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Pregnancy-associated Deaths: 31-year Experience

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Aim: The aim of the present study was to elucidate the clinical characteristics of pregnancy-associated maternal deaths.

Methods: We performed a retrospective analysis with medical records and autopsy reports of cases of pregnancy-associated deaths. We collected information on all maternal deaths related to pregnancy that occurred in 3 hospitals affiliated with Nippon Medical School in Japan from January 1, 1984, to December 31, 2014. Data analyzed were maternal age, past medical history, parity, gestational age, clinical signs and symptoms, cause of death, and maternal autopsy findings.

Results: A total of 26 maternal deaths occurred during the 31-year study period. Autopsies were performed for 16 patients (61.5%). The 26 deaths included 19 (73.1%) classified as direct maternal deaths and 7 (26.9%) classified as indirect maternal deaths. The mean maternal age at death was 33.1 ± 4.3 years (range, 26−41 years). The highest percentage of women was aged 35 to 39 years (38.5%). Of the 26 maternal deaths, 69% occurred at 32 to 41 weeks of gestation. In cases of direct maternal death, the leading causes were amniotic fluid embolism (7 cases, 27.0% of all deaths) and hemorrhage (6 cases, 23.1% of all deaths). In cases of indirect obstetric deaths, the causes included cardiovascular disorders, cerebrovascular disorders, sepsis due to group A streptococcal infection, and hepatic failure of unknown etiology.

Conclusions: Amniotic fluid embolism was the leading cause of maternal deaths and was followed by obstetric hemorrhage. To prevent and reduce the number of maternal deaths in Japan, further basic and clinical research on amniotic fluid embolism is required. (J Nippon Med Sch 2016; 83: 6−14)

Key words: amniotic fluid embolism, direct maternal death, maternal death, maternal mortality, pregnancy-associated deaths

Introduction

Maternal death is the most devastating event seen in obstetrics practice. The maternal mortality ratio is defined as the number of maternal deaths per 100,000 live births. This ratio is used as an overall quality indicator of national maternal health and can be used for international comparisons. Over the last 20 years the number of maternal deaths has declined worldwide by 34%[1]. However, declines in developed countries have been limited. Recent reports show increases in maternal mortality in the United States and the Netherlands[2-4].

In Japan, the maternal mortality rate has shown remarkable declines, with reported rates of 87.6 in 1965, 28.7 in 1975, 15.8 in 1985, 7.2 in 1995, and 4.1 in 2010[5]. In 2013, the Japan Society of Obstetrics and Gynecology announced an annual report by the subcommittee for the examination of causes of maternal death and their prevention[6]. This report showed that hemorrhage in the third stage of labor is the most frequent cause of maternal deaths in Japan.

To prevent future maternal deaths, individual cases of maternal death must be assessed. However, because maternal deaths are rare, insufficient information is available about the clinical signs and symptoms, causes of

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death, and the timing of onset. In the present study, we aimed to elucidate the clinical characteristics of patients who had maternal deaths. We retrospectively analyzed 26 cases of maternal death that occurred in patients treated in 1 of 3 hospitals affiliated with Nippon Medical School, Japan, during a 31-year period.

Materials and Methods

We performed a retrospective case study analysis of maternal deaths related to pregnancy using medical records and autopsy reports. Maternal death is defined by the World Health Organization as the death of a woman while pregnant or within 42 days of the end of pregnancy[7]. Maternal deaths are categorized as direct, indirect, or fortuitous. Direct deaths are defined as those resulting from obstetric complications of the pregnant state, interventions, omissions, incorrect treatment, or from a chain of events resulting from the above[7]. Indirect deaths are defined as deaths caused not by direct obstetric causes but by a previously existing disease or a disease that developed during pregnancy and was aggravated by the physiological effects of pregnancy[7]. Late maternal death was defined as the death of a woman from direct or indirect obstetric causes more than 42 days but less than 1 year after the completion of pregnancy.

To elucidate the clinical characteristics of maternal deaths, we collected information on all maternal deaths related to pregnancy that occurred from January 1, 1984, to December 31, 2014, in 3 hospitals affiliated with Nippon Medical School in Japan. These cases were analyzed with respect to maternal age, past medical history, parity, gestational age, clinical signs and symptoms, cause of death, and maternal autopsy findings if applicable. We excluded deaths caused by a traffic accident or malignancy.

Results

A total of 26 maternal deaths occurred during the 31-year study period (**Table 1**). Autopsies were performed for 16 patients (61.5%). The 26 deaths included 19 (73.1%) classified as direct maternal deaths and 7 (26.9%) classified as indirect maternal deaths. No late maternal deaths were identified.

At least 2 patients (7.7%) apparently had previously existing diseases that caused or influenced their deaths. The first patient was a woman who died at 32 weeks of gestation and had primary pulmonary hypertension (case 10); she died of cardiac decompensation immediately after delivery. The second patient, who died at 24 weeks of

gestation, presented with a ruptured dissecting aortic aneurysm associated with Marfan syndrome (case 21). Unfortunately, these preexisting medical conditions were not recognized until the patients became critically ill.

Regarding risk factors for maternal deaths, 2 women who died because of intracranial hemorrhage (cases 11 and 12) had family histories of cerebral aneurysm.

In 8 women (30.8%), including 1 patient with ectopic pregnancy, deliveries were not performed. These 8 women presented with symptoms before 29 weeks of gestation, with the exception of 1 woman who died suddenly at 32 weeks of gestation from an amniotic fluid embolism (case 1). Of the 18 deliveries, 9 were cesarean sections, 4 were vacuum extractions, and 5 were noninstrumental vaginal deliveries. No deaths were directly caused by the operative procedure of a cesarean section. Three deaths were directly related to vaginal delivery: 1 case of hemorrhagic shock after removal of the placenta (placenta accreta) (case 20), 1 case of severe postpartum hemorrhage due to uterine inversion (case 25), and 1 case of massive retroperitoneal hematoma due to shoulder dystocia (case 24). Two perimortem procedures (1 cesarean section and 1 vacuum extraction) were performed following maternal cardiopulmonary arrest caused by amniotic fluid embolism; the 2 fetuses survived, although 1 had a neurological disturbance.

Regarding fetal/neonatal outcomes, 14 fetuses (53.9%) died in utero, 1 neonate (3.8%) died soon after birth, 1 neonate (3.8%) survived with neurological damage, and 10 neonates (38.5%) survived without neurological impairment.

The mean maternal age at death was 33.1 ± 4.3 years (range, 26−41 years) (**Table 2**). The highest number of deaths occurred in women aged 35 to 39 years (38.5%), followed by women aged 30 to 34 years (34.6%). The mean age of the 19 women who direct maternal deaths was 33.0 ± 2.4 years (range, 26−41 years), and the mean age of the 7 women who died due to indirect maternal deaths was 33.3 ± 2.4 years (range, 30−37 years).

Twelve (46.2%) maternal deaths occurred at 37 to 41 weeks of gestation (**Fig. 1**). Of the 26 maternal deaths, 69% occurred at 32 to 41 weeks of gestation. After 31 weeks of gestation, the number of maternal deaths increased progressively. Fewer deaths occurred in the second trimester than in the first or third trimester.

The most common cause of the 19 direct maternal deaths was amniotic fluid embolism, which was present in 7 cases (27.0% of all deaths) (**Table 3**). In 6 of these 7 patients, amniotic fluid embolism was associated with

Table 1a Characteristics of 26 cases of maternal death

Case	Age (years)	Parity	Weeks of gestation	Mode of delivery	Signs and symptoms	Causes of death	Fetal/neonatal outcome
1	32	2	32	Undelivered	Seizure, cardiopulmonary arrest, intrauterine fetal death, DIC	Amniotic fluid embolism (autopsy)	Died in utero
2	34	1	36	Vacuum (to rescue the fetus)	Seizure, cardiopulmonary arrest, postpartum hemorrhage, DIC	Amniotic fluid embolism (autopsy)	Survived
3	35	0	41	Cesarean (to rescue the fetus)	Screaming, seizure, unconsciousness, fetal bradycardia, polyhydramnios, DIC, macrosomia,	Amniotic fluid embolism (autopsy)	Survived with neurological damage
4	31	2	40	Vacuum (due to NRFS)	Postpartum hemorrhage, uterine atony, DIC, chest pain, respiratory distress, unconsciousness	Amniotic fluid embolism (autopsy)	Survived
5	37	2	40	Vaginal	Postpartum hemorrhage, DIC, lumbago, Nausea, respiratory distress, pulmonary hemorrhage	Amniotic fluid embolism with Incomplete uterine rupture (autopsy)	Survived
6	39	1	40	Cesarean (due to placental abruption)	NRFS, placental abruption, postpartum hemorrhage, DIC, acute renal failure	Amniotic fluid embolism (autopsy)	Died in utero
7	35	1	39	Vacuum (due to NRFS)	Prolonged fetal bradycardia, postpartum hemorrhage, uterine atony, DIC	Amniotic fluid embolism, cervical laceration (autopsy)	Died in utero
8	28	1	28	Undelivered	Hypotension, shock	Bilateral pulmonary thromboembolism (autopsy)	Died in utero
9	31	?	12	Undelivered	Sudden respiratory distress, cardio-pulmonary arrest	Pulmonary thromboembolism (CT scan)	Abortion
10	34	2	32	Vaginal (breech extraction due to umbilical cord prolapse)	Hypotension, cyanosis, respiratory distress, edema, right sided cardiac failure	Primary pulmonary hypertension (autopsy)	Survived
11	35	1	32	Cesarean (to rescue the fetus)	Hypertension, pregnancy-induced Hypertension, family history of cerebral aneurysm	Intraventricular hemorrhage (CT scan), possibility of cerebral aneurysm	Survived
12	33	0	29	Cesarean (to rescue the fetus)	Headache for 1 month, incontinence of feces, family history of cerebral aneurysm	Subarachnoid hemorrhage (CT scan)	Survived
13	30	0	10	Undelivered	Nausea, vomiting	Cerebral infarction due to cerebral venous sinus thrombosis (autopsy)	Abortion
14	30	1	32	Cesarean (due to NRFS)	Placental abruption, HELLP syndrome, DIC, shock	Placental abruption	Died in utero
15	27	0	39	Cesarean (due to NRFS)	Placental abruption, DIC, hypovolemic shock, acute renal failure	Placental abruption, intra-abdominal hemorrhage (autopsy)	Died in utero
16	33	2	33	Cesarean (due to NRFS)	Sore throat, fever up to 40°C, placental abruption, DIC (intrauterine fetal death)	Sepsis due to group A streptococcal infection (autopsy)	Died in utero
17	31	?	35	Cesarean (due to NRFS)	Fever up, seizure, NRFS, unconsciousness	Sepsis due to group A streptococcal infection, septic shock	Died in utero
18	38	0	39	Cesarean (due to NRFS)	Pregnancy-induced hypertension, anuric acute renal failure (postcesarean section), DIC	Pregnancy-induced hypertension, bilateral renal cortical necrosis (autopsy)	Survived
19	41	3	40	Vaginal	Postpartum hemorrhage, uterine atony, shock, cardiopulmonary arrest	Incomplete uterine rupture (autopsy)	Survived
20	40	0	38	Vaginal	Placenta accreta, uterine atony after manual removal of the placenta, cardiopulmonary arrest during hysterectomy	Postpartum hemorrhage, placenta accreta	Survived

Table 1b Characteristics of 26 cases of maternal death

Case	Age (years)	Parity	Weeks of gestation	Mode of delivery	Signs and symptoms	Causes of death	Fetal/neonatal outcome
21	37	0	24	Undelivered	Back pain, upper abdominal pain, vomiting, hypotension	Ruptured dissecting aortic aneurysm with Marfan syndrome (autopsy)	Died in utero
22	26	1	7	Undelivered	Lower abdominal pain, massive intra-abdominal hemorrhage, hypovolemic shock, cardiac arrest	Ruptured right tubal pregnancy (autopsy)	Abortion
23	35	0	16	Undelivered	Severe hyperemesis gravidarum, unconsciousness	Wernicke's encephalopathy (autopsy)	Abortion
24	27	?	40	Vacuum (due to NRFS)	Shoulder dystocia, macrosomia	Retroperitoneal hematoma	Neonatal death
25	26	?	40	Vaginal	Postpartum hemorrhage, uterine atony, hypovolemic shock, DIC	Uterine inversion	Survived
26	35	?	18	Undelivered	Hepatic function disorder	Hepatic failure due to unknown etiology	Abortion

DIC, disseminated intravascular coagulation; NRFS, noreassuring fetal status; CT, computed tomography; HELLP, hemolysis, elevated liver enzymes, low platelet count; ?, unknown

Table 2 Age at maternal death

Maternal age (years)	Number	%
25–29	5	19.2
30–34	9	34.6
35–39	10	38.5
40–44	2	7.7
Total	26	100

disseminated intravascular coagulation. These 6 patients with amniotic fluid embolism also showed profound uterine bleeding as a presenting sign or a subsequent sign. The second most common cause of direct maternal death, with a total of 6 cases (23.1% of all deaths), was hemorrhage and hematoma or both, including placental abruption (2 cases), incomplete uterine rupture (1 case), uterine inversion (1 case), uterine atony (1 case), and shoulder dystocia (1 case). The third most common causes of direct maternal death, with a total of 2 cases each (7.7% of all deaths), were preeclampsia, which was associated with cerebral hemorrhage (1 case) or bilateral renal cortical necrosis (1 case), and pulmonary thromboembolism, which occurred at 28 and 12 weeks of gestation. No deaths due to pulmonary thromboembolism followed a cesarean delivery.

Also classified as direct maternal deaths were those of 1 patient (3.8% of all deaths) with Wernicke's encephalopathy and 1 patient with a ruptured ectopic pregnancy.

The 7 indirect maternal deaths were caused by cardiovascular disorders (primary pulmonary hypertension in 1 case, dissecting aortic aneurysm with Marfan syndrome in 1 case), cerebrovascular disorders (cerebral infarction due to cerebral venous sinus thrombosis in 1 case, subarachnoid hemorrhage in 1 case), sepsis due to group A streptococcal infection (2 cases), and hepatic failure of unknown etiology (1 case).

The date of occurrence of the 29 maternal deaths was the first half (1984−1999) of the 31-year study period for 20 cases (77.0%) (**Fig. 2**). No maternal deaths occurred in our hospitals from 2007 through 2014.

Three (11.5%) of the 26 maternal deaths (cases 18, 22, and 24) were judged to have been potentially preventable by the adequate management of pregnancy-induced hypertension (case 18), the earlier detection of ectopic pregnancy (case 22), and cesarean section for macrosomia (case 24).
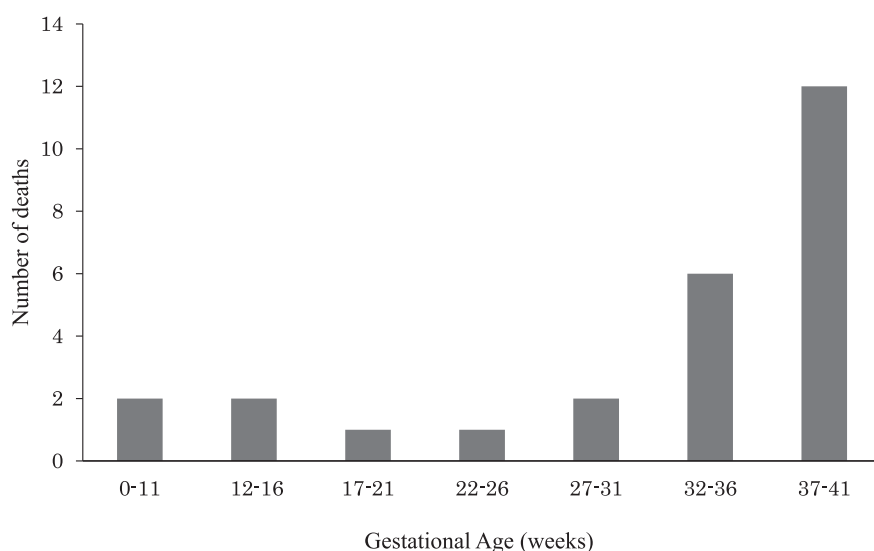
Fig. 1　Relationship between maternal death and gestational age
Twelve (46.2%) maternal deaths occurred at 37 to 41 weeks of gestation. Of all 26 maternal deaths, 69% occurred at 32 to 41 weeks of gestation. After 31 weeks of gestation, the number of maternal deaths increased progressively. Fewer deaths occurred in the second trimester than in the first or third trimester.

Table 3　Causes of maternal death, 1984–2014

Cause of death	Number	%
Direct maternal (obstetric) death	**19**	**73.1**
Amniotic fluid embolism	7	27.0
Hemorrhage	6	23.1
Placental abruption	2	
Incomplete uterine rupture	1	
Uterine inversion	1	
Uterine atony after manual removal of placenta	1	
Shoulder dystocia	1	
Complications of preeclampsia	2	7.7
Cerebral hemorrhage	1	
Bilateral renal cortical necrosis (due to preeclampsia)	1	
Pulmonary thromboembolism	2	7.7
Wernicke's encephalopathy	1	3.8
Ectopic pregnancy	1	3.8
Indirect maternal (obstetric) death	**7**	**26.9**
Cardiovascular condition	2	7.7
Primary pulmonary hypertension	1	
Dissecting aortic aneurysm with Marfan syndrome	1	
Cerebrovascular disorder	2	7.7
Sepsis due to group A streptococcal infection	2	7.7
Hepatic failure	1	3.8
Total	**26**	**100**

Discussion

We performed a retrospective analysis of 26 cases of pregnancy-related maternal deaths during a 31-year period in the affiliated hospitals of Nippon Medical School. Our study has 3 important findings. First, the leading cause of maternal deaths was amniotic fluid embolism and was followed by obstetric hemorrhage. Second, 69% of all 26 maternal deaths occurred at 32 to 41 weeks of gestation. Third, risk factors for maternal death included a family history of cerebral aneurysm in 2 women who
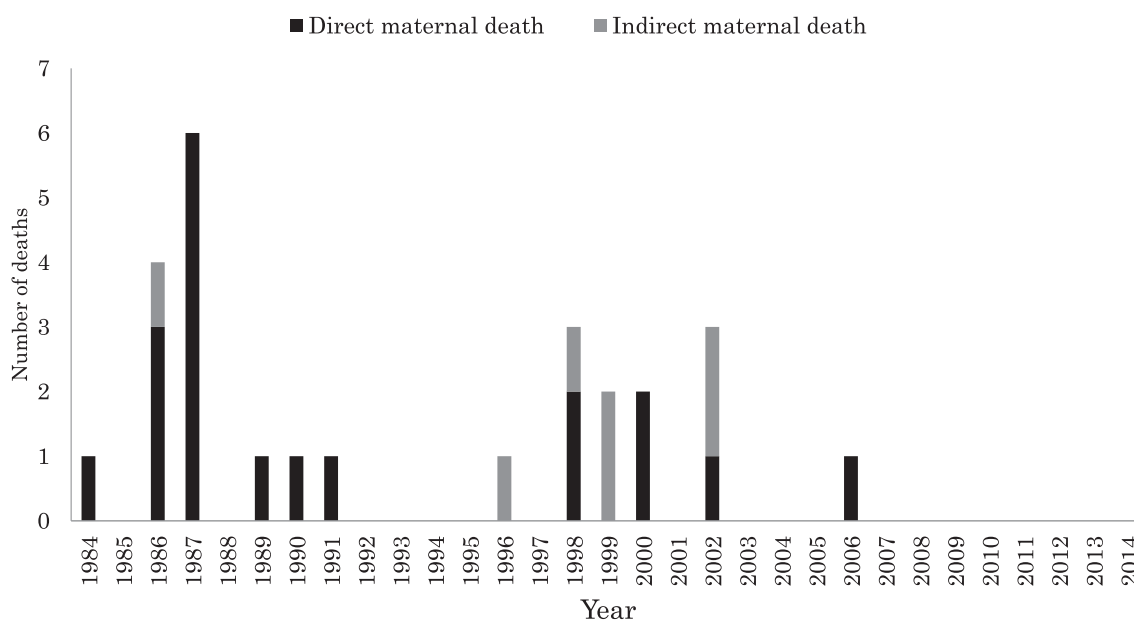
Fig. 2 Number of direct and indirect maternal deaths during a 31-year period.
Twenty (77.0%) maternal deaths occurred in the first half (1984–1999) of the present study. From 2007 through 2014, no maternal deaths were observed in our hospitals.

died of intracranial hemorrhage.

Amniotic fluid embolism, the most common cause of maternal death in the present study, accounted for 27.0% of cases. The percentage of maternal deaths from amniotic fluid embolism we observed was higher than the percentages in other studies in developed countries (13.1%–14.0%)[2,8].

Recently, we reported a retrospective study of 10 patients with amniotic fluid embolism from the past 29 years. Seven of these 10 women died of amniotic fluid embolism[9]. These 7 cases of maternal death were also included and analyzed in the present study. In our previous study, we noticed a difficulty in diagnosing amniotic fluid embolism at an early stage. Amniotic fluid embolism was suspected in only 2 of the 10 patients at the time of onset. However, all 7 women who died underwent postmortem examinations, and amniotic fluid embolism was diagnosed on the basis of the detection of fetal elements in the maternal pulmonary vasculatures. The autopsies were critical for establishing correct diagnoses of amniotic fluid embolism. We assume that the high autopsy rate of 61.5% in the present study is the main reason many cases of amniotic fluid embolism were reported.

Kanayama et al. investigated causes of direct maternal deaths by examining 193 autopsy cases from 1989 through 2004 in Japan[10]. They also reported that amniotic fluid embolism was the most common cause of direct maternal deaths, accounting for 24.3% of cases. This rate is consistent with our rate of 27.0%. The pathophysiology of amniotic fluid embolism remains poorly understood. To prevent and reduce the number of maternal deaths in Japan, further basic and clinical research on amniotic fluid embolism is required.

Our second key finding was that 69% of all 26 maternal deaths occurred during 32 to 41 weeks of gestation. After 31 weeks of gestation, the number of maternal deaths increased progressively. This finding is consistent with findings of previous studies[8]. We believe there are 3 possible explanations for this result. First, hemorrhage in the peripartum period is the major cause of maternal deaths. In a 2013 global study of worldwide maternal mortality, 24.6% of deaths occurred antepartum, 27.7% occurred intrapartum and immediately postpartum, and 35.6% occurred in the subacute and delayed postpartum period[11]. Second, all 7 cases of amniotic fluid embolism, which was the leading cause of maternal deaths in the present study, occurred at 32 to 41 weeks of gestation. Third, we believe that hypervolemia associated with pregnancy is a reason for the progressive increase in the number of maternal deaths after 31 weeks of gestation.

The blood volume of cases of hypervolemia associated with normal pregnancy was an average of 40% to 45% greater than the nonpregnant blood volume after 32 to 34 weeks[12]. Some women have only a modest increase in blood volume, but others have nearly a doubling of vol-

ume[12]. Pregnancy-induced hypervolemia can trigger a critically ill pregnancy status. For example, a woman of the present study who died at 32 weeks of gestation had primary pulmonary hypertension (case 10). Until 30 weeks of gestation, she had no symptoms. After 30 weeks of gestation, cyanosis, respiratory distress, edema, and hypotension developed. At 32 weeks of gestation the woman was transferred to the intensive care unit of our hospital. A Swan-Ganz catheter was inserted, and hemodynamic measurements suggested marked pulmonary hypertension and right-sided cardiac failure. Despite intensive management, she died of cardiac decompensation immediately after the delivery of her child at 32 weeks of gestation. A postmortem examination confirmed the diagnosis of primary pulmonary hypertension.

Pregnancy-induced hypervolemia might have also affected our cases of intraventricular hemorrhage (case 11, 32 weeks), subarachnoid hemorrhage (case 12, 29 weeks), and ruptured dissecting aortic aneurysm (case 21, 24 weeks).

Recently, the results of a survey of pregnancy-associated intracranial hemorrhage in Japan were reported by the Stroke and Pregnancy Survey Committee of the Japan Neurosurgical Society[13]. Ninety-seven hemorrhagic strokes associated with pregnancy were analyzed. In this survey, 50% of hemorrhagic strokes occurred after 32 weeks of gestation. Obstetricians should be aware of the increased risk of hemorrhagic stroke in the management of pregnant women, especially after 32 weeks of gestation.

Regarding risk factors for maternal death, we found that 2 women whose deaths were caused by intracranial hemorrhage had a family history of cerebral aneurysm. A history of aneurysmal subarachnoid hemorrhage in 2 or more first-degree relatives is reported to increase the lifetime risks of unruptured intracranial aneurysm and aneurysmal subarachnoid hemorrhage[14−16]. Therefore, screening for intracranial aneurysms should be considered for patients who have at least 2 first-degree relatives with aneurysmal subarachnoid hemorrhage according to guidelines from the European Stroke Organization and the American Heart Association[14,17,18]. In Japan, Okamoto and Horisawa have reported a case-control study of the relationship between family history and subarachnoid hemorrhage[19]. They showed that the risk of subarachnoid hemorrhage was elevated when (1) any first-degree relative had a positive episode of subarachnoid hemorrhage, (2) a mother or father had a relative with a positive episode of subarachnoid hemorrhage (an effect much greater in magnitude with a maternal rather than paternal history), and (3) any first-degree relative older than 50 years had a subarachnoid hemorrhage. They concluded that to prevent the onset of subarachnoid hemorrhage at a younger age, much more attention should be paid to individuals with any family members (first-degree relatives) who had episodes of subarachnoid hemorrhage.

In conclusion, we found that amniotic fluid embolism was the leading cause of maternal deaths, followed by obstetric hemorrhage. To prevent and reduce the number of maternal deaths in Japan, further basic and clinical research on amniotic fluid embolism is required. Of the 26 maternal deaths in our study, 69% occurred during 32 to 41 weeks of gestation. We also noted the effect of pregnancy-associated hypervolemia. To prevent the onset of subarachnoid hemorrhage during pregnancy, much more attention should be paid to patients with any family members (first-degree relatives) who had episodes of subarachnoid hemorrhage or cerebral aneurysms.

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