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Clinical Significance of Preterm Fetal Cardiotocography in Severe Fetal Acidemia due to Chorioamnionitis

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Abstract

Aim: At present, premature birth with chorioamnionitis is recognized as a social problem to be solved even in high-income countries. It is difficult to evaluate the preterm fetal condition using cardiotocography tracings. In this study, we compared the cardiotocographies in preterm fetus with or without chorioamnionitis.

Methods: The 22 subjects were recruited at three institutes between September 2010 and August 2016. To review the clinical importance of fetal cardiotocography tracings in preterm fetus with severe acidemia, we examined the baselines, variabilities, and decelerations of fetal heart rate（FHR）in preterm fetus with and without chorioamnionitis, with a pH <7.2 in the umbilical artery.

Results: In pregnant women with chorioamnionitis, some of the observed clinical features involved in uterine infection, e.g. heart rate, white blood cell count and CRP value, were significantly different compared with those in pregnant women without chorioamnionitis. In fetuses with chorioamnionitis, Apgar score at 5 minites after birth, frequency of abnormal variabilities of FHR, rapid restoration of FHR from the bottom of deceleration and short duration of deceleration were also found. Distinctly different patterns of cardiotocography tracings were observed between the fetuses with and without chorioamnionitis.

Conclusions: The rapid restoration of FHR from the bottom of deceleration might be the indicator of the preterm fetal acidemia wtih chorioamnionitis, even if variability of FHR were within normal.

Key words: Fetal Acidemia, Cardiotocography, Fetal Heart Rate, Preterm, Chorioamnionitis

Introduction

Early neonatal death, which is defined as the death of a newborn between zero and seven days after birth, represents 73% of all postnatal deaths worldwide[1)]. The etiology of early neonatal death is closely related to a country's industrialization. Prematurity and congenital anomalies are the leading causes for early neonatal death in high-income countries[2)]. Perinatal-related events such as hypoxia and infections are involved in prematurity. In high-income countries, according to current research evidence, survival has been improved by applying antenatal and perinatal therapies and immediate newborn resuscitation, as well as by centralizing at risk deliveries to centers with appropriate expertise available around the clock[3)]. However, premature birth has been the leading cause of child death in children younger than 5 years in high-income countries[4)].

Maintaining maternal oxygen supply is essential for fetal life. To diagnose the underlying cause of an unacceptable state, to judge the reversibility of the fetal condition *in*

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utero, and to determine the best timing for delivery, the signs is required to evaluate of reduced fetal oxygenation[5]. In term or near term, cardiotocography tracings have been available for the assessment of fetal state as a means of intrapartum fetal monitoring in high-income countries[6,7]. After 32 weeks of gestation, fetal condition is diagnosed as good in cases where the fetal heart rate (FHR) baseline ranges from 120 to 160 beats per minute and FHR displays a transient acceleration without deceleration in the cardiotocography tracings[6,7]. However, before 32 weeks of gestation, it is difficult to diagnose fetal well-being in cardiotocography tracings because of the prematurity of the sympathetic and parasympathetic nerve system[8-10]. To reduce neonatal death as well as child death, the exact evaluation of the preterm fetal condition, where birth may occur early because of hypoxia or infections, is required using cardiotocography tracings.

Fetal asphyxia is defined as "a condition of impaired gas exchange leading, if it persists, to progressive hypoxemia and hypercapnia with significant metabolic acidosis" [11]. Fetal asphyxia mainly consists of chronic or sub-chronic hypoxia due to the impairment of placental function such as fetal growth restriction and placental abruption, and metabolic acidemia due to infections such as chorioamnionitis[12]. In 1999, the international Cerebral Palsy Task Force stated that cord blood metabolic acidosis (pH < 7.00, basic deficit ≥ 12) is an essential requirement before cerebral palsy can be attributed to intrapartum events[13]. The analysis of > 50,000 consecutive cord samples suggested that a pH of 7.1 shows a risk of encephalopathy, an accepted precursor to cerebral palsy of intrapartum origin[14]. It is clinically important to assess how a preterm fetus with asphyxia indicates the cardiotocography tracings.

To investigate the clinical significance of fetal cardiotocography tracing in preterm fetus with severe acidemia, we examined the baselines, variabilities, and decelerations of FHR in preterm fetuses with and without chorioamnionitis, who had a pH < 7.2 in the umbilical artery.

Methods

Study design

We recruited 57 pregnant women who delivered at < 32 weeks' gestation and had fetal acidosis at three institutes (Fukuoka University Hospital, Saga National Hospital and Fukuoka Tokushukai Hospital) between September 2010 and August 2016. The study was approved by the review boards of the Fukuoka University Hospital, National Hospital Organization Saga Hospital and Fukuoka Tokushukai Hospital (protocol numbers 17-1-07, 27–4, and approval from the director of Fukuoka Tokushukai Hospital, respectively). Thirty-five subjects were excluded according to the following criteria: insufficient data (monitoring time <20 minutes) of FHR in cardiotocography (n=22), no histological data of placenta (n=11), twin pregnancy (n=3), and congenital anomalies (n=1, 21 trisomy) (Figure.1). We divided the 22 remaining subjects into two subgroups according to the degree of placental inflammation; the CAM group (n=12) had chorioamnionitis and the Non-CAM group (n=10) had no chorioamnionitis.

Definition

Chorioamnionitis was histologically diagnosed

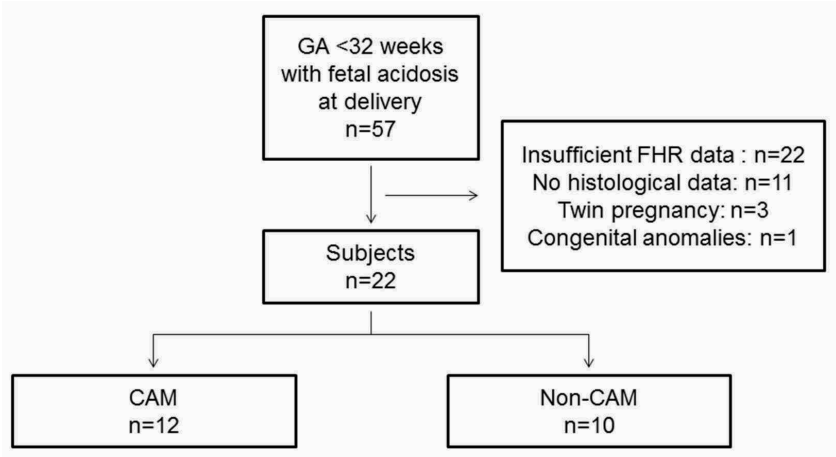

Figure 1. Flow chart of the study design. We recruited 57 pregnant women who delivered at < 32 weeks' gestation and had fetal acidosis. After excluding unsuitable subjects, 22 women were divided into two subgroups according to the degree of placental inflammation; CAM (n=12) has chorioamnionitis and Non-CAM (n=10) has no chorioamnionitis.

with Blanc's classification of 2 degrees or more. The details of Blanc's classification are as follows; stage I (sub-chorionitis): patchy or diffused accumulation of neutrophils within the subchorionic plate or decidua; stage II (chorionitis): more than a few scattered neutrophilic infiltrations in the chorionic plate or membranous chorionic connective tissue; and stage III (chorioamnionitis): neutrophilic infiltrates reaching subamniotic connective tissue and the amniotic epithelium.

The arterial blood pH in umbilical cord was used for assessing fetal acidosis. An umbilical artery pH < 7.20 was conventionally defined as fetal acidosis[15-17].

Premature rupture of the membranes was diagnosed if we observed evident outflow of alkaline amniotic fluid or detected insulin-like growth factor-binding protein 1 (IGFBP-1) in vaginal discharge.

Pregnancy-induced hypertension was diagnosed according to the major definitions in Japan; hypertension (blood pressure ≥ 140/90 mmHg) emerging between 20 weeks of gestation and 12 weeks of postpartum[18].

Fetal growth restriction was clinically diagnosed by obstetricians according to the clinical guidelines for obstetrical practice in Japan[19].

Placental abruption was diagnosed by histological examination of delivered placenta.

Small for gestational age was conventionally defined as infants with a birth weight below the 10th percentile for gestational age.

Clinical data and FHR data

All of the clinical data and FHR monitoring data were collected from clinical records. FHR monitoring data and uterine contractions were recorded with 30 beats/minutes (bpm) per centimeter vertical axis and paper speed at 3 cm/min horizontal axis by cardiotocography tracings at least for 20 minutes before delivery or the most recent 60 minutes before cesarean delivery. Baseline FHR, baseline FHR variability, accelerations, and decelerations were judged according to the research guidelines of the National Institute of Child Health and Human Development (NICHD)[20] and the clinical guidelines for obstetrical practice in Japan[19]. Baseline FHR was shown to be the approximate mean FHR rounded to increments of 5 bpm during a 10-minute window and the minimum baseline duration was at least 2 minutes. If the baseline FHR was <110 bpm, it was diagnosed as "bradycardia"; if the baseline FHR was >160 bpm, it was diagnosed as "tachycardia"; if the baseline FHR was 110-160 bpm, it was diagnosed as "normocardia".

Baseline FHR variability was defined as fluctuations in the baseline of two cycles per minute or greater, differing from the sinusoidal pattern, according to the previous guidelines[20]. If the amplitude range of FHR variability was undetectable, it was diagnosed as "undetectable"; if the amplitude was < 5 bpm, it was diagnosed as "minimal"; if the amplitude was 6 to 25 bpm, it was diagnosed as "moderate"; if the amplitude was >25 bpm, it was diagnosed as "marked" .

Accelerations were defined as having an acme ≥ 10 bpm above the baseline and a duration of ≥ 10 seconds and <2 minutes from onset to return to baseline, because our cases were limited to before 32 weeks of gestation. Decelerations were defined as decrease below the FHR baseline. The decrease in FHR is at least 15bpm and lasts at least 15 sec but <10min. Decelerations were divided into "early deceleration", "late deceleration", "variable deceleration", and "prolonged deceleration" according to the two previous guidelines[19,20]. Moreover, we analyzed decelerations in detail in the present study mainly according to the conventional methods[18]. The phase from onset of the deceleration to the nadir (bottom) was named the "falling phase" and the phase from the nadir (bottom) to recovery of the deceleration was named the "rising phase"; duration times in the "falling phase" were named "descending time" and those in the "rising phase" were named "ascending time" (Figure 2). The "ascending slope from bottom to

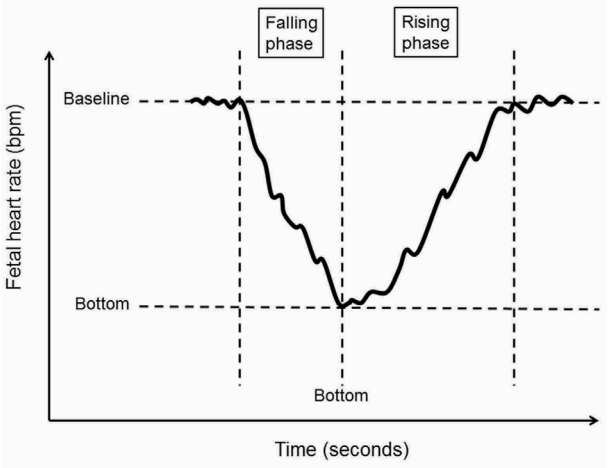

Figure 2. The naming conventions for analyzing the deceleration curve. The phase from onset of the deceleration to the nadir (bottom) is named the "falling phase" and the phase from the nadir (bottom) to recovery of the deceleration is named the "rising phase"; duration times in the "falling phase" are named "descending times" and those in the "rising phase" are named "ascending times".

baseline (bpm/seconds)" was named as the ascending rate (bpm) from the nadir (bottom) to recovery of the deceleration divided by "ascending time" (seconds).

Statistical analysis

Because of a small sample number, we calculated exact significance probabilities (two-tailed) as *P* values using the Mann-Whitney test for continuous variables and Fisher's exact test for categorical variables. To assess diagnostic accuracy, we constructed the receiver operating characteristic (ROC) curve and calculated the area under the curve (AUC), the Youden index, cut-off value, and diagnostic sensitivity and specificity. These analyses were performed using SPSS version 16.0J for Windows Base System SC (SPSS Japan Inc, Tokyo, Japan). Differences at $P < 0.05$ were considered statistically significant.

Results

Clinical characteristics in pregnant women in this study

Table 1 shows the clinically maternal characteristics. The pregnant women without chorioamnionitis were significantly older than the pregnant women with chorioamnionitis, although there were no significant differences in multigravida and the rate of cesarean section between the two groups. Nine of 10 pregnant women (90%) without chorioamnionitis contracted insufficiency of placental function including pregnancy-induced hypertension, placental abruption, and fetal growth restriction, compared with 3 of 12 pregnant women (25%) with chorioamnionitis. Nine of 12 pregnant women with chorioamnionitis and none of the pregnant women without chorioamnionitis indicated premature rupture of membrane.

The pregnant women with chorioamnionitis had significantly elevated heart rates, white blood cell counts and CRP values compared with those of pregnant women without chorioamnionitis, although there were no significant differences in fever between the two groups (Table 2). Taken together, these results suggested that most of the pregnant women without chorioamnionitis suffered from chronic placental dysfunction and that the infectious events occurred in pregnant women with chorioamnionitis.

Perinatal outcome in patients with chorioamnionitis and without chorioamnionitis

In perinatal outcome, there were no significant differences in gestational age at birth, neonatal body weight

Table 1. Maternal characteristics

	CAM (n=12)	Non-CAM (n=10)	*P*-value
Delivery Age (y) †	29.0 [27.3-34.5]	36.0 [34.3-39.5]	0.048
Multigravida	7 (58)	4 (40)	0.670
History of caesarean section	2 (17)	0 (0)	0.481
Caesarean section	7 (58)	6 (60)	1.000
Preterm premature rupture of membranes	9 (75)	0 (0)	<0.001
Pregnancy-induced hypertension	1 (8)	5 (50)	0.056
Fetal growth restriction	3 (25)	5 (50)	0.378
Placental abruption	0 (0)	2 (20)	0.195

Data shown as n (%).
†Data shown as median [interquartile range].
CAM; Chorioamnionitis

Table 2. Maternal clinical data

	CAM (n=12)	Non-CAM (n=10)	*P*-value
Body temperature (°C)	37.4 [36.9-37.7] (n=10)	36.9 [36.7-37.1] (n=10)	0.118
Heart rate (/min)	107.5 [94.3-117.0] (n=6)	80.0 [80.0-87.0] (n=9)	0.011
WBC count in maternal peripheral blood (cells/μL)	19,700 [12,898-22,698] (n=12)	11,000 [7,298-14,550] (n=10)	0.014
CRP in maternal peripheral blood (mg/dL)	2.1 [1.0-3.5] (n=12)	0.4 [0.2-1.0] (n=10)	0.026

Data shown as median [interquartile range].
CAM; Chorioamnionitis

at birth, the incidence of small for age date, the Apgar score at 1 minute after birth, and umbilical arterial pH values at birth between the infants with and without chorioamnionitis (Table 3). In the Apgar scores in 5 minute after birth, the infants with chorioamnionitis showed lower scores than the infants without chorioamnionitis. Accordingly, there were few alterations in perinatal outcome between the two groups under severe fetal acidemia.

Fetal monitor tracing in cardiotocography under severe fetal acidemia at preterm pregnancy

We compared the fetal heart rate data of cardiotocography between CAM and Non-CAM cases (Table4). In this study, there were no significant differences in the duration of the last cardiotocography tracing and interval time from the last fetal monitor tracing to delivery between the pregnant women with and without chorioamnionitis (Table 4). To assess the features in the cardiotocography tracings in both fetuses with and without chorioamnionitis, we examined the baseline of FHR, variability, acceleration and deceleration in the cardiotocography tracings. In the baseline of FHR, there was no significant differences between the two groups. However, 4 of 12 fetuses with chorioamnionitis indicated more than 180 beats per minute; that is, tachycardia. In the variability of baseline, 7 of 10 fetuses without chorioamnionitis indicated minimal variability, whereas all the 12 pregnant women with chorioamnionitis showed moderate variability. No significant differences in the incidence of acceleration or deceleration of FHR were found between the two groups.

Differences in deceleration curve in fetal monitor tracing

In this study, marked differences in the deceleration curve were found between the two groups. To evaluate the clinical significance of the deceleration curve in preterm

Table 3. Perinatal outcome

	CAM (n=12)	Non-CAM (n=10)	*P*-value
Gestational age at birth (weeks)	27.7 [25.9-29.6]	30.0 [27.5-30.0]	0.318
Neonatal body weight at birth (g)	912 [591-1,226]	977 [889-1,134]	0.539
Small for gestational age (n (%))	3 (25)	5 (50)	0.378
Apgar score 1min	3.0 [1.8-3.5]	4.0 [3.0-5.8]	0.190
Apgar score 5min	6.0 [4.5-6.3]	7.0 [6.0-8.0]	0.043
Umbilical arterial pH at birth	7.13 [7.07-7.18]	7.13 [7.09-7.16]	0.960

Data shown as median [interquartile range] except for small for gestatinal age.
CAM; Chorioamnionitis

Table 4. Fetal heart rate data of cardiotocography

	CAM (n=12)	Non-CAM (n=10)	*P*-value
Evaluating time of cardiotocography (min) †	60.0 [52.5-60.0]	60.0 [56.3-60.0]	1.000
Interval time between the cardiotocography and the delivery (min) †	28.0 [0.0-46.0]	27.5 [0.0-52.0]	0.829
Baseline of fetal heart rate (bpm) †	160.0 [138.8-170.0]	152.5 [141.3-155.0]	0.242
Fetal tachycardia ‡	4 (33)	0 (0)	0.096
Fetal normocardia ‡	8 (67)	10 (100)	0.096
Abnormal variability of baseline ‡	0 (0)	7 (70)	0.001
Undetectable variability of baseline ‡	0 (0)	1 (10)	0.455
Minimal variability of baseline ‡	0 (0)	6 (60)	0.003
Moderate variability of baseline ‡	12 (100)	3 (30)	0.001
Acceleration ‡	4 (33)	2 (20)	0.646
Deceleration ‡	8 (67)	6 (60)	1.000
Variable deceleration ‡	6 (50)	2 (20)	0.240
Late deceleration ‡	1 (8)	5 (50)	0.056
Prolonged deceleration ‡	2 (17)	2 (20)	1.000

† Data shown as median [interquartile range].
‡ Data shown as n (%).
Variability, Acceleration, Deceleratio; according to the two guidelines[19,20].
CAM; Chorioamnionitis

fetuses with severe fetal acidemia, we compared the above-mentioned components of maximum deceleration in each cardiotocography tracing between the two groups; we examined the descending rate from baseline to the bottom of FHR, the descending time from baseline to the bottom of FHR, the ascending time from the bottom to baseline of FHR, the duration time of deceleration, and the ascending slope from bottom to baseline of FHR (Fig. 2, Table 5). No significant differences in the maximum descending rate and time from baseline to the bottom of FHR were observed between the two groups, suggesting that the falling phase of deceleration curve in the cardiotocography tracing was almost the same between the two groups (Table 5). In the fetuses with chorioamnionitis, however, the maximum ascending time from the bottom to baseline of FHR, the longest whole duration time of deceleration, and the ascending slope from the bottom to baseline of FHR significantly decreased, compared with those in the fetuses without chorioamnionitis (Table 5), indicating that the rising phase of deceleration curve in the cardiotocography tracing was quite different between the two groups. These results suggested that the rapid restoration of FHR from the bottom of FHR may occur in cases of chorioamnionitis, and that the slow elevation of FHR from the bottom of FHR may be involved in placental insufficiency.

To confirm the relationship between severe fetal acidemia in chorioamnionitis and the factors associated with the rising phase of deceleration curve in the cardiotocography tracing, we evaluated the risk of developing chorioamnionitis using ROC curve analysis (Table 6). Each value of AUC in the ascending time from the bottom to the baseline, the duration time of deceleration, and the ascending slope from the bottom to the baseline of FHR was close to 1. The sensitivity or specificity was also beyond 80%. Taken together, these results suggested that the ascending time from the bottom to the baseline of FHR, the duration time of deceleration, and the ascending slope from the bottom to the baseline of FHR may be available for the diagnosis of fetal asphyxia in preterm chorioamnionitis.

Discussion

Under fetal acidemia (pH < 7.2), distinctly different cardiotocography tracings were observed between the fetuses with chorioamnionitis and without chorioamnionitis (e.g. placental insufficiency etc.). In fetuses with placental insufficiency, a lack of long-term variability as well as the gradual recovery occurring after the end of the contraction in cardiotocography tracing deceleration were recognized as diagnostic characteristics under severe fetal acidemia, whereas the moderate variabilities and the rapid restoration from the bottom of the FHR in the cardiotocography tracings showed severe acidemic conditions in the fetuses with chorioamnionitis.

When presenting with maternal fever, infants'

Table 5. Analysis of fetal heart rate pattern with deceleration

	CAM (n=12)	Non-CAM (n=10)	*P*-value
Descending rate from baseline to bottom (bpm)	40.0 [30.3-62.5]	31.0 [21.3-41.5]	0.543
Descending time from baseline to bottom (sec)	22.5 [13.0-32.8]	32.0 [26.3-43.0]	0.382
Ascending time from bottom to baseline (sec)	19.0 [12.0-27.8]	58.5 [47.5-67.3]	0.001
Duration of deceleration (sec)	47.0 [32.8-58.0]	94.0 [79.5-101.0]	0.024
Ascending slope from bottom to baseline (bpm/sec)	1.8 [1.3-3.7]	0.6 [0.4-0.7]	0.003

Data shown as median [interquartile range].
CAM; Chorioamnionitis

Table 6. Analysis of diagnostic accuracy which is preterm fetal academia due to chorioamnionitis with the parameters of deceleration

	AUC	95% confidence interval		Cutoff value	Sensitivity (%)	Specificity (%)
		Minimum	Maximum			
Descending rate from baseline to bottom	0.600	0.303	0.897	46.0 bpm	50	83.3
Descending time from baseline to bottom	0.642	0.335	0.948	24.0 sec	60	83.3
Ascending time from bottom to baseline	0.967	0.886	1.048	33.5 sec	90	100
Duration of deceleration	0.842	0.629	1.054	72.0 sec	90	83.3
Ascending slope from bottom to baseline	0.933	0.796	1.071	0.87 bpm/sec	100	83.3

AUC; area under the curve

metabolic demand is increased, which is associated with a simultaneous increase in cerebral blood flow[21]. For the fetus to acquire enough cerebral blood flow, hyperkinetic cardiac movement may be required because of the premature cardiovascular system in infants. In the case of chorioamnionitis, the preterm fetuses should also indicate a similar increase in metabolic demand as well as in cerebral blood flow, exposed to metabolic acidosis and inflammation-induced cytokinesis[22,23]. Accordingly, the fetal heart rate may transiently increase to maintain the excess of cerebral blood flow in fetuses with chorioamnionitis. Such phenomena may appear as an increased variation of FHR. When a deceleration of fetal heart rate occurs subsequently after cord compression, the FHR could quickly recover to baseline because of the hyperkinetic cardiac movement. It has been thought that the effects of intrauterine infection and potentially asphyxiating conditions are different between premature and near-term to term infants[24-26]. It is plausible, therefore, that premature infants may be vulnerable to intrauterine infection, resulting in neurological damage. In fetuses with chorioamnionitis, tachycardia, moderate variabilities, and rapid restoration from the bottom of the FHR in the cardiotocography tracings might play a pivotal role in determining the termination of pregnancy.

In severe preterm fetal growth restriction, a loss of variabilities in FHR in the cardiotocography tracings has been regarded as a critical sign for fetal asphyxia[27]. In animal models, umbilical stenosis induces a marked decrease from the placental supply, indicating that the cardiotocography tracings show a lack of variabilities of FHR[28-30]. Uterine contraction provokes exaggerated reduction of the placental flow. At that time, cardiotocography tracings reveal deceleration, displaying a rapid falling and gradual recovery of FHR[28-31]. These findings coincide with the fetal cardiotocography tracings in the fetuses without chorioamnionitis in this study. The fetuses without chorioamnionitis (e.g. placental insufficiency etc.) display a lack of variation of FHR and a slow rising phase of deceleration of FHR under severe fetal acidemia.

In this study, three pregnant women with chorioamnionitis who had severe fetal growth restriction showed moderate variation and rapid restoration of FHR from the bottom of the FHR. According to this findings, it is plausible that a decreased placental flow due to placental insufficiency is concealed by hyperkinetic cardiac movement and that prematurity induces fetuses to develop severe acidemia, independently of placental insufficiency.

This study had some limitations. First, statistical power was low because of small number of subjects. In recent years, the cases with severe fetal academia delivered at < 32 weeks' gestation were rarely occurred. We performed this study at three institutes in order to increase the number of subjects. Second, Non-CAM group were rich in variety cause of placental insufficiency which was roughly common. Third, assessment of cardiotocography tracing for preterm infants has been considered controversial. However, premature birth is an important issue to be solved even in high-income countries. Building on the findings in this study, a prospective study of the relationship between fetal acidemia and tachycardia or the rapid restoration of FHR from the bottom of the FHR should be performed in preterm and term fetuses with chorioamnionitis.

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