Preventing Vitamin K Deficiency Bleeding: An Evidence-Based Update for the Midwife

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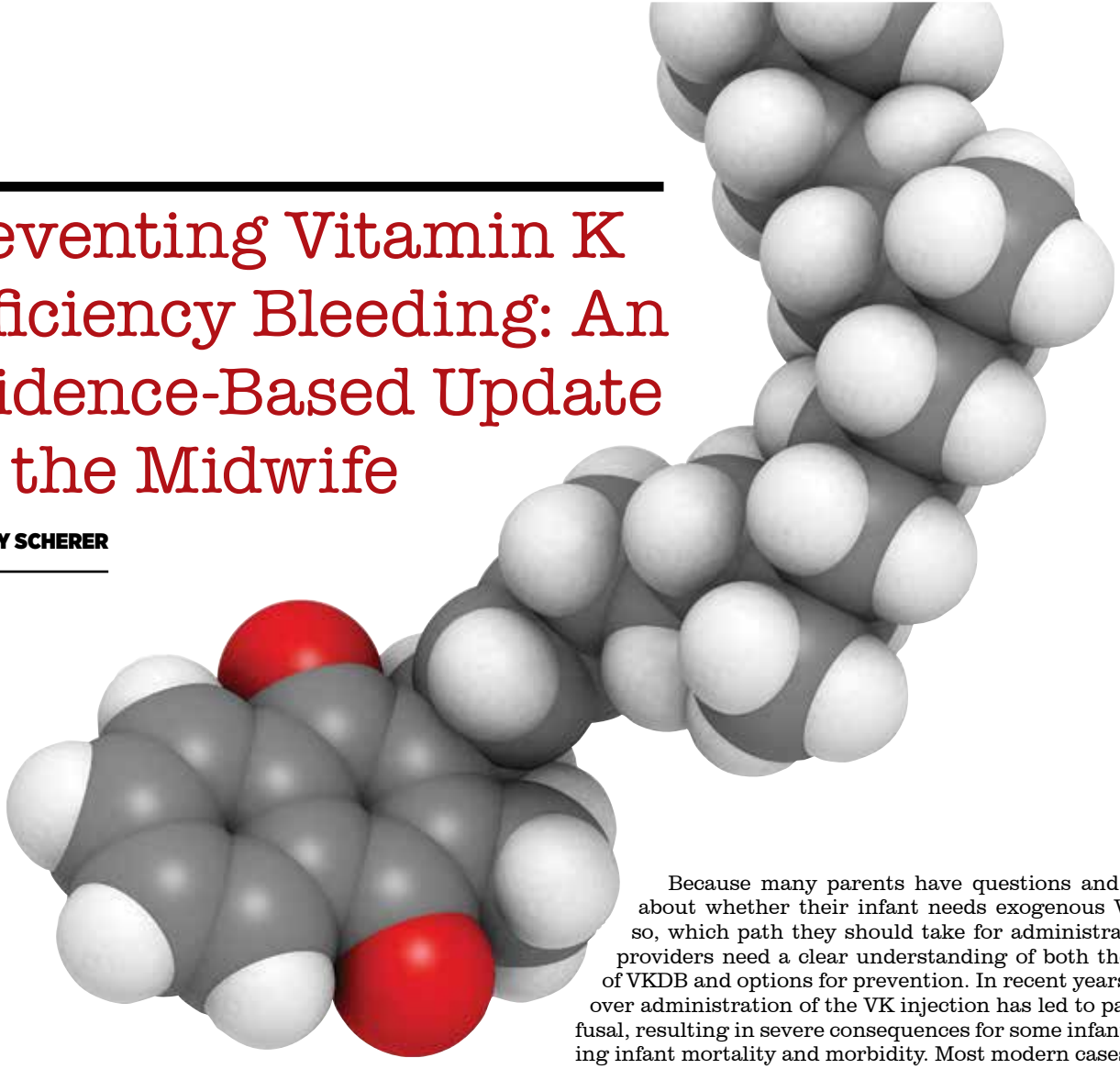

Vitamin K deficiency bleeding (VKDB) was first discovered in 1894 when spontaneous bleeding was observed in neonates who did not have any underlying disorders such as hemophilia, and it was named hemorrhagic disease of the newborn (HDN).[1] It was later renamed VKDB for accuracy, as it was discovered that VKDB is not unique to the newborn period, and hemorrhagic disease has multiple causes, though this particular manifestation is specific to vitamin K (VK) deficiency.[1,2] Although VKDB can occur across the lifespan, including in adults, it is most common in infants due to endogenous and exogenous factors that prevent them from developing and maintaining adequate VK levels. VKDB thus describes bleeding secondary to inadequate activity of VK-dependent coagulation factors that can be corrected by VK replacement.[3]

In 1961, the American Academy of Pediatrics began to recommend that all newborns be administered a VK injection at birth to help prevent them from developing VKDB.[4] Although another option exists for the prevention of VKDB—oral VK supplementation—for a variety of reasons this option is not offered as a standard of care in the United States. Midwives practicing in home and birth center settings frequently encounter parents who decline intramuscular VK for their newborns, leaving these infants vulnerable to the rare, though possible, outcome of developing VKDB and its serious sequelae, including brain damage and death. Oral VK is an evidence-based secondary option that can be offered to parents who are unwilling to accept an intramuscular VK injection for their infant. Although offering an oral VK protocol in the United States presents challenges, including lack of supplement regulation and no national standardized oral VK guidelines, it is an option that may be accepted by clients who decline intramuscular prophylaxis for their infant.

Because many parents have questions and concerns about whether their infant needs exogenous VK, and if so, which path they should take for administration, care providers need a clear understanding of both the etiology of VKDB and options for prevention. In recent years, concern over administration of the VK injection has led to parental refusal, resulting in severe consequences for some infants, including infant mortality and morbidity. Most modern cases of VKDB occur in infants whose parents decline prophylactic VK, often resulting in life-long implications for the infant. Case reports from hospitals around the country of infants who developed VKDB have led to an awareness that refusal of VK prophylaxis may be increasing. Although the following examples of infant hemorrhage following parental refusal of the VK injection are alarming, it is difficult to say how widespread VKDB is because there is no mandated reporting on or nationwide surveillance of its use in the United States. In 2004, a 5-week-old infant in Michigan developed a thymic hemorrhage and respiratory failure.[5] In 2013, a 3-week-old infant in North Carolina developed an umbilical stump bleed and hemorrhagic shock.[6] In 2006, two 5-week-old infants in Missouri developed intracranial hemorrhages (ICH).[7] In 2009, 2012, and 2015 respectively, a 6-week-old infant in Texas,[8] a 4-week-old infant in Virginia,[9] and a 3-week-old infant in Indiana[10] all also developed ICH. Perhaps most memorably, 7 infants who did not receive VK prophylaxis developed VK deficiency in Tennessee in 2013, drawing major attention and prompting a Centers for Disease Control and Prevention (CDC) investigation. Five of these infants exhibited bleeding, and 4 of those bleeds were intracranial hemorrhages.[11]

In all of the cases above, parents declined the VK injection, and it is unknown whether they were offered or aware of oral VK as a prophylactic option because it is not considered the standard of care. While there are no nationwide surveillance data on rates of VK refusal or place of birth for those infants not receiving VK, the CDC investigation in Tennessee revealed that in area hospitals, 96.6% of infants received VK injections, while in area out-of-hospital births, 72% of infants received VK.[11] Larger studies, such as a population-based study of nearly 300,000 births in Alberta, Canada, found that planned home births had

a parental VK refusal rate of 14.5%, birth center births a rate of 10.7%, and hospital births a rate of 0.2%.[12] While the midwifery model of care strongly emphasizes informed choice, it is crucial that parents understand the possibility of the rare yet devastating consequences that can occur in infants not receiving VK prophylaxis. In the Tennessee cases, for example, only 1 out of 7 infants' parents reported that they were aware that this type of emergency could result when they refused VK.[11]

Misinformation on VK abounds both in the midwifery community and more broadly, and many parents may decline prophylaxis without having the necessary information to make a truly informed decision. The full range of options for the prevention of VKDB may not even be available to parents depending on the provider they choose for their pregnancy and infant. To offer evidence-based, client-centered care, the midwifery community must ensure that all providers are well-educated and able to provide clients with comprehensive information on this topic. The following sections will explore the role of VK in the body and the unique physiology that puts infants at particular risk for VKDB; review the benefits and risks of intramuscular and oral VK prophylaxis; and present an evidence-based oral VK prophylactic protocol that care providers can offer parents for the prevention of infant VKDB.

Vitamin K in the Human Body

Vitamin K is one of the 4 fat-soluble vitamins, though in contrast to the other fat-soluble vitamins, there is little storage of it in the body. Naturally occurring forms of VK include a number of vitamers known as vitamin K1 and vitamin K2. Vitamin K1, or phylloquinone, is the predominant dietary form of VK and is found in green leafy vegetables and some plant oils. Vitamin K2 includes a wide range of VK forms called menaquinones. These forms of VK, known by their length, are designated by "MK-n," ranging from MK-2 to MK-14. Menaquinones are primarily of microbial origins and are found in fermented foods, dairy products, and animal liver. K2 is also produced in the human colon by bacteria, but this does not appear to be a major contributor to the body's coagulation status. Finally, there is a synthetic compound of VK known as vitamin K3 or menadione, originally used for newborn prophylaxis but rarely used today in any product for human use, as it can cause hemolytic anemia, hyperbilirubinemia, jaundice, and kernicterus in infants.[3,13,14]

Vitamin K performs many functions in the body, including an essential role in blood clotting. Vitamins K1 and K2 combine with enzymes, proteins, and minerals in the body to synthesize clotting factors II (prothrombin), VII, IX, and X in the liver, as well as Protein S, Protein C, and Protein Z.[3,13,15] These clotting factors make up the core of the clotting cascade. Both vitamins K1 and K2 are utilized by the body for clotting purposes, but K1 has been more robustly studied for its role in coagulation.[3]

Vitamin K Deficiency Bleeding

Infants may experience occasional internal bleeding as a spontaneous event or develop bleeding secondary to a traumatic event. VKDB can occur when the body experiences any type of bleeding, and due to a lack of available VK and VK-dependent coagulation factors, the bleeding persists. VKDB is diagnosed when VK replacement stops a bleeding event. VKDB is divided into three categories: early, classic, and late. Although these categories are based solely on the timing of bleeding, each type is also associated with a different pathogenic mechanism (Figure 1).[3]

Early VKDB develops in the first 24 hours of life and occurs secondary to placental transfer of maternal drugs, including anticonvulsants, cephalosporin antibiotics, tuberculostatic agents, and VK antagonists like warfarin, all of which inhibit VK activity in the infant. The incidence of VKDB in newborns of mothers who take any of the above drugs is as high as 6% to 12%.[2]

FIGURE 1. VITAMIN K DEFICIENCY BLEEDING[2,3,4,11,13,16,37,38]

	Early VKDB	Classic VKDB	Late VKDB
Age at onset	Less than 24 hours	Days 1-7 (most likely days 2-5)	Weeks 2-12 (possible up to 6 months)
Causes and risk factors	Drugs taken during pregnancy (anticonvulsants, anticoagulants, tuberculostatic agents, cephalosporins).	Low placental VK transfer; rapid VK excretion; low VK content of breast milk; inadequate milk intake for any reason, including but not limited to late onset of feeding and low milk supply.	Low VK content of breast milk; rapid VK excretion; immature VK cycle; liver stores dominated by phylloquinone rather than menaquinone; gut bacteria that do not contribute to VK status; physiologic slow rise of clotting factors until ~90 days after birth; VK malabsorptive disorders.
Location of bleeding (in order of frequency)	Cephalahematoma, umbilicus, intracranial, intra-abdominal, intrathoracic, gastrointestinal tract.	Gastrointestinal tract, umbilicus, nose, venipuncture site, circumcision, intracranial (rarely).	Intracranial (30-80%), skin, nose, gastrointestinal tract, venipuncture site, umbilicus, urogenital tract, intrathoracic.
Avoidance measures	Consult or refer prenatally to maternal-fetal medicine. Stop or replace problematic drugs if feasible. IM VK prophylaxis immediately after birth.	Ensure normal VK introduction to neonate by early and adequate breastfeeding. VK prophylaxis day of birth (IM and oral deemed equally effective).	VK prophylaxis (single IM dose on day of birth or oral dosing per Figure 3). Early recognition of predisposing conditions (jaundice, failure to thrive) and prompt investigation of warning bleeds.
Warning signs of VKDB or malabsorptive/ hepatobiliary disorders	Failure to thrive; vomiting; poor feeding; lethargy; hypothermia; pallor; tense or bulging fontanelle; jaundice beyond 2 weeks of age; warning bleeds: epistaxis, umbilical stump, urethral or gastrointestinal bleeding (blood in diaper, black stool), petechiae, bruising, circumcision site bleeding, mucosal bleeding (mouth, throat, gums), continuous bleeding of a small cut or abrasion.		
Management	All warning bleeds, jaundice beyond 2 weeks, and any other signs and symptoms should be taken seriously and evaluated. If VKDB is suspected, administer IM VK and send infant to hospital for immediate evaluation. IM VK may be administered to any infant regardless of previous VK status, though if already given IM VK, a bleed is unlikely to be due to VK deficiency. Ensure parents inform the hospital of the infant's VK prophylactic history upon arrival, as previous IM VK administration is likely assumed.[5,6,9,10]		

Classic VKDB develops from 24 hours after birth up to 1 week, most commonly on days 2 to 5. The incidence of classic VKDB is 0.25% to 1.7%, making it the most common manifestation of VKDB.[3,4,16] The etiology of classic VKDB is well understood. Newborns are born with negligible amounts of maternally acquired VK stored in their bodies, and deficiency intensifies in the first few days after birth because VK is a rapidly excreted vitamin. Newborns depend on continual nutritional intake for their VK needs, and colostrum is produced in physiologically small volumes, so in the first few days of life, newborns receive only small amounts of VK. Although delayed initiation of breastfeeding, low milk supply, and birth trauma can play a role in classic VKDB, the disease can occur in any newborn without the presence of these events as well.[2,3,16,17]

Late VKDB occurs on or after day 8, most often between 2 and 12 weeks of age.[2,4] The incidence of late VKDB ranges from 4.4 to 7.2 per 100,000 births.[4] While relatively rare, the bleeding is usually severe, with intracranial hemorrhages occurring in 30% to 80% of cases.[11] Bleeding can also occur from the nose, skin (petechiae, bruising, venipuncture sites), umbilicus, urogenital tract, gastrointestinal tract, or intrathoracically.[2,3,11] The etiology of late VKDB is complex. Limited placental VK transfer, low VK content in breast milk, rapid VK excretion, an immature VK cycle, liver stores dominated by K1 rather than K2, gut bacteria that do not contribute to VK status, a slow rise of clotting factors until about 90 days after birth, and the possibility of pathologic contributors such as hepatobiliary or malabsorptive disease all contribute to an infant's risk for late VKDB.

Physiologic Causes of VKDB in the Infant

Placental Transfer

Placental transfer of VK to the fetus is limited, as VK does not easily cross the placenta.[11] There is no evidence that delayed cord clamping increases a newborn's stores of VK, because as measured after birth, cord blood concentrations of VK are low to undetectable.[19] Prenatal maternal supplementation is not a reliable method of transferring VK to the newborn either,[20] as even large pharmacological doses of VK during pregnancy do not have reliable outcomes on cord blood concentrations.[19] Even if there were proven benefit to maternal supplementation during pregnancy or delayed cord clamping at birth, late VKDB occurs until 12 weeks of age, making this an event related to continued intake of VK rather than placental transfer.

Dietary Intake of Vitamin K

Because diet is the main source of VK for an infant, exclusively breastfed infants have a higher risk of VKDB than formula-fed infants, as formula in the United States is supplemented with VK.[11,15] In fact, late VKDB occurs almost exclusively in breastfed infants.[2] The Adequate Intake for VK is set at 2 mcg/day for infants 0 to 6 months of age.[20] Human breast milk contains relatively low concentrations of vitamin K1 and K2, with average concentrations of 0.25 mcg/dL to 0.5 mcg/dL,[21,22] whereas an average formula may have around 5.5 mcg/dL.[23] Therefore, an infant consuming 750 mL/day would have a total intake of 1.9 mcg to 3.8 mcg of VK via breast milk, or 41.3 mcg of VK via formula. Based on these total daily intakes, many breastfed infants may meet the Adequate Intake guidelines, while formula-fed infants exceed them.

It is important to consider that the Adequate Intake value is based on the premise that all infants receive an intramuscular VK injection at birth. When breast milk's VK content is combined with other endogenous factors present in the infant, this Adequate Intake value may not be enough to prevent bleeding in the infant who did not receive prophylactic VK. In the first week of life, breastfed infants are at particularly high risk of classic VKDB because of the low volume of colostrum or breast milk they receive. Some studies show colostrum can have a higher (even double) VK content as compared to mature milk,[22,24] while other studies show the content to be about the same or with a difference that is not statistically significant.[25] Regardless, the small volume of colostrum produced makes for a small transfer of VK.

Limited studies indicate that maternal supplementation can increase VK content in breast milk, but there are no evidence-based protocols. Two small studies of 20 and 32 breastfeeding women indicate that maternal intakes of 4 mg to 5 mg of K1 each day have been shown to increase breast milk VK content to formula levels.[23,26] Conversely, a study of 77 women showed that maternal intakes as high as 15 mg/day of K2 did not increase VK milk content as significantly as the smaller doses of K1.[27] The bioavailability of different supplements, each individual's ability to absorb supplements, and the reliability of this method of supplementation have not been clearly established.

Gut Flora

A common refrain among midwives is that gut-produced vitamin K2 is a main contributor to the body's VK needs. It is often repeated that infants are deficient in VK because of their immature, altered, or lack of gut flora, all of which may prevent them from producing K2, thereby putting them at risk for bleeding. Data now demonstrate that the main source of VK in infants and adults alike is dietary, not the gut. K2 production does occur in the adult and formula-fed infant gut because of production by bacteria such as ***Bacteroides fragilis*** and ***Escherichia coli***. Meanwhile, because the breastfed infant gut is colonized with bacteria like ***Bifidobacterium*** spp., ***Lactobacillus*** spp., and ***Clostridium*** spp., K2 is not readily produced.[18]

The amount of K2 the gut produces, however, is likely of little importance in the prevention of VKDB. Previously, data showed that up to 50% of the human VK requirement might be met by bacterial K2 synthesis, but it is now known that this figure is inaccurately high, with little evidence that gut-produced K2 contributes to coagulation at all.[13] Because VK is fat-soluble, it can only be absorbed from the small intestine in the presence of bile salts,[15] which are absent in the colon (large intestine) where K2 is produced.[33] There is no evidence that gut-produced K2 can be absorbed for use, though it may be possible it is absorbed through a mechanism currently unknown to researchers. The liver stores both vitamin K1 and K2, but just as liver stored K1 is from our diet, so is the majority of K2.[18,28,31] Although liver stores of VK help adults maintain coagulation status, reducing VK intake to zero or negligible levels depletes liver stores, and coagulation becomes abnormal.[28] Even in adults with fully developed gut bacteria, without dietary VK intake, gut-produced K2 is inadequate to maintain normal VK status.

Vitamin K Excretion and the Vitamin K Cycle

There are relatively low circulating and tissue stores of VK in the human body as compared to the other fat-soluble vitamins, because 60% to 70% of dietary VK intake is rapidly excreted from the body.[28] The adult body recycles VK, allowing it to be reused many times in the body, in part to compensate for the body's tendency to rapidly excrete VK. A single VK molecule is thought to be recycled ~1,000 times.[3,13] The vitamin K cycle may not yet be fully functional in newborns due to enzymes that are absent at birth.[29] Thus, when a breast-fed infant's marginally adequate levels of VK are excreted, the infant may not have sufficient VK to maintain normal coagulation. Formula levels

> Vitamin K deficiency in infants is part of the process of maturation—infants need time to develop their Vitamin K system much the same way they need time to develop their immune system.

of VK are higher and therefore a higher circulating level of VK remains in the formula-fed infant's body despite excretion.

Liver Storage of Vitamin K

Adults and infants have important differences in their liver storage of VK. In adults, liver storage is 10% phylloquinone (K1) and 90% menaquinone (K2).[28] In infants, liver storage is overall more limited, and phylloquinone predominates over menaquinone.[18,30] Menaquinone liver stores increase during the first year of life as complementary foods are added to the infant diet.[18] Because phylloquinone stores are more rapidly excreted from the body than menaquinone,[11,28] infants excrete VK at higher rates than do adults.

Slow Rise of Clotting Factors

Infant plasma concentrations of all VK-dependent clotting factors are 40% to 60% of adult values and rise slowly during infancy, taking up to 90 days to completely normalize even with adequate VK stores.[11,18,29,31] Data demonstrate that VK prophylaxis does not actually increase clotting factors in infants—it just ensures that there is enough VK available to produce clotting factors when the body needs them. As infants mature, they become more efficient producers of clotting factors.

Hepatobiliary and Malabsorptive Diseases

Hepatobiliary (liver/gallbladder) diseases, including cholestasis and biliary atresia, and malabsorptive diseases, such as cystic fibrosis, are the main pathologic causes of VKDB. Without proper liver, gallbladder, or small intestine function, VK cannot be absorbed or transported to the liver, and clotting factors cannot be produced.[2,11,32] Hepatobiliary and malabsorptive diseases are a main cause of late VKDB and can often result in the failure of oral VK prophylaxis, and though less common, can also result in the failure of IM VK prophylaxis.[33,34,35]

Wisdom of the Body

Although some may believe that there is a reason infants' bodies maintain a low level of VK, data demonstrate that VK deficiency in infants is simply a part of the process of maturation. Just as infants' immune systems are immature when they are born, so is their ability to clot. All humans would be deficient in VK without dietary intake—even adults develop bleeding problems when VK is removed from their diet. Breast milk, as infants' primary food source, happens to have minimally adequate levels of VK. With steady breast milk intake, most infants maintain an adequate though marginal supply of VK; however, when combined with other factors such as limited placental transfer, rapid excretion, an immature VK cycle, liver stores dominated by phylloquinone rather than menaquinone, gut bacteria that do not contribute to VK status, and the slow rise of clotting factors until about 90 days after birth, it seems that infants simply need time to develop their VK system to prevent bleeding, much the same way as they need time to develop their immune system. It doesn't mean they are unwise; it means they are developing.

Signs and Symptoms of VKDB

All practitioners responsible for infant care must be vigilant for symptoms of VKDB. Although VKDB most often occurs in infants who received no prophylaxis, it can occasionally occur in infants who received prophylaxis. Warning signs of VKDB, such as minimal bleeds and evidence of hepatobiliary disease, have often been present in infants diagnosed with VKDB but were overlooked by care providers.[36] The incidence of intracranial hemorrhage and long-term sequalae to VKDB can be reduced by recognizing the signs of predisposing conditions and promptly investigating warning bleeds.[2] Infants requiring further evaluation for early signs of VKDB or underlying hepatobiliary disease include those experiencing failure to thrive, vomiting, poor feeding, lethargy, hypothermia, pallor, a tense or bulging fontanelle, jaundice beyond 2 weeks of age, or warning bleeds (Figure 1).[3,11,13,16,37]

Jaundice should be of particular concern to the midwife, especially in the case of an infant who received no VK or oral VK, as this may be a sign there is an underlying hepatobiliary disorder preventing absorption of VK. Around 15% of breastfed infants have physiologic jaundice at 2 weeks. Referral for jaundice is recommended at 2 weeks if any of the following occur: dark urine; light stools; petechiae, bruising, or other signs of bleeding; poor feeding or weight gain; or if the midwife is unable to monitor the infant in the coming week.[38] Referral is recommended if jaundice persists for 3 weeks, even in the absence of any other symptoms.

Prophylactic Options for the Prevention of VKDB

The two options for preventing VKDB are intramuscular (IM) and oral VK prophylaxis, with the principal option in the United States being the IM injection. The American Academy of Pediatrics (AAP) recommends an IM injection of 0.5 mg to 1 mg of vitamin K1 after birth for all newborns.[4] Because the incidence of VKDB has gone down since the introduction of the VK injection in the United States, the injection has been deemed highly effective,[4] though there are no surveillance data determining exact past or current rates of effectiveness. Oral prophylaxis is not recommended by the AAP due to a lack of evidence to support it as an alternative to the highly effective IM injection.[4] IM vitamin K remains the standard of care in the US.

The effectiveness of VK prophylaxis varies depending on the type of VKDB it is used to prevent. Both oral and IM VK have been demonstrated to reduce the rate of classic VKDB to zero when administered immediately after birth.[15] As for late VKDB, neither oral nor IM prophylaxis provide complete protection, and neither has been tested in randomized controlled trials regarding efficacy in reduction of late VKDB.[3] Instead, population-based surveillance studies are used to determine effectiveness and show that when IM VK is given at birth, the rate of late VKDB is reduced from 4.4 to 7.2 cases per 100,000 births without prophylaxis,[4] to 0.24 to 3.2 cases per 100,000 births with prophylaxis.[11] There is variability in surveillance results due to the rarity of VKDB. For example, the most recent surveillance data from Canada and Australia reveal so few cases of late VKDB after IM prophylaxis that the incidence is 0 cases per 100,000 births.[41]

Late VKDB only occasionally occurs after IM VK, usually due to failure of uptake by the body or hepatobiliary disease.[41,42,43,44,45] The IM injection is thus highly effective in preventing late VKDB, though rarely it may fail. As for oral prophylaxis, population-based studies show that a single dose of oral VK prophylaxis at birth lowers the rate of late VKDB to 1.4 to 6.4 per 100,000 births,[4] which is less effective than a single IM VK dose at birth, and demonstrates that oral VK must be repeated to improve effectiveness. International data on the effectiveness of multiple doses of oral VK can be found in Figure 2, with nearly all countries' surveillance data demonstrating a comparable or lesser risk of VKDB after multi-dose oral prophylaxis when compared to IM prophylaxis.

Parental Refusal of Intramuscular Vitamin K

Parental concerns about IM VK do result in decline of this standard of care, as evidenced by multiple case studies and surveillance studies. Common concerns include high dosing, ingredients, and side effects.

High Dosing

High doses of VK are found in newborn serum after the IM injection. Some studies have shown infant VK serum levels to be 100 to 400 times the concentration of the normal adult range after the IM injection.[19,41,46] There is no evidence, however, that any amount of naturally occurring VK is toxic in the infant or adult body.[20]

Ingredients and Side Effects

Reports of rare side effects to the injection do occur and are

FIGURE 2. INTERNATIONAL VITAMIN K PROTOCOLS AND INCIDENCE OF VKDB

Country	Year Protocol Established & Product Used	Recommended Route of Prophylaxis	VKDB Prophylaxis Protocol	Incidence of VKDB
Australia	1999 Konakion MM Paediatric for IM and oral use.[36]	All newborns should receive VK. For healthy newborns, IM injection recommended, oral VK available. For unwell newborns or those whose mothers took medications that interfere with VK metabolism, IM injection recommended.[36]	**IM Dosing Protocol:**[36] Term newborns: 1 mg at birth Birth weight <1500 g: 0.5mg at birth **Oral Dosing Protocol:**[36] 2 mg birth 2 mg at 3-5 days 2 mg at exactly 4 weeks (no later)	**Classic VKDB:** Eliminated with VK administered via any route at birth.[36] **Late VKDB:** Incidence 0.3/100,000 births following IM injection.[36] Incidence 1.5/100,000 births following complete oral dosing protocol (using Konakion cremophor formulation from 1993-94).[37] Incidence 2.5/100,000 births following complete or incomplete oral dosing protocol.[37]
Canada	1997 Vitamin K1 IM product; no licensed oral VK product available.	IM injection highly recommended, oral VK available.[51]	**IM Dosing Protocol:**[51] IM dose within 6 hrs of birth based on weight. 1 mg VK if birth weight >1500 g 0.5 mg VK if birth weight <1500 g **Oral Dosing Protocol:**[51] Protocol varies by location. Canadian Paediatric Society and College of Family Physicians of Canada suggest: 2 mg within 6 hours after birth 2 mg at 2-4 weeks 2 mg at 6-8 weeks	**Early and Late VKDB:** [52] Incidence 0.45/100,000 births. 6 total cases of VKDB: 1 early and 5 late. 2 received no VK, 3 received IM VK, 1 received oral VK.
Denmark	1992 Konakion MM from 1992-2000 for IM and oral use; oral preparation currently unavailable.[44]	IM injection recommended. Oral previously recommended for all infants except those born before 33 wks gestation, with a difficult delivery, having asphyxia requiring resuscitation, and with mothers on antiepileptic drugs. In practice, often administered to all cesarean babies.[44]	**IM Dosing Protocol:**[44] 2 mg at birth **Oral Dosing Protocol:**[44] 2 mg after birth 1 mg/week until 3 months (parents administer) as long as baby is 50% or greater breastfed	**Late VKDB:** Incidence 0/100,000 births.[44]
Germany	1994 Konakion MM Paediatric since 1996 for IM and oral use.[39]	For healthy newborns, IM injection recommended, oral VK available. For unwell newborns or preterm infants <1500 g, IM injection recommended.[38]	**IM Dosing Protocol:**[38] Term newborns: 1 mg at birth Preterm or birth weight <1500 g: 0.2 mg/kg at birth **Oral Dosing Protocol:**[38] 2 mg after birth 2 mg at 3-10 days 2 mg at 4-6 weeks	**Late VKDB:** [39] Incidence following IM injection unavailable. Incidence 0.44/100,000 births following complete oral dosing protocol. Incidence 0.56/100,000 births following complete or incomplete oral dosing protocol. Majority of cases occurred secondary to cholestasis.
Japan	1988 Vitamin K2 menaquinone (MK-4) oral product.	Oral recommended.[41]	**Oral Dosing Protocol:**[41] 2 mg after birth 2 mg at discharge (usually 1 wk of age) 2 mg at 1 month	**Late VKDB:** Incidence 1.9/100,000 births (1999-2004).[41] 71 total reported cases: 11 received full oral prophylaxis.
Netherlands	1990 Three K1 products are licensed for IM and oral use.[49]	Oral recommended. IM injection recommended for unwell, preterm, and low birth weight infants.[50]	**Oral Dosing Protocol since 2011:**[50] 1 mg at birth 150 mcg/day until 12 weeks **Oral Dosing Protocol 1990-2011:**[49] 1 mg at birth 25 mcg/day until 13 weeks	**Late VKDB:** Incidence 1.1/100,000 births (1992-94).[49] Incidence 3.2/100,000 births (2005).[49] Incidence 2.1/100,000 births (2004-07).[45] Majority of cases secondary to cholestasis. The 2011 oral dosing protocol was implemented in light of these data suggesting that 25 mcg/day is insufficient to prevent late VKDB.
New Zealand	1995 Konakion mixed micellar (MM) Paediatric since 1999 for IM and oral use.[32]	IM injection recommended, oral VK available.[32]	**IM Dosing Protocol:**[32] Term newborns: 1 mg at birth Birth weight <1000g: 0.5mg at birth **Oral Dosing Protocol:**[32] 2 mg at birth 2 mg at 3-7 days 2 mg at 4-6 weeks	**Classic VKDB:** [33] Incidence 1.24/100,000 births. 8 total cases: 7 fully breastfed, none received VK prophylaxis. **Late VKDB:** [33] Incidence 1.4/100,000 births. 9 total cases: 8 received no VK, 1 received IM VK.
Switzerland	2003 Unspecified brand of mixed micellar (MM) VK since 1995 for IM and oral use.[42]	Oral recommended.	**Oral Dosing Protocol:**[43] 2 mg by hour 4 after birth 2 mg at 4 days 2 mg at 4 weeks Possible benefit to weekly oral doses recognized for preventing VKDB in infants with cholestasis, but more complex regimen may reduce compliance.	**Late VKDB:** [43] Incidence 0.87/100,000 births. 4 total cases: 3 had cholestasis, 3 refused all VK prophylaxis, 1 forgot third dose of oral VK
United Kingdom	2006 Konakion MM Pediatric for IM and oral use.[20]	IM VK is the most clinically and cost-effective method of administration. Parents declining IM VK should be offered oral VK as a second-line option.[55] In practice, pediatric units recommend preferred routes of administration, with those supporting oral dosing often recommending IM for high-risk newborns.[20]	**IM Dosing Protocol:**[55] 1 mg IM at birth **Oral Dosing Protocol:** Administer multiple oral doses according to manufacturer's instructions.[55] Maternity units usually recommend a minimum of three 2 mg doses of oral VK for breastfed babies.[20]	**Classic VKDB:** [20] No cases reported. **Late VKDB:** [20] Incidence 0.64/100,000 births. 11 total cases: 6 received no VK, 3 received IM VK (2 had biliary atresia, one was born preterm), 2 received incomplete oral VK. 4 of the 11 infants were jaundiced at presentation to clinic after 21 days.
United States	1961 Phytonadione for IM use.[77]	IM injection.[13]	**IM Dosing Protocol:**[13] 0.5-1.0 mg at birth	No data available.

generally attributed to other added ingredients in the VK injection.[47] Aluminum, benzyl alcohol and derivatives, polyoxyethlylated castor oil, polysorbate 80, and other ingredients may be among the inactive constituents of VK IM injections. All formulations containing benzyl alcohol or its derivates should be avoided in the neonate due to the possibility of "gasping syndrome," which consists of gasping respirations, respiratory distress, metabolic acidosis, hypotension, CNS dysfunction, and cardiovascular collapse.[39] Preservative-free IM formulations are available and may be administered by the midwife after review of the manufacturer's ingredient labeling. With any formulation of IM VK, there is the possibility of rarely reported side effects such as infection at the site of injection, hypersensitivity, shock, cardiac or respiratory arrest, anaphylaxis, or death. Data are scant on how often these side effects occur.[39]

Childhood Leukemia

A now readily-disproved study from 1992 reported that the IM injection led to a tripling of leukemia risk in children as opposed to the oral or complete refusal route.[48] This study led many countries to develop their oral VK protocols to find a method of administration that was acceptable to parents. While the leukemia connection has been disproven, parents may still be concerned about it.

Parental Preference

Due to the possible trauma of receiving an injection on the first day of life, a belief in the wisdom of the body not having VK at birth, unknown risks of the injection, and a general preference for avoiding interventions, some parents may not want to administer IM VK to their newborn.

Midwives may encounter clients with these concerns and can offer the most current, evidence-based information available, including information on the risks of VKDB, which IM VK is highly effective at preventing. The consequences for the small number of infants who develop uncontrolled bleeding are often catastrophic. Implications of any uncontrolled bleed in the infant include anemia, ischemia, shock, brain injury, disseminated intravascular coagulation, and death. Data from millions of births across the world demonstrate that VK prophylaxis is critical for the infant, and this prompted many countries including Australia, New Zealand, the United Kingdom, the Netherlands, Switzerland, Germany, and Japan to develop an oral VK product and protocol to ensure parents had an option besides the IM injection.[34,49,50,51,52,53,54] When parents decline the IM injection, a full range of options should be available to their infant for the prevention of VKDB, including oral VK prophylaxis.

An Optimal Vitamin K Protocol

An optimal vitamin K protocol incorporates parental acceptance, ease of use, and effective reduction of VKDB. While IM VK has been verified as simple and effective at preventing VKDB in a majority of cases, IM VK is not always accepted by parents. Because parents continue to refuse the injection, and because the majority of modern United States cases of VKDB occur in babies whose parents declined the injection,[34,42] an alternative option is essential.

Most other developed nations with excellent infant health outcomes offer an oral VK product and administration protocol with confidence, and their data demonstrate effective reduction of VKDB with these oral protocols (Figure 2). In the majority of these countries, the IM injection can also be given as an oral dose, and most utilize a mixed micellar (MM) formulation. This product uses a different solubilizing agent than the US IM formulation and was developed because there was some evidence that it may be better absorbed, especially in infants with cholestasis. However, data have not shown a significant improvement in the efficacy of the MM preparation to prevent late VKDB in infants with cholestasis.[34,50] Nonetheless the MM product has stayed on the market and continues to be used for IM and oral administration. In England,[55] Germany,[52] Australia,[51] New Zealand,[50] and Canada,[56] IM injections for the newborn are recommended, but oral administration is available. In Switzerland,[34] Japan,[53] Denmark,[57] and the Netherlands,[58] oral prophylaxis is recommended over IM injections, though IM injections may be recommended if the infant is preterm or unwell.[57,58] Although Denmark historically recommended oral prophylaxis, due to licensing issues, it lost its oral VK product in 2000 and now exclusively offers IM prophylaxis.[57] Vitamin K1 products for oral or IM administration are used in every country except Japan, where vitamin K2 is used.

Oral VK has high rates of parental acceptance and effectiveness based on population surveillance when given according to evidence-based dosing and timing protocols. Efficacy may be reduced by forgotten doses or infant sickness. Among infants with an undiagnosed hepatobiliary or malabsorptive disorder who received VK prophylaxis, oral prophylaxis is more likely to fail, but IM prophylaxis may fail as well.[34,42,49,59,60] Both IM and oral VK are effective options for the prevention of VKDB, especially when compared to no prophylaxis.

Limitations of Oral Vitamin K

Offering oral VK prophylaxis as an alternative to IM VK is a reasonable option when parents decline IM VK prophylaxis; however, both the midwife and client must understand the following limitations of oral prophylaxis.

Effectiveness

IM and oral VK are equally effective in preventing classic VKDB,[15] but IM VK is more effective than oral VK at preventing late VKDB, due to inconsistent administration and the possibility of hepatobiliary or malabsorptive disorders.

Undiagnosed Disorders

Not all infants who appear healthy are able to absorb oral VK, particularly infants with hepatobiliary or malabsorptive disorders. Many of these infants appear normal and have no external symptoms. If an infant is diagnosed with one of these diseases, the midwife must remind parents to inform their doctor if the infant did not receive IM VK at birth. These infants cannot absorb oral VK well, including VK from breast milk, and should receive the VK injection.

Premature or Low Birth Weight Infants

Preterm infants (<37 wks) and low birth weight infants (<2,000 g) should receive IM VK due to issues with limited intestinal absorption of oral VK and elevated risk for bleeds.[60] The IM injection may, however, contain ingredients such as aluminum and polysorbate 80 that are known to have serious side effects in premature neonates, and the manufacturer's ingredient label should be read to avoid these ingredients.[39] The standard IM VK dose of 1 mg has been found to cause excessively high serum levels of VK in premature or low birth weight infants,[61] and midwives may advocate for their clients to receive lower dosing. One study of 0.5 mg of IM VK in preterm infants found high serum VK values, and concluded that preterm infants should at most receive 0.5 mg of IM VK.[62] Another study of preterm infants found that 0.2 mg of IM VK maintained adequate VK status in preterm infants until a median age of 25 days, demonstrating that an even lower dose may be appropriate, with the potential to repeat small VK doses.[63]

Limited Product Options

The current IM VK product on the market is FDA-approved for injection but not oral use in the neonate.[39] Liquid oral VK products available in the United States include those found online or through compounding pharmacies. These products are not standardized, third-party verified, or FDA-approved, and therefore may not have the high level of effectiveness found in products used in foreign studies.

Parental Compliance

The midwife and parents must recognize that parental compliance with administration is key. Missed oral VK doses increase the risk for bleeding and related sequelae.

Maternal Risk Factors

The midwife must consider maternal risk factors. A mother

who has been taking anti-coagulants, anti-convulsants, cephalosporins, VK antagonists such as warfarin, or tubercolostatic agents during pregnancy will have a newborn requiring immediate IM VK prophylaxis. She will probably not be a candidate for out-of-hospital midwifery care because her infant will need special monitoring due to the high risk of developing VKDB in the first 24 hours of life.[2]

Circumcision

While there is little current data available, it can be reasonably inferred that an IM VK injection is ideal to mitigate post-surgical, circumcision-related bleeding risk, which is a common manifestation of classic VKDB.[2,3,17]

Special Circumstances

While there are scant data, in practice some countries recommend IM VK for infants with birth asphyxia requiring resuscitation, those born via cesarean section, and those who experience traumatic birth because trauma can contribute to cases of VKDB.[50,51,52,55,57,59]

Unknown Risks

Midwives and parents should recognize that while there may be unknown long-term risks to oral VK administration, none have been identified in the literature. The theoretical question remains as to whether oral VK preparations could harm the sensitive intestinal lining of the newborn.

An Oral Vitamin K Protocol

Based on maternal medical history and a discussion of plans for the infant, the midwife will be able to determine if a client is an appropriate candidate for an oral VK protocol. Eligibility criteria may include the requirements that the mother is not taking any high-risk medications, that the parents do not have plans for circumcision, and that they are committed to regular oral VK administration. If a client understands the main concerns with oral VK in the United States—lack of a licensed VK preparation for oral use and the possibility of poor absorption—then an oral protocol may be appropriate. Midwives may recommend the evidence-based oral VK protocol detailed in Figure 3 to their clients who decline IM VK prophylaxis.

This protocol is based on multiple countries' recommendations that 3-part oral VK dosing has demonstrated effectiveness in reducing VKDB according to surveillance studies of the largest populations. Late VKDB is so rare that large populations must be considered to determine the true effectiveness of any protocol, and 3-part dosing appears effective in the largest studied populations. Denmark and the Netherlands recommend daily or weekly dosing, but because the population of these countries is small, the results of their surveillance that show a rate of late VKDB at 0 cases per 100,000 births following the recommended oral prophylaxis protocol may not capture the true likelihood of cases of late VKDB. Combined data from 14 years of surveillance, however, do offer information about the benefit of continued weekly dosing for unwell infants. Denmark and the Netherlands are unique in that their surveillance looks retrospectively at cases of infants who were thought to be healthy but later diagnosed with hepatobiliary or malabsorptive disease. Data from 3.76 million births in Denmark and the Netherlands found that an oral VK dose of 1 mg/wk until week 13 is nearly as effective as IM VK at birth in preventing late VKDB in infants with a hepatobiliary or malabsorptive disease that has gone undiagnosed for a period of time since birth.[60]

FIGURE 3. ORAL VITAMIN K PROPHYLAXIS PROTOCOL AND ADMINISTRATION GUIDELINES

Oral Dosing Schedule:

2 mg at birth
2 mg on days 4-7
2 mg at 1 month
Optional continued dosage of 1 mg/wk from 5 weeks to 13 weeks

Determine the dose given in each drop of the oral vitamin K product being used. Dosages vary by drop, and correct dosing is critical. Because vitamin K1 products are the most robustly researched, it is recommended they should be used in this protocol.

Parameters for administration include:

- Midwife ensures infant receives critical doses at birth, on days 4-7, and at 1 month by scheduling an appointment or making a reminder call to the family.
- Midwife leaves optional continued weekly dosing from week 5 to week 13 up to parents.
- Midwife administers the at-birth dose, but parents must have their own bottle of Vitamin K to ensure the time-sensitive administration of the remaining doses. Midwife encourages parents to put dosing dates on the calendar. Timing is critical.
- Midwife instructs parents in proper administration technique. To administer, gently hold the infant's mouth open and place drops on tongue. Close the infant's mouth and observe for any of the dose leaking or being spit out.
- Re-administer dose if any spitting up, vomiting, or diarrhea occurs within 2 hours of administration.
- Encourage parents to administer the dose after feeding. Some studies suggest concurrent fat intake makes oral Vitamin K more absorbable.

Conclusion

VKDB continues to occur today, most often in infants who did not receive VK prophylaxis at birth. Both case studies and population data across the world demonstrate that VK administration is essential for preventing VKDB, both because there is no way to predict which infants will develop VKDB, and because all infants have physiologic factors that limit their ability to develop and maintain adequate VK stores, putting them at risk. VKDB can be life-threatening when it occurs, and parents deserve access to the full range of VK prophylactic options for the prevention of this event.

Misinformation about VK abounds, including in midwifery circles, and it is the midwife's responsibility to be educated and current on this topic and to ensure that clients are also well-educated and able to make the best decision for themselves and their infants. IM VK remains the standard of care due to its ease of administration and effective reduction of VKDB, but it may not be the option every parent is comfortable to choose. Oral administration of VK is a reasonable and effective option for parents choosing to decline IM VK. Each choice for prophylactic VK for the infant has benefits and risks. Evidence-based education covering the full range of options for the prevention of VKDB is critical in providing client-centered care that ensures access to the standard of care while also leaving space for clients to make the best decisions for themselves and their infants. ◉

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