Questionnaire

Intracerebral hemorrhage during pregnancy or that occurring within one year after delivery. Cases from January to December 2006 should be included.

| | |
|---|---|
| Years at onset | Years old |
| Previous delivery (over 22 weeks) | ( ) times |
| Delivery (weeks) of current pregnancy | Abortion (<22 weeks), Preterm (22-36 weeks), Full term (37-42 weeks) |
| Onset time | During pregnancy, Intrapartum, Within 24 h after delivery, Postpartum 1 to 42 days, Postpartum 43 days to 1 year |
| Delivery mode | Vaginal, Cesarean section, No delivery |
| Prognosis (Neonate) | Alive, Neonatal death, Still birth |
| Complications | PIH, Hypertension, DM, Hyperlipidemia, Smoking, Cardiovascular disease, Af, Arrhythmia, Deep vein thrombosis, APS, Habitual abortion, Headache |
| Type of cerebrovascular disease | TIA, Cerebral Infarction, Intracerebral hemorrhage [Category] Intraparenchymal hemorrhage, intraventricular hemorrhage, subarachnoid hemorrhage, subdural hemorrhage [Causes] Hypertension, AVM, aneurysm, Moyamoya disease, pre-eclampsia, vein sinus thrombosis |
| Diagnosed by | CT, MRI, Angiography, MRA |
| First symptoms | Headache, nausea, paralysis, seizure, consciousness disturbance, visual disturbance, speech disturbance |
| Place of first symptoms | Out of / In hospital |
| Department that first admitted the patient | Obstetrics and Gynecology, Internal Medicine, Neurosurgery, Emergency |
| Department that finally treated the patient | Obstetrics and Gynecology, Internal Medicine, Neurosurgery, Emergency |
| Onset to diagnosis time | Within 3 h, 3-24 h, More than 24 h |
| Patient JCS on arrival at your hospital | I-1, I-2, I-3, II-10, II-20, II-30, III-100, III-200, III-300, |
| At admission to hospital | Modified Rankin scale (0,1,2,3,4,5,6) Transferred to another hospital in the acute phase |

**Figure 1** Questionnaire. Intracerebral hemorrhage during pregnancy or that occurring within 1 year after delivery. Cases from January to December 2006 should be included. Af, atrial fibrillation; APS, antiphospholipid–antibody syndrome; AVM, arteriovenous malformation; CT, computed tomography; DM, diabetes mellitus; JCS, Japan Coma Scale; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; PIH, pregnancy-induced hypertension; TIA, transient ischemic attack.

and occurred mostly in the antepartum period, especially in the third trimester. Cesarean section was performed in 63.2% of women with ICH in the antepartum or intrapartum period. One stillbirth following maternal death was identified. In this case, putaminal hemorrhage occurred at 40 weeks of gestation. Eight premature live deliveries were identified. The condition of these infants is unknown as long-term follow-up was not performed due to the short observation period. The clinical features included headache in 22 cases, seizures in nine, and disturbance of consciousness in 26.

Pre-existing disorders and risk factors are shown in Table 2. Pre-eclampsia was identified in 10 cases (26.3%) and hemolysis elevated liver enzymes and low platelet count (HELLP) syndrome was present in five cases. Death occurred in four of the 10 cases with pre-eclampsia and in three of the four cases in which HELLP syndrome developed among cases of pre-eclampsia. HELLP syndrome occurred without prior pre-eclampsia in two cases, which resulted in one death and one case of subsequent severe disability in which the patient was bedridden. Three of the five cases of HELLP syndrome were diagnosed later than 3 h after onset of the disease. Thus, there is a possibility that a confounding factor (O–D time) could have influenced the outcome of ICH in these cases. Moyamoya disease occurred in four cases (10.5%) and arteriovenous malformation (AVM) was found in seven (18.4%). There were no pre-existing disorders in 16 (42.1%) of the cases of pregnancy-associated ICH. Collectively, these numbers reflect three cases with both pre-eclampsia and HELLP syndrome and one with pre-eclampsia and AVM (Table 2).

The relation between the consciousness disturbance level at onset and outcome was clear, with greater consciousness disturbance leading to a poor outcome (Table 3). The O–D time was also associated with the outcome. The survival rate was >90% for patients diagnosed within 3 h from onset of bleeding, although permanent moderate or severe disability remained in 68.2% of survivors (Table 3). The majority of patients ($n = 28$) first consulted (or were transferred to) a department of obstetrics. Of these patients, 21 (75%) were subsequently transferred to a neurosurgery department. Overall, 32 of the 38 patients were finally treated in neurosurgery. The O–D time in the 21 transferred patients was similar regardless of the location of the initial examination. Fourteen of these patients underwent surgery and this tended to be more common in patients who were first examined by

**Table 1** Baseline demographics and clinical characteristics of peripartum ICH patients

| Item | Value |
|---|---|
| Age (years, mean ± SD) | 31.5 ± 5.1 |
| Parity (primipara/multipara) | 26/12 |
| Gestational age at onset (mean, weeks) | 32.4 |
| Timing of onset in gestation | |
| Antepartum | 21 (55.2) |
| 1st, 2nd, 3rd trimester | 0, 7, 14 |
| Intrapartum | 7 (18.4) |
| Postpartum | 10 (26.3) |
| Mode of delivery | |
| Cesarean section | 24 (63.2) |
| Vaginal delivery | 14 (36.8) |
| Prognosis of newborn | |
| Alive | 37 (97.3) |
| Stillbirth | 1 (2.6) |
| Newborn death | 0 |
| Initial symptoms | |
| Headaches | 22 (58.0) |
| Nausea/vomiting | 4 (10.5) |
| Convulsion | 9 (23.7) |
| Disturbed consciousness | 25 (65.8) |
| Visual disturbance | 3 (7.9) |
| Paralysis | 9 (23.7) |

Values are shown as *n* (%). ICH, intracerebral hemorrhage.

**Table 2** Pre-existing disorders and Modified Rankin scale†

| | | Modified Rankin Scale§ | | |
|---|---|---|---|---|
| | Total (%)‡ | 0–2 | 3–5 | 6 |
| Pre-eclampsia | 10 (26.3) | 3 (30) | 3 (30) | 4 (40) |
| HELLP syndrome | 5 (13.2) | 0 (0) | 1 (20) | 4 (80) |
| Arteriovenous malformation | 7 (18.4) | 2 (28.6) | 4 (57.1) | 1 (14.3) |
| Moyamoya disease | 4 (10.5) | 1 (25) | 3 (75) | 0 (0) |
| No pre-existing disorder | 16 (42.1) | 9 (56.3) | 5 (31.3) | 2 (12.5) |

†Values are shown as *n* (%). ‡Percentage of all ICH cases, including three cases with pre-eclampsia and HELLP syndrome and one case with arteriovenous malformation and pre-eclampsia. §Modified Rankin Scale 0–2: good outcome, 3–5: poor outcome, 6: death. HELLP, hemolysis elevated liver enzymes and low platelet count.

**Table 3** Outcome based on consciousness disturbance at the onset of ICH or O–D time in patients who did and did not undergo neurosurgery†

| | | Neurosurgery | | Modified Rankin Scale‡ | | |
|---|---|---|---|---|---|---|
| | | | | 0–2 | 3–5 | 6 |
| Consciousness disturbance | None to mild | Yes | 17 | 2 (11.8) | 11 (64.7) | 4 (23.5) |
| | | No | 2 | 1 (50.0) | 0 (64.7) | 1 (50.0) |
| | Moderate to severe | Yes | 7 | 5 (71.4) | 2 (28.5) | 0 (0) |
| | | No | 12 | 9 (75.0) | 1 (8.3) | 2 (16.7) |
| O–D time | <3 h | Yes | 17 | 3 (17.6) | 14 (82.4) | 0 (0) |
| | | No | 7 | 4 (57.1) | 1 (14.3) | 2 (28.6) |
| | ≥3 h | Yes | 7 | 2 (28.6) | 1 (14.3) | 4 (57.1) |
| | | No | 5 | 4 (80.0) | 0 (0) | 1 (20.0) |

†Values are shown as *n* (%). ‡Modified Rankin scale 0–2: good outcome, 3–5: poor outcome, 6: death. ICH, intracerebral hemorrhage; O–D time, interval between onset and diagnosis.

**Table 4** Patient characteristics that are associated with mortality in pregnancy-associated ICH

| Item | Odds ratio (95%CI) | |
|---|---|---|
| | For poor outcome† | For death |
| Age ≥35 years old | 0.8 (0.2–3.4) | 2.2 (0.4–11.8) |
| Pre-eclampsia | 2.0 (0.4–9.5) | 5.6 (1.0–31.7) |
| HELLP syndrome | 21.5 (1.1–424.4) | 40.0 (3.3–483.7) |
| Moderate to severe disturbed consciousness‡ | 3.6 (1.7–7.8) | 0.8 (0.6–1.1) |
| O–D time ≥3 h | 0.4 (0.1–1.6) | 6.1 (1.0–37.5) |
| Neurosurgery | 0.8 (0.2–3.0) | 0.4 (0.1–1.9) |

Univariate logistic regression analysis was performed. †Poor outcome was defined as a modified Rankin scale score ≥3 (including 6, death). ‡Moderate to severe disturbed consciousness defined as JCS II-III. CI, confidence interval; HELLP, hemolysis elevated liver enzymes and low platelet count; ICH, intracerebral hemorrhage; O–D time, interval between onset and diagnosis.

a neurosurgeon. The outcome was poorer in women who were initially examined in a department of obstetrics. Neurosurgeries were performed in 26 cases, including four with pre-eclampsia, one with HELLP syndrome, seven with AVM, three with Moyamoya disease, and 14 with no pre-existing disorders. In most of these cases, the operation was either removal of the hematoma or drainage from the lateral ventricles. In AVM cases, the operation included removal of the AVM vessels. Treatment at a department of neurosurgery also tended to improve survival in severe cases of ICH based on classification by the consciousness level at the onset of the disease. However, severe disability persisted in survivors. Treatment at a department of neurosurgery also improved survival in cases with an earlier diagnosis, although still resulted in severe disability, but had no effect in those with a delayed diagnosis.

The odds ratios for each risk factor for poor outcome and mortality are shown in Table 4. HELLP syndrome and moderately or severely disturbed consciousness at onset of the disease was significantly associated with a poor outcome (mRS ≥3). Pre-eclampsia, HELLP syndrome and an O–D time >3 h were significantly associated with maternal mortality.

## Discussion

There are few data that specifically address pregnancy-associated ICH in Japan and this is the first nationwide study to examine the current status of this condition. The study covered all regions in Japan and more than 70% of facilities responded to our survey, which supports the reliability of the findings. The reported incidence of pregnancy-associated ICH is 3.8 to 18.1 per 100 000 deliveries[3,4,12–16] and the mortality rate is 9–38%,[2–6] both of which are consistent with the results of the current study. The mortality rate of ICH in pregnancy was higher than that in an age-matched

population of women who were not pregnant, based on vital statistics of the MHLW in Japan, but the difference was not significant. Ronsman *et al.*[17] described a 'healthy pregnant women effect' in a report on maternal death in the United Kingdom,[18] based on the observation that mortality during pregnancy or within 1 year after birth was four to five times lower than mortality in women without a recent pregnancy. Using the 2006 MHLW vital statistics, the mortalities of women with and without pregnancy were 5.1 and 47.7 per 100 000 in 2006. Thus, the 'healthy pregnant women effect' was even more evident in Japan. The finding that mortality from ICH was statistically equal in pregnant and non-pregnant women indicates that this effect does not apply in ICH.

The current study showed some differences in the cause of pregnancy-associated ICH compared with previous reports. We found that more primiparous women had ICH in Japan, in contrast to previous studies,[3,6] showing that the majority of pregnancy-associated ICH occurred in multiparous women. Another difference with these studies was the timing of ICH. In the current study, the antepartum rate of ICH was higher than the postpartum rate, but these rates were similar or higher than postpartum rates in other studies of risk factors for ICH.[3,4,12]

The rates of eclampsia or pre-eclampsia reported in patients with ICH have ranged from 14% to 50%.[3,4,14,15] We found a similar rate of 26.3% in patients with pregnancy-associated ICH. The mortality of ICH with pre-eclampsia followed by HELLP syndrome was higher than that of ICH without pre-eclampsia or HELLP syndrome. Horton *et al.*[19] found that 45% of maternal deaths due to HELLP syndrome were associated with cerebral hemorrhage. A JCS of III-300 was present at the onset of disease in three women with HELLP syndrome. Thus, the current findings confirm that HELLP syndrome complicated by ICH is associated with a poor maternal outcome. We speculate that in addition to hypertension, a decrease in platelet count or coagulation factors and endothelial dysfunction of the cerebral vasculature contribute to the high mortality of ICH with HELLP syndrome. However, as mentioned above, it should be noted that an influence of delayed diagnosis on the outcome of ICH with HELLP syndrome could not be eliminated.

It remains uncertain whether pregnancy increases the risk of rupture in pre-existing AVM.[12,19] In the current study, the incidence of AVM in pregnancy-associated ICH was lower than that of 20–67% found in other reports.[12] However, this was still the second most frequent risk cause and was also associated with a poor morbidity. Thus, AVM is an important risk factor in pregnancy-associated ICH. We also expected that a higher incidence of Moyamoya disease would influence the incidence of pregnancy-associated ICH, which is mainly caused by hemodynamic stress on fragile Moyamoya vessels. We found that 10.5% of cases with pregnancy-associated ICH had Moyamoya disease, which confirms that Moyamoya disease modifies the characteristics of pregnancy-associated ICH in Japan.

Consciousness at the onset of disease was found to be an important factor in the outcome of ICH. This factor did not influence mortality, but did affect morbidity in our study. O–D time was another important factor, with an increased mortality rate associated with a diagnosis made later than 3 h after onset of ICH. However, the functional outcome was also poor even if the diagnosis was made within 3 h after onset. In the current study, the majority of women with pregnancy-associated ICH initially presented to a department of obstetrics. In particular, all patients with pre-eclampsia were initially examined by obstetricians, and a substantial percentage of all the patients with ICH had pre-eclampsia. Pre-eclampsia can be followed by eclampsia, which shows similar clinical features to those in ICH: convulsion, headaches, and disturbed consciousness. Eclampsia is also more common than ICH and greater familiarity with the disease may have caused many physicians to consult with obstetricians for cases with pre-eclampsia. Many maternity centers in Japan do not have CT or MRI facilities and this may be a limitation in an initial examination made by an obstetrician.

One limitation in the current study was that multivariate regression analysis could not be performed because of the small number of subjects. We classified the subgroups of risk factors into two (consciousness level at onset of ICH and O–D time) that significantly influenced the outcome of patients. However, the influence of confounding factors could not be eliminated.

In summary, we found a mortality rate of 18.4% in 38 patients with pregnancy-associated ICH. This rate was higher than our initial expectations and we did not observe a 'healthy pregnant effect' in women with pregnancy-associated ICH. Early diagnosis may prevent maternal death, even in severe cases of ICH, but survivors still had neurological disabilities. For diagnosis of ICH, imaging such as CT or MRI is the most prompt and accurate diagnostic tool. In this decade, regional maternal–fetal care centers have been established in Japan and the perinatal care network has

become more sophisticated by placing the regional maternal–fetal care center at the core of the network. However, these centers do not always have full-time neurosurgeons or imaging tools for ICH diagnosis. Therefore, another network is required to link maternity centers with departments of neurosurgery that have CT or MRI available at all times. Pregnant women with neurological symptoms could then be transferred to regional facilities that are suitable for management of such patients.

## Acknowledgments

This work was supported by the Ministry of Health, Labor and Welfare of Japan, H18-children-general-006. We would like to thank Dr Akiko Kada for statistical support.

## Disclosure

None of the authors has a financial or other conflict of interest regarding the contents of this study.

## References

1. Minematsu K, Yamaguchi T. Management of intracerebral hemorrhage. In: Fisher M (ed.). *Stroke Therapy*, 2nd edn. Boston: Butterworth Heinemann, 2001; 287–299.
2. Awada A, Al Rajeh S, Duarte R, Russell N. Stroke and pregnancy. *Int J Gynaecol Obstet* 1995; **48**: 157–161.
3. Sharshar T, Lamy C, Mas JL. Incidence and causes of strokes associated with pregnancy and puerperium. A study in public hospitals of Ile de France. Stroke in Pregnancy Study Group. *Stroke* 1995; **26**: 930–936.
4. Jaigobin C, Silver FL. Stroke and pregnancy. *Stroke* 2000; **31**: 2948–2951.
5. Hu HH, Sheng WY, Chu FL, Lan CF, Chiang BN. Incidence of stroke in Taiwan. *Stroke* 1992; **23**: 1237–1241.
6. Liang CC, Chang SD, Lai SL, Hsieh CC, Chueh HY, Lee TH. Stroke complicating pregnancy and the puerperium. *Eur J Neurol* 2006; **13**: 1256–1260.
7. Nagaya K, Fetters MD, Ishikawa M *et al.* Causes of maternal mortality in Japan. *JAMA* 2000; **283**: 2661–2667.
8. Kubo M, Kiyohara Y, Kato I *et al.* Trends in the incidence, mortality, and survival rate of cardiovascular disease in a Japanese community: The Hisayama study. *Stroke* 2003; **34**: 2349–2354.
9. Kuroda S, Houkin K. Moyamoya disease: Current concepts and future perspectives. *Lancet Neurol* 2008; **7**: 1056–1066.
10. Rankin J. Cerebral vascular accidents in patients over the age of 60. *Scott Med J* 1957; **2**: 200–215.
11. Ohta T, Kikuchi H, Hashi K, Kudo Y. Nozofenone administration in the acute stage following subarachnoid hemorrhage. *J Neurosurg* 1986; **64**: 420–426.
12. Bateman BT, Schumacher HC, Bushnell CD *et al.* Intracerebral hemorrhage in pregnancy: Frequency, risk factors, and outcome. *Neurology* 2006; **67**: 424–429.
13. Simolke GA, Cox SM, Cunningham FG. Cerebrovascular accidents complicating pregnancy and the puerperium. *Obstet Gynecol* 1991; **78**: 37–42.
14. Salonen Ros H, Lichtenstein P, Bellocco R, Petersson G, Cnattingius S. Increased risks of circulatory diseases in late pregnancy and puerperium. *Epidemiology* 2001; **12**: 456–460.
15. Jeng JS, Tang SC, Yip PK. Incidence and etiologies of stroke during pregnancy and puerperium as evidenced in Taiwanese women. *Cerebrovasc Dis* 2004; **18**: 290–295.
16. James AH, Bushnell CD, Jamison MG, Myers ER. Incidence and risk factors for stroke in pregnancy and the puerperium. *Obstet Gynecol* 2005; **106**: 509–516.
17. Khlat M, Ronsmans C. Deaths attributable to childbearing in Matlab, Bangladesh: Indirect causes of maternal mortality questioned. *Am J Epidemiol* 2000; **151**: 300–306.
18. Ronsmans G, Lewis G, Hurt L, Physick N, Macfarlane A, Abrahams C. Mortality in pregnant women in England and Wales 1997–2002: Are pregnant women healthy. In: Lewis G (ed.). *Why Mothers Die 2000–2001*, 6th edn. London: RCOG Press at the Royal College of Obstetricians and Gynecologists, 2004; 272–278.
19. Horton JC, Chambers WA, Lyons SL, Adams RD, Kjellberg RN. Pregnancy and the risk of hemorrhage from cerebral arteriovenous malformations. *Neurosurgery* 1990; **27**: 867–871.

Original Paper

Neonatology

Neonatology 2014;106:81–86
DOI: 10.1159/000358189

Received: August 14, 2013
Accepted after revision: December 23, 2013
Published online: May 10, 2014

# 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

Yoshihito Sasaki[a] Tomoaki Ikeda[b] Kunihiro Nishimura[c] Shinji Katsuragi[d] Kazuo Sengoku[e] Satoshi Kusuda[f] Masanori Fujimura[g]

[a]Department of Neonatology, Otsu Red Cross Hospital, Otsu, [b]Department of Obstetrics and Gynecology, Mie University, Tsu, Departments of [c]Preventive Medicine and Epidemiology and [d]Perinatology and Gynecology, National Cerebral and Cardiovascular Center, Suita, [e]Department of Obstetrics and Gynecology, Asahikawa Medical University, Asahikawa, [f]Department of Neonatology, Tokyo Women's Medical University, Tokyo, and [g]Department of Neonatology, Osaka Medical Center and Research Institute for Maternal and Child Health, Izumi, Japan

**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

KARGER


1661–7800/14/1062–0081$39.50/0

E-Mail karger@karger.com
www.karger.com/neo

Yoshihito Sasaki, MD, PhD
Department of Neonatology
Otsu Red Cross Hospital
1-1-35 Nagara, Otsu 520-8511 (Japan)
E-Mail yosasaki@otsu.jrc.or.jp

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.

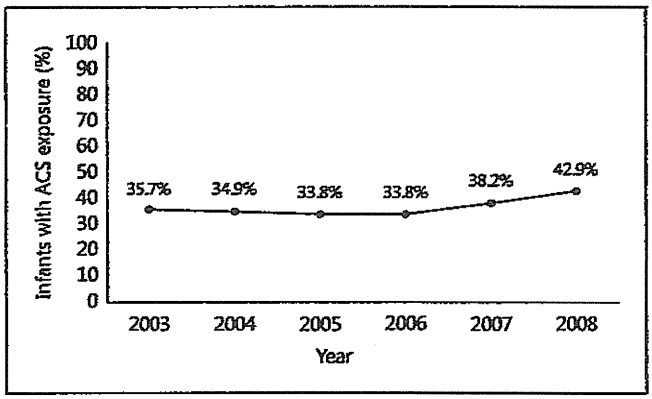


**Fig. 1.** Frequency of exposure to ACS by year of birth.

**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.


## Acknowledgements

My heartfelt appreciation goes to Kaoru Ishikawa, Yoshihiro Miyamoto, Akira Miyazaki, Akihiko Kai, Hiroshi Ishikawa, Kazutoshi Hayashi and Rintaro Mori, whose comments and suggestions were of inestimable value to my study and to the subsequent publication.

## References


1 National Institutes of Health: Report of the consensus development conference on the effect of corticosteroids for fetal maturation on perinatal outcomes. Bethesda, US Department of Health and Human Services, National Institutes of Health, 1994, pub. No. 95-3784.

2 Roberts D, Dalziel S: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev 2006;3:CD004454.

3 Miracle X, Di Renzo GC, Stark A, Fanaroff A, Carbonell-Estrany X, Saling E, Coordinators of WAPM Prematurity Working Group: Guideline for the use of antenatal corticosteroids for fetal maturation. J Perinat Med 2008; 36:191–196.

4 Kusuda S, Fujimura M, Sakuma I, Aotani H, Kabe K, Itani Y, et al: Morbidity and mortality of infants with very low birth weight in Japan: center variation. Pediatrics 2006;118: e1130–e1138.

5 Mori R, Kusuda S, Fujimura M, Neonatal Research Network Japan: Antenatal corticosteroids promote survival of extremely preterm infants born at 22 to 23 weeks of gestation. J Pediatr 2011;159:110–114.

6 Lee HC, Gould J: Survival advantage associated with cesarean delivery in very low birth weight vertex neonates. Obstet Gynecol 2006; 107:97–105.

7 Bottoms SF, Paul RH, Mercer BM, MacPherson CA, Caritis SN, Moawad AH, et al: Obstetric determinants of neonatal survival: antenatal predictors of neonatal survival and morbidity in extremely low birth weight infants. Am J Obstet Gynecol 1999;180:665–669.

8 Wilson-Costello D, Friedman H, Minich N, Siner B, Taylor G, Schluchter M, et al: Improved neurodevelopmental outcomes for extremely low birth weight infants in 2000–2002. Pediatrics 2007;119:37–45.

9 Malloy MH: Impact of cesarean section on neonatal mortality rates among very preterm infants in the United States, 2000–2003. Pediatrics 2008;122:285–292.

10 Durie DE, Sciscione AC, Hoffman MK, Mackley AB, Paul DA: Mode of delivery and outcomes in very low-birth-weight infants in the vertex presentation. Am J Perinatol 2011; 28:195–200.

11 Batton B, Burnett C, Verhulst S, Batton D: Extremely preterm infant mortality rates and cesarean deliveries in the United States. Obstet Gynecol 2011;118:43–48.

12 Lee HC, Gould JB: Survival rates and mode of delivery for vertex preterm neonates according to small- or appropriate-for-gestational-age status. Pediatrics 2006;118:e1836–e1844.

13 Stoll BJ, Hansen NI, Bell EF, Shankaran S, Laptook AR, Walsh MC, et al: Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. Pediatrics 2010;126:443–456.

14 Pietz J, Achanti B, Lilien L, Stepka EC, Mehta SK: Prevention of necrotizing enterocolitis in preterm infants: a 20-year experience. Pediatrics 2007;119:e164–e170.

15 Karna P, Muttineni J, Angell L, Karmaus W: Retinopathy of prematurity and risk factors: a prospective cohort study. BMC Pediatr 2005; 5:18.

16 Yinon Y, Mazkereth R, Rosentzweig N, Jarus-Hakak A, Schiff E, Simchen MJ: Growth restriction as a determinant of outcome in preterm discordant twins. Obstet Gynecol 2005; 105:80–84.

17 Garite TJ, Clark R, Thorp JA: Intrauterine growth restriction increases morbidity and mortality among premature neonates. Am J Obstet Gynecol 2004;191:481–487.

18 Darlow BA, Hutchinson JL, Henderson-Smart DJ, Donoghue DA, Simpson JM, Evans NJ, et al: Prenatal risk factors for severe retinopathy of prematurity among very preterm infants of the Australian and New Zealand Neonatal Network. Pediatrics 2005;115:990–996.

19 Choi SJ, Song SE, Seo ES, Oh SY, Kim JH, Roh CR: The effect of single or multiple courses of antenatal corticosteroid therapy on neonatal respiratory distress syndrome in singleton versus twin pregnancies. Aust NZ J Obstet Gynaecol 2009;49:173–179.

20 Turrentine MA, Wilson PD, Wilkins IA: A retrospective analysis of the effect of antenatal steroid administration on the incidence of respiratory distress syndrome in preterm twin pregnancies. Am J Perinatol 1996;13:351–354.

21 McEvoy C, Schilling D, Spitale P, Peters D, O'Malley J, Durand M: Decreased respiratory compliance in infants less than or equal to 32 weeks' gestation, delivered more than 7 days after antenatal steroid therapy. Pediatrics 2008;121:e1032–e1038.

22 Mizuno M, Takeba Y, Matsumoto N, Tsuzuki Y, Asoh K, Takagi M, et al: Antenatal glucocorticoid therapy accelerates ATP production with creatine kinase increase in the growth-enhanced fetal rat heart. Circ J 2010;74:171–180.

23 Arai M: Antenatal glucocorticoid therapy for fetal heart development. Circ J 2010;74:47–48.

24 Vinukonda G, Dummula K, Malik S, Hu F, Thompson CI, Csiszar A, et al: Effect of prenatal glucocorticoids on cerebral vasculature of the developing brain. Stroke 2010;41:1766–1773.

TECHNICAL NOTE doi: 10.2176/nmc.tn.2013-0359
Neurol Med Chir (Tokyo) 54, 819–823, 2014 Online April 23, 2014

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

Kenji FUKUDA,[1,2] Jun MASUOKA,[1] Shigeki TAKADA,[1] Shinji KATSURAGI,[3] Tomoaki IKEDA,[3] and Koji IIHARA[1]

*Departments of [1]Neurosurgery and [3]Perinatology and Gynecology, National Cerebral and Cardiovascular Center, Suita, Osaka; [2]Department of Neurosurgery, Faculty of Medicine, Fukuoka University, Fukuoka, Fukuoka*

## 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

Received November 27, 2013; Accepted January 13, 2014

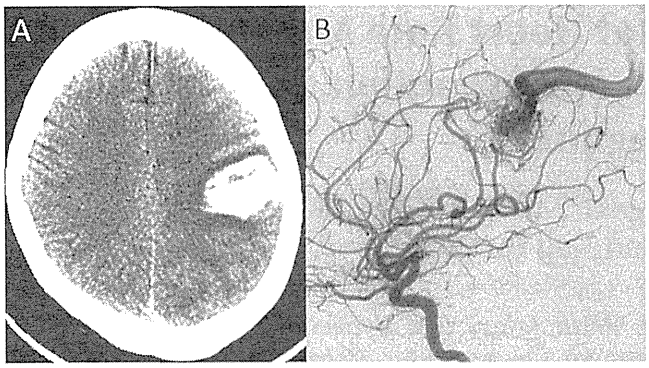


**Fig. 1 Case 1: A: Computed tomography scan showing a left parietal intraparenchymal hematoma. B: Digital subtraction angiogram showing a grade 2 left parietal arteriovenous malformation.**

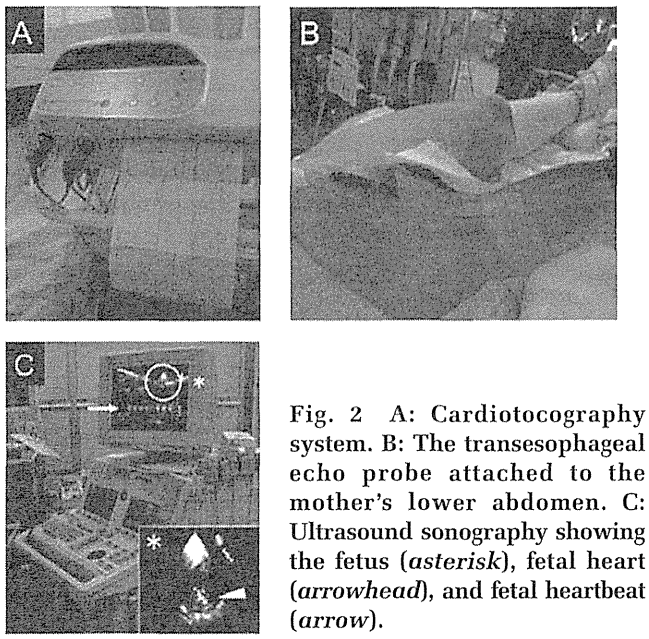


**Fig. 2 A: Cardiotocography system. B: The transesophageal echo probe attached to the mother's lower abdomen. C: Ultrasound sonography showing the fetus (*asterisk*), fetal heart (*arrowhead*), and fetal heartbeat (*arrow*).**

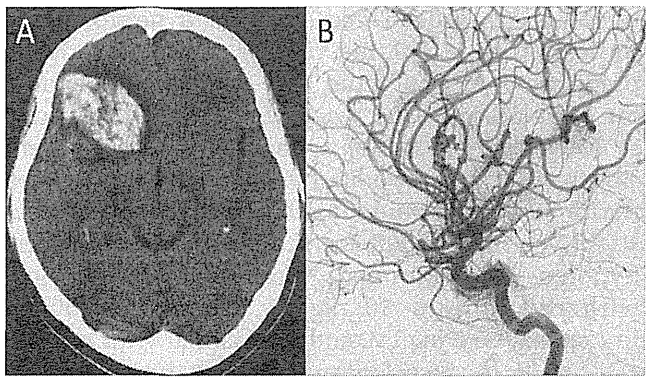


**Fig. 3 Case 2: A: Computed tomography scan showing a right frontal intraparenchymal hematoma. B: Digital subtraction angiogram showing a grade 1 right frontal arteriovenous malformation.**

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

vision, without FHR monitoring.[5] They did not use FHR monitoring because there was no preparation for emergency cesarean delivery with the mother's consent. The American College of Obstetrics and Gynecology Committee opinion on "Non-Obstetric surgery in Pregnancy" stated that "although there are no data to support specific recommendations regarding non-obstetric surgery and anesthesia in pregnancy, it is important for non-obstetric physicians to obtain obstetric consultation before performing non-obstetric surgery, and the decision to use fetal monitoring should be individualized and each case warrants a team approach for optimal safety of the woman and her baby."[28] FHR monitoring facilitates the best possible care for the fetus, especially when the mother wishes to continue the pregnancy or deliver the fetus if fetal asphyxia is suspected. In this line, we were able to operate safely, stably, and successfully for both mother and fetus under monitoring of FHR with the cooperation of obstetrician and anesthesiologist.

## Conclusion

FHR monitoring is useful for AVM surgery during pregnancy. CTG is an appropriate method in the third trimester, whereas ultrasonography, using a transesophageal echo probe, can be used in the second trimester. These methods could have a wider application for cerebrovascular surgery during pregnancy.

## Conflicts of Interest Disclosure

The authors declare no conflict of interest concerning the materials or methods used in this study or the findings specified in this article.

## References


1) Dias MS, Sekhar LN: Intracranial hemorrhage from aneurysms and arteriovenous malformations during pregnancy and the puerperium. *Neurosurgery* 27: 855–865; discussion 865–866, 1990
2) Graf CJ, Perret GE, Torner JC: Bleeding from cerebral arteriovenous malformations as part of their natural history. *J Neurosurg* 58: 331–337, 1983
3) Robinson JL, Hall CS, Sedzimir CB: Arteriovenous malformations, aneurysms, and pregnancy. *J Neurosurg* 41: 63–70, 1974
4) Tuncali B, Aksun M, Katircioglu K, Akkol I, Savaci S: Intraoperative fetal heart rate monitoring during emergency neurosurgery in a parturient. *J Anesth* 20: 40–43, 2006
5) Balki M, Manninen PH: Craniotomy for suprasellar meningioma in a 28-week pregnant woman without fetal heart rate monitoring. *Can J Anaesth* 51: 573–576, 2004
6) Berman MF, Sciacca RR, Pile-Spellman J, Stapf C, Connolly ES, Jr, Mohr JP, Young WL: The epidemiology of brain arteriovenous malformations. *Neurosurgery* 47: 389–396; discussion 397, 2000
7) Fleetwood IG, Steinberg GK: Arteriovenous malformations. *Lancet* 359: 863–873, 2002
8) Horton JC, Chambers WA, Lyons SL, Adams RD, Kjellberg RN: Pregnancy and the risk of hemorrhage from cerebral arteriovenous malformations. *Neurosurgery* 27: 867–871; discussion 871–872, 1990
9) Gross BA, Du R: Rate of re-bleeding of arteriovenous malformations in the first year after rupture. *J Clin Neurosci* 19: 1087–1088, 2012
10) Gross BA, Du R: Hemorrhage from arteriovenous malformations during pregnancy. *Neurosurgery* 71: 349–355; discussion 355–356, 2012
11) Trivedi RA, Kirkpatrick PJ: Arteriovenous malformations of the cerebral circulation that rupture in pregnancy. *J Obstet Gynaecol* 23: 484–489, 2003
12) Salvati A, Ferrari C, Chiumarulo L, Medicamento N, Dicuonzo F, De Blasi R: Endovascular treatment of brain arteriovenous malformations ruptured during pregnancy—a report of two cases. *J Neurol Sci* 308: 158–161, 2011
13) Fukuda K, Hamano E, Nakajima N, Katsuragi S, Ikeda T, Takahashi JC, Miyamoto S, Iihara K: Pregnancy and delivery management in patients with cerebral arteriovenous malformation: a single-center experience. *Neurol Med Chir (Tokyo)* 53: 565–570, 2013
14) Spetzler RF, Martin NA: A proposed grading system for arteriovenous malformations. *J Neurosurg* 65: 476–483, 1986
15) Gross BA, Du R: Surgical and radiosurgical results of the treatment of cerebral arteriovenous malformations. *J Clin Neurosci* 19: 1001–1004, 2012
16) Parer JT, Ikeda T: A framework for standardized management of intrapartum fetal heart rate patterns. *Am J Obstet Gynecol* 197: 26.e1–6, 2007
17) Parer JT, King T, Flanders S, Fox M, Kilpatrick SJ: Fetal acidemia and electronic fetal heart rate patterns: is there evidence of an association? *J Matern Fetal Neona* 19: 289–294, 2006
18) Zuspan FP, Quilligan EJ, Iams JD, van Geijn HP: Predictors of intrapartum fetal distress: the role of electronic fetal monitoring. Report of the National Institute of Child Health and Human Development Consensus Development Task Force. *Am J Obstet Gynecol* 135: 287–291, 1979
19) Rosen MA: Management of anesthesia for the pregnant surgical patient. *Anesthesiology* 91: 1159–1163, 1999
20) Goodman S: Anesthesia for nonobstetric surgery in the pregnant patient. *Semin Perinatol* 26: 136–145, 2002
21) Gianopoulos JG: Establishing the criteria for anesthesia and other precautions for surgery during pregnancy. *Surg Clin North Am* 75: 33–45, 1995

22) Macarthur A: Craniotomy for suprasellar meningioma during pregnancy: role of fetal monitoring. *Can J Anaesth* 51: 535–538, 2004
23) Reitman E, Flood P: Anaesthetic considerations for non-obstetric surgery during pregnancy. *Br J Anaesth* 107(Suppl 1): i72–78, 2011
24) Minielly R, Yuzpe AA, Drake CG: Subarachnoid hemorrhage secondary to ruptured cerebral aneurysm in pregnancy. *Obstet Gynecol* 53: 64–70, 1979
25) Newman B, Lam AM: Induced hypotension for clipping of a cerebral aneurysm during pregnancy: a case report and brief review. *Anesth Analg* 65: 675–678, 1986
26) Ito T, Toyoshima N, Takahashi H, Ozasa A, Nakajima K, Tatsumura M, Teragawa N, Nobuhara H, Iwanaga M: [Study by fetal movement meter of effects of general anesthesia on fetal movement and fetal cardiac rate]. *Obstetrical and Gynecological Practice* 39: 1115–1118, 1990 (Japanese)
27) Immer-Bansi A, Immer FF, Henle S, Spörri S, Petersen-Felix S: Unnecessary emergency caesarean section due to silent CTG during anaesthesia? *Br J Anaesth* 87: 791–793, 2001
28) ACOG Committee on Obstetric Practice: ACOG Committee Opinion Number 284, August 2003: Nonobstetric surgery in pregnancy. *Obstet Gynecol* 102: 431, 2003
29) Horrigan TJ, Villarreal R, Weinstein L: Are obstetrical personnel required for intraoperative fetal monitoring during nonobstetric surgery? *J Perinatol* 19: 124–126, 1999

*Address reprint requests to*: Kenji Fukuda, MD, Department of Neurosurgery, Faculty of Medicine, Fukuoka University, 7-45-1 Nanakuma, Jonan-ku, Fukuoka, Fukuoka 814-0180, Japan.
*e-mail*: kefukuda@fukuoka-u.ac.jp

Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

ORIGINAL ARTICLE
Myocardial Disease

# Cardiovascular Events in Pregnancy With Hypertrophic Cardiomyopathy

Hiroaki Tanaka, MD; Chizuko Kamiya, MD, PhD; Shinji Katsuragi, MD, PhD; Kayo Tanaka, MD; Takekazu Miyoshi, MD; Mitsuhiro Tsuritani, MD, PhD; Masashi Yoshida, MD, PhD; Naoko Iwanaga, MD; Reiko Neki, MD, PhD; Jun Yoshimatsu, MD, PhD; Tomoaki Ikeda, MD, PhD

***Background:*** The influence of the physiological circulatory changes during pregnancy on hypertrophic cardiomyopathy (HCM) is unclear. There have been no comprehensive studies of pregnant women with HCM in the Japanese population.

***Methods and Results:*** A total of 27 pregnancies (23 women with HCM) were retrospectively reviewed. A total of 18 cardiovascular events occurred in 13 of the 27 pregnancies (48%), and 13 of these events (76%) were related to arrhythmia. The cardiovascular events tended to occur in the early stage of pregnancy (≈30 gestational weeks) or postpartum. The events related to arrhythmia mainly occurred in the early stage of pregnancy or at approximately 30 gestational weeks. Four pregnancies were terminated because of cardiovascular events. Cardiovascular events occurred in 8 of 9 pregnancies in women on medication before pregnancy (88%), 7 of 10 pregnancies with high CARPREG score (70%), and in 9 of 12 pregnancies with high ZAHARA score (75%).

***Conclusions:*** Cardiovascular events occurred in more than half of the pregnant women complicated with HCM, and the arrhythmia is the most common cardiovascular event. Medication in the pre-pregnancy period, and CARPREG or ZAHARA score ≥1 were identified as risk factors of cardiac events during pregnancy or postpartum. (*Circ J* 2014; **78:** 2501–2506)

**Key Words:** Arrhythmia; CARPREG score; Hypertrophic cardiomyopathy; Pregnancy; ZAHARA score

Hypertrophic cardiomyopathy (HCM) is a disease that presents as cardiac muscle dilation with asymmetric diversity. The complications of HCM include arrhythmia, left ventricular outflow obstruction, and diastolic and partial systolic dysfunction because of the myocardial thickening. HCM may result in heart failure, thrombosis, atrial and ventricular arrhythmias, and sudden death, but is often asymptomatic. HCM is thought of as a rare disease, but a recent investigation showed a prevalence of approximately 1.8% in Japan, corresponding to an estimated 21,900 patients with HCM in Japan.[1,2] Therefore, HCM may be more common than previously thought, and this is a matter of concern in the context of pregnancy.

Editorial p2386

There are few reports on pregnancy in women with exacerbated cardiomyopathy, and the perinatal prognosis of this condition is unclear. The available reports include 7 studies of pregnancy with HCM.[3–9] In the first of these studies, which examined 13 pregnancies with HCM, Turner et al found that vaginal birth was not possible in 2 cases because of worsening angina and in 1 because of breathing difficulties.[3] Autore et al identified 98 survivors and 2 deaths during pregnancy among 100 women with HCM (199 pregnancies),[5] giving a maternal mortality of 10 in 1,000 live births (95% confidence interval 1.1–36.2/1,000), which is higher than that in normal pregnancy. An investigation of the morbidity rate in 40 pregnancies with HCM showed deterioration in New York Heart Association cardiac performance (NYHA class) in 1 of 28 women who were asymptomatic before pregnancy, and in 5 of 12 women who were symptomatic, thus indicating that the perinatal prognosis is excellent in patients who are asymptomatic before becoming pregnant.[5] In a comparison of nonpregnant and pregnant (n=23) women with HCM, the incidence of arrhythmia was higher in those who were pregnant (33.3% vs. 13.4%), but

Received May 12, 2014; revised manuscript received June 23, 2014; accepted July 9, 2014; released online August 6, 2014 Time for primary review: 17 days
Department of Perinatology, National Cerebral and Cardiovascular Center, Suita (H.T., C.K., S.K., K.T., T.M., M.T., M.Y., N.I., R.N., J.Y.); Department of Obstetrics and Gynecology, Faculty of Medicine, Mie University, Tsu (H.T., T.I.), Japan
Mailing address: Hiroaki Tanaka, MD, Department of Perinatology, National Cerebral and Cardiovascular Center, 5-7-1 Fujishirodai, Suita 565-8565, Japan. E-mail: h_tanaka@med.miyazaki-u.ac.jp
ISSN-1346-9843 doi:10.1253/circj.CJ-14-0541

**Table 1. Background of the 27 Pregnancies in 23 Women With HCM**

| Case no. | Age (years) | Parity | Complication | HOCM | D-HCM | Medication pre-pregnancy | NYHA class (pre-pregnancy) |
|---|---|---|---|---|---|---|---|
| 1 | 25 | 0 | TOF | – | – | – | 1 |
| 2 | 25 | 0 | No | + | – | Metoprolol, Verapamil | 1 |
| 3 | 31 | 0 | ITP | – | – | – | 1 |
| 4 | 33 | 1 | ITP | – | – | – | 1 |
| 5 | 33 | 1 | – | – | – | – | 1 |
| 6 | 32 | 2 | – | – | – | – | 1 |
| 7 | 21 | 0 | Bartter syndrome | – | – | – | 1 |
| 8 | 32 | 0 | – | + | – | Verapamil | 1 |
| 9 | 39 | 0 | – | + | – | – | 1 |
| 10 | 30 | 0 | – | + | – | Diltiazem | 2 |
| 11 | 33 | 1 | – | – | – | – | 1 |
| 12 | 25 | 0 | – | + | – | Mexiletine, Metoprolol | 1 |
| 13 | 30 | 1 | – | + | – | Mexiletine, Metoprolol | 1 |
| 14 | 33 | 0 | – | – | – | – | 1 |
| 15 | 32 | 0 | – | – | – | – | 1 |
| 16 | 34 | 1 | – | – | – | – | 1 |
| 17 | 32 | 0 | – | – | – | Propranolol | 1 |
| 18 | 32 | 0 | – | + | – | – | 1 |
| 19 | 33 | 0 | – | – | – | Diltiazem, Enalapril | 1 |
| 20 | 34 | 1 | – | – | – | – | 1 |
| 21 | 29 | 0 | – | – | – | – | 1 |
| 22 | 33 | 1 | – | – | – | – | 1 |
| 23 | 31 | 1 | – | – | – | – | 1 |
| 24 | 27 | 0 | – | – | – | – | 1 |
| 25 | 33 | 0 | – | – | – | Propranolol | 1 |
| 26 | 35 | 1 | – | – | – | – | 1 |
| 27 | 28 | 0 | – | – | – | Propranolol, Verapamil | 1 |

D-DCM, dilated phase of hypertrophic cardiomyopathy (HCM); HOCM, hypertrophic obstructive cardiomyopathy; LADs, atrial diameter in endsystole; LVEF, left ventricular ejection fraction; LVOTO, left ventricular outflow tract obstruction; MR, mitral regurgitation; NYHA, New York Heart Association.

(**Table 1** continued the next page.)

heart failure and cardiac infarction rates did not differ significantly.[6] There were no deaths in either group, and pregnancy was assumed to have had no influence on the natural course of HCM. Cardiovascular events that required hospitalization increased when there was a family history (71.4% vs. 25.0%), which indicates the need to obtain a family medical history in the case of pregnancy with HCM.[6]

Pregnancy increases the circulating blood volume and cardiac output because of increases in the ventricular rate and stroke volume, while the peripheral vascular resistance decreases. The circulating blood volume increases more rapidly after 20 gestational weeks and reaches a plateau at 32 gestational weeks of 40–45% of the nonpregnant volume.[10,11] In HCM, the preload increase, afterload decrease and increase in cardiac contraction are precipitating factors because the ventricular blood volume decreases and left ventricular outflow obstruction deteriorates. The influence of these pregnancy-related physiologic changes on the circulation in HCM is not well understood. Therefore, in this the first study of this condition in Japan, we investigated the cardiovascular events that occurred during pregnancy with HCM.

## Methods

We examined the outcomes of 27 pregnancies (23 women with HCM) between 1995 and 2013 at the Department of Perinatology, National Cerebral and Cardiovascular Center, Japan. HCM was diagnosed using the definition and type classification of cardiomyopathy published by the World Health Organization/International Society and Federation of Cardiology Joint Committee in 1995, by a cardiovascular physician based on medical history, physical findings, ECG, chest X-rays, an echocardiogram, and Doppler ultrasound. Radionuclide scans, computed tomography, magnetic resonance imaging, a cardiac catheter test, coronary arteriography, myocardial biopsy, and genetic diagnosis were performed when necessary. HCM was subcategorized into hypertrophic nonobstructive cardiomyopathy (HNCM), hypertrophic obstructive cardiomyopathy (HOCM), and dilated phase of HCM (D-HCM) with systolic dysfunction such as left ventricular ejection fraction (LVEF) <50%.

Information on maternal background was collected, including age, parity, complications, medications before pregnancy, NYHA class before pregnancy, family history of HCM, echocardiographic parameters; maximum wall thickness, LVEF, left atrial diameter in endsystole (LADs), mitral regurgitation (MR), and the pressure gradient (PG) of the left ventricular outflow tract obstruction (LVOTO), CARPREG score[12] and ZAHARA score[13] were retrospectively calculated. The CARPREG score is a contemporary assessment of maternal and neonatal risks

| Case no. | LVEF <50% | Family history | LADs >50 mm | MR ≥moderate | LVOTO >50 mmHg | Maximau wall thickness >30 mm | ZAHARA score | CARPREG score |
|---|---|---|---|---|---|---|---|---|
| 1 | – | – | – | – | – | – | 0 | 0 |
| 2 | – | – | – | – | – | – | 1.5 | 0 |
| 3 | – | + | – | – | – | – | 0 | 0 |
| 4 | – | + | – | – | – | – | 0 | 0 |
| 5 | – | + | – | – | – | – | 0 | 0 |
| 6 | – | + | – | – | – | – | 0 | 0 |
| 7 | – | – | – | – | – | – | 1.5 | 0 |
| 8 | – | – | – | – | – | – | 3 | 1 |
| 9 | – | – | – | – | – | – | 0 | 0 |
| 10 | – | + | + | + | + | + | 4.75 | 1 |
| 11 | – | – | – | – | – | – | 0 | 0 |
| 12 | – | – | – | – | – | – | 3 | 1 |
| 13 | – | – | – | – | – | – | 3 | 2 |
| 14 | – | – | – | – | – | – | 0 | 0 |
| 15 | – | + | – | – | – | – | 0 | 0 |
| 16 | – | + | – | – | – | – | 0 | 0 |
| 17 | – | – | – | – | – | – | 3 | 1 |
| 18 | – | + | – | – | – | – | 0 | 0 |
| 19 | – | – | – | – | – | – | 3 | 1 |
| 20 | – | – | – | – | – | – | 0 | 0 |
| 21 | – | – | – | – | – | – | 0 | 0 |
| 22 | – | – | – | – | – | – | 0 | 0 |
| 23 | – | – | – | – | – | – | 0 | 0 |
| 24 | – | – | – | – | – | – | 1.5 | 1 |
| 25 | – | – | – | – | – | – | 3 | 1.5 |
| 26 | – | – | – | – | – | – | 1.5 | 1 |
| 27 | – | – | – | – | – | – | 3 | 1.5 |

associated with pregnancy in women with heart disease who are receiving comprehensive prenatal care. Frequency of maternal primary cardiac events, as predicted by the risk index and observed in the derivation and validation groups, is expressed as a function of the number of cardiac predictors or points. The ZAHARA score is a modified risk score for cardiac complications during completed pregnancies in women with congenital heart disease.

Maternal and neonatal outcomes were examined, including cardiovascular events, NYHA class during pregnancy, NYHA class postpartum, gestational age, delivery mode, indication for cesarian section, birth weight, pH of the umbilical artery, and Apgar score at 5 min. Cardiovascular events were defined as new onset or worsening of arrhythmia, heart failure, endocarditis, or thromboembolic events that required medication, hospitalization, or termination of pregnancy. The gestational week of the occurrence of all cardiovascular events was recorded. Cardiovascular events were also classified as those related to arrhythmia or other than arrhythmia. The type of arrhythmia, gestational week of occurrence, and the detection method were recorded for each cardiovascular event related to arrhythmia.

### Statistical Analysis

Univariate analysis by chi-squared test and the Cochran-Armitage trend test was used for statistical analysis. $P<0.05$ was considered significant.

## Results

### Maternal Background

Maternal background data for the 27 pregnancies (23 women) with HCM are shown in **Table 1**. The median age was 32 years (21–39 years). The mother was nulliparous in 17 pregnancies (63%) and multiparous in 10 (48%). Cases 3 and 4, 12 and 13, 15 and 16, and 21 and 22 relate to the same woman in each pair of cases (4 women). There were 17 women with HNCM, 6 with HOCM, and none D-HCM. One woman was complicated with tetralogy of Fallot after repair. Other maternal complicating diseases were idiopathic thrombocytopenic purpura and Bartter syndrome in 1 woman each. The medications administered before pregnancy were verapamil in 3 women, diltiazem in 2 women, $\beta$-blocker in 6 women, mexiletine in 2 women and angiotensin-converting enzyme inhibitor in 1 woman. A family history of HCM was identified in 6 women (26%). The NYHA class before pregnancy was I in all except 1 woman in class II (case 10) and that woman had LADs >50 mm, moderate MR, and a PG of LVOTO >50 mmHg. Among the other women with HOCM, the PG of LVOTO before pregnancy or in early pregnancy was between 15 and 35 mmHg. Therefore, all of the patients, except for the woman in case 10, were in good general condition.

### Pregnancy Outcomes

Maternal and neonatal outcomes for the 27 pregnancies (23 women) with HCM are shown in **Tables 2,3**. A total of 17 cardiovascular events occurred in 13 pregnancies (48%), includ-

**Table 2. Outcomes of the 27 Pregnancies in 23 Women With HCM**

| Case no. | Cardiovascular event | Gestational week | NYHA class (pregnancy) | NYHA class (postpartum) | Gestational age (weeks) | Delivery mode | Indication of CS | Birth weight (g) | UA pH | APS (5 min) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | No | | 1 | 1 | 36 | VD | | 2,690 | 7.36 | 9 |
| 2 | Yes | 30 | 1 | 1 | 38 | VD | | 2,822 | 7.33 | 9 |
| 3 | Yes | 30 | 1 | 1 | 38 | CS | NRFS | 2,286 | 7.28 | 9 |
| 4 | Yes | 13 | 1 | 1 | 37 | CS | Previous CS | 2,940 | 7.35 | 9 |
| 5 | Yes | 32 | 1 | 1 | 40 | VD | | 3,190 | 7.32 | 9 |
| 6 | No | | 1 | 1 | 38 | VD | | 2,724 | 7.25 | 9 |
| 7 | Yes | 32 | 1 | 1 | 36 | VD | | 2,426 | 7.31 | 9 |
| 8 | Yes | 12, 31 | 1 | 1 | 31 | CS | Heart | 1,512 | 7.25 | 6 |
| 9 | No | | 1 | 1 | 40 | VD | | 3,016 | 7.32 | 9 |
| 10 | Yes | 13, 27 | 3 | 2 | 27 | CS | Heart | 850 | 7.29 | 5 |
| 11 | Yes | 32, 36 | 3 | 1 | 36 | CS | Heart | 2,250 | 7.21 | 7 |
| 12 | Yes | 13, 29 | 1 | 1 | 29 | CS | Heart | 1,013 | 7.33 | 3 |
| 13 | Yes | Postpartum | 1 | 1 | 37 | CS | Previous CS | 2,070 | 7.35 | 8 |
| 14 | No | | 1 | 1 | 37 | VD | | 2,326 | 7.24 | 10 |
| 15 | No | | 1 | 1 | 39 | VD | | 2,562 | 7.25 | 9 |
| 16 | No | | 1 | 1 | 38 | VD | | 3,124 | 7.38 | 10 |
| 17 | Yes | 31 | 1 | 1 | 39 | VD | | 2,250 | 7.306 | 9 |
| 18 | No | | 1 | 1 | 37 | VD | | 2,874 | 7.201 | 8 |
| 19 | Yes | Postpartum | 1 | 1 | 37 | VD | | 2,533 | 7.26 | 9 |
| 20 | No | | 1 | 1 | 37 | VD | | 3,364 | 7.35 | 9 |
| 21 | No | | 1 | 1 | 38 | VD | | 2,858 | 7.27 | 8 |
| 22 | No | | 1 | 1 | 40 | VD | | 3,054 | 7.29 | 8 |
| 23 | No | | 1 | 1 | 39 | CS | Previous CS | 3,008 | 7.28 | 9 |
| 24 | No | | 1 | 1 | 34 | VD | | 2,434 | 7.35 | 10 |
| 25 | Yes | 24 | 1 | 1 | 39 | CS | CPD | 3,994 | 7.34 | 9 |
| 26 | No | | 1 | 1 | 37 | VD | | 2,674 | 7.29 | 10 |
| 27 | Yes | Postpartum | 1 | 1 | 38 | VD | | 2,646 | 7.27 | 8 |

CPD, cephalopelvic disproportion; CS, cesarean section; NRFS, non-reassuring fetal status; UA, umbilical artery; VD, vaginal delivery. Other abbreviations as in Table 1.

**Table 3. Summary of Maternal Outcomes of 27 Pregnancies With HCM**

| | |
|---|---|
| Cardiovascular event | 14/27 (52%) |
| Termination of pregnancy because of cardiovascular event | 4/27 (15%) |
| Worsening of NYHA class during pregnancy | 2/27 (7%) |
| Preterm birth | 7/27 (26%) |

Abbreviations as in Table 1.

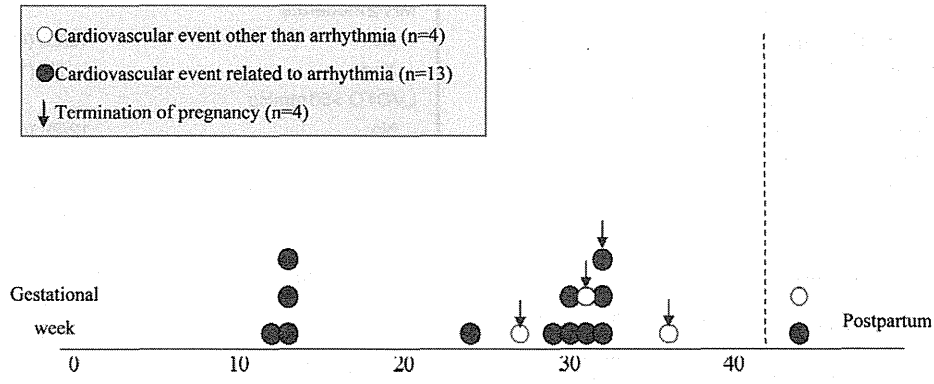


**Figure.** Cardiovascular events and gestational weeks (n=18).