Editorial

Vitamin K and the newborn

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Vitamin K comprises several molecular forms that have a common 2-methyl-1,4-naphthoquinone ring but differ in the structures of the side chain at the 3-position[1]. Vitamin K_1 or phylloquinone is the principal form in plants and vegetable oils[2]. Most commercial formulae contain >50µg/L of vitamin K_1. In contrast, vitamin K content of human milk is generally <20µg/L and often <5µg/L[3]. Vitamin K_1 absorption occurs in the small intestine and requires the presence of bile acids[2]. The intestinal flora synthesizes vitamin K as vitamin K_2 or menaquinone[4]. Bacteria vary widely in this ability: *Bacteroides fragilis* and some strains of *Escherichia coli* are efficient producers of vitamin K_2 whereas some lactobacilli and pseudomonas organisms are incapable of its synthesis[4]. Absorption of vitamin K_2 from neonatal colon has been demonstrated[5], but the relative importance of intestinal flora in providing vitamin K to infant is unknown.

Vitamin K is required for modification and activation of a number of important proteins, best known of which are coagulation factors II, VII, IX and X[6]. Protein C, an inhibitor of coagulation, is also vitamin K dependent[7] as are other proteins with less understood specific functions[8]. The specific action of vitamin K is the posttranslational carboxylation of glutamic acid residues on vitamin K-dependent proteins[9]. This conversion of glutamic acid to gamma-carboxyglutamic acid creates effective calcium binding sites on these proteins. Noncarboxylated proteins are functionally defective because they cannot bind calcium. In absence of vitamin K, synthesized coagulation factors circulate in their noncarboxylated, functionally defective form[1]. The vitamin K-dependent carboxylation of coagulation factors occurs in the endoplasmic reticulum of the hepatocyte[1].

Vitamin K_1 does not cross the placenta easily. Its concentration in cord blood is <10% of mean maternal values[10] and mean concentrations of vitamin K dependent clotting factors (II, VII, IX and X) are 30% to 60% of normal adult values[11]. These low levels gradually increase until they reach normal adult values by 6 weeks of age[1].

In the past, assessment of vitamin K status in infancy relied on functional assays of vitamin K-dependent factors or prothrombin time (PT) and comparison of these values with those of normal newborn infants.

Unfortunately, levels seen in mild vitamin K deficiency may overlap normal physiologic values. An increase in these factor levels or decrease in the PT following administration of vitamin K has also been used to suggest a deficiency state. More specific tests measure the abnormal, noncarboxylated prothrombin that circulates in vitamin K-deficient patients. This abnormal prothrombin is antigenically intact but functionally defective[1]. One method compares level of prothrombin measured functionally (II coagulant) with that measured antigenically (II antigen)[12]. A low coagulant/antigen ratio indicates vitamin K deficiency. Other methods measure this abnormal prothrombin or PIVKA more directly[13]. In these assays carboxylated prothrombin is absorbed from plasma and any remaining noncarboxylated prothrombin is assayed immunologically.

Vitamin K deficiency bleeding (VKDB) in infancy (formerly known as haemorrhagic disease of the newborn) comprises early (0-24 hours), classical (1-7 days) and late (2-12 weeks) syndromes according to the time of presentation[14].

1. ***Early VKDB*** - These infants have severe and often life-threatening haemorrhage at time of delivery or during first 24 hours after birth. Although idiopathic cases have been reported[15,16], it is typically seen in infants whose mothers have taken drugs that affect vitamin K metabolism. Warfarin taken during pregnancy may result in severe early VKDB[17]. Maternal anticonvulsants have also been linked to early VKDB[18,19]. Most cases have involved barbiturates, phenytoin or both. Infants born to women taking rifampicin and isoniazid during pregnancy may also be at risk for early VKDB[20]. The extent of bleeding varies from skin bruising or umbilical bleeding to widespread and fatal intra-cranial, intrathoracic, intra-abdominal and gastrointestinal haemorrhage[1].

2. ***Classical VKDB*** - This typically occurs at 2 to 5 days of age[21]. Affected infants are normal at birth but subsequently develop generalized ecchymoses or gastrointestinal bleeding. Nasal bleeding or bleeding following circumcision may also be the initial manifestation[1]. Intracranial haemorrhage is less common at this age. Breast feeding plays an important role in its pathogenesis. Breast milk is relatively deficient in vitamin K. The incidence of moderate to severe bleeding among breast fed infants who do not receive vitamin K is 15 to 20 times greater than in infants who receive cow's milk, vitamin K or both[22].

3. ***Late VKDB*** - This was first described in Thailand in 1963[23]. The bleeding manifestations occur after first week of life. Of major concern is its sudden and unpredictable onset and the high (50-82%) frequency of intracranial haemorrhage as the presenting feature[24]. Another common initial feature is widespread deep ecchymoses or 'nodular purpura'[25]. Known risk factors include breast feeding and failure to give vitamin K prophylaxis at birth. An association between late VKDB and undiagnosed abnormalities of liver function has been reported in surveillance programmes from several countries[26,27,28]. Evidence for liver dysfunction in some cases has rested on transient, mildly abnormal biochemical indices[26,29], but several surveys have indicated that certain cholestatic liver diseases such as biliary atresia and alpha1 antitrypsin deficiency may be responsible for the majority of cases of late VKDB[27,28,30].

The efficacy of newborn intramuscular (IM) vitamin K prophylaxis in prevention of classical and late VKDB has been well established[31]. In 1990 Golding et al reported a study of a 1970 birth cohort in Britain in which they noted an unexpected association between childhood cancer and pethidine given in labour and neonatal administration of vitamin K[32]. Subsequently, Golding and others conducted a case-control study designed to examine the risk of cancer associated with IM vitamin K administration among infants born in two hospitals in Avon between 1965 and 1987 and diagnosed with cancer between 1971 and 1989[33]. They reported a significant association between IM vitamin K and cancer when compared to no vitamin K or oral Vitamin K. They recommended exclusive use of oral vitamin K. A study from the United States of America found no association between neonatal IM vitamin K and an increased risk of any childhood cancer[34]. The American Academy of Paediatrics has thus recommended continued use of IM vitamin K for prophylaxis[35]. The British Paediatric Association, on the other hand, recommended routine use of oral vitamin K in all healthy neonates, reserving IM prophylaxis for those at greatest risk of VKDB[36]. 4 subsequent studies from Great Britain, whilst ruling out solid tumours, could not completely exclude a small risk of leukaemia[37,38,39,40].

The most efficacious oral vitamin K regimen for prevention of late VKDB remains to be established. Experience from small populations suggests that 0.025 mg given daily, as in Netherlands[40], or 1 mg doses given weekly, as in Denmark[41], may be almost as effective as 1 mg given IM at birth. Three oral doses of 2 mg vitamin K have been given to a substantial population of newborns in Europe under surveillance for late VKDB. The incidence of VKDB in these children was 0.56 (95% confidence interval 0.33-0.89)/100,000 live births, suggesting that this regimen is quite effective. Most of the infants who did not respond to prophylaxis had cholestatic disease[42].

Since 1994, the original Konakion, which contained the non-ionic detergent Cremophor EL as solubiliser, has been superseded by a mixed micellar formulation (Konakion MM) in which phylloquinone (vitamin K1) is solubilised in glycocholic acid and phosphatidylcholine. A paediatric Konakion MM formulation is now in wide use for oral vitamin K prophylaxis of VKDB and in healthy babies has been shown to give higher serum levels than the earlier preparation, suggesting a superior bioavailability[43]. It has also been claimed that Konakion MM is well absorbed in infants with severe cholestasis[44]. In a recent randomized controlled trial comparing breast fed infants given either 1 mg vitamin K, IM or 2 mg mixed micellar preparation orally at birth, on day 7 and day 30, good or even higher plasma vitamin K, concentrations up to the eighth week of life were observed in children on the oral regimen[45].

In Sri Lanka the paediatric Konakion MM formulation has been available from 1996. As this is supplied only in glass vials it is unsuitable for routine administration by mothers and so professional administration of each dose is specified in the data-sheet. However, most neonatal units continue to use IM vitamin K rather than the oral preparation because, in the normal newborn population, giving three doses of vitamin K_1 to breast feeding infants, two of which would be given after hospital discharge, is problematic. Poor compliance in administering the three doses has already been reported from elsewhere[46].

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