

Effects of Vitamins K in Neonates and Young Infants

*Gian Maria Pacifici¹

¹ Via San Andrea 32, 56127 Pisa, Italy.

Abstract

Vitamin K is required for the hepatic production of blood coagulation factors II, VII, IX and X. The term vitamin K refers to a variety of fat-soluble 2-methyl-1, 4-naphthoquinone derivatives. Vitamin K1 (phylloquinone) occurs in green plants, while vitamin K2 (menaquinone) is synthesized by microbial in the gut. The recommended dose of vitamin K in neonates is 1 mg intramuscularly. For infants below 2.5 kg, the dose is 0.3 mg/kg to a maximum dose of 1 mg. Vitamin K crosses the placenta poorly, and neonates are relatively deficient of vitamin K at birth. Human milk contains about 1.5 µg/l of vitamin K, whereas most formula milks contain about three times as much as this. Vitamin K1 prophylaxis with 0.2 mg administered intramuscularly maintains adequate vitamin K1 status of preterm infants until a median age of 25 postnatal days and did not cause early vitamin K1 2, 3-epoxide accumulation. There is need for intramuscularly vitamin K prophylaxis for all newborns in order to eradicate hemorrhagic disease of the newborn. Some authors found that the antenatal administration of vitamin K1 to pregnant women in preterm delivery increases the blood coagulation activity in neonates whereas other authors found that the antenatal administration of vitamin K1 has no effects on neonates. Vitamin K1 crosses the placenta poorly and it is not surprising that vitamin K1 has limited effects on neonates. The aim of this study was to review the effects of vitamins K in neonates and young infants.

Key Words: Effects, Neonates, Vitamin K, Vitamin K1.

*Please cite this article as: Maria Pacifici G. Effects of Vitamin K in Neonates and Young Infants. Int J Pediatr 2016; 4(3): 1611-24.

***Corresponding Author:**

Gian Maria Pacifici, MD, Via San Andrea 32, 56127 Pisa, Italy.

Email: pacificigm@tiscali.it

Received date Jan 17, 2016 ; Accepted date: Feb 22, 2016

1-INTRODUCTION

The term vitamin K refers to a variety of fat-soluble-2-methyl-1, 4-naphthoquinone derivatives. Vitamin K1 (*phytonadione*), isolated in 1939, occurs in green plants, while K2 (menaquinone) is synthesized by microbial flora in the gut. Human milk contains about 1.5 µg/l of vitamin K. Most formula milks contain 4.39 to 5.99 ng/ml vitamin K. Vitamin K crosses the placenta poorly, and neonates are relatively deficient of vitamin K at birth. Any resultant vitamin-responsive bleeding used to be called "hemorrhagic disease of the newborn", but is now, more informatively, called "vitamin K deficiency bleeding" because it can occur at any time in the first 3 months of life. Any unexplained bruise or bleed in a young infant calls for immediate attention if catastrophic cerebral bleeding is to be avoided (1).

Vitamin K is required for the hepatic production of coagulation factors II, VII, IX and X. Later vitamin K deficiency bleeding can, however, cause potentially lethal intracranial bleeding, and there is 1:6,000 risk of this in the unsupplemented breastfed infants. Malabsorption, usually due to unrecognized liver disease, accounts for most of this increased risk. A single 1 mg intramuscular dose of vitamin K provides almost complete protection, probably by providing a slow-release intramuscular depot, but a dose this large causes some liver overload in the very preterm infant.

Vitamin K1 promotes formation of the following clotting factors in the liver: active prothrombin (factor II), proconvertin (factor VII), and Stuart factor (factor X). Vitamin K1 does not counteract the anticoagulant action of heparin (2).

Healthy newborn infants show decreased plasma concentrations of vitamin K-dependent clotting factors for a few days after birth, the time required to obtain an

adequate dietary intake of the vitamin K and to establish a normal intestinal flora. In premature infants and in infants with hemorrhagic disease of the newborn, the concentrations of clotting factors are particularly depressed. The degree to which these changes reflect true vitamin K deficiency is controversial. Measurements of non-gamma-carboxylated (non-γ-carboxylated) prothrombin suggest that vitamin K deficiency occurs in about 3% of live births (3). Hemorrhagic disease of the newborn has been associated with breast-feeding; human milk has low concentrations of vitamin K (4). In addition, the intestinal flora of breast-fed infants may lack microorganisms that synthesize the vitamin K (5). Commercial infant formulas are supplemented with vitamin K. In the neonate with hemorrhagic disease of the newborn, the administration of vitamin K raises the concentration of these clotting factors to the level normal for the newborn infant and controls the bleeding tendency within about 6 hours. The routine administration of 1 mg phytonadione intramuscularly at birth is required by law in the United States. This dose may have to be increased or repeated if the mother has received anticoagulant drug therapy or if the infant develops bleeding tendencies. Alternatively, some clinicians treat mothers who are receiving anticonvulsants with oral vitamin K prior to delivery (20 mg per day) for 2 weeks.

2- MATERIALS AND METHODS

2-1. Literature Search

The following databases were searched for relevant papers and reports: MEDLINE, CINAHL, Embase, Google scholar and PubMed as search engines; January 2016 was the cutoff point. Key references from extracted papers were also hand-searched.

2-2. Search Terms

Combinations of search terms from three categories ("Neonates" keyword AND "Effects vitamin K neonate" keyword AND "Effects vitamin K1 neonate AND Infants" keyword) were used to search for the relevant literature. In addition, the books Neonatal Formulary (1) and NEOFAX by Young and Mangum (2) were consulted.

3-RESULTS

3-1. Monitoring

Check prothrombin time when treating clotting abnormalities. A minimum of 2 to 4 hours is needed for measurable improvement (2).

3-2. Prophylaxis

3-2-1. Intramuscular prophylaxis

1 mg is the dose traditionally given to every infant at birth. Intravenous administration does not give the sustained protection provided by intramuscular injection. For infants below 2.5 kg, give 0.3 mg/kg to a maximum dose of 1 mg (1).

3-2-2. Oral prophylaxis

Infants born to mothers on carbamazepine, phenobarbital, phenytoin, rifampicin or warfarin and those too ill for early feeding should be offered intramuscular prophylaxis at birth, but all other infants can, with parental consent, be given a 1 or 2 mg dose of vitamin K by mouth instead (1).

3-3. Effects of vitamin K and vitamin K1 supplementation in neonates and young infants and their mothers

Two groups of 165 healthy breast-fed infants who received at random 1 mg vitamin K1 orally or intramuscularly after birth were studied at 2 weeks and 1 and 3 months of age (6). Although vitamin K1 concentrations were statistically significantly higher in the intramuscular group, blood coagulation activities of

factors VII and X and proteins induced by vitamin K absence and clotting factors did not reveal any difference between the two groups. At 2 weeks of age vitamin K1 concentrations were raised compared with reported unsupplemented concentrations and no proteins induced by vitamin K absence was detectable. At 3 months vitamin K1 concentrations were back at unsupplemented values and proteins induced by vitamin K absence were detectable in 11.3% of infants. Therefore, a repeated oral prophylaxis will be necessary to completely prevent vitamin K deficiency beyond the age of 1 month.

Busfield et al. (7) surveyed vitamin K deficiency bleeding and documented vitamin K prophylaxis practice, and compared this with findings predating withdrawal of Konakion Neonatal and guidance from the National Institute of Health and Clinical Excellence, both occurring in 2006. All newborns and infants were under 6 months with suspected vitamin K deficiency. Eleven cases of vitamin K deficiency bleeding were found: six (55%) infants received no vitamin K prophylaxis, in five (45%) because parents withheld consent; three (27.5%) infants with vitamin K deficiency bleeding received intramuscular Konakion MM (two had biliary atresia, and one was delivered preterm); two (18%) infants received incomplete oral prophylaxis. Nine infants (62%) were breast fed. Three (27%) infants had liver disease; four (36%) infants had intracranial hemorrhage, two probably suffering long-term morbidity. Vitamin K prophylaxis practice was defined in 236 (100%) units. All units recommended prophylaxis for every newborn: 169 (72%) intramuscularly, 19 (8%) oral, and 48 (20%) offered parental choice. All units that recommended intramuscular prophylaxis used Konakion MM. Oral prophylaxis always involved multidose regimens for breastfed infants; 61 (91%) units used Konakion MM, and

six (9%) used unlicensed products suitable for administration by parents. Intramuscular Konakion MM is efficacious, but parents withholding consent for recommended intramuscular prophylaxis reduces effectiveness. Reappraisal of National Institute of Health and Clinical Excellence guidance would be appropriate. Prolonged jaundice demands investigation. Late vitamin K deficiency bleeding occasionally occurs after intramuscularly prophylaxis.

Strehle et al. (8) investigated the acceptability and tolerability of the oral food supplement Neokay for the prevalence of vitamin K deficiency bleeding in newborns. One dose of Neokay was given to 1,794 healthy newborns at birth and further daily doses were given to 812 breastfed infants for 3 months. The midwives listed as the main advantages ease of administration, no need for prescription or written consent, and transfer of responsibility to parents. As disadvantages, they mentioned possible confidence in breast-feeding and technical issues with packaging. A prophylaxis vitamin K dosage regimen of 1 mg oral vitamin K (Konakion MM Pediatric or Orakay) given to all healthy neonates at birth, combined with daily doses of 50 µg Neokay for 3 months for breast-fed infants at birth, combined with daily doses of 50 µg Neokay for 3 months for breastfed infants is well tolerated and acceptable to midwives and parents.

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. Van Hasselt et al. (9) compared the risk of vitamin K deficiency bleeding under different prophylactic regimens in infants with biliary atresia. These authors determined the absolute and relative risk of severe vitamin K deficiency and vitamin K deficiency bleeding on diagnosis in breast-

fed infants on each prophylactic regimen and in formula-fed infants. Vitamin K deficiency bleeding was noted in 25 of 30 breast-fed infants on 25 µg of daily oral prophylaxis, in 1 of 13 on 1 mg weekly oral prophylaxis, in 1 of 10 receiving 2 mg of intramuscular prophylaxis at birth, and 1 of 98 formula-fed infants ($P < 0.05$). The relative risk of bleeding in breast-fed compared with formula-fed infants was 77.5 for 25 µg of daily oral prophylaxis, 7.2 for 1 mg of weekly oral prophylaxis, and 9.3 for 2 mg of intramuscular prophylaxis at birth. A daily dose of 25 µg of vitamin K fails to prevent bleedings in apparently healthy infants with unrecognized cholestasis because of biliary atresia. One mg of weekly oral prophylaxis offers significantly higher protection to these infants and is of similar efficacy as 2 mg of intramuscular prophylaxis at birth. These data underline the fact that event analysis in specific population at risk can help to evaluate and improve prophylactic regimens.

Clarke et al. (10) assessed vitamin K status and metabolism in preterm infants after 3 regimens of prophylaxis. Infants <32 weeks' gestation were randomized to receive 0.5 mg (control) or 0.2 mg of vitamin K1 intramuscularly or 0.2 mg intravenously after delivery. Primary outcome measures were serum vitamin K1, its epoxide metabolite (vitamin K1 2,3-epoxide), and under-carboxylated prothrombin assessed at birth, 5 days, and after 2 weeks of full enteral feeds. Secondary outcome measures included prothrombin time and factor II concentrations. On day 5, serum vitamin K1 concentrations in the 3 groups ranged widely (2.9-388 ng/ml) but were consistently higher than adult range (0.15-1.55 ng/ml). Presence of vitamin K1 2, 3-epoxide on day 5 was strongly associated with higher vitamin K1 bolus doses. Vitamin K1 2, 3-epoxide was detected in 7 of 29 and 4 of 29 infants from the groups

that received 0.5 mg intramuscularly and 0.2 mg intravenously, respectively. After 2 weeks of full enteral feeding, serum vitamin K1 was lower in the infants who received 0.2 mg intravenously compared with the infants in the control group. Three infants from the 0.2-mg groups had undetectable serum vitamin K1 as early as the third postnatal week but without any evidence of even mild functional deficiency, as shown by their normal under-carboxylated prothrombin concentrations. Vitamin K1 prophylaxis with 0.2 mg administered intramuscularly maintained adequate vitamin K status of preterm infants until a median age of 25 postnatal days and did not cause early vitamin K1 2, 3-epoxide accumulation. In contrast, 0.2 mg administered intravenously and 0.5 mg administered intramuscularly led to vitamin K1 2, 3-epoxide accumulation possibly indicating overload of the immature liver. To protect against late vitamin K1 deficiency bleeding, breast preterm infants given a 0.2 mg dose of prophylaxis should receive additional supplementation when feeding has been established.

Costakos et al. (11) studied infants (22 to 32 week gestational age) of mothers wishing to breast-feed. Group 1, received 1 mg of vitamin K and group 2 received 0.5 mg vitamin K. The day 2 plasma levels of vitamin K were 1,900 to 2,600 times higher on average, and the day 10 vitamin K levels were 550 to 600 times higher on average, relative to normal adult plasma values, whether an initial prophylaxis dose of 0.5 mg or 1 mg was used. These authors conclude that 0.5 mg as the initial dose of vitamin K intramuscularly or intravenously would likely be more than adequate to prevent hemorrhagic disease of the newborn, and that 0.3 mg per day may be used for infants with birth weights below 1,000 grams. Kumar et al. (12) assessed vitamin K status in premature infants by measuring plasma vitamin K and plasma

protein-induced in vitamin K absence from birth until 40 weeks' postconceptional age (PCA). Premature infants (≤ 36 weeks' gestation) were divided at birth into groups by gestational age (group 1, ≤ 28 weeks; group 2, 29-32 weeks; group 3, 33-36 weeks). Supplemental vitamin K (1 mg intramuscularly) was administered at birth followed by 60 $\mu\text{g}/\text{day}$ (weight $< 1,000$ grams) or 130 $\mu\text{g}/\text{day}$ (weight $\geq 1,000$ grams) via total parenteral nutrition. Of the 44 infants enrolled, 10 infants in each gestational age group completed the study. The patient characteristics for group 1, 2, and 3 were as follows: gestational age, 26.3 ± 1.7 , 30.3 ± 1.3 , and 33.9 ± 1.1 weeks; birth weight, 876 ± 176 , $1,365 \pm 186$, and $1,906 \pm 163$ grams; and days of hyperalimentation, 28.9 ± 16 , 16.8 ± 12 , and 4.3 ± 4 days, respectively. At 2 weeks of age, the vitamin K intake and plasma levels were highest in group 1 versus group 3 (intake: 71.2 ± 39.6 versus 13.4 ± 16.6 $\mu\text{g}/\text{kg}$ per day; plasma levels: 130 ± 125.6 versus 27.2 ± 24.4 ng/ml). By 40 weeks' postconception, the vitamin K intake and plasma levels were similar in all 3 groups (group 1, 2, and 3: intake, 11.4 ± 2.5 , 15.4 ± 6.0 , and 10.0 ± 7.0 $\mu\text{g}/\text{kg}$ per day; plasma levels, 5.4 ± 3.8 , 5.9 ± 3.9 , and 9.3 ± 8.5 ng/ml). None of the post plasma samples had any detectable protein-induced in vitamin K absence. Premature infants at 2 weeks of age have high plasma vitamin K levels compared with those at 40 weeks' postconceptional age secondary to the parenteral administration of large amounts of vitamin K. By 40 weeks' postconception, these values are similar to those in term formula-feed infants. Confirming "adequate vitamin K status" was undetectable by 2 weeks of life in all the premature infants. With the potential for unforeseen consequences of high vitamin K levels, consideration should be given to reducing the amount of parenteral vitamin K supplementation in the first few weeks of life in premature infants.

Newborn infants are born vitamin K deficient; however, the deficiency is not sufficiently severe to cause a coagulopathy due to vitamin K deficiency and hemorrhagic disease of the newborn (13). Severe vitamin K deficiency can develop quickly in breast-fed newborns and can result in the appearance of classic hemorrhagic disease of the newborn during the first week of life or late hemorrhagic disease of the newborn during the first 2 months of life. Both forms of the disease can be severe, causing brain damage and death. Classic and late hemorrhagic disease of the newborn are prevented by the intramuscular vitamin K prophylaxis. There have been concerns about the need for, and safety of, this therapy. There is need for intramuscular vitamin K prophylaxis for all newborns in order to eradicate hemorrhagic disease of the newborn.

Hemorrhage in the infant from vitamin K deficiency is still a concern in pediatrics. Vitamin K give intramuscularly will largely prevent hemorrhagic disease in the newborn, even in infants who are exclusively breast-fed and are thus at greater risk for bleeding (14). The vitamin K content of human milk is very low compared with standard infant formulas. The role of vitamin K in the prevention of intravenous hemorrhage in premature infants has not been sufficiently demonstrated. Ongoing developments in this field will lead to improving methods of detecting early vitamin K deficiency and perhaps suitable alternatives to intramuscular vitamin K prophylaxis in the newborn.

A study was undertaken to increase the phylloquinone (vitamin K₁) concentration of human milk with maternal oral phylloquinone supplements such that both the phylloquinone intake of breast-fed infants and their serum concentrations of phylloquinone would approach those of formula-fed infants who are known to be

at much less risk for hemorrhagic disease of the newborn (15). The study had 2 stages. Stage I: ten mothers received 2.5 mg per day oral phylloquinone, and 10 mothers received 5.0 mg per day oral phylloquinone. Stage II: sequential sampling of 22 human milk-fed infants and lactating mothers. All infants received 1 mg of phylloquinone at birth. Eleven mothers received a placebo and 11 mothers received 5 mg per day phylloquinone. Stage I, longitudinal, randomized study of 6 weeks' duration; and stage II, longitudinal, randomized, double-blind, placebo-controlled study of 12 weeks' duration. In stage I, both 2.5 and 5.0 mg per day phylloquinone significantly increased the phylloquinone content of human milk at both 2 and 6 weeks. As expected, 5.0 mg had a greater effect (mean±SD, 58.96±25.39 versus 27.12±12.18 ng/ml at 2 weeks). In stage II, the vitamin K-supplemented group had significantly higher maternal serum phylloquinone concentrations, higher phylloquinone milk concentrations, and higher infant plasma phylloquinone concentrations at 2, 6, and 12 weeks compared with the placebo group. At 12 weeks infant phylloquinone intakes were significantly higher for the vitamin K group of (9.37±4.55 versus 0.15±0.07 µg/kg per day). This corresponded to a plasma phylloquinone concentration in the vitamin K group of 2.84±3.09 versus 0.34±0.57 ng/ml in the placebo group. At 12 weeks, the prothrombin times did not differ between the groups, but the Des-gamma carboxyprothrombin (DCP), (partially decarboxylated prothrombin thought to be a measure of vitamin K deficiency) was significantly elevated in the placebo group compared with the vitamin K group (1.48±1.19 versus 0.42±0.55 ng/ml). In exclusively breast-fed infants who receive intramuscular phylloquinone at birth, the vitamin K status as measured by plasma phylloquinone and Des-gamma

carboxyprothrombin, concentrations is improved by maternal oral supplements of 5 mg per day phylloquinone through the first weeks of life.

Vitamin K traverses the placenta from mothers to infant very poorly and is present only in very low concentrations in human milk (16). Thus, it is not surprising that the newborn infant has undetectable vitamin K serum levels with abnormal amounts of the coagulation proteins and undercarboxylated prothrombin. Hemorrhagic disease of the newborn, secondary to vitamin K deficiency, remains largely a disease of breastfed infants. Lactating mothers easily achieve the recommended dietary allowance for vitamin K (1 µg/kg per day) and the breast milk concentration is increased by increasing maternal vitamin K intake. Breastfed infants do not receive the recommended vitamin K intake via human milk. To prevent vitamin K deficiency in the newborn, intramuscular or oral vitamin K prophylaxis is necessary.

Eleven lactating mothers, who received 20 mg of phylloquinone (vitamin K1) orally, had rises in plasma (less than 1 to 64.2 ng/ml by 6 hours) and breast milk concentrations (from 1.11 ± 0.82 to 130 ± 188 ng/ml by 12 hours) (17). Twenty-three lactating mothers and their infants were observed longitudinally along with a formula-fed control group of infants (n=11). Mean breast milk concentrations of phylloquinone at 1, 6, 12, and 26 weeks were 0.64 ± 0.43 , 0.86 ± 0.52 , 1.14 ± 0.72 , and 0.87 ± 0.50 ng/ml, respectively, in the infants fed human milk. Maternal phylloquinone intakes (72-hour dietary recalls) exceeded the recommended daily allowance of 1 µg/kg per day. Infant phylloquinone intakes did not achieve the recommended daily allowance of 1 µg/kg per day in any infant. Plasma phylloquinone concentrations in the infants fed human milk remained extremely low (less than 0.25 ng/ml) throughout the first

6 months of life compared with formula-fed infants (4.39 to 5.99 ng/ml). In this small sample, no infant demonstrated overt vitamin K deficiency. Despite very low plasma phylloquinone concentrations, vitamin K supplements (other than in the immediate newborn period) cannot be recommended for exclusively breast-fed infants based on these data.

3-4. Antenatal supplementation of vitamin K1 and vitamin K2 to pregnant women and effects in their neonates

Pregnant women in preterm labor at less than 35 weeks of gestation were randomly selected to receive antenatal vitamin K1 10 mg per day injection intramuscularly or intravenously for 2-7 days (vitamin K1 group, n=40), or no such treatment (control group, n=50). At the same period, cord blood samples were collected from 30 full-term neonates to compare the factor levels with those of premature infants. Intracranial ultrasound was performed by the same sonographer to determine the presence and severity of periventricular-intraventricular hemorrhage (18). The actives of vitamin K-dependent coagulation factors in umbilical blood in the control group were: factor II $25.64 \pm 9.49\%$, factor VII $59.00 \pm 17.66\%$, factor IX $24.67 \pm 8.88\%$, and factor X $30.16 \pm 5.02\%$. In full-term infants, the respective values were: factor II $36.70 \pm 4.88\%$, factor VII $64.54 \pm 10.62\%$, factor IX $30.18 \pm 5.69\%$, and factor X $34.32 \pm 12.63\%$. In vitamin K1 these factors were: factor II $36.35 \pm 6.88\%$, factor VII $69.59 \pm 16.55\%$, factor IX $25.71 \pm 10.88\%$, and factor X $39.26 \pm 8.02\%$. These data suggest the absence of vitamin K-dependent coagulation factors in preterm infants, and that antenatal supplement of vitamin K1 may increase the cord blood activity of factors II, VII and factor X ($P < 0.05$). In addition, the overall rates of periventricular-intracranial hemorrhage in the vitamin K1 group and in controls were 32.4 and 52.0%, respectively ($P = 0.036$),

and the frequency of severe periventricular-intracranial hemorrhage was 5.0% and 20.0%, respectively ($P=0.038$). Administration of vitamin K1 to pregnant women at less than 35 weeks' gestation age may result in improved coagulation and may reduce the incidence as well as the severity degree of periventricular-intracranial hemorrhage in neonates.

El-Ganzoury et al. (19) determined the effects of maternal antenatal administration of vitamin K1 on activity levels of vitamin K-dependent coagulation factors and on the occurrence of periventricular-intraventricular hemorrhage. A total of 90 infants who were classified into Group A: 30 preterms whose mothers received antenatal vitamin K1, Group B: 30 preterms whose mothers did not receive antenatal vitamin K1, and Group C: 30 healthy full term newborns as a control group. All newborns were subjected to measurement of the activity level of vitamin K-dependent coagulation factors (II, VII, IX, and X). Cranial ultrasound was done on the 1st, 3rd, and 7th days of life. Group B showed significantly lower activity level of factors II and X with higher incidence of periventricular-intraventricular hemorrhage. Neonates who developed periventricular-intraventricular hemorrhage by the 7th day in both group A and B had significantly lower activity level of vitamin K-dependent coagulation factors. When antenatal vitamin K1 was given to pregnant women at imminent risk of preterm labor, their preterm neonates were able to achieve a clotting status approaching that of full term neonates and are less liable to develop periventricular-intraventricular hemorrhage. Preterm infants are at risk of periventricular hemorrhage.

This can damage the brain and lead to neurodevelopment abnormalities, including cerebral palsy. It has been suggested that vitamin K might improve coagulation in preterm infants. Crowther and Henderson-Smith (20) assessed the effects of vitamin K administered to women at risk of imminent very preterm birth to prevent periventricular hemorrhage and associated neurological injury in the infant. The primary outcomes were neonatal mortality, neurological morbidity and any maternal side effects. Five trials were included, involving more than 420 women. Antenatal vitamin K was associated with a non-significant trend to a reduction in all grades of periventricular hemorrhage (relative risk 0.82, 95% confidence interval 0.67-1.00) and in severe periventricular hemorrhage (grades 3 and 4) (relative risk 0.75, 95% confidence interval 0.45-1.25) for infants receiving prenatal vitamin K compared with control infants. Information on neurodevelopment was given for a small sample of children in one trial and no differences were seen. Vitamin K administered to women prior very preterm birth does not appear to be able to significantly prevent periventricular hemorrhage in preterm infants.

Dickson et al. (21) determined whether maternal vitamin K1 administered antenatally improved global coagulation parameters and the levels of specific vitamin K-dependent proteins in low birth-weight infants. Thirty-three preterm mothers admitted in labor were assigned in a prospective, blinded fashion to receive either intramuscular vitamin K1 ($n=17$) or placebo ($n=16$). At delivery cord blood samples were tested for prothrombin time, activated partial thromboplastin time, factor II and protein C activity, and antigen

levels. No statistically significant differences could be demonstrated with regard to group mean values for global tests (prothrombin time, activated partial thromboplastin time) or specific vitamin K-dependent protein levels (factor II, protein C) in newborns whose mothers received antenatal vitamin K1 compared with those who did not. These results would suggest that antenatal vitamin K1 therapy to mothers <32 weeks' gestation has no significant effect on the level of vitamin K-dependent factors in the fetus.

The null hypothesis of the study by Cornelissen et al. (22) is that extra vitamin K administered to pregnant women on a regimen of enzyme-induced anticonvulsant therapy will not decrease the frequency of symptoms of vitamin K deficiency in their neonates. A multicenter case-control study was performed on 16 pregnant women on anticonvulsant therapy who received 10 mg of vitamin K1 daily from 36 weeks of pregnancy onward. Concentrations of protein induced by vitamin K absence for factor II and vitamin K1 were determined in cord blood and compared with those in 20 controls. In none of 17 cord samples was protein induced by vitamin K absence for factor II detectable, compared with 13 of 20 in controls ($P=0.001$). Median cord vitamin K1 level was 530- pg/ml compared with below detection limit in most controls. Antenatal vitamin K1 treatment decreases the frequency of vitamin K deficiency in neonates of mothers on anticonvulsant therapy.

Levels of plasma vitamin K1 and vitamin K2 and protein-induced vitamin K protein-induced vitamin K absence-II were measured in Japanese mothers and their infants ($n=33$) (23). Twenty mg of vitamin K1 ($n=11$) or vitamin K2 ($n=12$) were given orally to random selected mothers 7 to 10 days prior delivery. Means of plasma vitamin K1 and vitamin K2 concentrations were significantly higher in vitamin K1

($P<0.01$) and vitamin K2 ($P<0.01$) treated mothers than in the controls at delivery, respectively. Similarly, these levels were significantly elevated in cord plasma in vitamin K1 ($P<0.05$) and vitamin K2 ($P<0.05$) treated groups, compared with findings in the control group, although there was a large concentration gradient between maternal and cord plasma (mostly less than one-tenth). A significant positive correlation was found in vitamin K1 concentration between maternal and cord plasma ($n=33$, $P<0.01$), and the protein-induced vitamin K absence II infants was significantly lower in vitamin K treated groups than in the control group at birth ($P<0.05$). On the fifth postnatal day, mean levels of vitamin K1 ($P<0.01$) and vitamin K2 ($P<0.01$) in breast milk were significantly higher in the vitamin K1 and vitamin K2 treated mothers than in the control mothers, respectively. In the control group 9 of 10 infants had a positive protein-induced vitamin K absence-II, but no one in the treated groups was positive, thereby indicating significant differences between control and treated groups ($P<0.01$ and $P<0.01$, respectively).

Yang et al. (24) determined the maternal-fetal vitamin K1 transport in premature infants after vitamin K1 was given to mothers antenatally and the vitamin K1 effects on blood coagulation in neonates. Women in labor at less than or equal to 34 weeks of gestation were randomly selected to receive antenatal vitamin K1, 5 mg given intramuscularly (vitamin K1 group), or no vitamin K1 (control group). Eight infants, including one set of twins, were in the vitamin K1 group and six in the control group. Vitamin K1 concentrations were higher in the vitamin K1 group than in the control group ($P=0.06$). Activated partial thromboplastin time was prolonged, and factor II coagulation activity and factor II antigen were proportionately decreased in cord plasma in both groups. The average ratio of factor II coagulation activity to

antigen was not decreased in either group. Protein induced by vitamin K absence-II was not detectable in any cord plasma sample in either group. These findings suggest that the decreased vitamin K-dependent coagulation activity in premature infants is the result of reduced synthesis of precursor proteins, rather than the result of vitamin K deficiency, and suggest that additional vitamin K1 is not likely to improve coagulation activity. Among those infants who underwent cranial ultrasonography, all four in the vitamin K1 group and one of five in the control group had mild intraventricular hemorrhage.

Morales et al. (25) established the effect of antenatal vitamin K on the incidence and severity of intraventricular hemorrhage in 92 patients destined to deliver infants less than 32 weeks' gestation. Group 1, received 10 mg of vitamin K1 intramuscularly every 5 days until delivery. Group 2 received no antenatal vitamin K1 therapy. There were 100 neonates less than 1,500 grams, equally divided between groups 1 and 2 with respect to gestational age, birth weight, race, gender, presentation, route of delivery, duration of labor, Apgar scores, and arterial umbilical cord acid-base balance. The antenatal use of vitamin K resulted in significant reduction in prothrombin time (12.7 versus 15.2 seconds) and partial thromboplastin time (42.6 versus 58.9 seconds; $P < 0.05$). Furthermore, group 1 experienced a lower incidence of total (16% versus 36%) and severe (0% versus 11%) grades of intraventricular hemorrhage ($P < 0.05$). This study suggests that the antenatal use of vitamin K may result in a reduction and severity of intraventricular hemorrhage in the neonate less than 1,500 grams. Kazzi et al (26) investigated the effect of maternal administration of vitamin K1 on cord blood prothrombin time, activated partial thromboplastin time, activity of factors II,

VII, and X, and antigen levels of factors II and X in infants of less than 35 weeks' gestation. Pregnant women in preterm labor were randomly assigned to receive 10 mg of vitamin K1 intramuscularly or no injection. If delivery did not occur in 4 days, the dose of vitamin K1 was repeated. Women who continued their pregnancy 4 days beyond the second dose received 20 mg of vitamin K1 orally daily until the end of the 34th week of gestation. The birth weights of infants ranged from 370 to 2,550 grams and the gestational age ranged from 22 to 34 weeks. The prothrombin time, activated partial thromboplastin time, factors II, VII, and X activity, and factors II and X antigen levels were not statistically different in either group of infants. Intraventricular hemorrhage occurred in 25 of 51 control infants and 25 of 47 vitamin K-treated infants. More control infants had grade III intraventricular hemorrhage on day 1 ($P = 0.032$), but on day 3 and 14 of life, the severity of intraventricular hemorrhage was comparable in both groups. Infants in whom an intraventricular hemorrhage developed were significantly smaller, younger, and more critically ill than infants without intraventricular hemorrhage. Administration of vitamin K1 to pregnant women at less than 35 weeks' gestation does not improve the haemostatic defects nor does it reduce the incidence or severity of intraventricular hemorrhage in their infants.

4-DISCUSSION

Prematurity is associated with bronchopulmonary dysplasia and vitamin A is an alternative therapy to reduce bronchopulmonary dysplasia morbidity and mortality. Intramuscular administration of 5,000 IU of vitamin A three times per week for 4 weeks decreased the risk of chronic lung disease in extremely-low-birth infants (21). Bronchopulmonary dysplasia was diagnosed in 9 of 20 infants given vitamin

A supplementation and 17 of 20 control infants ($P=0.008$) (19).

Supplementation of vitamin A in late pregnancy increases the cord blood vitamin A concentration and decreases the incidence of bronchopulmonary dysplasia in newborns. Combining antenatal vitamin A supplementation with postnatal supplementation to the newborn prevents bronchopulmonary dysplasia better than the postnatal preventive therapy alone. Vitamin A deficiency may increase the responsiveness of the respiratory tract infection, resulting in airway obstruction and wheezing (20).

Preterm infants have low vitamin A status at birth and this has been associated with increased risk of developing chronic lung disease (2). Infants with serum retinol values below $0.70 \mu\text{mol/l}$ were significantly ($p<0.001$) lower in the vitamin A group than in the control group. In regions where at least 22% of pregnant women have vitamin deficiency of vitamin A, giving neonates vitamin A supplements will have a protective effect against death (7). Reduction in breast milk retinol was observed in the control group compared with the pre-supplementation levels (1.93 and $1.34 \mu\text{mol/l}$, respectively; $P=0.003$) (9). Postpartum vitamin A supplementation is used to combat vitamin A deficiency and to reduce maternal and infant morbidity and mortality. The World Health Organization recommends a dose of 200,000 IU of vitamin A to pregnant women. Infants born to women whose vitamin A levels were in the lowest quartile ($<0.32 \mu\text{mol/l}$) had three-fold higher likelihood of mortality than infants born to mothers whose vitamin A levels were in the higher quartiles ($P<0.03$). These results suggest that maternal vitamin A deficiency during pregnancy may contribute to higher infant mortality rates (13). Klemm et al. (14) observed that supplementation of vitamin A reduces by 15% mortality compared with controls.

The kidneys are target organs for vitamin A action (24). Retinoic acid, a vitamin A metabolite, is involved in embryonic kidney patterning. Vitamin A status of the mother affects kidney organogenesis of the neonate. Retinoic acid regulates nephron mass during nephrogenesis. The newborns born to mothers with vitamin A deficiency have significantly lower mean values of cord retinol concentrations and dimensions of kidneys than the newborns delivered to mothers with vitamin A sufficiency. The maternal serum retinol concentrations were positively correlated with the cord retinol concentrations, the dimensions of kidney, and the renal volume of their respective newborns. Maternal vitamin A deficiency during pregnancy may decrease renal size in the infant at birth. Preterm infants have a reduced retinal sensitivity compared with term infants. Mactier et al. (27) administered intramuscularly a vitamin A dose of 10,000 IU 3 times weekly from day 2 for a minimum of 2 weeks. Retinal sensitivity was greater in supplemented infants than in controls ($P<0.03$). Early high-dose vitamin A supplementation for infants at risk of retinopathy of prematurity improves retinal function at 36 weeks' postmenstrual age.

Vitamin A increases the body weight of term infants. A statistically significant ($P=0.001$) correlation was observed between vitamin A concentration in cord blood and birth weight, length, chest circumference, mid-upper arm circumference, triceps skinfold thickness and head circumference of neonates (5). Tolba et al. (6) observed a trend of increasing birth weight with increasing cord plasma vitamin A.

Miller et al. (28) observed that doses of 10,000 IU vitamin A (retinyl esters and retinol) per day are safe and do not cause teratogenicity. Doses $>10,000$ IU vitamin-A per day, as supplements, have been reported to cause malformations. Using a smoothed regression curve, Rothman et al.

(29) found an apparent threshold near 10,000 IU per day of supplemental vitamin A. The increased frequency of defects was concentrated among neonates born to mothers who consumed high levels of vitamin A before the seventh week of pregnancy. Czeizel and Rockenbauer (30) stated that doses of vitamin A (<10,000 IU) during the first trimester of pregnancy is not teratogenic but presents some protective effects to the fetus. Mills et al. (31) observed no association between periconceptional vitamin A exposure at doses >8,000 or >10,000 IU per day and malformations in general. If vitamin A is a teratogen, the minimum teratogenic dose appears to be well above the level consumed by most women during organogenesis. In conclusion, vitamin A consists of four fat-soluble compounds namely retinol (the alcohol form), retinyl esters, retinaldehyde and retinol acid. Vitamin A is used to combat bronchopulmonary dysplasia and mortality in infants. Preterm infants have lower vitamin A status than term infants at birth and this has been associated with increased risk of developing chronic lung disease. Supplementation of vitamin A to mothers and infants reduces the risk of infant mortality. Vitamin A concentration correlates in cord and maternal sera. Retinoic acid regulates the nephron mass during nephrogenesis. Vitamin A deficiency reduces the dimensions of neonatal kidneys. Supplementation of 10,000 IU vitamin A increases the retinal sensitivity in preterm infants. Vitamin A cord concentration correlates with the neonatal body size. Doses of vitamin A \leq 10,000 IU are not teratogenic. Although there are several studies on the effects of vitamin A in neonates and young infants, more studies are needed to administer vitamin A for an evidence-based treatment of neonates and infants with this vitamin.

5-CONCLUSION

Vitamin A deficiency remains a public health problem among women, affecting an estimated 19 million pregnant women (33), with the highest burden found in the WHO regions of Africa and South-East Asia. During pregnancy, vitamin A is essential for the health of the mother as well as for the health and development of the fetus. This is because vitamin A is important for cell division, fetal organ and skeletal growth, maintenance of the immune system to strengthen defences against infection, and development of vision in the fetus as well as maintenance of maternal eye health and night vision (34, 35). During pregnancy, serum retinol levels decline, particularly in the third trimester; this may be due to the physiological increment in blood volume or due to an acute phase response, and it can be exacerbated by an inadequate vitamin A intake (36, 37). Night blindness, an early sign of vitamin A deficiency, is associated with infectious diseases (37, 38). In countries where vitamin A deficiency is a public health problem, WHO recommends periodic administration of high-dose vitamin A supplements to children 6–59 months of age to reduce mortality (39). Although vitamin A supplements are not recommended as part of routine antenatal care for the prevention of maternal and infant morbidity and mortality, they are recommended in pregnant women for the prevention of night blindness in areas where there is a severe public health problem of vitamin A deficiency (40).

6-CONFLICT OF INTERESTS

Prof. Gian Maria Pacifici declares no conflicts of financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employments, gifts and honoraria.

7-ACKNOWLEDGMENTS

The author thanks Dr. Patrizia Ciucci and Dr. Francesco Varricchio of the Medical Library of the University of Pisa for retrieving the scientific literature.

8-REFERENCES

1. Neonatal Formulary. Sixth edition. John Wiley & Sons, Limited European Distribution Centre New Era Estate, Oldlands Way Bognor Regis. West Sussex, PO22 9NQ, UK. 2011. p.531-2.
2. Darlow BA, Graham PJ. Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birthweight infants. *Cochrane Database Syst Rev* 2007; (4):CD000501.
3. Chytil F. Vitamin A and lung development. *Pediatr Pulmonol* 1985;1(3 Suppl):S115-17.
4. Young TE, Mangum B. Neofax, Vitamins & minerals. In: a manual of drugs used in neonatal care. Edition 23rd. Montvale: Thomson Reuters; 2010. P. 339.
5. Rondó PH, Abbott R, Tomkins AM. Vitamin A and neonatal anthropometry. *J Trop Pediatr* 2001;47(5):307-10.
6. Tolba AM, Hewedy FM, al-Senaidy AM, al-Othman AA. Neonates' vitamin A status in relation to birth weight, gestational age, and sex. *J Trop Pediatr* 1998; 44(3):174-77.
7. Rotondi MA, Khobzi N. Vitamin A supplementation and neonatal mortality in the developing world: a meta-regression of cluster-randomized trials. *Bull World Health Organ* 2010; 88(9):697-702.
8. Henderer JD and Rapuano CJ. Ocular Pharmacology. In L. Brunton, B. Chanber and B. Knollman eds. *Goodman & Gilman's, The Pharmacological Basis of Therapeutics*. 12th Edition. New York: Mc Graw Hill; 2011. P. 1798.
9. Martins TM, Ferraz IS, Daneluzzi JC, Martinelli CE Jr, Del Ciampo LA, Ricco RG, et al. Impact of maternal vitamin A supplementation on the mother-infant pair in Brazil. *Eur J Clin Nutr* 2010;64(11):1302-7.
10. Agarwal K, Dabke AT, Phuljhele NL, Khandwal OP. Factors affecting serum vitamin A levels in matched maternal-cord pairs. *Indian J Pediatr* 2008;75(5):443-46.
11. Ambalavanan N, Wu TJ, Tyson JE, Kennedy KA, Roane C, Carlo WA. A comparison of three vitamin A dosing regimens in extremely-low-birth-weight infants. *J Pediatr* 2003;142(6):656-61.
12. Fernandes TF, Figueiroa JN, Grande de Arruda IK, Diniz Ada S. Effect on infant illness of maternal supplementation with 400 000 IU vs 200 000 IU of vitamin A. *Pediatrics* 2012;129(4):e960-66.
13. Semba RD, Miotti PG, Chiphangwi JD, Dallabetta G, Yang LP, Saah A, et al. Maternal vitamin A deficiency and infant mortality in Malawi. *J Trop Pediatr* 1998;44(4):232-34.
14. Klemm RD, Labrique AB, Christian P, Rashid M, Shamim AA, Katz J, et al. Newborn vitamin A supplementation reduced infant mortality in rural Bangladesh. *Pediatrics* 2008;122(1):e242-50.
15. Meyer S, Gortner L. NeoVitaA Trial Investigators. Early postnatal additional high-dose oral vitamin A supplementation versus placebo for 28 days for preventing bronchopulmonary dysplasia or death in extremely low birth weight infants. *Neonatology* 2014; 105(3):182-88.
16. Babu TA, Sharmila V. Vitamin A supplementation in late pregnancy can decrease the incidence of bronchopulmonary dysplasia in newborns. *J Matern Fetal Neonatal Med* 2010; 23(12):1468-69.
17. Guimarães H, Guedes MB, Rocha G, Tomé T, Albino-Teixeira A. Vitamin A in prevention of bronchopulmonary dysplasia. *Curr Pharm Des* 2012; 18(21):3101-13.
18. Chan V, Greenough A, Cheeseman P, Gamsu HR. Vitamin A levels at birth of high risk preterm infants. *J Perinat Med* 1993; 21(2):147-51.
19. Shenai JP, Kennedy KA, Chytil F, Stahlman MT. Clinical trial of vitamin A supplementation in infants susceptible to bronchopulmonary dysplasia. *J Pediatr* 1987;111(2):269-77.
20. Luo ZX, Liu EM, Luo J, Li FR, Li SB, Zeng FQ, et al. Vitamin A deficiency and wheezing. *World J Pediatr* 2010; 6(1):81-4.
21. Tyson JE, Wright LL, Oh W, Kennedy KA, Mele L, Ehrenkranz RA, et al. Vitamin A supplementation for extremely-low-birth-weight infants. National Institute of Child Health and Human Development Neonatal Research Network. *N Engl J Med* 1999;340(25):1962-68.
22. Ambalavanan N, Tyson JE, Kennedy KA, Hansen NI, Vohr BR, Wright LL, et al.

- National Institute of Child Health and Human Development Neonatal Research Network. Vitamin A supplementation for extremely low birth weight infants: outcome at 18 to 22 months. *Pediatrics* 2005; 115(3):e249-54.
23. Kaplan HC, Tabangin ME, McClendon D, Meinzen-Derr J, Margolis PA, Donovan EF. Understanding variation in vitamin A supplementation among NICUs. *Pediatrics* 2010; 126(2):e367-73.
24. Bhat PV, Manolescu DC. Role of vitamin A in determining nephron mass and possible relationship to hypertension. *J Nutr* 2008;138(8):1407-10.
25. El-Khashab EK, Hamdy AM, Maher KM, Fouad MA, Abbas GZ. Effect of maternal vitamin A deficiency during pregnancy on neonatal kidney size. *J Perinat Med* 2013;41(2):199-203.
26. Goodyer P, Kurpad A, Rekha S, Muthayya S, Dwarkanath P, Iyengar A, et al. Effects of maternal vitamin A status on kidney development: a pilot study. *Pediatr Nephrol* 2007;22(2):209-14.
27. Mactier H, McCulloch DL, Hamilton R, Galloway P, Bradnam MS, Young D, et al. Vitamin A supplementation improves retinal function in infants at risk of retinopathy of prematurity. *J Pediatr* 2012;160(6):954-59.
28. Miller RK, Hendrickx AG, Mills JL, Hummler H, Wiegand UW. Periconceptional vitamin A use: how much is teratogenic? *Reprod Toxicol* 1998; 12(1):75-88.
29. Rothman KJ, Moore LL, Singer MR, Nguyen US, Mannino S, Milunsky A. Teratogenicity of high vitamin A intake. *N Engl J Med* 1995;333(21):1369-73.
30. Czeizel AE, Rockenbauer M. Prevention of congenital abnormalities by vitamin A. *Int J Vitam Nutr Res* 1998; 68(4):219-31.
31. Mills JL, Simpson JL, Cunningham GC, Conley MR, Rhoads GG. Vitamin A and birth defects. *Am J Obstet Gynecol* 1997; 177(1):31-6.
32. Johansen AM, Lie RT, Wilcox AJ, Andersen LF, Drevon CA. Maternal dietary intake of vitamin A and risk of orofacial clefts: a population-based case-control study in Norway. *Am J Epidemiol* 2008; 167(10):1164-70.
33. Global prevalence of vitamin A deficiency in populations at risk 1995–2005. WHO Global Database on Vitamin A Deficiency. Geneva: World Health Organization; 2009. Available at: http://whqlibdoc.who.int/publications/2009/9789241598019_eng.pdf. Accessed Dec 2015.
34. Downie D, Antipatis C, Delday MI, Maltin CA, Sneddon AA. Moderate maternal vitamin A deficiency alters myogenic regulatory protein expression and perinatal organ growth in the rat. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology* 2005; 288:73–9.
35. Food and Nutrition Board, Institute of Medicine. Vitamin A. In: Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. Washington, DC: National Academy Press; 2001:82–146.
36. Indicators for assessing vitamin A deficiency and their application in monitoring and evaluation intervention programmes. Geneva: World Health Organization; 1996. Available at: http://www.who.int/nutrition/publications/micronutrients/vitamin_a_deficiency/WHONUT96_10.pdf. Accessed, Dec 2015.
37. Dibley MJ, Jeacocke DA. Vitamin A in pregnancy: impact on maternal and neonatal health. *Food and Nutrition Bulletin* 2001; 22: 267–84.
38. Coutosoudis A. The relationship between vitamin A deficiency and HIV infection: review of scientific studies. *Food and Nutrition Bulletin* 2001; 22:235–47.
39. Guideline: vitamin A supplementation in infants and children 6–59 months of age. Geneva, World Health Organization. Available at: http://whqlibdoc.who.int/publications/2011/9789241501767_eng.pdf. Accessed, Dec 2015.
40. Guideline: vitamin A supplementation in pregnant women. Geneva: World Health Organization; 2011. Available at: http://whqlibdoc.who.int/publications/2011/9789241501781_eng.pdf. Accessed, Dec 2015.