Vitamin K for Newborns: a conundrum

Vitamin K is a clotting factor that all humans need to maintain the ability of the blood to clot when injury occurs. There are two naturally occurring types of Vitamin K: K1 and K2. Vitamin K1, or Phylloquinone, is found in food sources including dark leafy greens, broccoli, some whole grains, asparagus, kiwi, nuts, olive oil, soybean oil and others. However, Vitamin K2, or Menaquinone, is synthesized from many bacteria that colonize the intestinal tract. Liver, butter, eggs, chicken and some fermented products are main food sources contributing to K2. While adults get most of our vitamin K from our diet in the form of Vitamin K1, a significant amount is also created in out guts by beneficial bacteria.

As it turns out, newborn babies are born with very low levels of vitamin K, at least in comparison to adult levels. One reason for this is that very little Vitamin K crosses the placenta during pregnancy. The other reason is that a newborn's gut is nearly sterile – with minimal bacteria – at birth. The meconium present there is made up mainly of dead skin cells sloughed throughout gestation into the amniotic fluid and then swallowed by the baby. But normally, very little beneficial bacteria. So at birth, babies don't have the beneficial bacteria needed to create vitamin K2 for them.

The fact that babies are born low in vitamin K was discovered in the early-mid 1900's. There were a couple of U.S. childbirth practices happening at the time that caused undue stress on babies. One was the fact that most women were being completely knocked out for delivery, and since they couldn't push, the babies were being pulled out by forceps – like metal salad tongs applied to the sides of baby's head and then traction placed to literally PULL the baby out. This obviously resulted in lots of trauma to those babies' heads, both inside and outside the skull. At the same time, it was the height of infant circumcision. Virtually all baby boys were being circumcised within hours of birth, which was surely another big trauma. And what they observed was increased bleeding, difficulty getting bleeding to stop, in babies with these traumas. Blood tests revealed the new information that babies were born with 20-50% of the blood-clotting activity of adults, including the vitamin-K-dependent factors. Viewing this as a design flaw (during the era when it was deeply believed that Nature was faulty and needed to be improved upon), modern medicine quickly came up with a solution – give all babies a dose of vitamin K at birth.

When vitamin K supplementation began in the mid-1940s, babies were supplemented orally. However, by the mid-1950's, this method fell out of favor due to the fact that the version given at the time caused hemolytic anemia and jaundice at high dosages. By the 1960-1970s, injectable vitamin K was the standard route. Oral vitamin K came back into greater use in the 1990's when a study linked injectable vitamin K as a potential factor in childhood leukemia or other cancers. As a result, alternative oral protocols were developed and entire countries switched to giving predominately oral vitamin K. During the leukemia scare, the US still recommended injectable vitamin K, but consumers in the US began to look for alternatives. Oral vitamin K offered a middle ground for many in this debate, being that it was less invasive yet still protected babies against Vitamin K Deficiency Bleeding (VKDB).

Vitamin K Deficiency Bleeding (VKDB) is defined as bleeding from any source stopped by vitamin K administration. There are three types of VKDB: early, classic, and late.

- Early VKDB, occurring on the first day of life, is rare and confined to infants born to mothers who have received medications that interfere with vitamin K metabolism. These include the anticonvulsants Phenytoin, barbiturates or Carbamazepam, the anti-tubercular drugs Rifampicin or Isoniazid and the vitamin K antagonists Warfarin and Phenprocoumarin. The reported incidence of VKDB in infants of mothers who have received such medications without vitamin K supplementation is between 6 and 12 percent. Women taking these drugs definitely need the injection for their babies.

- Classic onset VKDB occurs between 2 to 7 days of life, and is more common in infants who had a traumatic delivery (forceps, vacuum extraction), are unwell at birth or who have delayed onset of feeding. It may also be related to premature clamping/cutting of the umbilical cord deprives babies of up to 40% of their natural blood volume, including platelets and other clotting factors. Bleeding is usually from the umbilicus, gastrointestinal tract, skin punctures, surgical sites and uncommonly in the brain. Severe intracranial hemorrhage may occur suddenly and result in death or severe CNS dysfunction. The incidence reported in the literature is variable, with rates of 0.25 to 1.5 percent in early reports of both sick and well infants to 0 to 0.44 percent in recent reviews predominantly of well infants. Babies born with obvious trauma to the head – including forceps or vacuum extraction or even just unusual bumps or bruising – or whose cord was cut before 3 minutes after birth will benefit from the injection within a few hours of birth or at any time in the first week if suspicious signs develop.

- Late onset VKDB is the focus for prevention and key reason for vitamin K supplementation. It occurs from eight days to six months after birth, with most presenting at one to three months. It is almost completely confined to fully breast-fed infants because formulas are supplemented with unnaturally high levels of vitamin K. The cause of this bleeding trauma is generally liver disease that has not been detected until the bleeding occurs. Several liver problems can reduce the liver's ability to make blood-clotting factors out of vitamin K; therefore extra K helps this situation. Several recent reports emphasize a late form of hemorrhagic disease occurring at 4-6 weeks of age, often manifesting as intracranial bleeding. Symptoms of intracranial bleeding include:

    - Paleness
    - glassy eyed look
    - irritability or high pitched crying
    - loss of appetite
    - vomiting
    - fever
    - prolonged jaundice
    - lethargy

Other signs suggesting clotting deficiency and possible internal bleeding are:

- bleeding from the umbilicus, nose, mouth, ears, urinary tract, rectum or surgical sites (circumcision?) – known as warning bleeds
- any bruise not related to a known trauma
- pinpoint bruises called petechiae
- black tarry stools after meconium has already been expelled
- black vomit
- bleeding longer than 6 minutes from any open wound, even after there has been pressure on the wound

Late-onset VKDB is by far the most challenging form, since the baby doesn't usually have any obvious symptoms. That's why I've detailed the info on the warning signs. This form, while rare, is often fatal (20%) or leaves serious morbidity (40%) due to intracranial hemorrhage, which characterizes late onset VKDB in 50% of cases. During late onset, bleeding in the brain is often the first sign of VKDB; 30% of cases have a warning bleed (bleeding or bruising that appears elsewhere). Prolonged jaundice after 14- 21 days may be linked to late onset. In up 60% of cases, there was undiagnosed liver disease (cholestasis, biliary atresia, 1-antitrypsin etc.) or another disorder causing malabsorption (cystic fibrosis, impaired secretion of bile salts, repeated antibiotics, etc).

Recent data indicates that the rate of late VKDB is about 1/15,000 to 1/20,000 without any vitamin K. If an infant has a single **oral** dose of 1-2 milligrams at birth, their risk is 1/25,000 to 1/70,000. The rates of late VKDB for an infant given a 1.0 mg IM **injection** at birth is 0.1/100,000, and for an infant given an **oral** 2mg dose at birth followed by a 1 mg dose weekly through 12 weeks, there was a similar rate of 0-0.9/100,000 (Van Hasselt 2008).

There is a perspective, common among "natural living" advocates, that questions whether these naturally-occurring low levels of Vitamin K in newborns is normal physiology rather than a design flaw. If there were actually design flaws in the process of birth and the body of the normal newborn, wouldn't our species have died out many centuries ago? Instead, look how many of us there are!! If all babies are born with these so-called "low" levels, maybe that is actually NORMAL! There is a big difference between noticing that babies have relatively lower levels than adults and deeming this a pathological condition which needs routine treatment.

In fact, toward the end of gestation, the fetus begins developing some of the other clotting factors, developing two key factors just before term birth. It has recently been shown that this tight regulation of vitamin K levels helps control the rate of rapid cell division during fetal development. Apparently, high levels of vitamin K can allow cell division to get out of hand, leading to cancer. So Mother Nature has provided a mechanism for babies to develop vitamin K when the time is right. The birth canal is full of beneficial bacteria, as is the mother's own bowel, and it's no accident that babies are nearly always born facing their mother's rectum. In addition, the colostrum that baby gets in the first days of nursing is FULL of beneficial bacteria as well. The birth and breastfeeding process "seeds" the baby's gut with the bacteria needed for so many aspects of health, including those that manufacture vitamin K2 for baby. So by the end of the first week, most breastfed babies are making some of their own vitamin K2.

In theory, I actually agree with this argument. We are likely not born without parts we need. Nature doesn't make mistakes in the design of our bodies – FOR THE MOST PART. But, Nature also doesn't care if an occasional baby – one out of 20,000 – might die. It's survival of the fittest. As a midwife, I do care. And it's likely that as a parent, so do you.

The newborn clotting system is considered immature until 6 months of age. So, what can we do to minimize the risk that any baby might develop late VKDB?

The standard recommendation by the American Academy of Pediatrics is to give all term newborns injectable Vitamin K1 1 mg/ 0.5mL within the first six hours of birth regardless of route of delivery, intent to breastfeed or formula feed, or lack of trauma at birth. Developed countries recommend injectable vitamin K to be given to newborns or at least "at risk newborns" (ie: premature, low-birth weight babies, or mothers on certain vitamin K depleting medications and instrument delivery, vacuum or c-section. Injectable Vitamin K1 comes in many forms, but the most natural option is called Phytonadione by Amphastar Pharmaceuticals, which comes in a prefilled syringe of 1mg/.5mL. It costs around $20, about the same as oral Vitamin K. It contains 10 mg polysorbate 80, 10.4 mg propylene glycol, sodium acetate anhydrous, and glacial acetic acid. It must be protected from light and kept at room temperature (50-86 degrees) as with all oral vitamin K. Both polysorbate 80 and propylene glycol are generally classified as not expected to be harmful but are considered mild non-reproductive toxins, rated a 3 on the Environmental Working Group database (www.ewg.com).

Many countries recognize oral vitamin K as an alternative option, especially if parents decline the injection and infants are low risk. The Netherlands still exclusively gives oral vitamin K. Other countries like the UK, Australia, many EU countries, New Zealand, and Canada offer oral as an alternative, but prefer injection.

Many oral protocols have been used, from using only one 1-2 mg bolus dose at birth, to adding two additional doses-typically one at day 7-8 and one at 4-6 weeks, to weekly and daily dosing. Currently, there is no unified

cross-country oral protocol or recommendation. Those countries that continue to give oral vitamin K do so with a more effective multidose regimen rather than giving oral once at birth. The most effective protocol appears to be the Danish protocol of a 2 mg dose at birth, followed by a 1 mg dose weekly for 12 weeks; this protocol showed a similar efficacy for low risk infant to the IM injection prophylaxis for classic and late onset VKDB, especially for babies with cholestasis.

It is important to ensure baby has indeed gotten the oral dose; therefore, if baby throws up within 60 minutes after the dose is given, it is suggested to repeat the dose. Some breastfeeding advocates have argued that oral vitamin K has the potential to disrupt the sealing of the gut lining that occurs in a breastfed baby. Research has not been focused on this issue, but we do know that IM injection is a direct and sustained route as the muscle acts as a reservoir for the medication and works faster in the body rather than having to navigate the gut. Concern has been raised around compliance of parents with oral vitamin K multi-dosing, as missing a dose could be critical, but one study in Denmark showed 94% completion.

The option for oral vitamin K in the US is manufactured by Biotics Research Division, called Bio-Kmulsion. It contains 500 mcg (.5 mg) of Vitamin K1 per drop, in an emulsion of gum arabic, water and sesame oil.

No oral vitamin K in the US is FDA-approved for use with newborns. The FDA has no reason to recommend its use, as injection is the recognized form of vitamin K for newborns in the US. None of the oral vitamin K products that have been used in Europe and in the majority of studies are available in the US.

Since the AAP does not recommend oral vitamin K, providers are at the mercy of the products available by nutraceutical companies for clinical use, as it is costly to research and assemble evidence for efficacy to obtain FDA approval, especially for newborns. We find ourselves in a situation where evidence cannot fully be carried out by the consumer or provider, therefore limiting the real-life options. This is not a new conundrum, as researcher Hey points out, "policies for giving babies Vitamin K prophylactically at birth have been dictated, over the last 60 years, more by what manufacturers decided on commercial grounds to put on the market, than by any informed understanding of what babies actually need or how it can most easily be given".

Another possible source of Vitamin K would be the baby's nutrition. Late VKDB occurs almost exclusively in breastfed infants, as breast milk is naturally low in vitamin K. The milk of mothers who do not take a vitamin K1 supplement averages around 2 mcg/liter with colostrum, and 1-2 mcg/liter with mature milk (Shearer 2009), However, based on a few small studies, we know that a supplement of 5 mg daily of vitamin K to lactating mothers will increase the concentration in human milk to 40-80 mcg/L and significantly increase what passes to her baby. Therefore, it would be reasonable to assume that a mother can increase the amount in her breastmilk by enough to make a difference by taking a vitamin K1 supplement daily.

Of the fat-soluble vitamins and their relation to newborns and maternal intake, vitamin D is the one in the spotlight of late, and thus receiving the funding. For vitamin D, one pilot-study showed that when nursing mothers' levels of Vitamin D are high enough or when nursing mothers supplemented Vitamin D in high levels, newborn's levels were equivalent to those who had received vitamin D drops directly (Wagner et al 2006). Vitamin D and Vitamin K may have some similarities, as they are both fat soluble in the body and transported through our lymph breast tissue. If research could look at high levels of maternal supplementation and its impact on VKDB, and results were positive, the debated issue of oral vitamin K in regards to newborn gut health could potentially be eliminated.

Although there is no law in the state of Wisconsin pertaining to Vitamin K administration, the routine administration of this substance to newborns by injection is still considered "standard of care" to prevent vitamin K deficiency bleeding (VKDB). At home, I can provide the same injection your baby would receive at the hospital. It is given in the thigh within hours of birth, and I have occasionally given it at the first postpartum visit

when baby exhibited unexpected swelling or bruising to the head that appeared on that day. Mainstream medical research indicates that the disorders associated with VKDB are almost completely preventable if the vitamin K injection is given at birth.

However, not all parents are comfortable with having their newborns injected with vitamin K. One mg of vitamin K, preserved with chemicals, may not be a completely benign substance. And providing a level of vitamin that is 20,000 times the normal newborn level may cause complications we don't even know about yet.

For this reason, and after experiencing one late-onset case in my own practice, I researched options and can provide a form of oral vitamin K. The product available for this in the US is Bio-Kmulsion the form mentioned above. Each drop provides .5 mg of vitamin K-1 activity. This particular product has not been studied by the medical community but may provide some degree of protection against VKDB, although it will probably not be effective against vitamin K deficiency caused by a liver disorder.

Oral vitamin K is given in a series of doses over the first 12 weeks of life. **After the initial dose of 2 mg (4 drops), I suggest that baby receive TWO drops (1 mg) per week for the first 12 weeks, and that mother takes 8-10 drops per day (4-5 mgs), for the first several weeks, until the bottle is empty. If it appears that the bottle will run out before the baby has had a full 12 doses, then mother should discontinue in order for there to be enough left for baby's doses.**

This oral vitamin K product can be purchased online or directly from Well-Rounded Maternity for about $20 for a 1-oz bottle. A new bottle is needed for each new baby, as the product loses potency over time.

Midwives have few early signs to know when to transfer care. We cannot always identify which babies will have a difficult time nursing, and there are few clear signs of liver disorders in a newborn. If one compares known pros and cons to giving some form of Vitamin K to a baby after birth to dynamics such as repeated early antibiotic use and its lifelong impact on our microbiome, the issues with vitamin K supplementation seem trivial.

To date, the oral protocol from Denmark offers midwives a comparable protective alternative to injectable vitamin K against late VKDB. While the products available in the US have not been approved for newborns, reason stands to argue they offer a reasonable alternative while we wait on research and pharmaceutical companies to demonstrate efficacy. In light of all the arguments, parents and midwives must walk of fine line of both continuing to understand the medical model, navigating research, understand risk and gaps in knowledge and give the best informed consent we can while looking for bias.

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Prevention of vitamin K deficiency bleeding in breastfed infants: lessons from the Dutch and Danish biliary atresia registries.

van Hasselt PM, de Koning TJ, Kvist N, de Vries E, Lundin CR, Berger R, Kimpen JL, Houwen RH, Jorgensen MH, Verkade HJ; Netherlands Study Group for Biliary Atresia Registry. Pediatrics. 2008 Apr;121(4):e857-63.

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Aim: Newborns routinely receive vitamin K to prevent vitamin K deficiency bleeding. The efficacy of oral vitamin K administration may be compromised in infants with unrecognized cholestasis. We aimed to compare the risk of vitamin K deficiency bleeding under different prophylactic regimens in infants with biliary atresia.

Patients and Methods: From Dutch and Danish national biliary atresia registries, we retrieved infants who were either breastfed and received 1 mg of oral vitamin K at birth followed by 25 microg of daily oral vitamin K prophylaxis (Netherlands, 1991-2003), 2 mg of oral vitamin K at birth followed by 1 mg of weekly oral prophylaxis (Denmark, 1994 to May 2000), or 2 mg of intramuscular prophylaxis at birth (Denmark, June 2000-2005) or were fed by formula. We determined the absolute and relative risk of severe vitamin K deficiency and vitamin K deficiency bleeding on diagnosis in breastfed infants on each prophylactic regimen and in formula-fed infants.

Results: Vitamin K deficiency bleeding was noted in 25 of 30 of breastfed infants on 25 microg of daily oral prophylaxis, in 1 of 13 on 1 mg of weekly oral prophylaxis, in 1 of 10 receiving 2 mg of intramuscular prophylaxis at birth, and in 1 of 98 formula-fed infants ($P < .001$). The relative risk of a bleeding in breastfed compared with formula-fed infants was 77.5 for 25 microg of daily oral prophylaxis, 7.2 for 1 mg of weekly oral prophylaxis, and 9.3 for 2 mg of intramuscular prophylaxis at birth.

Conclusions: A daily dose of 25 micrograms of vitamin K fails to prevent bleedings in apparently healthy infants with unrecognized cholestasis because of biliary atresia. One milligram of weekly oral prophylaxis offers significantly higher protection to these infants and is of similar efficacy as 2 mg of intramuscular prophylaxis at birth. Our data underline the fact that event analysis in specific populations at risk can help.

Weekly oral vitamin K prophylaxis in Denmark

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Aim: To evaluate oral vitamin K prophylaxis at birth by giving 2 mg phytomenadione, followed by weekly oral vitamin K prophylaxis; 1 mg was administered by the parents until 3 mo of age.

Methods: A total of 507 850 live babies were born in Denmark during the study period, November 1992 to June 2000. Of these infants, 78% and 22% received oral and intra-muscular prophylaxis, respectively; i.e. about 396000 neonates received oral prophylaxis at birth. Weekly oral prophylaxis was recommended for all infants as long as they were mainly breastfed. A survey of possible cases of vitamin K deficiency bleeding (VKDB) was carried out by repeated questionnaires to all Danish paediatric departments and by checking the National Patient Register.

Results: No cases of VKDB were revealed, i.e. the incidence was 0–0.9:100000 (95% CI). The questionnaires were used to evaluate compliance with the regimen. Parents of 274 infants participated. A dose of vitamin K was regarded as having been given if the infant received a drop of vitamin K or was mostly formula-fed that week, and the prophylaxis was regarded as completed if the infant had received at least 9 doses. Compliance was good, with 94% of the infants completing the course of prophylaxis.

Conclusion: Weekly oral vitamin K supplementation during the first 3 mo of life was an efficient prophylaxis against VKBD. Parental compliance with the regimen was good.