INTRODUCTION

Hemorrhagic disease of the newborn (HDN) is one of the most common causes of acquired haemostatic disorder in early infancy ***(Pooni et al., 2003).***

It is a form of bleeding that is caused by reduced activity of vitamin k dependant coagulation factors (II, VII, IX, X), has normal or even increased activity of vitamin K-independent coagulation factors and responds to vitamin K ***(Sutor, 2007).***

Newborns have only 20-50% of adult coagulation activity. Lack of vitamin bK administration at birth, exclusive breast feeding, chronic diarrhea and prolonged use of antibiotics make them more prone to vitamin K deficiency bleeding ***(Pooni et al., 2003).***

It is categorized as early, classical or late depending on the time of onset. Late HDN usually occurs between 2-12 weeks. Rare cases occur also after week 15; therefore the upper age limit should be 6 months and not 3 months ***(Sutor, 2007).***

The common manifestations of late HDN reported are evidence of intracranial hemorrhage, deep ecchymosis, bleeding from gastrointestinal tract and/or bleeding from mucus membrane, skin punctures or surgical incisions ***(Bor et al., 2000).***

Important issues to be considered in prevention of VKDB are administration of vitamin K prophylaxis to all

newborns, alertness about the symptoms of any disease that would predispose to bleedings (prolonged jaundice, growth retardation, and chronic diarrhea) and any warning bleeds (nose, umbilicus, and skin), and consideration of repeated vitamin K doses especially if a hepatic or intestinal disease is present ***(Cekinmez et al., 2008).***

A study done on Egyptian infants revealed higher prevalence of late onset vitamin K deficiency bleeding than the international rates, the serum level of vitamin K was thought to be responsible, with the two main risk factors being the misuse of antibiotics and diarrhea. ***(Elalfy et al., 2014).***

The role of antibiotics in the pathogenesis of vitamin K deficiency and the mechanism of production of hypoprothrombinemia is not fully understood. Discovering vitamin K deficiency in children hospitalized in a large tertiary care center shows that physicians lack the knowledge about this important and preventable cause of bleeding. Vitamin K deficiency contributing to morbidity and mortality of hospitalized patients is a preventable condition. Awareness and recognition are the only requirements precluding effective treatment and prevention. A significant incidence of hypoprothrom-binemia is present; although the incidence of actual bleeding is low. It is a factor to be considered in children on prolonged antibiotic therapy. Mechanisms causing vitamin K deficiency include a combined effect of a diet low in vitamin K and a loss of normal bowel flora by antibiotic therapy, which synthesize the vitamin ***(Firkin et al., 1989).***

AIM OF THE STUDY

We are a developing country where there are a lot of mistakes from healthcare givers regarding prescription of antibiotics in both dosage and duration with the subsequent events of this on the wellbeing of children, our research aiming to:

- Provide a proof that prolonged antibiotic usage is an important risk factor for VKDB
- Provide proof for importance of vitamin K supplementation for certain populations of children and with prescription of antibiotics for longer than 10 days

Chapter (1):

VITAMIN K DEFICIENCY BLEEDING

The term hemorrhagic disease of the newborn was used to describe bleeding disorders in neonates associated with a traumatic birth or hemophilia. The proper diagnostic term that has been adopted is currently vitamin K deficiency bleeding because vitamin K deficiency is not the sole cause of hemorrhagic disorders in preterm and term infants ***(Clarke and Shearer, 2007).***

Vitamin K Deficiency Bleeding (VKDB) in infancy is a potentially serious worldwide problem with a high risk of mortality or permanent disability, primarily due to the high incidence of intracranial haemorrhage (ICH) of the later onset syndrome ***(Elalfy et al., 2014).***

Newborn infants are at risk of developing vitamin K deficiency, and this coagulation abnormality leads to serious bleeding. Transplacental transfer of vitamin K is very limited during pregnancy, and the storage of vitamin K in neonatal liver is also limited. This makes the newborn infant uniquely vulnerable to hemorrhagic disorders unless exogenous vitamin K is given for prevention of bleeding immediately after birth ***(Pichler and Pichler, 2008).***

It is a disease of breastfeeding infants and can be prevented by administration of vitamin K to newborns shortly after birth ***(Martin-Lopez et al., 2011).***

Vitamin K deficiency bleeding

Coagulation factors do not cross the placental barrier but are synthesized independently by the conceptus. At birth, activities of the vitamin K dependent factors II, VII, IX, and X and the concentrations of the contact factors XI and XII are reduced to about 50% of normal adult values. The levels of the factors V, VIII, XIII, and fibrinogen are similar to adult values ***(Girolami et al., 2012).***

Plasma concentrations of the naturally occurring anticoagulant proteins (antithrombin, protein C, and protein S) are significantly lower at birth than during the adult years. Plasminogen is reduced by approximately 50%. Platelet counts are within the normal range, regarding function, however, neonatal platelets seem to be hyporeactive. The von Willebrand factor contains large multimers and its concentration is increased ***(Yang et al., 2010).***

Historical background:

Before the identification of Vitamin K as an essential cofactor for the production of functional coagulation factors, Townsend, (1894) reported 50 cases of a generalized bleeding tendency in neonates in a condition that was named the

hemorrhagic disease of the newborn (HDN). He described that HDN differed from hemophilia in its earlier presentation, the lack of a family history and in its self-limiting course. Townsend, (1894) suggested a link between the mother's capacity to breast-feed and the hemostatic capacity of the newborn infant.

After the identification of the role of VK in blood coagulation, the disease was shown to be related to VK nutritional deficiency and was renamed as VK deficiency bleeding (VKDB) by the International Society on Thrombosis and Haemostasis (ISTH) Pediatric/ Perinatal Subcommittee in 1999 ***(Sutor et al., 1999).***

Although VK deficiency can occur in adults, it is common in newborns because of their limited VK storage, immature gastrointestinal absorption and due to the low placenta transfer of VK ***(Shearer, 2009).***

Classification:

VKDB is classified according to the age of presentation as early, classical and late. Early VKDB occurs in the first 24 h after birth, it is generally rare and often associated with maternal anticoagulant and or anticonvulsant usage during pregnancy. Classical occurs between days 2 to 7, and late VKDB days 8 to 6 months of life ***(Shearer, 2009).*** In classical VKDB, bleeding typically occurs from the gastrointestinal tract, umbilicus, skin,

nose or after circumcision while in late VKDB, bleeding predominantly occurs within the brain with prevalence rates of ICH as high as 60%–80% ***(Santorino et al., 2015).***

Table (1): Classification of vitamin K deficiency bleeding

	Early onset	**Classic disease**	**Late onset**
Incidence	Very rare	≈2% if not given vitamin K	Dependent on primary disease
Age	0–24 hours	2–7 days	1–6 months
Site of hemorrhage	Cephalohematoma	Gastrointestinal	Intracranial
	Subgaleal	Ear-nose-throat–mucosal	Gastrointestinal
	Intracranial	Intracranial	Cutaneous
	Gastrointestinal	Circumcision	Ear-nose-throat–mucosal
	Umbilicus	Cutaneous	Injection sites
	Intra-abdominal	Gastrointestinal	Thoracic
		Injection sites	
Etiology/risks	Maternal drugs (phenobarbital, phenytoin, warfarin, rifampin, isoniazid) that interfere with vitamin K	Vitamin K deficiency	Cholestasis malabsorption of vitamin K (biliary atresia, cystic fibrosis, hepatitis)
	Inherited coagulopathy	Breast-feeding	Abeta-lipoprotein deficiency
			Idiopathic in Asian breast-fed infants
			Warfarin ingestion
Prevention	Possible vitamin K at birth or to mother (20 mg) before birth	Parenteral vitamin K at birth. Oral vitamin K regimens require repeated dosing over time	Parenteral and high-dose oral vitamin K during periods of malabsorption or cholestasis
	Avoid high-risk medications		

(Fischer et al., 2010)

- ***Early-onset vitamin K deficiency***

Early-onset vitamin K deficiency bleeding usually occurs during first 24 hours after birth. It is seen in infants born to mothers taking anticonvulsant or antituberculosis medication. Serious hemorrhagic complications can occur in this type of hemorrhage ***(Darlow et al., 2011).***

Numerous maternal medications and/or exposure to toxins during pregnancy are associated with vitamin K deficiency bleeding in neonates (eg, anticonvulsants [eg, phenytoin, barbiturates, carbamazepine], antituberculous drugs [eg, rifampin, isoniazid], vitamin K antagonists [eg, warfarin, phenprocoumon]) ***(Pichler and Pichler, 2008).***

The mechanisms by which anticonvulsant and antituberculosis medications cause vitamin K deficiency bleeding in neonates is not clearly understood, but limited studies suggest that vitamin K deficiency bleeding is a result of vitamin K deficiency and can be prevented by administration of vitamin K to the mother during the last 2-4 weeks of pregnancy. Vitamin K supplementation given after the birth for early onset vitamin K deficiency bleeding may be too late to prevent this disease, especially if vitamin K supplementation was not provided during pregnancy ***(Steinho, 2008).***

- ***Classic vitamin K deficiency***

Classic vitamin K deficiency bleeding usually occurs after 24 hours and as late as the first week of life. However, it can occur during first month and sometimes overlaps with late-onset vitamin K deficiency bleeding. Classic vitamin K deficiency bleeding is observed in infants who have not received prophylactic vitamin K at birth ***(Clarke and Shearer, 2007)***.

The incidence of classic vitamin K deficiency bleeding ranges from 0.25-1.7 cases per 100 births**.** Bleeding commonly occurs in the umbilicus, GIT (ie, melena), skin, nose, surgical sites (ie, circumcision) and, uncommonly, in the brain ***(Scott and Montgomery, 2007).***

The efficacy of neonatal vitamin K prophylaxis (oral or parenteral) at birth in the prevention of classic VKDB is firmly established ***(Shearer, 2012).***

- ***Late-onset vitamin K deficiency***

Late vitamin K deficiency bleeding in young infants is a rare disorder which occurs almost exclusively in breast-fed infants who did not receive proper vitamin K prophylaxis at birth and who might additionally suffer from cholestasis. Its impact on morbidity is high since it presents with intracranial hemorrhage in 50% of the cases with a mortality rate of 20% and life-long neurologic sequelae in 30% of the affected infants ***(Ozdemir et al., 2012).***

Supplementation of vitamin K at birth has been recommended since 1961 and successfully reduced the risk of major bleeding. Refusal or omission of vitamin K prophylaxis is increasing and puts newborn infants at risk for life-threatening bleeding ***(Schulte et al., 2014).***

Siauw et al. (2015) reported 2 male infants that both admitted to their unit at the age of 5 weeks with subdural hematoma with midline shift due to late vitamin K deficiency bleeding. Both infants did not receive the recommended Vitamin K prophylaxis. One patient presented with cholestatic jaundice on admission as an additional risk factor. They found that parents refused the recommended and well established vitamin K prophylaxis at birth leading to the reappearance of late vitamin K deficiency bleeding. They concluded that: it is the responsibility of health-care takers to show increased awareness to the growing number of parents refusing vitamin K prophylaxis at birth and educate them properly about the devastating consequences of late vitamin K deficiency bleeding.

Apart from breast-feeding, there is a lot of evidence of an association of late VKDB and hepatobiliary dysfunction. The most common causes of neonatal cholestasis are biliary atresia, sepsis, idiopathic neonatal hepatitis, alpha-1 antitrypsin deficiency, and intrahepatic cholestasis syndromes. Infantile choledochal cyst (CC) usually presents as jaundice, vomiting, acholic stools, and hepatomegaly, and it can resemble biliary

atresia. Although bleeding tendency is a rare clinical presentation of CC, it may be the first symptom, especially in infants less than 12 months of age ***(Krstovski et al., 2010).***

- ***Hereditary combined vitamin K-dependent clotting factors deficiency***

Hereditary combined vitamin K-dependent clotting factors deficiency (VKCFD) is a rare inherited coagulation defect that forms part of a wider group of rare disorders named Familial Multiple Coagulation Factor Deficiencies (FMCFDs). FMCFDs are characterized by the simultaneous decrease in the levels of two or more coagulation factors. The first classification of FMCFDs was proposed by Soff and Levin in 1981. A new classification has been outlined and defined FMCFDs as the*presence of more than one coagulation factor deficiency arising from a genetic defect or defects and transmissible as a familial trait* ***(Robson and Mumford, 2009).***

The development of this new classification required both laboratory and genetic recognition of patients affected by concomitant independent defects as well as the identification of multiple defects related to one single gene mutation. Three subgroups of disorders are therefore included: i) FMCFDs arising from single coagulation factor deficiencies ii) FMCFDs arising from a single genetic defect iii) FMCFDs arising from cytogenetic abnormalities. Since VKCFD arises from a single genetic defect of either *γ-glutamyl carboxylase* (*GGCX*)

or *vitamin K 2,3-epoxide reductase complex* (*VKORC*) - two proteins of the vitamin K cycle - in the revised classification it obviously falls in the second subgroup ***(Napolitano et al., 2010).***

Epidemiology of late onset vitamin K deficiency bleeding

There is evidence that the incidence of VKDB reflects economic and nutritional status, social customs such as male circumcision, and probably genetic variations such as those known to influence the metabolism and intracellular recycling of VK ***(Plank et al., 2013).***

A high frequency of ICH due to late onset VKDB was reported in Egyptian infants aged two to twenty four weeks, with poorer outcomes than international studies ***(Elalfy et al., 2014).***

Epidemiological studies of the incidence of late VKDB have indicated that China, Japan, and countries within Southeast Asia such as Thailand and Vietnam have higher rates of VKDB than in the rest of the world. This is most accurately exemplified by comparing the incidence of VKDB between countries that have published data from nationally representative surveillance programs such as those carried out in the UK, The Netherlands, Germany, Switzerland, Australia, New Zealand, and Japan ***(Shearer, 2009).***

In other countries such as Thailand, China, and Vietnam, regional surveys have also yielded valuable incidence data of

VKDB. Care needs to be taken in comparing incidence data because of the different methodologies and case definitions. Where acceptable criteria for international comparisons have been met, the incidence of late VKDB in infants not given vitamin K prophylaxis has been shown to be ~5 cases/10^5 births in Western European countries compared to 11 and 72/10^5 births in Japan and Thailand, respectively ***(Shearer, 2009).***

Causes of neonatal deficiency of vitamin k:

Vitamin K-dependent coagulation factors are synthesised exclusively in the liver and so the maintenance of adequate hepatic vitamin K reserves is essential for normal haemostasis. Preterm as well as term babies are born with extremely low hepatic stores of vitamin K ***(Clarke, 2008).***

Unlike in adults, the major hepatic form of vitamin K in neonates is phylloquinone (vitamin K_1) which is also the major form of the vitamin in human breast milk. After birth, the combination of low hepatic reserves and relatively low concentrations of phylloquinone in breast milk (compared to formula milks) places the breast-fed infant at increased risk of developing vitamin K deficiency. They are consequently dependent upon adequate intakes of vitamin K postnatally and during early infancy to keep them healthy. Supplementary vitamin K prophylaxis is offered at birth to protect against vitamin K deficiency bleeding (VKDB), a now rare but still

potentially lethal disorder which may cause devastating brain injury and lifelong impairment in survivors **(*Shearer, 2009*).**

Preterm infants may be at higher risk of developing VKDB without adequate ongoing phylloquinone intakes following birth, so a baseline understanding of their current typical intakes from various sources during the neonatal period is clearly important ***(Clarke, 2010).***

In both term and preterm infants the very large bolus dose of phylloquinone given prophylactically at birth is considered to be the major source of phylloquinone in early infancy, and, therefore, to provide the mainstay of protection provided against VKDB during early infancy. Preterm neonates receive an on-going supply of phylloquinone from dietary sources, including from enteral and often parenteral feeding ***(Shearer et al., 2012).***

Transplacental transfer of vitamin K is very limited during pregnancy. Only 10% of maternally administered vitamin K is delivered to the fetus. Low levels of vitamin K have been noted in cord blood and in livers of aborted fetuses ***(Hubbard and Tobias, 2006).***

The gastrointestinal tract is sterile at birth, and its population with vitamin K-producing flora occurs after feedings are instituted ***(Lori et al., 2006).***

Management:

The diagnosis of VKDB can be made in infants younger than 6 months of age who present spontaneous bleeding, bruising, or intracranial hemorrhage (ICH) with a prolonged clotting time but with a normal or elevated platelet count ***(Jinghe et al., 2015).***

Since the VKDB patients who present with intracranial bleeding are exclusively breastfed, ***Greer (2010)*** investigated phylloquinone intakes in exclusively breast-fed infants in a North America and found that the average daily intake was one-tenth of that in healthy adults while formulated milk contained 50-fold higher concentration of phylloquinone than human milk.

- ***Symptoms and signs:***

1- Symptoms of intracranial haemorrhage:

ICH in this age group typically present with focal seizures; focal neurologic deficits are rarely present but may evolve over weeks to months. Almost 80% of ICH in children younger than 2 years present with seizures and hemiparesis; seizures can be focal or generalized; single, recurrent, or status epilepticus; responsive to acute treatment or refractory. Fever and altered consciousness are common at the onset of ICH ***(Mangunatmadja et al., 2003).***