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CASE REPORT

Late-onset vitamin K deficiency bleeding in an extremely preterm infant fed an exclusively human milk–based diet

Vimal Vasu[1,2] | Shaveta Mulla[1] | Atisha Pandya[1] | David Card[3] | Martin J. Shearer[4] | Paul Clarke[5,6]

[1]Department of Neonatal Medicine, William Harvey Hospital, Ashford, Kent, UK

[2]School of Biosciences, University of Kent, Canterbury, UK

[3]Human Nutristasis Unit, Synnovis, Guy's and St. Thomas's NHS Trust, London, UK

[4]Centre for Haemostasis and Thrombosis, Guy's and St. Thomas's NHS Foundation Trust, London, UK

[5]Neonatal Unit, Norfolk and Norwich University Hospitals NHS Foundation Trust, Norwich, UK

[6]Norwich Medical School, University of East Anglia, Norwich, UK

Correspondence
Vimal Vasu, Department of Neonatal Medicine, William Harvey Hospital, Kennington Rd, Willesborough, Ashford, Kent, TN24 0LZ, UK.
Email: vimal.vasu@nhs.net

Abstract

All newborns need extra phylloquinone (vitamin K_1; K_1) to prevent vitamin K deficiency bleeding (VKDB). In preterm babies, the main sources are prophylactic K_1 given at birth and parenteral and/or enteral feeding thereafter. Preterm babies are at risk of late-onset VKDB if ongoing K_1 supplementation is inadequate. For extremely preterm infants fed an exclusive human milk diet, the low K_1 content of human milk may predispose them to vitamin K deficiency. Human milk fortification with either bovine milk–derived fortifier or human milk–based fortifier (HMF) made from pooled donor milk is a widely used strategy to improve the micronutrient and growth status of preterm infants. However, the K_1 content of HMF is markedly lower than that of bovine-based preparations. We present an unusual case of late-onset VKDB in an extremely preterm infant who received an exclusive human milk diet and HMF and quantify total K_1 intake prior to the bleeding.

KEYWORDS
hemorrhage, human, milk, nutrients, nutrition, premature birth, vitamin K

CASE REPORT

An extremely preterm female infant (23 weeks + 5 days of gestation) was born via spontaneous vaginal delivery, with a birth weight of 555 g (25th centile). There were no relevant maternal medications or medical conditions. After birth, she received a standard intramuscular 400 μg/kg phylloquinone (vitamin K_1; K_1) dose (Konakion MM Paediatric, Neon Healthcare) for prophylaxis of vitamin K deficiency bleeding (VKDB). She received parenteral nutrition for 8 days while enteral feeds were established with her mother's own expressed breast milk. On reaching a full enteral feed volume (150 mL/kg/d) on day 13, a commercially available liquid human milk–based fortifier (HMF) (Prolact + H^2MF, Prolacta Bioscience) was added to supplement her mother's expressed breast milk as part of a clinical trial [1]. Cranial ultrasonography in the first postnatal week revealed only minor bilateral germinal matrix hemorrhages (Papile stage 1) [2]. Between days 13 and 73, she remained fully enterally fed with maternal expressed breast milk plus human milk fortifier between 150 to 180 mL/kg/day. Her weight gain was satisfactory (∼15.3 g/kg/d).

On day 73 (postmenstrual age, 33 weeks + 6 days; weight, 1521 g), after routine capillary blood gas sample collection, she had unexpected significant oozing of blood from the heel-prick puncture site lasting for a few hours. A venous blood sample demonstrated markedly deranged coagulation with prothrombin time of 150 seconds (reference range, 13-16 seconds) and activated partial thromboplastin

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time of 84 seconds (reference range, 22-35 seconds). Assay of coagulation factors (F) showed very low activity of vitamin K–dependent factors II (<0.03 IU/mL) and VII (<0.06 IU/mL) and low-normal activity of FX (0.31 IU/mL). Reference means (95% CIs) in international units per milliliter are as follows: FII, 0.57 (0.36-0.95); FVII, 0.83 (0.21-1.45); and FX, 0.56 (0.20-0.92) [3].

Late-onset VKDB was suspected. She was immediately treated with K_1 (Konakion MM Paediatric) 1 mg orally, followed by ongoing daily oral K_1 supplementation with 2 mg for 3 days and 1 mg thereafter. A repeat clotting profile conducted within 24 hours of K_1 treatment demonstrated normalized coagulation parameters (prothrombin time, 13.5 seconds; activated partial thromboplastin time, 40 seconds). Three days after the bleeding episode, blood samples were collected and sent to the Nutristasis Unit, St Thomas' Hospital, London, United Kingdom, for analysis of serum protein induced by vitamin K absence or antagonism; undercarboxylated FII (PIVKA-II) and K_1, assayed as previously described [4]. An elevated PIVKA-II indicates present or recent vitamin K deficiency. With the chemiluminescence assay we used [4], the adult reference range is 0.01 to 0.05 arbitrary units (AU)/mL. This infant's PIVKA-II concentration was very elevated at 13.4 AU/mL. Because the half-life of disappearance of PIVKA-II from the circulation in newborns is of the order of 50 hours [5], this value would have been even higher (at least double) when the infant had been first bled 3 days earlier. The concomitant K_1 concentration was 40 μg/L (adult nonfasting K_1 reference range, 0.15 to 1.55 μg/L [6,7]). This markedly elevated concentration reflected the recent K_1 treatment and ongoing high-dose daily supplementation at the time of sampling. The baby subsequently remained stable, and further cranial ultrasound scans showed no new hemorrhage. She had no clinical signs of liver disease. During her neonatal course, maximum values for alanine aminotransferase and alkaline phosphatase were 12 U/L (reference range, 5-45 U/L) and 506 U/L (reference range, 60-425 U/L), respectively. A follow-up PIVKA-II concentration 3 weeks after the VKDB episode was 0.03 AU/mL, confirming the expected normalization after K_1 treatment. She was discharged home at 39 weeks + 4 days postmenstrual age. Neurodevelopmental assessment at 2 years corrected age was normal.

1.1 | Review of dietary vitamin K intake between birth and the bleeding episode

We retrospectively determined this baby's total K_1 intake from all sources between birth and the VKDB event on day 73 using the information below:

(i) The prophylactic intramuscular K_1 dose given at birth (200 μg; ie, 400 μg/kg).
(ii) The documented daily and weekly maternal milk feed volumes received, with dietary K_1 intake estimated based on a maternal human milk K_1 content of 2.0 μg/L [8].
(iii) Parenteral nutrition–derived K_1 provided by the Vitlipid N emulsion component given at a dose of 4 mL/kg/d (20 μg K_1 per mL of Vitlipid N), which provided 80 μg/kg/d of K_1.
(iv) K_1 intakes in micrograms per kilogram per day were calculated using the infant's weight at birth and updated weekly weights until day 70 by dividing successive cumulative total weekly K_1 intakes by 7 (μg/d) and then by the corresponding week's weight.

The Table shows the estimated total weekly K_1 intake received from all sources between birth and the VKDB episode.

2 | DISCUSSION

This proven case of VKDB in an extremely preterm infant occurred secondary to dietary K_1 deficiency associated with an exclusive human milk diet (EHMD) with no extra K_1 supplementation of milk feeds. To our knowledge, this is the first time that the total intake of K_1 from all sources has been quantified in any infant prior to a VKDB presentation. This case highlights that without adequate ongoing dietary K_1 supplementation, extremely preterm infants are at risk of clinical late-onset VKDB despite receiving the recommended prophylaxis K_1 dose at birth. The case also shows the value of retrospective PIVKA-II analyses to confirm definitively a suspected clinical diagnosis of VKDB biochemically—a conclusion enabled by the slow disappearance rate of PIVKA-II from the circulation [5].

The HMF added as a daily supplement to the mother's own milk from day 13 provided essentially no further additional dietary K_1 because the commercial product "*is not a significant source of this nutrient*" (Prolacta Bioscience, Nutrition brochure). The K_1 content of the mother's own milk would only have been ~2.0 μg/L [8]. Based on the baby's actual daily intake of 180 mL/kg/d of milk from week 5, without additional K_1 provided by the HMF, her daily K_1 intake in the weeks preceding the bleeding episode approximated only 0.3 μg/kg/d. This is approximately 30 times lower than the current minimum recommended adequate daily K_1 intake of 8 to 10 μg/kg/d for preterm infants [9]. In contrast, had the mother's milk been fortified with a commercially available bovine milk–based fortifier (which typically supplements human milk by an additional ≥6 μg K_1/100 mL milk) [8], this baby would have received at least the recommended daily K_1 intake (in this case ≥11 μg/kg/d), and VKDB would almost certainly have been avoided.

Without extra K_1 supplementation, an infant's dietary K_1 intake with an EHMD is significantly lower than the required daily intake to meet the demands for the post-translational conversion of specific glutamate residues to γ-carboxyglutamate, which is needed for biological activity of vitamin K–dependent proteins. Further, the routinely administered single prophylactic intramuscular dose of K_1 given at birth did not protect against VKDB at ~10 weeks postnatal age. Adequate ongoing dietary intake of vitamin K is therefore essential, particularly for preterm infants receiving an EHMD [4,8].

Using EHMDs incorporating commercially available HMFs has gained popularity in recent years, with proponents citing a lower incidence of necrotizing enterocolitis and mortality in extremely preterm infants [10,11]. HMFs are comparable to bovine-derived fortifiers in terms of macronutrient content, minerals, and some

TABLE Estimated total weekly K_1 intake received from all sources between birth and the vitamin K deficiency bleeding episode on day 73.

Day (week of life)	Weight (kg)[a]	Human milk volume (mL)	Human milk volume (mL/kg/d)[b]	K_1 intramuscular (μg)	PN Vitlipid K_1 (μg)[c]	Human preterm milk K_1 (μg)[d]	Total K_1 intake (μg)[e]	K_1 intake (μg/kg/d)[f]
D0-D7 (wk 1)	0.555	21.5	5.5	200	176	0.04	376.04	96.79
D8-D14 (wk 2)	0.528	308	83.3	0	176	0.62	176.62	47.79
D15-21 (wk 3)	0.608	667	156.7	0	0	1.33	1.33	0.31
D22-D28 (wk 4)	0.719	545	108.3	0	0	1.09	1.09	0.22
D29-D35 (wk 5)	0.815	1027	180.0	0	0	2.05	2.05	0.34
D36-D42 (wk 6)	0.990	1247	179.9	0	0	2.49	2.49	0.36
D43-D49 (wk 7)	1.050	1323	180.0	0	0	2.65	2.65	0.36
D50-56 (wk 8)	1.280	1613	180.0	0	0	3.23	3.23	0.36
D57-63 (wk 9)	1.385	1745	180.0	0	0	3.49	3.49	0.36
D64-D70 (wk 10)	1.510	1902	179.9	0	0	3.80	3.80	0.36
D71-D73 (wk 11 to VKDB event)	1.570	543	49.4	0	0	1.09	1.09	0.35
Cumulative totals				200	352	22	**574**	

The total (absolute) amount of K_1 dose she received between birth and the vitamin K deficiency bleeding episode was approximately 574 μg, a daily average of 5 μg/kg/d from birth to day 73 based on her weight (1.57 kg) at the time of bleeding, but an average of only ~0.3 μg/kg/d from week 3 until day 73.

D, day; PN, parenteral nutrition; VKDB, vitamin K deficiency bleeding.

[a]Based on birth weight (week 1) and infant's weight at the end of each completed week until the day 73 bleeding episode.

[b]Feed volumes were ~180 mL/kg/d from week 5 onwards.

[c]Parenteral nutrition Vitlipid intake was 80 μg/kg/d.

[d]Based on human preterm milk K_1 content of 2.0 μg/L [8].

[e]Total K_1 from prophylactic bolus parenteral, parenteral nutrition solution intake, and enteral human milk intake.

[f]Averaged daily total K_1 intake for each week (part week for days 71-73) from all sources based on the infant's weight at the end of each completed week.

vitamins. However, the K_1 content in the HMF fed to this baby was negligible, and therefore, she had a significantly reduced dietary supply of K_1 compared to what would have been provided by a bovine-derived fortifier. Though it is biologically plausible that an EHMD is beneficial for extremely preterm infants, future research should better establish the unintended but potential risks of vitamin K and other micronutrient deficiencies alongside important outcomes (eg, necrotizing enterocolitis/neurodevelopment).

VKDB is rare after intramuscular prophylaxis, with a reported incidence in epidemiological surveillance studies of ~1/100 000 births [12,13]. However, a recent prospective study indicated that ~two-thirds of human milk–fed preterm infants have subclinical vitamin K deficiency in early infancy [4]. Based on these data and this case, we recommend that exclusively preterm infants receiving an EHMD be given routine daily K_1 supplementation during early infancy. Meanwhile, neonatal units currently using EHMDs for preterm infants and those that do not routinely supplement maternal milk using bovine-derived milk fortifiers should remain vigilant for possible signs of late-onset VKDB. Maternal K_1 supplementation also effectively increases breast milk K_1 concentrations [14] and could therefore provide an alternative strategy to improve an infant's K_1 status during early infancy.

In this case, the prompt clinical suspicion and treatment of VKDB may have prevented sentinel bleeding from progressing to life-threatening intracranial bleeding. The recommended reversal of VKDB is rapid therapy with intravenous/subcutaneous vitamin K_1 [15]. Our patient received oral vitamin K_1, which stopped the clinical oozing within hours and normalized the coagulation profile within <24 hours. This illustrates that, in an infant tolerating enteral feeds and without underlying hepatobiliary insufficiency, jaundice, or malabsorption, oral K_1 supplementation can treat VKDB successfully. However, because minor bleeding may be the first sign of dangerous vitamin K deficiency, with such warning bleeds sometimes occurring only a few hours or days before life-threatening intracranial hemorrhage [16], prompt treatment with intravenous/subcutaneous vitamin K_1 is preferable.

3 | CONCLUSION

Extremely preterm infants fed an EHMD receive significantly less than the recommended daily vitamin K_1 intake and so are at increased risk of VKDB. Routine ongoing daily dietary K_1 supplementation is therefore indicated for these infants. Practitioners should remain vigilant for signs of possible K_1 deficiency and have a low threshold for urgent parenteral K_1 treatment of infants who have unexplained minor bleeds as these may be the harbingers of imminent life-threatening hemorrhage.

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AUTHOR CONTRIBUTIONS

V.V. wrote the first manuscript draft. All coauthors provided additional intellectual input and contributed to manuscript revision. All authors approved the final manuscript version. D.C. supervised the vitamin K_1 and protein induced by vitamin K absence or antagonism; undercarboxylated FII analyses. V.V. is guarantor.

DECLARATION OF COMPETING INTERESTS

V.V. was involved in recruitment to a clinical trial that randomized preterm-born infants to an exclusively human milk diet [1]. P.C. declares unrestricted research funding paid to his employing institution (Norfolk and Norwich University Hospitals NHS Foundation Trust) by Danone Early Life Nutrition and conference travel and accommodation reimbursements received from Nutricia and Nestle in 2018 to 2019 and, in 2018 to 2020, was local principal investigator recruiting to a commercial trial of a novel bovine-derived breast milk fortifier sponsored by Danone Nutricia Research. M.J.S. has acted as a medicolegal expert witness in cases of vitamin K deficiency bleeding. The authors have no other potential conflicts of interest relevant to this article to disclose.

ORCID

Vimal Vasu https://orcid.org/0000-0003-2606-9797
Shaveta Mulla https://orcid.org/0000-0002-1008-0767
Atisha Pandya https://orcid.org/0009-0009-7108-5498
David Card https://orcid.org/0000-0002-4967-4343
Martin J. Shearer https://orcid.org/0000-0003-2509-0818
Paul Clarke https://orcid.org/0000-0001-6203-7632

TWITTER

Vimal Vasu @vimalvasu

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