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Subsequent pregnancy outcomes according to the presence of acute histologic chorioamnionitis in women with spontaneous preterm delivery

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Objective
To compare subsequent pregnancy outcomes according to the presence of acute histologic chorioamnionitis (HCA) in women with spontaneous preterm delivery (SPTD).

Methods
Among 1,706 women who gave birth twice or more at our institution, 138 women delivered spontaneously at preterm (<37.0 weeks). Subsequent deliveries occurred at our institution and placental biopsy results were available. The study population was categorized into 2 groups based on the presence of acute HCA at the time of SPTD: HCA group (n=52) and non-HCA group (n=86). The primary outcome measures were gestational age at delivery, birthweight, and frequency of preterm delivery in subsequent pregnancies.

Results
The median gestational age at the time of SPTD was 34.0 weeks (interquartile range [IQR], 28.9–35.3 weeks), and the frequency of acute HCA was 52/138 (38%). There were no differences in gestational age at delivery, birthweight, and frequency of preterm delivery between the HCA group and non-HCA group (median gestational age at delivery, 38.0 weeks (IQR, 36.7–38.8 weeks) in the HCA group vs. 37.9 weeks (IQR, 35.7–39.0 weeks) in the non-HCA group; frequency of preterm delivery, 14/52 (27%) in the HCA group vs. 33/86 (38%) in the non-HCA group; and median birthweight, 3.14 kg (IQR, 2.64–3.45 kg) in the HCA group vs. 2.95 kg (IQR, 2.44–3.36 kg) in the non-HCA group; *P*>0.1 for all.

Conclusion
The presence of acute HCA in women at prior SPTD did not significantly affect their subsequent pregnancy outcomes.

Keywords: Acute histologic chorioamnionitis; Preterm delivery; Recurrent preterm delivery; Placenta; Funisitis

Introduction

A history of prior preterm delivery is a well-known risk factor for preterm delivery in subsequent pregnancies [1]. Preterm delivery can be divided into spontaneous preterm delivery (SPTD) and medically indicated preterm delivery caused by maternal, fetal, or placental conditions. Spontaneous preterm labor (PTL) with intact membranes, preterm premature rupture of membranes (PPROM), and acute cervical insufficiency are included in the major causes of SPTD.

Intra-amniotic infection (isolation of microbes in the amni-

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otic fluid) and sterile intra-amniotic inflammation (condition accompanied by increased pro-inflammatory cytokines in the amniotic fluid without isolation of microbes) are generally considered to be mechanisms of acute histologic chorioamnionitis (HCA) [2] and are known to be associated with SPTD [3]. It has been reported that the frequency of HCA was more than 50% in women with preterm delivery [4,5]. The rate of HCA in patients with PPROM was 37.5–42% in the group without intra-amniotic infection/inflammation, 50–85% in the group with sterile inflammation, and 93% in the group with infection [6,7]. The rate of HCA in PTL patients with intact membranes was 21–27% in the group without intra-amniotic infection/inflammation, 58–86% in the group with sterile inflammation, and 79–83% in the group with infection [8,9]. HCA is related to an increase in neonatal complications such as intraventricular hemorrhage, cerebral palsy, sepsis, pneumonia, necrotizing enterocolitis, and death [4,5].

Because acute HCA is associated with an earlier preterm delivery and a poorer prognosis for neonates [2,7,9-11], it is important to evaluate whether acute HCA in a prior preterm delivery is associated with poor outcomes of subsequent pregnancy. The results of the analysis will be helpful to clinicians when counseling pregnant women with a prior preterm birth and acute HCA. Previous studies have shown that acute inflammatory lesions of the placenta increased the risk of recurrent preterm delivery in women who have a past preterm delivery [12,13]. However, these studies included all preterm deliveries due to spontaneous labor and iatrogenic causes. Therefore, it is not clear whether the increased risk of recurrent preterm delivery is directly or indirectly associated with acute inflammatory lesions in the placenta. There are no studies evaluating the relationship between the presence of acute HCA in prior preterm delivery and the recurrence of SPTD in patients with a history of SPTD. The objective of this study was to compare subsequent pregnancy outcomes according to the presence of acute HCA in women with SPTD.

Materials and methods

We conducted a retrospective cohort study that included all women who had given birth 2 or more times in our institu-

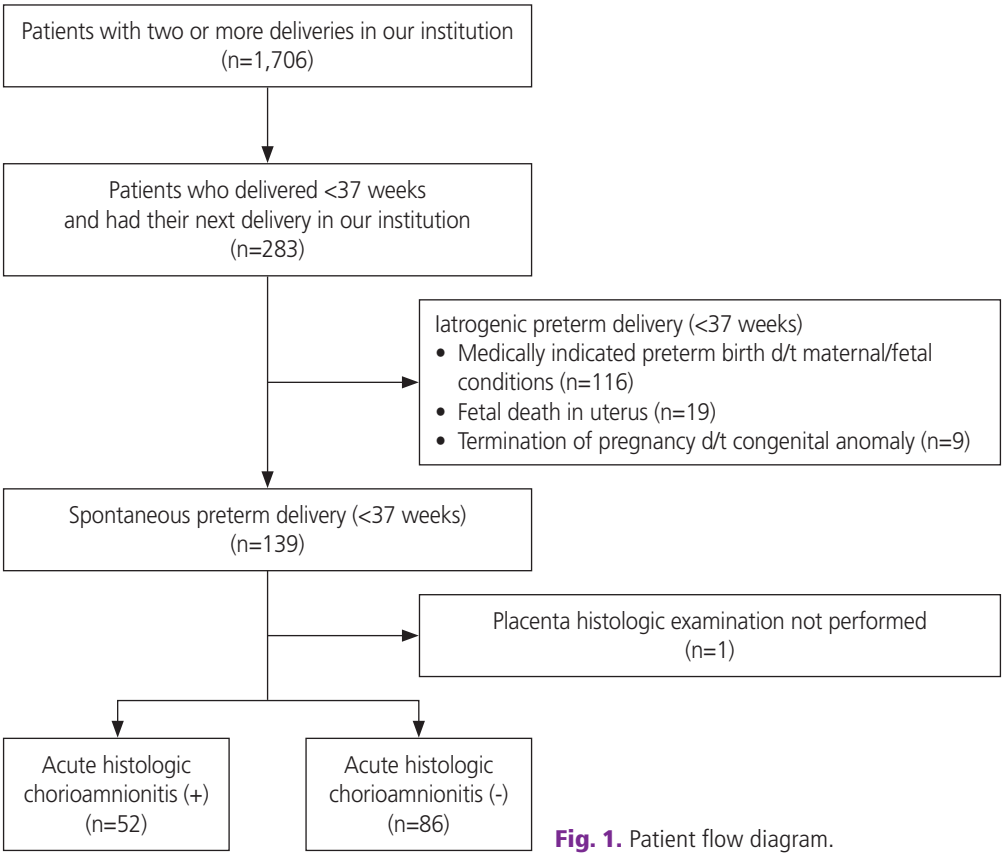

Fig. 1. Patient flow diagram.

tion from May 2003 to March 2018. Of the 1,706 women, 139 delivered spontaneously at preterm (<37.0 weeks of gestation) and had their subsequent delivery at our institution (Fig. 1). SPTD was defined as preterm birth caused by PTL with intact membranes, PPROM, or acute cervical insufficiency. The exclusion criteria were as follows: 1) medically indicated preterm delivery caused by maternal or fetal conditions (n=116), 2) fetal death in utero (n=19), and 3) termination of pregnancy due to a congenital anomaly (n=9). The study population was categorized into 2 groups based on the presence of acute HCA from their preterm delivery: group 1, patients with HCA from their preterm delivery; and group 2, patients without HCA from their preterm delivery (Fig. 1). The institutional review board of our institute approved this research. We followed the ethical standards for human experimentation established in the Declaration of Helsinki.

The diagnosis of acute HCA was made by using criteria previously published [2,5,14,15]. Acute HCA was defined as the presence of acute inflammatory lesions by infiltration of neutrophils into the chorion-decidua and amnion. Acute funisitis was defined as the infiltration of neutrophils into the walls of umbilical vessels or Wharton's jelly. The subsequent pregnancies were managed similarly for patients with and without previous HCA. Clinical characteristics of the study population including parity, maternal age at previous preterm delivery, gestational age at delivery, cause of SPTD, neonatal birthweight, amniotic fluid analysis if amniocentesis was performed, and the interval between SPTD and subsequent delivery were reviewed. Primary outcome measures were the rate of SPTD and gestational age at subsequent deliveries.

Continuous variables and categorical variables were analyzed by the Mann-Whitney *U*-test and the Fisher's exact test, respectively. Continuous variables are presented as the median and interquartile range (IQR). Categorical variables are expressed as the percentage and number of patients in each group. Probability values less than 0.05 were considered statistically significant. All statistical analyses were carried out using SPSS 22.0 for Windows (IBM, Armonk, NY, USA).

Results

During the study period, 139 women delivered spontaneously at preterm and had a subsequent delivery at our institution (Fig. 1). One woman who was unavailable for placenta histology was excluded. Therefore, this study included 138 women. Clinical characteristics of the study population are summarized in Table 1. The median gestational age at preterm delivery was 34.0 weeks (IQR, 28.9–35.3 weeks). The causes of preterm delivery were PTL (82/138 [59%]), PPROM (47/138 [33%]), and cervical insufficiency (10/138 [7%]). The frequency of preterm delivery in the subsequent pregnancy was 47/138 (34%). The frequencies of acute HCA and funisitis were 52/138 (38%) and 29/138 (21%), respectively. Among the 66 women who had transabdominal amniocentesis, the rate of a positive result in amniotic fluid culture was 18/66 (27%).

Table 2 presents the clinical characteristics of the study population according to the presence or absence of acute HCA at the time of preterm delivery. The median gestational age and birthweight at prior SPTDs were significantly lower in the HCA group than in the non-HCA group (median gestational age: 28.5 weeks (IQR, 22.9–34.0 weeks) vs. 34.7 weeks (IQR, 33.4–35.9 weeks), $P<0.001$; median gestational birthweight: 1.25 kg (IQR, 0.57–2.01 kg) vs. 2.38 kg (IQR, 2.00–2.65 kg), $P<0.001$). Acute cervical insufficiency

Table 1. Demographic and clinical characteristics of the study population at the time of preterm delivery

Clinical characteristics	Value (n=138)
Maternal age (yr)	30 (28–32)
Nulliparity	109 (79)
Gestational age at preterm delivery (wk)	34.0 (28.9–35.3)
20.0–27.9	26 (19)
28.0–31.9	23 (17)
32.0–36.9	89 (64)
Birth weight (kg)	2.11 (1.28–2.58)
Cause of preterm delivery	
Preterm labor	82 (59)
Preterm rupture of membranes	46 (33)
Cervical insufficiency	10 (7)
Preterm delivery at subsequent pregnancy	47 (34)
Delivery mode	
Vaginal delivery	93 (67)
Cesarean delivery	45 (33)
Acute histologic chorioamnionitis	52 (38)
Funisitis	29 (21)
Positive amniotic fluid culture	18/66 (27)

Data are median (interquartile range) or number (%).

was significantly higher in the HCA group than the non-HCA group (9/52 [17%] vs. 1/86 [1%], *P*<0.001). The culture-proven amniotic fluid infection rate was higher in the HCA group, as expected (HCA group, 15/36 [42%] vs. non-HCA group, 3/30 [10%], *P*=0.005).

Table 3 shows the subsequent pregnancy outcomes of the study population. The frequency of preterm delivery in the subsequent pregnancy was 14/52 (27%) in the HCA group

Table 2. Clinical characteristics of study population according to the presence of histologic chorioamnionitis (HCA) at the time of preterm delivery

Clinical characteristics	Acute HCA		
	Yes (n=52)	No (n=86)	*P*-value
Maternal age (yr)	31 (28–33)	30 (27–32)	0.048
Nulliparity	37 (71)	72 (84)	0.089
Gestational age at previous spontaneous preterm delivery (wk)	28.5 (22.9–34.0)	34.7 (33.4–35.9)	<0.001
Birth weight (kg)	1.25 (0.57–2.01)	2.38 (2.00–2.65)	<0.001
Cause of preterm delivery			
Preterm labor	29 (56)	53 (62)	0.592
Preterm rupture of membranes	14 (27)	32 (37)	0.265
Cervical insufficiency	9 (17)	1 (1)	0.001
Delivery mode			0.268
Vaginal delivery	38 (73)	55 (64)	
Cesarean delivery	14 (27)	31 (36)	
Positive amniotic fluid culture	15/36 (42)	3/30 (10)	0.005

Data are median (interquartile range) or number (%).

Table 3. Subsequent pregnancy outcome of study population according to the presence of histologic chorioamnionitis (HCA) in previous preterm delivery

Characteristics	HCA		
	Yes (n=52)	No (n=86)	*P*-value
Gestational age at delivery (wk)	38.0 (36.7–38.8)	37.9 (35.7–39.0)	0.313
Birth weight (kg)	3.14 (2.64–3.45)	2.95 (2.44–3.36)	0.100
Interval between pregnancies (mon)	23 (17–37)	30 (22–47)	0.002
Progesterone use[a)]	19 (37)	18 (21)	0.050
Cervical length at level II ultrasound (mm)[b)]	36.5 (31.0–40.0)	35.3 (31.6–39.0)	0.462
Delivery mode			0.852
Vaginal delivery	30 (58)	51 (59)	
Cesarean delivery	22 (42)	35 (41)	
Preterm delivery (<37 wk)	14 (27)	33 (38)	0.197
Spontaneous preterm delivery	12 (23)	24 (28)	0.556
Medically indicated preterm delivery	2 (4)	9 (11)	0.208
20.0–27.9 wk	1 (2)	2 (2)	1.000
28.0–31.9 wk	0 (0)	3 (4)	0.442
32.0–36.9 wk	13 (25)	28 (33)	1.000

Data are median (interquartile range) or number (%).
[a)]Progesterone administration begins before 24 weeks' gestation; [b)]Data was available in 97 women.

and 33/86 (38%) in the non-HCA group (*P*=0.197). The rate of SPTD in the HCA group was similar to that in the non-HCA group (12/52 [23%] vs. 24/86 [28%], *P*=0.556). There were no significant differences in gestational age at subsequent delivery, cervical length, frequency of preterm delivery, or birthweight between the 2 groups. Patients in the HCA group had a significantly shorter interval between pregnancies than those in the non-HCA group (23 months [IQR, 17–37] vs. 30 months (IQR, 22–47), *P*=0.002). Progesterone was more frequently administered in women with HCA from their preterm delivery than those without HCA from their preterm delivery, but the difference was statistically insignificant (19/52 [37%] vs. 18/86 [21%], *P*=0.050).

Discussion

The principal finding from this study is that there was no significant difference in the subsequent pregnancy outcomes according to the presence or absence of acute HCA from their previous preterm delivery regarding the median gestational age at delivery, rate of SPTD, cervical length at Level II ultrasonography, and neonatal birthweight.

A few studies have demonstrated the relationship between histologic placental lesions and recurrent preterm delivery. Himes and Simhan [13] reported that recurrence of preterm delivery is more frequent among women who had inflammatory changes on the placenta from a prior preterm delivery and that these women are more likely to have placental inflammatory lesions with their subsequent delivery. Ghidini and Salafia [12] examined the placental lesions of women whose past obstetrical history was available and who delivered at <32 weeks of gestational age. They showed that women with an obstetrical history of one or more preterm births had more frequent placental pathologies, implying both acute and chronic inflammatory changes of the uterine cavity, compared to those without history of preterm birth. The results of our study contrast the previous studies. One possible explanation is that our study included only patients with a prior history of SPTD, whereas the other studies included all preterm deliveries (SPTD and medically indicated preterm delivery). Therefore, the association between recurrent preterm delivery and acute HCA in prior preterm delivery shown in previous studies might be due to a higher rate of recurrent SPTD in patients with previous SPTD than in those with a medically indicated preterm delivery. According to a study by Ananth et al. [16], the rate of SPTD in subsequent pregnancies was 20.7% in patients with a prior SPTD and 10.4% in those with a prior medically indicated preterm delivery. Another possible explanation for the difference is that the previous studies were performed before 2005, which means that preventive medicine such as progesterone might not have been administered to patients with a prior preterm delivery. In the current study, the rate of progesterone administration was 27% in prior SPTDs <37.0 weeks and 39% in prior SPTDs <34.0 weeks. Moreover, the rate of progesterone administration was higher in women with HCA from their preterm delivery, although the difference had no statistical significance (HCA group, 37% vs. non-HCA group, 21%; *P*=0.050). Substantial evidence shows that progesterone administration reduces recurrence of preterm birth by 34% in women with a prior preterm delivery [17,18]. Therefore, preventive medicine using progesterone might affect the rate of recurrent preterm deliveries in the current study. Interestingly, the cervical length from the level II ultrasound, one of the most powerful predictors of preterm delivery [19-21], was similar regardless of the presence of acute HCA in prior SPTDs.

Table 3 shows the interval between pregnancies in the HCA group was significantly shorter than that in the non-HCA group. It is generally understood that short interpregnancy intervals are associated with increased risks of preterm birth. Therefore, it is possible that the difference between the interpregnancy intervals in the 2 groups could have an influence on the subsequent pregnancy outcomes in this study.

The major clinical implication of this study is that there is no association between acute HCA and subsequent pregnancy outcomes including gestational age at delivery, rate of SPTD and neonatal birthweight in women with a prior SPTD. This may help clinicians when counseling patients with a history of SPTD. One of the weaknesses of this study is the small sample size and the single center design. However, no trend was observed with respect to the frequency of recurrent preterm birth and the presence of acute HCA in women with prior SPTDs. We hope that larger population studies will confirm the association between acute HCA and subsequent pregnancy outcomes with consideration of tocolytics use, progesterone use, cervical cerclage operation, and other variables which may affect the recurrence of preterm birth.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Ethical approval

The Institutional Review Board of our institute approved the use of electronic obstetrical medical records for this research (protocol No. B-1811/504-106).

Patient consent

This study approved the patient consent waiver due to the retrospective study design.

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