

# Vitamin K Deficiency in Infants

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## History

Vitamin K (VK) is an essential fat-soluble vitamin or micronutrient.

1895 Charles Townsend (Boston, USA) first described syndrome of "Hemorrhagic Disease of the Newborn (HDN)".

1929 VK was discovered by Henrick Dam, the Danish biochemist. K stands for "Koagulation".

1939 VK was synthesized for clinical use.

1974 Definite action of VK in carboxylation process was known.

1995 One hundred year celebration of Dam's birth: International Symposium on "Vitamin K in Infancy" in Basel, Switzerland by Sutor, Hathaway et al<sup>(1)</sup>.

## Physiology and Metabolism of VK

Types of natural VK:

1. K<sub>1</sub> Phyloquinone from plant, fat-soluble.
2. K<sub>2</sub> Menaquinone from GI flora, water-soluble.

K<sub>2</sub> has longer half-life in the liver storage than K<sub>1</sub>.

Adults receive VK half from diet and half from gastrointestinal (GI) flora. For newborn and infants the main source of VK comes from diet (milk) and small amounts from GI flora.

## Metabolism.

Vitamin K is an essential fat-soluble vitamin that is required for the post-translational gamma carboxylation of the coagulation factors II, VII, IX, X and Proteins C and S. These proteins contain the unique amino acid, gamma carboxyl glutamic acid, which is necessary for calcium binding and essential for their function. The process occurs in the liver cells. The enzymes necessary for the vitamin K epoxide cycle are vitamin K epoxide reductase and vitamin K quinone reductase. Undercarboxylated vitamin K dependent proteins which are produced and released in the absence of VK are named protein induced by VK absence or PIVKA II.

## Vitamin K dependent proteins:

1. Clotting factors II, VII, IX, X or prothrombin complex (PC).
2. Protein C inhibits VIIa, Va and increases fibrinolysis.
3. Protein S, cofactor of protein C.
4. Osteocalcin for calcium metabolism: increases calcium deposition in bone, tissue and increases renal tubular reabsorption and etc.

## Physiologic deficiency of prothrombin complex in newborn babies.

Newborn babies received VK in small amounts from the

mother at birth. PC levels will decrease at 1-2 weeks of age and becomes normal at 6 week to 6 month of age.

Etiology of physiologic PC deficiency in infants:

1. Low vitamin K level in the newborn babies.
  - 1.1 low plasma K<sub>1</sub> level and K<sub>1</sub> has short half-life during storage in the liver.
  - 1.2 low K<sub>1</sub> concentration in the liver tissue.
  - 1.3 low K intake from breast milk (low VK content in breast milk).
  - 1.4 low VK producing bacteria from GI tract.
2. Prematurity of liver function which decreases production of prothrombin Ag.
3. Low liver enzyme K epoxide reductase for vitamin K metabolism.
4. Placental barrier to the transport of VK from mother to neonate. VK administered to mother does not effect the level of coagulation factors in cord blood<sup>(2)</sup>.

## Laboratory test for VKP deficiency:

1. Blood coagulation test:

- Prothrombin time (Quick's method) is the most useful and practical test.
- Thrombotest.
- Assay for VK dependent coagulation factors II, VII, IX, X.

2. Direct test using 2 markers: descarboxy prothrombin, descarboxy osteocalcin. Noncarboxylated prothrombin or descarboxy prothrombin (PIVKA II) by

- latex agglutination.
- EIA electroimmunoassay.
- CIE closed immune electrophoresis.
- RIA radioimmunoassay.
- ELISA enzyme-linked immunosorbant assay.

3. Vitamin K assay: high performance liquid chromatography fluorometric detection.

## Vitamin K Deficiency Bleeding (VKDB) in infants.

Definition of VKDB<sup>(1)</sup>. Hemorrhage in infants due to VK deficiency shown by low activity of VK dependent coagulation factors (II, VII, IX, X), normal activity of VK independent coagulation factors (I, V, VIII, XI, XII, XIII) and the presence of PIVKA II. Administration of VK is followed by shortening of the prothrombin time after 30-60 minutes and corrects the coagulation abnormalities.

## Classification of VKDB in infants.

VKDB can be classified by etiology and by the age at onset into four groups (see Table 1):

1. Early HDN.
2. Classic HDN.

3. Late HDN or Acquired PC deficiency (APCD) in infants.  
 4. Secondary PC deficiency.  
 A series of patients seen in Thailand including classic HDN, late HDN and secondary VKDB of the authors' report is shown in **Table 2**.

**1. Early HDN.**

Etiology. Baby born of mother who has been on certain drugs:

- anticonvulsant: barbiturate, phenytoin.
- antituberculous drug: rifampin, isoniazide.
- antibiotics.
- VK antagonist anticoagulant.

Clinical manifestation: Bleeding usually occurs within 2 days and not more than 5 days of life.

Organs of bleeding are reported to be gastrointestinal, liver, intracranial, etc.

Mortality is rather high. Deblay et al<sup>(3)</sup> reported 8 out of 111 neonates born to epileptic women treated with anticonvulsants develop early HDN (7%) and three cases died (37% mortality).

Management. VK parenterally can correct coagulation defect and stop bleeding.

Prevention. The mechanism of production of VK deficiency is not known but it can be prevented by administra-

tion of VK to the mother antepartum for 2 weeks. VK given to the infant immediately after delivery may be too late.

**2. Classic HDN.**

Occurs during 2 to 7 day of life when the prothrombin complex is low.

Etiology. VK deficiency from low intake and low storage at birth. It was found in babies who do not received VKP or VK supplemented.

The incidence is thought to be 0.4-1.7/100 birth in babies not receiving VKP at birth<sup>(4)</sup>.

Clinical manifestation. Among 75 cases of the author's series, bleeding was found in GI tract in 70%, skin in 27%, intracranial in 19% and the mortality rate was 1-2%<sup>(5)</sup>.

Management. VK and plasma infusion.

Prevention. VKP at birth intramuscularly or by oral route can prevent classic HDN.

**3. VKDB from secondary causes.**

Etiology. Definite etiology inducing VKP is found in association with bleeding:

- 1) Malabsorption of VK ie gut resection.
- 2) Biliary atresia.
- 3) Severe liver disease-induced intrahepatic biliary obstruction, cholestatic disease. etc.

Table 1: Vitamin K deficiency bleeding in infancy<sup>(1)</sup>

	Early HDN	Classic HDN	Late HDN or APCD	Secondary PC deficiency
Age	within 1-2 days of birth	days 2-7 (mostly days 3-5)	2 wk.- 6 mo. (mostly wk. 2-8)	any age
Causes and risk factors	- maternal medication during pregnancy - rarely idiopathic	- late onset of feeding - inadequate VK intake - marginal VK content in breast milk - no VKP at birth	- inadequate VK intake - marginal VK content in breast milk - no VKP at birth	- biliary obstruction - hepatic disease - malabsorption, etc. - low intake, i.e. parenteral nutrition
Incidence per 100,000 births	very rare	80 in Thailand	- 20-80 in Asia - 4-7 in Europe	
Prophylaxis	VKP antepartum to mother	- VKP oral or IM - adequate VK supply	- VKP IM - adequate VK supply	

Table 2: Vitamin K deficiency bleeding in infants<sup>(5)</sup>

	Classic HDN 75 cases	Late HDN 691 cases	Secondary PC deficiency 31 cases
Age	1-7 days	2 wk – 6 mo	2 wk – 1 yr
Etiology	idiopathic	idiopathic	malabsorption, bile obstruction, etc.
Risk factors	no VKP at birth, low VK intake	no VKP at birth, low VK intake	known cause
Common bleeding site	GI, skin	intracranial 80%	intracranial 65%
Mortality (%)	1 – 2	25	26
Sequelae	rare	50	28

Clinical manifestations: The age onset of bleeding is varied from 2 weeks to over 1 year according to the primary disease. Intracranial bleeding was found in 65%, mortality rate was 26% and permanent neurological handicap 28% (see Table 2)<sup>(5,6)</sup>.

Management. Plasma and VK will correct coagulation defect. Removal of primary cause is the most important treatment. In chronic cases in which primary disease could not be treated i.e. permanent gut resection, total parental nutrition; long term VK administration is recommended.

Prognosis depends on the primary disease.

#### 4. Late HDN.

Synonyms.

- Acquired prothrombin complex deficiency (APCD) syndrome in infants is common in Southeast Asia. It was named by Bhanchet in 1966<sup>(7)</sup>.

- Idiopathic vitamin K deficiency in infants (IVKDI) is named in Japan<sup>(8-11)</sup>.

Definition. Late HDN is an acquired bleeding disorder in the 2 week to 6 month age infant caused by reduced vitamin K dependent clotting factor (II, VII, IX, X) with a high incidence of intracranial hemorrhage and responds to VK.

History. It was first reported in 23 Thai babies by

Bhanchet et al in 1966<sup>(7)</sup>. Cases were reported by Chan and Wong in Singapore<sup>(12)</sup> and Lovric in Australia in 1967<sup>(13)</sup> and both papers referred to Bhanchet's first report from Thailand<sup>(7)</sup>. Nammacher et al reported 4 cases in USA in 1970<sup>(14)</sup>. APCD or late HDN was described in detail in 93 reported cases by Bhanchet-Isarangkura in 1977 and 1975<sup>(15-16)</sup>. Since then attention has been drawn to this disease as one of major health problems in infants in Southeast Asian countries because of the high prevalence (30-80 per 100,000 births), high incidence of intracranial bleeding (80%), high mortality (25%) and permanent neurological handicap (50-65%)<sup>(17)</sup>.

In early 1980s it apparently became a major problem in Europe and Japan.<sup>(8-11,18)</sup> VKDB and VKP were described and discussed in detail in the "International Symposium of VK in Infancy" in Basel, Switzerland 1994 for the celebration on the "100<sup>th</sup> birthday of Henrik dam" who discovered VK<sup>(1)</sup>. Prevention of VKDB in infants was thoroughly reviewed by Zipursky in 1999<sup>(19)</sup>.

The incidence, risk factors, clinical manifestations and outcome are shown in **Table 3**<sup>(6,15,20)</sup>. The incidence of late HDN is most commonly found in 2 week to 2 month old infants (75%<sup>(15)</sup>). It may range between 2 weeks to 11 months for babies receiving late additional food which is the main source of VK. The disease occurs in male more than female at a ratio of about 2:1<sup>(6,15)</sup>. Almost all of them received breast feeding (90-95%) and did not receive VKP at birth (80-96%)<sup>(6,20)</sup>.

#### Pathogenesis of late HDN<sup>(9,21,22)</sup>.

Infants have very limited VK reserve at birth, depending largely on milk for their supply. The supply from intestinal bacteria is limited particularly in breast fed infants. Low VK content in breast milk from some mothers and no additional VKP are important causes of VK deficiency in late HDN.

The etiologic factors:

Table 3: Incidence and risk factors of late HDN<sup>(6,6)</sup>

	Thailand	Other Countries
No. of cases	691	922
Year	1953-1995	1967-1988
Incidence		
Age		
½ to 2 month	85%	75%
>2 to 6 month	15%	25%
Sex M:F	2.5:1	2:1
Risk factors:		
Infant feeding		
Breast	92	91
Breast + formula	8	9
VK prophylaxis		
Not receiving	80	96
Intramuscular	3	-
Oral	7	-
Undetermined	10	4
Clinical manifestation.		
Hemorrhage	100	100
Intracranial	82	91
Skin and muscle	24	24
Gastrointestinal tract	17	26
Anemia	74	90
Convulsion	64	
Outcome		
Mortality	24	17
Sequelae	50	50

Table 4: Plasma VK level in newborn and adult<sup>(23)</sup>.

	Plasma K <sub>1</sub> level	
	ng/mL	range
Normal adult	0.26	0.10-0.66
Pregnant woman at term	0.2	0.01-0.29
Cord blood	not detected (< 0.01)	

Table 5: Vitamin K<sub>1</sub> level in human and cow's milk<sup>(24)</sup>.

	Vitamin K <sub>1</sub> level	
	mg/L	range
Human colostrum	2.5	
Breast milk	2.3	< 5
Cow's milk	4.9	
Formula milk	33	50-60

1. Low vitamin K in plasma and liver storage at birth (see **Table 4**). K level of cord blood is below 0.01 ng/mL or undetectable while adult K level is 0.26 ng/mL<sup>(23)</sup>. Main source of VK in infant is K<sub>1</sub> from diet which has shorter half life than K<sub>2</sub> from GI flora<sup>(19)</sup>.

2. Low vitamin K intake in breast-fed infant (see Table 5). VK content in breast milk is below 5 mg/mL while formula milk has 50-60 mg/mL<sup>(24)</sup>. Breast milk of mothers with late HDN contains lower vitamin K<sub>1</sub> and K<sub>2</sub> level than that of the control mothers<sup>(25,26)</sup>.

3. In formula fed infants, the bowel contains *Bacteriodes fragillis* which can produce vitamin K<sub>2</sub> whereas in breast-fed babies, the bowel contains *Lactobacillus* which can not produce K<sub>2</sub>. The endogenous bowel production of VK in formula fed infants can correct the VK deficiency in the newborn<sup>(21)</sup>.

Risk factors:

1. Low intake from low K content in breast milk.
2. No VKP giving at birth for supplementation.

### Prevalence of late HDN and its health problem.

It should be noted that the incidence of late HDN in the eastern world is 25-80 per 100,000 births<sup>(6,8,27,28)</sup> which is higher than that in the western world (4-25 per 100,000 births<sup>(18)</sup>) as shown in **Table 6**.

The observation in England and Japan, summer temperature were associated with a doubling in incidence.

It should be noted that VKDB in infant in the first year of life manifested with a high incidence of intracranial hemorrhage (ICH), as observed in late HDN and secondary prothrombin complex deficiency (65%) as shown in Table 2. Late HDN has the highest incidence of ICH (80-90%) among any bleeding disorders. The reason could not be definitely explained. It is hypothesized that during the first year of life, the brain develops rapidly while the bony and supportive tissue structures cannot expand accordingly. ICH is found in subdural, subarachnoid and intracerebral space in 100, 80, 30 percent respectively<sup>(20)</sup> of cases.

Late HDN is one of the important health problems in infant morbidity, mortality and socio-economic problem of

the country. More attention should be drawn to physicians and health authorities to prevent this serious disease.

### Management of late HDN:

1. Vitamin K<sub>1</sub> 1-2 mg iv daily for 1-3 days.
2. FFP 10 mL/kg/dose in severe bleeding.
3. PRC transfusion in moderate to severe anemia.
4. Treat intracranial bleeding : anticonvulsant, dexamethasone iv, subdural tap daily-until no obtainable fluid, lumbar puncture when neurological symptoms improved.
5. Follow up neurological complications and early stimulation for neurological handicap.

### Prevention of classic and late HDN by vitamin K prophylaxis.

VKP to all newborn babies was started from 1961 in USA and from 1960-1970 in Europe. At the beginning, the intramuscular route was routinely practiced by giving 1 mg i.m. to all newborn babies.

For developing countries such as Thailand about 30 to 40 years ago (1960-1970), around half of the deliveries were carried out by traditional birth attendants or midwives. Parenteral injection could not be carried out by midwives. The first author asked a pharmaceutical company to provide VK pediatric drops (Konakion, Roche, Basel, Switzerland) and conducted research studies of VKP by the oral route, 2 mg single dose which can be practiced routinely. The high efficacy, low toxicity, low cost, the long expiration date, the simple way of storage and administration of VK pediatric drops made it practical for developing countries at that time<sup>(17)</sup>. VKP 2 mg oral route for normal newborn and 0.5-1 mg intramuscular route for unwell babies has been routinely practice in Thailand since 1988 and has been compulsorily practiced all over the country from 1994 until 1998. The incidence of late HDN decreased from 30-70 to 4-7 per 100,000<sup>(6)</sup> birth. Since 1999, VKP 1 mg intramuscularly is mandatory to all newborn babies while most deliveries are carried out in the hospitals. VKP i.m. route is given together with routine vaccination ie. Hepatitis B, BCG.

In the developed world, VKP has changed from time to

Table 6: Incidence of late HDN in different countries.

	Year of study	Country	VKP giving		Prevalence per 100,000 birth
			Yes	No	
1. Ungchusak K. <sup>(27)</sup>	1983	Thailand		✓	35
2. Khanjanathiti P. <sup>(28)</sup>	1977-78	Thailand		✓	80
3. Chuansumrit A and Isarangkura P.	1977-87	Thailand		✓	80
4. Nakayama K. <sup>(8)</sup>	1978-80	Japan	✓ (mostly)	-	4.2-7.8
5. Hanawa Y. <sup>(10)</sup>	1981-85	Japan	±	-	25
6. Hanawa Y. <sup>(11)</sup>	1985-88	Japan	✓	-	20
7. Von Kries R. <sup>(18)</sup>	1998	Europe		✓	6
8. Victora CG. <sup>(18)</sup>	1998	USA	✓	✓	4-10
					4.4-7.2

time. In 1992 Jean Golding<sup>(29)</sup> reported an unexpected association between childhood cancer and neonatal VKP intramuscularly but not by oral route. Intramuscular VKP doubled the incidence of leukemia in children under 10 years of age. Since then VKP by oral route has become more and more practiced in Europe in different dosages. The result shows that the VKP intramuscular route gives the most promising results in protecting late HDN<sup>(19)</sup> (as shown in **Table 7**). It should be noted that following several studies there was no evidence of an increased incidence of childhood cancer after the administration of VK i.m. at birth<sup>(19)</sup>.

**VKP by the intramuscular route:**

Advantages:

1. Produces higher and more sustained plasma VK levels than oral administration<sup>(30,31)</sup>.
2. Giving a “depot” effect with delay release of VK for week after injection<sup>(32)</sup>.
3. More reliability in term of intake and absorption.
4. Only single dose is required.

Disadvantages: It may induce bleeding, infection, injur vessels and nerves at the injection site rarely.

**VKP by oral route.**

Advantages :

1. Simple way of administration but it is costly and troublesome to give many doses repeatedly.
2. No bleeding, infection, injured vessels and nerves at the injection site.
3. Parental request.

Disadvantages:

1. Less reliable in term of intake.
2. Unpredictable absorption.
3. Unnoticed regurgitation.
4. Danger of lipid aspiration.
5. Requires skilled person for drug administration

**Vitamin K mixed micelles (KMM)** is a new form of K<sub>1</sub>. It has been used for intramuscular and oral route. The composition of K<sub>1</sub> and KMM is shown in **Table 8**. KMM

has no cremophor which may induce anaphylactic shock for intravenous injection. Glycocholic acid and lecithin are added in KMM to enhance absorption despite biliary obstruction.

It is now clear that the administration of VK 1 mg i.m. immediately after birth will prevent both classic and late HDN. Oral VKP given at birth and supplemented during the neonatal period for 1-5 month did not entirely prevent late HDN (see Table 7).

**Cost effectiveness of VKP in preventing late HDN.**

Most infants affected by late HDN are fully or exclusively breast-fed. However, breast feeding should be continuously and strongly promoted together with the promotion of giving VKP to all newborn babies at birth.

The expense of VKP 1 mg i.m. single dose would cost US\$ 0.5-1 per dose per newborn baby. The World Bank classifies intervention of disability-adjusted life years (DALY) below US\$ 100 is most effective<sup>(33)</sup>.

**Conclusion.**

It can be concluded that there is need for a single dose of VKP 1 mg intramuscularly at birth for all newborn babies in order to eradicate classic and late HDN and there is no evidence that this therapy is harmful. For developing countries, VKP must be given 1 mg i.m. as early as possible if it cannot be given at birth because of home delivery. VKP given within 2 weeks of delivery will prevent late HDN.

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Table 7: The prevalence of late HDN by VKP im VS oral route.

Type of VKP	Prevalence	
	Rate/ total births	per 100,000 births
Intramuscular:		
K <sub>1</sub> 1 mg at birth: single dose <sup>(19)</sup>	0:325,000	0
Oral route:		
K <sub>1</sub> 1 mg x 3 D0, W1, W4-6 <sup>(19)</sup>	32:1,200,000	2.7
K <sub>1</sub> 1 mg x 3 D0, D3, W3-4 <sup>(19)</sup>	8:325,000	2.5
KMM 2 mg D1, D4 <sup>(30)</sup>	4:83,000	4.8
K <sub>1</sub> 1 mg D0, 25 µg/day x 3 mo. <sup>(19)</sup>	5:439,000	1.1
K <sub>1</sub> 2 mg: single dose Thailand <sup>(6)</sup>	4-7:100,000	4-7
No VKP Thailand <sup>(27,28)</sup>	35-80:100,000	30-80

Table 8: Composition of Vitamin K<sub>1</sub> and K<sub>1</sub> mixed micelles.

Konaktion(K <sub>1</sub> ) *		K <sub>1</sub> Mixed Micelles*	
Phytomenadione	1 mg	Vitamin K	10 mg
Phenol crist	5 mg	Glycocholic acid	54.6 mg
Cremophor EL	10 mg	NaOH 1 N	123.2 µl
Propylene glycol	10 mg	Lecithin	75.6 mg
Aq. inject. ad	1 mg	HCl 1 N	10 µl
		NaOH 0.1 N, pH 6	
		Aq. inject. ad	1 mg

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