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Funisitis as a Risk Factor for Adverse Neonatal Outcomes in Twin Neonates with Spontaneous Preterm Birth: A Retrospective Cohort Study

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Purpose: Funisitis, inflammation of the umbilical cord, is considered a strong risk factor for adverse neonatal outcomes; however, a clinical definition of funisitis has not been established. In this study, we aimed to determine the clinical significance of funisitis in twin neonates with spontaneous preterm birth.

Materials and Methods: The study included preterm twin neonates (<35 weeks) delivered after spontaneous preterm labor and/or preterm premature rupture of amniotic membranes. The presence of funisitis was examined in the umbilical cord of each twin. We analyzed the risk of adverse neonatal outcomes according to the presence and absence of funisitis. Adverse neonatal outcomes were defined as the occurrence of neonatal mortality, significant morbidity, or both.

Results: Among 474 preterm neonates (237 twin pairs) included in this study, the frequency of funisitis was 6.5% (31 cases). Funisitis was significantly associated with neonatal mortality and adverse neonatal outcomes after adjustment for confounding variables [neonatal mortality, odds ratio (OR) 9.043, 95% confidence interval (CI) 2.620–31.204; adverse neonatal outcome, OR 2.445, 95% CI 1.017–5.875]. The concordance rate of funisitis between the twins was 10.7%, and in the absence of funisitis in one twin, the risk of neonatal mortality or adverse neonatal outcome was not influenced by the presence of funisitis in the other twin.

Conclusion: The presence of funisitis appears to be associated with an increased risk for adverse neonatal outcomes in twin neonates with spontaneous preterm birth.

Key Words: Chorioamnionitis, funisitis, preterm birth, twin pregnancy

INTRODUCTION

In twin pregnancies, preterm delivery occurs in more than 50% and is associated with an increased risk of adverse neonatal outcomes.[1-3] The pathophysiology of preterm delivery in twin gestation is not well understood, despite speculated mechanisms of preterm birth in twin gestation differing from those in singleton gestation: various etiologies of preterm birth in twin preg-

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nancies have been reported, including uterine over-distension, cervical insufficiency, fetal distress, placenta abruption, intrauterine infection, and inflammation.[3] In singleton pregnancies, intrauterine infection and inflammation are considered significant causes of preterm delivery, and they are known to be associated with adverse neonatal outcomes.[4-6] As a subset of intrauterine inflammation, funisitis (inflammation of the umbilical cord) arises as a fetal inflammatory response and is known to be a strong risk factor for adverse neonatal outcomes in singleton preterm neonates.[7-9] In the literature, there have been anecdotal reports on placental inflammation in twin preterm births; however, the significance of intrauterine inflammation as a cause of preterm birth in twin pregnancies and the relationship between placental inflammation and adverse neonatal outcomes in twin pregnancies have not been well established.

In this study, we aimed to determine the clinical significance of funisitis in twin neonates with spontaneous preterm birth. In addition, we sought to evaluate whether neonatal outcomes are influenced by the presence of funisitis in twins.

MATERIALS AND METHODS

Study design

This retrospective cohort study included twin preterm neonates born between 23 0/7 weeks gestation and 34 6/7 weeks gestation due to spontaneous preterm labor, preterm premature rupture of the membranes, or both at Seoul National University from January 2008 to December 2015. Cases with higher-order pregnancy, fetal demise in utero, major fetal malformation, or unique monochorionic complications, including twin-to-twin transfusion syndrome, were excluded. The management of preterm labor and preterm premature rupture of the membranes was determined by attending physicians, usually based on the American College of Obstetricians and Gynecologists guidelines.[10,11] The study population was divided into two groups: group 1, neonates without funisitis; group 2, neonates with funisitis. We compared neonatal mortality rates and morbidity between the two groups. In addition, we analyzed the risk of neonatal mortality and adverse neonatal outcomes according to the presence or absence of funisitis in the co-twin. The Institutional Review Board of Seoul National University Hospital approved the collection and use of clinical information for research purposes on February 2, 2018 (No. 1301-129-462). We followed the ethical standards for human experimentation established in the Declaration of Helsinki.

Analysis of co-twin effects on the risk of funisitis and adverse neonatal outcomes

To discover how much a twin is affected by the co-twin, we evaluated the concordance rate of funisitis and histologic chorioamnionitis between the twins. To calculate the concordance rate, we used pairwise concordance rates, which reflects the proportion of concordant twin pairs among the affected pairs. For analysis of co-twin effects on the risk of neonatal mortality and adverse neonatal outcomes, we divided group 1 into group 1-1 and group 1-2 depending on the presence of funisitis in the co-twin: group1-1, both neonates without funisitis; group 1-2, one neonate without funisitis and the co-twin with funisitis. We compared rates of neonatal mortality and adverse neonatal outcomes among group 1-1, group 1-2, and group 2 (both twins with funisitis).

Histologic chorioamnionitis and funisitis

Histopathologic examination was performed for tissue samples obtained from the umbilical cord, chorionic plate, and chorion and amnion of each twin. Funisitis was diagnosed in the presence of neutrophils on the umbilical vessel walls or Wharton's jelly. Histologic chorioamnionitis was defined as the presence of acute inflammatory change in the amnion, chorion-decidua, or the chorionic plate of the placenta; acute inflammation of those tissues was defined according to criteria previously described.[12]

Neonatal outcomes

Adverse neonatal outcomes were defined as the presence of neonatal mortality and/or significant morbidity. Neonatal mortality was defined as death before 28 days of life after birth. Neonatal morbidity was defined as the presence of at least one of the following: respiratory distress syndrome, bronchopulmonary dysplasia, pneumonia, intraventricular hemorrhage, and necrotizing enterocolitis in neonates.[12]

Statistical analysis

Chi-square or Fisher's exact test was used to compare categorical variables between the groups, and Mann-Whitney U test was used for continuous variables. For multivariate analysis, a generalized estimating equation was used to account for familial correlation between the twin pairs from a single mother and to adjust for confounding variables.[13] Variables with a p value <0.05 in univariate analysis were chosen for inclusion in multivariate analysis (Supplementary Tables 1 and 2, only online). The difference in concordance rates between funisitis and histologic chorioamnionitis was evaluated using an approximate z-test. A p-value of less than 0.05 was considered significant. All analyses were performed using SPSS version 20 (IBM Corp., Armonk, NY, USA) and R version 3.0.2 (http://www.r-project.org).

RESULTS

Study population

During the study period, a total of 301 pregnant women delivered preterm twin neonates after preterm labor, preterm premature rupture of the membranes, or both. Among them, 24 pairs of fetal demise in utero, 13 pairs with major anomalies, and 8

pairs with twin-to-twin transfusion syndrome were excluded. In 19 pairs, the result of placental histopathology was not available. Finally, 474 (237 twin pairs) neonates were included in this study. Supplementary Fig. 1 (only online) shows the patient flow diagram and the study population.

Clinical and obstetric characteristics of the study population

In the study population, the frequency of funisitis was 6.5% (31 cases), and that of histologic chorioamnionitis was 32.9% (156 cases). Table 1 presents the clinical and obstetric characteristics according to the presence of funisitis. Neonates with funisitis (group 2) had a significantly younger gestational age at delivery (GAD) than those without. However, there was no significant difference in maternal age, parity, history of preterm birth, chorionicity, proportion of presenting twin, use of antenatal corticosteroids, use of antenatal antibiotics, cause of preterm delivery, cesarean delivery, and sex of neonates among the groups. The clinical and obstetric characteristics according to the presence of histologic chorioamnionitis are presented in Supplementary Table 3 (only online).

Adverse neonatal outcomes

Table 2 shows the risks of neonatal mortality and adverse neonatal outcomes between the study groups. Neonates with funisitis (group 2) had higher risks for neonatal mortality and adverse neonatal outcomes than those without (neonatal mortality, 19.4% vs. 2.3%, $p<0.001$; adverse neonatal outcome, 51.6% vs. 28.4%, $p<0.05$). This association between funisitis and the risk of neonatal mortality or adverse neonatal outcome remained signifi-

Table 1. Characteristics of the Study Population according to the Presence of Funisitis

	Group 1 Neonates without funisitis (n=443)	Group 2 Neonates with funisitis (n=31)	*p* value
Maternal age (yr)*	33 (30–35)	33 (30–37)	NS
Nulliparity	348 (78.6)	27 (87.1)	NS
History of preterm birth	30 (6.8)	3 (9.7)	NS
Chorionicity-monochorionic†	91/439 (20.7)	5/31 (16.1)	NS
In vitro fertilization‡	131/394 (33.2)	8/28 (28.6)	NS
Presenting twin	219 (49.4)	18 (58.1)	NS
Antenatal corticosteroid	296 (66.8)	24 (77.4)	NS
Antenatal antibiotics	313 (70.7)	25 (80.6)	NS
Cause of preterm delivery			NS
Preterm PROM	257 (58)	21 (67.7)	
Preterm labor	186 (42)	10 (32.3)	
Gestational age at delivery (weeks)*	32.9 (29.6–34.1)	30.9 (26.7–33.3)	<0.05
Birthweight (g)*	1740 (1250–2040)	1480 (970–1940)	0.062
Cesarean delivery	185 (41.8)	15 (48.4)	NS
Male sex	244 (55.1)	13 (41.9)	0.156

PROM, preterm rupture of membranes; NS, not significant.
Data are presented as n (%).
*Median and interquartile range, †Four neonates (two twin pregnancies) had unknown Chorionicity, ‡Twenty-six pregnancies lacked information on whether in vitro fertilization was performed.

Table 2. Neonatal Outcomes according to the Presence of Funisitis

	Group 1 Neonates without funisitis (n=443)	Group 2 Neonates with funisitis (n=31)	*p* value
Adverse neonatal outcome (neonatal mortality and/or morbidity)	126 (28.4)	16 (51.6)	0.006
Neonatal mortality	10 (2.3)	6 (19.4)	<0.001
Neonatal morbidity*	122 (27.8)	13 (44.8)	0.050
Respiratory distress syndrome	99 (22.6)	11 (37.9)	0.059
Bronchopulmonary dysplasia	86 (19.9)	9 (33.3)	0.093
Necrotizing enterocolitis	25 (5.8)	1 (3.6)	NS
Intraventricular hemorrhage	18 (4.1)	2 (7.1)	NS
Sepsis	5 (1.2)	1 (3.6)	NS
Pneumonia	0 (0)	0 (0)	(-)

NS, not significant.
Data are presented as n (%).
*Six neonates died shortly after delivery and thus could not be evaluated with respect to the presence or absence of neonatal complications.

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cant even after adjustment for confounding variables [neonatal mortality, odds ratio (OR) 9.043, 95% confidence interval (CI) 2.620–31.204, $p<0.001$; adverse neonatal outcome, OR 2.445, 95% CI 1.017–5.875, $p<0.05$] (Table 3).

In terms of histologic chorioamnionitis, neonates with histologic chorioamnionitis had higher risks for neonatal mortality and adverse neonatal outcome than those without (Supplementary Table 4, only online). The association between histologic chorioamnionitis and neonatal mortality remained significant after adjustment for confounding factors; however, the association between histologic chorioamnionitis and adverse neonatal outcome was not significant after adjustment [Supplementary Table 5 (only online), neonatal mortality, 8.3% vs. 0.9%, $p<0.001$ (adjusted OR 7.207, 95% CI 1.847–28.118, adjusted $p=0.09$); adverse neonatal outcome, 42.3% vs. 23.9%, $p<0.001$ (adjusted OR 1.578, 95% CI 0.749–3.325, adjusted $p<0.05$)].

Table 3. Relationship between Adverse Neonatal Outcomes (Neonatal Mortality and/or Morbidity) and the Presence of Funisitis Analyzed Using a Generalized Estimating Equation

	OR	95% CI	*p* value
Neonatal mortality			
Funisitis	9.043	2.620–31.204	<0.001
Gestational age at delivery	0.667	0.560–0.706	<0.001
Cesarean delivery	4.304	1.355–13.677	<0.05
Adverse outcomes			
Funisitis	2.445	1.017–5.875	<0.05
Gestational age at delivery	0.443	0.382–0.513	<0.001
Chorionicity-monochorionic	0.514	0.229–1.149	NS
Antenatal corticosteroids	0.569	0.235–1.378	NS

OR, odds ratio; CI, confidence interval; NS, not significant.

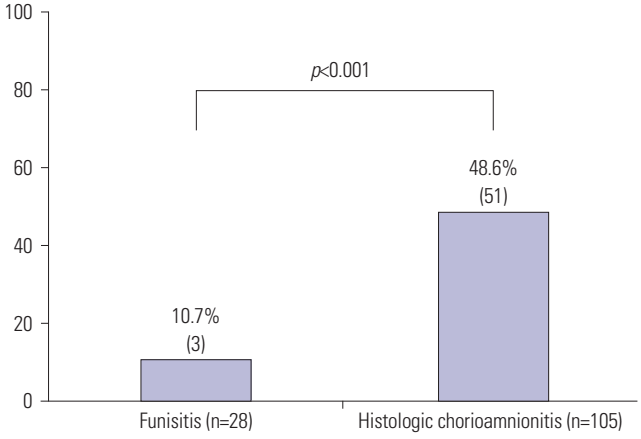

Fig. 1. Twin concordance rate for funisitis and histologic chorioamnionitis.

Effect of the presence of funisitis in the co-twin

The concordance rate of funisitis was 10.7%, and that of histologic chorioamnionitis was 48.6%. The concordance rate of funisitis was significantly lower than that of histologic chorioamnionitis ($p<0.001$) (Fig. 1). We analyzed these results according to chorionicity. In dichorionic twin pregnancy, the concordance rate of funisitis was significantly lower than that of histologic chorioamnionitis, similar to the results for the entire cohort. In monochorionic twin pregnancies, the concordance rate of funisitis and acute histologic chorioamnionitis showed a similar pattern; however, it did not reach statistical significance due to the small number of cases (Supplementary Fig. 2, only online). To evaluate the risk of neonatal mortality and adverse neonatal outcomes in the co-twin according to the presence or absence of funisitis, the risk of neonatal mortality and adverse neonatal outcome was compared among the three groups after stratification for GAD (Figs. 2 and 3). There were no differences in neonatal mortality between groups 1-1 and 1-2, indicating that funisitis in the co-twin does not influence the risk of neonatal mortality in the twin without funisitis. Moreover, the risk of adverse neonatal outcomes was also not different between groups 1-1 and 1-2. We also analyzed these results according to chorionicity. In dichorionic twin neonates, the risk of neonatal mortality and adverse outcomes in the twin without funisitis was also not influenced by the presence of funisitis in the co-twin; this was the same as the results for the total population (Supplementary Fig. 3, only online). However, we could not obtain

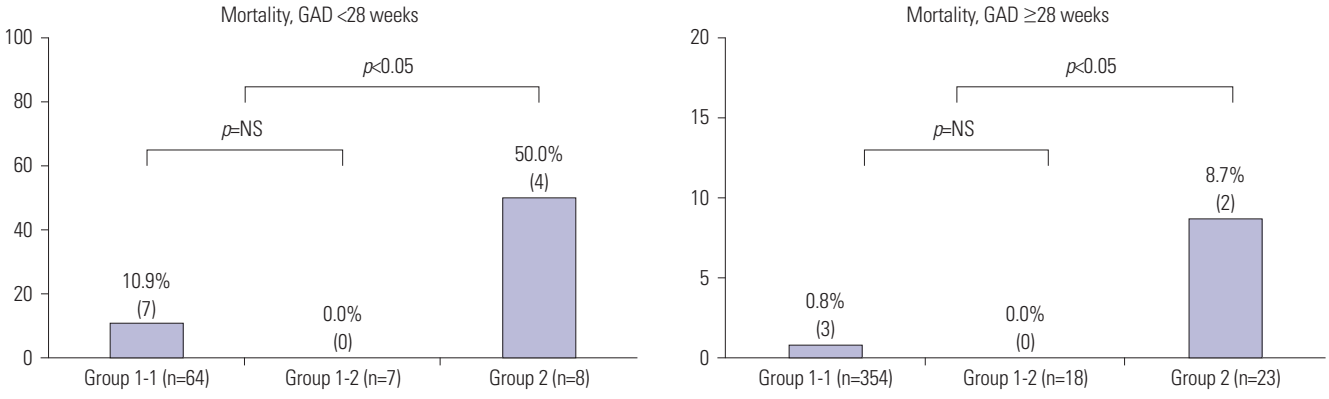

Fig. 2. Neonatal mortality according to the presence of funisitis in the co-twin. When the GAD was stratified by 28 weeks, there was no difference in neonatal mortality between neonates without funisitis & co-twin without funisitis (group 1-1 and 1-2) in both before and after 28 weeks. Neonates with funisitis (group 2) had a higher risk for neonatal mortality than neonates without funisitis regardless of co-twin funisitis both before and after 28 weeks. GAD, gestational age at delivery; NS, not significant.

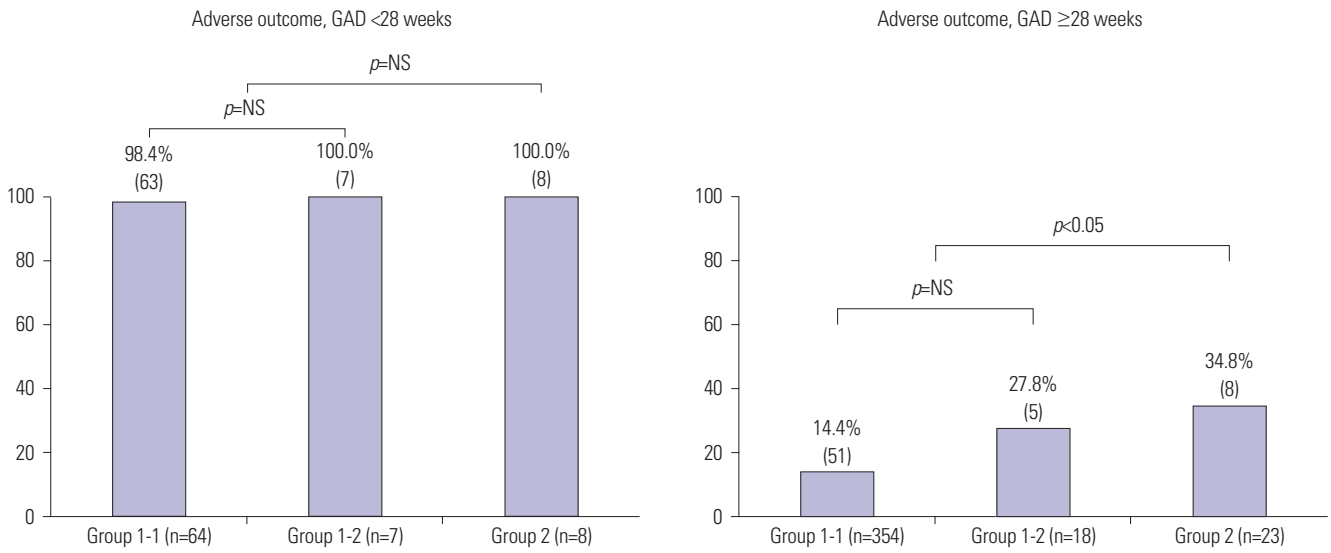

Fig. 3. Adverse neonatal outcomes according to the presence of funisitis in the co-twin. When the GAD was stratified by 28 weeks, there was no difference in adverse neonatal outcomes between neonates without funisitis & co-twin without funisitis (group 1-1 and 1-2) both before and after 28 weeks. Neonates with funisitis (group 2) exhibited a higher risk for adverse neonatal outcomes than neonates without funisitis regardless of co-twin funisitis if they were born after 28 weeks of gestation. GAD, gestational age at delivery; NS, not significant.

any significant findings after analyzing monochorionic twin pregnancies because only a small number of monochorionic twin pregnancies were included.

DISCUSSION

First, we found that the frequency of funisitis was 6.5% in twin preterm neonates. Second, we noted an association between funisitis and adverse neonatal outcome, which remained significant after adjustment for confounding factors. Third, the concordance rate of funisitis was 10.7%, which was lower than that of histologic chorioamnionitis. Finally, the presence of funisitis in the co-twin did not impact neonatal outcomes in the other twin without funisitis.

Funisitis, an acute inflammation of the umbilical cord, is a histopathologic hallmark of fetal inflammatory response syndrome and is associated with fetal organ damage and an increased risk for short-term and long-term sequelae in preterm neonates.[7-9,14,15] Previous studies on funisitis have primarily been focused on singleton pregnancies; and to the best of our knowledge, the clinical implication of funisitis in twin pregnancies has not been well evaluated. A previous anecdotal report found that funisitis is increased in twin pregnancies after laser surgery for twin-to-twin transfusion syndrome.[16] Recently, one report evaluated the association between positive results on screening tests for preterm delivery (short cervical length and positive fetal fibronectin) and funisitis in twin gestations. The authors reported that these positive screening results were associated with funisitis,[17] although neonatal outcomes were not evaluated in this report.

Our study suggests that the presence of funisitis could be used as a major indicator for adverse neonatal outcomes in preterm twin pregnancies. The results of our study are consistent with previous reports showing the role of intra-amniotic infection and inflammation in twin pregnancies with preterm labor.[18] Oh, et al.[18] reported that intra-amniotic inflammation in twin pregnancies showed a similar frequency to singleton gestation with preterm labor, and the presence of intra-amniotic inflammation increased the risk for preterm delivery and neonatal morbidities in twin pregnancies.

In our study, the concordance rate of histologic chorioamnionitis was higher than that of funisitis. Intrauterine inflammation is thought to spread from one twin to the other twin through choriodecidual space. According to the results of our study, the presence of histologic chorioamnionitis in each twin is strongly correlated, which indicates that histologic chorioamnionitis could extend through the choriodecidua and, subsequently, affect the co-twin. However, funisitis showed a lower correlation between each twin than histologic chorioamnionitis. Funisitis is a fetal response to infection or inflammation, and the presence of funisitis in one twin may have less influence on the other twin, because funisitis may be an individual inflammation response of the fetus.

To the best of our knowledge, our study is the first to evaluate neonatal outcomes in a twin according to the presence of funisitis in the co-twin. The presence of funisitis in the co-twin did not appear to increase the risk for adverse neonatal outcomes in the twin without funisitis. Adverse neonatal outcomes might be affected only by one's own inflammatory response. Meanwhile, previous studies have reported that the presenting twin has a higher rate of intra-amniotic infection than the non-presenting twin, which supports the hypothesis of ascending infection in twin pregnancies.[19,20] Like those reports, our research

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indicated a trend of a higher rate of funisitis in the presenting twin, although this difference was not statistically significant due to our small sample size.

To clarify the clinical significance of funisitis in twin pregnancies with preterm birth as a subset of intra-amniotic infection and inflammation, further studies 1) that investigate the relationship of funisitis, inflammatory mediators, and cytokines of amniotic fluid or umbilical cord plasma between each twin and 2) that examine the effects thereof on neonatal outcomes are warranted. Furthermore, in twin neonates born by premature birth with funisitis, long-term outcomes, such as cerebral palsy and neurodevelopmental consequence, should be further assessed.

In conclusion, the presence of funisitis appears to be associated with increased risks of neonatal mortality and adverse neonatal outcomes in twin pregnancies with preterm birth, although the presence of funisitis of the co-twin does not seem to influence adverse neonatal outcomes in the other twin.

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AUTHOR CONTRIBUTIONS

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