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.

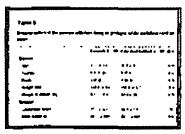

Table 1

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.

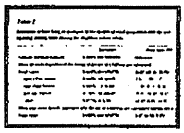

Table 2

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

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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

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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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References

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1. Holbrook BD, Phelan ST. Umbilical cord prolapse. Obstet Gynecol Clin N Am. 2013;40(1):1–14. doi: 10.1016/j.ogc.2012.11.002. [PubMed] [Cross Ref]

2. Koonings PP, Paul RH, Campbell K. Umbilical cord prolapse A contemporary look. The Journal of reproductive medicine. 1990;35(7):690–2. [PubMed]

3. Gannard-Pechin E, Ramanah R, Cossa S, Mulin B, Maillet R, Riethmuller D. [Umbilical cord prolapse: a case study over 23 years] J Gynecol Obstet Biol Reprod. 2012;41(6):574–83. doi: 10.1016/j.jgyn.2012.06.001. [PubMed] [Cross Ref]

4. Traore Y, Dicko TF, Teguete B, Mulbah JK, Adjobi R, N'Guessan E, Tegnan A, Kouyate S, Kouakou F, Anongba S. Frequency of cord prolapse: etiological factors and fetal prognosis in 47 cases in a health center. Le Mali medical. 2006;2(1):25–2. [PubMed]

5. Dufour P, Vinatier D, Bennani S, Tordjeman N, Fondras C, Monnier JC, et al. Cord prolapse. Review of the literature. A series of 50 cases. J Gynecol Obstet Biol Reprod. 1996;25(8):841–5. [PubMed]

6. Qureshi NS, Taylor DJ, Tomlinson AJ. Umbilical cord prolapse. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2004;86(1):29–30. doi: 10.1016/j.ijgo.2003.11.013. [PubMed] [Cross Ref]

7. Kahana B, Sheiner E, Levy A, Lazer S, Mazor M. Umbilical cord prolapse and perinatal outcomes. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2004;84(2):127–32. doi: 10.1016/S0020-7292(03)00333-3. [PubMed] [Cross Ref]

8. Usta IM, Mercer BM, Sibai BM. Current obstetrical practice and umbilical cord prolapse. Am J Perinatol. 1999;16(9):479–84. doi: 10.1055/s-1999-6809. [PubMed] [Cross Ref]

9. Critchlow CW, Leet TL, Benedetti TJ, Daling JR. Risk factors and infant outcomes associated with umbilical cord prolapse: a population-based case–control study among births in Washington State. Am J Obstet Gynecol. 1994;170(2):613–8. doi: 10.1016/S0002-9378(94)70238-1. [PubMed] [Cross Ref]

10. Huang JP, Chen CP, Chen CP, Wang KG, Wang KL. Term pregnancy with umbilical cord prolapse. Taiwanese journal of obstetrics & gynecology. 2012;51(3):375–80. doi: 10.1016/j.tjog.2012.07.010. [PubMed] [Cross Ref]

11. Boyle JJ, Katz VL. Umbilical cord prolapse in current obstetric practice. The Journal of reproductive medicine. 2005;50(5):303–6. [PubMed]

12. Uygur D, Kis S, Tuncer R, Ozcan FS, Erkaya S. Risk factors and infant outcomes associated with umbilical cord prolapse. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2002;78(2):127–30. doi: 10.1016/S0020-7292(02)00140-6. [PubMed] [Cross Ref]

13. Murphy DJ, MacKenzie IZ. The mortality and morbidity associated with umbilical cord prolapse. Br J Obstet Gynaecol. 1995;102(10):826–30. doi: 10.1111/j.1471-0528.1995.tb10850.x. [PubMed] [Cross Ref]

14. Yamada T, Kataoka S, Takeda M, Kojima T, Yamada T, Morikawa M, et al. Umbilical cord presentation after use of a trans-cervical balloon catheter. The journal of obstetrics and gynaecology research. 2013;39(3):658–62. doi: 10.1111/j.1447-0756.2012.02008.x. [PubMed] [Cross Ref]

15. Dilbaz B, Ozturkoglu E, Dilbaz S, Ozturk N, Sivaslioglu AA, Haberal A. Risk factors and perinatal outcomes associated with umbilical cord prolapse. Arch Gynecol Obstet. 2006;274(2):104–7. doi: 10.1007/s00404-006-0142-2. [PubMed] [Cross Ref]

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ORIGINAL ARTICLE
Peripheral Vascular Disease

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

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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-

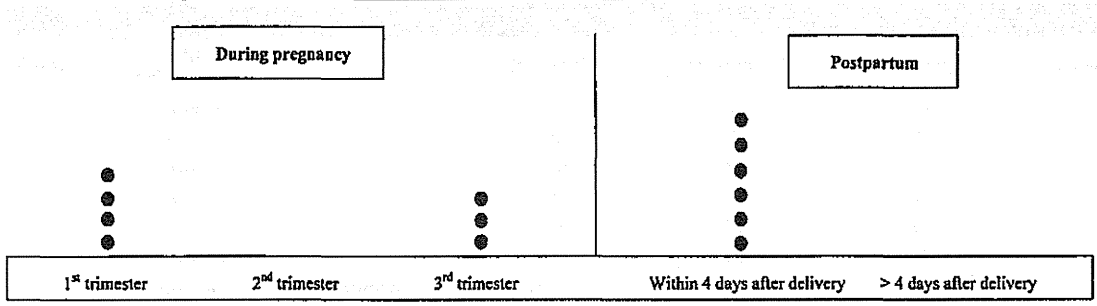

Figure 1. Time of occurrence of maternal-death-related venous thromboembolism.

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.

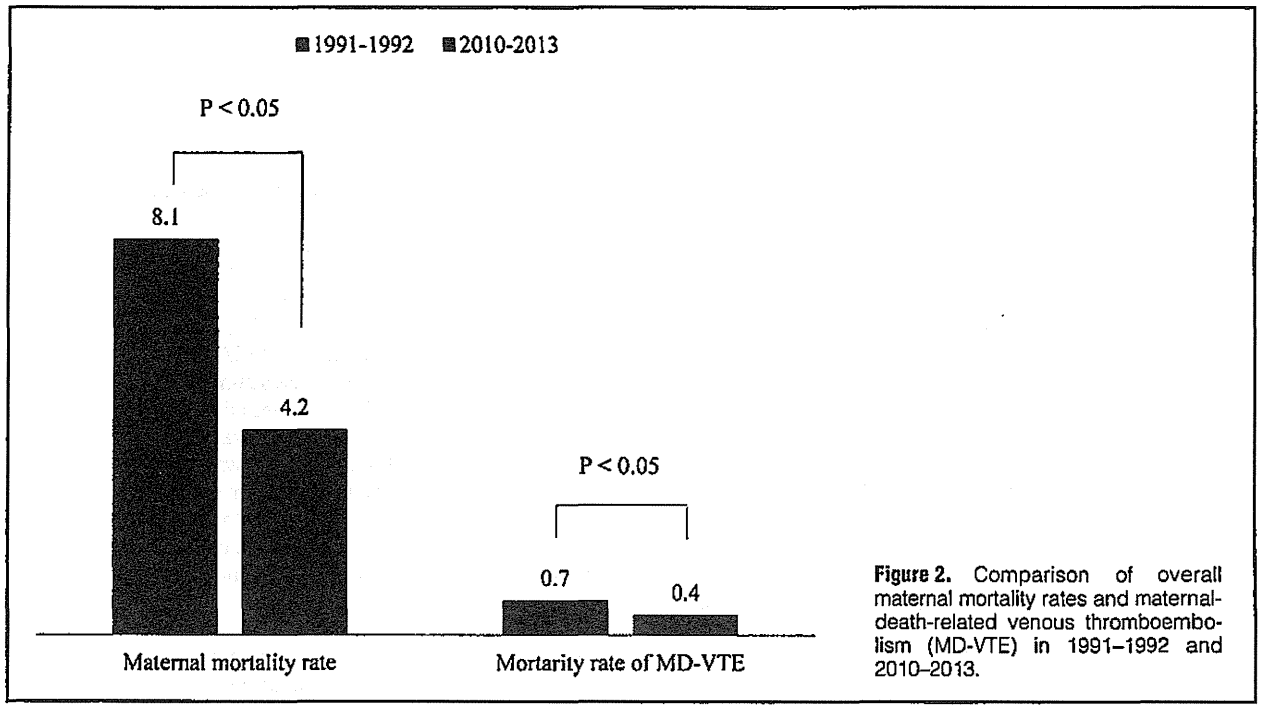

Figure 2. Comparison of overall maternal mortality rates and maternal-death-related venous thromboembolism (MD-VTE) in 1991–1992 and 2010–2013.

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.

Acknowledgments

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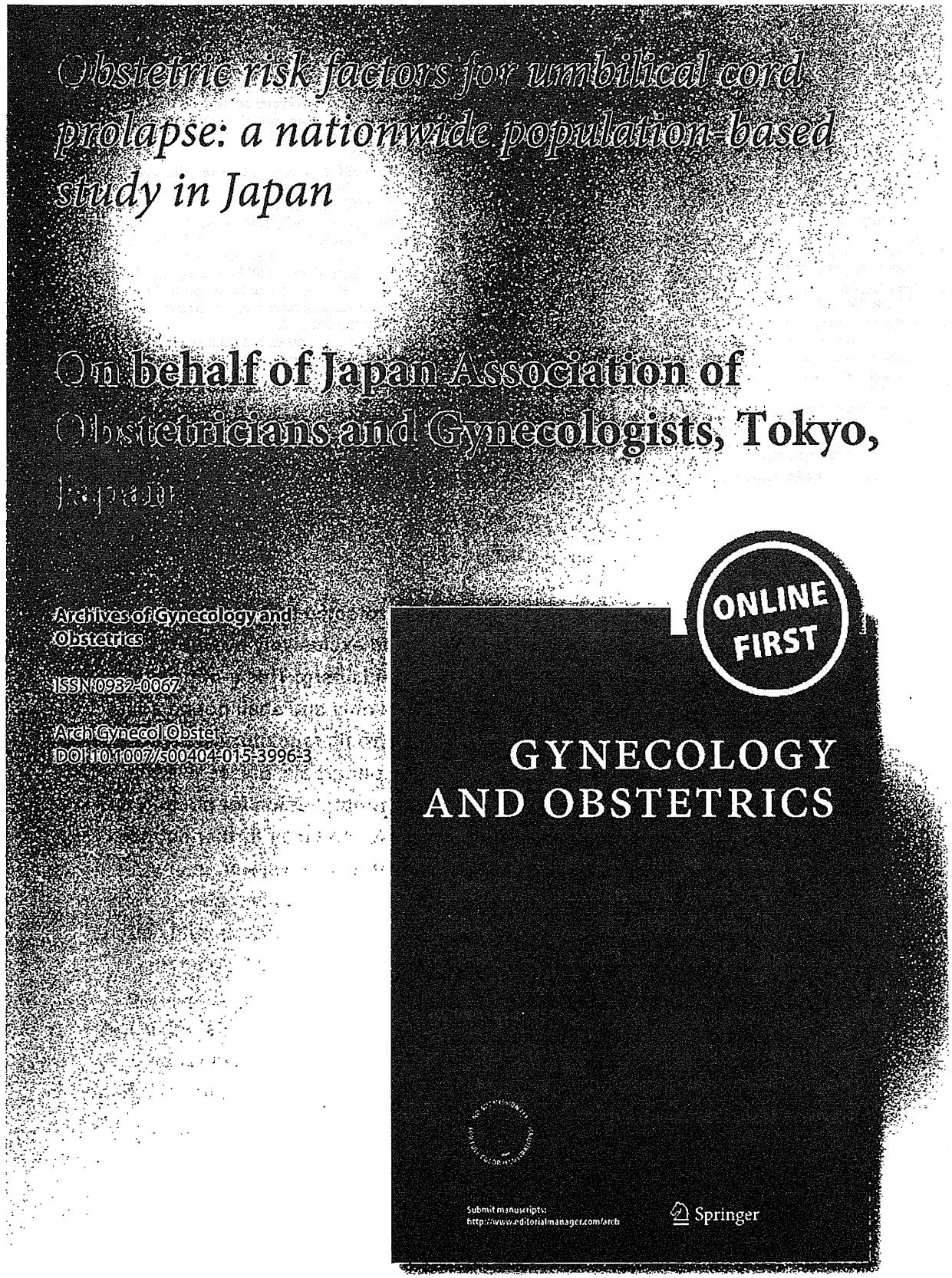
References

1. Katsuragi S, Yamanaka K, Neki R, Kamiya C, Sasaki Y, Ikeda T. Maternal outcome in pregnancy complicated with pulmonary arterial hypertension. *Circ J* 2012; **76:** 2249–2254.
2. Tanaka H, Kamiya C, Katsuragi S, Tanaka K, Miyoshi T, Ikeda T. Cardiovascular events in pregnancy with hypertrophic cardiomyopathy. *Circ J* 2014; **78:** 2501–2506.
3. Tanaka H, Tanaka K, Kamiya C, Iwanaga N, Katsuragi S, Yoshimatsu J. Analysis of anticoagulant therapy by unfractionated heparin during pregnancy after mechanical valve replacement. *Circ J* 2014; **78:** 878–881.
4. Greer IA. Thrombosis in pregnancy: Maternal and fetal issues. *Lancet* 1999; **353:** 1258–1265.
5. Bates SM, Ginsberg JS. Thrombosis in pregnancy. *Curr Opin Haematol* 1997; **4:** 335–343.
6. Bergqvist A, Bergqvist D, Hallbook T. Thrombosis during pregnancy: A prospective study. *Acta Obstet Gynecol Scand* 1983; **62:** 443–448.
7. Rutherford SE, Phelan JP. Deep venous thrombosis and pulmonary embolism in pregnancy. *Obstet Gynecol Clin North Am* 1991; **18:** 345–370.
8. Heit JA, Kobbervig CE, James AH, Petterson TM, Bailey KR, Melton LJ. Trends in the incidence of venous thromboembolism during pregnancy or postpartum: A 30-year population-based study. *Ann Intern Med* 2005; **143:** 697–706.
9. Kobayashi T, Nakabayashi M, Ishikawa M, Ikenoue T, Adachi T, Maeda S. Final reports of deep vein thrombosis/pulmonary thromboembolism between 1991 and 2000 in obstetrics and gynecology. *Jpn J Obstet Gynec Neonatal Hematol* 2005; **14:** 1–24.
10. Kobayashi T, Nakabayashi M, Ishikawa M, Adachi T, Kobashi G, Ikenoue T. Pulmonary thromboembolism in obstetrics and gynecology increased by 6.5-fold over the past decade in Japan. *Circ J* 2008; **72:** 753–756.
11. Battinelli EM, Marshall A, Connors JM. Thrombosis: The role of thrombophilia in pregnancy. *Thrombosis* 2013; **2013:** 516420, doi:10.1155/2013/516420.
12. Nagaya K, Fetters MD, Ishikawa M, Kubo T, Koyanagi T, Neki R. Causes of maternal mortality in Japan. *JAMA* 2000; **283:** 2661–2667.
13. Mothers' and Children's Health Organization. Maternal and child health statistics of Japan (2013). Tokyo, The Mothers and Children's Health and Welfare Association in Japan, 2014.
14. Goldhaber SZ. Risk factors for venous thromboembolism. *J Am Coll Cardiol* 2010; **56:** 1–7.
15. Goldhaber SZ, Grodstein F, Stampfer MJ, Manson JE, Colditz GA, Speizer FE. A prospective study of risk factors for pulmonary embolism in women. *JAMA* 1997; **277:** 642–645.
16. Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ 3rd. Risk factors for deep vein thrombosis and pulmonary embolism: A population-based case-control study. *Arch Intern Med* 2000; **160:** 809–815.
17. Kinsella SM, Lohmann G. Supine hypotensive syndrome. *Obstet Gynecol* 1994; **83:** 774–788.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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.

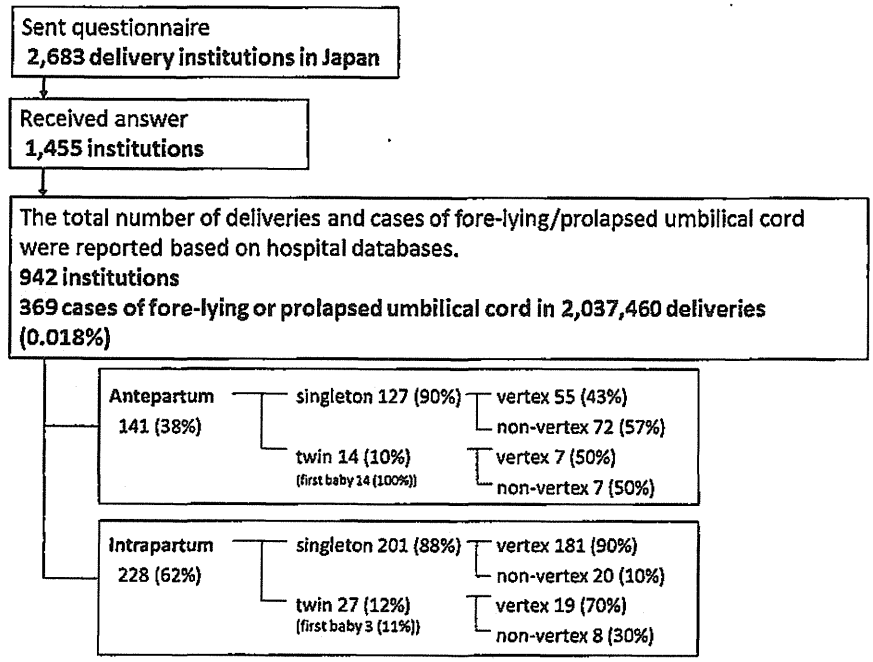

Fig. 1 Study flow diagram

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

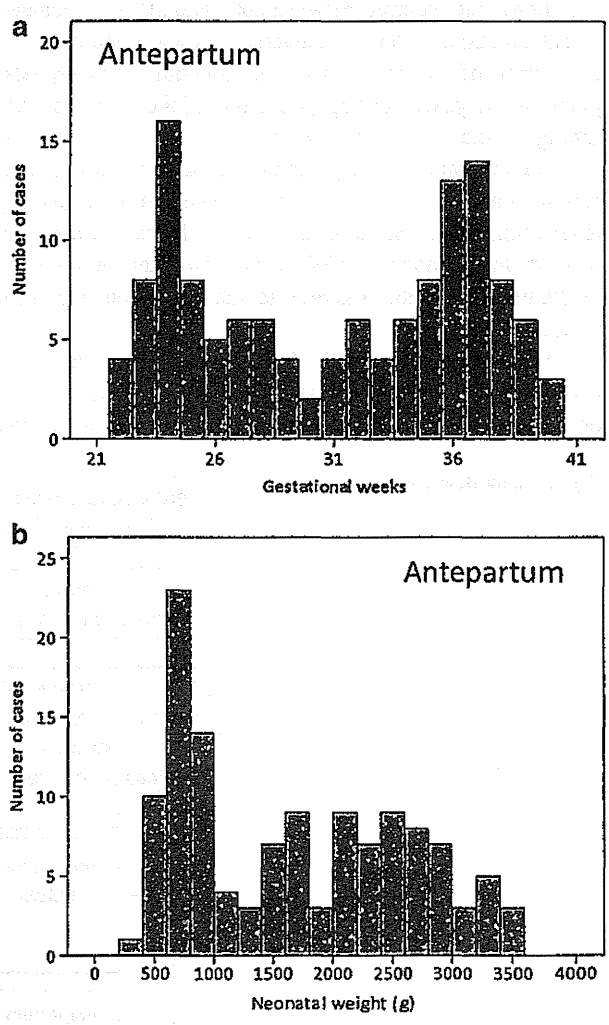

Fig. 2 The distributions of gestational age (a; $n = 131$) and neonatal birth weight (b; $n = 125$) in 141 cases of fore-lying/prolapsed umbilical cord during the antepartum period. There were some missing data

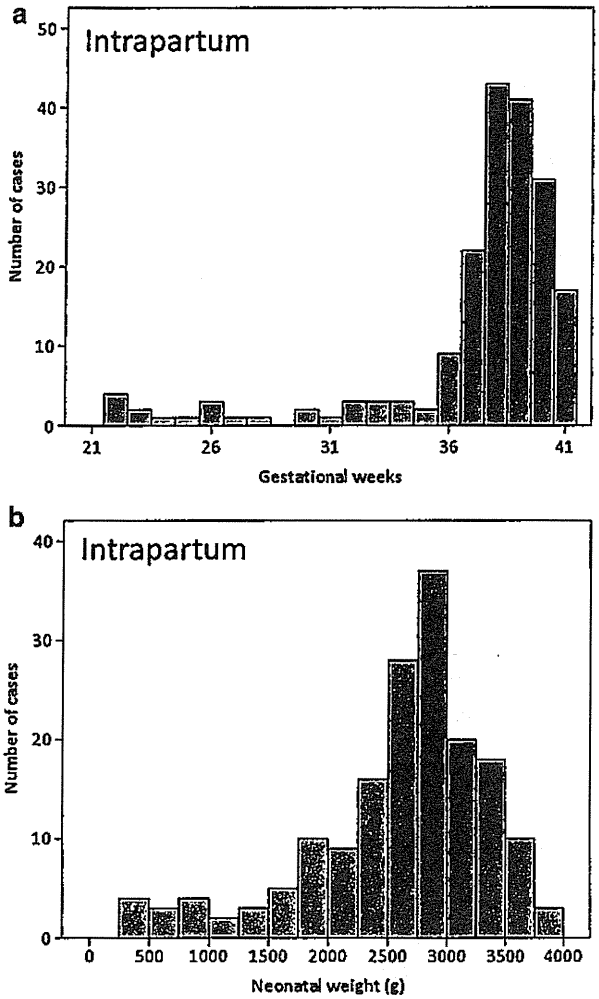

Fig. 3 The distributions of gestational age (a; $n = 191$) and neonatal birth weight (b; $n = 174$) in 228 cases of fore-lying/prolapsed umbilical cord at the induction of labor and in the intrapartum period. There were some missing data

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.

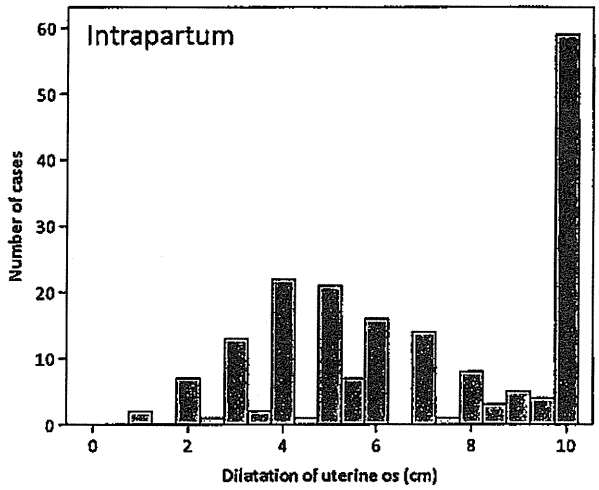

Fig. 4 The distributions of the dilatation of the uterine os ($n = 186$) at the time at which fore-lying/prolapsed umbilical cord occurred during labor (including twin births and non-vertex presentations). There were some missing data

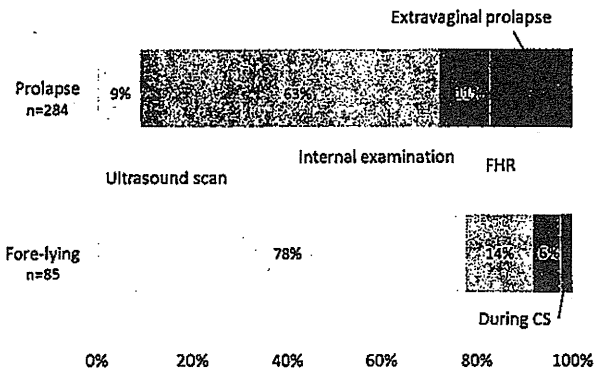

Fig. 5 The responses to a question on how fore-lying/prolapsed umbilical cord was diagnosed in all cases ($n = 369$). *FHR* fetal heart rate. *CS* Cesarean section

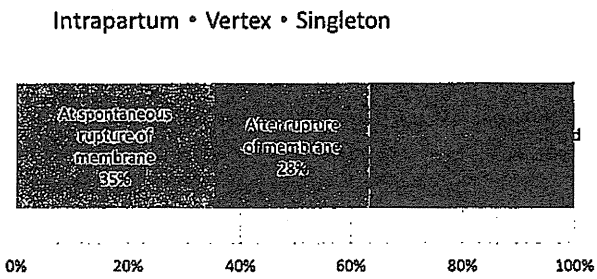

Fig. 6 The responses to a question on when fore-lying/prolapsed umbilical cord was diagnosed during labor in vertex singleton babies ($n = 181$)

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

Table 2 The frequency of clinical risk factors in cases of umbilical cord prolapse in the Japanese population

Risk factors ratio	Cases $n = 369$	Cohort [10] $n = 116{,}569$	Odds (95 % confidence interval)
Multiple pregnancy	11.9 % (44)	3.7 % (4256)	3.57 (2.60, 4.90)
Non-vertex presentation	29.0 % (107)	8.0 % (9370)	4.67 (3.73, 5.86)
Induction labor	25.5 % (98)	25.3 % (29,520)	1.07 (0.85, 1.34)
Preterm labor	32.8 % (121)	17.6 % (20,559)	2.28 (1.83, 2.83)
Premature rupture of membrane	34.4 % (127)	12.0 % (14,002)	3.84 (3.10, 4.77)
Prolapsed amniotic bag	12.5 % (46)	1.1 % (1333)	12.31 (9.00, 16.85)
Cervical cerclage	2.4 % (9)	n/a	
Polyhydramnios	2.4 % (9)	0.9 % (1000)	2.89 (1.49, 5.61)
Oligohydramnios	3.3 % (12)	1.8 % (2152)	1.79 (1.00, 3.18)
Low-lying placenta	2.2 % (8)	n/a	
Abnormal cord insertion	5.7 % (21)	n/a	
Birth weight $\geq$ 3500 g	4.3 % (16)	8.0 % (9272)	0.52 (0.32, 0.87)
Birth weight <2500 g	40.4 % (149)	23.0 % (26,868)	2.26 (1.84, 2.79)

The data values indicate the mean $\pm$ standard deviation, median (range) or frequency (n). *n/a* not available

umbilical cord without the rupture of the membranes. On the other hand, umbilical cord prolapse was diagnosed at the time of the spontaneous rupture of membranes and amniotomy in 35 % and 24 % (respectively) of cases that occurred in vertex singleton babies during labor; it was diagnosed after the rupture of membranes in 28 % of such cases.

The frequency of the clinical risk factors in cases of umbilical cord prolapse and the nationwide cohort [11] are demonstrated in Table 2. The analyses of the whole study population revealed the following variables to be risk factors for umbilical cord prolapse: 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).

Discussion

The incidence of umbilical cord prolapse ranges from 0.12 to 0.62 % evaluated before 2000 in various part of the world [1, 7, 12, 13]. In the present study, the overall incidence of fore-lying/prolapsed umbilical cord was less (0.018 %) than that of previous reports. The frequency of the umbilical cord prolapse has been previously reported to be decreasing: it was reported to be 0.6 % in 1932 [7], 0.2 % in the 1990s [14] and 0.12 % in 2003, thus this study showed that the decreasing incidence was explained by an increasing trend to deliver babies of breech and multiple pregnancies by Cesarean section [7]. Better quality of ultrasound equipment also might to be the reason of decreasing incidence of umbilical cord prolapse. However, since the present study was based on a multi-institutional questionnaire survey, it is possible that the prevalence was underestimated.

Similar to previous reports [1, 7], the variables that were associated with preterm labor and the premature rupture of membranes were frequently reported to be associated with umbilical cord prolapse. Thus, umbilical cord prolapse during the antenatal period was more likely to be observed in small babies. In fact, our results suggested that prolapsed amniotic bag, preterm labor, and premature rupture of membrane were strongly associated with umbilical cord prolapse. Peak incidence occurred at two points in the gestational period, 24 and 37 weeks. It revealed that umbilical cord prolapse during the antenatal period tended to occur not only in the mid-trimester, but also shortly before the full term of small fetus pregnancies (Table 2).

An abnormally positioned fetus is less likely to be engaged in the maternal pelvis, thus allowing space for the cord to prolapse [5], thus malpresentation is associated with umbilical cord prolapse. Non-vertex presentation was reported in 29 % of the subjects of the present study. Multiple gestation is also a known risk factor [1], likely due to the increase in abnormal positioning of the fetuses. In the present study, 89 % (328/369) of cases were singleton pregnancies, and 4.6 % (17/369) and 6.5 % (24/369) of cases occurred in the first and second twin. Similar to our report, it is reported that 77 % of cases occurred in singleton pregnancies, and in twin pregnancies, 9 and 14 % of cases occurred in the first and second twin [12]. Moreover, fore-lying/prolapsed umbilical cord occurred in the first baby in all twin cases that occurred during the antepartum period. In

contrast, fore-lying/prolapsed umbilical cord occurred in the first baby in only 11 % cases during labor. It is also known that polyhydramnios [1, 6] is a risk factor. In the present study, 2.4 % of the subjects were diagnosed with polyhydramnios (OR 2.89).

Fore-lying/prolapsed umbilical cord occurred in one-third of cases when the uterine cervix was at 10 cm of dilatation. In other cases, they were likely to occur when at around 4–5 cm of dilatation. It is supposed that such cases were associated with the use of a cervical ripening balloon catheter, because the association of the use of a cervical ripening balloon catheter with umbilical cord prolapse was previously reported in same study subjects, and in one-fourth of them umbilical cord prolapse occurred during or after the use of a cervical ripening balloon catheter [9]. Especially, the use of disk-type and ball-type balloons filled with large amounts of water for cervical ripening were likely to involve umbilical cord prolapse [9] as same as natural removal when at 4-5 cm of dilatation of the uterine cervix.

Most of the fore-lying umbilical cord cases were diagnosed by an ultrasound scan (78 %), whereas umbilical cord prolapse was frequently diagnosed during internal examinations (63 %). It is considered that most cases of umbilical cord prolapse occur shortly after the rupture of membranes [7]. In the present study, 24 and 35 % of umbilical cord prolapses were diagnosed at the time of amniotomy during labor and spontaneous rupture of membranes, respectively. Since neonatal prognosis was better when fore-lying cord could be found ultrasonically than when umbilical cord prolapse occurred after rupture of membrane [8], an ultrasound evaluation to screen for fore-lying umbilical cord or occult prolapse of the umbilical cord in high risk situations, before the occurrence of an overt cord prolapse, may improve the neonatal outcomes associated with umbilical cord prolapse.

Conclusion

To our knowledge, this is the largest study in Japan to demonstrate the clinical course and relevant risk factors that are 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 should be considered as high risk situation for umbilical cord prolapse.

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Author's contribution Hasegawa J., Sekizawa A. and Kinoshita K. designed the research. Hasegawa J., Sekizawa A., Ikeda T., Ishiwata I. and Kinoshita K. collected the data. Hasegawa J. and Sekizawa A. analyzed and interpreted the data, and drafted the manuscript. Hasegawa J. performed the statistical analyses.

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Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest in association with the present study. The authors do not receive any financial support, nor do they own stock in any of the companies related to the present study.

Ethical approval This study was approved by the ethical board in the Japan Association of Obstetricians and Gynecologists. The present study was a retrospective analysis based on a questionnaire survey. Thus, the confidentiality of the patients involved was protected and no personal data was required for the present study.

References

1. Kahana B, Sheiner E, Levy A, Lazer S, Mazor M (2004) Umbilical cord prolapse and perinatal outcomes. Int J Gynaecol Obstet Off Organ Int Fed Gynaecol Obstet 84:127–132
2. Usta IM, Mercer BM, Sibai BM (1999) Current obstetrical practice and umbilical cord prolapse. Am J Perinatol 16:479–484
3. Critchlow CW, Leet TL, Benedetti TJ, Daling JR (1994) Risk factors and infant outcomes associated with umbilical cord prolapse: a population-based case-control study among births in washington state. Am J Obstet Gynecol 170:613–618
4. Huang JP, Chen CP, Chen CP, Wang KG, Wang KL (2012) Term pregnancy with umbilical cord prolapse. Taiwan J Obstet Gynecol 51:375–380
5. Holbrook BD, Phelan ST (2013) Umbilical cord prolapse. Obstet Gynecol Clin N Am 40:1–14
6. Boyle JJ, Katz VL (2005) Umbilical cord prolapse in current obstetric practice. J Reprod Med 50:303–306
7. Koonings PP, Paul RH, Campbell K (1990) Umbilical cord prolapse. A contemporary look. J Reprod Med 35:690–692
8. Hasegawa J, Sekizawa A, Ikeda T, Koresawa M, Ishiwata I, Kawabata M, Kinoshita K (2015) Group: Japan Association of O, Gynecologists (in press) Clinical risk factors for poor neonatal outcomes in umbilical cord prolapse. J Matern Fetal Neonatal Med 16:1–5 (Epub ahead of print)
9. Hasegawa J, Sekizawa A, Ikeda T, Koresawa M, Ishiwata I, Kawabata M, Kinoshita K, Group: Japan Association of O, Gynecologists (2015) The use of balloons for uterine cervical ripening is associated with an increased risk of umbilical cord prolapse: population based questionnaire survey in Japan. BMC Pregnancy Childbirth 15:4
10. Hayashi M, Nakai A, Satoh S, Matsuda Y (2012) Adverse obstetric and perinatal outcomes of singleton pregnancies may be related to maternal factors associated with infertility rather than the type of assisted reproductive technology procedure used. Fertil Steril 98:922–928
11. Unno S, Masuzaki H, Kanayama N, Kubo T, Fujimori K, Matsuda Y (2013) Report of perinatology committee. Acta Obstet Gynaecol Jpn 65:1377–1387
12. Murphy DJ, MacKenzie IZ (1995) The mortality and morbidity associated with umbilical cord prolapse. Br J Obstet Gynaecol 102:826–830
13. Katz Z, Lancet M, Borenstein R (1982) Management of labor with umbilical cord prolapse. Am J Obstet Gynecol 142:239–241
14. Lin MG (2006) Umbilical cord prolapse. Obstet Gynecol Surv 61:269–277

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Histological characteristics of the myometrium in the postpartum hemorrhage of unknown etiology: a possible involvement of local immune reactions

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ABSTRACT

The aim of this study was to evaluate the histological characteristics of the myometrium obtained in postpartum hemorrhage (PPH) of unknown etiology secondary to uterine atony. These characteristics were selected from among registered cases of clinically suspected amniotic fluid embolism (AFE) and classified as PPH of unknown etiology because of no obvious cause of PPH at Hamamatsu University School of Medicine, a registration center for clinical AFE in Japan. Immunohistochemical studies were performed on myometrium using anti-mast cell tryptase, anti-neutrophil elastase, anti-CD68, anti-CD88, anti-CD3, and anti-ZnCP-1 antibodies. Massive infiltrations of inflammatory cells with mast cell degranulation within the myometrium secondary to complement activation were observed in PPH of unknown etiology ($n=34$), but not in control pregnant women ($n=15$) or after delivery in women without PPH ($n=18$). The concomitant immunohistochemical detection of meconium in myometrium suggests that amniotic fluids or fetal materials are one of the candidates for inducing maternal local immune activation in the PPH of unknown etiology. Postpartum acute myometritis in the absence of an infective etiology may be a histological characteristic of PPH of unknown etiology.

1. Introduction

Postpartum hemorrhage (PPH) is the leading cause of maternal mortality in the world, with an incidence estimated to be up to 10% (Oyelese et al., 2007; Mousa et al., 2014; Cunningham et al., 2010). Various conditions such as abnormal placentation, trauma to the genital tract, uterine atony, and coagulation defects are known causes of PPH (Cunningham et al., 2010). Among the above, uterine atony is a major cause of PPH, estimated to be responsible for 70% (Karoshi and Keith, 2009; Oyelese and Ananth, 2010); however, the etiology remains to be clarified in cases of PPH secondary to uterine atony. Over-distended uterus and exhausted myometrium are considered to be causes of uterine atony; however, it has yet been clarified why myometrium suddenly stops contraction after delivery, because most patients presenting with uterine atony have no explainable risk factors (Rouse et al., 2006).

The authors, at a registration center for clinical amniotic fluid embolism (AFE) in Japan, and others, have proposed clinical criteria for AFE with the main clinical symptom of

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massive PPH not explained by other diseases (Kanayama et al., 2011; Benson, 2012). Furthermore, from the data accumulated on registering cases of clinical AFE in Japan, massive PPH frequently accompanied by coagulopathy and uterine atony has been considered pathognomonic for clinical AFE (Benson, 2007). In other words, a number of cases of 'PPH of unknown etiology' have been regarded and managed as clinical AFE according to the criteria but with no physical evidence. Although the causative mechanism of clinical AFE is still unclear, a previous study demonstrating maternal complement activation in clinical AFE suggested that a pathological maternal immune reaction might be associated with the pathogenesis of 'PPH of unknown etiology' including clinical AFE (Kanayama and Tamura, 2014).

In the present study, we hypothesized that a maternal immune reaction localized in the myometrium might deteriorate the myometrial function of contraction and cause PPH of unknown etiology secondary to uterine atony. To identify immunoreactive cells in myometrium with PPH of etiology, we carried out immunohistochemical examinations.

2. Materials and methods

2.1. Subjects

Cases of 'PPH with unknown etiology' were originally registered at Hamamatsu University School of Medicine from January 2011 to December 2012 as having clinically suspected AFE according to the Japan consensus criteria for the diagnosis of AFE, whereby the major symptom was PPH except for cardiac arrest or respiratory failure (Tamura et al., 2014a). They were retrospectively and carefully selected as 'PPH with unknown etiology' secondary to uterine atony according to the reports of physicians in charge. Exclusion criteria were multiple fetuses, rupture of membranes, preterm labor, chorioamnionitis, uterine or cervical laceration, placenta previa, placenta accreta, preceding DIC such as sepsis, placental abruption, and preceding sudden maternal cardiac deterioration.

Tissues after abdominal hysterectomy after the onset of PPH were collected and stored at Hamamatsu University School of Medicine. Mean time interval between deliveries and hysterectomy was 4.6 h in PPH cases. Control tissues were obtained at Hamamatsu University Hospital after receiving written informed consent. The myometrial tissues were obtained by partial resection of the anterior wall of the uterine body, 3–5 mm beneath the serosa, during ($n=15$) or soon after ($n=18$) the delivery of neonates by cesarean section after an uncomplicated pregnancy. 9 nulliparous and 6 multiparous pregnant women were selected for controls with mean gestational age (37.8 ± 0.7), mean parity (0.79 ± 1.05) and mean gravida (1.14 ± 1.10). Myometrial tissues from 6 nulliparous to 12 multiparous women were also obtained after delivery of neonates as controls with a mean gestational age (38.3 ± 1.5), mean parity (1.29 ± 1.11), and mean gravida (1.57 ± 0.98). All control cases were free from massive hemorrhage, hock, DIC, uterine atony, and any kind of allergic reaction. Patients' demographic data are shown in Table 1.

2.2. Immunohistochemistry

All specimens were fixed in 10% buffered formalin solution, embedded in paraffin, and cut into 3-μm-thick sections. Sections were stained with hematoxylin and eosin. For immunohistochemistry, the antigen was retrieved in a high-pressure cooker for 20 min (temperature: 95 °C) using citrate buffer (pH 6) for tryptase and CD68 and Tris/EDTA buffer (pH 9) for CD88 and CD3. Endogenous peroxidase activity was blocked by H_2O_2 for 5 min. Primary antibody was applied at a ratio of 1:10,000 for tryptase (abcam®, UK), 1:200 for elastase (DakoCytomation, Denmark), 1:200 for CD68 (Thermo, UK), 1:200 for CD3 (Novocastra™ liquid, UK), 1:4000 for CD88 (Cosmo Bio Co. Japan) with 120 ng/mL of mouse IgG for meconium-specific zinc coproporphyrin I (ZnCP-I) (Furuta et al., 2012), and incubated for 30 min. A positive reaction was visualized by 3,3-diaminobenzidine, counterstained with hematoxylin, coverslipped, and observed with an Olympus BX51 optical microscope. Halo patterns of the tryptase "golden reaction" around mast cells were considered to represent activated mast cells with degranulation (Fineschi et al., 2009; Tamura et al., 2014b).

2.3. Method for cell counts

Numbers of muscle cells and positively stained cells on a total of four digital images in each case under microscopic fields of 50 mm^2 were counted and analyzed.

2.4. Statistical analysis

All values are presented as the median ± standard error (SE). Significant differences were assessed using the Mann–Whitney *U* test. A P value of less than 0.05 was considered significant.

2.5. Approval

The Ethics Committee of Hamamatsu University School of Medicine approved all the procedures of this study (#24-130).

3. Results

3.1. Backgrounds of the subjects

Thirty-four cases were examined after being selected as 'PPH of unknown etiology', regarded as atonic uterine bleeding by excluding uterine or cervical laceration, placenta previa, placenta accreta, preceding DIC such as sepsis, placental abruption, and preceding sudden maternal cardiac deterioration.

3.2. Histological findings

Significant infiltration of inflammatory cells in myometrial stroma with a sparse structure due to edema was observed in cases of PPH of unknown etiology (Fig. 1C and F).