Table 3 Maternal and neonatal outcomes in 27 pregnancies with Moyamoya disease

Case no.	Presence of symptoms due to Moyamoya disease intrapartum	Mode of delivery	Obstetrics event	Gestational age (week)	Birthweight (g)	Apgar score at 5 min	pH of umbilical artery
1	No	VD	No	40	2562	9	7.39
2	No	VD	No	39	2804	8	7.34
3	No	VD	No	38	2890	10	7.29
4	No	VD	No	39	2984	10	7.35
5	No	VD	No	41	2978	9	7.37
6	No	VD	No	40	3306	8	7.37
7	No	VD	No	39	3208	9	7.37
8	No	VD	No	39	3116	9	7.33
9	No	VD	No	38	3498	9	7.27
10	No	VD	No	37	2362	10	7.37
11	No	VD	No	40	3226	9	7.38
12	No	VD	No	41	3144	10	7.37
13	No	VD	No	40	3510	9	7.32
14	No	VD	No	40	3170	9	7.39
15	No	VD	No	39	3006	8	7.3
16	No	VD	No	39	2490	9	7.34
17	No	VD	No	37	2377	9	7.29
18	No	VD	TPL	38	2300	9	7.3
19	No	VD	TPL	35	2296	9	7.09
20	No	VD	FGR	37	2024	9	7.23
21	No	CS	Breech presentation	37	2698	9	7.34
22	No	CS	Superimposed pre-eclampsia	32	1370	7	7.24
23	No	CS	Pre-eclampsia	36	2420	10	7.28
24	No	CS	No	37	2508	10	7.27
25	No	CS	No	37	2486	9	7.24
26	No	CS	Previous CS	38	2570	9	7.27
27	No	CS	No	40	3156	9	7.16

CS, cesarean section; FGR, fetal growth restriction; TPL, threatened premature labor; VD, vaginal delivery.

delivery is possible if cerebral blood flow can be controlled, and this may be achieved by controlling blood flow to the brain with epidural anesthesia. In the current study, SPECT in seven women (37%) showed good cerebral circulation, while the absence of frequent symptoms due to Moyamoya disease within 1 year before pregnancy in 12 women (63%) who did not undergo SPECT was also taken to indicate normal cerebral circulation. When vaginal delivery as a mode of delivery is selected, we think that evident good cerebral circulation is important. These findings may explain the absence of intrapartum symptoms of Moyamoya disease in our patients.

We had thought that patients with favorable cerebral hemodynamics without ischemic symptoms as confirmed 1 year before delivery and the finding of good perfusion of the brain blood flow by SPECT were of the same value. However, our present finding that the patients had favorable cerebral hemodynamics without ischemic symptoms as confirmed 1 year before delivery is objective scientific proof. In a future study, we will evaluate the cerebral blood flow by SPECT in all patients.

It was recently reported that increased thyroid function and elevated thyroid autoantibodies are associated with Moyamoya disease, and thus the monitoring of thyroid function and thyroid autoantibodies in patients with Moyamoya disease was suggested.[15,16] Three of the mothers in the present study had hyperthyroidism, but all of them showed normal thyroid function during pregnancy and post-partum.

We cannot be certain that vaginal delivery with epidural anesthesia is safe in pregnancies with Moyamoya disease because this study was performed as a retrospective analysis. The greatest limitation is the small number of patients and the rarity of the condition. However, our findings indicate that a patient with no symptoms of Moyamoya disease within 1 year before pregnancy or with SPECT findings indicating normal cerebral circulation is a good candidate for vaginal

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Therapeutic application of C1 esterase inhibitor concentrate for clinical amniotic fluid embolism: a case report

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Key Clinical Message

Go to:

We present the successful application of C1 esterase inhibitor (C1INH) concentrate to a patient with clinical amniotic fluid embolism (AFE).

Keywords: Amniotic fluid embolism, C1 esterase inhibitor, disseminated intravascular coagulopathy, kallikrein, uterine atony

Introduction

Go to:

Amniotic fluid embolism (AFE) is one of the most serious causes of maternal death 1. AFE is recognized as a syndrome characterized by the abrupt onset of hypoxia, hypotension, disseminated intravascular coagulopathy (DIC), and uterine atony due to mechanical obstruction of the maternal pulmonary artery or anaphylactic reaction to amniotic fluid 2.

In Japan, AFE was defined based on the Japan consensus criteria for the diagnosis of AFE based on the United States of America and the United Kingdom criteria as shown in Fig.1 3,4. A pathological diagnosis was determined when fetal debris was found in the maternal pulmonary arteries. On the other hand, the diagnosis of clinical AFE depended on clinical manifestations and was done when factors B1–B3 were all present, but more than one of the signs and symptoms listed in B1 needed to be present.

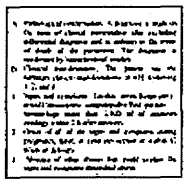

Figure 1
The Japan consensus criteria for the diagnosis of AFE.

Previously, we reported that C1 esterase inhibitor (C1INH) activity levels were significantly low in clinical AFE patients. On performing lifesaving treatment for patients with AFE, C1INH activity levels were increased after the administration of fresh frozen plasma 5. Therefore, we hypothesized that the administration of C1INH concentrate could be effective for patients with AFE. We describe the first reported case of C1INH treatment for a patient

clinically diagnosed AFE. The Ethics Committee of Hamamatsu University School of Medicine approved all the procedures in this study (No. 25-107).

Case

Go to:

The patient was a 36-year-old Japanese woman, eight Gravida, three parous (3 × normal vaginal deliveries, 1 × stillbirth, 4 × spontaneous abortions). The family histories showed nothing of note. She had no allergy to food or drugs. She became pregnant spontaneously, and the pregnancy course was normal before the third trimester. At the 28th week of gestation, vaginal spotting appeared, and placental previa was diagnosed on ultrasound examination. At the 31st week of gestation, a moderate amount of vaginal bleeding occurred. She was admitted for bed rest and tocolysis. At 36 weeks and 1 day, she underwent uneventful cesarean section. The operation time was 86 min, and blood loss was 770 g. About 400 mL of autologous blood was transfused. When the operation was completed, the levels of hemoglobin and hematocrit were 9.5 g/dL and 31%, respectively. Massive vaginal bleeding and hypotension occurred suddenly just after the operation. We increased the transfusion and administrated oxytocin and prostaglandin F2α intravenously. We also conducted Bakri balloon tamponade for hemostasis. She was refractory to these treatments, and uterine bleeding continued. At 2.0 h after the operation, the total bleeding amount reached 2100 mL and the blood pressure decreased to 76/38 mmHg with fainting. The size of the uterus was large; the fundus of the uterus was over 3 fingers above the umbilicus and the myometrium was very soft. Severe atonic uterus was observed. Clot formation was not observed in vaginal blood. At this point, the levels hemoglobin and hematocrit were 8.7 g/dL and 27%, respectively, however, the fibrinogen concentration was 67 mg/dL. The level of FDP was over the normal range (more than 300 μg/dL). The complement C3 was 59 mg/dL and C4 was 7 mg/dL, which were both very low levels. From this quite unusual condition, we diagnosed her with clinical amniotic fluid embolism according to the Japanese criteria, as the patient developed marked hemorrhage of more than 1500 mL with DIC within 2 h after delivery and there were no other medical explanations for the clinical course. We administered 1000 units of C1INH (Berinert R) intravenously at 2.5 h after the operation. After administration of C1INH, uterine contraction rapidly improved and uterine bleeding decreased. Thirty minutes after treatment with C1INH, not only uterine bleeding had almost stopped, but also vital signs and the consciousness level had markedly improved. At 3.5 h after the operation (1 h after C1INH administration), we started to give fresh frozen plasma (FFP) and red blood cell concentrates (RBCs) to restore the blood coagulation factor levels. At 4.5 h after the operation, uterine bleeding had stopped completely. The total bleeding amount was 2800 mL and total amount of FFP and RBCs required were 12 U (1680 mL) and 16 U (1920 mL), respectively.

The plasma C1INH activity was 29% at onset, increased to 72% at 30 min after the administration of C1INH. The levels of blood fibrinogen and antithrombin were 67 mg/dL and 38% at the onset of AFE and 72 mg/mL and 52% at 30 min after C1INH administration, respectively. She was discharged 8 days after the operation/delivery without any side effects.

Discussion

Go to:

We describe the first case of the clinical application of C1INH to a patient with AFE. The present case demonstrated that C1INH concentrate was sufficient to prevent the aggravation of symptoms with shock vitals, a bleeding tendency, and an atonic uterus. Particularly in the present case, we did not apply any anti-DIC agents such as fibrinogen, antithrombin or FFP before the administration of C1INH concentrate, however, the levels of blood fibrinogen and antithrombin showed marginal change and increased, suggesting the independent effect of C1INH to cease the progression of DIC from AFE.

Recently, AFE has been generally characterized by a rapidly progressive clinical course with dyspnea, hypoxemia, hypotension, and fetal bradycardia with subsequent and acute cardiorespiratory collapse, DIC, neurological compromise, and maternal and fetal death 6. Mechanical obstructions of the maternal pulmonary artery and an anaphylactic reaction to amniotic fluid have been suggested as pathological causes of AFE 2. Although there are no universal diagnostic criteria to confirm AFE other than autopsy, the United States of

America, the United Kingdom and Japan have similar clinical diagnostic criteria and national registries 7. In the present case, massive hemorrhage developed of more than 1500 mL with DIC within 2 h after delivery and there were no other medical explanations for the clinical course, meeting the clinical criteria for AFE in Japan.

As for the treatment of AFE, there have been only palliative treatments such as airway management, vascular management, fluid replacement, blood transfusion, and the administration of anti-shock and anti-DIC agents. C1INH, a major inhibitor of C1 esterase, FXIIa, and kallikrein, is capable of not only inhibiting the complement system but also modulating the coagulo-fibrinolytic and kallikrein-kinin systems 8. We previously reported that mean C1INH activity level in clinical AFE cases was 30.0 ± 1.8%, which was significantly lower than those of normal postpartum women with 62.0 ± 2.0%, suggesting that C1INH administration would be effective for AFE 5. As we expected, the present patient's uterus quickly contracted, resulting in the stopping of uterine bleeding, and DIC conditions were gradually alleviated after the administration of C1INH. Although the mechanism of the downregulation of C1INH activity in AFE is not clear, this observation paradoxically suggests that an abnormal uterine hemorrhagic type of AFE is a kind of syndrome of disorders in complement, coagulo-fibrinolytic, and kallikrein-kinin systems due to a decrease in C1INH activity.

Clinically, the use of 500–1500 units of human plasma-derived C1INH concentrates can reverse hereditary angioedema (HAE) in C1INH-deficient patients 9. Since the present case of AFE showed a significantly lower level of C1INH activity, similar to C1INH deficiency, we administrated 1000 units of C1INH. We must consider the amount and number of administrations of C1INH in further studies.

Our experience is limited and further cases are required; however, in conclusion, we suggest that the administration of C1INH in the early phase of AFE may be very effective for uterine atony with DIC, subsequently preventing the deterioration of conditions associated with AFE.

Consent

Go to:

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Acknowledgments

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Conflict of Interest

Go to:

None declared.

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ORIGINAL ARTICLE

High frequency of decreased antithrombin level in pregnant women with thrombosis

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Abstract Venous thromboembolism (VTE) occurs frequently in pregnant women and is a significant cause of maternal death. Hemostatic abnormalities were examined in 18 pregnant women with thrombosis. We studied five families with congenital antithrombin (AT) deficiency, and two families with congenital protein C (PC) deficiency. One woman with PC deficiency showed protein S (PS) Tokushima. The AT activity levels were significantly lower at the onset of thrombosis in the pregnant women than during the stable state. The PS activity and antigen levels were also significantly lower at the onset of thrombosis. In the patients with congenital AT deficiency, AT activity was significantly low in the stable state and decreased further at the onset of thrombosis. Although AT levels were normal before pregnancy, they subsequently decreased and in two cases the patients required the administration of AT after pregnancy. Gene analysis revealed one family with AT Budapest, one family with AT Toyama, and three families with AT Glasgow. Additionally, there were one family with PC Tochigi and one family with combined heterozygous of PC deficiency and PS Tokushima. In conclusion, the deficiency of natural anticoagulants, especially AT, is an important cause of pregnancy-related VTE.

Keywords Pregnancy · Thrombosis · AT · PC · Thrombophilia

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Introduction

During normal pregnancy, the pro-coagulant activity is increased, while the anticoagulant activity is reduced [1, 2], resulting in a prothrombotic environment that predisposes toward venous thromboembolism (VTE). As a consequence, VTE continues to be one of the leading causes of maternal morbidity and mortality in countries with good perinatal care [3, 4]. The incidence of pregnancy-related VTE is approximately one per 1000 pregnancies [5]. Fatal pulmonary embolism (PE) accounts for 1.1 deaths per 100,000 deliveries, which is approximately 10 % of all maternal deaths [6]. Deficiencies of natural anticoagulants, including antithrombin (AT), protein C (PC) and protein S (PS), are rare, and the strong association of such deficiencies with VTE has mainly been described in family studies [7–9]. Although Gerhardt et al. [10] found AT, but not PC or PS, deficiency, to be an independent risk factor for pregnancy-related VTE, there is a paucity of information on the risk of pregnancy-related VTE related to low levels of natural anticoagulants. While the impact of heritable and acquired thrombophilia in the non-pregnant

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Table 1 Subjects

Name	Age	Pregnancy weeks	Frequency of TH	TH	Pregnancy	Cause	Abortion	Live birth
1	27	10	1	CVST, DVT	Frist time	AT deficiency	1	1
2	26	After delivery	1	DVT	First time	AT deficiency	0	1
3-a	30	30	3	DVT	First time	AT deficiency	0	1
3-b	30	36	1	DVT	Second time	AT deficiency	0	2
4	32	20	1	DVT	Second time	AT deficiency	0	2
5	22	37	1	DVT	First time	AT deficiency	0	1
6	38	10	2	DVT	Forth time	a-AT deficiency	4	1
7	35	13	1	DVT	First time	PC deficiency	0	1
8	35	8	1	CVST	First time	APS	0	1
9	27	After delivery	1	DVT	First time	Bed rest	0	3
10	29	17	1	CVST	First time	Unknown	0	2
11	30	12	1	DVT	Second time	a-AT deficiency	0	2
12	34	14	1	DVT	Forth time	Dehydration	0	4
13	28	11	1	DVT	First time	PC and PS deficiency	0	On going
14	35	40	1	TIA	First time	Suspected PIH	0	1
15	32	8	1	DIC	First time	APS	0	2
16	34	23	1	DVT	Second time	Unknown	0	2
17	30	29	1	DVT	First time	Unknown	0	On going

TH thrombosis, *PIH* pregnancy-induced hypertension, *DVT* deep vein thrombosis, *CVST* cerebral venous sinus thrombosis, *TIA* transient ischemic attack, *AT* antithrombin, *PC* protein C, *PS* protein S, *a-AT* acquired AT deficiency, *APS* antiphospholipid antibody syndrome

population is generally considered to be low, evidence of thrombophilia is found to be present in as many as 50 % of women who develop pregnancy-related VTE [6]. Whereas the *F5* R506Q (Factor V Leiden; FVL) and *F2* G20210A (prothrombin G20210A) mutations [11] are the most prevalent types of inherited thrombophilia in Europe and North American, there are no reports of these mutations in Japanese patients. The thrombotic risk is greater in association with homozygous or compound genetic defects of natural anticoagulants [12]; however, these cases are rare. The most common acquired thrombophilia associated with an increased risk of VTE in pregnancy is antiphospholipid antibody syndrome (APS) [13]. APS has been reported to be associated with the risk of thrombosis during pregnancy, with an odds ratio (OR) of 15.8 [14]. Furthermore, a Canadian population-based study found APS to be associated with PE, with an OR of 12.9 (95 % CI 4.4–38.0), and DVT, with an OR of 5.1 (95 % CI 1.8–14.3) [15].

In this study, we examined hemostatic abnormalities in 18 pregnant women with thrombosis to evaluate the role of AT in thrombosis due to pregnancy in comparison to that observed in DVT patients undergoing major orthopedic surgery.

Materials and methods

The thrombotic risk factors were examined in 18 pregnant women with thrombosis at Mie University Hospital treated from January 1, 1998 to March 28, 2015 (Table 1) compared to that observed in 35 patients with DVT undergoing major orthopedic surgery (75.0 years: 68.0–80.0 years). The study protocol was approved by the Human Ethics Review Committee of the Mie University School of Medicine and a signed consent form was obtained from each subject. This study was faithfully carried out in accordance with the Declaration of Helsinki. DVT was diagnosed using echography or venography, and disseminated intravascular coagulation (DIC) was diagnosed according to the International Society of Thrombosis and Haemostasis overt-DIC diagnostic criteria [16]. Cerebral vascular disease was diagnosed with computed tomography or magnetic resonance imaging (MRI), and cerebral venous sinus thrombosis (CVST) was diagnosed based on MRI, magnetic resonance venography (MRV) or cerebral angiography (CAG).

Measurement of the AT, PC, PS and antiphospholipid antibody concentrations

Peripheral blood samples were collected in a 1/10 volume of 3.13 % sodium citrate. The free PS antigen concentration was measured using a monoclonal antibody-based enzyme-linked immunosorbent assay (ELISA) with the Asserachrom free PS kit (Diagnostica Stago, Asnières, France). The plasma PS and PC activity levels were measured according to the clotting time method using STA®-Staclot® Protein S and STA®-Staclot® Protein C kit

(Diagnostica Stago, respectively). The plasma PC antigen concentration was measured based on a latex agglutination test using a LPIA-ACE PC kit (Mitsubishi Chemical Medience Corporation, Tokyo, Japan). The plasma AT activity was measured according to a synthetic substrate assay using a Chromorate ATIII (C) kit (Mitsubishi Chemical Medience Corporation). The dilute Russell's viper venom time (DRVVT) was measured with the clotting time method using a Gradipore LA test (Gradipore, Sydney, Australia). The titers of anti-cardiolipin-β2 glycoprotein I (ACL-β2GPI) antibodies were measured with an ELISA kit (Yamasa Co, Tokyo, Japan) [17].

Gene analysis of AT, PC and PS

Genomic DNA was prepared from peripheral blood leukocytes using a QIAamp DNA Blood Mini Kit (QIAGEN) according to the manufacturer's instructions. Each exon and exon/intron boundary of the gene was amplified from genomic DNA using polymerase chain reaction (PCR), as previously described. The PCR products were directly sequenced using a Big-Dye Terminator Cycle Sequencing Kit and Applied Biosystems 3130 Genetic Analyzer (Applied Biosystems, Foster City, CA, USA) [17]. Gene analyses were carried out in cases with AT, PC or PS levels less than 70 %.

Statistical analysis

The data are expressed as the median (25th–75th percentile). Differences between the groups were examined for statistical significance using the Mann–Whitney *U* test. A *p* value of <0.05 denoted the presence of a statistically significant difference.

Results

There were 17 patients with pregnancy-related VTE, including one woman with congenital AT deficiency and her mother. There were five families with congenital AT deficiency and two families with congenital PC deficiency. One woman with PC deficiency showed PS Tokushima (Table 1). These patients were diagnosed as having thrombophilia based on a genetic analysis after developing VTE. The age of onset of thrombosis was 30.0 years (28.8–34.3 years), and thrombosis appeared during first trimester in eight cases, during second trimester in three cases, during third trimester in five cases and after delivery in two cases. Fourteen of the eighteen women demonstrated thrombosis at the first pregnancy. There were 14 cases of DVT, three cases of CVST, one case of DIC and one case of TIA. The cause of thrombosis was considered to be AT

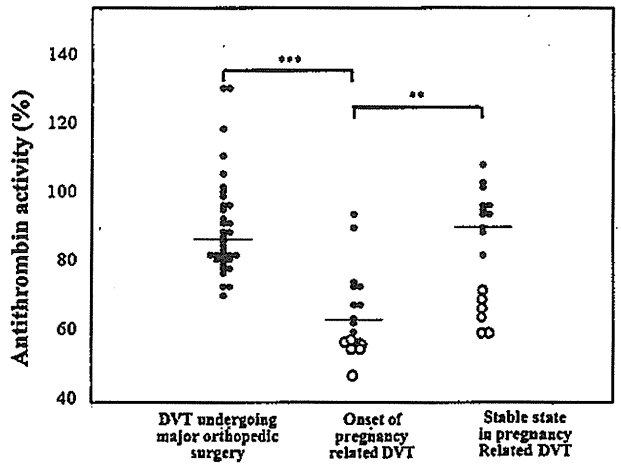

Fig. 1 AT activity at onset and in the stable state of pregnancy-related VTE and in the DVT patients undergoing major orthopedic surgery. $^{**}p < 0.01$, $^{***}p < 0.005$. *Open circle* congenital AT deficiency. *DVT* deep vein thrombosis, *VTE* venous thromboembolism

deficiency in eight cases, APS in two cases, PC deficiency in one case, PC and PS deficiency in one case, bed rest in one case, pregnancy-induced hypertension in one case, dehydration in one case and unknown in three cases. An abortion occurred in only two cases.

The AT activity levels were significantly lower at the onset of thrombosis (62.0 %: 56.8–72.5 %) than after delivery and anticoagulant therapy (89.2 %: 67.7–95.7 %, $p < 0.005$) and in the DVT patients undergoing major orthopedic surgery (86.2 %; 80.7–96.4 %, $p < 0.001$, Fig. 1). The PS activity and antigen levels were also significantly lower at the onset of thrombosis (50.0 %: 40.2–60.4 % and 60.0 %: 49.4–81.4 %) than after delivery and without warfarin therapy (83.2 %: 69.8–95.3 % and 90.9 %: 73.6–114.0 %, $p < 0.01$ and $p < 0.05$). There were no significant differences in the PC activity or antigen levels between the onset of thrombosis and the stable state after delivery and without warfarin therapy (Table 2). In cases 1–5, the AT activity was significantly low in the stable state and became lower at the onset of thrombosis. Although the AT levels were normal before pregnancy, they subsequently decreased and the patients required the administration of AT after pregnancy in Cases 6 and 11. Table 3 shows the veins in which thrombosis related to pregnancy occurred. The frequency of DVT was relatively higher in the left vein than in the right vein. In the DVT patients undergoing major orthopedic surgery, DVT occurred in the form of soleus vein thrombosis.

In the gene analyses (Table 4), AT Budapest [18] was noted in case 1, AT Toyama [19] was noted in case 2 and AT Glasgow [20] was noted in cases 3-a and 3-b, 4 and 5. Although the patients in cases 3-a and 3-b were from the same family, the patients in cases 3–5 were from different

Table 2 AT, PC and PS levels at the onset of thrombosis

	AT activity (%)		PC activity (%)		PC antigen (%)		PS activity (%)		PS antigen (%)	
	Onset	Stable	Onset	Stable	Onset	Stable	Onset	Stable	Onset	Stable
1	55.5	63.6	–	107	–	108	–	127	–	120
2	56.0	70.0	–	–	98	–	–	–	60	–
3-a	–	59.1	–	147	–	135	–	–	97	114
3-b	59.0	59.4	113	–	–	–	24	–	–	–
4	57.4	71.4	–	89.0	–	–	–	66	–	73
5	47.5	65.4	–	126	–	116	61	89	51	79
6	56.8	108	105	100	91	96	56	77	–	–
7	56.9	89.8	61	60	56	58	61	–	–	–
8	94.2	102	105	102	–	–	49	98	91	102
9	–	93.0	–	98.0	–	–	–	49 ([a])	–	–
10	63.9	82.0	138	–	134	–	50	73	36	63
11	72.0	96.8	104	–	95	–	57	–	58	–
12	62.0	92.9	97	–	90	–	39	–	44	–
13	67.9	–	55	–	39	–	43	–	62	–
14	72.6	96.8	–	–	–	–	–	–	–	–
15	73.3	88.6	109	–	95	–	39	–	–	–
16	89.7	94.6	109	103	100	104	66	92	78	–
17	66.8	103	134		128		27		61	

AT antithrombin, *PC* protein C, *PS* protein S

[a] Pregnant state

Table 3 Thrombosis

Name	Vein
1	DVT (left femoral and soleus vein), CVST (straight sinus)
2	DVT (left femoral and soleus vein)
3-a	DVT (right iliac and femoral vein)
3-b	DVT (left femoral vein)
4	DVT (left iliac, femoral and soleus vein)
5	DVT (left iliac, femoral and soleus vein)
6	DVT (left external iliac and femoral vein), DVT (left and right femoral and soleus vein)
7	DVT (inferior vena cava, left iliac, femoral and soleus vein)
8	CVST (right transverse sinus)
9	Left DVT ([a])
10	CVST (right transverse sinus)
11	DVT (inferior vena cava, left iliac, femoral, superficial femoral and popliteal vein)
12	DVT (right common iliac, external iliac and common femoral vein)
13	DVT (right external iliac vein)
14	No findings in MRI
15	DIC
16	DVT (right soleus vein)
17	DVT (left external iliac and femoral vein)

DVT deep vein thrombosis, *CVST* cerebral venous sinus thrombosis, *MRI* magnetic resonance imaging

[a] Data were not available

families and were not relatives. Protein C Tochigi [21] was observed in case 7 and combined heterozygous PC deficiency [22] and PS Tokushima [23] was observed in case 13. There were no cases in which the AT, PC or PS levels were less than 70 % of among the DVT patients undergoing major orthopedic surgery.

Table 4 Gene analysis

Name			cDNA change	Amino acid change
1	AT Budapest [18]	Type II	c.1382C>T	p.Pro461Leu
2	AT Toyama [19]	Type II	c.235C>T	p.Arg79Cys
3-a	AT Glasgow [20]	Type II	c.1274G>A	p.Arg425His
3-b	AT Glasgow [20]	Type II	c.1274G>A	p.Arg425His
4	AT Glasgow [20]	Type II	c.1274G>A	p.Arg425His
5	AT Glasgow [20]	Type II	c.1274G>A	p.Arg425His
7	Protein C Tochigi, Protein C Osaka-1 [21]	Type I	c.631C>T	p. Arg211Trp
13	Protein C [22]	Type I	c.400G>T	p.Glu134X
	Protein S Tokushima [23]	Type II	c.586A>G	p.Lys196Glu

AT antithrombin, *PC* protein C, *PS* protein S

Discussion

Maternal factors are important for the onset of pregnancy-related VTE [14]. In the current study, the median age of pregnancy-related VTE was 30.0 years, suggesting that late child bearing is not a main cause of pregnancy-related VTE.

Several previous reports [24, 25] have suggested that the onset of pregnancy-related VTE in cases of thrombophilia occurs in early pregnancy. In our study, pregnancy-related VTE tended to occur during the first and second trimesters, and most case of pregnancy-related VTE appeared during the patient's first pregnancy, suggesting that thrombophilia is an important factor for the onset of thrombosis during pregnancy. VTE, such as DVT and CVST, was observed in this study. Although DVT is the most frequent type of VTE, CVST [26, 27] is rare among cases of VTE. The diagnosis of CVST provides an important clue to suspect CVST. Most lesions of pregnancy-related VTE involved proximal DVT in this study; however, DVT was distal in the patients undergoing major orthopedic surgery, as patients undergoing major orthopedic surgery are treated with anticoagulants [28]. Although patients with pregnancy-related VTE have a risk of developing fatal PE, pregnant women are usually not treated with anticoagulants such as warfarin. Therefore, these patients require intravenous heparin administration.

In terms of the causes of thrombosis, hemostatic abnormalities were noted in 12 cases (approximately 66 %). In particular, congenital or acquired AT deficiencies were observed in eight cases (approximately 44 %). The AT activity was significantly low in the stable state of congenital AT deficiency and decreased further at the onset of thrombosis. Although the AT levels were normal before pregnancy in the cases of acquired AT deficiency, they subsequently decreased and the patients required the administration of AT during pregnancy and after delivery. AT deficiency has been reported to be an independent risk factor for pregnancy-related VTE [10]. AT deficiency is also observed in patients with pregnancy-induced hypertension [29]. Congenital or acquired AT deficiency may be important for the onset of pregnancy-related VTE. However, AT deficiency was not observed in the DVT patients undergoing major orthopedic surgery in this study, and the PS activity and antigen levels were also significantly low at the onset of pregnancy-related VTE in comparison to that observed in the stable state or in the DVT patients undergoing major orthopedic surgery. Although the decreased PS levels noted in pregnant women have been reported to be caused by estrogen [30], the relationship between decreased PS levels and pregnancy-related VTE remains unclear. APS is also important for pregnancy-related VTE, as reported in Case 15 [31]. While there were two cases of congenital PC deficiency, in the current study, there were no significant differences in the PC levels between the onset of VTE and in the stable state, suggesting that pregnancy may not decrease the PC levels.

In the gene analyses, six pregnant women with VTE were diagnosed as having congenital AT deficiency, indicating that the rate of congenital AT deficiency is markedly high in cases of pregnancy-related VTE. A previous study [10] reported that AT deficiency is a risk factor for pregnancy-related VTE. Notably, AT Budapest [18], AT Toyama [19] and AT Glasgow [20] were noted in this study. Although the patients in Cases 3–5 from different families were not relatives, the far ancestors of these families may be the same. There were two cases of congenital PC deficiency in this report; however, the relationship between PC deficiency and pregnancy-related VTE was not clarified.

In conclusion, a deficiency of natural anticoagulants, especially AT, is frequently observed in patients with pregnancy-related VTE and is an important cause of pregnancy-related VTE.

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Compliance with ethical standards

Conflict of interest There are no conflicts of interest for any of the authors in association with this study.

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ORIGINAL ARTICLE
Stroke

Maternal Death Due to Stroke Associated With Pregnancy-Induced Hypertension

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Background: The aim of this study was to clarify the clinical features of maternal death due to stroke associated with pregnancy-induced hypertension (PIH) in Japan.

Methods and Results: Reported maternal deaths occurring between 2010 and 2012 throughout Japan were analyzed by the Maternal Death Exploratory Committee. Among a total of 154 reports of maternal death, those due to stroke with (n=12) or without (n=13) PIH were compared. Cerebral stroke occurred more frequently in the third trimester and during the second stage of labor in deaths with PIH, whereas it occurred at any time point in deaths not involving PIH. Although 83% of patients with PIH who died had experienced initial symptoms in a hospital, more than half of them required maternal transport due to lack of medical resources. Among the patients without PIH, some vascular abnormalities were identified, but no evidence was found among the patients with PIH. In addition, 58% of PIH cases resulting in stroke were complicated by hemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome.

Conclusions: Appropriate management of PIH during pregnancy and labor, including anti-hypertensive therapy and early maternal transport to tertiary hospital, may reduce the maternal death rate. (*Circ J* 2015; **79:** 1835–1840)

Key Words: Hemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome; Intracerebral hemorrhage; Maternal death; Pregnancy-induced hypertension; Stroke

The pathophysiology of pregnancy-induced hypertension (PIH) is complex and involves multiple systems. In this disorder, increasing resistance of maternal systemic blood vessels adversely affects the blood flow in many organ systems, including the liver, kidneys, brain and placenta in pregnant women.[1,2] Women with pre-eclampsia and eclampsia have a 3–25-fold increased risk of serious complications such as pulmonary edema, abruption, aspiration pneumonia, renal failure, hepatic failure, disseminated intravascular coagulation (DIC) and stroke.[3,4] Without appropriate management, PIH progresses to severe maternal and fetal pathologies resulting in stillbirth as well as maternal death. Especially, pre-eclampsia is a known risk factor in 25–45% of stroke cases during pregnancy.[5,6]

Editorial p1695

Although the maternal mortality rate in Japan is not high (4:100,000)[7] compared with that observed in other developed countries, in order to reduce the mortality rate, the Japan Association of Obstetricians and Gynecologists (JAOG) established a registration system for tracking maternal deaths in 2010. Subsequent JAOG analysis has shown that PIH remains an important cause of maternal death.[8]

Therefore, we believe that it is necessary to clarify the clinical course and features of maternal death due to PIH in order to make recommendations and thus reduce the maternal mortality rate. The purpose of the present study was to clarify the clinical features of maternal death associated with PIH in Japan.

Methods

Maternal deaths associated with PIH in Japan between 2010 and 2012 were reviewed to clarify patient clinical features. Then, the clinical characteristics in maternal death due to stroke

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Table 1. Characteristics of Maternal Death Associated With PIH

ID no.	Age (years)	G	P	Height (cm)	Weight (kg)		BMI at delivery	Before onset	Direct cause of death	Onset	
					At delivery	Before pregnancy		BP (mmHg)/ medication		GA (weeks)	BP (mmHg)
1	40	0	0	162	67		25.5	150/90 (No)	ICH (R nucleus caudatus)	34	190/115
2	23	1	0		62	49		141/94 (No)	ICH (bl. basal ganglia)	37	201/126
3	32	1	1	165	53		19.5	150/90 (No)	ICH (L frontal lobe)	39	170/100
4	30	1	1	147	55	42	25.2	150/100 (No)	ICH (L thalamus)	38	179/116
5	36	1	1	158	60	54	24	164/100 (AMD)	ICH (R lateral ventricle)	36	158/108
6	35	2	2	153	79	74	33.7	181/102 (No)	ICH	41	181/131
7	27	0	0		62	49		173/114 (hydralazine)	ICH (bl. cerebrum)	38	184/130
8	45	9	2	155	57	43	23.6	155/98 (No)	ICH (L frontal, occipital)	39	192/100
9	33	0	0	152	62		26.8	194/134 (No)	ICH (bl. temporal lobe)	38	222/123
10	38	1	0	164	66		24.5	141/81 (No)	ICH (brainstem)	40	166/95
11	28	0	0	155		63		166/108 (No)	ICH (L lateral ventricle)	36	180/110
12	34	1	1	158	64		25.6	170/98 (No)	ICH (diffuse cerebrum)	33	170/107
13	36	2	2	155	57		23.7	164/86 (No)	Pulmonary edema	38	219/110
14	34	2	2	158	70	57	28.1	154/95 (No)	Cardiomyopathy	38	160/110
15	29	3	3	156	56	52	23	140/90 (No)	Amniotic fluid embolism	35	80/22
16	34	0	0	156	67		27.7	141/81 (No)	Unexplained	40	NR
17	33	1	1	161	102	104	39.4	200/140 (hydralazine)	Unexplained	36	90/40

AMD, α-methyldopa; bl., bilateral; BMI, body mass index; BP, blood pressure; CS, cesarean section; G, gravida; GA, gestational age (GA at delivery used in cases of puerperium onset); HELLP, hemolysis, elevated liver enzymes and low platelet count; ICH, intracerebral hemorrhage; JNS, Japan Neurosurgical Society; L, left; NR, not reported; P, parity; PIH, pregnancy-induced hypertension; R, right.

(Table 1 continued the next page.)

associated with PIH were compared with that without PIH collected by the JAOG and analyzed by the Maternal Death Exploratory Committee.

When maternal death occurs in Japan, a detailed report is submitted to JAOG and the individual data are analyzed by the Maternal Death Exploratory Committee (Chairman: T. Ikeda). This committee consists of 15 obstetricians, 4 anesthesiologists, 2 pathologists, an emergency physician and various specialists who attend review sessions each month to make annual recommendations to reduce the maternal mortality rate. The present study was performed as part of a series analyzing maternal deaths in Japan by this committee.[9]

In cases of maternal death in which the mother died during pregnancy or within 1 year after delivery, report forms are submitted to the registration system. The report form contains 22 pages of approximately 100 questions to elicit detailed information regarding the clinical history of each death and the characteristics of the facility and personnel that participated in the patient's care (**Supplementary File 1**). All anonymized reports are analyzed for factors associated with maternal mortality and the circumstances of death.

The definition and classification of PIH followed the guidelines published by the Japan Society for the Study of Hypertension in Pregnancy for Japanese obstetric care providers.[10] PIH was defined as hypertension (blood pressure ≥140/90 mmHg) with or without proteinuria (≥300 mg/24 h) emerging after 20 weeks of gestation and resolving up to 12 weeks after delivery. Furthermore, it is recommended in the guidelines proposed by the Japan Society of Obstetrics and Gynecology that hypotensive drugs, including α-methyldopa (250–2,000 mg/day), hydralazine (30–200 mg/day), nifedipine (20–40 mg/day) or labetalol (150–450 mg/day), should be administered, if systolic blood pressure is ≥160 mmHg or if the diastolic blood pressure is ≥110 mmHg. When a sudden elevation of blood pressure occurs during labor (≥160/110 mmHg), the use of hydralazine or nicardipine should also be considered.[11]

In Japan, pregnant women usually undergo regular prenatal checkups, which include blood pressure measurement and a urine test every 2 weeks after 26 weeks' gestation and every week after 36 weeks. Thus, patients are evaluated for PIH at least every 2 weeks. Therefore, in the present study, "patients without PIH" were defined as those in whom PIH had not appeared by the final examination in a hospital or in the recent prenatal checkups.

The diagnosis and location in the brain of intracerebral hemorrhage (ICH), subarachnoid hemorrhage and ischemic stroke

ID no.	Onset				Maternal transfer (duration from onset to admission)	Hospital characteristics (JNS category)	HELLP syndrome	Complication
	Timing	Time (h)	Symptom	Location				
1	During pregnancy	17:30	Hypertension	Outside	Yes (5h)	Medical center (branch)	Yes	
2	During pregnancy	2:30	Headache	Outside	Yes (3h)	Medical center (branch)	Yes	
3	During pregnancy	4:55	Chest pain	General hospital	Yes (1h)	City hospital (branch)	Yes	
4	During pregnancy	13:20	Consciousness disorder	General hospital	Yes (18h)	University hospital (core)	Yes	
5	During pregnancy	23:50	Headache	General hospital	Yes (4.5h)	City hospital (branch)	No	
6	During labor (1st stage)	17:50	Consciousness disorder	Private clinic	Yes (4h)	City hospital (branch)	No	
7	During labor (2nd stage)	18:15	Consciousness disorder	Private clinic	Yes (2h)	University hospital (core)	No	
8	During labor (2nd stage)	3:00	Consciousness disorder	General hospital	No	University hospital (core)	No	Depression, asthma
9	During labor (2nd stage)	14:25	Consciousness disorder	General hospital	No	City hospital (branch)	Yes	Uterine myoma
10	During labor (2nd stage)	23:35	Headache	General hospital	No	Medical center (branch)	No	Basedow disease
11	Puerperium (4h)	18:30	Consciousness disorder	General hospital	No	General hospital (branch)	Yes	
12	Puerperium (9h)	17:00	Consciousness disorder	General hospital	No	Medical center (core)	Yes	
13	During pregnancy	11:00	Cough	Private clinic	Yes (33h)	Medical center	No	
14	Puerperium (day 10)	9:00	Edema	General hospital	No	University hospital	No	von Recklinghausen type I
15	During CS	10:00	Consciousness disorder	General hospital	No	City hospital	No	
16	During labor (2nd stage)	21:30	Consciousness disorder	Private clinic	Yes (3h)	University hospital	No	
17	Puerperium (9h)	1:15	Dyspnea	General hospital	No	Medical center	No	

were based on the interpretation of imaging by a radiologist and/or neurosurgeon using computed tomography (CT) and/or magnetic resonance imaging (MRI), and/or based on the findings during surgery or autopsy.

Statistical significance was defined as $P<0.05$. The data were entered into SPSS (Windows version 20.0 J; SPSS, Chicago, IL, USA). Continuous variables are reported as the median and range according to Mann-Whitney U-test. Categorical variables are reported as frequencies and were compared using Fisher's exact test.

Ethics

This study was approved by the ethics board of National Cerebral and Cardiovascular Center, Osaka, Japan and the JAOG. This investigation was conducted according to the principles expressed in the Declaration of Helsinki. Informed consent was not obtained from patients and their family, because this study was based on analysis of reported forms from institution, and patient records/information was anonymized and de-identified prior to analysis.

Results

A total of 154 reports of maternal death (reports sent from 151 institutions in a total of 2,683 institutions that provide maternity services across Japan identified from a hospital list of the JAOG) were analyzed by the Maternal Death Exploratory Committee between 2010 and 2012. The maternal death rate (per 100,000 births) was 4.8 in 3,236,452 births after 12 weeks of pregnancy in Japan between 2010 and 2012.[7] Of these, 17 met the criteria for PIH at the onset of initial symptoms (11% of all maternal deaths). The characteristics of the patients with maternal death associated with PIH are given in Table 1. The final diagnosis of the direct cause of maternal death was cerebral stroke in 12 cases (71%) of maternal death associated with PIH. Of the remaining 5 maternal deaths associated with PIH, direct cause of death was pulmonary edema in 1 case, cardiac myopathy in 1 case, amniotic fluid embolism in 1 case, and not clearly explained due to the presence of multifactorial factors in 2 cases.

The clinical characteristics of the maternal deaths due to stroke associated with PIH were compared with those of the 13 cases without PIH collected by the JAOG and analyzed by the Maternal Death Exploratory Committee. The characteristics of the maternal deaths due to stroke without PIH are listed in Table 2.

The clinical features of the maternal deaths due to stroke vs. the presence of PIH are listed in Table 3. The maternal characteristics did not differ between the patients with and without PIH. The median gestational age at the onset of ICH was 38 weeks (range, 33–41 weeks) in the patients with PIH, whereas stroke occurred at any time point, ranging from 9 to 39 weeks'

Table 2. Characteristics of Maternal Death Due to Stroke Without PIH

ID no.	Age (years)	G	P	Height (cm)	Weight (kg)		BMI at delivery	Direct cause of death	Onset		
					At delivery	Before pregnancy			GA (weeks)	BP (mmHg)	Timing
1	33	1	1					ICH (brainstem)	9	140/90	After artificial abortion
2	22	0	0	162	100	97	38.1	ICH (thalamus)	17	Unknown	During pregnancy
3	32	2	2	154	62		26.1	Subarachnoid bleeding	22	Unknown	During pregnancy
4	33	1	1					Subarachnoid bleeding	23	Unknown	During pregnancy
5	28	1	1	155	47	37	19.6	ICH	29	Unknown	During pregnancy
6	40	2	2	161	80		30.9	ICH	31	Unknown	During pregnancy
7	32	0	0	152	60		26	ICH (bl. lateral ventricle)	33	203/146	During pregnancy
8	40	3	3	156	72		29.6	ICH (bl. lateral ventricle)	37	NR	During pregnancy
9	37	0	0			47		ICH (R frontal lobe)	39	119/76	During labor (1st stage)
10	35	1	1	155	53	44	22.1	ICH (L frontal lobe)	38	146/70	Puerperium (9h)
11	37	0	0	157	54		21.9	Subarachnoid bleeding	33	200/100	Puerperium (1 day)
12	38	1	0	175	72	62	23.5	Subarachnoid bleeding	38	195/120	puerperium (1 day)
13	32	0	0	166	62	54	22.5	Ischemic stroke	35	NR	puerperium (9 days)

ID no.	Onset			Maternal transfer (duration from onset to admission)	Hospital characteristics (JNS category)	HELLP syndrome	Complication
	Time (h)	Symptom	Location				
1	11:00	Consciousness disorder	Private clinic	Yes (50 min)	University hospital (core)	No	
2	NR	Consciousness disorder	Outside	Yes (3h)	City hospital (branch)	No	
3	14:15	Consciousness disorder	Outside	Yes	Medical center (branch)	No	
4	14:00	Consciousness disorder	Outside	Yes (50 min)	University hospital (core)	No	
5	20:30	Headache	Outside	Yes	City hospital (branch)	No	
6	NR	Convulsion, dyspnea	Outside	Yes	University hospital (core)	No	
7	7:00	Headache	Private clinic	No	Medical center (branch)	No	
8	14:00	Headache	General hospital	No	University hospital (core)	No	ITP, moyamoya
9	6:50	Convulsion, dyspnea	Private clinic	Yes (2h)	University hospital (core)	No	AVM
10	22:00	Consciousness disorder	General hospital	Yes (3h)	General hospital (branch)	No	Suspected AVM
11	11:00	Hypertension	General hospital	Yes (30 min)	City hospital (branch)	No	Aneurysm, PA, DIC
12	7:18	Headache	General hospital	Yes (2h)	City hospital (branch)	No	
13	12:00	Consciousness disorder	General hospital	No	Medical center (branch)	No	Massive bleeding, DIC

AVM, arteriovenous malformation; DIC, disseminated intravascular coagulation; ITP, idiopathic thrombocytopenic purpura; moyamoya, moyamoya disease; PA, placental abruption. Other abbreviations as in Table 1.

Table 3. Clinical Features of Maternal Death Due to Stroke vs. Presence of PIH

	With PIH (n=12)	Without PIH (n=13)	P-value
Maternal characteristics			
Age (years)	34 (23–45)	33 (20–44)	0.810
Gravida	1 (0–9)	1 (0–3)	1.000
Parity	1 (0–2)	1 (0–3)	0.769
Height (cm)	157 (147–165)	157 (152–175)	0.631
Weight before pregnancy (kg)	49 (42–74)	51 (39–97)	1.000
At delivery (kg)	62 (53–79)	65 (47–100)	0.863
BMI at delivery	25.2 (19.5–33.7)	24.7 (19.6–38.1)	1.000
Onset of cerebral stroke			
Gestational weeks at onset (delivery)	38 (33–41)	33 (9–39)	0.009
Blood pressure (mmHg) at initial symptom			
Systolic	170 (112–192)	171 (119–203)	0.750
Diastolic	100 (89–134)	95 (70–146)	0.616
Timing of onset			
Before onset of labor	42 (5)	54 (7)	0.695
During first stage of labor	8 (1)	8 (1)	1.000
During second stage of labor	33 (4)	0 (0)	0.039
Puerperium	17 (2)	31 (4)	0.363
Location at onset			
Outside hospital	17 (2)	38 (5)	0.223
Private clinic	17 (2)	23 (3)	1.000
General Hospital	67 (8)	38 (5)	0.238
Maternal transport	58 (7)	77 (10)	0.411

Data given as median (range) or % (n). Abbreviations as in Table 1.

gestation, in the patients without PIH. Cerebral stroke occurred more frequently during the second stage of labor (33%) among the patients with PIH, whereas this symptom was more likely to occur after delivery (40%) among the patients without PIH.

Stroke occurred outside of the hospital in 38% of patients without PIH, and in 17% of those with PIH. Whereas 83% of patients with PIH who died had experienced initial symptoms in a general or private hospital, more than half of these patients required maternal transport due to a lack of medical resources, such as specialists (brain surgeons and/or emergency physicians), medical staff, stored blood, imaging modalities, such as CT and MRI, and/or intensive care units.

The cause of cerebral stroke was ICH in all patients with PIH, whereas, in the patients without PIH, ICH was noted in 8 (62%), with subarachnoid hemorrhage being diagnosed in 4 of the 13 patients (31%) and hemorrhagic infarction in 1. Among the patients without PIH, moyamoya disease, cerebral aneurysm, arteriovenous malformation and protein S deficiency were considered to be causes of cerebral stroke and maternal death. Moreover, there were 2 cases of stroke possibly induced by massive bleeding complicated by DIC during delivery. Among patients with PIH, however, no evidence of vascular abnormalities was found except for PIH itself. In addition, 7 of the 12 PIH patients who had ICH (58%) also had hemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome.

Discussion

In this review of maternal deaths in Japan between 2010 and 2012, 11% of all maternal deaths were associated with PIH. More than 70% of the causes of maternal death associated with PIH was due to stroke (ICH), and 12 of 25 deaths (48%) due to stroke were associated with PIH, similar to the previous reported rate of eclampsia and pre-eclampsia in patients with ICH ranging from 14% to 50%.[12–15]

Stroke associated with PIH occurred more frequently in the third trimester, especially during the pushing stage of labor, and less frequently after delivery in the patients with PIH, in comparison with maternal deaths due to stroke without PIH.

It is thought that pre-existing cerebral vascular disease plays a significant role in the onset of pregnancy-associated hemorrhagic stroke.[16] In the present case series, stroke occurred at any time period, ranging from 9 to 39 weeks' gestation in the patients without PIH. It has also been reported that hemorrhagic stroke without pre-existing cerebral vascular disease occurred significantly later than that associated with such disorders (mean, 33.7±8.7 weeks vs. 25.3±9.6 weeks, respectively).[16] In patients without PIH, pre-existing brain vascular abnormalities with possible associations with stroke, such as moyamoya disease, cerebral aneurysm and arteriovenous malformation, were reported at imaging facilities in the present study.

ICH is a subtype of stroke that occurs within the brain tissue itself and is a serious medical emergency, because it can increase intracranial pressure.[17] Pregnancy-related ICH has an estimated mortality rate of 9–38%.[13,14,17–19] Because PIH is a disease involving damaged endothelial cells, cerebral ischemia due to spasms and the leakage of cerebral blood vessels may cause cerebral edema and hemorrhage. The higher rate of ICH observed in patients with PIH may be explained by these changes induced by PIH.

More than half of all cases of PIH in our series involved ICH complicated by HELLP syndrome. A previous report showed that 45% of maternal deaths due to HELLP syndrome are associated with cerebral hemorrhage.[20] In addition to hypertension and endothelial dysfunction of the cerebral vasculature, decreased platelet count and coagulation factors may contribute to the high mortality of ICH associated with HELLP syn-

drome.[17]

The physiological changes that occur during pregnancy have a significant impact on the vasculature in cases of arteriovenous malformation, and rupture during pregnancy is by no means coincidental.[16] The significance of pregnancy-associated ischemic and hemorrhagic stroke has been emphasized in patients with moyamoya disease.[21] It should also be noted that not only hypertension during labor, but also pregnancy itself induced stroke in patients with pre-existing vascular abnormalities in the brain.[22]

After a review of these case series, the Maternal Death Exploratory Committee considered most of the cases of stroke without PIH to be unpreventable as a result of sudden unforeseen onset without control outside of the hospital. In contrast, given that most of the cases of ICH occurred around delivery in women with PIH that was not treated using hypotensive drugs before the onset of initial symptoms, such as headache and consciousness disorder, there may be a possibility to avoid maternal death by allowing for the appropriate control of hypertension, termination of the pregnancy or improvement of the medical resources (transfer to a different hospital). Clark et al reported the results of a retrospective evaluation of maternal deaths from 2007 to 2012 after the introduction of disease-specific protocols that included blood pressure management for severe intrapartum or postpartum hypertension based on 2000–2006 data, and noted that there was a significant decline in the rate of deaths from pre-eclampsia.[23] We feel that better recommendations for blood pressure control during pregnancy are needed in Japan.

There are limitations, however, associated with the prevention of maternal death, because it remains unclear whether the ICH in women with PIH was associated with pre-existing brain vascular abnormalities. It was previously reported that the detection rate of hemorrhage in patients with cerebral vascular disease is 71.7% during pregnancy, 23.1% at delivery and 33.5% in the postnatal period.[22] In addition, even if diagnostic imaging of women with pre-existing occult brain vascular diseases was performed during pregnancy, it is unclear whether these diseases can be detected. It also might be difficult to evaluate the details of the blood pressure control in the present case series, because this study was based on analyses of report forms sent from each institution.

Conclusions

ICH was the final causative disease in more than two-thirds of maternal deaths associated with PIH. Although many women were hospitalized due to delivery or the management of PIH, they could not be appropriately treated for PIH at their local hospital, and thus initially experienced serious symptoms. As a result, such women had to be transported to tertiary medical centers due to a lack of medical resources and such delays in receiving proper treatment sometimes resulted in maternal death. Although most maternal deaths are not preventable after the onset of ICH, an increased recognition of PIH, which is directly associated with maternal death, is needed.

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Supplementary Files

Supplementary File 1

Report form for submitting to the maternal death registration system (in Japanese)

Please find supplementary file(s);
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The use of balloons for uterine cervical ripening is associated with an increased risk of umbilical cord prolapse: population based questionnaire survey in Japan

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Abstract

Go to:

Background

To clarify whether the use of balloons for cervical ripening is associated with the incidence of umbilical cord prolapse.

Methods

A postal questionnaire survey was distributed in Japan. Cases of umbilical cord prolapse occurring during labor in association with the use of balloons for cervical ripening between 2007 and 2011 in Japan were analyzed.

Results

Answers from 942 institutions were obtained. The subjects included 369 patients with fore-lying or prolapse of the umbilical cord among a total of 2,037,460 deliveries. Among the singleton vertex cases, fore-lying or prolapse of the umbilical cord during labor were observed in 88 (0.005%) of 1,891,189 deliveries not associated with the use of balloons for cervical ripening and in 93 (0.064%) of 146,271 deliveries associated with the use of balloons for cervical ripening (Odds ratio 13.67, 95% confidence interval 10.21, 18.30). All types of balloons were significantly associated with the occurrence of fore-lying or prolapse of the umbilical cord. A total of 39% of cases of umbilical cord prolapse occurred during manual or spontaneous balloon removal, while 53% of cases occurred after a while not directly associated with balloon removal.

Conclusion

The risk of umbilical cord prolapse was significantly increased during the use of balloons for cervical ripening, especially in cases involving the use of disk-type and ball-type balloons filled with large amounts of water.

Keywords: Cervical ripening balloon, Emergency cesarean section, Fore-lying cord, Perinatal mortality, Umbilical cord prolapse

Background

Go to:

Umbilical cord prolapse can result in poor neonatal outcomes because it may cause the cord to be compressed between the fetus and the maternal bony pelvis or soft tissue, inducing fetal hypoxia [1]. It is previously reported that incidence of umbilical cord prolapse ranges from 0.1 to 0.6% [2-6]. Although the total perinatal mortality and morbidity rates have been decreasing in Japan in association with improvements in neonatal resuscitation and newborn care, umbilical cord abnormalities including umbilical cord prolapse are still remaining causes of unfavorable perinatal outcomes, because cord prolapse can quickly lead to fetal compromise, with resultant long-term disability or death [1,7-10].

Several risk factors associated with umbilical cord prolapse, including fetal anomaly, fetal malpresentation, multiple pregnancy, polyhydramnios, preterm delivery, a birth weight less than 2500 g, preterm premature rupture of membranes [1,2,7,11,12]. Iatrogenic risk factors for umbilical cord prolapse also have been previously reported. Such factors are related to interventions that cause the fetal presenting part to be elevated out of the pelvis or occur following the rupture of the amniotic sac [1]. These interventions include artificial rupture of the membranes, attempted rotation of the fetal head, amnioinfusion, external cephalic procedures in a patient with ruptured membranes, placement of an intrauterine pressure catheter or fetal scalp electrode and the use of cervical ripening balloon catheters [1]. It has been reported that approximately 47% of cases of umbilical cord prolapse can be attributed to iatrogenic factors [8,13].

In these iatrogenic factors, cervical ripening balloons are often used to induce labor in Japan. Although the occurrence of umbilical cord prolapse during the antenatal period is not preventable in most cases, we believe that it is necessary to clarify the relationship between the incidence of umbilical cord prolapse and the use of cervical balloons in order to reduce the morbidity and mortality associated with umbilical cord prolapse. Hence, the accumulation of evidence regarding the relationship between umbilical cord prolapse and the use of balloons for cervical ripening is needed.

Therefore, we conducted a population-based survey of cases of umbilical cord prolapse collected from throughout Japan. The purpose of the present study was to clarify whether the use of balloons for cervical ripening is associated with the occurrence of umbilical cord prolapse.

Methods

Go to:

We conducted a postal questionnaire survey in Japan between August 2012 and June 2013 as an investigation of the Japan Association of Obstetricians and Gynecologists. A total of 2,683 institutions that provide maternity services across Japan were identified from a hospital list. Three pages of questionnaires regarding cases of umbilical cord prolapse and the total number of deliveries in each institution between 2007 and 2011 were sent to these hospitals.

The questions regarding umbilical cord prolapse after 22 weeks' gestation included maternal characteristics and complications, timing of prolapse, use of a balloon for cervical ripening, fetal presentation, gestational age and timing of rupture of the membranes. Answers were based on respective medical records and databases which each hospital held. Each questionnaire was accompanied by a cover letter outlining the aims of the study and was addressed by name to the director, chief obstetrician or consultant in fetomaternal medicine. Answers to the questionnaires were received via facsimile.

Only fully completed answers regarding the number of cases with fore-lying or prolapse of the cord, the number of deliveries and the number of cases involving the use of balloons for cervical ripening during the study period were included in the present study. Among these cases involving fore-lying or prolapse of the cord during intrapartum, singleton vertex of the subjects were divided into cases which were associated with the use of

balloons for cervical ripening and controls which were not associated with the use of balloons (Figure 1). The incidence of fore-lying or prolapse of the umbilical cord was then compared between the cases and the controls.

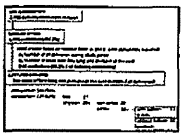

Figure 1
Study flow diagram.

Umbilical cord prolapse was defined as a rupture of the fetal membranes and protrusion of the cord in advance of the fetal presenting part through the cervical os and into or beyond the vagina. Fore-lying of the umbilical cord was defined as the occurrence of an intact fetal membrane in cases in which the umbilical cord preceded the presenting part diagnosed using palpation through the membrane and/or transvaginal ultrasonography.

In most hospitals in Japan, the following three types of balloons are used for cervical ripening: (a) Intra-cervix balloons (usually filled with 40 ml of water and inserted into the uterine cervix), (b) Disk-type balloons (usually filled with 100 ml of water and placed into the uterine isthmus), (c) Ball-type balloons (usually filled with more than 100 ml of water and placed into the uterine isthmus). In cases involving the use of these balloons, the type and amount of water employed to inflate the balloon were recorded (Figure 2). Other types of balloons included double balloon catheter and gourd shape balloon.

Figure 2
Balloons for cervical ripening: (a) Intra-cervix balloon (usually filled with 40 ml of water and inserted into the uterine cervix), (b) Disk-type balloon (usually filled with 100 ml of water and placed into the uterine isthmus), (c) Ball-type ...

Statistical analysis

The frequency of fore-lying or prolapse of the umbilical cord was reported as the percentage and compared using Fisher's exact test. Continuous variables were compared using Student's *t*-test. Ordered variables were compared using the Mann–Whitney *U* test. Statistical significance was defined as a p-value of less than 0.05. The Statistical Package for Social Science (SPSS; Windows version 20.0 J; Chicago, IL, USA) was used for the analyses.

Ethics statement

This study was performed as an investigation of the Japan Association of Obstetricians and Gynecologists (JAOG) and approved by the ethics board of JAOG. Because this was a retrospective analysis based on a questionnaire survey, patient information was anonymized and de-identified prior to answer to questions. Therefore, confidentiality of the patients involved was protected and no personal data were required for the present study.

Results

Go to:

We sent questionnaire to 2,683 delivery institutions in Japan and received replies from 1,455 (54.2%) institutions which had detail database associated with their delivery information. Following exclusion of answers with a deficient number of cases of fore-lying or prolapse of the cord and/or number of deliveries and cases involving the use of balloons for cervical ripening during the study period, answers from 942 institutions were collected in the present study. They included 369 patients with fore-lying or prolapse of the umbilical cord among a total of 2,037,460 deliveries.

A diagnosis of fore-lying or prolapse of the cord during intrapartum was made in 228 (62%) cases, while a diagnosis of them during antepartum period was made in 141. For final analysis, after exclusion of 27 twin