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MATERNAL-FETAL MEDICINE

The effects of antenatal corticosteroids therapy on very preterm infants after chorioamnionitis

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Abstract
Purpose To evaluate the effectiveness of antenatal corticosteroids (AC) therapy on outcomes of very low birthweight infants with histologic chorioamnionitis.
Methods We performed a retrospective analysis of 10,935 single infants born at a gestational age between 22 + 0 and 33 + 6 weeks and birth weight <1,500 g. Clinical data were obtained from the Neonatal Research Network that included the tertiary neonatal intensive care units throughout Japan between 2003 and 2008.
Results Data of 7,896 infants were available for the period 2003–2008 and were included in the analysis. According to logistic regression analysis, AC were significantly associated with reduced mortality [odds ratio (OR) = 0.50; $p < 0.001$], lower incidence of respiratory distress syndrome (OR = 0.72; $p < 0.001$), neonatal seizure (OR = 0.65; $p = 0.003$) and intraventricular hemorrhage (OR = 0.68; $p = 0.001$) in cases after histologic chorioamnionitis compared with the cases had no AC therapy ($n = 3,271$ vs. 4,625). Antenatal corticosteroids were significantly associated with reduced mortality [odds ratio (OR) = 0.60; $p < 0.001$] among the cases without histologic chorioamnionitis.
Conclusion In the retrospective population-based study in Japan, AC exposure was significantly associated with a lower rate of death and neurological morbidity in cases with histologic chorioamnionitis. These outcome data in Japan will be important for further improvement of antenatal practice and care.

Keywords Chorioamnionitis · Antenatal corticosteroids · Outcome · Preterm infants · Very low birthweight infants

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Introduction

Maternal administration of antenatal corticosteroids (AC) is effective to decrease respiratory distress syndrome (RDS) and it improves neurological morbidity and mortality in preterm infants [1–4]. AC therapy has become one of common interventions for threatened preterm delivery [1]. However, most obstetricians are concerned about AC administration and fear adverse effects in cases of suspected infection represented by chorioamnionitis [3, 5]. Major guidelines have indicated that the benefits of AC outweigh the infection risk and recommend AC therapy for pregnant women as long as they show no clinical evidence of infection [4, 5]. However, no evidence has been reported that AC make maternal or fetal infections worse [5]. Pregnant women with signs suggestive of chorioamnionitis have been excluded from randomized control trials [1, 6–9] according to the recommendation. To the best of our knowledge, a randomized clinical trial about the effects of

AC therapy in cases of chorioamnionitis does not exist; only small observational studies or cohort studies are available on the efficacy of AC therapy in cases of chorioamnionitis [10–14].

Chorioamnionitis is associated with the incidence of preterm birth, especially in spontaneous preterm birth at very low gestation (<30 weeks) [15], and this association increases with decreasing gestational age [13]. The presence and severity of chorioamnionitis have been diagnosed by pathological examinations of the placenta (histologic chorioamnionitis). Although accurate, this histological diagnosis can only be made after birth. Antenatal infection can be diagnosed in various ways from clinical signs such as elevated temperature, increased white blood cell (WBC) counts, and uterine tenderness. Clinicians are concerned about AC therapy, particularly in cases where the mother already has chorioamnionitis.

The most significant morbidities such as intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), and chronic lung disease (CLD) are associated with infants weight <1,500 g [10, 16]. In previous studies, AC therapy for women in preterm labor at <34 weeks of gestation decreases neonatal problems, including RDS, IVH, and death [2, 3]. Therefore, the efficacy of AC is much more expected for very low birthweight (VLBW) infants.

The purpose of the study was to evaluate the effectiveness of AC therapy for women we could get postnatal information regarding histologic chorioamnionitis on outcomes of VLBW infants by analyzing a large database (the Neonatal Research Network Japan) and to accumulate one of the largest body of evidence at present.

Materials and methods

This was a retrospective analysis of 7,896 single infants born at a gestational age between 22 + 0 and 33 + 6 weeks and birth weights <1,500 g. Clinical data between 2003 and 2008 were obtained from the Neonatal Research Network Japan which collects data on >50 % of neonates born in Japan. All tertiary neonatal units designated by the government participate in this database. 63 Level III perinatal centers out of the 73 participating facilities were registered for the Neonatal Research Network Japan in the year 2008. This database contains information on morbidity and mortality of VLBW infants <1,500 g and born in participating hospitals.

Data for infants who were born alive but died in the delivery room were included. The clinician's perspective on active treatment or withdrawal of care to preterm infants born at 22 and 23 weeks of gestation depended on the status of infants. After 23 weeks of gestation, most clinicians make an effort to save infants [17].

Data were analyzed according to presence of histologic chorioamnionitis. We analyzed the effect of AC therapy on mortality as the main outcome and studied secondary outcomes with neurological morbidities such as neonatal seizure, IVH, PVL, respiratory morbidities such as RDS, CLD, and adverse effects such as sepsis, late-onset adrenal insufficiency, patent ductus arteriosus (PDA), and necrotizing enterocolitis (NEC).

Non-reassuring fetal status (NRFS) was diagnosed when there is persistent bradycardia or recurrent decelerations. The presence and severity of histologic chorioamnionitis were examined on the basis of Blanc's criteria [18, 19]. IVH was reported according to the classification of Papile et al. [20]. PVL was diagnosed by either cranial ultrasonography or head magnetic resonance imaging scan, performed at 2 weeks or later. RDS was diagnosed on the basis of clinical presentation and characteristic radiographic appearance. CLD was diagnosed on the basis of dependency on oxygen supplementation at a corrected age of 28 days. Neonatal sepsis was documented by a positive blood culture. Late-onset adrenal insufficiency was clinically diagnosed by systematic hypotension with oliguria, hyperkalemia, and myocardial dysfunction [21]. PDA was defined as persistence of an open ductus arteriosus after birth with clinical symptoms. NEC was defined according to Bell classification stage II or greater [22]. Neonatal mortality was defined as death of an infant before discharge.

Statistical analysis

Data are presented as means ± standard deviations for continuous data and median and range for ordinal data. Differences between the AC and no-steroid groups were tested using a Chi-square test and *t* test, as appropriate. Multivariable logistic regression analyses were performed to assess the effect of AC therapy on neonatal mortality and morbidity. Odds ratios or coefficients adjusted for confounding variables and 95 % confidence intervals were calculated. Multivariate logistic regression analysis was performed after adjusting for maternal age, parity, diabetes, preeclampsia, premature rupture of the membranes (PROM), non-reassuring fetal status (NRFS), mode of delivery, gestational age at delivery, and sex of the infant.

Statistical analyses were performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). Statistical tests were considered significant at a p value of <0.05.

Results

A total of 19,226 infants were registered in the database between 2003 and 2008 (Fig. 1). In total, 5,156 infants

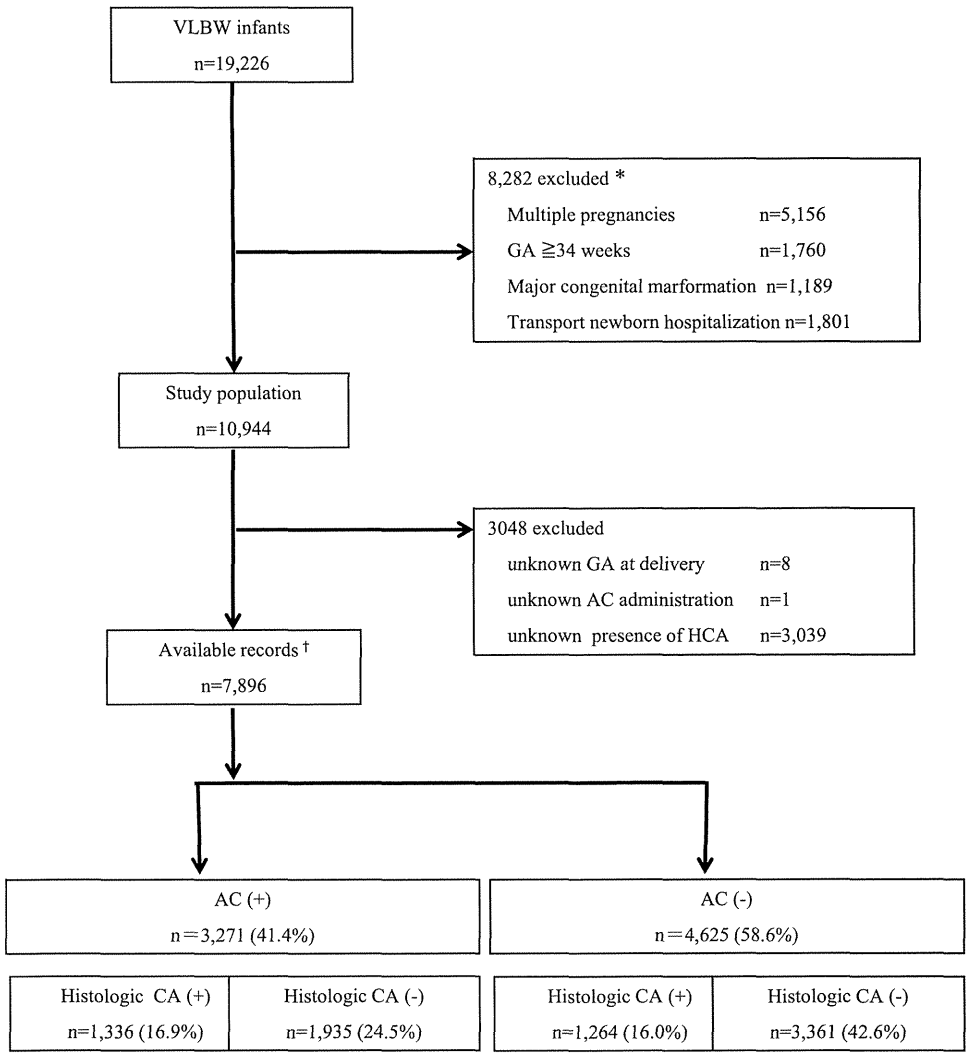

Fig. 1 Flow of study population. *Asterisk* some terms are crossover

were excluded because of multiple pregnancies, 1,189 infants were excluded because of major congenital malformation, and 1,801 infants were excluded because they were born outside participant centers. In study population, 3,039 infants were excluded due to lack of the information about the presence and severity of histologic chorioamnionitis. Data of 7,896 (72.1 %) single infants born at gestational ages between 22 + 0 and 33 + 6 weeks were available, of which only 3,271 (41.4 %) received AC therapy.

Maternal and delivery characteristics for the groups are described in Table 1. The AC group had significantly higher rates of PROM ($p < 0.001$), and lower rates of NRFS ($p = 0.02$), higher rates of cesarean delivery ($p = 0.001$), lower gestational age at delivery ($p < 0.001$), and lower birthweight ($p < 0.001$).

As the main outcome, the effect of AC therapy on neonatal mortality is shown in Table 2. The mortality rate was 6.2 and 13.3 % in the AC and no-steroid groups, respectively, in pregnant women with histologic chorioamnionitis. Similarly, the mortality rate was 5.7 and 9.1 % in the AC and no-steroid groups, respectively, in pregnant women with no histologic chorioamnionitis. In the logistic regression analysis, AC therapy was associated with a significant decrease in mortality of infants whose mothers had histologic chorioamnionitis [adjusted odds ratio (OR), 0.50; 95 % confidence interval (CI); 0.37–0.68; $p < 0.001$].

Regarding neurological morbidities, AC therapy resulted in a significant decrease in neonatal seizures (adjusted OR 0.65; CI 0.44–0.95; $p = 0.03$), IVH (adjusted OR 0.72; CI 0.58–0.89; $p = 0.002$), but no significant association with PVL (adjusted OR 0.74; CI 0.52–1.11; $p = 0.15$) in infants of mothers with histologic chorioamnionitis (Table 2).

The effect of AC therapy on respiratory outcome is shown in Table 2. AC therapy was associated with a significant decrease in RDS in cases of histologic chorioamnionitis (adjusted OR 0.72; CI 0.60–0.85; $p < 0.001$).

AC therapy was associated with a significant decrease in neonatal sepsis in women with histologic chorioamnionitis (adjusted OR 0.72; CI 0.56–0.93; $p = 0.01$). No significant

Table 1 Demographics and baseline characteristics

	Steroid (n = 3,271)	No steroid (n = 4,625)	P value
Maternal age (years)[a]	31.1 ± 5.2	31.1 ± 5.4	0.67
Parity[a]	0.68 ± 0.86	0.67 ± 0.89	0.77
Diabetes	1.1 %	1.8 %	0.006
Preeclampsia	17.5 %	22.7 %	<0.001
PROM	41.8 %	26.2 %	<0.001
NRFS	25.8 %	27.7 %	0.02
Mode of delivery			0.001
Vaginal	26.8 %	28.5 %	
With manipulation	0.5 %	1.0 %	
Cesarean section	72.7 %	70.5 %	
GA at delivery (weeks)[a]	27.6 ± 2.6	27.8 ± 3.0	<0.001
Birth weight (g)[a]	970.2 ± 290.6	995.7 ± 306.3	<0.001
Male sex	52.8 %	51.2 %	0.11

PROM preterm rupture of membranes, *NRFS* non-reassuring fetal status

[a] Mean ± SD

differences were seen for late-onset adrenal insufficiency, PDA, or NEC in women with histologic chorioamnionitis in the logistic regression analysis (Table 2).

Discussion

The current study was an extremely large population-based cohort study that sought to determine the effectiveness of AC therapy in pregnant women who were diagnosed as histologic chorioamnionitis after delivery.

AC therapy was administered to only 41.4 % of women delivered prematurely. This is low rate of AC use in this high-risk population compared with other countries, because in Japan AC therapy was covered under National Health Insurance since 2009. AC therapy decreased neonatal mortality rate and neurological complications regardless of chorioamnionitis in pregnant women (Table 2). The effect was more apparent in pregnant women with histologic chorioamnionitis than those without them. The decrease in neurological complications with the use of AC therapy might lead to a decrease in mortality rate. Hemorrhage in cases of IVH occurs when venous pressure is elevated [23]. PVL is caused by reactive oxygen toxicity resulting from reperfusion or ischemia/hypoxia occurring in the immature fetal brain [24]. AC therapy stabilizes the hemodynamic parameters of the fetus such as blood pressure [25], prevents congestion, ischemia, or reperfusion damage, thus decreasing neurological complications [26].

We experienced decrease in RDS as a result of AC therapy in pregnant women with histologic chorioamnionitis. Fetuses are reportedly stressed by the presence of intrauterine infection/inflammation such as chorioamnionitis, which thereby accelerates lung maturity by encouraging the secretion of endogenous corticosteroids resulting in the production of surfactant [27]. However, we could find AC therapy decreased RDS in the group with histologic chorioamnionitis. In contrast, AC therapy increased RDS in the group without histologic chorioamnionitis. The finding differs from the trend reported in past reports with respect to RDS [1]. This could be because various factors such as the period from steroid administration to delivery had not been adjusted, and RDS has often been subjectively diagnosed by clinical symptoms other than chest X-ray. CLD tended to increase in infants receiving AC therapy, although not significantly. This result possibly occurred because the mortality rate decreased and a larger number of infants in serious condition required long-term ventilation management, oxygen administration, and artificial nutrition [27].

The current study had several limitations. First, the database used in this study had little information about mothers. Aspects such as the type of corticosteroid used during AC therapy, the number of doses of corticosteroids, the period from corticosteroid administration to delivery, maternal sepsis, and maternal mortality were not studied. Second, we analyzed data from multiple facilities; hence, the timing of AC therapy may have differed depending on the facility. However, since this database is very large, the neonatal information associated with AC therapy obtained in the present study is beneficial.

PROM is a higher risk condition for maternal, fetal, and neonatal infection. Intrauterine infection is strongly associated with PROM and particularly complicates 30–50 % of mid-trimester PROM in previous reports [28, 29]. There have been concerns about promoting this risk because of corticosteroid use. However, some recommendations show that AC therapy for pregnant women with PROM before 32 weeks of gestation is beneficial [4, 7, 8]. In this regard, treatment did not increase the risk of maternal death and infection in a systematic review about AC therapy in pregnancies complicated by PROM [1, 30]. As stated above, administration of corticosteroids to pregnant women who have a higher possibility of intrauterine infection is believed to be acceptable without significant maternal adverse effects.

In future, data including information about mothers must be examined, differences in the effectiveness of AC therapy depending on gestational age, and differences among different steroids, dosage, and other variations in treatments regimes must be studied. The effectiveness of AC therapy must be ascertained in a study of multiple pregnancies. In addition, the data on long-term prognosis of cases included in this study are being analyzed.

Table 2 Effects of antenatal corticosteroid on neonatal outcomes after histologic chorioamnionitis

	Affected/total (%)					
	Steroid	No steroid	Crude OR	Adjusted OR[a]	95 % CI	*P* value
Neonatal mortality						
Histologic CA(+)	83/1,336 (6.2)	168/1,264 (13.3)	0.43	0.50	0.37–0.68	<0.001
Histologic CA(−)	111/1,935 (5.7)	306/3,361 (9.1)	0.61	0.60	0.47–0.78	<0.001
Overall	194/3,271 (5.9)	474/4,625 (10.2)	0.65	0.56	0.48–0.67	<0.001
Neurological outcomes						
Neonatal seizure						
Histologic CA(+)	49/1,336 (3.7)	80/1,264 (6.3)	0.56	0.65	0.44–0.95	0.03
Histologic CA(−)	49/1,935 (2.5)	122/3,361 (3.6)	0.69	0.69	0.48–0.97	0.03
Overall	98/3,271 (3.0)	202/4,625 (4.4)	0.66	0.56	0.45–0.71	<0.001
IVH						
Histologic CA(+)	224/1,336 (16.8)	294/1,264 (23.3)	0.67	0.72	0.58–0.89	0.002
Histologic CA(−)	217/1,935 (11.2)	433/3,361 (12.9)	0.85	0.87	0.72–1.05	0.14
Overall	441/3,271 (13.3)	727/4,625 (15.7)	0.87	0.74	0.65–0.83	<0.001
PVL						
Histologic CA(+)	56/1,336 (4.2)	66/1,264 (5.2)	0.79	0.74	0.52–1.11	0.15
Histologic CA(−)	61/1,935 (3.2)	125/3,361 (3.7)	0.84	0.80	0.56–1.10	0.18
Overall	117/3,271 (3.6)	191/4,625 (4.1)	0.95	0.83	0.67–1.03	0.09
Respiratory outcomes						
RDS						
Histologic CA(+)	686/1,336 (51.3)	762/1,264 (60.3)	0.70	0.72	0.60–0.85	<0.001
Histologic CA(−)	1,121/1,935 (57.9)	1,759/3,361 (52.3)	1.25	1.17	1.03–1.33	0.02
Overall	1,807/3,271 (55.2)	2,521/4,625 (54.5)	1.16	0.92	0.84–1.00	0.06
CLD						
Histologic CA(+)	727/1,256 (57.9)	621/1,122 (55.3)	1.11	1.05	0.84–1.31	0.66
Histologic CA(−)	685/1,810 (37.8)	866/2,972 (29.1)	1.48	1.38	1.18–1.61	<0.001
Overall	1,412/3,066 (46.1)	1,487/4,094 (36.3)	1.55	1.16	1.04–1.28	0.01
Other outcomes						
Sepsis						
Histologic CA(+)	135/1,336 (10.1)	183/1,264 (14.5)	0.66	0.72	0.56–0.93	0.01
Histologic CA(−)	120/1,935 (6.2)	223/3,361 (6.6)	0.93	0.98	0.76–1.25	0.85
Overall	255/3,271 (7.8)	406/4,625 (8.8)	0.97	0.86	0.74–0.99	0.05
Late-onset adrenal insufficiency						
Histologic CA(+)	163/1,295 (12.6)	149/1,180 (12.6)	0.99	1.05	0.81–1.36	0.70
Histologic CA(−)	156/1,873 (8.3)	241/3,146 (7.7)	1.10	0.92	0.73–1.15	0.47
Overall	319/3,168 (10.1)	390/4,326 (9.0)	1.27	1.02	0.88–1.19	0.77
PDA						
Histologic CA(+)	515/1,336 (38.5)	465/1,264 (36.8)	1.08	1.16	0.97–1.39	0.09
Histologic CA(−)	639/1,935 (33.0)	950/3,361 (28.3)	1.25	1.17	1.02–1.33	0.02
Overall	1,154/3,271 (35.3)	1,415/4,625 (30.6)	1.34	1.13	1.04–1.24	0.01
NEC						
Histologic CA(+)	26/1,336 (1.9)	25/1,264 (2.0)	0.98	1.13	0.63–2.02	0.68
Histologic CA(−)	28/1,935 (1.4)	39/3,361 (1.2)	1.25	1.35	0.81–2.25	0.25
Overall	54/3,271 (1.7)	64/4,625 (1.4)	1.23	1.13	0.82–1.57	0.45

CA chorioamnionitis, *OR* odds ratio, *CI* confidence interval

[a] Adjusted for maternal age, parity, diabetes, preeclampsia, preterm rupture of membrane (PROM), non-reassuring fetal status (NRFS), mode of delivery, gestational age of delivery, birthweight, and sex of the infant

Conclusion

Based on this body of the evidence and the results of our study, we propose that active use of AC therapy is recommended for women with a single pregnancy at the very preterm and even those with chorioamnionitis. These outcome data in Japan will be important for further improvement of antenatal practice and care.

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Conflict of interest The authors declare no conflict of interest.

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C1 Esterase Inhibitor Activity in Amniotic Fluid Embolism

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AQ3 **Introduction:** Amniotic fluid embolism exhibits activation of the complement system and the kallikrein-kinin and coagulofibrinolytic systems. C1 esterase inhibitor is a major inhibitor of C1 esterase and can inhibit plasma kallikrein and also factors XIIa and XIa. Its activity has been shown to be significantly lower in pregnancy and labor than in the nonpregnant state. The purpose of this study was to determine C1 esterase inhibitor activity levels in amniotic fluid embolism.

Methods: This study was retrospectively conducted on 194 singleton pregnant women. One hundred six cases of amniotic fluid embolism had applied to the Japan amniotic fluid embolism registration center in Hamamatsu University School of Medicine between January 2010 and December 2011. In amniotic fluid embolism cases, 85 cases were nonfatal and 21 cases were fatal. Eighty-eight women who delivered without amniotic fluid embolism were regarded as a control. C1 esterase inhibitor activity levels at the onset of amniotic fluid embolism in amniotic fluid embolism cases and at the completion of labor in control cases were measured and compared using the Mann-Whitney *U* test.

Results: C1 esterase inhibitor activity levels were significantly lower in amniotic fluid embolism patients (30.0% ± 1.8%) than in control women (62.0% ± 2.0%) ($p < 0.0001$). C1 esterase inhibitor activity levels in fatal amniotic fluid embolism cases (22.5% ± 3.4%) were significantly lower than those in nonfatal amniotic fluid embolism cases (32.0% ± 2.1%) ($p < 0.05$).

Conclusions: These results demonstrated that low C1 esterase inhibitor activity levels were closely associated with the pathogenesis of amniotic fluid embolism suggesting that C1 esterase inhibitor activity levels have potential as a prognosis factor of amniotic fluid embolism. (*Crit Care Med* 2014; XX:00–00)

Key Words: amniotic fluid embolism; C1 esterase inhibitor; disseminated intravascular coagulopathy; kallikrein; postpartum hemorrhage; serpin

Amniotic fluid embolism (AFE) is one of the most serious complications of obstetrics, anesthetics, and critical care. Despite earlier recognition and intensive critical care, the mortality of AFE remains high and has been estimated at between 5% and 15% of all maternal deaths (1). Maternal mortality rates due to AFE have been estimated at between 37% and 80% (2, 3). Maternal death has been decreasing year by year in Japan; however, the prevalence of maternal death due to AFE has remained unchanged. The maternal mortality rate due to AFE has increased to 24.3% in Japan (4). AQ4

AFE is recognized as a kind of syndrome characterized by the abrupt onset of hypoxia, hypotension, and disseminated intravascular coagulopathy (DIC) (5). Benson et al (6) reported that maternal complement levels were significantly decreased in AFE. These findings suggested a disorder in the coagulofibrinolytic system as well as the complement system that may play important roles in the pathogenesis of AFE.

We developed the Japan AFE registration system in 2003 and collected clinical data, maternal serum, and uterine tissue from nearly all cases of fatal AFE in Japan (4, 7). Under the system, maternal serum has been applied to determine mainly the levels of specific amniotic fluid complements such as Sialyl Tn and zinc coproporphyrin 1 (8, 9). These clinical and histopathological observations demonstrated that AFE was frequently associated with uterine atony due to angioedema (unpublished data). AQ5

C1 esterase inhibitor (C1INH), belonging to the serpin group/family, is a major inhibitor not only of C1 esterase but also of kallikrein and factors XIIa and XIa (10–12). Its deficiency has been known to be a direct cause of hereditary angioedema (HAE) as well as acquired angioedema (13). Since

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C1INH has the potential to regulate the coagulofibrinolytic system, complement system, and kallikrein-kinin system, we have become greatly interested in C1INH activity levels in AFE in Japan.

MATERIALS AND METHODS

Definition of AFE

AFE was defined based on the Japan consensus criteria for the diagnosis of AFE based on the United States/United Kingdom criteria as shown in **Figure 1** (7, 14). A pathological diagnosis was determined when fetal debris was found in the maternal pulmonary arteries. The diagnosis of nonfatal AFE depended on clinical manifestations and was done when factors B1–B3 were all present, but more than one of the signs and symptoms listed in B1 needed to be present. Consumptive coagulopathy/DIC due to evident etiologies such as abnormal placentation (placental abruption, etc.), trauma during labor and delivery, and severe preeclampsia/eclampsia should be excluded from the criteria.

Patients

The Japan AFE registration system was started in 2003 (7). This system has included the procedure of consent to apply and analyze their clinical data and blood samples. Consent was obtained from patients or patient's family, when physicians regarded their patients with significant symptoms as AFE based on the diagnostic criteria of AFE. Clinical data and serum from nearly all cases of AFE have accumulated in Hamamatsu University School of Medicine. Subjects of the present study were extracted from entry cases in the Japan AFE registration center in Hamamatsu University School of Medicine, Shizuoka, between January 2010 and December 2011. Women with multiple pregnancies, preeclampsia, thrombophilia, preterm labor, uterine disorder such as uterine myoma, and a history of systemic disease were excluded from this study. Cesarean section was carried out due to obstetrical indications, such as breech presentation, history of cesarean section, arrest of labor, and nonreassuring fetal status. Women, who delivered at Hamamatsu University Hospital between April 2011 and September 2011, without AFE and any medical intervention other than general birth and surgical assistances were analyzed as the control subjects. One hundred six cases of AFE and 88 cases of control were defined (**Table 1**). Among the AFE cases, 85 cases survived and 21 cases died due to AFE.

The Japan consensus criteria for the diagnosis of AFE

A. Pathological confirmation; A diagnosis is made on the basis of clinical presentation after excluding differential diagnosis and at autopsy in the event of death of the parturient. The diagnosis is confirmed by histochemical studies.

B. Clinical manifestation; The patients has the hallmark clinical manifestations of AFE following 1, 2, and 3:
1. Signs and symptoms: Cardiac arrest/ Respiratory arrest/ Consumptive coagulopathy
2. Onset of all of the signs and symptoms during pregnancy, labor, or cesarean section or within 12 hours of delivery
3. Absence of other illness that could explain the signs and symptoms described above

Figure 1. The Japan consensus criteria for the diagnosis of amniotic fluid embolism (AFE). A pathological diagnosis was determined when fetal debris was found in the maternal pulmonary arteries. The diagnosis of nonfatal AFE depended on clinical manifestations and was done when factors B1–B3 were all present, but more than one of the signs and symptoms listed in B1 needed to be present.

Blood Collection and Measurement of C1INH Activity

Blood samples from registered AFE patients were collected at the Japan AFE registration center in Hamamatsu, and serum and plasma samples were then kept at −30°C until use. Time points of blood samples obtained were at onset of and before interventions against AFE. Control blood samples were obtained at the completion of labor. The determination of C1INH activity was performed using the Berichrom C1 inhibitor kit (Siemens Healthcare Diagnostics) according to the manufacturer's instructions. The intra-assay coefficients of variation (CV) ranged between 1.8% and 7.9% and the interassay CV were between 3.2% and 6.6%. We analyzed all the samples at the same time under a blind fashion. In the present study, we demonstrated the measurement of C1INH activity in serum. Furthermore, C1INH activity was measurable in serum as well as plasma; there were no significant differences ($p < 0.0001$, $R^2 = 0.9881$) in the activity level between serum and plasma under the Berichrom C1 inhibitor kit (data not shown).

Approval

Written informed consent was obtained after full explanation of the study. The study was carried out under the approval of the Ethics Committee of Hamamatsu University School of Medicine (Number 24–130 and 25–107), which conforms to the provisions of the Declaration of Helsinki (as revised in Tokyo 2004).

Data Analysis

Values of C1INH activity (%) were presented as the median ± SE. Significant differences were assessed with the Mann-Whitney U test. A p value of less than 0.05 was considered significant.

RESULTS

As shown in **Figure 2**, C1INH activity levels in the controls and AFE cases were 62.0% ± 2.0% and 30.0% ± 1.8%, respectively. C1INH activity levels in the AFE cases were significantly lower than those in the controls ($p < 0.0001$). C1INH activity levels in fatal and nonfatal AFE cases were 22.5% ± 3.4% and 32.0% ± 2.1%, respectively. A significant difference was observed between the two groups ($p = 0.0121$).

Changes in C1INH activity levels in one survivor case and one case that died due to AFE are shown in **Figure 3**. Both cases were defined as AFE by the Japan consensus criteria for the diagnosis of AFE shown in Figure 1. C1INH activity levels were potentially very low before the onset of AFE. C1INH activity in the survivor case was at its lowest level at the onset 3 hours after the selective cesarean section due to history of cesarean section when AFE was defined due to the development of DIC. Immediate replacement therapy with FFP successfully increased the activity of C1INH. In the case that died,

AQ6 **TABLE 1. XXX**

AQ7

	Control	Total AFE	Nonfatal AFE	Fatal AFE
No. of subjects	88	106	85	21
Age (yr)	31.0±4.8	33.8±5.8	33.3±5.4	35.6±3.8
Gravida[a]	1.27±1.02	1.64±1.77	1.74±1.82	1.23±1.47
Parity[a]	0.72±0.63	0.83±1.06	0.89±1.12	0.57±0.72
Nulliparous (%)	28 (31.8)	52 (49.0)	41 (48.3)	11 (52.4)
Multiparous (%)	60 (68.2)	54 (51.0)	44 (51.7)	10 (47.6)
Gestational period (d)	273±12	268±19	267±20	270±17
Delivery methods				
Vaginal delivery (%)	60 (68.2)	52 (49.0)	44 (51.7)	10 (47.6)
Cesarean section (%)	28 (31.8)	54 (51.0)	41 (48.3)	11 (52.4)
Blood loss at delivery (mL)				
Vaginal delivery	395±170	4,864±3,039	5,038±3,111	4,097±2,569
Cesarean section	840±279	4,270±2,988	4,314±2,657	4,107±3,961

AFE = amniotic fluid embolism.
[a]Woman without previous history of pregnancy and delivery was determined as gravida 0 and parity 0, respectively.

C1INH activity was also low before the manifestation of AFE symptoms. In this case, amniotic fluid, fetal substance, and gram-positive coccus were observed and autopsy diagnosis was AFE and bacteremia.

DISCUSSION

AFE is an unpredictable and serious disorder of pregnancy characterized by hypotension, hypoxia, and coagulopathy (5). In most pregnant women, the entry of small amounts of amniotic fluid into the maternal circulation may be innocuous; however, such exposure is associated with a fatal outcome in other women. Anaphylactic reactions have been suggested as a concept of AFE to explain such an individual difference in the response to amniotic fluid (2, 15). Benson (6, 16) reported that serum tryptase and urinary histamine increased and complement levels decreased in AFE patients, suggesting that contact and maternal immune activation played important roles in the pathophysiology of AFE.

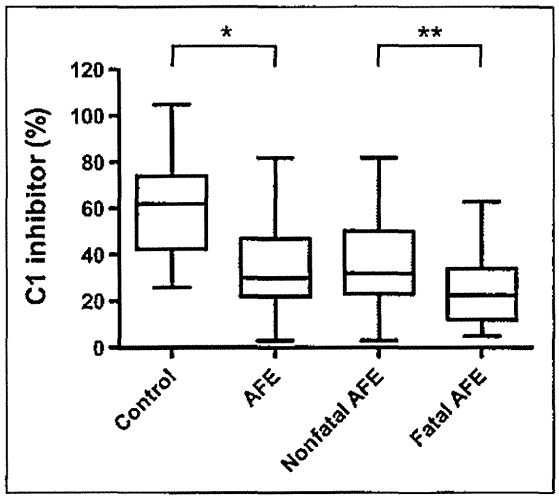

Figure 2. C1 esterase inhibitor (C1INH) activity levels in control, amniotic fluid embolism (AFE), nonfatal AFE, and fatal AFE cases. Columns indicate the medians and whiskers represent the minimum and maximum values. Significant differences were $^{*}p < 0.0001$ and $^{**}P = 0.0121$, respectively.

Clinically, DIC-type postpartum hemorrhage accompanying uterine atony is one of the recognized symptoms of AFE (4, 17). To explain this, coagulation factor XII (FXII) may be responsible for the pathological condition as it is activated by contact with various artificial or biological negatively charged surfaces, resulting not only in blood coagulation but also in the activation of the complement system and kallikrein-kinin system to produce bradykinin (18). We demonstrated that FXII inactivated plasminogen activator inhibitor 1 and enhanced fibrinolysis (19). Interestingly, bradykinin has strong vasodilation effects, a hypotensive effect, and causes an increase in vascular permeability resulting in a hypotonic uterus (20, 21). These findings suggest that FXII activation by contact triggers the subsequent catastrophic chain of AFE. We are continuing to investigate the possible role of FXII in AFE.

C1INH, which is mainly synthesized in hepatocytes and endothelial cells and belongs to serpin family, is a major inhibitor of not only C1 esterase but also FXIIa and kallikrein (11, 12). Its deficiency is known to be a specific cause of HAE (13). Since C1INH is capable of not only inhibiting the complement system but also modulating the coagulofibrinolytic and kallikrein-kinin systems (22, 23), we hypothesized that C1INH was key in the pathophysiology of AFE.

Halbmayer et al (24) reported that basal C1INH activity levels decreased markedly with pregnancy up to labor. Although the mechanism remains unclear, estradiol (E2) was shown to suppress the potential activity of C1INH (25, 26).

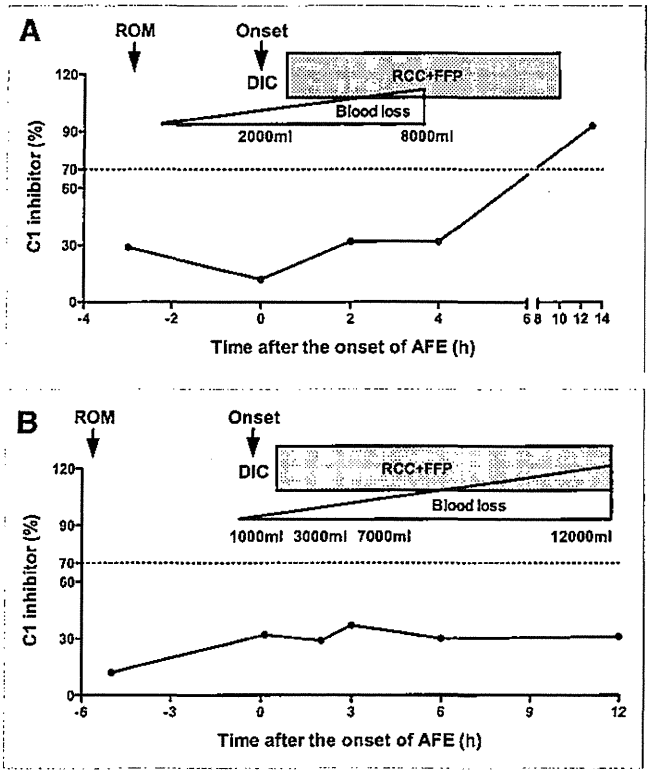

Figure 3. Chronological changes in C1 esterase inhibitor (C1INH) activity levels in amniotic fluid embolism (AFE) cases. A survivor of AFE (**A**) and a case that died due to the coexistence of AFE with bacteremia (**B**). Potential C1INH activity levels were low before the onset of AFE. In case A, the sudden onset of AFE presented disseminated intravascular coagulopathy (DIC) 3 hr after rupture of membrane (ROM) under a selective cesarean section. When AFE was recognized as abnormal coagulopathy, blood replacement therapy was immediately administrated resulting in an increase in C1INH activity levels. In case B, despite intensive care including adequate blood transfusions, C1INH activity levels did not recover. A *dotted line* indicates 70% of C1INH activity. Normal AQ10 C1INH activity is more than 70%. RCC =, FFP =.

The increase in E2 levels during pregnancy may be associated with the decrease in C1INH activity levels in pregnant women. They also observed that C1INH activity levels were significantly lower in preeclampsia patients than in normal pregnant women (24). Increases in C3a and C5a have been reported not only in AFE patients but also in patients with preeclampsia and eclampsia (27), which suggests that the consumption of C1INH is due to activation of the complement system. This may explain the high risk of AFE associated with preeclampsia and eclampsia as risk factors of AFE (28, 29).

The present study demonstrated that C1INH activity levels in AFE cases were significantly lower than those of controls. Furthermore, when we compared fatal cases to nonfatal cases using Pearson chi-square test for C1INH activity less than 25% as a cutoff value almost comparable to "attack of angioedema," there was a significant difference with p equal to 0.026 (degree of freedom 1 and chi-square value 4.956). In addition, the chronological assessment of C1INH activity levels in two AFE patients indicated that their basal C1INH activity levels before delivery and onsets of AFE were also lower at 29% and 12% than that of healthy pregnant controls at 74.3% ± 15.5% during the third trimester (24). These results suggest that low C1INH activity levels before onset of AFE could be a predictive factor as well as low levels at onset and the persisting low levels of C1INH activity could be a prognostic factor of AFE.

It has been reported that the levels of C1INH may be increased during infection as an acute phase protein, then cleaved and inactivated by neutrophil elastase and bacterial proteases under developing inflammatory conditions due to bacteremia and sepsis resulting in a functional C1INH deficiency (30–32). As demonstrated in the fatal case in **Figure 3B**, we should note here that not only C1INH consumption under AFE condition but also C1INH inactivation under inflammatory conditions due to bacteremia may be involved in the persistent low levels of C1INH activity (32).

As a treatment for DIC with AFE, the rapid administration of FFP or cryoprecipitate was sufficient to extricate the patient from a critical situation. FFP contains several essential proteins such as ATIII and fibrinogen. One hundred units AQ11 of C1INH are contained in FFP derived from 200 mL blood. Our chronological assessment of C1INH activities in the AFE patient shown in **Figure 3A** demonstrated that a suited blood transfusion including FFP was able to improve C1INH activity. Clinically, the use of 500–1,500 U of human plasma–derived C1INH concentrates can revert HAE in C1INH-deficient patients (33–35). Since AFE patients certainly have significant lower levels of C1INH activity, similar to a C1INH deficiency, the clinical application of human plasma–derived C1INH concentrates may become one of the promising candidates for the treatment of AFE.

In summary, we reported here that C1INH activity levels were significantly lower in AFE cases, particularly in fatal cases. These results indicate that C1INH activity levels reflect the severity of AFE and can be a prognostic factor of AFE. We speculate that the clinical application of C1INH concentrates will be effective for the treatment of AFE. Although the chronological measurement of C1INH activity was small, our results suggest that pregnant women with potentially low C1INH activity levels may be at a high risk of the onset of AFE. Further clinical studies are required to elucidate the etiological role of C1INH in AFE and determine whether C1INH activity may be a predictive factor of AFE.

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Association of Antenatal Corticosteroids and the Mode of Delivery with the Mortality and Morbidity of Infants Weighing Less than 1,500 g at Birth in Japan

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Key Words
Antenatal corticosteroids · Very low birth weight · Cesarean section · Vaginal delivery

Abstract
Objective: This study aimed to re-evaluate the effectiveness of antenatal corticosteroids (ACS) and to analyze the association between ACS and the mode of delivery in the context of perinatal morbidity and mortality in very-low-birth-weight (VLBW) infants. ***Study Design:*** This retrospective cohort study involved 15,765 VLBW infants born between 2003 and 2008 at less than 34 weeks of gestation and weighing less than 1,500 g at birth. Data were obtained from the Japanese neonatal research network database. Univariate and multivariate logistic regression analyses were performed to evaluate the impact of ACS and mode of delivery on the risk of infant mortality and morbidity. ***Results:*** Administration of ACS was associated with decreases in mortality rate, intraventricular hemorrhage (IVH) and retinopathy of prematurity (ROP), and was not associated with the incidence of respiratory distress syndrome (RDS), periventricular leukomalacia or necrotizing enterocolitis (NEC). When the administration of ACS was analyzed in the context of different modes of delivery, the incidence of IVH and ROP tended to decrease with cesarean section deliveries, whereas the incidence of RDS tended to decrease and the incidence of NEC tended to increase for infants delivered vaginally. The incidence of chronic lung disease tended to increase in association with both delivery methods. ***Conclusions:*** This large cohort study reconfirms that ACS treatment is associated with decreases in infant mortality and severe morbidity. Furthermore, the delivery method may be associated with severe morbidity in VLBW infants exposed to ACS.

Introduction

A neonatal research network (NRN) database was established in Japan in 2003 with a grant from the Japanese Ministry of Health, Labour and Welfare. Recommendations regarding the use of antenatal corticosteroids (ACS) have been published, and they indicate that all fetuses at

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risk of delivery between 24 and 34 weeks of gestation should be considered as candidates for ACS [1]. Recent studies have confirmed that the use of ACS is associated with decreases in infant mortality and reduced incidence of respiratory distress syndrome (RDS), necrotizing enterocolitis (NEC) and intraventricular hemorrhage (IVH) in preterm infants [2, 3]. Our group has previously reported the differences in morbidity and mortality in very-low-birth-weight (VLBW) infants and the effects of ACS on the survival of these infants at tertiary centers registered with the NRN database in Japan [4, 5].

The optimal delivery method for preterm infants is controversial. Some studies report lower mortalities or morbidities in VLBW infants following deliveries by cesarean section (CS) compared with vaginal delivery (VD) [6–9], whereas other investigators have found no improvements in perinatal outcomes on the basis of the delivery method [10–12].

The present study aimed to re-evaluate the effectiveness of ACS and to analyze the association between ACS and the mode of delivery in the context of perinatal morbidity and mortality in VLBW infants using the large volume of population data available on the NRN database. The results from this study should encourage ACS use in Japan and should help determine the appropriate mode of delivery for VLBW infants.

Materials and Methods

For this retrospective cohort study, patient data were obtained from the Japanese NRN database that contains maternal and neonatal data collected in accordance with common database definitions (http://plaza.umin.ac.jp/nrndata/hyo1.pdf). All government-designated tertiary neonatal units in Japan contribute to this database. The NRN database contains information on the morbidity and mortality of infants weighing less than 1,500 g at birth and born in or admitted to participating hospitals within 28 days of birth. Data on infants who were born alive but died in the delivery room were also included in this study, but data on infants born with congenital anomalies or chromosomal aberrations were excluded. All information about the infants was collected anonymously and independently from the original data. The infants were categorized according to whether or not their mothers had received ACS and whether they were delivered by CS or VD. Data about the administration of full and partial courses of ACS were collected, but data about the timings of ACS administration and the doses given were not available. Central internal review board approval of this study was obtained from Tokyo Women's Medical University, where all data were collected and stored.

Definitions

We studied the effects of ACS on the risk of infant death or the risk of infants being born with RDS, IVH, periventricular leukomalacia (PVL), chronic lung disease (CLD), NEC or retinopathy of prematurity (ROP) when ACS were administered to mothers who were at risk of experiencing preterm births at 22–34 weeks of gestation. Infant death was defined as the death of an infant before discharge and included death in the delivery room. RDS was diagnosed on the basis of clinical and radiographic findings. The IVH grade was determined using cranial echography and the classification system developed by Papile. CLD was defined as a persistent need for supplemental oxygen for the first 28 days after birth or at 36 weeks postmenstrual age. NEC was defined as Bell's stage II or higher. The stage of ROP was determined in accordance with the classification endorsed by the Japanese Ministry of Health, Labour and Welfare, which directly correlates with ICROP (International Classification of ROP). In this study, the presence of ROP was defined as ophthalmoscopic findings consistent with ICROP stages 2, 3, 4, or 5.

Statistical Analysis

To investigate the effects of exposure to ACS, all infants on the Japanese NRN database who died or were born with RDS, IVH, PVL, CLD, NEC or ROP were compared with infants who had not died or did not have these complications. All outcomes were measured at the time of discharge from the neonatal unit. Missing data were excluded from the analyses.

For the first analysis, the demographic characteristics of the mothers treated with ACS were compared with those of the mothers who were not administered ACS, using Student's t test and the Wilcoxon rank-sum test, as appropriate. Univariate and multivariate logistic regression analyses were used to determine the correlations between ACS treatment and the risk of infant death, RDS, IVH, PVL, CLD, NEC or ROP. Maternal age, infant gender, gestational age at delivery (in weeks), birth weight, the presence of twins, intrauterine growth restriction (IUGR) occurrence, delivery by CS, and the occurrence of premature rupture of the membrane (PROM) were included as adjustments in the multivariate model.

For the second analysis, the demographic characteristics of the mothers who delivered their infants by CS were compared with those of the mothers who delivered their infants by VD, using Student's t test and the Wilcoxon rank-sum test, as appropriate. Univariate and multivariate logistic regression analyses were applied to determine correlations between ACS treatment and the risk of infant death, RDS, IVH, PVL, CLD, NEC or ROP in the CS and VD subgroups. Maternal age, infant gender, gestational age at delivery (in weeks), birth weight, the presence of twins, IUGR occurrence, and PROM occurrence were included as adjustments in the multivariate model. We also tested the interaction between the effect of ACS and mode of delivery for all outcomes.

All tests were two-tailed and differences were considered significant for $p < 0.05$. Stata statistical software, release 12 (StataCorp LP, College Station, Tex., USA) was used for all of the statistical analyses.

Results

The study population comprised 15,765 infants born between 2003 and 2008 (fig. 1); of these, 6,400 (40.6%) had been exposed to ACS. Betamethasone is generally used for ACS therapy in Japan. Table 1 shows the demographic and clinical characteristics of the study population categorized

Table 1. Demographic and baseline clinical characteristics categorized according to ACS exposure

Variable	ACS exposure (n = 6,400)	No ACS exposure (n = 9,365)	p value
Female	48.5	50.1	0.0461
Gestational week	27.9±2.67	28.3±3.15	<0.001
Birth weight, g	994.5±293.6	1,025.6±309.2	<0.001
Birth length, cm	34.9±3.85	35.3±4.05	<0.001
Twin pregnancy	31.6	26.4	<0.001
CS	78.8	74.3	<0.001
PROM	35.4	23.6	<0.001
Mother's age, years	31.1	31.0	0.618
Death	6.1	9.0	<0.001
RDS	56.8	52.6	<0.001
IVH	12.2	14.3	0.001
IVH grade 3 or 4	3.9	5.7	<0.001
CLD	38.6	30.8	<0.001
PVL	3.5	3.7	0.652
NEC	1.6	1.3	0.229
ROP stage >II	51.1	57.8	<0.001
IUGR	33.1	38.6	<0.001

Data are presented as mean ± standard deviation or percentage.

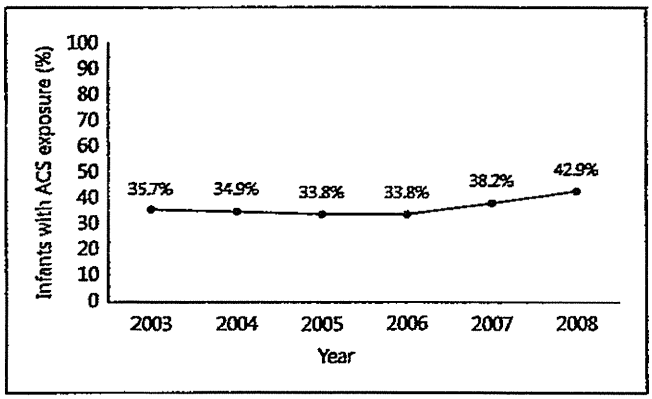

Fig. 1. Frequency of exposure to ACS by year of birth.

Table 2. Association between ACS administration and infant mortality and morbidity

Variable	OR	p value	95% CI
Death	0.632	<0.001	0.54–0.72
RDS	0.99	0.721	0.92–1.06
IVH	0.76	<0.001	0.68–0.84
IVH grade 3 or 4	0.64	<0.001	0.54–0.75
CLD	1.18	<0.001	1.08–1.30
PVL	0.87	0.117	0.73–1.04
NEC	1.15	0.309	0.88–1.52
ROP	0.74	<0.001	0.69–0.79

Data are adjusted for maternal age, infant gender, gestational age, birth weight, the presence of twins, delivery by CS, occurrence of IUGR and PROM.

Table 3. Demographic and baseline clinical characteristics classified according to delivery method

Variable	CS (n = 12,006)	VD (n = 3,759)	p value
Female	50.0	47.6	0.010
Gestational week	28.5±2.86	27.1±3.09	<0.001
Birth weight, g	1,019.3±296.8	992.9±322.5	<0.001
Birth length, cm	35.3±3.89	34.7±4.24	<0.001
PROM	25.1	39.0	<0.001
Mother's age, years	31.3	30.2	<0.001
Steroid therapy	42.0	36.0	<0.001
IUGR	42.6	16.2	<0.001
Death	6.6	11.6	<0.001
RDS	55.9	49.0	<0.001
IVH	11.7	18.9	<0.001
IVH grade 3 or 4	4.3	7.1	<0.001
CLD	33.1	37.3	<0.001
PVL	3.6	3.5	0.674
NEC	1.4	1.6	0.281
ROP stage >II	53.1	61.5	<0.001

Data are presented as mean ± standard deviation or percentage.

according to the use of ACS. Significant differences in some characteristics were observed between the group that received ACS and the group that did not receive ACS (table 1). Results from the univariate and multivariate logistic regression analyses performed to determine the correlations between ACS treatment and the risk of infant mortality, RDS, IVH, PVL, CLD, NEC or ROP are presented in table 2. The use of ACS significantly decreased the odds ratio (OR) of infant mortality (OR 0.63; 95% CI 0.54–0.72; $p < 0.001$). With respect to infant morbidity, ACS was associated with a decreased incidence of IVH (OR 0.76; 95% CI 0.68–0.84; $p < 0.001$) and ROP (OR 0.74; 95% CI 0.69–0.79; $p < 0.001$). We did not note any improvement in the risk of RDS with ACS use (OR 0.99; 95% CI 0.92–1.06; $p = 0.721$). The CLD rate increased with the use of ACS (OR 1.18; 95% CI 1.08–1.30; $p < 0.001$).

Table 3 shows the demographic and baseline characteristics of the study population categorized according to

Table 4. Association between ACS and infant mortality and morbidity categorized according to the delivery method

Outcome	CS (n = 12,006)			VD (n = 3,759)			p value for interaction
	OR	p value	95% CI	OR	p value	95% CI	
Death	0.68	<0.001	0.57–0.80	0.53	<0.001	0.41–0.70	0.103
RDS	1.09	0.056	1.00–1.18	0.71	<0.001	0.61–0.82	<0.001
IVH	0.65	<0.001	0.58–0.74	1.03	0.770	0.85–1.24	<0.001
IVH grade 3 or 4	0.54	<0.001	0.44–0.66	0.9	0.490	0.68–1.21	0.004
CLD	1.14	0.013	1.03–1.27	1.3	0.006	1.08–1.57	0.188
PVL	0.88	0.192	0.72–1.07	0.8	0.263	0.55–1.18	0.855
NEC	0.96	0.797	0.69–1.32	1.73	0.042	1.02–2.92	0.048
ROP	0.71	<0.001	0.65–0.76	0.9	0.153	0.77–1.04	0.006

Data are adjusted for maternal age, infant gender, gestational age, birth weight, the presence of twins, the occurrence of IUGR and PROM.

delivery method. Significant differences were observed between the CS and VD groups in some characteristics. Compared with the VD group, the CS group showed significantly higher rates of ACS use and IUGR, and higher gestational age at birth. Infant mortality and the incidence of IVH, CLD and ROP were significantly lower in the CS group than in the VD group. The associations between ACS and infant mortality and morbidity in relation to the mode of delivery are shown in table 4. Regardless of the delivery method, administration of ACS was associated with lower infant mortality rates (CS: OR 0.68; 95% CI 0.57–0.80; $p < 0.001$; VD: OR 0.53; 95% CI 0.41–0.70; $p < 0.001$). The interaction term between the mode of delivery and ACS for mortality was not significant ($p = 0.103$). CS delivery was associated with decreased incidence of IVH (OR 0.65; 95% CI 0.58–0.74; $p < 0.001$) and ROP (OR 0.71; 95% CI 0.65–0.76; $p < 0.001$). VD was associated with decreased incidence of RDS (OR 0.71; 95% CI 0.61–0.82; $p < 0.001$) and increased incidence of NEC (OR 1.73; 95% CI 1.02–2.92; $p = 0.042$). The incidence of CLD tended to increase in association with both delivery methods (CS: OR 1.14; 95% CI 1.03–1.27; $p = 0.013$; VD: OR 1.30; 95% CI 1.08–1.57; $p = 0.006$). The interaction term between the mode of delivery and ACS for RDS, IVH, NEC and ROP became significant (table 4).

Discussion

This retrospective study shows that the dissemination rate of ACS was low from 2003 until 2008, and was low compared with data published by the National Institute of Child Health and Human Development Neonatal Research Network [13], which reported that ACS were used for almost 80% of VLBW infants. Socioeconomic factors may influence the administration of ACS, but we have no data on the socioeconomic statuses of the mothers investigated in this study. We have also experienced a high level of apprehension about the adverse effects to mothers of ACS and that this may also limit the administration of ACS, especially when using obstetric tocolytic agents. The administration of betamethasone as ACS therapy is now covered by the Japanese National Medical Insurance Program, so we expect that the use of ACS therapy will soon gain momentum and become more widely used in Japanese tertiary care centers.

In this study, we analyzed data from a larger study population than was previously reported by our group [5], and we demonstrated that the use of ACS significantly reduced infant mortality and the incidence of IVH and ROP. However, sources of potential bias should be considered in the results obtained from this study because the data used included infants who died in the delivery room as well as inborn and outborn patients. Some publications report that the use of ACS is associated with overall reductions in the incidence of neonatal death, RDS, IVH, NEC and the need for respiratory support [2, 3, 5, 14, 15]. In this study, we obtained similar results regarding mortality, IVH and ROP, but the results differed from those previously described regarding RDS, CLD, NEC and PVL. The benefit of ACS in reducing the incidence of RDS has been recognized, and a recent Cochrane review reported the effectiveness of ACS in accelerating fetal lung maturation in women at risk of preterm birth [2]. One reason for the differences in the results between the present study and previously published studies may be

that the data analyzed in the present study contained information about multiple pregnancies and IUGR; several reports have indicated that ACS are less effective at reducing morbidity and mortality in patients with IUGR [16–18] and in infants from multiple pregnancies [19, 20]. Furthermore, the timings of ACS administration and the doses of ACS administered may have led to differences between the results from our study and those from previous studies [21]. The data analyzed in the current study included data on both completed and partially completed courses of ACS, but data about the timings of ACS administration and the doses of ACS administered were not available. Regarding the increase in the occurrence of CLD in this study, it might be necessary to take into account recent improvements in infant prognoses. These improvements may have influenced the respiratory status of the study population overall. In particular, improvements in neonatal mortality can affect the incidence of CLD, because the affected infants would not have survived if they had been administered conventional treatment. This result also suggests that ACS treatment is more strongly associated with reductions in infant mortality and in the incidence of IVH and ROP, rather than merely reducing the incidence of respiratory problems. We also believe that the use of ACS helps to stabilize the systemic circulation because of improvements in systematic angiogenesis and the maturation of cardiac function in premature infants. Some authors have reported that ACS administration may play a significant role in the maturation of premature hearts [22, 23] and the cerebral vasculature [24]. Further studies are needed to determine the mechanisms underlying the effects of ACS on the systemic circulation in premature infants.

The second analysis undertaken in this study anticipated that the delivery method may be associated with infant outcomes. When pregnancies are associated with complications, including IUGR, severe pregnancy-induced hypertension, clinical chorioamnionitis and preterm deliveries, CS is the likely delivery option. Furthermore, ACS is more likely to be administered in complicated pregnancies when CS deliveries are anticipated. In the current study, the gestational week of delivery was significantly later, and the rates of IUGR and ACS were significantly higher in the CS group compared with the VD group (table 3). These selection biases should be considered in the analysis. Several reports have suggested that CS deliveries are associated with improvements in mortality and morbidity in preterm infants [6–9]. The increased incidence of CLD irrespective of the delivery method may be associated with improvements in neonatal prognoses overall, as discussed previously in the context of the first analysis. With regard to the association between the mode of delivery and the incidence of RDS in our study, this result should be interpreted prudently because the study data included both complete and incomplete courses of ACS, and data concerning the timings of ACS administration and the doses administered were not available, as discussed previously. Although it is unclear how ACS affects outcomes in relation to the mode of delivery, our results suggest that obstetric intervention may influence the morbidity of VLBW infants. As pointed out in a previous report [12], CS delivery may be associated with the improved survival of preterm SGA (small-for-gestational-age) neonates, which suggests that VD is stressful for physiologically vulnerable SGA neonates. The data from this study and previous reports [6–9] suggest that CS delivery may be preferable for VLBW infants, especially when they weigh less than 800–1,300 g or have a gestational age of 24–26 weeks, or if there is IUGR and the fetus is aged less than 30 weeks. However, it remains unclear whether CS delivery is directly associated with reduced stress and trauma compared with VD, and tertiary care centers in Japan have not developed guidelines regarding selection of mode of delivery for VLBW infants. Physicians have to select the optimal delivery method while taking into account the multiple variables associated with a preterm birth, which include fetal status and vulnerability, the mother's condition, the infant's morbidity or mortality and the potential for long-term disabilities, as well as their institution, in an effort to avoid unnecessary CS. Therefore, improvements in the technologies to support very small and premature infants have to be accompanied by changes in treatment practices during premature deliveries. In this study, we reported the importance of optimizing the obstetric management of immature infants, and we hope that future advances in obstetric management will improve infant mortality and morbidity rates. More clinical evidence regarding ACS treatment will be available from the NRN database in Japan in the future.

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Utility of Intraoperative Fetal Heart Rate Monitoring for Cerebral Arteriovenous Malformation Surgery during Pregnancy

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Abstract

We report two methods of intraoperative fetal heart rate (FHR) monitoring in cases of cerebral arteriovenous malformation surgery during pregnancy. In one case in her third trimester, cardiotocography was used. In another case in her second trimester, ultrasound sonography was used, with a transesophageal echo probe attached to her lower abdomen. Especially, the transesophageal echo probe was useful because of the advantages of being flexible and easy to attach to the mother's lower abdomen comparing with the usual doppler ultrasound probe. In both cases, the surgery was successfully performed and FHR was monitored safely and stably. The use of intraoperative FHR monitoring provides information about the influence of induced maternal hypotension and unexpected bleeding on fetus during surgery. These monitoring techniques would be especially emphasized in cerebrovascular surgery for the safe management of both mother and fetus.

Key words: arteriovenous malformation, pregnancy, fetal heart rate monitoring

Introduction

Intracranial hemorrhage due to rupture of a cerebral arteriovenous malformation (AVM) during pregnancy, although rare, is associated with significant maternal and fetal mortality and morbidity.[1)] Several studies have reported an increased rebleeding rate during the course of pregnancy and it is considered desirable to remove the AVM, if possible.[2,3)] While performing surgery for AVM during pregnancy, monitoring the fetal heart rate (FHR) is important to avoid uterine and placental hypoperfusion and fetal asphyxia. Although many cases of neurosurgery during pregnancy have been reported, the reference of intraoperative FHR monitoring was in few reports of brain tumor.[4,5)] So, we describe the role of intraoperative FHR monitoring in two cases of maternal AVM surgery at different stages of pregnancy, and additionally in cerebrovascular surgery.

Illustrative Cases

I. Case 1

A healthy 27-year-old woman (gravida 1, para 1) presented with sudden right hemiparesis and sensory aphasia at 25th week of gestation. Computed tomography (CT) and magnetic resonance imaging (MRI) revealed an intracerebral hemorrhage in the left parietal lobe (Fig. 1A). Given the mild neurological symptoms, emergency removal of the hematoma was not indicated. Obstetrically, there was no indication for pregnancy termination. At 27th week of gestation, cerebral angiography revealed a left parietal AVM of Spetzler and Martin grade 2 (Fig. 1B). AVM removal was judged necessary on a neurosurgical indication to avoid the risk of rebleeding during pregnancy. As the fetus was not mature enough for extra-uterine life, we performed AVM removal at 30 weeks of gestation with the patient's consent. The patient was operated on under general anesthesia in the supine position with her abdomen slightly turned to left for the prevention of supine hypotensive syndrome. Anesthesia was induced with rocuronium 50 mg i.v., propofol 100 mg i.v., fentanyl 0.2 mg i.v., and maintained with propofol 1–4 mg/kg/h, remifentanyl 0.15–0.30 μg/kg/min, and 0.5–1.2% sevoflurane in oxygen. During the operation, the fetal status was monitored using cardiotocography (CTG) (Fig. 2A). The obstetrics team was prepared for an emergency cesarean section

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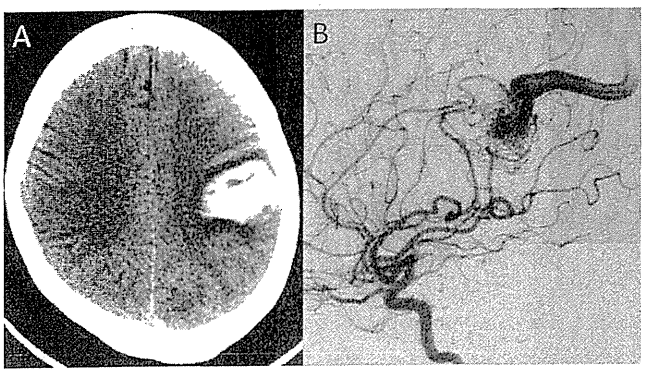

Fig. 1 Case 1: A: Computed tomography scan showing a left parietal intraparenchymal hematoma. B: Digital subtraction angiogram showing a grade 2 left parietal arteriovenous malformation.

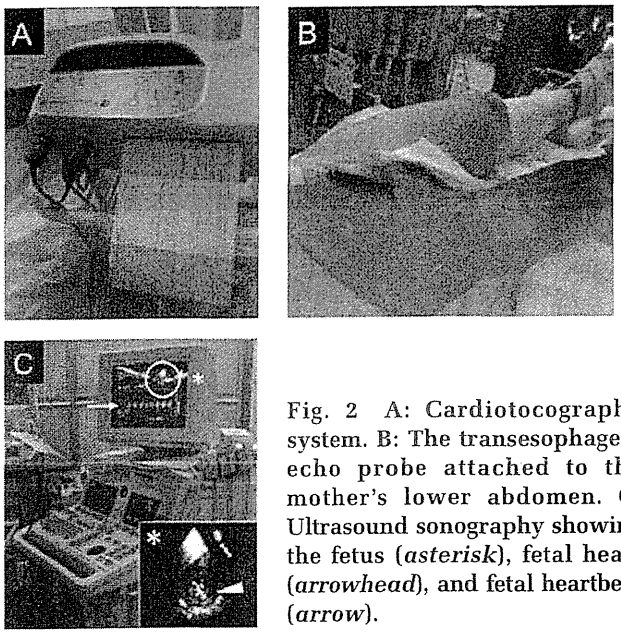

Fig. 2 A: Cardiotocography system. B: The transesophageal echo probe attached to the mother's lower abdomen. C: Ultrasound sonography showing the fetus (*asterisk*), fetal heart (*arrowhead*), and fetal heartbeat (*arrow*).

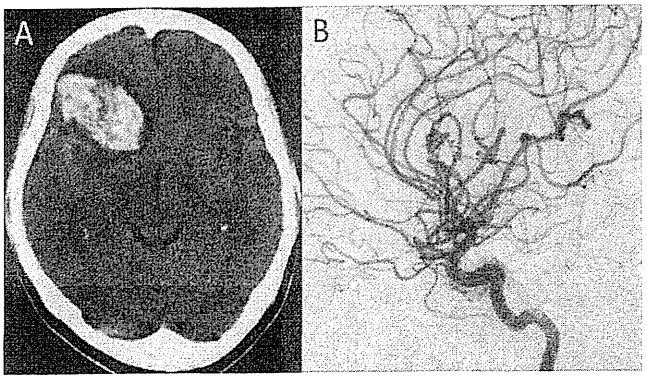

Fig. 3 Case 2: A: Computed tomography scan showing a right frontal intraparenchymal hematoma. B: Digital subtraction angiogram showing a grade 1 right frontal arteriovenous malformation.

in the same operating room. The patient's systolic blood pressure (SBP) was maintained between 90 and 100 mmHg during surgery, and the lowest SBP was 82 mmHg during the resection of the nidus by deliberate depression of maternal blood pressure. Her uterine contraction was restrained by anesthetic agents. The FHR remained between 130 and 140 beat per minute (bpm) and FHR variability decreased less than 6 bpm throughout the operation. The FHR decreased between 5 and 10 bpm under general anesthesia compared to pre-operative value. The surgery was completed without any problems. The amount of blood loss was 560 ml. The patient showed a slight right sensory disturbance, but the symptom improved rapidly. The remaining course of the pregnancy was favorable, and the patient successfully delivered via spontaneous vaginal delivery with epidural anesthesia in the 40th week of gestation.

II. Case 2

A 34-year-old woman (gravida 1, para 1) was admitted to our hospital in the 16th week of gestation because of sudden left hemiparesis. CT and MRI revealed an intracerebral hemorrhage in the right frontal lobe. Cerebral angiography showed a right frontal AVM of Spetzler and Martin grade 1 on the same day (Fig. 3A, B). The mother wished to continue the pregnancy and consented to the AVM resection. The surgery was performed in the 18th week of gestation. General anesthesia was induced with rocuronium 50 mg i.v., thiopental 250 mg i.v., fentanyl 0.2 mg i.v., and maintained with remifentanyl 0.20–0.25 μg/kg/min, and 1.0–1.5% sevoflurane in oxygen. During the procedure, FHR was directly monitored using ultrasonography, with a transesophageal echo probe attached to the mother's lower abdomen (Fig. 2B, C). The patient's SBP was maintained between 90 to 100 mmHg during surgery, and the lowest SBP was 84 mmHg during the resection of the nidus. Her oxygenation level was good and no fetal bradycardia occurred during surgery. The FHR remained between 150 and 160 bpm throughout the perioperative period. The surgery was completed without any problems. The amount of blood loss was only 200 ml. The mother complained of no new abnormal neurological symptom. The remaining course of the pregnancy was favorable, and a cesarean section was performed in the 40th week of pregnancy because of macrosomia and a history of cesarean section.

Discussion

The prevalence of AVM is estimated at 0.01–0.50%

of the population.[6,7] AVM is generally present in patients aged between 20 years and 40 years, and especially in those over 30 years, which is a childbearing age for women. AVM rupture during pregnancy is associated with maternal mortality of 28% and fetal mortality of 14%.[1] The implication of pregnancy in AVM rupture is controversial, but the bleeding rate appears to increase up to three-fold.[1–3,8] Although the rebleeding rate during the first year in the natural course of a ruptured AVM varied from 6% to 15.8%, the frequency of rebleeding during the same pregnancy could be as high as 27%.[3,9] Moreover, in a recent report by Gross and Du, the annual hemorrhage rate during pregnancy was 10.8%, the hemorrhage rate per pregnancy was 8.1%, and the hazard ratio for intracerebral hemorrhage during pregnancy was 7.91.[10] In view of these very high rates, cases of AVM in pregnant women should be treated with great care.

Here, we described the role of intraoperative FHR monitoring in two cases of elective surgery for AVM presenting with intracerebral hemorrhage at different stages of pregnancy. Although radical treatment for ruptured AVM tended to be performed after delivery in many case reports and case series, early surgical intervention for patients with an immature fetus before delivery would lead to improved maternal and fetal prognosis if the surgical risk is low.[3,11–13] The indication of surgery for AVM is determined primarily by the Spetzler-Martin grading scale.[14,15] The removal of AVM was supposed to be completed safely in our cases because the AVM grade was low. However, one of the anxieties for neurosurgeon is about fetal well-being during perioperative period. Although many cases of neurosurgery during pregnancy have been reported, the reference of intraoperative FHR monitoring was in few reports of brain tumor.[4,5] FHR monitoring is important for the assessment of reassuring fetal status in the antepartum as well as intrapartum stage.[16–18] Several reports have recommended continuous intraoperative FHR monitoring if non-obstetric surgery is performed after the 16th week of pregnancy.[19–22] Prolonged deceleration or bradycardia caused by maternal hypoperfusion, maternal hypoxia, compression of the umbilical cord, or the depression of the fetal cardiovascular system by anesthetic agents reflects a decreased uterine and placental circulation that can result in fetal asphyxia, acidosis, and death.[4,19] Loss of FHR variability does not always indicate fetal distress under general anesthesia because it may occur by the effect of anesthetic agents on the fetal autonomic nervous system.[19,23] Unexpected intraoperative bleeding or induced maternal hypotension would lead to the risk of mother and fetus during cerebrovascular surgery, especially in the timing as resection of AVM or clipping of cerebral aneurysm.[24,25] A mean arterial pressure of < 70 mmHg or a reduction in systolic arterial pressure of 25–30% is sufficient to reduce utero-placental blood flow.[23] We can adjust the maternal blood pressure, maternal oxygenation, and anesthetic agents as soon as possible if FHR abnormality occurs. Nevertheless, cesarean section is required unless the fetal distress improves. Our indication for emergency cesarean section is the incidence of prolonged deceleration or bradicardia with < 80 bpm for 2 minutes, based on the framework by Parer and Ikeda.[16] This value is correlated with the lower limit thresholds of pH 7.1 and base excess of −12 mEq/L in umbilical arterial blood, which indicates the fetal hypoxic damage. In these circumstances, FHR monitoring can be especially valuable for cerebrovascular surgery.

In the third trimester, CTG is widely used to monitor the FHR for fetal well-being. Being safe, easy, and quick, CTG has become very popular. In our case, the patient was in the supine position and her abdomen was left unobstructed so that emergent cesarean section could be performed if fetal asphyxia was suspected. In the second trimester, the transesophageal echo probe was useful because of the advantages of being flexible and easy to attach to the mother's lower abdomen comparing with the usual doppler ultrasound probe. Both these approaches allowed easy, stable, and successful FHR monitoring. The problem associated with FHR monitoring in the late stage of pregnancy is the movement of the fetus. The CTG sensor would have to be repositioned when the fetus moves. However, fetal movement tends to be reduced under general anesthesia as our first case.[26] The problem with FHR monitoring in the early stage of pregnancy is that the fetus cannot be rescued directly when non-reassuring fetal status is suspected. In addition, the usefulness of intraoperative FHR monitoring during pregnancy is controversial, because no large systematic study has been conducted. Maternal anesthesia may decrease the baseline FHR and variability.[19,23] Misinterpretation of FHR data could result in interventions that endanger the fetus, such as an unnecessary cesarean section.[27] So, a trained obstetrician team is needed to read it and prepare for an urgent cesarean delivery during surgery.[28] Horrigan et al. reviewed that no fetal hypoxic condition has been documented without the occurrence of a maternal hypoxic complication, whether FHR monitoring is used or not.[29] Balki and Manninen reported a successful craniotomy for suprasellar meningioma in a 28-week pregnant woman who suffered from rapidly deteriorating