Eur J Pediatr (2009) 168:127–134
DOI 10.1007/s00431-008-0856-1

REVIEW

Vitamin K, an update for the paediatrician

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Received: 9 August 2008 / Accepted: 7 October 2008 / Published online: 4 November 2008

Abstract
Introduction This review summarizes current knowledge on vitamin K for the paediatrician. Vitamin K is a fat-soluble vitamin, present in plants as phylloquinone and produced by bacteria as menaquinone. It is acting as a co-factor for γ-glutamyl carboxylase. This enzyme is responsible for post-translational modification of some glutamate side chains to γ-carboxyglutamate. The majority of γ-carboxylated proteins function in blood coagulation; others play a role in calcium homeostasis.
Data Newborn babies are at particular risk of vitamin K deficiency, as placental transfer is limited and human milk is a poor source. Vitamin K prophylaxis at birth effectively prevents vitamin K deficiency bleeding (VKDB), formerly known as "haemorrhagic disease of the newborn". Recent epidemiological studies provide data on the effectiveness of different administration routes and dosing schemes. Infants of mothers taking drugs that inhibit vitamin K are at risk of early VKDB and should receive 1 mg intramuscular (IM) as soon as possible after birth. Classic VKDB is prevented by intramuscular as well as by oral administration of 1 mg vitamin K. In exclusively breast-fed infants, single IM administration at birth is also effectively preventing (rare) late VKDB but single oral administration is not. If given orally, prophylaxis should be continued by either weekly administration of 1 mg till 12 weeks or repeating 2 mg at weeks 1 and 4. Daily administration of 25 μg offers insufficient protection. The only infants not fully protected in this way are those with yet unrecognised liver disease.
Conclusions Further work is needed before firm recommendations can be made regarding dose in preterm infants and in patients with fat malabsorption/cholestasis or regarding the role of vitamin K in the prevention of osteoporosis.

Keywords Vitamin K · Phylloquinone · Vitamin K deficiency bleeding · Prophylaxis

Abbreviations

IM	intramuscular
GGCX	γ-glutamyl carboxylase
VKOR	vitamin K-epoxide reductase
VKD	vitamin K deficiency
VKDB	vitamin K deficiency bleeding
VKCFD	Vitamin K dependent clotting factor deficiency
MM preparation	mixed micellar preparation
PT	prothrombin time
INR	international normalised ratio
PIVKA	protein induced by vitamin K absence
ucOC	under-γ-carboxylated osteocalcin
BMD	bone mineral density

Structure and function of vitamin K

In 1929, Henrik Dam, a Danish biochemist, showed that hens fed a fat- and sterol-free diet developed a lethal bleeding disorder [15]. By feeding them the same diet supplemented with the fat fraction of hemp seed or hog liver, the bleeding disorder was cured. He called the anti-

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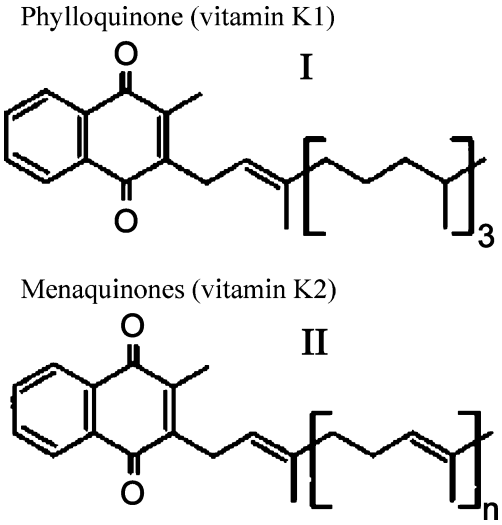


Fig. 1 Chemical structure of vitamin K

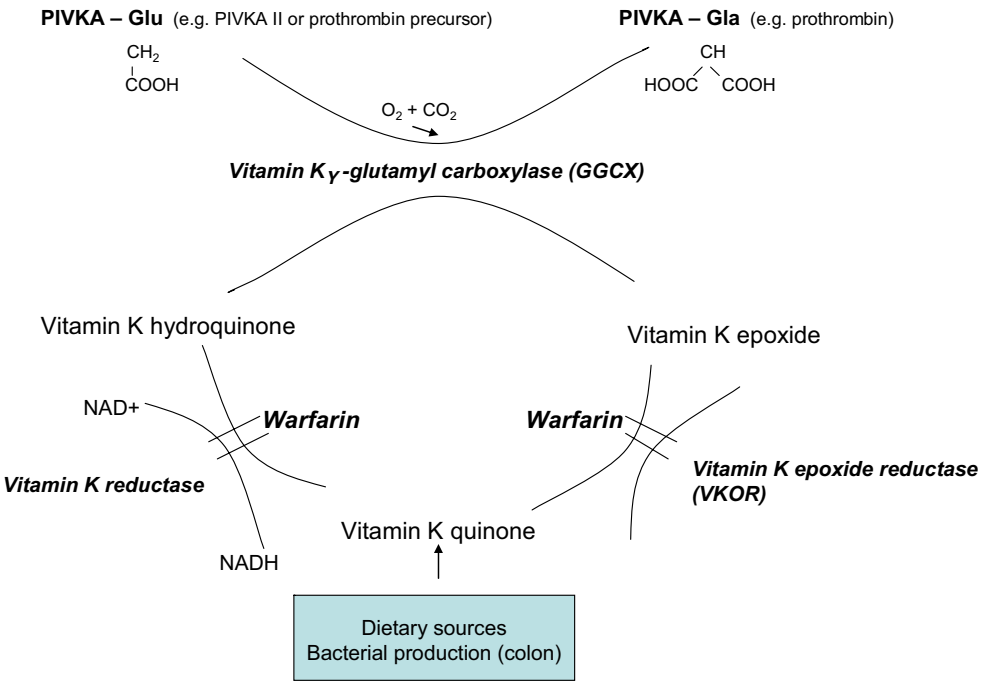
haemorrhagic fat-soluble component "vitamin K" referring to "Koagulation" [16]. Together with Edward Doisy, who elucidated the structure of vitamin K, he received the Nobel prize of Medicine in 1943 for his work on vitamin K.

Vitamin K is the common denominator of several molecular forms, all sharing a 2-methyl-1,4-naphtoquinone ring but differing regarding the structures of the side chain at the 3-position (Fig. 1). Phylloquinone (or vitamin K_1) is the only important form from plant origin and has a phytyl side chain. The group of menaquinones (or vitamin K_2) differs in the number of isoprenyl units in the side chain and are synthesized by bacteria in human and animal intestine. Finally, menadion (or vitamin K_3) is a synthetic and water-soluble vitamin K without a side chain [38]. Use of menadion or vitamin K_3 has been abandoned after reports showing that its use in high doses was associated with haemolytic anaemia, indirect hyperbilirubinemia and kernicterus [22, 27].

Vitamin K acts as a cofactor for γ-glutamyl carboxylase (GGCX), serving as an electron donor for the post-translational conversion of protein-bound glutamate into γ-carboxyglutamate (Gla; Fig. 2). During this process, it is oxidized to vitamin $K_{2,3}$-epoxide. Gla residues are calcium-binding groups which are essential for the biological activity of the proteins in which they are found. Gla-containing proteins are the vitamin K-dependent coagulation factors II, VII, IX and X but also protein C, protein S, protein Z, osteocalcin, matrix Gla protein, Gas6, Prolin Rich Gla Protein1, Prolin Rich Gla Protein 2, Conantokin G and Conantokin T. These Gla proteins are found in a variety of tissues. The function of some of these proteins is still unknown [18, 28, 31].

Vitamin K deficiency leads to the synthesis of under-carboxylated proteins unable to bind calcium and hence inactive. In vitamin K-deficient individuals, undercarboxylated forms of vitamin K-dependent coagulation proteins (proteins induced by vitamin K absence (PIVKA)) are released from the liver into the blood, where they can be dosed. Their level increases with the severity of the deficiency. PIVKA are inactive in the coagulation cascade. PIVKAII or undercarboxylated prothrombin is a marker of subclinical vitamin K deficiency

Fig. 2 The vitamin K cycle



and becomes measurable before the development of abnormal coagulation tests [49].

Vitamin K-epoxide is recycled to vitamin K by vitamin K-epoxide reductase (VKOR). This recycling process is inhibited by coumarin and warfarin, explaining their anticoagulant activity which can be antagonised by high doses of vitamin K [31]. Autosomal recessive vitamin K-dependent clotting factor deficiencies (VKCFD) have been described either caused by a mutation in γ-glutamylcarboxylase (VKCFD1) or in vitamin K-epoxide reductase (VKCFD2). Both coumarin sensitivity and coumarin resistance have been linked to mutant alleles of these enzymes. Recently, Oldenburg et al. published a detailed description of these conditions, which falls outside the scope of this review [31].

Key message 1	The recommended dietary intake of vitamin K: 1 μg/kg body weight per day

Requirement and sources of vitamin K

The recommended dietary intake of vitamin K is 1 μg/kg body weight/day [28]. This means a daily requirement for infants of 5–10 μg/day, for children of 15–30 μg/day, for adolescents of 55–65 μg/day, for adult women of 90 μg/day and for adult males of 120 μg/day [29]. Although these intakes are sufficient to maintain normal plasma prothrombin levels in healthy subjects, it has been suggested that they may be suboptimal for adult bone health [8].

Natural sources

Phylloquinone (vitamin K_1) is provided by dietary sources, whereas intestinal bacterial synthesis is a source of menaquinones (vitamin K_2). The relative contribution of these two sources in humans is unclear. Most of the vitamin K directly measured in plasma is phylloquinone, whereas more than 90% of the human liver content of vitamin K consists of menaquinone [38].

Since the 1980s, the availability of specific and sensitive assays based on high-performance liquid chromatography has enabled reliable measurement of the phylloquinone content of foods, including human milk. Table 1 summarizes the vitamin K content of different foods [6, 43]. The best sources are green leafy vegetables, certain legumes and some vegetable oils such as rapeseed, soybean and olive oils. Other vegetable oils such as corn, peanut, sunflower and safflower oil have much lower phylloquinone content. Human milk is a poor source of vitamin K, containing 1–4 μg/l, with high intra- and interindividual variability and the average concentrations near the lower end of this range [28, 48]. A small placebo-controlled trial has shown that supplementing lactating mothers with high-dose vitamin K (5 mg/day) increases the level in their breast milk and is associated with lower PIVKAII levels in their infants [20]. Infant formulas are fortified and contain ≥50 μg/l.

Little is known on the bio-availability of phylloquinone from different food sources. Bio-availability from the same food source (e.g. spinach) is better if ingested together with fat [6].

Controversy also persists regarding the contribution of bacterial production of menaquinones in the intestine to the requirements of vitamin K. Menaquinone content of foods, with the exception of animal liver and some fermented products (e.g. “natto”, a Japanese fermented soy product) is negligible. As vitamin K is highly liposoluble, its absorption needs the presence of conjugated bile salts. These bile salts are lacking in the colon, considered as the main site of intestinal production. Despite the fact that more than 90% of vitamin K store in the liver consists of menaquinones, it is unclear what their relative contribution is to overall vitamin K status, and their absorption from the colon is probably very limited [41].

Placental transfer of vitamin K is limited, and phylloquinone levels in cord blood are very low, about 1/30 of the levels in maternal plasma. Liver reserve also is substantially lower than in adults, estimated at 1/5. Menaquinones are not present in the liver of infants before the age of 2 to 3 months [38, 40]. It is not clear why vitamin K levels at birth are so tightly regulated.

Pharmacological sources

In Europe and North America, a pharmaceutical preparation of phylloquinone or vitamin K_1 has been marketed for more than 50 years, whereas in Japan, the main product is menaquinone-4 or a member of the vitamin K_2 series.

Table 1 Vitamin K content of different foods (adapted from [43])

Phylloquinone content (μg/100 g edible portion)	
800–900	Kale, parsley
600–700	Collards
400–500	Spinach
100–200	Sprouts, broccoli, onions, lettuce, cabbage, endives
50–100	Asparagus, olive oil
20–50	Peas, kiwi, blackberries, nuts, soy oil
10–20	Carrot, cucumber, grapes
5–10	Tomato, whole bread
1–5	Potato, eggplant, apricot, peach, apple, pear, strawberries, white bread, meat, egg, cheese
<1	Rice, fish, milk

Since the 1960s, a phylloquinone preparation with polyethoxylated castor oil (cremophor) as emulsifier was marketed. Occasionally, intravenous use of this preparation in adults has been associated with serious anaphylactic reactions. Also, because of safety concerns regarding phenol content, a new formulation was developed in the 1990s, using natural components (glycocholic acid and phophatidylcholine) as solubilizers. This mixed micellar (MM) preparation, commercialised in a concentration of 10 mg/ml, has replaced the cremophor form, which is no longer available in most European countries. Initially, the MM preparation was expected to be better absorbed than the cremophor solution. Although this might be true in healthy infants [36], epidemiological data do not show an improved efficacy of the MM preparation [47]. Absorption after oral administration remains poor in cholestatic patients, those most at risk for late vitamin K deficiency bleeding (VKDB) [32, 37, 47].

In the Netherlands, Belgium and Luxemburg, a low-dose preparation 25 μg/5 drops is available for daily oral administration [12].

Vitamin K deficiency and vitamin K deficiency bleeding

VKDB is defined as a bleeding disorder where coagulation is rapidly restored by vitamin K supplementation. Diagnosis is suggested by international normalised ratio (INR) ≥4 or a prothrombin time ≥4 control value in the presence of a normal platelet count and normal fibrinogen level. Confirmation is given by a rapid (within 2 h) normalisation of coagulation tests after parenteral administration of 1 mg vitamin K and/or the presence of PIVKA in plasma. The presence of PIVKA without coagulation deficit is a marker of subclinical vitamin K deficiency (VKD) but is not equivalent to VKDB [4].

As a consequence of limited stores at birth, neonates are prone to vitamin K deficiency if no sufficient intake is provided. Formerly less specifically known as "haemorrhagic disease of the newborn" [42], three presentations of VKDB are described [4, 40].

Early VKDB presents within 24 h of birth and is almost exclusively seen in infants of mothers taking drugs which inhibit vitamin K. These drugs include anticonvulsants (carbamazepin, phenytoine and barbiturates but not valproic acid), tuberculostatica (isoniazid, rifampicin), some antibiotics (cephalosporins) and vitamin K antagonists (coumarin, warfarin). Clinical presentation is often severe with cephalic haematoma and intracranial and intra-abdominal haemorrhage. The incidence in an at-risk group without vitamin K supplementation is 6–12%.

Classical VKDB occurs between 24 h and 7 days of life and is associated with delayed or insufficient feeding. Clinical presentation is often mild, with bruises, gastrointestinal blood loss or bleeding from the umbilicus and puncture sites. Blood loss, however, can be significant, and intracranial haemorrhage, although rare, has been described. Without vitamin K supplementation, incidence in older reviews is estimated at 0.25–1.5% [1], whereas more recent reviews mention lower estimates of 0.01–0.44% [4, 40].

Late VKDB is associated with exclusive breast-feeding. It occurs between the ages of 2 and 12 weeks. Clinical presentation is severe, with a mortality rate of 20% and intracranial haemorrhage occurring in 50%. Persistent neurological damage is frequent in survivors. In fully breast-fed infants who did not receive vitamin K at birth, the incidence is between 4.4/100,000 and 7.2/100,000 births (or between 1/15,000 and 1/20,000). Infants with cholestasis or malabsorption syndromes are at particular risk. Often, VKDB is the first sign of this underlying condition. [4].

Vitamin K prophylaxis in the newborn

In 1939, soon after the discovery of vitamin K, it was shown that treatment with vitamin K could abolish haemorrhagic disease of the newborn [16, 22]. Routine prophylaxis with 1 mg vitamin K at birth was adopted as a universal measure in North America and most European countries, although 1 mg represents a massive dose compared to the daily requirement of 5–10 μg in infants [1]. Quoting E. Hey [23], no formal studies were ever performed to establish what dose might be appropriate before it became standard practice to give every infant a 1-mg dose at birth and to give it intramuscularly simply because that was the only product available. In 1990 [19], an epidemiological study described an association between intramuscular (IM) vitamin K at birth and childhood cancer and leucemia. In response to these findings, several European countries, Australia and New Zealand changed their policy to oral prophylaxis. In the following years, new studies failed to confirm the association between IM vitamin K at birth and childhood cancer. A risk of solid tumours can now almost definitely be ruled out, but a small risk of leukaemia cannot be excluded. [17, 35]. When cases of late VKDB started to reappear, Denmark, Canada, Australia and New Zealand responded by reintroducing universal IM prophylaxis, offering oral prophylaxis with repeated doses to those parents refusing the IM injection at birth. Oral prophylaxis with repeated doses has remained the policy in the Netherlands and in Germany, using different products and dosing schemes [12, 47]. The American Academy of Pediatrics has always endorsed the IM route [1–3] also because no vitamin K preparation is licensed for oral use in the USA. IM prophylaxis has the

advantage of not depending on parents' compliance for administration. Disadvantages are pain caused by the injection, the risk of medication error by confusing maternal ergotamin with vitamin K [5] and the dependence on compliance by the medical staff [7]. However, although an injection is painful, the risk of local neuromuscular damage is very low; no significant complications after 420,000 IM injections were reported [46].

Key message 2	There is no doubt that all newborns need vitamin K

Last year, several carefully conducted epidemiological studies were published, providing data on the effectiveness of different administration routes and dosing schemes [7, 24, 44]. There is no doubt that all infants need vitamin K at birth in order to prevent early and classic VKDB. In at-risk groups (premature infants, mothers taking medications interacting with vitamin K, instrumental delivery), vitamin K is given parenterally.

Key message 3	Classic VKDB is prevented by the administration of 1 mg vitamin K at birth; IM administration is the preferred route in at-risk groups

In healthy term exclusively breast-fed infants, oral prophylaxis with a single 1 mg dose at birth prevents classic VKDB but not late VKDB, whereas IM administration offers protection for both. Table 2 summarizes the incidence of late VKDB in relation to different prophylaxis schemes. Oral prophylaxis with repeated doses protects almost all healthy breast-fed infants from late VKDB [12, 21, 37, 47]. Infants with cholestasis or malabsorption are, however, not protected by daily repeated low doses of 25 μg [24]. Comparing data from the Dutch and Danish biliary atresia registries enabled to establish the efficacy in protecting cholestatic infants from VKD (disordered coagulation but no bleeding) and from late VKDB with three regimens [44]. In all breast-fed infants with biliary atresia, the Dutch regimen of 1 mg orally at birth followed by 25 μg daily failed to protect from VKD, and 25 of 30 suffered VKDB. The relative risk for a VKDB was 77.5 (95%CI 11–548) compared to formula-fed infants. Both Danish regimens of a weekly oral dose of 1 mg (1994–2000) or 2 mg IM at birth (2000–2005) offered substantially better protection: the risk of VKD but not of VKDB was elevated compared to formula-fed infants [44]. As a consequence of these findings, the Netherlands is now considering daily oral administration of 50 μg, a dose comparable to what formula-fed infants receive. At this moment however, no evidence is available to endorse this choice.

Key message 4	IM administration of vitamin K at birth is effective in preventing both classic and late VKDB

In summary, there is no discussion about the necessity of universal vitamin K prophylaxis at birth. Both IM and oral administration of 1 mg protect against classic VKDB [34]. In exclusively breast-fed infants, single IM administration at birth is effectively preventing (rare) late VKDB, but oral administration should be continued by either weekly administration of 1 mg till 12 weeks or 2 mg at weeks 1 and 4. Daily administration of 25 μg offers insufficient protection. The only infants not fully protected in this way are those with yet unrecognised liver disease.

Key message 5	In exclusively breast-fed infants, oral vitamin K administration should be continued. Weekly oral administration of 1 mg vitamin K is more effective in preventing late VKDB than daily administration of 25 μg

Vitamin K prophylaxis in preterm infants

Ever since the discovery of vitamin K, it has been clear that premature infants are at particular risk of VKDB [22]. Although there is consensus on the fact that all premature infants should receive vitamin K, neonatology units use a variety of doses, dosing schedules, routes and formulations

Table 2 Incidence of late VKDB with different administration schemes of vitamin K

	Administration scheme	Incidence (per 100,000)
The Netherlands [24]	1 mg oral at birth followed by 25 μg daily till 12 weeks	3.2 (95%CI 1.2–6.9)
Germany [47]	2 mg oral at birth followed by 2 mg at 1 and 4 weeks (MM preparation)	0.44 (95%CI 0.19–0.87)
Denmark [21]	2 mg oral at birth followed by 1 mg weekly till 12 weeks	0 (95%CI 0–0.9)
Great Britain [7]	1 mg IM	0.1
	1 mg oral, continuing after 1 week	0.43
	1 mg oral, not beyond 1 week	2.9
	Nil	6.2

[9]. Reports have shown very high plasma vitamin K levels in preterm infants receiving 0.5 to 1 mg at birth [13, 25]. Although no toxic effects of these excessively high serum levels have been recognised, caution is warranted because the functions of some Gla proteins are not fully understood. A recent randomised trial shows adequate serum vitamin K levels in preterm infants receiving 0.2 mg at birth [10]. In this trial, preterm infants receiving 0.5 mg have elevated levels of vitamin K epoxide, suggesting inefficient recycling of vitamin K by VKOR in the immature liver. These findings support current empirical dosage recommendations for preterm infants advising a reduced dose of 0.3 mg for birth weights <1,000 g and 0.5 mg for those >1,000 g and <1,500 g [3].

Vitamin K administered to women prior to very preterm birth has not been shown to significantly prevent periventricular haemorrhages in preterm infants [14].

Vitamin K prophylaxis in patients with fat malabsorption and/or cholestasis

Due to fat malabsorption and inadequate intake, infants with cholestatic liver disease are especially at risk for vitamin K deficiency. Infantile cholestasis is frequently unrecognized, and once the diagnosis is made, these children are often referred without having received extra vitamin K supplementation. As mentioned above, some of the current standard regimens of oral vitamin K prophylaxis are mostly insufficient in cholestatic patients making them extremely vulnerable for VKDB. More than 80% of breast-fed infants with biliary atresia who received the Dutch oral vitamin K prophylaxis (1 mg oral vitamin K at birth followed by 25 mg daily) developed a VKDB at the time of diagnosis. Forty-three per cent presented with an intracranial haemorrhage [44]. These data can be explained by the finding that the intestinal absorption of mixed micellar K_1 is unreliable in children with conjugated hyperbilirubinaemia [32].

Key message 6	Infantile cholestasis = extra vitamin K supplementation

The empirical dosing guideline for oral vitamin K_1 in infants and children with chronic cholestasis is 2.5–5 mg given two to seven times per week [39]. Nevertheless, with this regimen, subclinical vitamin K deficiency seems prevalent despite normal prothrombin time (PT). In a group of 43 cholestatic children supplemented following this schedule, 23 (54%) had elevated plasma PIVKA II levels (>3 ng/ml) with normal PT [26].

Vitamin K doses sufficient to maintain normal coagulation may not be sufficient to maximize carboxylation of osteocalcin. This might further increase the risk for osteopenia and osteoporosis in children with chronic cholestatic liver disease.

Based on the above-mentioned data, it is thus of uttermost importance that, as soon as the diagnosis of cholestasis is made in an infant, extra vitamin K supplementation should be given to prevent VKDB with its serious consequences. However, the best strategy for vitamin K supplementation in chronic childhood cholestasis still remains a critical issue. Current regimens may underestimate the optimal dosage of vitamin K.

Possible role of vitamin K in the prevention of osteoporosis

The bone defect present in the fetal warfarin syndrome [33] led to the search for Gla proteins in bone. Osteocalcin and matrix Gla protein are both dependent on post-translational modification involving vitamin K. Although the exact function of these proteins is not yet completely understood, they play an important role in the formation of bone matrix. [8]. As for other PIVKAs, the circulating concentration of under-γ-carboxylated osteocalcin (ucOC) is a sensitive marker of vitamin K nutritional status and has been reported to be a predictor of low bone mineral density (BMD) in adults [8]. In children with cystic fibrosis however, ucOC levels were correlated significantly with bone turnover markers but not with bone density [11]. One year supplementation of 10 mg vitamin K per week in a small group of children with cystic fibrosis had no influence on BMD but resulted in lower parathormone levels [30]. In healthy children, a marked elevation of the ratio of ucOC/carboxylated OC compared to adults is observed [45]. Although it has been suggested that dietary vitamin K intakes sufficient to maintain normal blood coagulation may be suboptimal for adult bone health, no evidence is available to prove this statement. Further well-designed controlled trials are needed before recommendations regarding the role of vitamin K in the prevention of osteoporosis in different population and patient groups can be formulated.

Conclusion

Since its discovery more than 70 years ago, it has been clear that vitamin K plays an essential role in maintaining normal coagulation. Recent work has elucidated its role as a co-factor for GGCX, an important enzyme not only for the activation of vitamin K-dependent coagulation factors but for a range of other Gla proteins. The function of several of these Gla proteins is not yet elucidated. More basic research

on the maturation of these enzymes in the fetus and newborn and on the activity of their different phenotypes remains to be done. It is not clear how menaquinones are absorbed from the colon and what their relative contribution is to overall vitamin K status. Carefully conducted epidemiological studies using valuable registries have enabled to end some controversies concerning vitamin K and the newborn. It remains, however, unclear what the optimal dosing regimen is for preterm infants or for patients with cholestasis. The same holds true regarding the role for vitamin K in the prevention and treatment of osteoporosis.

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