Vitamin K Is Necessary for Newborns

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Fat-soluble vitamin K is a critical part of the activation of coagulation factors II (prothrombin), VII, IX, and X. Compared with adults and older children, newborns have much lower levels of vitamin K: approximately 40% to 60% of normal adult values, which are not typically reached until approximately 6 months of age. This phenomenon is multifactorial, driven in part by low transplacental transfer of vitamin K, low levels of vitamin K excreted in human milk, and a physiologic delay in the acquisition of gut microflora that synthesize vitamin K, which is actually active in several forms. Vitamin K_1, or phylloquinone, is present in green leafy vegetables and is the most common source of vitamin K for humans. Vitamin K_2, or menaquinone, is synthesized by bacteria and is found in some animal and fermented products.

Vitamin K was first discovered in 1929 by Henrik Dam, who observed hemorrhages in chicks fed fat-free diets. Edward Doisy identified the structure and forms of vitamin K in the 1940s, and both men received the Nobel Prize for their collective work on vitamin K in 1943. Because of its critical role in hemostasis, vitamin K deficiency can cause bleeding in the infant. Vitamin K deficiency bleeding (VKDB) was first described in the 1930s shortly after the compound's discovery, with the first infants given vitamin K to treat clinical bleeding later that decade. Swedish researcher Jörgen Lehmann compared the use of oral and intramuscular (IM) vitamin K in the 1940s and concluded that a low dose of 0.5 to 1 mg was effective in reducing the risk of hemorrhage in the newborn. As more institutions began to use vitamin K prophylaxis, the appropriate dosing of vitamin K came into question, with some researchers recommending doses upward of 5 mg for prophylaxis, which seemed to be a causative factor in several cases of neonatal hyperbilirubinemia and kernicterus. In the 1950s, a water-soluble (rather than fat-soluble) version of vitamin K was introduced and was thought to have a better safety profile. The American Academy of Pediatrics (AAP) first recommended the routine use of IM vitamin K prophylaxis in 1961, and the current recommendation widely accepted in America and Europe is for prophylaxis with water-soluble vitamin K.

VKDB was differentiated in the 1980s into 3 typical patterns: early, classic, and late. Early VKDB occurs within the first 24 hours of life, usually secondary to maternal vitamin K deficiency, often complicated by maternal medication use. Although rare, this variant is often life-threatening because it frequently involves intracranial and internal bleeding. Classic VKDB presents during the first week of life, with bleeding commonly occurring in the gastrointestinal tract, umbilicus, and other cutaneous sites, including postcircumcision bleeding; intracranial bleeding is possible but rare. Late VKDB can occur as late as 6 months of age, with most cases occurring between 3 and 8 weeks. Although occasionally

AUTHOR DISCLOSURE Drs Stachowiak's spouse works for GenomOncology. Dr Furman serves on the editorial board and is an associate editor for *Pediatrics,* an American Academy of Pediatrics journal. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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idiopathic, late VKDB more commonly occurs in exclusively breastfed infants with inadequate prophylaxis, and most often in infants with underlying gastrointestinal or hepatobiliary disease from secondary fat malabsorption.

Most VKDB can be prevented by routine prophylaxis with vitamin K after birth. In 1961 and 1993, the AAP recommended the early use of either parenteral or oral vitamin K_1; however, in 2003 the recommendation was changed to advocate for the exclusive use of IM vitamin K. Oral vitamin K has been used for neonatal prophylaxis in some parts of Europe, with some studies suggesting that oral prophylaxis is effective in preventing early and classic VKDB. However, infants with conjugated hyperbilirubinemia, which may not be diagnosed immediately after delivery, do not have reliable intestinal absorption of oral vitamin K. The incidence of late-onset VKDB is higher with oral vitamin K administration than with a single IM dose, particularly in infants with hepatobiliary disease. In addition, adherence is a concern with oral regimens of vitamin K because most require several doses of vitamin K over weeks to months, in contrast to a single IM dose at birth. The AAP currently recommends 0.5 to 1 mg of vitamin K_1 given IM at birth as the sole standard of care for newborns.

Despite the convincing evidence-based case for IM vitamin K prophylaxis at birth, rates of parental refusal range from 0.5% to 3%. In a recent study conducted by the BORN (Better Outcomes Through Research for Newborns) network, which included just more than 8% of live deliveries in the United States (95 newborn nurseries in 34 states with ~330, 000 infants), demographic factors significantly associated with parental declination included parental non-Hispanic white ethnicity, older maternal age, and exclusive breastfeeding; public versus private insurance as a proxy for socioeconomic status was not significantly related to refusal.

The history of current vitamin K refusal may have roots in a now well-refuted association between IM vitamin K administration and leukemia reported in 1990 by Golding et al in the *British Journal of Cancer*. In addition, rare episodes of hemolysis occurred in infants with glucose-6-phosphate dehydrogenase deficiency who were treated with oral synthetic vitamin K_3, or menadione, which is no longer used for this purpose.

On interview, a range of parental concerns have been shared, including pain of injection, concern for harmful ingredients in the preparation, desire for "all natural" birth care, mistrust of the medical and pharmaceutical communities, and incomplete or no knowledge about the risk of VKDB to their infant. Unfortunately, vitamin K refusal is associated with hepatitis B vaccine refusal, as well as with refusal of ocular prophylaxis. Simply providing information may not overcome parental vitamin K refusal when it is reinforced by nonmainstream or non–evidence-based approaches to health that are promulgated on the Internet or within the family's social circle. However, pediatricians have a meaningful opportunity to provide evidence-based counseling about the purpose of vitamin K prophylaxis, and about the risks of refusal, to parents whose knowledge base is incomplete; we can also work to continue nonjudgmental engagement with any who decline regardless of reason.

In summary, vitamin K prophylaxis at birth given IM as 1 mg of K_1 (phylloquinone) prevents VKDB in infants and is the current standard of care for infants in the United States and much of the world.

COMMENTS: As Drs Stachowiak and Furman point out, vitamin K refusal is not isolated. In the narrow perspective of the nursery, it is associated with refusal of hepatitis B vaccine as well as ocular prophylaxis; but, of course, it is also akin to the broader rise in vaccine refusal that has led to the most significant epidemic of measles, both in the United States and Europe, that we have seen in decades. On a cultural level, though, these refusals of medical intervention are part of a broader and more frightening phenomenon—the denial of evidence-based science that extends beyond medicine, generating a reality of "alternative facts." In a 2017 Gallup poll, 38% of Americans believed that God created humans in our present form, denying evolution. Troubling enough in itself, but of more concern when that belief is legislated into a place in science textbooks. On a somewhat lighter note, a 2018 Pew poll found that nearly a third of Americans believed in astrology. But surely most disastrous is the denial of climate change, either by its rejection altogether or by disbelief in the causality of human activity, which has led to policies that threaten the safety and security of our children, their very future.

– Henry M. Adam, MD
Associate Editor, *In Brief*

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