# Vitamin K: A Brief Review of Maternal and Infant Supplementation Research

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## Abstract

Vitamin K supplementation in newborns and/or their mothers has been the topic of recent debate. This topic is particularly relevant to infants who are breastfed exclusively because they are at increased risk for hemorrhagic disease of the newborn (HDN). Hospitals, in general, strongly recommend intramuscular (IM) injections for all newborns. Midwives and others who attend out-of-hospital births have a wide array of recommended treatments. These run the gamut from doing nothing, increasing vitamin K in the mother's diet, maternal oral supplementation (pre- and/or post birth), to oral or IM supplementation to the infant. This article will review recent literature, areas of debate and proposed treatment strategies.




## Background

Vitamin K is an essential co-factor in coagulation factors II, VII, IX and X. There are three basic types of vitamin K. Vitamins K1 and K2 are found in nature and are hydrophobic. Vitamin K1 (phylloquinone) is present in green plants. Vitamin K2 (a group of manaquinones) is produced by intestinal bacteria. Vitamin K3 (menadione) is synthetic, water soluble, less effective than K1 and K2, toxic and no longer in use. Intramuscular injections are now either K1 or K2.

It was discovered in 1952 that vitamin K deficiency was related to hemorrhagic disease of the newborn (HDN). In 1961, the American Academy of Pediatrics Committee on Nutrition recommended supplementation, either oral or parenteral, for all newborns after birth (1). The problem was not to be solved so simply. Initially, large doses of synthetic vitamin K were used and actually contributed to hemorrhagic anemia, hyperbilirubinemia and kernicterus (2). Since then, concerns have been raised about cancer, either from the IM injection itself, the high plasma levels of vitamin K obtained, or the adjuvants in the solution (1). Until recently, there were no conclusive studies investigating the efficacy of oral supplementation in pregnant women.

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## Hemorrhagic Disease of the Newborn

Hemorrhagic disease of the newborn has several manifestations with varying degrees of severity. Early onset HDN occurs within the first 24 hours after birth and is usually severe and often fatal. Although some idiopathic cases do appear, it is mostly seen in infants whose mothers have taken drugs that interfere with vitamin K metabolism, especially barbiturates, warfarin, isoniazid, and diphantoine (1).

Classic HDN occurs between day two and day seven after birth. Infants initially appear healthy but bleed from the GI tract, umbilical cord, nose, penis if circumcision has been performed and venipuncture site. Estimates of incidence without vitamin K supplementation are from 0.25% to 1.7% in term infants. Sequelae are usually not severe with vitamin K treatment (1).

Late HDN occurs after the first week of life. "The mortality is high and most survivors have severe neurologic sequelae. Late HDN is almost exclusively confined to breastfed infants and is not prevented by [a single dose of] oral vitamin K prophylaxis at birth" (1). In the early 1980s in England, there was a dramatic increase in cases of late-onset HDN, which has been attributed to the increased rate of breastfeeding there (1).

Formula fed infants have elevated levels of vitamin K because all formulas contain higher levels of vitamin K than breastmilk. Cow's milk formulas contain about 55-58 µg/ml of vitamin K, whereas breastmilk contains an average of 2.1 µg/ml. Formula fed infants are at lower risk for HDN. However, preterm infants, infants unable to tolerate oral feedings and infants with malabsorption syndromes (e.g., cystic fibrosis, biliary atresia) are all at increased risk for vitamin K deficiency (2).

## Concerns regarding cancer

Concern has been raised whether injections of vitamin K increase the risk of childhood cancer. In 1990, the British Journal of Cancer (3) published a study that found positive independent statistical associations with both maternal smoking (odds ratio 2.5), and prescription drugs (mostly vitamin K administration) (odds ratio 22.6). In another study in England and Wales, 597 children born between 1968 and 1985 and diagnosed with cancer between 1969 and 1986 were selected with matched controls. The association between overall cancer incidence and intramuscular vitamin K was of borderline significance (odds ratio 1.44, P=0.05); the association was strongest for leukemia. The authors concluded that "... the risk, if any, attributable to the use of vitamin K cannot be large, but the possibility that there is some risk cannot be excluded" (3). Another study (4) looking at British children who developed cancer before their fifteenth birthday found "... no association between IM vitamin K and all childhood cancers and all acute lymphocytic leukemias ... but there was a raised odds ratio for acute lymphocytic leukemia developing 1-6 years after birth ... It is not possible, on the basis of currently published evidence, to refute the suggestion that neonatal intramuscular vitamin K ...increases the risk of early childhood cancer" (4). These studies raise concerns regarding vitamin K injections. In both studies cited, the authors conclude that a much larger study is needed to rule out an association with cancer.

## Oral Vitamin K

Oral vitamin K appears to avoid the possible link between vitamin K and childhood cancers. Many health care providers have been reluctant to forego IM vitamin K due to a lack of studies showing the efficacy of oral vitamin K. Recently, however, some studies have been done using various oral regimens. A Danish group looked at all cases of late onset vitamin K deficiency by sending questionnaires to pediatricians. Of 134,500 infants given a single 1 mg oral dose at birth, six cases of late onset HDN were reported (one death and three severely handicapped). There were no cases of HDN (among 163,000 infants) when 2 mg of vitamin K was administered orally at birth, with weekly follow-up doses of 1 mg for the first three months of life (5).

In a retrospective survey (6), 38 cases of HDN (27 in Britain and 11 in Germany) were analyzed. Of the 38 cases, 33 of the infants were exclusively breastfed. Twenty-one babies had no vitamin K treatment, seven received a single oral dose at birth, six had two oral doses in the first week, and four had three oral doses in the first six weeks of life. The authors conclude that oral doses of K prevent HDN in the first week of life. They also conclude that exclusively breastfed infants should have two doses of K1 in the first week of life, and three doses in the first three months of life. "For longer breastfed (beyond two months) ... more doses are probably needed." However, they also admit that " ... there are few reports of bleeding in babies who have received parenteral vitamin K1" (6).

## Measuring Vitamin K Levels

No single standard for measuring the effects of vitamin K currently exists. Levels of PIVKA (protein induced by vitamin K absence) are used as a marker for vitamin K deficiency and to indicate the need for vitamin K prophylaxis, since levels in supplemented infants tend to drop. However, there has been some speculation that PIVKAs don't correlate well with bleeding, because supplemented infants who are exclusively breastfed have higher levels of PIVKAs without a corresponding increased risk of HDN (1).

In a Japanese study (7) investigating the efficacy of maternal vitamin K supplementation, vitamin K levels in infants were measured via the Normotest (which measures the total activity of Vitamin K dependent coagulant factors II, VII, and X) and noncarboxylated prothrombin (a form of prothrombin found in the plasma of those who are vitamin K deficient or receiving a vitamin K antagonist). Pregnant women were supplemented with vitamin K (10 mg/day for two weeks). There was no significant difference in the noncarboxylated prothrombin levels, however there was a significant difference (P<0.001) in Normotest values (59.6+/-10.1% with treatment, and 53.4 +/- 9.9% for controls). Even though vitamin K has a half life of 2.0 - 2.8 hours, the relatively high levels of K1 concentration during the first week after oral administration may be attributable to storage of vitamin K in the fetal liver. The authors conclude that prenatal vitamin K1 persists in neonates until at least the fifth day after birth (7). Cornelissen et al. (8) found that although IM treated infants had significantly higher levels of vitamin K, there was no difference in PIVKA-II (acarboxy prothrombin) or in the activities of factors VII and X. The authors conclude that repeated oral prophylaxis is necessary to completely prevent vitamin K deficiency beyond the age of one month (8).

## Breastfeeding and Vitamin K Supplementation

Although it goes against the grain of naturopathic thought to consider that breastfeeding may create a health problem, the evidence is pretty convincing that unless mothers are supplemented with vitamin K, breast milk alone does not protect all infants from HDN. Evidence suggests that some supplementation for breastfed infants is advisable. Whether a vitamn K deficiency is exacerbated by (or another result of) overuse of antibiotics and a corresponding decrease in the bacterial flora that produce vitamin K, is at this point purely speculative. In their thorough review article, Huysman & Sauer (1) conclude the following:

1. Vitamin K orally or intramuscularly is effective in preventing all classic and most cases of late HDN.
2. Repeated oral prophylaxis is effective in preventing late HDN.
3. The risk of cancer after intramuscular vitamin K prophylaxis is uncertain.

4. Recommended vitamin K administration :
   all newborns–1 mg orally;
   breastfed babies–25 micrograms daily from the second to 13th week of age;
   newborns weighing less than 1500 g–0.5 mg orally or intramuscularly;
   maternal supplementation in mothers treated with anticonvulsants, anticoagulants, antitubercular antibiotics–10 mg daily from the 36th week of gestation until delivery.
5. Further studies are needed regarding the optimal dose for term and preterm neonates and the optimal route of administration in perinatal problems.

## Conclusion

For solely breastfed infants, there does appear to be a significant risk of late HDN which, although rare, can have devastating consequences. Vitamin K supplementation poses many questions, including difficulty in determining optimum levels. What is the best marker for evaluating risk? Which vitamin K, by which route, should be used? Why are there such lowered levels in solely breastfed infants? Why, if the half life of vitamin K is 2.0 - 2.8 hours, are there differences in levels in supplemented versus non-supplemented infants for up to one week post supplementation? What is the optimum newborn level? Although a very good argument can be made against routine IM vitamin K to newborns, an equally strong argument can be made for some sort of supplementation in pregnancy and beyond. After reviewing current research, a strong recommendation can be made to include more counseling regarding vitamin K in pregnant women's diets and to offer vitamin K supplementation during pregnancy starting at 36 weeks, and for newborns until three months after birth. The benefits of breastfeeding remain impressive. Encouragement and support for breastfeeding continues to be an important part of preventive medicine.

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## Biography

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