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Severe Early-Onset Vitamin K Deficiency Bleeding in a Neonate Born to a Mother with Crohn's Disease in Clinical Remission: A Case Report

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Abstract

Vitamin K deficiency bleeding (VKDB) in neonates is a significant disorder that causes skin, gastrointestinal, and intracranial hemorrhaging. Early-onset VKDB occurs within 24 hours of birth, and its prognosis is poor due to severe hemorrhage. The causes of early-onset VKDB include maternal intake of warfarin and anticoagulants, and maternal vitamin K deficiency. We report the case of a neonate with early-onset VKDB born to a mother with Crohn's disease. The neonate developed severe cerebellar hemorrhage on the day of birth and subsequent noncommunicating hydrocephalus requiring a ventriculoperitoneal shunt. The mother had a 14-year history of Crohn's disease and short bowel owing to intestinal resection. She was in complete remission during pregnancy according to the Crohn's Disease Activity Index. Endoscopic examination performed shortly before pregnancy revealed inflammatory findings in the residual small intestine. Her blood tests at delivery showed an elevated prothrombin induced by vitamin K deficiency or antagonist II (PIVKA-II) level of 26,900 mAU/mL. A definitive protocol to prevent early-onset VKDB in mothers with Crohn's disease complicated by a short bowel is lacking. Administering vitamin K to mothers with elevated PIVKA-II levels before delivery may help prevent early-onset VKDB.

Keywords
- cerebellar hemorrhage
- Crohn's disease
- PIVKA-II
- short bowel syndrome
- vitamin K deficiency bleeding

Background

Vitamin K deficiency bleeding (VKDB) is a significant disorder in neonates that has serious sequelae and can be fatal. VKDB is caused by coagulopathy owing to vitamin K deficiency resulting from factors such as low vitamin K levels in breast milk and low vitamin K production in the intestinal tract of neonates. VKDB in neonates is classified into three types: early onset, classical, and late onset.[1] Classical VKDB often occurs within a few days of birth and can be largely prevented by administering vitamin K after birth. In contrast, early-onset VKDB occurs during the fetal period or within the

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first 24 hours of life; it is mainly caused by maternal factors and cannot be prevented by vitamin K administration after birth. Maternal Crohn's disease is one of the risk factors for maternal and fetal vitamin K deficiency. Cases have been reported of infants born to mothers with Crohn's disease who developed early-onset VKDB.[2,3] In all these reports, the mothers had active Crohn's disease or required total parenteral nutrition.

Here, we report a case of early-onset VKDB with severe cerebellar hemorrhage in a neonate born to a mother with Crohn's disease. In our case, the mother's Crohn's disease was in clinical remission throughout the pregnancy and her dietary intake was normal. No definitive protocol for preventing early-onset VKDB in neonates born to mothers with Crohn's disease is available; however, we believe that our case may have implications for the management of mothers with this disease and their neonates.

Case Report

A neonate was born at 40 weeks of gestation to a gravida 2 para 0, 35-year-old mother via emergency cesarean section because of nonreassuring fetal heart rate tracings. The mother was diagnosed with Crohn's disease at the age of 21 years and had undergone intestinal resection twice (at 21 and 24 years), leaving her with only 120 cm of residual small intestine. Despite the absence of symptoms, the mother's most recent endoscopy performed 5 years before the current pregnancy showed inflammation in the residual intestine, including multiple ulcerations in the ileocecal sac. Throughout the pregnancy, the mother had no clinical symptoms, such as abdominal pain or diarrhea, and she ate a normal, well-balanced diet in sufficient quantities. She gained weight as an average pregnant woman would. The Harvey–Bradshaw Index, one of Crohn's disease clinical indices, was 0 (clinical remission < 5) and the levels of the serum biomarkers hemoglobin and C-reactive protein were almost normal.[4] Complete clinical and serum remission were achieved. Intestinal ultrasound during the pregnancy showed no inflammatory findings, such as intestinal edema, and her gastroenterologist considered that Crohn's disease had become less severe following pregnancy. Throughout this pregnancy, which was established through in vitro fertilization, the mother was treated with high-dose adalimumab (80 mg/2 wk) with concomitant azathioprine for Crohn's disease; clinical remission was maintained. She also received oral folic acid during pregnancy and was administered intravenous ampicillin before delivery to prevent group B streptococcus infection. The neonate's birth weight was 4,188 g (+ 2.96 standard deviation [SD]) without any congenital anomaly and was in good general condition at birth, with Apgar scores of 8 and 9 points at 1 and 5 minutes, respectively. The neonate was breastfed several times for early skin-to-skin contact and stimulating breast secretion. However, the neonate developed bilateral cephalohematoma and vomited fresh blood and was admitted to the neonatal intensive care unit 15 hours after birth. The neonate did not receive vitamin K before the admission as Japan's guideline recommend the first vitamin K be administered orally in syrup when suckling is established (usually the morning of day 1). The vital signs on admission were within the normal range and breathing was stable without respiratory support. We considered that the vomited blood was the baby's blood, not the mother's, as the blood volume was large and fresh at 15 hours after the birth and the baby had normocytic anemia. Physical examination revealed irritability and bulging of the anterior fontanelle in addition to a bilateral large cephalohematoma. A head computed tomography scan (►**Fig. 1**)

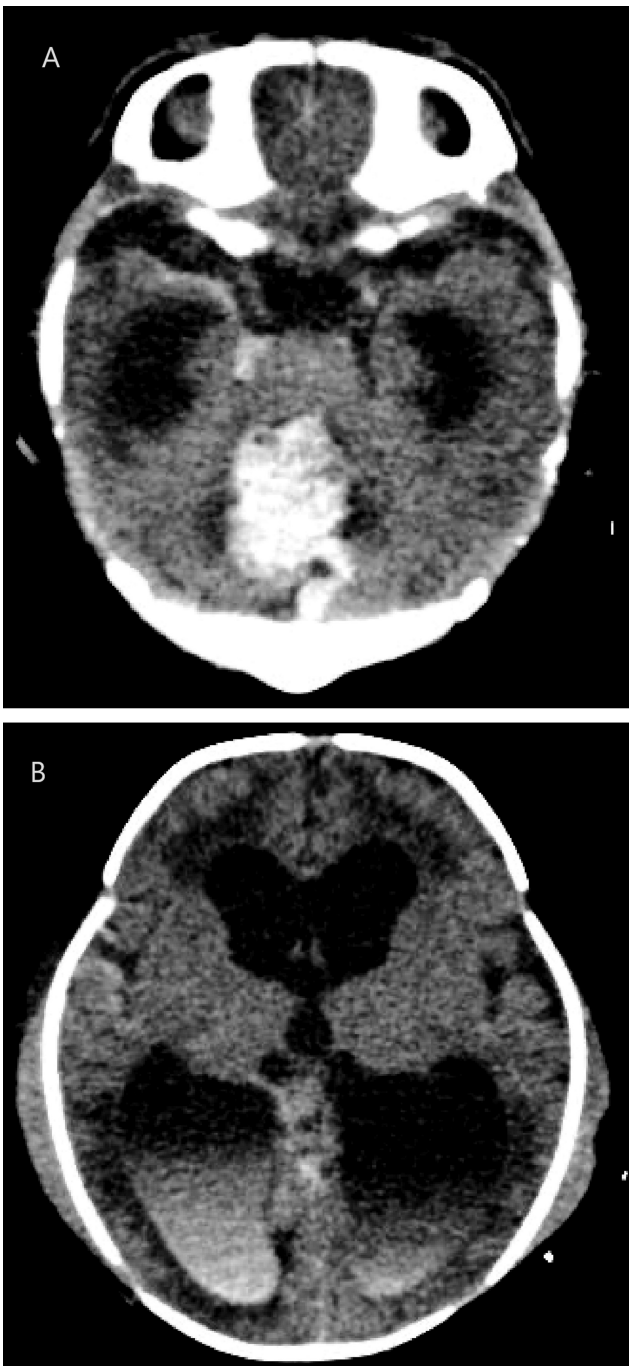

Fig. 1 Computed tomography image captured on day 1 showing (**A**) cerebellar hemorrhage involving the vermis and bilateral cerebellar hemispheres and (**B**) hydrocephalus due to perforation of the cerebellar hemorrhage.

Table 1 Blood test results of the neonate before vitamin K infusion and blood transfusion

		Our institutional normal value			Our institutional normal value
White blood cell count (/μL)	14,780	3,300–8,600	APTT (s)	> 200.0	24.0–34.0
Red blood cell count ($\times 10^4$/μL)	215	435–555	PT (s)	> 100.0	9.6–13.1
Hemoglobin (g/dL)	8.1	13.7–16.8	PT-INR	> 10.00	0.9–1.1
Hematocrit (%)	25.1	40.7–50.1	Fibrinogen (mg/dL)	224	200–400
Platelets ($\times 10^4$/μL)	21.6	15.8–34.8	Fibrin degradation products (μg/mL)	19.0	< 5.0
T-Bil (mg/dL)	6.9	0.4–1.5	D-dimer (μg/mL)	8.9	< 1.0
D-Bil (mg/dL)	0.2	< 0.2	PIVKA-II (mAU/mL)	68,400	< 28
			Clotting factors		
			II (%)	14	27–64
			V (%)	39	50–140
			VII (%)	< 3	28–78
			VIII (%)	111	38–150
			X (%)	16	21–65
			Protein C antigen (%)	24	21–47
			Protein S antigen (%)	29	33–67

Abbreviations: APTT, activated partial thromboplastin time; D-Bil, direct bilirubin; PIVKA-II, prothrombin induced by vitamin K deficiency or antagonist II; PT, prothrombin time; PT-INR, international normalized ratio of prothrombin time; T-Bil, total bilirubin.

showed cerebellar hemorrhage involving the vermis and bilateral cerebellar hemispheres, and expanded ventricles, which suggested noncommunicating hydrocephalus owing to perforation of the cerebellar hemorrhage.

Blood tests before vitamin K infusion and blood transfusion (►**Table 1**) showed anemia and abnormal coagulation capacity with a prothrombin time (PT) international normalized ratio of greater than 10.00 and an activated partial thromboplastin time (aPTT) of greater than 200.0 seconds. In addition, prothrombin induced by vitamin K deficiency or antagonist II (PIVKA-II) level was extremely high at 68,400 mAU/mL (normal, < 28 mAU/mL).[5] The mother's blood tests at delivery (►**Table 2**) showed that the PT and aPTT were normal, but her PIVKA-II level, at 26,900 mAU/mL, was also elevated. The neonate was administered 2 mg of vitamin K infusion, 15 mL/kg of frozen fresh plasma transfusion, and red blood cells. The coagulopathy promptly recovered to within the normal range 24 hours after the neonate was born. The cephalohematoma began to shrink and hematemesis stopped the day after the vitamin K was infused. A follow-up computed tomography scan on day 2 showed that the cerebellar hemorrhage had not expanded (►**Fig. 2**). Based on the patient's clinical course and laboratory data, the patient was diagnosed with early-onset VKDB. Supporting the diagnosis, magnetic resonance imaging (MRI), including magnetic resonance angiography and magnetic resonance venography on day 8, showed no congenital abnormalities that could cause brain bleeding, such as cerebral arteriovenous malformation or venous sinus thrombosis. MRI findings also showed a high-intensity area with only a small low-intensity area in the center of the cerebellum on T1-weighted images, suggesting that it was approximately 1 to 2 weeks since the hemorrhage had occurred (►**Fig. 3**). A fetal ultrasound, performed by an obstetrician at 38 weeks of gestation, showed no hydrocephalus; however, the patient's head circumference at birth (40 cm + 5.3 SD) was asymmetrically enlarged for the birth weight of 4,188 g (+ 2.96 SD), indicating that the neonate already had hydrocephalous at birth. Therefore, we considered that the baby may have developed the cerebellar hemorrhage during the perinatal period from 39 weeks of gestation to birth and that the progression of posthemorrhagic hydrocephalus probably led to fetal dysfunction.

Table 2 The mother's blood test results at delivery

APTT (s)	31.1
PT (s)	13.2
PT-INR	1.21
PIVKA-II (mAU/mL)	26,900

Abbreviations: APTT, activated partial thromboplastin time; PIVKA-II, prothrombin induced by vitamin K deficiency or antagonist II; PT, prothrombin time; PT-INR, international normalized ratio of prothrombin time.

No further enlargement of the cerebellar hemorrhage was observed; however, on day 9, the hydrocephalus gradually worsened, causing coma and severe apnea due to brainstem compression. The patient was ventilated and emergency cerebrospinal fluid drainage was performed through the anterior fontanelle the following day (day 10). Pediatric neurosurgeons performed Ommaya reservoir placement surgery on the neonate at another hospital. Cerebrospinal

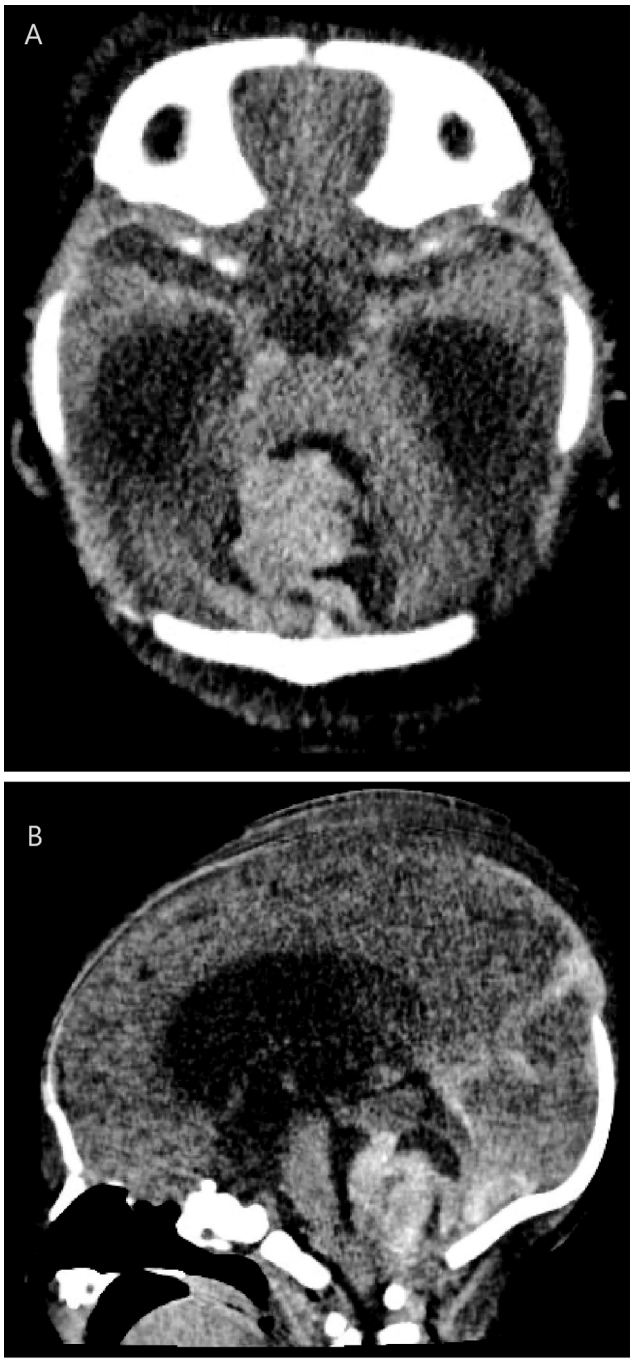

Fig. 2 Computed tomography image captured on day 2 showing that (**A**) the cerebellar hemorrhage has not expanded and (**B**) the hemorrhage occupies the fourth ventricle.

fluid was drained from the patient every 8 to 12 hours and the patient's consciousness improved. The patient was extubated on day 11, when shrinking of the brain ventricles was observed. The PIVKA-II levels were normalized on day 46 (►**Table 3**). As the patient required continuous cerebrospinal fluid drainage, a ventriculoperitoneal shunt was placed on day 58. MRI findings on day 70 revealed shrinkage of the hematoma and improved ventricular enlargement. The patient was discharged without any medical devices on day 82, when the patient showed abnormal writhing movements but had not started eye tracking.

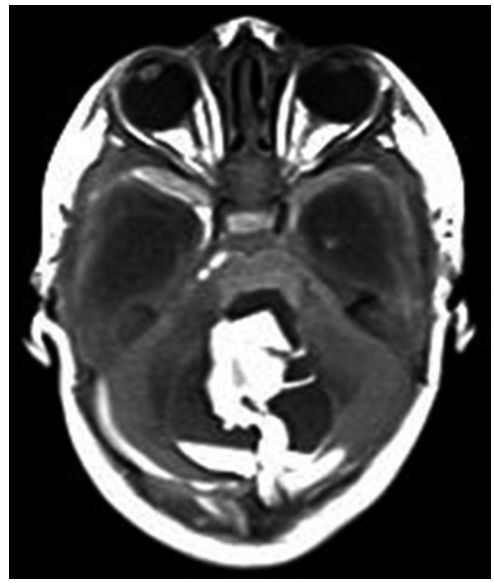

Fig. 3 Magnetic resonance image captured on day 8. The T1-weighted image shows a high-intensity area with only a small low-intensity area in the center of the cerebellum.

Table 3 Laboratory data for the infant

	15 h	24 h	Day 3	Day 46
APTT (s)	> 200.0	44.1	31.1	26.8
PT (s)	> 100.0	15.2	11.2	10.5
PT-INR	> 10.00	1.41	1.00	0.94
PIVKA-II (mAU/mL)	68,400	Not available	32,800	22

Abbreviations: APTT, activated partial thromboplastin time; PIVKA-II, prothrombin induced by vitamin K deficiency or antagonist II; PT, prothrombin time; PT-INR, international normalized ratio of prothrombin time.

Discussion

We report the case of a neonate with severe early-onset VKDB born to a mother with Crohn's disease. The mother had a short bowel, but was in clinical remission.

VKDB is a bleeding disorder caused by insufficient activity of the vitamin K–dependent coagulation factors, and prompt recovery can be achieved with vitamin K supplementation. PIVKA-II is an abnormal protein produced when vitamin K is deficient and is an indicator of VKDB.[6] To prevent VKDB, early vitamin K administration is recommended after birth. In Japan, since 1989, oral syrup administration of vitamin K_2 has been advocated three times: at the time that suckling is established, at 1 week of age, or at the time of obstetric discharge, whichever comes first and at the 1-month check-up, which dramatically decreased the incidence of VKDB.[7] However, there were reports of VKDB incidence even with the three-time method, and the 2011 guideline of Japan Pediatric Society described an alternative method of once a week until 3 months of age, based on the method used in European Union (EU) countries.[8] Then, the once-a-week

Table 4 Recommendations for prophylaxis of the vitamin K deficiency bleeding in neonates and infancy (2021) by the Japan Pediatric Society

Recommendations
Neonates and early infants can have vitamin K deficiency bleeding, and among them, infants with hepatobiliary diseases are at high risk of intracranial hemorrhage owing to vitamin K deficiency. Intracranial hemorrhage is associated with poor life prognosis and neurological complications. We recommend all pediatricians to keep the following two points in mind
1. For early detection of hepatobiliary diseases, physicians should understand the significance of the stool color card in the Maternal and Child Health Handbook and instruct parents on how to use of this card
2. Vitamin K_2 should be administered orally in syrup at the time that suckling is established (usually the morning of day 1), at 1 wk of age, or at the time of obstetric discharge, whichever comes first, and, then, once a week until the age of 3 mo

dosing method was widely spread. However, the two dosing methods were mixed. In the 2021 "recommendations for prophylaxis of the VKDB in neonates and infancy," the Japan Pediatric Society recommend the once-a-week dosing method until the age of 3 months (►**Table 4**). However, vitamin K administration cannot prevent early-onset VKDB, which occurs during the fetal period or within 24 hours of birth.

Early-onset VKDB is caused by poor placental transfer of vitamin K to the fetus, even in the absence of maternal coagulation abnormalities. This disorder may be associated with the mother taking vitamin K–inhibiting drugs (such as antiepileptic and antituberculosis drugs, warfarin, and continuous antibiotics) during pregnancy or continued low nutrition owing to maternal malabsorption disorders, severe hyperemesis gravidarum, or eating disorders during pregnancy.[8,9]

Crohn's disease is a chronic inflammatory disease of the gastrointestinal tract that often affects the terminal ileum and colon. Patients often have abnormal mucosal immune response and compromised epithelial barrier function, caused by many factors including genetic susceptibility, environmental factors, and intestinal microflora.[10] Symptoms of Crohn's disease include diarrhea, abdominal pain, nausea, weight loss, chronic fatigue, and gastrointestinal bleeding, which can lead to malnutrition. In addition, small bowel resection or small intestinal ulcers reduce the intestinal absorptive surface and cause fat-soluble vitamin deficiencies.[11] Therapeutic elemental diets, which contain small amounts of lipids, also contribute to the failure to absorb fat-soluble vitamins.

In the reported cases of VKDB owing to maternal Crohn's disease, Crohn's disease was active or total parenteral nutrition was required.[2,3] In our case, the mother was in complete clinical and serum remission of Crohn's disease. Furthermore, she consumed a normal diet that included lipids, gained weight, and did not take vitamin K–inhibiting drugs or continuous antibiotics throughout the pregnancy. To the best of our knowledge, no cases of VKDB caused by maternal Crohn's disease in clinical remission have been reported. We believe that a short intestinal tract and residual inflammation in the intestine might cause VKDB in infants. As observed in the present case, early-onset VKDB associated with maternal Crohn's disease can cause severe bleeding symptoms, such as intracranial and intra-abdominal hemorrhages, and prediction and prevention methods for VKDB should be established.

Between January 2012 and December 2022, 33 mothers with Crohn's disease were admitted to our hospital. Of these, 14 mothers underwent partial resection of the ileum or small intestine, three of these mothers consequently had a short bowel. Of the three cases of short bowel, the mother in the current case had the shortest residual small intestine at 120 cm. Of the 33 cases, our case was the only one in which the neonate developed VKDB. Maternal short bowel does not commonly cause VKDB in infants.

The European Crohn's and Colitis Organisation Guidelines, revised in 2022, include a new statement that special attention regarding nutritional requirements should be paid to pregnant women with inflammatory bowel disease.[12] However, no definitive protocol exists regarding which mothers with Crohn's disease are at risk of developing VKDB or how to treat these mothers. In addition to mothers who are undernourished or require an elemental diet, we propose that clinicians recognize that pregnant women with the disease who have undergone intestinal resection or have residual intestinal inflammatory findings are at risk of VKDB, even if the disease is in clinical remission. Assessing the PIVKA-II levels in such patients to check for vitamin K deficiency might help identify patients at risk of early-onset VKDB.[13]

Treatment for mothers identified as having a vitamin K deficiency remains unclear. A systematic review and meta-analysis by Shahrook et al reported that antenatal administration of vitamin K1 to a mother has low placental transit and increases the vitamin K level of maternal and newborn plasmas, cord serum, and breast milk, but does not directly reduce neonatal bleeding.[14] However, Japanese guidelines suggest prophylactic administration of vitamin K to the mother before delivery as an option when risk factors for early-onset VKDB are recognized.[8] Although further studies are needed, measuring the PIVKA-II levels of mothers with risk factors, and administering vitamin K to these mothers, might be a method of preventing early-onset VKDB.

Conclusion

Mothers with Crohn's disease can cause severe VKDB in neonates, even if the mothers are in clinical remission. When mothers with Crohn's disease have a short bowel or inflammatory findings in the residual small intestine, obstetricians and neonatologists should be aware that the infant is at risk of developing VKDB. Measuring the PIVKA-II levels to

detect mothers with potential vitamin K deficiency and administering vitamin K to these mothers may help prevent early-onset VKDB.

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Conflict of Interest
None declared.

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References

1 Lane PA, Hathaway WE. Vitamin K in infancy. J Pediatr 1985;106 (03):351–359
2 Ohishi A, Nakashima S, Ogata T, Iijima S. Early vitamin K deficiency bleeding in a neonate associated with maternal Crohn's disease. J Perinatol 2014;34(08):636–639
3 Hirose M, Akiyama M, Takakura K, Noda Y. Active Crohn disease with maternal vitamin K deficiency and fetal subdural hematoma. Obstet Gynecol 2001;98(5, Pt 2):919–921
4 Turner D, Ricciuto A, Lewis A, et al; International Organization for the Study of IBD. International Organization for the Study of IBD. STRIDE-II: an update on the selecting therapeutic targets in inflammatory bowel disease (STRIDE) initiative of the International Organization for the Study of IBD (IOIBD): determining therapeutic goals for treat-to-target strategies in IBD. Gastroenterology 2021;160(05):1570–1583
5 Hunnali CR, Devi U, Kitchanan S, Sethuraman G. Three different regimens for vitamin K birth prophylaxis in infants born preterm: a randomized clinical trial. J Pediatr 2023;255:98–104
6 Ringoringo HP, Tambunan KR, Ananda FK, Nawati F, Permana YN. Gastrointestinal bleeding due to idiopathic early onset of vitamin K deficiency bleeding in a girl baby 50 min after birth: a rare case. BMC Pediatr 2022;22(01):663
7 Shirahata A. Vitamin K deficiency in newborn and young infants. J Pediatr Hematol Oncol 2008;22:95–103
8 Shirahata A, Itou S, Takahashi Y, Nishiguchi T, Mastuda Y. Modified guideline of vitamin K administration for vitamin K deficiency in infancy. J Jpn Pediatr Soc 2011;115:705–712
9 Araki S, Shirahata A. Vitamin K deficiency bleeding in infancy. Nutrients 2020;12(03):780
10 Torres J, Mehandru S, Colombel JF, Peyrin-Biroulet L. Crohn's disease. Lancet 2017;389(10080):1741–1755
11 Fabisiak N, Fabisiak A, Watala C, Fichna J. Fat-soluble vitamin deficiencies and inflammatory bowel disease: systematic review and meta-analysis. J Clin Gastroenterol 2017;51(10):878–889
12 Torres J, Chaparro M, Julsgaard M, et al. European Crohn's and colitis guidelines on sexuality, fertility, pregnancy, and lactation. J Crohn's Colitis 2023;17(01):1–27
13 Sotodate G, Matsumoto A, Konishi Y, Toya Y, Endo M, Oyama K. Fetal intracranial hemorrhage due to maternal subclinical vitamin K deficiency associated with long-term eating disorder. J Obstet Gynaecol Res 2019;45(02):461–465
14 Shahrook S, Ota E, Hanada N, Sawada K, Mori R. Vitamin K supplementation during pregnancy for improving outcomes: a systematic review and meta-analysis. Sci Rep 2018;8(01): 11459

