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The combined exposure to intra-amniotic inflammation and neonatal respiratory distress syndrome increases the risk of intraventricular hemorrhage in preterm neonates

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Abstract

OBJECTIVE—To evaluate the impact of combined exposure to intra-amniotic inflammation and neonatal respiratory distress syndrome (RDS) on the development of intraventricular hemorrhage (IVH) in preterm neonates.

METHODS—This retrospective cohort study includes 207 consecutive preterm births (24.0–33.0 weeks of gestation). Intra-amniotic inflammation was defined as an amniotic fluid matrix metalloproteinase-8 concentration >23 ng/mL. According to McMenamin's classification, IVH was defined as grade II or higher when detected by neurosonography within the first weeks of life.

RESULTS—1) IVH was diagnosed in 6.8% (14/207) of neonates in the study population; 2) IVH was frequent among newborns exposed to intra-amniotic inflammation when followed by postnatal RDS (33% [6/18]). The frequency of IVH was 7% (8/115) among neonates exposed either to these conditions—intra-amniotic inflammation or RDS—and 0% (0/64) among those who were not exposed to these conditions; and 3) neonates exposed to intra-amniotic inflammation and postnatal RDS had a significantly higher risk of IVH than those with only intra-

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amniotic inflammation [odds ratio (OR), 4.6; 95% confidence interval (CI), 1.1–19.3) and those with RDS alone (OR, 5.6; 95% CI, 1.0–30.9), after adjusting for gestational age.

CONCLUSION—The combined exposure to intra-amniotic inflammation and postnatal RDS markedly increased the risk of IVH in preterm neonates.

Keywords

brain injury; hypoxic-ischemic injury; intra-amniotic inflammation; periventricular-intraventricular hemorrhage; preterm birth

Introduction

Intraventricular hemorrhage (IVH) remains one of the leading causes of morbidity and mortality in the preterm neonate [1–13]. A substantial body of evidence indicates that IVH is a predictor of periventricular leukomalacia [14–17], neurodevelopmental delay [3, 12, 13, 18] and cerebral palsy [19–23]. Even low-grade IVH is associated with poor neurodevelopmental outcomes [12, 24]. Risk factors that have been linked to the development of IVH include early gestational age at birth [4, 25–28], intrauterine/fetal inflammation [1, 4, 5, 29–33], spontaneous preterm birth [4, 34], early onset of neonatal sepsis [35], respiratory distress syndrome (RDS) [25, 36–39], hypoxia-ischemia [40, 41], and non-use of antenatal corticosteroids [26, 35].

Substantial evidence indicates that intra-amniotic infection/inflammation is causally linked to preterm delivery [5, 42–62]. The inflammatory response has been implicated in the genesis of fetal brain injury in humans [1, 5, 15, 29, 30] as well as in experimental animal models [63–67]. However, some recent studies [4, 68–70] reported that acute histologic chorioamnionitis was not an independent risk factor for the development of IVH. Moreover, reports suggest that antenatal exposure to an inflammatory response accelerates fetal lung maturation [71, 72] and decreases the risk of developing of RDS [73–75]. In a nationwide population-based study, spontaneous preterm infants were at increased risk of cerebral palsy but at decreased risk of RDS [76]. These findings raise the question of how the inflammatory response increases the risk of IVH despite decreasing the risk of RDS, which is known as a risk factor for IVH.

The purpose of this study was to evaluate the relationship among the antenatal inflammatory response, the postnatal occurrence of RDS, and the development of IVH in preterm neonates.

Materials and methods

Study design

This retrospective cohort study includes 207 consecutive singleton preterm neonates who were born in the Seoul National University Hospital from 1995 to 2007 and met the following criteria: 1) gestational age at birth between 24.0 and 33.0 weeks; 2) absence of chromosomal abnormalities and major structural anomalies; 3) collection of amniotic fluid (AF) within 120 hours of delivery, either by abdominal amniocentesis or at the time of

cesarean delivery; and 4) neurosonographic examination within seven days of birth. We reviewed the medical records to determine the clinical and demographic characteristics of the mothers and their neonates. The demographic characteristics included age, parity, and gestational age at birth. The clinical characteristics consisted of antenatal corticosteroid administration, histopathological evaluation of the placenta, cause of preterm birth (spontaneous vs. medically indicated preterm birth) and delivery mode (cesarean vs. vaginal delivery). We also included gender, umbilical arterial blood gas analysis, and Apgar scoring at 1 minute and 5 minutes.

Diagnosis of neonatal respiratory distress syndrome and intraventricular hemorrhage

Neonatal RDS was defined as the presence of respiratory distress, increased oxygen requirement ($FiO_2 > 0.4$), and diagnostic radiological findings in the absence of evidence of any other causes of respiratory distress as described previously [74].

Neurosonographic examinations were performed as part of routine clinical care in preterm neonates. Sonographic findings of periventricular-intraventricular hemorrhage (PV-IVH) were graded into three categories according to McMenamin's classification [2]: 1) grade I: subependymal hemorrhage with minimal or no IVH; 2) grade II: IVH, but neither lateral ventricle completely filled with blood, with or without mild ventricular dilatation; and 3) grade III: IVH completely filling and distending at least one lateral ventricle. IVH was defined as Grade II or higher by McMenamin's classification of PV-IVH. For a meaningful temporal relationship among intra-amniotic inflammation, neonatal RDS, and the development of IVH, the results of neurosonographic examinations performed within seven days of birth were included.

Definition of intra-amniotic inflammation

Amniotic fluid not used for clinical studies was stored at −70°C for future research purposes. The stored AF was analyzed for matrix metalloproteinase-8 (MMP-8), which was measured with a commercially available enzyme-linked immunosorbent assay (Amersham Pharmacia Biotech, Inc., Amersham, UK), as previously reported [77]. The measurement was not performed in 10 patients because of the lack of available AF. The sensitivity of the test was 0.3 ng/mL. Intra- and inter-assay coefficients of variation for each were <10%. Intra-amniotic inflammation was defined as an elevated AF MMP-8 concentration (>23 ng/mL), as previously reported [77]. The Institutional Review Board of the Seoul National University Hospital approved the collection and use of these samples for research purposes. This University Hospital has a Federal Wide Assurance with the Office for Human Research Protection of the Department of Health and Human Services of the United States.

Diagnosis of acute histologic chorioamnionitis and acute funisitis

Acute histologic chorioamnionitis was defined in the presence of acute inflammatory changes upon examination of the choriodecidua and amnion, respectively; acute funisitis was diagnosed in the presence of neutrophil infiltration into the umbilical vessel walls or Wharton's jelly with the use of criteria previously reported [5, 59].

Statistical analysis

The Mann-Whitney *U*-test was used for comparison of continuous variables. For the dichotomized variables, a Fisher's exact test was performed. Multiple logistic regression analysis was used to examine the relationship of intra-amniotic inflammation and RDS to the probability of the occurrence of IVH after adjusting for variables that had a significant correlation or a tendency ($P < 0.1$) including gestational age at birth, male gender, and acute histologic chorioamnionitis. A probability value < 0.05 was considered as significant. SPSS 21.0 for Windows (IBM, Armonk, NY, USA) was used for statistical analyses.

Results

Characteristics of the study population

Table 1 describes the characteristics and results of the neurosonographic examinations performed in the study population. A total of 258 neurosonographic examinations were performed on 207 neonates (mean 1.3 ±0.5 neurosonographic examinations/neonate) within seven days of birth; 43 (31%) newborns received multiple scans. IVH was diagnosed in 6.8% (14/207) of neonates in the study population.

Table 2 compares the clinical characteristics according to the development of IVH. Gestational age was significantly lower in neonates with IVH than those without IVH ($P < 0.005$). Neonates with IVH had higher rates of RDS and the presence of histologic chorioamnionitis than those without IVH ($P < 0.05$ for each). Spontaneous preterm birth and male gender were more frequent in neonates with IVH than in those without IVH, but the differences did not reach statistical significance. The rates of antenatal corticosteroid use and cesarean delivery were not significantly different between groups. Among the 197 neonates whose AF was measured for MMP-8 concentrations, neonates with IVH had a significantly higher median AF MMP-8 concentration ($P < 0.05$) and a higher rate of intra-amniotic inflammation ($P < 0.01$) than those without IVH.

The relationship among intra-amniotic inflammation, respiratory distress syndrome and intraventricular hemorrhage

Table 3 shows the multivariate analysis for the factors that had a probability of < 0.1 in the univariate analysis. Because the presence of intra-amniotic inflammation was closely linked to the occurrence of histologic chorioamnionitis, they were included separately in the multivariate analysis model. When acute histologic chorioamnionitis was included in the multivariate analysis, gestational age at birth was an independent risk factor for the development of IVH [odds ratio (OR), 0.70; 95% confidence interval (CI), 0.52–0.94). When the presence of intra-amniotic inflammation was included in the analysis, this factor (OR, 7.88; 95% CI, 1.63–38.1) and the occurrence of RDS (OR, 6.50; 95% CI, 1.69–25.1) were independent risk factors for the development of IVH. When these two variables (intra-amniotic inflammation and acute histologic chorioamnionitis) were included together in the multivariate analysis, the presence of intra-amniotic inflammation (OR, 25.3; 95% CI, 1.89–338.6) and the occurrence of RDS (OR, 4.63; 95% CI, 1.10–19.4) were independently associated with the development of IVH.

The effect of combined exposure to intra-amniotic inflammation and postnatal respiratory distress syndrome on intraventricular hemorrhage

Table 4 presents the clinical characteristics and outcomes of the study population according to the presence or absence of intra-amniotic inflammation and the occurrence of neonatal RDS. IVH was frequent among newborns exposed to intra-amniotic inflammation when followed by postnatal RDS (33% [6/18]). The frequency of IVH was 7% (8/115) among neonates exposed to either of these conditions (intra-amniotic inflammation or RDS) and 0% (0/64) among those who were not exposed to these conditions. Figure 1 displays the comparison of rates of IVH among groups according to the presence or absence of intra-amniotic inflammation and the occurrence of RDS. Neonates who were exposed to both of these conditions had a significantly higher risk of IVH than those with RDS alone (OR, 5.63; 95% CI, 1.03–30.87) and those with intra-amniotic inflammation alone (OR, 4.56; 95% CI, 1.08–19.26) after adjusting for the gestational age at birth.

Discussion

Principal findings of this study

IVH occurred in 6.8% (14/207) of the preterm singleton neonates (gestational age between 24.0–33.0 weeks). Intra-amniotic inflammation and neonatal RDS were independent risk factors for the development of IVH. Moreover, the impact of the combined exposure to intra-amniotic inflammation and postnatal RDS was considerably greater than that of separate exposures to either of the conditions.

Intra-amniotic inflammation and intraventricular hemorrhage

Strong evidence suggests that prenatal exposure to an inflammatory response is associated with the development of IVH [1, 5, 29–34, 78, 79]. The germinal matrix zone of preterm neonates is supported by a single cell layer of endothelium without muscle coats and is prone to hemorrhage [80]. The inflammatory response exerts a direct neurotoxic effect [81–83], leads to circulatory disturbances [80], and induces adhesion of leukocytes to fragile vessels [84], all of which may increase the risk of IVH. The findings of our study support the view that prenatal exposure to an inflammatory response plays an important role in the development of IVH in preterm neonates.

Prenatal exposure to an inflammatory response can be determined by elevated concentrations of AF inflammatory mediators [49, 54, 77, 85–104], AF white blood cell count [105–107], the presence of inflammatory changes in the fetal membranes or acute histologic chorioamnionitis [59, 78, 106, 108–111], and the concentration of cytokines in umbilical cord blood [1, 48, 112–116]. In the study herein, intra-amniotic inflammation was defined as an elevated AF MMP-8 concentration (>23 ng/mL); previous studies have shown that the concentration of AF MMP-8 is an excellent marker of intra-amniotic infection and/or inflammation, the fetal inflammatory response syndrome, impeding preterm delivery, and neonatal morbidity [54, 57, 58, 77, 86, 100, 117]. The measurement of AF cytokine concentrations has some advantages over other tools: 1) histologic examination cannot be performed antenatally and the results may not be available in time for clinical management

decisions; 2) histologic chorioamnionitis is frequently found in patients with active labor [118]; and 3) amniocentesis is frequently used for the assessment of lung maturity.

Recent reports have claimed that acute histologic chorioamnionitis is not an independent risk factor for the development of IVH [4, 68–70], which is consistent with our findings (Table 3). However, upon further analysis, we found that intra-amniotic inflammation was an independent risk factor, even after adjusting for other confounding variables. Acute histologic chorioamnionitis represents a maternal inflammatory response in the fetal membranes in response to chemotactic stimuli within the amniotic cavity [108]. Therefore, intra-amniotic inflammation is a better index of the risk of fetal systemic inflammation than histologic chorioamnionitis. Indeed, most neutrophils in the amniotic cavity are of fetal origin [59, 119].

The relationship between neonatal respiratory distress syndrome and intraventricular hemorrhage

Several studies support that RDS is a risk factor for the development of IVH [25, 36, 37, 120, 121]. RDS is associated with the fluctuation of cerebral blood flow [122–124], low blood pressure [125], use of mechanical ventilation and hypoxia-ischemia [126], all of which increase the risk of IVH. In the current study, neonates with RDS had an OR of 3.71 (95% CI, 1.20–11.5; $P<0.05$) for the development of IVH. Moreover, neonates with combined exposure to intra-amniotic inflammation and subsequent RDS had a significantly higher risk of developing IVH than those with intra-amniotic inflammation alone, even after adjusting for gestational age at birth.

Does intra-amniotic inflammation sensitize the immature brain to postnatal injury?

An important question is whether combined exposure to intra-amniotic inflammation and postnatal RDS has a synergistic effect on the development of IVH and brain damage in preterm neonates. Our findings showed that combined exposure of intra-amniotic inflammation and postnatal RDS markedly increases the risk for the development of IVH. Such findings are in keeping with the results of other studies in humans [127] as well as in animals [128–135]. In animal models, the impact of combined exposure to inflammation and postnatal hypoxic-ischemic injury was greater than when either of the conditions was induced separately [128–135]. Indeed, Nelson and Grether [127] found that the risk of unexplained spastic cerebral palsy in neonates with exposure to both infection/birth-asphyxiating conditions was considerably greater than the risk in those with either condition alone, and was 78 times greater than the risk in those without exposure to either of these conditions.

Other factors related to the development of intraventricular hemorrhage

In the study herein, corticosteroid use and cesarean delivery did not show protective effects against the development of IVH. Roberts and Dalziel [136] demonstrated that antenatal corticosteroid treatment decreases the occurrence of cerebroventricular hemorrhage in their meta-analysis, which included 2,872 infants from 13 studies. However, we could not detect this effect in the present study. Possible explanations for this finding include: 1) the small sample size in our study population; 2) selection bias of corticosteroid use (in the study

period, all patients were eligible for receiving antenatal steroids); 3) there was no adjustment for an incomplete course of steroids.

Whether cesarean delivery can prevent IVH is controversial. Although some have reported that cesarean delivery prevents the development of IVH [137–140], other investigators [4, 26, 78, 141] have found that the risk of IVH was not influenced by mode of delivery. In our study, the mode of delivery was not associated with the development of IVH.

Clinical implications

The major clinical implication of our study is that the presence or absence of intra-amniotic inflammation contributes to the estimate of risk for the subsequent development of IVH. Moreover, if RDS occurs in the neonates who were exposed to intra-amniotic inflammation, the risk of IVH is greatly increased. It seems paradoxical that intra-amniotic inflammation decreases the risk of neonatal RDS but increases the risk of IVH. In the current study, neonates with intra-amniotic inflammation had a significantly lower rate of the occurrence of RDS than those without intra-amniotic inflammation [21% (18/84) in the intra-amniotic inflammation group vs. 43% (49/113) in the non-intra-amniotic inflammation group; $P<0.001$ after adjusting for gestational age at birth]. However, although 9% (18/197) of preterm neonates were affected by combined intra-amniotic inflammation and postnatal RDS, 43% (6/14) of cases with IVH were from those neonates. These findings suggest that preterm neonates exposed to intra-amniotic inflammation and subsequent postnatal RDS are at great risk of the development of IVH and require evaluation and more intense surveillance.

In conclusion, antenatal intra-amniotic inflammation and postnatal RDS are independent risk factors for the development of IVH, and the combined exposure of these two factors markedly increases the risk of IVH in preterm neonates.

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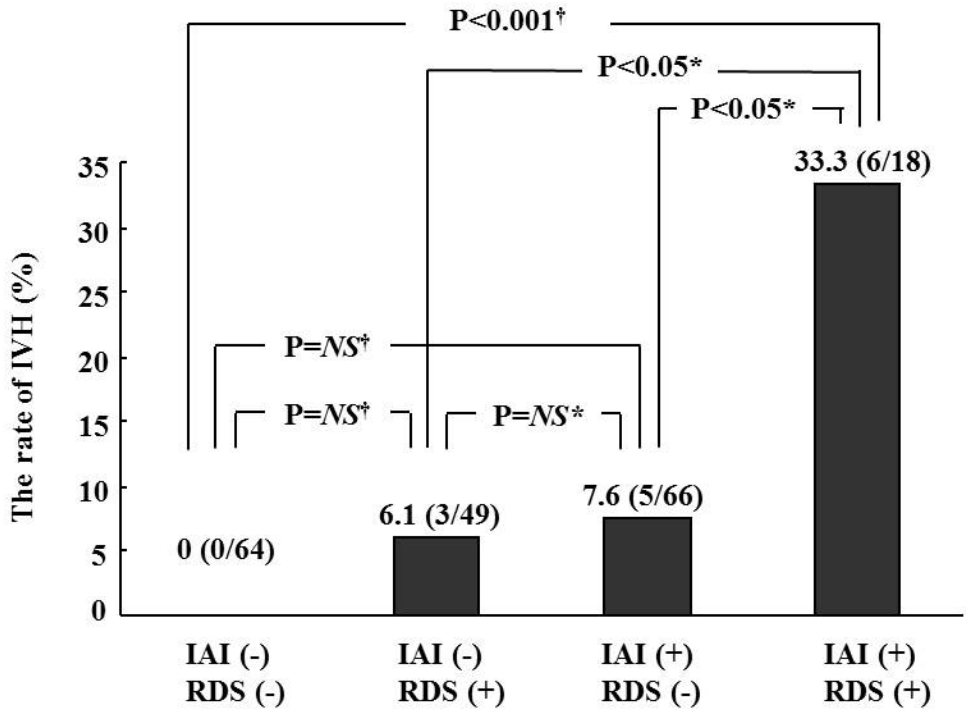

Figure 1. The rate of the development of intraventricular hemorrhage (IVH) according to the presence or absence of intra-amniotic inflammation and the occurrence of neonatal respiratory distress syndrome (RDS)

Intra-amniotic inflammation was defined as an elevated amniotic fluid MMP-8 concentration (>23 ng/mL). *Each P-value was adjusted for gestational age at birth. †P-value could not be adjusted for gestational age at birth because no patient without intra-amniotic inflammation and RDS had an IVH. Patients with intra-amniotic inflammation and neonatal RDS had a higher risk of the development of IVH than those with neonatal RDS alone [odds ratio (OR), 5.63; 95% CI, 1.03–30.9; P<0.05] and those with intra-amniotic inflammation alone [OR, 4.56; 95% CI, 1.08–19.3; P<0.05) after adjusting for gestational age at birth.

Table 1

Characteristics of neurosonographic examinations performed in the study population

Characteristics	Number of neonates (n=207)
No. of neurosonographic examinations	
1	79.2% (164)
2	17.9% (37)
3	1.9% (4)
4	1.0% (2)
Postnatal day at neurosonographic examination	
≤ 3days	63.8% (132)
4–7days	21.3% (44)
Both (≤ 3days and 4–7days)	15.0% (31)
Grade of PV-IVH by neurosonographic examination *	
0	67.6% (140)
I	25.6% (53)
II	4.8% (10)
III	1.9% (4)
IVH †	
Yes	6.8% (14)
No	93.2% (193)

Values are given as % (n).

* Sonographic finding of PV-IVH was graded by McMenamin's classification.

† IVH was defined as PV-IVH of grade II or higher by McMenamin's classification.

IVH: intraventricular hemorrhage; PV-IVH: periventricular-intraventricular hemorrhage.

Table 2

Clinical characteristics of the study population according to the development of intraventricular hemorrhage

Characteristics	IVH (−) (n=193)	IVH (+) (n=14)	P-value
Maternal age (years)	31.4 ± 4.4	31.6 ± 4.3	NS
Nulliparity	48.2% (93/193)	35.7% (5/14)	NS
Gestational age at birth (weeks)	29.8 ± 2.2	27.8 ± 2.3	0.003
Antenatal corticosteroid use	74.1% (143/193)	92.9% (13/14)	NS
Cesarean delivery	69.4% (134/193)	64.3% (9/14)	NS
Spontaneous preterm birth	55.4% (107/193)	78.6% (11/14)	NS
Male	46.1% (89/193)	71.4% (10/14)	0.095
Birthweight, grams	1282 ± 427	1086 ± 456	0.095
Fetal growth restriction	26.9% (52/193)	21.4% (3/14)	NS
Apgar score <4 at 1min	27.5% (53/193)	42.9% (6/14)	NS
Apgar score <7 at 5min	44.6% (86/193)	64.3% (9/14)	NS
Umbilical arterial pH <7.15 *	10.2% (18/176)	15.4% (2/13)	NS
Respiratory distress syndrome (RDS)	32.6% (63/193)	64.3% (9/14)	0.022
AF MMP-8 concentration (ng/mL) †	6.0 (0.3–6386.3)	358.0 (0.3–4202.7)	0.011
AF MMP-8 >23 ng/mL †	39.9% (73/183)	78.6% (11/14)	0.009
Acute histologic chorioamnionitis ‡	41.4% (72/174)	75.0% (9/12)	0.033
Acute funisitis §	20.5% (36/176)	41.7% (5/12)	NS

Values are given as mean ± standard deviation or median (range) or % (n/N).

* Eighteen patients whose umbilical arterial pH was not measured were excluded from the analysis.

† MMP-8 concentration was not measured in 10 patients because of the lack of remaining AF.

‡ Twenty-one patients were excluded because their placental histologic examinations were not performed.

§ Nineteen patients were excluded because the presence or absence of funisitis was not determined.

AF: amniotic fluid; IVH: intraventricular hemorrhage; MMP-8: matrix metalloproteinase-8; NS, not significant.

Table 3

Relationship among various variables with the development of intraventricular hemorrhage analyzed by overall logistic regression

	Univariate analysis	Multivariate analysis		
	OR (95% CI)	OR (95% CI)*	OR (95% CI)†	OR (95% CI)‡
Gestational age at birth (weeks)	0.69 (0.55–0.88)	0.70 (0.52–0.94)	0.87 (0.66–1.16)	0.77 (0.56–1.05)
Male gender	2.92 (0.89–9.64)	2.62 (0.69–10.0)	3.30 (0.90–12.1)	1.98 (0.49–7.96)
Respiratory distress syndrome	3.71 (1.20–11.5)	2.70 (0.69–10.5)	6.50 (1.69–25.1)	4.63 (1.10–19.4)
Acute histologic chorioamnionitis	4.25 (1.11–16.2)	3.80 (0.84–17.3)		0.70 (0.11–4.43)
Intra-amniotic inflammation (defined as AF MMP-8 concentration >23 ng/mL)	5.53 (1.49–20.5)		7.88 (1.63–30.1)	25.3 (1.89–338.6)

*All variables of P<0.1 in the univariate analysis except the presence or absence of intraamniotic inflammation were included.

†All variables of P<0.1 in the univariate analysis except the presence or absence of histologic chorioamnionitis were included.

‡All variables of P<0.1 in the univariate analysis were included.

AF: amniotic fluid; MMP-8: matrix metalloproteinase-8; OR: odds ratio.

Table 4

Clinical characteristics and outcomes of the study population according to the presence or absence of intra-amniotic inflammation and the occurrence of neonatal respiratory distress syndrome

Characteristics	IAI (−)/RDS (−) (n=64)	IAI (−)/RDS (+) (n=49)	IAI (+)/RDS (−) (n=66)	IAI (+)/RDS (+) (n=18)	P-value*
Gestational age at birth (weeks)	31.0 ± 2.4§	29.5 ± 4.2††	29.3 ± 2.4‡‡	27.1 ± 4.8	<.001
Birthweight, gram	1255 ± 457	1245 ± 434	1349 ± 422	1086 ± 391	NS
Fetal growth restriction	54.7% (35/64)†,‡,§	24.5% (12/49)**,††	7.6% (5/66)	0% (0/18)	<.001
Cesarean delivery	85.9% (55/64)‡,§	91.8% (45/49)**,††	43.9% (29/66)	38.9% (7/11)	<.001
Spontaneous preterm birth	34.4% (22/64)‡,§	24.5% (12/49)**,††	95.5% (63/66)	100% (18/18)	<.001
Male	48.4% (31/64)	46.9% (23/49)	47.0% (31/66)	50.0% (9/18)	NS
Apgar score <4 at 1 minute	25.0% (16/64)	40.8% (20/49)**,††	16.7% (11/66)‡‡	50.0% (9/18)	.005
Apgar score <7 at 5 minutes	37.5% (24/64)†,§	61.2% (30/49)**,††	36.4% (24/66)‡‡	66.7% (12/18)	.007
Umbilical arterial pH <7.15	11.7% (7/60)	22.4% (11/49)**	1.9% (1/54)	5.9% (1/17)	.009
Intraventricular hemorrhage	0% (0/64)§	6.1% (3/49)††	7.6% (5/66)‡‡	33.3% (6/18)	<.001

Values are given as mean ± standard deviation or % (n/N).

*P value for the overall group comparison.

†Significant difference between IAI (−)/RDS (−) and IAI (−)/RDS (+)

‡Significant difference between IAI (−)/RDS (−) and IAI (+)/RDS (−)

§Significant difference between IAI (−)/RDS (−) and IAI (+)/RDS (+)

**Significant difference between IAI (−)/RDS (+) and IAI (+)/RDS (−)

††Significant difference between IAI (−)/RDS (+) and IAI (+)/RDS (+)

‡‡Significant difference between IAI (+)/RDS (−) and IAI (+)/RDS (+)

IAI: intra-amniotic inflammation; NS: not significant; RDS, respiratory distress syndrome.