—Case Reports—

A Case of Maternal Vitamin K Deficiency Associated with Hyperemesis Gravidarum: Its Potential Impact on Fetal Blood Coagulability

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Vitamin K deficiency is associated with malnutrition in some complications, such as hyperemesis gravidarum, active gastrointestinal diseases, and psychological disorders. Maternal vitamin K deficiency can cause fetal bleeding, in particular, fetal intracranial hemorrhage. Although fetal hemorrhage is uncommon, severe damage to the fetus may be inevitable. We describe a pregnant woman with vitamin K deficiency possibly due to hyperemesis gravidarum. The patient was treated for the deficiency, and no fetal or neonatal hemorrhagic diseases were manifested. (J Nippon Med Sch 2015; 82: 54–58)

Key words: maternal vitamin K deficiency, fetal bleeding, hyperemesis gravidarum

Introduction

Vitamin K deficiency can lead to hemorrhagic diseases in newborns and adults. Although relatively rare, maternal vitamin K deficiency can cause fetal bleeding, in particular, intracranial hemorrhage. Fetal hemorrhagic diseases can develop because fetal vitamin K is derived from the mother[1]. Vitamin K deficiency can result from malnutrition associated with complications, such as hyperemesis gravidarum, active gastrointestinal diseases, and psychological disorders. We report a case of vitamin K deficiency due to hyperemesis gravidarum.

Case Report

A 39-year-old woman (gravida 0, para 0) was admitted to our hospital because of hyperemesis gravidarum at 8 weeks' gestation. Her past medical history was uneventful, except for infertility requiring artificial insemination by husband. There was no family history of a coagulation disorder. Her height and weight were 160 cm and 64.1 kg, respectively. Her body weight at admission was almost the same as her prepregnancy weight. She had not been able eat or drink anything for 1 week and had recurrent vomiting.

Evaluations performed at admission included transvaginal ultrasonography; blood tests, including complete blood count and electrolyte measurements; and renal and liver function tests. Fetal assessment showed a viable embryo with a normal crown-rump length (15 mm). Blood tests showed a mild elevation of alanine aminotransferase (ALT; 52 IU/L; normal range, 4–37 IU/L) and mild hypokalemia (3.1 mmol/L; normal range, 3.6–5.0 mmol/L); however, no clinical abnormality was detected. The levels of fibrin/fibrinogen degradation products were normal. Urinalysis showed moderate ketonuria.

From the first day of admission (day 0; 8 weeks' gestation), a daily intravenous drip infusion (2,500 mL/day), including 522 kcal and sufficient quantities of vitamins B_1, B_6, B_{12}, and C, was started via a peripheral vein. There was no oral ingestion. On day 7 (9 weeks' gestation), increases in aspartate aminotransferase (AST; 76 IU/L; normal range, 9–32 IU/L), ALT (183 IU/L), and γ-glutamyltransferase (γ-GTP; 74 IU/L; normal range, <32 IU/L) were observed. Coagulation studies showed a normal activated partial thromboplastin time (APTT) level, but the prothrombin time (PT) was prolonged (15.2 seconds; normal range, 12–15 seconds). On day 21 (11 weeks' gestation), liver enzyme levels had improved (AST, 32 IU/L; ALT, 72 IU/L; and γ-GTP, 84 IU/L). However, the PT had become further prolonged (19.7 seconds). There was no change in APTT. An abnormal PT/APTT pattern indicated the presence of a vitamin K deficiency, a clotting factor VII deficiency, severe impaired

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liver function, or a rare lupus anticoagulant disease. Therefore, we performed an additional blood clotting test and demonstrated vitamin K deficiency (vitamin K_1 <0.05 ng/mL; normal range, 0.15–1.25 ng/mL) and a low level activity of clotting factor VII (33%; normal range, 75%–140%). There was no apparent maternal hemorrhage. Because the prolonged PT appeared to be associated with vitamin K deficiency, oral administration of vitamin K_1 (15 mg per day) was started on day 21 to prevent maternal and fetal hemorrhagic diseases. This treatment was effective, and the PT gradually improved (16.1 seconds on day 26 and 13.8 seconds on day 34). Oral ingestion was started on day 39, and the patient was discharged on day 43 (14 weeks' gestation). At 16 weeks' gestation, vitamin K_1 administration was stopped because of the improvement in the activity of clotting factor VII and sufficient levels of vitamin K.

At 20 weeks' gestation, the PT, APTT, and the level of prothrombin induced by vitamin K absence II (PIVKA-II) were 10.6 seconds, 26.9 seconds, and 33 mAU/mL (normal range, <40 mAU/mL), respectively. Together, these factors indicated the absence of vitamin K deficiency.

At 32 weeks' gestation, we recommended the patient consult an internist because she had had a loss of appetite. Upper gastrointestinal endoscopy revealed a gastric polyp and esophageal hiatus hernia. The esophageal hiatus hernia may have contributed to her eating disorder. We selected a noninvasive treatment based on informed consent.

At 38 weeks' gestation, labor was induced because of arrested fetal growth (no increase in fetal body weight for 2 weeks). Ultrasonography also revealed no fetal structural abnormalities. Oxytocin was administered for 5 days starting at 38 weeks' gestation, and a 2,644-g female infant was delivered vaginally with Apgar scores of 9 at 1 minute and 9 at 5 minutes. The newborn had no intracranial or intestinal bleeding at birth.

Results of analysis of neonatal blood samples collected immediately after delivery were: PT, 17.6 seconds; APTT, 50.8 seconds; fibrinogen, 145 mg/dL (normal range, 150–400 mg/dL); and hepaplastin, 42% (normal range,13%–31% on day 0[2] and 41.8%–61.6% on day 5[3]). There was no evidence of clinical hemorrhage. Vitamin K syrup, containing 2 mg of vitamin K2, was orally administered to the neonate within 24 hours after birth. The mother and the neonate were discharged without any problems 5 days after delivery.

Discussion

Vitamin K deficiency is a complication of malnutrition, liver dysfunction, and gastrointestinal diseases. It is also a cause of coagulopathy because vitamin K is essential for the synthesis of active clotting factors II, VII, IX, and X[4]. These clotting factors are produced in the liver. In humans, vitamin K is supplied primarily by the diet and especially from green vegetables. Healthy, well-nourished persons generally obtain sufficient quantities of vitamin K every day, but only a small amount of vitamin K is stored. Therefore, vitamin K deficiency is easily caused by the absence of a dietary source and by impaired absorption associated with gastrointestinal diseases[1].

In the present case, vitamin K deficiency appeared to have been produced by long-term discontinuation of oral ingestion due to hyperemesis gravidarum. The bacteria and the aseptic conditions in the fetal intestine result in the reduced synthesis of vitamin K compounds. Maternal vitamin K deficiency sometimes causes fetal vitamin K deficiency because fetal vitamin K is derived from the mother. Placental transfer of vitamin K from the mother is limited, and the fetus takes up less than 10% of maternal vitamin K[5]. Therefore, maternal vitamin K deficiency can result in fetal hemorrhagic disease. Fortunately, in the present case, no hemorrhagic disease was apparent in the mother or the neonate.

Table 1 shows previous cases of fetal hemorrhagic disease associated with maternal vitamin K deficiency and abnormal fetal signs[6–20]. Six cases were found with a PUBMED search from 2001 through 2011[8,12,14–17], and 10 cases were found with an Igaku Chuo Zasshi search (Japanese literature only) from 1994 through 2013[6,7,9–11,13,18–20]. These cases do not include those in pregnant women treated with warfarin or with an enzyme-inducing antiepileptic drug. Four cases were in neonates with coagulopathy associated with maternal vitamin K deficiency but without abnormal fetal signs (**Table 2**)[20–23]. Japanese reports (14 cases) accounted for most of the 16 cases involving fetal hemorrhagic disease. In an East Asian population, including Japanese, there was a high incidence of hyperemesis gravidarum during pregnancy[24]. In the 16 cases reported maternal complications were hyperemesis gravidarum (4 cases), Crohn's disease (4 cases), loss of oral feeding without obvious disease (2 cases), an eating disorder (2 cases), postbariatric surgery (1 case), gastric cancer (1 case), hepatic dysfunction (1 case), and a somatoform disorder (1 case). Nonreassuring fetal status (9 cases) and an intracranial hyperechoic area (8 cases) were common fetal signs. In these 16 cases subdural hema-

Table 1 Previous cases of fetal hemorrhagic diseases due to maternal vitamin K deficiency

Year	Author	Maternal complications	Stop of dietary intake (weeks of gestation)	Maternal supplementation with vitamin K	Delibery age (weeks of gestation)	Neonatal body weight (g)	Apgar score (1/5 minutes)	Fetal abnormal signs	Neonatal hemorrhagic diseases	Neonatal outcome
1994	Yamamoto[6]	CD	Unknown	–	36	2,756	1/3	Intracranial HEA	Multiple intracranial hemorrhage	unknown
2001	Shimabukuro[7]	Gastric carcinoma	31	–	35	1,950	6/7	NRFS, FGR	Subdural hemorrhage	Discharge at 2.5 months of age
2001	Hirose[8]	CD	–	+	36	2,588	9/10	HEA at temporal lobe	Subdural hemorrhage	Intact at 3 months of age
2001	Nishino[9]	CD	24	–	28	Unknown	Unknown	Increased ventricle and BPD	Subdural hemorrhage	Death at 2 days of age
2001	Tamura[10]	HG	6	–	35	2,426	1/1	Intracranial HEA	Subdural hemorrhage	Death at 75 minutes of age
2002	Kunikata[11]	Hepatic dysfunction	25	–	27	Unknown	1/2	NRFS, HEA in ventricle	Cerebral hemorrhage	Death at 12 hours of age
2002	Kunikata[11]	CD	–	–	36	Unknown	1/3	NRFS, intracranial HEA	Cerebral hemorrhage, IVH	tetraplegia
2003	Sakai[12]	HG with Esophageal hiatal hernia	28	–	31	1,702	1/2	NRFS, HEA at parietal lobe	Subdural hemorrhage	tetraplegia
2004	Kato[13]	Eating disorder	Unknown	–	34	1,978	1/2	NRFS, HEA at brainstem	Intracranial hemorrhage, PVL	tetraplegia
2008	Minami[14]	Eating disorder	28	–	40	2,288	Unknown/10	HEA in ventricle	IVH, cerebral atrophy, deficit of left cerebellum	auditory disorder
2008	Van Mieghem[15]	Post-bariatric surgery	28	–	31	2,094	4/7	NRFS, reverse of MCA	Subdural hemorrhage, SAH	Death at 7 days of age
2008	Kawamura[16]	HG	10	+	20	Unknown	Unknown	Increased BPD and ventricle	SAH	Artificial abortion
2009	Eventov-Friedman[17]	HG	–	–	32	2,198	1/1	NRFS	Subdural hemorrhage, IVH, cerebral hemorrage	unknown
2009	Morikawa[18]	Loss of oral feeding	36	–	37	2,734	1/6	NRFS	Bleeding tendency	Discharge at 17 days of age
2012	Fujimaki[19]	Somatoform disorder	10	–	29	766	Unknown	LEA at temporal lobe, increased BPD	Subdural hemorrhage	unknown
2013	Morikawa[20]	Loss of oral feeding	30	–	34	2,714	2/3	NRFS	Cerebral hemorrhage, IVH, hemorrhagic shock	unknown

CD: Crohn disease HG: hyperemesis gravidarum HEA: hyperechoic area NRFS: non reassuring fetal status
MCA: middle cerebral artery IVH: intraventricular hemorrhage SAH: subarachnoid hemorrhage FGR: fetal growth restriction
PVL: periventricular leukomalacia

Table 2 Previous cases of neonatal hemorrhagic diseases due to maternal vitamin K deficiency

Year	Author	Maternal complications	Stop of dietary intake (weeks of gestation)	Maternal supplementation with vitamin K	Delibery age (weeks of gestation)	Neonatal body weight (g)	Apgar score (1/5 minutes)	Fetal abnormal signs	Neonatal hemorrhagic diseases	Neonatal outcome
2003	Kitamura[21]	HG	22	–	27	1,054	3/4	None	Hemorrhagic diathesis	Unknown
2010	Odaka[22]	Choledochal cyst	32	–	34	2,097	8/9	None	Hemorrhagic diathesis	Discharge with no complication
2011	Bersani[23]	Post-bariatric surgery	–	+	34	2,480	Unknown	None	Coagulopathy	Intact at 6 months of age
2013	Morikawa[20]	Loss of oral feeding	30	–	34	2,352	8/9	None	Hemorrhagic diathesis	Discharge at 23 days of age

HG: hyperemesis gravidarum

toma (8 cases) was the most common neonatal disease. The neonatal outcomes were: death, 4 cases (25%); tetraplegia, 3 cases (18.8%); auditory disorder, 1 case (6.3%); and induced abortion, 1 case (6.3%).

There have been, to our knowledge, only 2 previous reports detailing the diagnosis of maternal vitamin K deficiency and its treatment with maternal vitamin K supplementation[6,10]. In our hospital (1,800 deliveries per year), 3 pregnant women with prolonged PT and hyperemesis gravidarum were identified from May 2013 through April 2014 (unpublished data).

Detecting low maternal vitamin K levels can be difficult before the appearance of fetal abnormalities. Also unclear are the level of maternal vitamin K that leads to fetal hemorrhage and whether this level produces hemorrhagic symptoms in both the mother and fetus. Because the vitamin K concentration is much lower in umbilical cord blood than in maternal blood, the fetus can be exposed to severe hypovitaminosis even though the vitamin K deficit in the mother is slight. In the present case, inadequate fetal levels of vitamin K may be prevented by early diagnosis and treatment of the maternal vitamin K deficiency. Pregnant women undergoing treatment with total parenteral nutrition and prophylactic supplementation for vitamins A, B, C, or E should also receive supplemental vitamin K to avoid possible hemorrhagic complications in the fetus.

We performed a coagulation test during pregnancy because maternal coagulopathy and fetal intracranial hematoma due to hyperemesis gravidarum were evident[10,12,16,17]. Although a maternal coagulation test yielded abnormal results during pregnancy, the maternal coagulopathy did not precede fetal bleeding in every case. Previous studies have shown that PT has a low sensitivity for detecting vitamin K deficiency and that a decrease in the prothrombin level of greater than 50% is needed to prolong PT[25]. Revised Japanese guidelines for possible vitamin K deficiency-induced bleeding in neonates and infants recommend either one or both of the following: administration of vitamin K to the neonate immediately after delivery or administration of supplemental vitamin K for at least 1 week after 36 or 38 weeks' gestation to pregnant women with a high risk for giving birth to neonates with such bleeding. Pregnant women with such a high risk include those being treated with an anticoagulant, antiepileptic, or antituberculotic drug and those with a complicating gastrointestinal disease, such as celiac sprue. The guidelines also suggest that vitamin K supplementation should be considered for pregnant women requiring long-term intravenous nutrition[26].

In conclusion, hyperemesis gravidarum can induce maternal and fetal vitamin K deficiency. Although fetal intrauterine cerebral bleeding associated with maternal vitamin K deficiency is rare, it can have a catastrophic outcome. Effective methods for predicting, preventing, and treating fetal hemorrhagic diseases due to low maternal vitamin K are unclear. However, prophylactic treatment with vitamin K during pregnancy should be considered to avoid potential fetal bleeding.

Conflict of Interest: None of the authors have any conflicts of interest associated this paper.

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