Personal Practice

Vitamin K During Infancy: Current Status and Recommendations

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Vitamin K is usually the first vitamin given at birth. Dietary deficiency of vitamin K in healthy subjects is rare because it is indigenously produced in the gut by bacterial flora. In clinical practice, deficiency of micro-nutrients usually occur in various combinations but vitamin K deficiency though rare, often occurs in an isolated form. Vitamin K is essential for synthesis of coagulation factors II (prothrombin), VII, IX and X by a process of carboxylation of glutamic acid in vitamin K-dependent proteins which results in creation of effective calcium binding sites which helps in the process of coagulation. Vitamin K exists in three forms: naturally occuring vitamin K-I (Phylloquinone) which is provided through dietary sources like green leafy vegetables (50-800 (ig/100 g) and vegetable oils; vitamin K-II (menaquinone) which is indigenously produced in the gut by bacteroides fragilis and E. *coli* and synthetic vitamin K-III (menadoine sodium bisulfite) which is water soluble and has the potential risk of producing serious jaundice in newborn babies especially those with instability of glutathione and deficiency of G6 PD. Vitamin K is absorbed through the jejunum and ileum with the help of bile and pancreatic juice. In newborn babies, around 30% of ingested vitamin K is absorbed as compared to 50 to 70% in adults. It is believed that plasma half life of vitamin K is less than 72 hours but it may be stored in the healthy liver for upto one month. The half life of prothrombin is only for few hours. Daily requirement of vitamin K is around 5 µg/d and an intake of around 10 µg/d is sufficient to provide for daily needs. Blood PIVKA II (protein induced in vitamin K absence) is an excellent marker of vitamin K deficiency. Hemorrhagic disease of the newborn, which is a manifestation of vitamin K deficiency in a newborn baby, is conventionally suspected by prolonged partial thromboplastin time and prothrombin time. These laboratory abnormalities are also seen in patients with disseminated intravascular coagulation (DIC) but in DIC, factor V, fibrinogen and platelets are also low and there are circulating fibrin degradation products in the blood.

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Hemorrhagic Disease of the Newborn

The term hemorrhagic disease of the newborn (HDN) was first used in 1894 when Townsend(l) reported 50 infants with bleeding manifestations during the first 2 weeks of life. Hemorrhagic disease of the newborn is the commonest manifestation of vitamin K deficiency in infancy. On the basis of age of onset, there are three types of hemorrhagic disease of the newborn:

(a)Early HDN

Onset is usually during first 24 hours of life. Fetal hemorrhage and early HDN is limited to offsprings of mothers receiving anticonvulsants, antituberculous agents, coumarin derivatives, salicylates, *etc.* during pregnancy.

(b) Classical HDN

It has onset between 1-7 days of life and is usually limited to exclusively breastfed infants. The common clinical manifestations include bleeding from umbilical stump and gastrointestinal tract. Its reported incidence in the literature varies between 0.25-0.5% while our own observations and data by Jelliffe(2) suggests that it's incidence is around 0.1% in breastfed babies.

(c) Late HDN

It has onset between 1-16 weeks of life. It is rare in top fed infants and in infants who had received injectable vitamin K at birth. Its incidence is reported to be around one in 14,000 infants when no vitamin K prophylaxis is used at birth. In a nation wide survey conducted in Germany by Dusseldorf, it has been documented that when vitamin K is administered parenterally at birth, incidence of late HDN drops to 1:4,20,00 population(3). Intracranial bleeding is seen in over 50% cases of late-onset HDN which carries a relatively high mortality and high incidence of neuromotor sequelae among the survivors. Most cases of late HDN are idiopathic. It may occur following prolonged use of broad spectrum antibiotic therapy, chronic diarrhea and malabsorption. Cholestatic hepatitis due to diverse etiology may be associated with late onset HDN due to malabsorption of vitamin K from the gut. It has been postulated that immaturity of carboxylase system in the liver and increased vitamin K requirements due to ineffective vitamin K-I epoxide reductase system may be responsible for some cases(4,5).

Should Healthy Breastfed Neonates be Given Vitamin K Supplementation at Birth?

Transplacental passage of vitamin K is minimal with maternal to cord blood vitamin K ratio of 30:1. Hepatic content of vitamin K in a neonate is 25% of an adult. It is believed that precarious coagulation status of a newborn baby may be further jeopardized by breastfeeding because vitamin K content of human milk (15 Mg/1) is one-fourth of cow's milk. Moreover, exclusively breastfed babies are often starved during first three days of life due to insufficiency of lactation. On the basis of these observations, The American academy of Pediatrics recommended in 1961 that all healthy term newborn babies should receive 0.5-1.0 mg vitamin K-I intramuscularly at birth(6). However, these recommendations are not uniformly accepted and adopted because many workers do not routinely give prophylactic vitamin K at birth to healthy term babies.

We have not followed the recommendations of American Academy of Pediatrics in our Neonatal Unit for the past 15 years(7). There are numerous biological advantages of human milk and despite the available scientific evidence pertaining to HDN, it is difficult to comprehend that healthy term babies fed on breastmilk are predisposed to develop classical HDN. It is against the basic principles of nature and commonsense that a readymade food produced by nature is deficient in an important nutrient and is unable to serve the nutritional needs of a healthy baby(8). The incidence of classical HDN is merely 0.1% in our neonatal unit. It is well known that colostrum has higher content of vitamin K and it is

possible that vitamin K in the human milk has enhanced bioavailability and absorption. Due to the common practice of giving prelacteal and prolacteal feeds, despite specific instructions against their use, it is possible that there is early colonization of gut in our babies resulting in reduced incidence of classical HDN. Moreover, oral preparation of vitamin K is not available in India and one would have to give 1000 injections of vitamin K to prevent one case of classical HDN which can be easily diagnosed and promptly managed by therapeutic administration of vitamin K. There are logistic difficulties, inherent risks of intramuscular injections (sepsis, hepatitis B virus and HIV infections) and above all danger of inadvertent administration of high dose of vitamin K-III (menadione sodium bisulphite available as 10 mg/ml in Indian market) which can lead to severe hemolysis, jaundice and even kernicterus. In view of relatively high incidence of G6 PD deficiency in India, administration of synthetic vitamin K to all newborn babies may have a potential risk for occurrence of hemolytic jaundice. In view of the fact that plasma half life of vitamin K is only 72 hours and its storage in a healthy liver is limited upto one month, it is difficult to comprehend that parenteral administration of one dose of vitamin K can prevent late-onset HDN which may occur as late as 16 weeks (even upto one year by some workers!). There is some controversial evidence that administration of vitamin K through intramuscular route may enhance the risk of cancer during childhood(9). Two recent case control studies have refuted the increased risk of cancer in association with intramuscular administration of vitamin K(10,11).

Despite its controversial status, the American Academy of Pediatrics recommends that 1.0 mg vitamin K should be administered intramuscularly at birth to all healthy term babies. Most workers, however, recommend administration of 1.0-2.0 mg vitamin K-I (phylloquinone) orally at birth. Water soluble vitamin K is easily absorbed through the gut while fat soluble vitamin K requires bile salts for its absorption. Vitamin K_3 (menadione sodium bisulfite) is readily absorbed in the gut and is effective in correcting vitamin K deficiency(12,13). Some workers consider this routine prophylactic administration of vitamin K to healthy term babies as unnecessary.

Vitamin K in High Risk Newborn Babies

We are following a selective policy of giving prophylactic vitamin K 0.5-1.0 mg IM to high risk newborn babies *(Table I)*.

It is recommended that infants receiving total parenteral nutrition should be given biweekly parenteral supplementation of vitamin K and those receiving broad spectrum antibiotics should receive exogenous vitamin K once a week because of sterilization of the gut. In view of the fact that vitamin K is stored in the liver upto one month, it would appear logical and desirable to administer supplemental vitamin K parenterally once a month till the high risk situation resolves.

Vitamin K in Infancy

Infants with prolonged diarrhea (more

TABLE I- *Indications for Giving Vitamin K to High Risk Newborn Babies*

1. High risk newborn babies: Preterm, <2.0 kg, traumatic delivery, birth asphyxia, grossly SFD/LFD babies
2. Maternal intake of coumarin derivatives (warfarin), anticonvulsants, salicylates and antituberculous drugs during pregnancy
3. Surgical neonate
4. Broad spectrum antibiotics
5. Total parenteral nutrition

than 2 weeks), malabsorption syndrome, cholestatic hepatits and those receiving prolonged broad spectrum antibiotics should be given 1.0 mg vitamin K intramuscular once every month or 50-100 µg daily. Breastfed infants of mothers receiving drugs which are known to cause vitamin K dependent coagulation disorder, should also be administered monthly supplements of vitamin K(14).

In the light of available information in the literature, the current recommendations for prophylactic use of vitamin K to prevent HDN are summarized in *Table II.*

Epilogue

In view of the current controversies and lack of unanimity in the prophylactic use of vitamin K in early life, it is desirable to undertake additional prospective studies to resolve some of the issues. Studies should be undertaken to assess PIVKA-II levels during first week of life and at the age of 16 weeks in breastfed infants with or without vitamin K supplementation at birth (oral and parenteral). There is a need to study the efficacy, safety and optimal dosage of orally administered synthetic vitamin K-III which is the only vitamin available in the Indian market. Colonization of the gut should be studied among exclusively breastfed babies during first week of life. In order to reduce the incidence of late-onset HDN, which is a potentially fatal and disabling disorder, it is desirable to study whether oral supplementation of vitamin K to the mother during lactation can enhance vitamin K content of the breastmilk and prevent occurrence of late HDN. It is hoped that ongoing research will provide answers to the clinically relevant crucial questions that needs to be answered to ensure rational use of vitamin K during infancy and childhood. In view of the efficacy of oral vitamin K_3 in correcting PIVKA-II abnormalities(13), we have approached several pharmaceutical companies to market vitamin K_3 in an oral drops formulation in 10 ml dropper vials in a concentration of 10 mg/m *i.e.* 0.5 mg/drop. Administration of two drops at birth to healthy term babies should prevent classical HDN. Precise dosing of oral vitamin K for prevention of late-onset HDN also needs to be studied.

TABLE II-*Prophylaxis Regimens for Administration of Vitamin K*

1. Early HDN	:	Vitamin K 20 mg daily to the high risk pregnant woman with potential risk of fetal hemorrhage (those receiving anticonvulsants, antituberculous agents, coumarin derivatives, salicylates) for 2 weeks before delivery. Vitamin K 1.0-2.0 mg IV to the baby at birth.
2. Classical HDN	:	Vitamin K 0.5-1.0 mg IM at birth (high risk group) Vitamin K 1.0-2.0 mg oral at birth (healthy term babies).
3. Late HDN	:	Vitamin K 1.0 mg IM at birth. Vitamin K 1.0 mg IM once every month or 50-100 µg daily supplements in high risk infants.

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