hematopoiesis in neonates and/or fetuses.

The objective of this study was to determine if systemic inflammation in fetuses with FIRS is associated with a fetal hematologic response.

PATIENTS AND METHODS

Patients and eligibility

This retrospective cross-sectional study included women who were admitted at Hutzel Hospital with preterm labor and intact membranes or with preterm PROM between March 1992 and March 1996. They were offered amniocentesis for the diagnosis of MIAC and assessment of fetal lung maturity. Patients who consented to have an amniocentesis were asked to participate in a research management protocol that included the collection of additional amniotic fluid for research purposes and cordocentesis. Criteria for eligibility into this study included (1) preterm labor with intact membranes or with preterm PROM, (2) written informed consent to have amniocentesis and cordocentesis, and (3) availability of skilled medical staff to perform amniocentesis and cordocentesis. Exclusion criteria were: (1) clinical chorioamnionitis, (2) multiple gestation, (3) fetal distress, or (4) significant vaginal bleeding. Oligohydramnios was not an exclusion criterion.

Clinical definition

The diagnosis of preterm labor was made in the presence of regular uterine contractions (at least 3 in 30 minutes) and documented cervical change in patients with a gestational age of 20 to 36 6/7 weeks. Preterm PROM was diagnosed with sterile speculum examination with a combination of vaginal pooling and nitrazine and ferning tests. Intra-amniotic infection was defined as a positive microbiological culture in amniotic fluid. Clinical chorioamnionitis was diagnosed in the presence of a temperature elevation to 37.8°C or higher and two or more of the following criteria: uterine tenderness, malodorous vaginal discharge, fetal tachycardia (fetal heart rate >160 beats/min), and maternal leukocytosis (leukocyte count >15,000/μL) 55,56].

Since blood cell count varies with gestational age, the observed values were corrected for fetal age by calculating a ratio between the observed and expected mean value for gestational age. The reference ranges for each gestational age of fetal hemoglobin concentrations, nucleated red blood cell, white blood cell and platelet counts were obtained from previous studies [148–151]. The corrected eosinophil and basophil counts were not obtained since they do not change with gestational age [150]. Neutrophilia was defined as a neutrophil count >95th centile of gestational age and neutropenia was defined as a neutrophil count <5th centile of gestational age [150]. The results of nucleated red blood cell count were reported as count per 100 WBC.

All patients provided written informed consent prior to the performance of procedures and collection of samples. The collection and utilization of the samples for research 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.

Amniocentesis, cordocentesis and assays for IL-6

All patients had a detailed ultrasonographic examination before amniocentesis and cordocentesis were performed. Electronic fetal monitoring was performed before and after the procedure to evaluate fetal well-being. Amniocentesis and cordocentesis procedures were performed under ultrasound guidance with the "free-hand technique" as previously described [152]. Gram stain and microbial cultures for aerobic and anaerobic bacteria, and mycoplasmas were performed in amniotic fluid. The results of these tests were used for subsequent clinical management. Fetal blood was collected in ethylenediaminetetra-acetic acid (EDTA). Kleihauer-Betke stains were performed on fetal blood, and all specimens were found to be free of maternal blood. Fetal blood was analyzed for hemoglobin concentration, platelet and nucleated red blood cell count, as well as WBC and differential count, including neutrophils, monocytes, lymphocytes, basophils, and eosinophils. The hemoglobin concentration, platelet, and total nucleated cell count (WBC and nucleated red blood cell counts) were obtained with a Coulter S-Plus IV (Coulter Electronics, Hialeah, Fla., USA) analyzer. The blood films were stained by Giemsa-Wright method. The nucleated red cell and the differential leukocyte counts were determined by morphological classification of 100 cells.

Fetal plasma IL-6 concentrations were determined with commercially available enzyme-linked immunoassays (R&D Systems, Minneapolis, USA). The sensitivity of the assay was 0.06 pg/mL. The intra-assay and inter-assay coefficients of variation were 3.3% and 8.3%, respectively. The results of IL-6 concentrations in fetal plasma reported herein were neither available nor used for clinical decision-making.

Statistical analysis

The Kolmogorov-Smirnov test and Shapiro-Wilk test were used to determine if the data was normally distributed. A two-tailed Mann-Whitney U test was used to compare continuous nonparametric variables. Comparisons between proportions were performed using Chi-square or Fisher's exact tests. Correlation between fetal plasma IL-6 concentrations and fetal hematologic parameters was determined using Spearman's rank correlation test. A p-value <0.05 was considered statistically significant. Analysis was performed with SPSS, version 15 (SPSS Inc., Chicago, USA)

RESULTS

Demographic and clinical characteristics

This study included 102 women, of which 67% (102/152) were presented with preterm labor and intact membranes and 33% (50/152) were presented with preterm PROM. Seventy nine percent (121/152) delivered at <37 weeks of gestation. The prevalence of intra-amniotic infection and FIRS was 27% (41/152) and 28.9% (44/152), respectively. FIRS was diagnosed more frequently in patients with preterm PROM than in those with preterm labor [preterm PROM 42% (21/50), vs. preterm labor 22% (23/102); p=0.01]. Patients with FIRS had a higher rate of intra-amniotic infection, clinical chorioamnionitis, and preterm delivery than those without FIRS (all $p<0.05$ see Table I). There was no significant difference in the frequency of exposure to antenatal steroids, tocolysis (magnesium sulfate, indomethacin or

terbutaline) or antibiotics prior to cordocentesis between patients with and without FIRS (all p>0.05; see Table I). All patients except five (97%), had information on hemoglobin concentrations, platelet, NRBC and differential WBC counts.

FIRS is associated with leukocytosis and neutrophilia

Fetuses with FIRS have a higher median total WBC count and corrected WBC count for gestational age than those without FIRS (total WBC: FIRS median 6.3 $\times 10^9$L; range 1.3–23.1 $\times 10^9$L vs. without FIRS median 5.4 $\times 10^9$L; range 2–12.6 $\times 10^9$L; p=0.008 and corrected WBC: FIRS median 1.4; range 0.3–5.6 vs. without FIRS median 1.1; range 0.4–2.9; p=0.001; Table II and Figure 1).

Similarly, the median absolute and corrected neutrophil counts were higher in fetuses with FIRS than in those without FIRS (median absolute neutrophil count 2.8 $\times 10^9$cells/ mL; range 0.1–17 $\times 10^9$cells/ mL vs 1.6 $\times 10^9$cells/ mL; range 0.1–7.2 $\times 10^9$cells/ mL; median corrected neutrophil count 3.6; range 0.1–57.5 vs 1.8; range 0.2–13.9, all p<0.05; see Table II, Figure 2). Neutrophilia was significantly more common in fetuses with FIRS than in those without FIRS [71% (30/42), vs. 35% (37/104), p<0.001, Table II]. However, neither the prevalence of neutropenia [4.8% (2/42), vs 7.7% (8/105), p>0.05; Table II] nor the median lymphocyte, monocyte, eosinophil and basophil counts were significantly different between fetuses with and without FIRS (all p>0.05, Table II).

Fetuses with FIRS had a tendency of enhanced erythropoiesis

Fetuses with FIRS have a median absolute fetal NRBC count higher than those without FIRS (FIRS: median 0.5/100WBC; range 0-14/100WBC vs. without FIRS: median 0.3/100WBC; range 0-14/100WBC; p=0.01). The median fetal NRBC count corrected for gestational age in FIRS was higher than that in fetuses without FIRS. However, the difference did not reach statistical significance (FIRS: median 0.07; range 0–1.3 vs. without FIRS: median 0.04; range 0–2.3; p=0.06; see Table II and Figure 3). The median hemoglobin concentration and platelet count were not significantly different between fetuses with and without FIRS (all p>0.05, Table II).

Correlation between fetal blood IL-6 concentration and fetal blood hematologic parameters

The absolute and corrected fetal WBC counts were correlated with fetal plasma IL-6 concentrations (Spearman's rho 0.2; p=0.004 and Spearman's rho 0.3; p<0.001, respectively). Among the various WBC lineages, only the absolute and corrected neutrophil counts were correlated with an elevated fetal plasma IL-6 concentration (Spearman's rho = 0.2 for both; p=0.01 and 0.006, respectively). There was a significant relationship between fetal plasma IL-6 concentration and both absolute and corrected NRBC counts (Spearman's rho 0.3 for both; p<0.001 and p=0.001, respectively).

DISCUSSION

Principal findings of the study

1) Fetuses with FIRS had a higher median total WBC and neutrophil count than those without FIRS; 2) more than two thirds of fetuses with FIRS had neutrophilia, while neutropenia was present in only 4.8%; 3) FIRS was not associated with significant changes in hemoglobin concentration, platelet, lymphocyte, monocyte, basophil or eosinophil counts; and 4) there was a tendency for fetuses with FIRS to have an elevated NRBC count when compared to those without FIRS after adjustment for gestational age.

More than two thirds of fetuses with FIRS have neutrophilia

Neutrophils are part of the innate immune system and play a critical role in the acute inflammatory response and host defense against infection. During human fetal development, neutrophils first appear in the clavicular bone marrow at 12–13 weeks of gestation [153]. However, the lymphocyte is the predominant WBC type in the preterm fetus [154]. After 32 weeks of gestation, the proportion of neutrophils increases to become the predominant leukocyte at term [150,154]. It is interesting that while hematopoiesis in the fetal liver is characterized by proliferation of erythrocytes rather than neutrophils, the early bone marrow behaves differently – hypocellular for erythrocytes but rich in neutrophils [153].

The finding that fetuses with FIRS had elevated neutrophil counts is consistent with several previous studies from our group and others. Carroll and Nicolaides demonstrated that fetuses with bacteremia had higher leukocyte and neutrophil counts than those without bacteremia in patients with preterm PROM [155]. Fetuses with FIRS also have phenotypic evidence of monocyte-neutrophil activation in patients who delivered within 72 hours of cordocentesis [156]. Moreover, umbilical cord blood from patients with acute funisitis, the histological counterpart of FIRS [157], had phenotypic and metabolic changes on leukocytes [higher median mean channel brightness (MCB) of CD14, CD64, and CD66b on granulocytes and of CD64 on monocytes and increased basal intracellular reactive oxygen species and oxidative burst in monocytes) [158]. These findings suggest that fetuses with FIRS had a hematologic profile consistent with activation of the innate limb of the immune response.

More than two-thirds of fetuses with FIRS had neutrophilia, and only 4.8% had neutropenia. These observations seem to contradict the findings in septic preterm neonates who frequently present with neutropenia. The mechanism of fetal neutrophilia is not completely understood. However, it has been proposed that granulocyte colony stimulating factor (G-CSF), the primary physiologic regulator of neutrophil production and emergency signal of neutrophil release, may participate in these mechanisms [159–163]. Indeed, fetuses with FIRS had higher plasma concentrations of G-CSF than those without FIRS [162]. It is possible that fetal infection causes elevation of G-CSF and mobilization of neutrophils from bone marrow resulting in fetal neutrophilia. Subsequently, the neutrophil storage pool in these fetuses is depleted, and the neonates become neutropenic after birth. This hypothesis is consistent with a chronic nature of infection-related preterm birth [164–174].

Erythropoiesis and nucleated red blood cell count in FIRS

Erythropoiesis, a process of red blood cell production, is a component of hematopoiesis which is crucial from a developmental perspective. The development of an erythropoietic system allows growth of the higher organisms to a size not otherwise possible due to inadequate supply of oxygen by simple diffusion, a key mechanism for oxygen transport in lower organisms [175]. Humans have four principal sites of erythropoiesis: yolk sac, ventral aspect of the aorta, liver and bone marrow. Hepatic hematopoiesis diminishes with advancing gestational age, as the bone marrow becomes the primary site of erythropoiesis [176]. The main regulator of this process is erythropoietin. This growth factor maintains red blood cell production during fetal, neonatal and adult life by inhibiting apoptosis of erythroid progenitors and by stimulating their proliferation and differentiation into normoblasts.

In contrast to adults, the primary source of erythropoietin in fetal life is the liver, and it is not until approximately the 30th week of gestation that renal erythropoietin production begins [175,176]. This hematopoietic factor can be stimulated by hypoxia-inducible factors -1 and -2, IL-6 and tumor necrosis factor–α. Elevated erythropoietin has been reported in several pathologic conditions such as hypoxia [177–179], anemia [180,181], placental

insufficiency [178,182] or infants of diabetic mothers [183,184]. In these conditions, erythropoietin is correlated with an elevated NRBC count in umbilical cord blood [185,186]. Recently, the administration of recombinant erythropoietin to mothers or fetuses ameliorated the fetal liver and white matter injury in endotoxin treated animals [187,188].

Fetuses with FIRS tend to have higher NRBC counts than those without FIRS

One of the principal findings of this study is that the fetuses with FIRS had a higher absolute NRBC count than those without FIRS. However, when NRBC counts were adjusted for gestational age, the difference fell short of reaching statistical significance ($p=0.06$). Since NRBC counts in this study were expressed as numbers of NRBC per 100 WBC, the real magnitude of the changes in NRBC counts observed herein may have been underestimated. The increase in the total leukocyte count in FIRS may artificially lead to an underestimation of the number of NRB cells when using this ratio.

Elevated neonatal NRBC counts have been reported in patients with prolonged rupture of fetal membranes (>24 hours) [189], histologic chorioamnionitis [190], high acute placental inflammation score [146] and early-onset neonatal sepsis [122]. Since we have reported that FIRS is not associated with changes in the umbilical vein blood gas pH and PaO_2 [191], hypoxia and metabolic acidosis is unlikely to cause the increased erythropoiesis observed herein. We propose that the increased number of NRBC represents the action of selected cytokines such as IL-6.

Interleukin-6 is a cytokine with a broad range of biological activities produced by macrophages, T cells and B cells [192,193]. This cytokine is a major mediator of the host response to infection and tissue damage that plays a central role in the defense mechanism, acute phase reaction, and hematopoiesis [192,193]. Studies in animals [145] and humans [194] indicate that IL-6 can stimulate erythropoiesis. Intrauterine administration of endotoxin to pregnant mice increases circulating NRBC in the fetal blood without significant elevations in erythropoietin concentrations [195]. Therefore, we propose that an elevated IL-6 in FIRS is responsible, at least in part, for the increased erythropoiesis reflected in the NRBC count.

Alternatively, the effect of IL-6 may be indirect. This cytokine can stimulate erythropoietin production and, through this mechanism, indirectly increase NRBC count. Evidence in support of this hypothesis includes: 1) umbilical venous blood erythropoietin and umbilical arterial blood IL-6 concentrations are higher in infants born to mothers with both histologic and clinical chorioamnionitis than those born to mothers without chorioamnionitis [196]; 2) neonates with acute funisitis have higher erythropoietin concentrations than those without acute funisitis [186]; and 3) in hospitalized adult patients, NRBC count is correlated with plasma erythropoietin as well as inflammation related cytokine (IL-3, IL-6 and IL-12p70) concentrations [197]. Patients with elevated NRBC counts have higher mortality rates than those with elevated erythropoietin or IL-6 concentration alone. Stachon et al. proposed that the NRBC count may be considered as a parameter which expresses the combined effects of hypoxia (erythropoietin) and inflammation (IL-6) [197].

Strength and limitations of the study

This is the first study describing the hematologic profiles of human fetuses with FIRS. The limitations of this study are: 1) a subset of patients received medication including antenatal steroids, tocolysis and antibiotics prior to the procedure. However, there was no significant difference in the frequency of these confounders between fetuses with and without FIRS; and 2) the NRBC count in the current study was reported as NRBC per 100WBC. This parameter has been criticized as being susceptible to under- or over-estimation of the

absolute value of NRBC, especially in conditions where there is an increase or decrease in leukocyte counts, respectively [198]. Even if we wished to report the results as absolute numbers of NRBC per unit volume, an accurate adjustment of NRBC counts as a function of gestational age cannot be performed since there is no published reference standard for gestational age for the absolute number of NRBC per unit volume (e.g. cells/mm^3 or cells / L) available.

Conclusion

The hematological response of the fetus with FIRS is characterized by significant changes in the total WBC and neutrophil counts. The NRBC count in fetuses with FIRS tends to be higher than that of fetuses without FIRS, and this cannot be attributed to the effect of hypoxia. In contrast to septic preterm neonates, the majority of fetuses with FIRS have neutrophilia. This study contributes to characterizing the hematologic parameters in fetuses with FIRS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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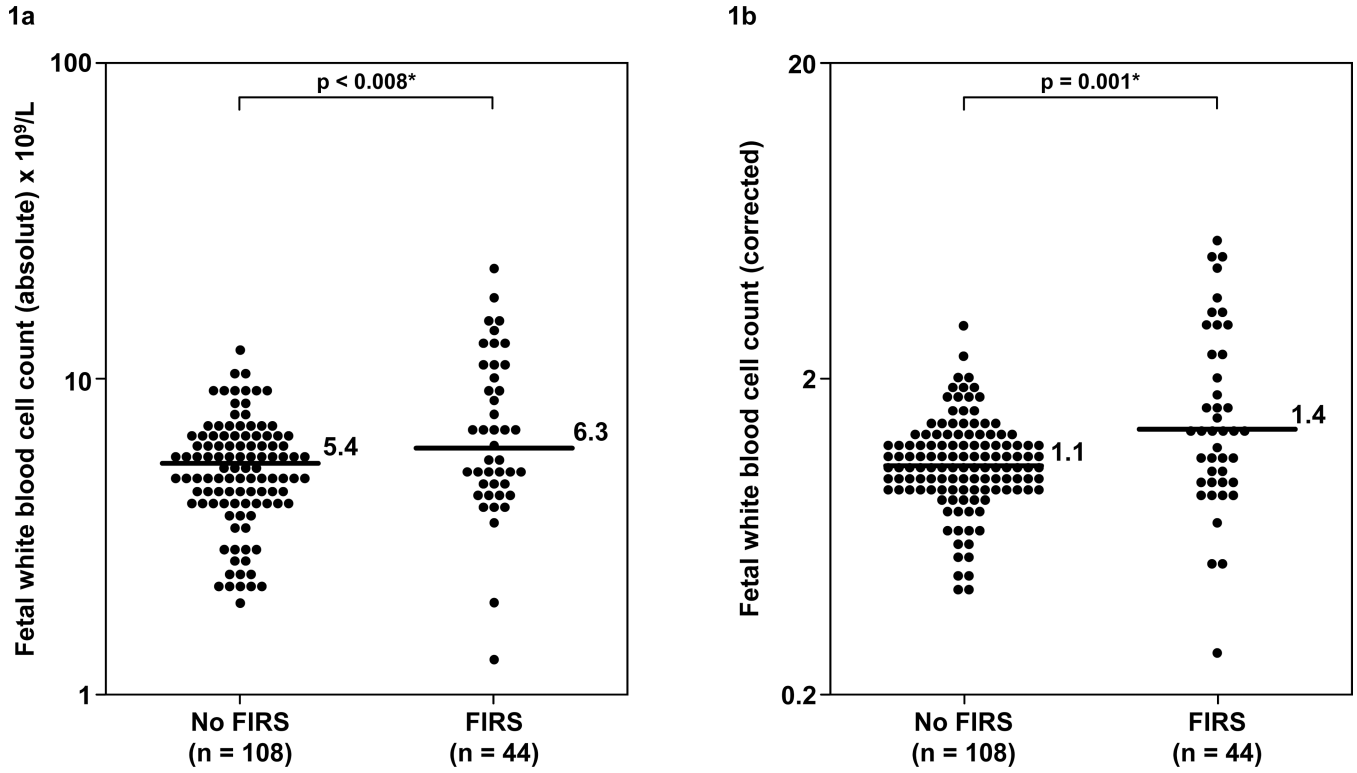

Figure 1. Comparison of the fetal blood absolute and corrected white blood cell counts between fetuses with FIRS and those without FIRS

Fetuses with FIRS have a higher median absolute WBC count (FIRS: median 6.3 $\times 10^9$/L; range 1.3–23.1 $\times 10^9$/L vs. without FIRS: median 5.4 $\times 10^9$/L; range 2–12.6 $\times 10^9$/L; p=0.008, Figure 1a) and corrected WBC count (FIRS: median 1.4; range 0.3–5.6 vs. without FIRS median 1.1; range 0.4–2.9; p=0.001; Figure 1b) than those without FIRS. The y-axis is depicted in log scale.

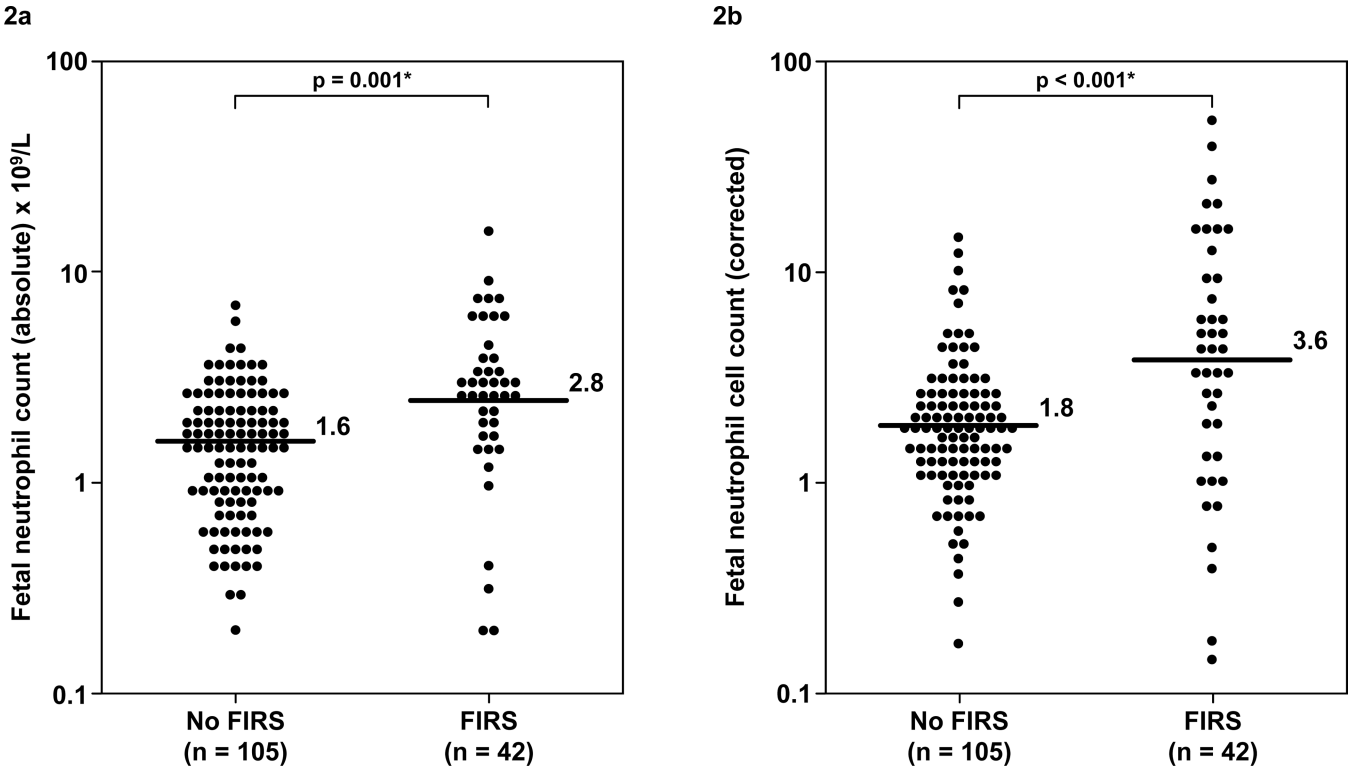

Figure 2. Comparison of the fetal blood absolute and corrected neutrophil counts between fetuses with FIRS and those without FIRS

The median absolute and corrected neutrophil counts were higher in fetuses with FIRS than that of those without FIRS [median for absolute neutrophil count 2.8 $\times 10^9$/L; range 0.1–17 $\times 10^9$/L vs 1.6 $\times 10^9$/L; range 0.1–7.2 $\times 10^9$/L (Figure 2a); median for corrected neutrophil count 3.6; range 0.1–57.5 vs 1.8; range 0.2–13.9, all $p<0.05$; (Figure 2b)]. The y-axis is depicted in log scale.

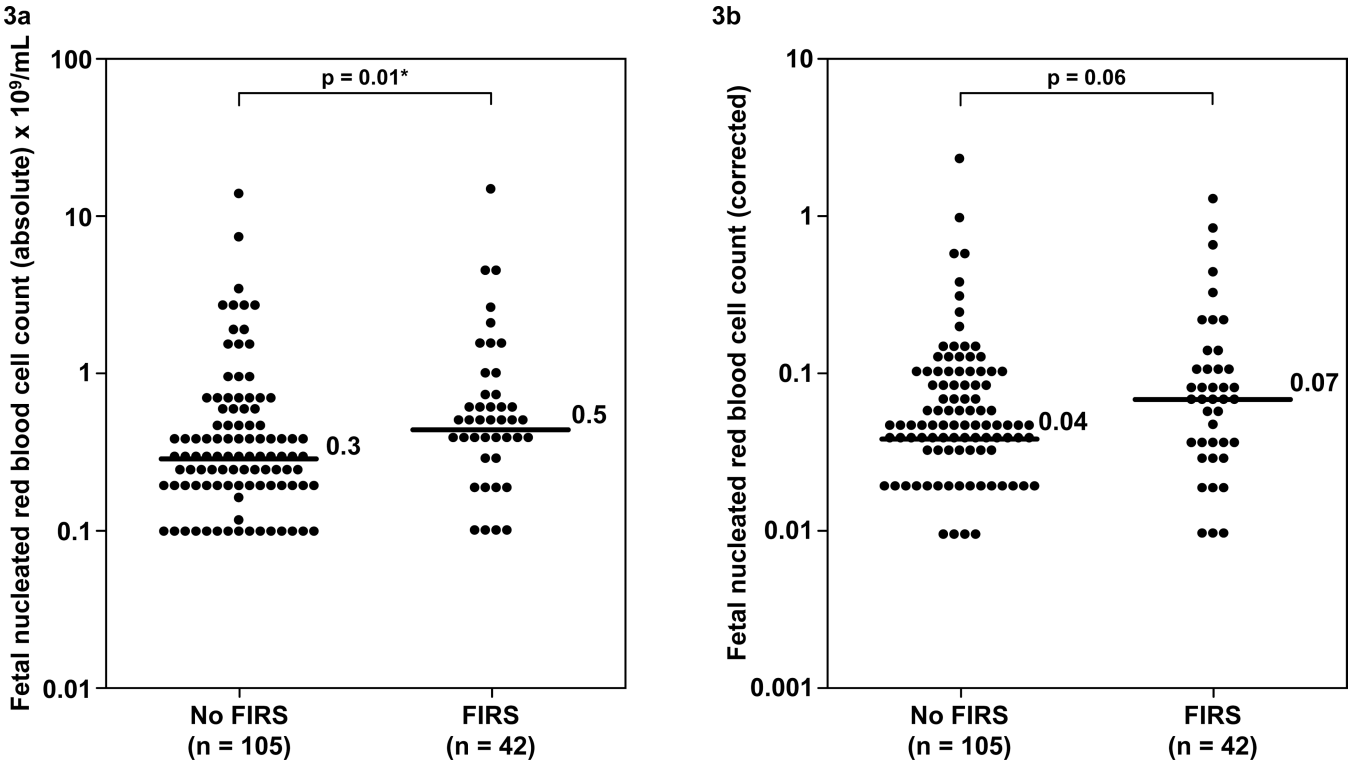

Figure 3. Comparison of the fetal blood absolute and corrected nucleated red blood cell counts between fetuses with FIRS and those without FIRS

Fetuses with FIRS have a median absolute fetal NRBC count higher than those without FIRS. (FIRS: median 0.5 / 100WBC; range 0–14 / 100WBC vs. without FIRS: median 0.30 / 100WBC; range 0–14 / 100WBC; p=0.01, Figure 3a). The median fetal NRBC count corrected for gestational age in FIRS was higher than that in fetuses without FIRS. However, the difference did not reach statistical significance (FIRS: median 0.07; range 0–1.3 vs. without FIRS: median 0.04; range 0–2.3; p=0.06; Figure 3b). The y-axis is depicted in log scale.

Table I

Clinical characteristics of the study population

	NO FIRS (n=108)	FIRS (n=44)	p
Age (years)	24.3 (15–38)	24.5 (15–39)	0.8
GA at cordocentesis (weeks)	30.7 (18.2–35.5)	29.2 (20–36)	0.02
Preterm PROM	29 (26.9%)	21 (47.7%)	0.01
Intra-amniotic infection	14 (13%)	27 (61.4%)	<0.001
Clinical chorioamnionitis	6 (5.6%)	10 (62.5%)	0.002
Antenatal steroids prior to cordocentesis	29 (26.9%)	13 (29.5%)	0.7
Tocolysis prior to cordocentesis	71 (65.7%)	23 (52.3%)	0.1
Antibiotics prior to cordocentesis	27 (25%)	13 (30.2%)	0.5
Preterm delivery	79 (73.1%)	42 (95.5%)	0.002
Delivery within 72 hours	22 (20.4%)	35 (79.5%)	<0.001
GA at delivery (weeks)	34.3 (24–41.8)	30.1 (20–38.3)	<0.001
Interval to delivery (hours)	608.2 (2–3384)	149.7 (1–1368)	<0.001
Birthweight (grams)	2327 (490–4337)	1568 (360–3480)	<0.001
Fetal blood IL-6 (pg/mL)	4.8 (0.3–10.8)	171.6 (11.5–900)	<0.001

Values were expressed as number (percent) or median (range)
FIRS: Fetal inflammatory response syndrome
GA: Gestational age; PROM: prelabor rupture of membranes

TABLE II

Hematologic profile of the fetuses with and without FIRS

	NO FIRS (n=108)	FIRS (n=44)	p
WBC (×10^9/L)	5.4 (2–12.6)	6.3 (1.3–23.1)	0.008
Corrected WBC	1.1 (0.4–2.9)	1.4 (0.3–5.6)	0.001
Neutrophil (×10^9/L)	1.6$^{\alpha}$ (0.1–7.2)	2.8$^{\beta}$ (0.1–17)	0.001
Corrected Neutrophil	1.8$^{\alpha}$ (0.2–13.9)	3.6$^{\beta}$ (0.1–57.5)	<0.001
Neutrophilia	37 (35%)$^{\alpha}$	30 (71%)$^{\beta}$	<0.001
Neutropenia	8 (7.7%)$^{\alpha}$	2 (4.8%)$^{\beta}$	0.5
Lymphocyte (×10^9/L)	3.2$^{\alpha}$ (1–6.1)	2.8$^{\beta}$ (0.9–8.4)	0.6
Corrected Lymphocyte	0.8$^{\alpha}$ (0.3–1.8)	0.7$^{\beta}$ (0.3–1.8)	0.9
Monocyte (×10^9/L)	0.3$^{\alpha}$ (0–0.9)	0.3$^{\beta}$ (0–1.9)	0.4
Corrected Monocyte	1.1$^{\alpha}$ (0–4.7)	1.2$^{\beta}$ (0–21.1)	0.2
Eosinophil (×10^9/L)	0.1$^{\alpha}$ (0–1.1)	0.1$^{\beta}$ (0–0.6)	0.4
Basophil (×10^9/L)	0$^{\alpha}$ (0–0.2)	0$^{\beta}$ (0–0.2)	0.7
NRBC/100 WBC	0.3$^{\alpha}$ (0–14)	0.5$^{\beta}$ (0–14)	0.01
Corrected NRBC	0.04$^{\alpha}$ (0–2.3)	0.07$^{\beta}$ (0–1.3)	0.06
Platelet (×10^9/L)	249$^{\alpha}$ (73–394)	229$^{\beta}$ (28–368)	0.1
Corrected Platelet	1.03$^{\alpha}$ (0.3–1.6)	0.9$^{\beta}$ (0.1–1.5)	0.3
Hemoglobin (g/dl)	13.1$^{\alpha}$ (0–15.8)	12.9$^{\beta}$ (9.8–16)	0.4
Corrected hemoglobin	0.9$^{\alpha}$ (0–1.2)	0.9$^{\beta}$ (0.7–1.2)	0.7

Values were expressed as median (range) and number (percent)
FIRS: Fetal inflammatory response syndrome
WBC: White Blood Cell, NRBC: Nucleated Red Blood Cell

$^{\alpha}$n=105,

$^{\beta}$n=42