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.

Acknowledgments

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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);
http://dx.doi.org/10.1253/circj.CJ-15-0297

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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.

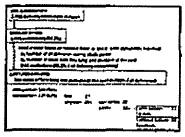

Figure 1
Study flow diagram.

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.

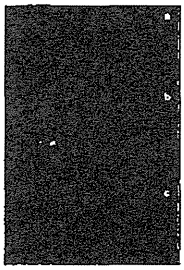

Figure 2
Balloons for cervical ripening: (a) Intra-cervix balloon (usually filled with 40 ml of water and inserted into the uterine cervix), (b) Disk-type balloon (usually filled with 100 ml of water and placed into the uterine isthmus), (c) Ball-type ...

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

pregnancies and 20 non-vertex presentations, a total of 181 singleton vertex cases with fore-lying or prolapse of the cord during labor were enrolled in the present study, and then 93 cases and 88 controls were analyzed. The demographics of these two groups did not differ except gestational weeks, as demonstrated in Table 1.

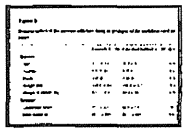

Table 1

Demographics of the patients with fore-lying or prolapse of the umbilical cord among the singleton vertex cases

Balloons for cervical ripening were used in 146,271 cases (7.2% of all deliveries). The mean ± standard deviation of the amount of water used to inflate the balloon for cervical ripening was as follows: 43.0 ± 6.7 ml for intra-cervix balloons, 106.5 ± 9.3 ml for disk-type balloons and 130.9 ± 60.3 ml for ball-type balloons, respectively.

The incidence of fore-lying or prolapse of the umbilical cord in singleton vertex cases involving the use of balloons for cervical ripening is demonstrated in Table 2. Among the singleton vertex cases, fore-lying or prolapse of the umbilical cord during labor was 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 (OR; Odds ratio 13.67, 95% CI; 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.

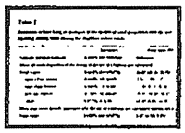

Table 2

Incidence of fore-lying or prolapse of the umbilical cord associated with the use of balloons for cervical ripening during labor among the singleton vertex cases

When only cases directly associated with the use of a balloon (during use and at the time of removal) were calculated, the incidence of fore-lying or prolapse of the umbilical cord was 0.030% (OR 6.47, 95% CI 4.50, 9.29). In this analysis, the frequency of fore-lying or prolapse of the cord did not differ between the cases in which intra-cervix balloons were used and the controls. Fore-lying or prolapse of the cord was diagnosed during the use of balloon in 3% (3/93) of the cases, during spontaneous balloon removal in 25% (23/93) of the cases and during manual balloon removal in 14% (13/93) of the cases, respectively. On the other hand, 53% (49/93) of the cases of umbilical cord prolapse occurred after a while (at least 15 min) not directly associated with balloon removal (not reported in 5% (5/93) of cases).

Discussion

Go to:

To our knowledge, this is the first large population-based investigation to demonstrate the exact prevalence of umbilical cord prolapse in association with the use of balloons for cervical ripening. In the present study, of all 369 cases, one-fourth of the present subjects (93 cases) experienced umbilical cord prolapse during and after the use of a balloon. The prevalence of fore-lying or prolapse of the umbilical cord was only 0.005% in cases not associated with the use of a balloon for cervical ripening, compared to 0.064% (OR 13.67) in the cases associated with the use of a balloon.

A previous study suggested that the use of a trans-cervical balloon catheter with 180–250 ml of saline increases the risk of cord presentation [14]. Similar to previous study, in particular, the use of a ball-type balloon filled with large amount of water (130.9 ± 60.3 ml) was associated with a remarkably high risk (OR 25.83). This odds ratio is highest among those of known risk factors in previous reports [3,4,7,12,15]. However, it is supposed that the increased risk of umbilical cord prolapse in cases involving the use of an intra-cervix balloon filled with approximately 40 ml of water was limited, as the incidence of umbilical cord prolapse after balloon removal did not differ between the patients treated with and without an intra-cervix balloon.

According to the answers to questions in which prolapse of the umbilical cord occurring during labor associated with the use of balloons for cervical ripening, umbilical cord prolapse occurred after a while balloon removal in

more than half of the cases (53%). Even when umbilical cord prolapse did not occur during the use of a balloon or at removal, it may be possible to preserve the elevating fetal presenting part out of the pelvis and induce the wrong rotation of the fetal head, resulting in umbilical cord prolapse. Furthermore, the use of a balloon may involve occult umbilical cord prolapse during the procedure, after which umbilical cord prolapse is detected due to the identification of the descending fetal presenting part or rupture of the membranes. Unfortunately, only 57% of doctors participated in the present study answered that umbilical cord presentation was routinely confirmed using ultrasound scans during the use of a balloon for cervical ripening (data are not shown). Thus, the ultrasound confirmations of the umbilical cord presentation to diagnose fore-lying and occult prolapse of the umbilical cord before balloon placement, after and prior to removal might improve perinatal outcomes.

Questionnaire surveys in large population to obtain enough examples of a rare occurrence have limitations. Compared to western countries, there are a lot of small private hospitals that provide maternity services across Japan. Doctors worked such small hospitals did not retrospectively obtain detail obstetric information and did not answer to this questionnaire survey, because they were unlikely to have computerized database. Therefore, although we believe that the quality of obtained answers was good, this survey was limited by number of response.

Alternatively, since cases whose umbilical cord prolapse was found at just before delivery resulting in delivery without any neonatal complications might not be reported, prevalence of the umbilical cord prolapse might be underestimated. Besides, since the purpose of the present study was to clarify adverse effect of cervical balloon itself such as cord prolapse, the subjects were collected only singleton vertex cases complicated with fore-lying or prolapse of the cord during labor. Therefore, prevalence of fore-lying or prolapse of the cord in the present study was lower (0.005-0.064%) than in some former studies reported a prevalence of them ranging from 0.1 to 0.6% [2-6].

Conclusion

Go to:

Our findings revealed that 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.

Acknowledgements

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We are grateful to everyone who answered the present questionnaire survey and everyone who helped to conduct the present study.

Footnotes

Go to:

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

JH, AS and KK conceived the study, JH wrote the initial protocol, analyzed the data, and wrote the first draft of the manuscript. All authors collected data. JH and AS coordinated the study and, with JH produced the database and analyzed the data. All authors contributed to writing the paper. TI, MK, II, MK and KK are the guarantors for the study. All authors had full access to all of the data in the study, can take responsibility for the integrity of the data and the accuracy of the data analysis, and read and approved the final manuscript.

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ORIGINAL ARTICLE
Peripheral Vascular Disease

Increase in Maternal Death-Related Venous Thromboembolism During Pregnancy in Japan (2010–2013)

Hiroaki Tanaka, MD; Shinji Katsuragi, MD, PhD; Kazuhiro Osato, MD; Junichi Hasegawa, MD, PhD; Masahiko Nakata, MD, PhD; Takeshi Murakoshi, MD, PhD; Jun Yoshimatsu, MD, PhD; Akihiko Sekizawa, MD, PhD; Naohiro Kanayama, MD, PhD; Isamu Ishiwata, MD, PhD; Tomoaki Ikeda, MD, PhD

Background: The aim of the present work was to understand the current circumstances of maternal-death-related venous thromboembolism (MD-VTE) in Japan. We retrospectively investigated the characteristics of cases of MD-VTE, and compared past and present rates of occurrence.

Methods and Results: We examined the Japanese data for MD-VTE in 2010–2013, and compared it with that from 1991–1992. MD-VTE occurred in 17 women in 1991–1992, and in 13 women in 2010–2013. The maternal mortality ratio of MD-VTE was 0.7 per 100,000 in 1991–1992 and 0.4 per 100,000 in 2010–2013. Both the maternal mortality ratio and rate of MD-VTE in 2010–2013 deceased significantly compared with 1991–1992 ($P<0.05$). However, the number of cases of MD-VTE during pregnancy was 6 among 13 women (41%) in 2010–2013, but 1 in 17 women (6%) in 1991–1992, showing an increase ($P<0.05$). In the present study, cesarean delivery was more frequently associated with MD-VTE.

Conclusions: MD-VTE overall has decreased within the past 20 years in Japan. But, MD-VTE during pregnancy in 2010–2013 increased relative to 1991–1992. Future guidelines for prevention of VTE may need to extend beyond the perioperative period to decrease the incidence of MD-VTE. (*Circ J* 2015; 79: 1357–1362)

Key Words: Maternal death; Pregnancy; Pulmonary embolism; Venous thromboembolism

Pregnancy induces numerous physiological changes, which can increase the possibility of thrombosis (eg, increased circulating blood volume).[1–3] In addition, hypercoagulable condition, reduction of fibrinolytic capacity, venous smooth-muscle relaxation, pressure from the uterus, and supine position during delivery can contribute to thrombosis. Therefore, pregnancy has been defined as a risk factor for thrombosis.[4–7]

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Heit et al reported an incidence of thrombosis during pregnancy and postpartum of 199.7 in 100,000 pregnancies.[8] Further, they reported that deep venous thrombosis (DVT) was 5-fold more likely to occur in the postpartum period than during pregnancy (postpartum: 511.2 per 100,000 vs. pregnancy: 95.8 per 100,000), and that pulmonary embolism (PE) was 15-fold more likely to occur postpartum (postpartum: 159.7 per 10,000 vs. pregnancy: 10.6 per 10,000).[8] In Japan, Kobayashi et al[9,10] carried out a questionnaire survey of venous thromboembolism (VTE)-related obstetrics cases at 102 hospitals in 1991–1992 and reported a total number of 76, with a mortality rate of 13.2% (10/76 cases). The time of occurrence of VTE was during pregnancy in 17 of the 76 cases (22.4%), and postpartum in 59 of the 76 cases (77.6%).

Analysis according to delivery mode has confirmed that VTE is more likely to occur with cesarean rather than vaginal delivery.[8–10] Kobayashi et al[9,10] reported pregnancy-associated VTE occurrence rates of 0.003% (9/348.702 pregnancies) for vaginal delivery and 0.06% (50/87,382 pregnancies) for cesarean

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Table 1. Clinical Characteristics of Pregnant Women in Cases of MD-VTE in Japan (2010–2013)

Case no.	Age (years)	Height (cm)	Weight (kg)	BMI	Inherited thrombophilia	Medication
1	28	156	70	29	Unknown	–
2	29	156	80	33	Unknown	–
3	27	153	67	29	Unknown	–
4	39	162	62	23	Unknown	–
5	29	159	66	26	Unknown	–
6	43	160	62	24	Unknown	–
7	39	Unknown	Unknown	Unknown	Unknown	–
8	33	153	53	23	Unknown	–
9	27	156	51	21	Unknown	–
10	34	158	60	24	Unknown	–
11	35	161	62	23	Unknown	–
12	33	Unknown	Unknown	Unknown	Unknown	–
13	32	161	42	16	Unknown	Steroid

Case no.	Maternal complication	Obstetric and gynecologic complications	Familial history of VTE	Time of occurrence	Episode of bed rest and/or dehydration
1	–	CPD	–	Postpartum 3rd day	+
2	–	–	+	14 weeks of pregnancy	+
3	–	NRFHR	Unknown	Postpartum 2nd day	+
4	–	CPD	Unknown	Postpartum 4th day	+
5	–	–	Unknown	Postpartum 30 min	–
6	–	–	Unknown	Post induced abortion 4th day	+
7	–	–	Unknown	9 weeks of pregnancy	+
8	Epilepsy	–	Unknown	39 weeks of pregnancy	–
9	Epilepsy, Cardiovascular disease	–	+	12 weeks of pregnancy	+
10	–	–	–	Postpartum 1 st day	–
11	–	Myoma	Unknown	Postpartum 4th day	+
12	–	Myoma	–	37 weeks of pregnancy	–
13	–	TPL	Unknown	33 weeks of pregnancy	+

BMI, body mass index; CPD, cephalopelvic disproportion; MD, maternal-death-related; NRFHR, non-reassuring fetal heart rate; TPL, threatened premature labor; VTE, venous thromboembolism.

delivery.

As for inherited thrombophilia, the known associated factors include antithrombin deficiency, protein C deficiency, protein S deficiency, Factor V Leiden, and prothrombin gene mutation. Battinelli et al reported that among their cases of pregnancy-associated VTE, patients with a deficiency in antithrombin, protein C or protein S comprised 4.1% (95% confidence interval (CI): 1.7–8.3%), Factor V Leiden comprised 2.1% (95% CI: 0.7–4.9%), and prothrombin gene mutation comprised 2.3% (95% CI: 0.8–5.3%).[11] Factor V Leiden has not be reported in Japan.

Pregnancy-associated VTE has gradually emerged as a topic of further research and discussion, but there are few reports of maternal-death-related VTE (MD-VTE). The aim of the present work was to understand the current circumstances of MD-VTE by retrospectively investigating the characteristics of cases of MD-VTE, and comparing past and present rates of its occurrence in Japan.

Methods

Since 2010, information on all maternal deaths in Japan has been gathered by the Japan Association of Obstetricians and Gynecologists (JAOG). When a maternal death occurs in Japan, a detailed report is submitted to the JAOG and the individual data are analyzed by the Maternal Death Exploratory Committee (Chairman: T. Ikeda). The committee consists of 15 obstetricians, 4 anesthesiologists, 2 pathologists, 1 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. We extracted the data concerning MD-VTE in 2010–2013 from the database.

Data on maternal background, including maternal age, body height and weight, body mass index (BMI), inherited thrombophilia (antithrombin deficiency, protein C deficiency, protein S deficiency, Factor V Leiden, and prothrombin gene mutation), medication during pregnancy, maternal complications, obstet-

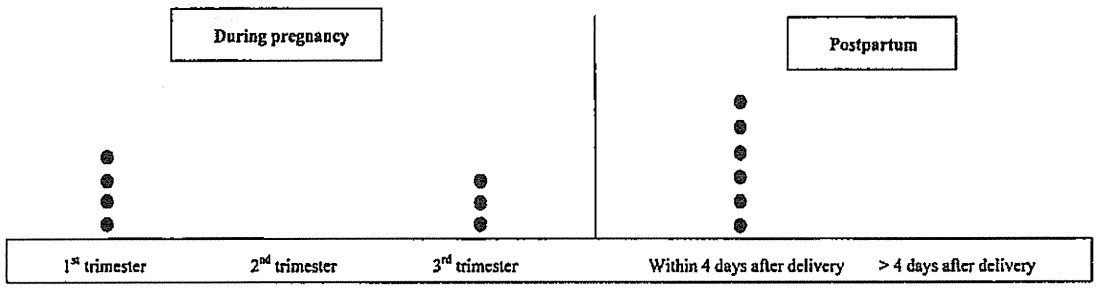

Figure 1. Time of occurrence of maternal-death-related venous thromboembolism.

Table 2. Inciting Episode for Developing MD-VTE and Risk Factors for VTE During Pregnancy (2010–2013)

Case no.	Inciting episode	Risk factors of VTE			
		Obesity	Smoking	Late pregnancy	Other
2	Bed rest because of muscle strain	+	–	–	–
7	Bed rest and dehydration because of hyperemesis	Unknown	Unknown	+	–
8	–	–	Unknown	–	Protein someone deficiency suspected
9	Bed rest and dehydration because of hyperemesis	–	Unknown	–	Cardiovascular disease
12	Dehydration because of common cold	+	–	–	Myoma
13	Bed rest because of TPL	–	Unknown	–	Prescribed steroids for mastocytoma

Abbreviations as in Table 1.

ric complications, familial history of VTE, time of occurrence, and episodes of bed rest, were collected. In cases of postpartum VTE, delivery mode and thromboprophylaxis after delivery were investigated.

For cases of MD-VTE during pregnancy (2010–2013), further details about the inciting episode and risk factors for VTE were investigated.

For analysis of prior cases of MD-VTE we used the data gathered by Nagaya et al, who analyzed all maternal deaths in Japan from 1991 to 1992.[12] Points of comparison included age, BMI, time of occurrence, delivery mode, maternal and obstetric complications, time from onset to cardiac arrest, and maternal mortality ratio. The maternal mortality ratio was defined as the value of all maternal deaths divided by the sum of all live births and fetal deaths, multiplied by 100,000.

In both temporal groups, MD-VTE was defined as VTE demonstrated by contrast enhanced computed tomography, pulmonary arteriography, lung scintigraphy, ultrasound sonography, autopsy imaging, and/or autopsy, and either a number of expert obstetricians in the Maternal Death Exploratory Committee (2010–2013) or Nagaya's group (1991–1992) judging VTE as the cause of death. Time of occurrence was defined as the time symptoms first occurred.

Univariate analysis was performed using the chi-squared test, and the Mann-Whitney U-test and paired t-test were used for statistical analysis. $P<0.05$ was considered significant.

Results

The total number of maternal deaths from January, 2010 through December, 2013 was 184. The cause of maternal death was VTE in 13 women (7.0%). Maternal background data for the MD-VTE cases are shown in Table 1. The median maternal age was 33 years (27–43 years), median maternal height was 158 cm (153–162 cm), median maternal weight was 62 kg (42–80 kg) and median BMI was 24 (16–33). Inherited thrombophilia was unknown in any of the women. None were taking medication that would increase the risk of thrombosis. Diseases complicating maternity were epilepsy in 2 women, but medication for epilepsy was discontinued before pregnancy, as long as the patients remained in good condition. Two women had a familial history of thrombosis; in 1 case, the sister had experienced thrombosis and in the other, an uncle had had a juvenile brain infarction. The period during which VTE occurred was pregnancy in 6 women (46.1%), postpartum in 6 women (46.1%), and after induced abortion in 1 woman (7.6%). None of the women experienced VTE during the 2nd trimester of pregnancy (Figure 1). In all postpartum cases, VTE occurred within 4 days after delivery: delay of early ambulation after delivery in 4 cases; bed rest for a strained muscle in 1 case; bed rest and dehydration because of hyperemesis in 2 cases; long-term bed rest because of threatened premature labor (TPL) in 1 case(Table 2).

The inciting episode for MD-VTE and risk factors for VTE during pregnancy (2010–2013) are shown in Table 2; 5 of 6 women (83.3%) had had an episode of bed rest and/or dehy-

Table 3. Mode of Delivery and Thromboprophylaxis in Postpartum Cases of MD-VTE

Case no.	Mode of delivery	Thromboprophylaxis	Method of prophylaxis		
			Compression stockings	Intermittent pneumatic compression	Heparin
1	Cesarean delivery	−	−	−	−
3	Cesarean delivery	+	+	−	−
4	Cesarean delivery	+	+	+	−
5	Vaginal delivery	−	−	−	−
10	Cesarean delivery	+	+	−	−
11	Cesarean delivery	+	+	−	−

Abbreviations as in Table 1.

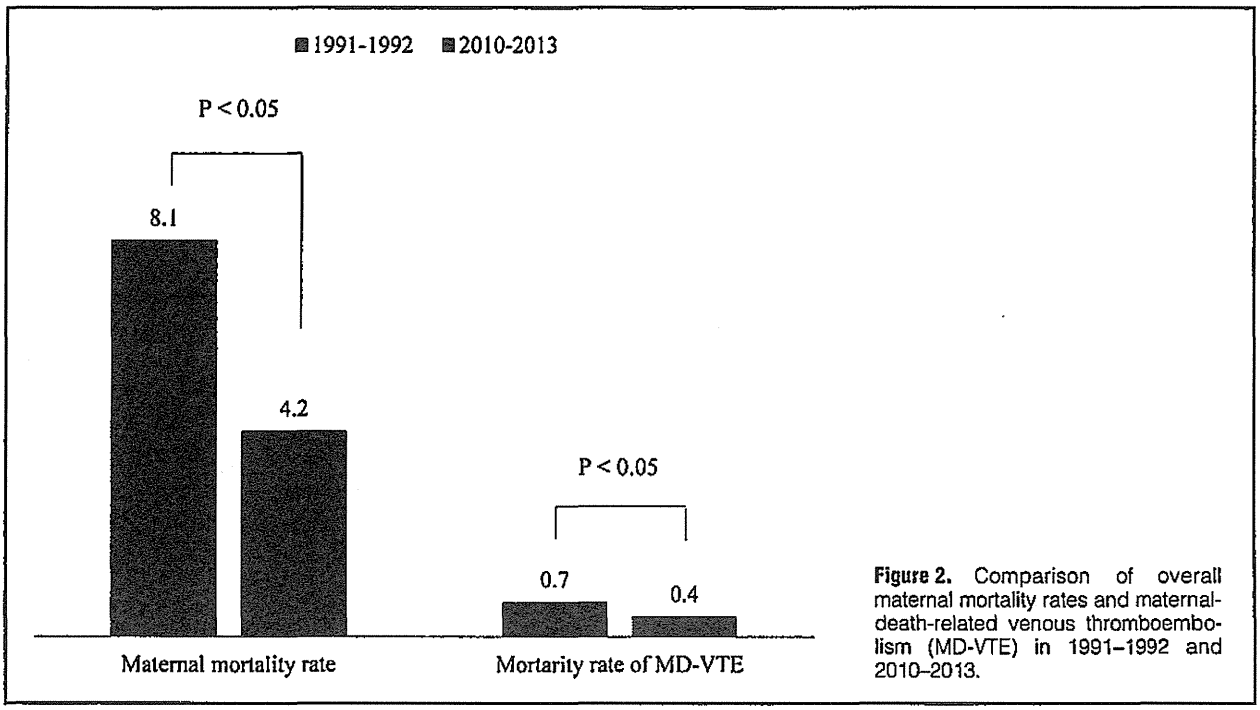

Figure 2. Comparison of overall maternal mortality rates and maternal-death-related venous thromboembolism (MD-VTE) in 1991–1992 and 2010–2013.

dration; 5 of 6 women (83.3%) had had a risk factor for VTE. In case 8 in which there was no inciting episode for developing MD-VTE, the patient was suspected to have protein S deficiency because the value measured at 11 weeks of pregnancy was 28%. The patient in case 2 was obese; case 7 was an older woman; in case 9 there was cardiac depression after Kawasaki's disease; the patient in case 12 was obese and had myoma (height and weight unknown, but obesity suspected from medical record); in case 13 the patient had taken steroids for mastocytoma.

The delivery mode of the postpartum MD-VTE cases was cesarean delivery in 5 of 6 women (83.3%) and vaginal delivery in 1 of 6 women (16.6%). In 3 of 6 women (50.0%), DVT after delivery was prevented by the use of compression stockings (cases 1, 3) or intermittent pneumatic compression (case 4). Heparin was not used to prevent DVT in any case (Table 3).

Comparisons of maternal deaths and MD-VTE in 2010–2013 with those in 1991–1992 are shown in Figure 2 and Table 4. The sum of all live births and fetal deaths in Japan was 2,423,923 in 1991–1992 and 4,291,452 in 2010–2013. Total number of maternal deaths in Japan was 197/2,423,923 in 1991–1992 and 184/4,291,452 in 2010–2013. Total number of MD-VTE cases in Japan was 17/2,423,923 in 1991–1992 and 13/4,291,452 in 2010–2013. The maternal mortality ratio was 8.1 per 100,000 population in 1991–1992 and 4.2 per 100,000 population in 2010–2013. The maternal mortality ratio of MD-VTE was 0.7 per 100,000 population in 1991–1992 and 0.4 per 100,000 population in 2010–2013. Both the overall maternal mortality ratio and the rate of MD-VTE in 2010–2013 showed significant decreases from 1991–1992 ($P<0.05$). However, the rate of VTE among maternal death cases remained static: 8.6% (17 of 197 women) in 1991–1992 and 7.0% (13 of 184 women) in 2010–2013. The BMI in 2010–2013 decreased from that in 1991–1992 ($P<0.05$). MD-VTE during pregnancy was 6/13 (46.6%) in 2010–2013, and 1/17 (5.8%) in 1991–1992. In 2010–2013; the occurrence of MD-VTE during pregnancy increased compared with 1991–1992 while the occurrence of MD-VTE in the postpartum period decreased ($P<0.05$).

Discussion

The present study investigated the characteristics of cases of MD-VTE in Japan and compared current statistics (2010–2013) with those of the past (1991–1992). MD-VTE occurs more

Table 4. Comparison of the Characteristics of MD-VTE Cases in 2010–2013 and 1991–1992

	1991–1992 (n=17)	2010–2013 (n=13)
Age (years)	30 (24–40)	33 (27–43)
BMI	30.5 (19.1–38.6)	24.2 (16.4–33.2)*
Occurrence time		
During pregnancy	1 (5.8%)	6 (46.1%)*
During delivery	0 (0%)	0 (0%)
Postpartum	16 (94.1%)	7 (53.8%)*
Cesarean delivery	13/16 (81.2%)	5/6 (83.3%)
Obstetric and gynecologic complications		
Pregnancy-induced hypertension	3 (17.6%)	0 (0%)
Placental abruption	2 (11.7%)	0 (0%)
Threatened premature delivery	1 (5.8%)	1 (7.6%)
Myoma of the uterus	2 (11.7%)	2 (15.3%)
Median time from onset to cardiac arrest (min)	20 (0–850)	60 (0–11,520)

*P<0.05. Abbreviations as in Table 1.

frequently in the postpartum period, especially after cesarean delivery. MD-VTE during pregnancy occurred mainly in the 1st and 3rd trimesters. The maternal mortality ratio of MD-VTE decreased from 1991–1992 to 2010–2013, but the rate of MD-VTE during pregnancy increased. The decrease in postpartum cases of MD-VTE was the reason for the overall decrease in MD-VTE. MD-VTE has decreased, but the proportion of VTE cases among total maternal deaths did not differ between 1991–1992 and 2010–2013.

The period of onset of MD-VTE appeared to have 3 peaks in the present study: the 1st and 3rd trimesters, and postpartum. These results are similar to findings regarding the onset of VTE in general.[11] VTE onset in the 1st trimester could be related to dehydration from hyperemesis or bed rest because of TPL. VTE in the 3rd trimester is believed to be the result of prolonged immobilization because of complications of severe preeclampsia, TPL, or the pregnacy is multiple (twin or more).[11] Risk of VTE is reported to be 22-fold higher with cesarean delivery than with vaginal delivery.[11] In the present study, cesarean delivery was more frequently associated with MD-VTE (cesarean, 4; vaginal, 1).

The incidence of MD-VTE in Japan has decreased within the past 20 years. The Japanese Society on Thrombosis and Hemostasis developed the Japanese Guideline for Prevention of Venous Thromboembolism in 2004, and VTE has now been universally recognized as significant complication after delivery in Japan. Second, use of anticoagulant therapy such as unfractionated heparin as a thromboprophylaxis after delivery. However, we found that MD-VTE had occurred in cases of thromboprophylaxis for DVT, so further decreases in MD-VTE may depend on improvements in the guidelines for thromboprophylaxis in the field of obstetrics.

The rate of MD-VTE during pregnancy in 2010–2013 increased relative to that in 1991–1992 and in almost all cases the women had an inciting episode for the development of MD-VTE. They also had the risk factors for VTE. Therefore, particularly for pregnant women with potential inciting episodes for the development of MD-VTE in addition to risk factors for VTE, and a thrombotic predisposition, we should carefully manage their pregnancy to prevent significant VTE. The present results suggest that despite advancements in reproductive medicine, the increasing number of late pregnancies is a factor.[13] Therefore, the number of pregnant women with risk factors of VTE may also increase. Future guidelines for the prevention of VTE may need to extend beyond the perioperative period to decrease the incidence of MD-VTE.

We cannot be certain of the rationale underlying the decision to perform cesarean delivery, because this study was a retrospective analysis. However, these are official statistics because almost all obstetricians in Japan will have participated in the study through their association with JAOG.

In the present study, there were a number of cases (11 cases) in which the woman's BMI was less than 25. The mean BMI in MD-VTE cases in 1991–1992 was 30.9. Moreover, the odds ratio for VTE with a BMI ≥27 was 3.47 in the report by Kobayashi et al,[9,10] whereas that for a BMI <25 was 1.89. Obesity has been reported as a risk factor for the development of VTE.[14,15] In the obese, the pumping function of skeletal muscle contraction is reduced, so blood stagnation can occur. On the other hands, Heit et al reported that only obesity without other complications was not a risk factor for developing VTE.[16] Generally, thin people are considered not at risk of VTE.[14,15] However, for a pregnant woman, being thin reduces the amount of perivascular fat and the inferior vena cava can become vulnerable to being compressed by uterus, thus predisposing the woman to supine hypotensive syndrome.[17]

In the present study, inherited thrombophilia was not examined, but the possibility that it plays a role in MD-VTE is incontrovertible. It will be necessary to investigate inheritance and the primary causes of thrombosis in future cases of MD-VTE.

Conclusions

The ratio of MD-VTE in Japan has decreased within the past 20 years, but the rate of MD-VTE during pregnancy in 2010–2013 had increased relative to the rate in 1991–1992. These results suggest that despite advancements in reproductive medicine, the increasing numbers of late pregnancies is a causative factor. Pregnant women with risk factors of VTE may be increase in number, as will the number of cesarean deliveries. In the future, the Guideline for Prevention of VTE may need to extend beyond the perioperative period to decrease the incidence of MD-VTE.

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Obstetric risk factors for umbilical cord prolapse: a nationwide population-based study in Japan

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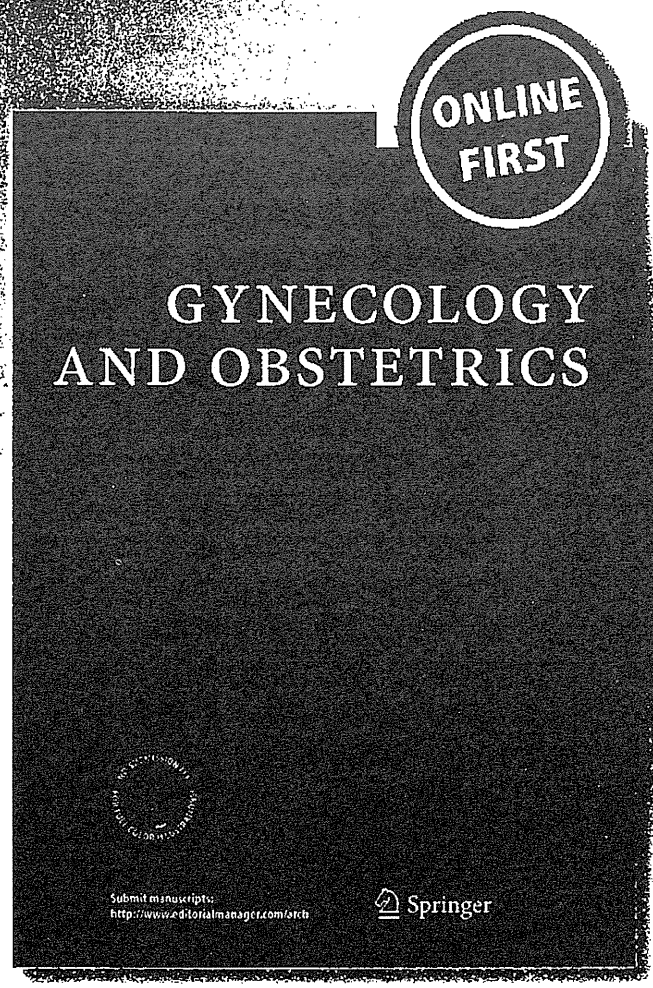

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MATERNAL-FETAL MEDICINE

Obstetric risk factors for umbilical cord prolapse: a nationwide population-based study in Japan

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Abstract

Objectives To demonstrate the clinical course and the obstetric risk factors for umbilical cord prolapse.

Methods The clinical course of reported cases of umbilical cord prolapse that occurred in Japan between 2007 and 2011 was retrospectively analyzed. The obstetric risk factors for umbilical cord prolapse were investigated by a nationwide population-based case-cohort study.

Results Three hundred and sixty-nine cases (0.018 %) of fore-lying/prolapsed umbilical cord in 2,037,460 deliveries were analyzed. Most cases of fore-lying umbilical cord were diagnosed by an ultrasound scan (78 %), whereas umbilical cord prolapse was most frequently diagnosed by an internal examination (63 %). Umbilical cord prolapse was found to be significantly associated with the following factors: multiple pregnancy [odds ratio (OR) 3.57; 95 % confidence interval (CI) 2.60, 4.90], non-vertex presentation (OR 4.67; 95 %CI 3.73, 5.86), preterm labor (OR 2.28; 95 %CI 1.83, 2.83), premature rupture of membranes (OR 3.84; 95 %CI 3.10, 4.77), prolapsed amniotic bag (OR 12.31; 95 %CI 9.00, 16.85), polyhydramnios (OR 2.89; 95 %CI 1.49, 5.61), and a birth weight of <2500 g (OR 2.26; 95 %CI 1.84, 2.79).

Conclusion The current study is the largest in Japan to demonstrate the obstetric clinical course and risk factors associated with umbilical cord prolapse. Prolapsed amniotic bag, labor and rupture of membrane during premature period, and fetal abnormal presentation induced by multiple pregnancy, and polyhydramnios were high risk situation for umbilical cord prolapse.

Keywords Umbilical cord prolapse · Fore-lying cord · Cord presentation · Cervical balloon · Emergency Cesarean section · Fetal death · Non-reassuring fetal status · Fetal heart rate tracing · Pregnancy complication

Introduction

Umbilical cord prolapse is still associated with unfavorable perinatal outcomes because it can quickly lead to fetal compromise, resulting in long-term disability or death [1–5]. Several risk factors are associated with umbilical cord prolapse, including fetal malpresentation, multiple pregnancy, polyhydramnios, preterm delivery, a birth weight of <2500 g, premature rupture of the membranes, amniotomy, attempted rotation of the fetal head, external cephalic version, placement of an intrauterine pressure catheter or fetal scalp electrode, and placement of a cervical ripening balloon catheter [1, 5–7]. However, these risk factors have only been reported in small case series due to the low prevalence of umbilical cord abnormalities. We therefore conducted a nationwide population-based study of umbilical cord prolapse in Japan. The purpose of the present study was to clarify the relevant obstetric risk factors for umbilical cord prolapse in the Japanese population.

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Methods

This study was performed as part of a series to investigate the incidence of umbilical cord prolapse throughout Japan. The present study, along with previously reported studies [8, 9], was performed by the Japan Association of Obstetricians and Gynecologists (JAOG). In the present study, the clinical course of umbilical cord prolapse was retrospectively analyzed, and obstetric risk factors for umbilical cord prolapse were investigated in a nationwide population-based case-cohort study.

Cases of umbilical cord prolapse were enrolled based on the answers to a three-page questionnaire that was sent to 2683 Japanese institutions which offer delivery and maternity services. The institutions, which were located across Japan, were identified from a JAOG hospital list. The questionnaire covered cases of umbilical cord prolapse (after 22 weeks of gestation) that occurred between 2007 and 2011. It included questions about maternal characteristics and complications, the timing of the occurrence, the induction of labor, fetal presentation, gestational age, dilatation of the uterine cervix, timing of the rupture of membranes, diagnostic methods, neonatal outcomes, and placenta and umbilical cord complications. Each questionnaire was accompanied by a covering letter outlining the aims of the study and was addressed by name to the director, the chief obstetrician or the fetomaternal medicine consultant. Answers to the questionnaires were received via facsimile.

To compare cases with the controls, the cohort was derived from the perinatal database of the Japanese Society of Obstetrics and Gynecology (JSOG) which is the nationwide registry in Japan established in 1974. For the JSOG database, attending physicians at 192 secondary and tertiary care centers of the Perinatal Research Network in Japan have collected yearly data for each pregnant woman through an off-line clinical database system using a common format. The data are stored by the Perinatal Committee of the JSOG following strict quality control of the information contained in the database [10]. The cohort using JSOG database included 116,569 deliveries after 22 weeks' gestation that took place throughout Japan between January and December 2011 [11].

Umbilical cord prolapse was defined as having occurred after the rupture of the fetal membranes, with the protrusion of the umbilical cord prior to the presentation of the fetus through the cervical os and into or beyond the vagina by pelvic examination. In contrast, a fore-lying umbilical cord was defined as the umbilical cord preceding the fetus with an intact fetal membrane, as diagnosed by palpitation through the membrane and/or transvaginal ultrasonography.

The categorical variables were reported as percentages and compared using Fisher's exact test. A p value of <0.05 was considered to be statistically significant. The Statistical Package for Social Science (SPSS) software program (Windows version 20.0J; Chicago, IL, USA) was used for the analyses.

This study was approved by the ethical board in Japan Association of Obstetricians and Gynecologists. The present study was a retrospective analysis based on an anonymized hospital database. Therefore, the confidentiality of the patients involved was protected and no personal data were required.

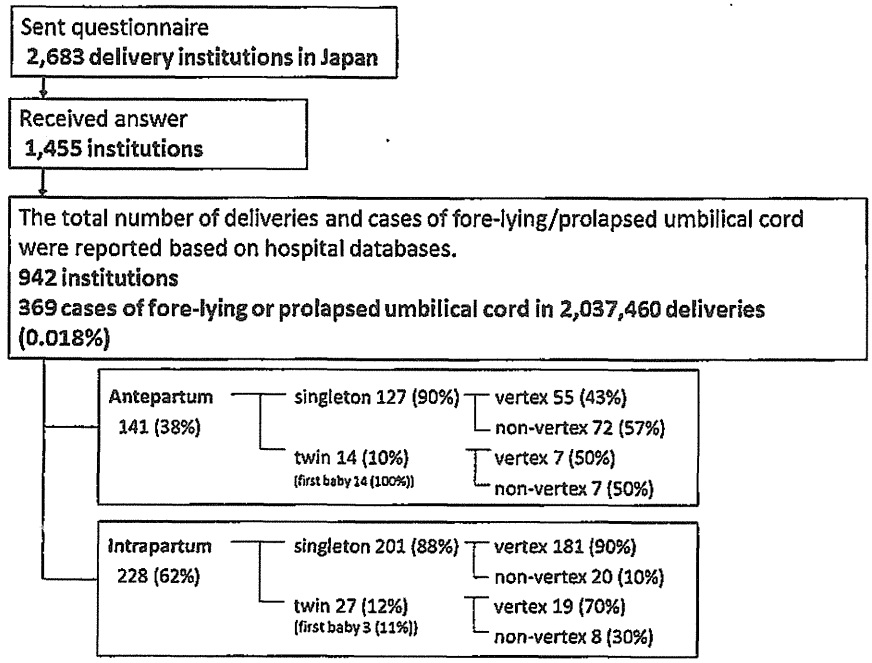

Fig. 1 Study flow diagram

Results

For the collection of cases, questionnaires were sent to 2683 delivery institutions in Japan, and received from 1455 institutions. Following exclusion of answers with a deficient number of cases of fore-lying or prolapse of the cord and/or number of deliveries during the study period, answers from 942 institutions were collected in the present study. For the final analyses, there were 369 cases of fore-lying/prolapsed umbilical cord in the present study (0.018 % of 2037,460 deliveries) (Fig. 1). A total of 141 (127 singletons and 14 twins) of these cases (38 %) were diagnosed with fore-lying/prolapsed umbilical cord during the antepartum period, while 228 (201 singletons and 27 twins) cases (62 %) were diagnosed during labor. In twin pregnancy, fore-lying/prolapsed umbilical cord occurred in only 11 % of the first baby during intrapartum period, whereas they did in 100 % of the first baby during antepartum period.

The maternal demographics of the subjects with fore-lying/prolapsed umbilical cord are shown in Table 1. The maternal characteristics were mostly similar to the other Japanese population-based study [11]. Among the neonates, there were two cases of trisomy 21, two cases of trisomy 18 and one case with lateral curvature. Fore-lying/prolapsed cord occurred during labor in 61.8 % (228) of cases. The adverse clinical outcomes were as follows: intra-uterine fetal death (2.4 %), neonatal death (4.3 %) and survival with disability (6.5 %).

Table 1 The maternal demographics of the subjects ($n = 369$)

Maternal	
Age at delivery	31.5 ± 5.4
Height (cm)	158.0 ± 5.7
Weight (kg)	61.6 ± 9.9
Gravida	1 (0–9)
Parity	1 (0–7)
Multiparous	59.9 % (221)
Spontaneous abortion	0 (0–4)
Pre-eclampsia	4.3 % (16)
Neonatal	
Multiple pregnancy	11.1 % (41)
Intrapartum fore-lying/prolapsed cord	61.8 % (228)
Gestational weeks at delivery	37 (22–42)
Non-vertex presentation	29.0 % (101)
Apgar score	
1 min	7 (0–10)
5 min	9 (0–10)
Umbilical arterial blood pH	7.24 ± 0.13
Base excess	−6.2 ± 5.1
Intact survival	81.0 % (299)
Survival with disability	6.5 % (24)
Neonatal death	4.3 % (16)
Intra-uterine death	2.4 % (9)
Unknown	5.7 % (21)

The data values indicate the mean ± standard deviation, median (range) or frequency (n)

The distributions of the gestational period (in weeks) and neonatal birth weight in the cases of fore-lying/prolapsed umbilical cord that occurred during the antepartum period and during labor are shown in Figs. 2 and 3. During intrapartum period, two peaks distribution were observed in the gestational period at 24 and 37 weeks of gestation, and small fetuses were likely to complicate fore-lying/prolapsed umbilical cord.

The distribution of the dilatation of the uterine os when fore-lying/prolapsed umbilical cord occurred is demonstrated in Fig. 4. Fore-lying/prolapsed umbilical cord

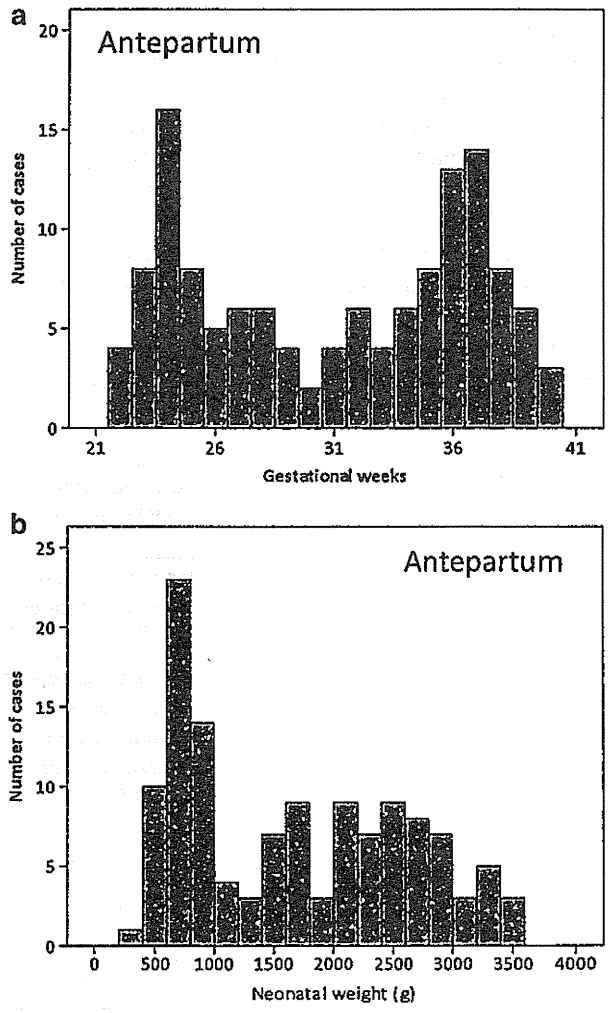

Fig. 2 The distributions of gestational age (a; $n = 131$) and neonatal birth weight (b; $n = 125$) in 141 cases of fore-lying/prolapsed umbilical cord during the antepartum period. There were some missing data

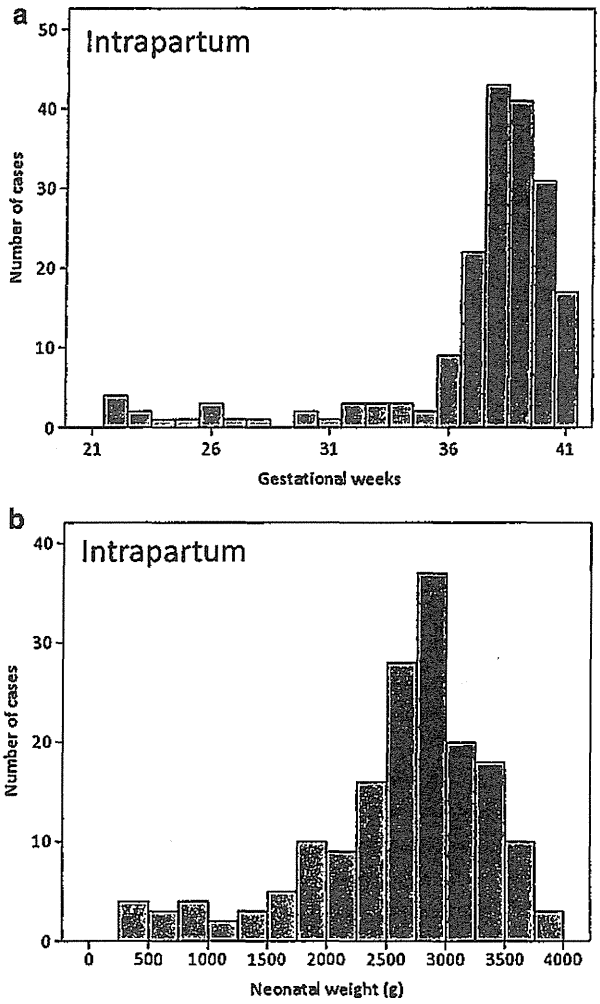

Fig. 3 The distributions of gestational age (a; $n = 191$) and neonatal birth weight (b; $n = 174$) in 228 cases of fore-lying/prolapsed umbilical cord at the induction of labor and in the intrapartum period. There were some missing data

occurred in one-third of the cases when uterine cervix dilatation was 10 cm. In most of the other cases it occurred at around 4–5 cm dilatation.

The responses to a question about how fore-lying/prolapsed umbilical cord was diagnosed are shown in Fig. 5. In most cases, a fore-lying umbilical cord was diagnosed by an ultrasound scan (78 %), whereas umbilical cord prolapse was frequently diagnosed during internal examinations (63 %). A fore-lying and prolapsed umbilical cord were often found after abnormal fetal heart rate tracing (11 % of prolapsed and 6 % of fore-lying umbilical cord). One case of a fore-lying umbilical cord and two cases of umbilical cord prolapse were diagnosed during Cesarean section operations that were performed due to unexplained fetal bradycardia (occult umbilical cord prolapse). Sixteen percent of the umbilical cord prolapse were primarily diagnosed as extravaginal prolapse.

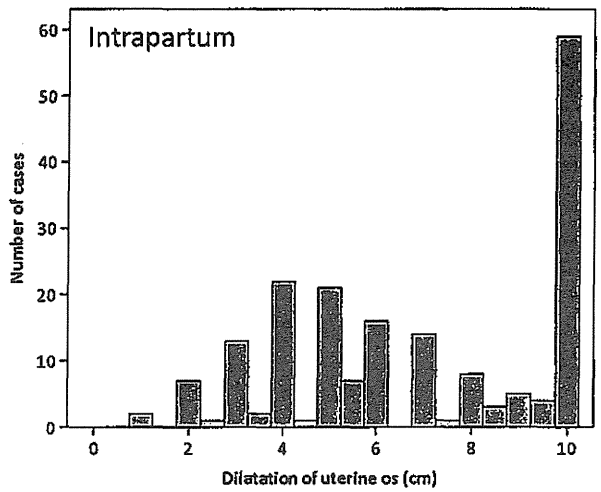

Fig. 4 The distributions of the dilatation of the uterine os ($n = 186$) at the time at which fore-lying/prolapsed umbilical cord occurred during labor (including twin births and non-vertex presentations). There were some missing data

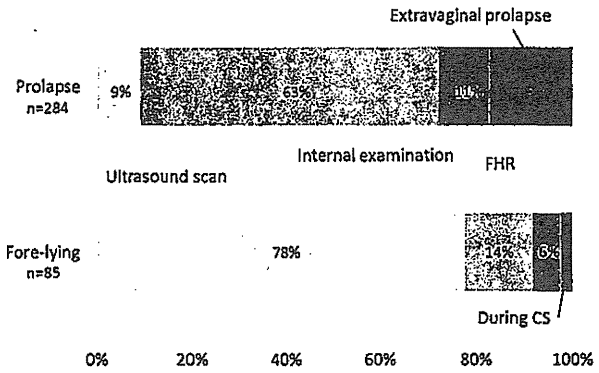

Fig. 5 The responses to a question on how fore-lying/prolapsed umbilical cord was diagnosed in all cases ($n = 369$). *FHR* fetal heart rate. *CS* Cesarean section

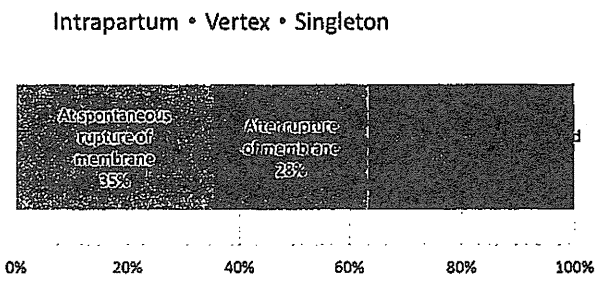

Fig. 6 The responses to a question on when fore-lying/prolapsed umbilical cord was diagnosed during labor in vertex singleton babies ($n = 181$)

The responses to a question about the diagnosis of fore-lying/prolapsed umbilical cord during labor in vertex singleton babies are shown in Fig. 6. Among these cases, 13 % of cases were diagnosed with fore-lying of the