VITAMIN-K STATUS BEYOND THE NEONATAL PERIOD, A PROSPECTIVE STUDY IN NORMAL BREAST-FED AND FORMULA-FED INFANTS

THESIS

SUBMITTED FOR PARTIAL FULFILMENT OF
M.S. DEGREE IN PEDIATRICS

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1993

ACKNOWLEDGEMENT

A word of thanks giving to ***ALLAH*** *, the source of all the knowledgement, by whom abundant aid this work has come to fruition.*

I would like to express my deep thanks to ***Prof. Dr. FOUAD EL-BADRAWAY,*** *Professor of Pediatrics, for his general supervision, continuous encouragement and general help.*

I'm deeply indebted to ***Prof. Dr. TARIF HAMZA SALAAM,*** *Professor of Clinical Pathology, for his creative guidance and unlimited help throughout this work.*

I'm also indebted to ***Prof. Dr. MOHAMED FARID,*** *Professor of Pediatrics, for all the help he offered me, for his wise direction and constructive suggestions.*

I'm grateful to ***Dr. GAMAL AHMED HELMY MOTTIER,*** *Lecturer of Pediatrics, for his moral help and wise advises that helped me too much in this work.*

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INTRODUCTION

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Hemorrhagic disease of the newborn is a self limited bleeding disorder resulting from a deficiency of the coagulation factors depending upon vitamin K namely factor II (prothrombin), VII, IX and X ***(Shapiro et al., 1986)***. The levels of these factors are about 50% of normal adult value in umbilical cord blood and decline rapidly to reach nadir at 48-72 hours of life ***(Sann et al., 1985)***. In 0.25-0.5% of infants the decline is so extreme that severe hemorrhage may result ***(McDonald et al., 1984)***. Thereafter, the levels of these factors slowly increase due to vitamin K absorption from the diet. Vitamin K is approximately four times more concentrated in cow milk than in breast milk ***(John and William, 1982)***. That is why breast feeding has been implicated as a necessary factor in the pathogenesis of hemorrhagic disease of the newborn infants unless vitamin K prophylaxis is given ***(Cornelissen et al., 1992)***. Deficiency of vitamin K-dependent clotting factors with

Introduction

clinical bleeding has occasionally been reported in the breast fed infants beyond the neonatal period ***(Hogenbirk et al., 1993)***.

AIM OF THE WORK

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The aim of this work is to determine whether the type of feeding, breast or formula fed, beyond the neonatal period is associated with changes in the level of vitamin K-dependent clotting factors.

REVIEW OF

LITERATURE

HISTORICAL REVIEW

The term hemorrhagic disease of the newborn was first used in *1894* when ***Townsend*** reported 50 infants with bleeding during the first two weeks of life. The hemorrhage usually began on the second or third day of life and most commonly was from gastrointestinal tract. The observation that this disorder was self-limiting led Townsend to differentiate acquired hemorrhagic disease from inherited hemophilia.

Vitamin K was not discovered until *1929* when ***Dam Seren*** observed bleeding in chickens fed a fat-free diet. Afterward, ***Brinkhous et al., (1937)*** documented low prothrombin levels in normal newborn infants. Others demonstrated that these low levels could be elevated by the administration of vitamin K ***(Waddell and Guerry, 1939)***. Hemorrhagic disease caused by vitamin K deficiency was subsequently differentiated from bleeding secondary to other causes; ***(Aballi and de Lamerens, 1962)***, and the effectiveness of vitamin K administration in the preven-

tion of vitamin K deficiency bleeding was established by ***Wefring in 1962.***

Banchet et al., (1966) and Goldman and Desposito (1966) described a "new" bleeding syndrome in infants from the age of two months up to one year.

Several publications have appeared presenting the syndrome under a variety of descriptive terms such as "hemorrhagic" diathesis in children associated with vitamin K-deficiency ***(Taj-Eldin et al., 1966),*** "hemorrhagic syndrome of early childhood" ***(Loveric and Jones., 1967),*** "Vitamin K-deficiency in infants beyond the neonatal period" ***(Nammacher et al., 1970).***

The syndrome has been well established as a vitamin K-deficiency and the administration of vitamin K has a dramatic effect with restoration to normal of vitamin K-dependent clotting factors ***(Lizuka et al., 1975).***

Most striking in the clinical picture is the prevalence of intracranial bleeding which occurs in about

60% of all cases. This is in sharp contrast to the bleeding syndrome of newborn which occurs on the 2nd to 5th day of life and is dominated by hematemesis or gastrointestinal bleedings (melena neonatorum). The reason for this different predilection of bleeding sites remains a mystery *(Chaou et al., 1984)*.

SOURCES OF VITAMIN K IN INFANTS

The human neonate is not endowed with a surplus of vitamin K, and some are vitamin K deficient at birth *(Shapiro et al., 1986)*. This precarious vitamin K status may be the result of a placental gradient for vitamin K. Using high-performance liquid chromatography, *Shearer et al., (1982)* found that vitamin K was undetectable in the cord blood of nine term infants despite levels of 0.13 to 0.29 ng/ml in their mothers. Six additional mothers received vitamin K intravenously prior to delivery, which raised their vitamin K concentration to between 45 and 93 ng/ml. The values found in the cord blood of their infants ranged from undetectable to only 0.14 ng/ml.

The diet is an important source of vitamin K immediately after birth. It is appreciated that early supplemental feeding could reduce the incidence of hemorrhage during the first week of life *(Widder Shoven et al, 1988)*.

Fat soluble vitamin K_1, or phylloquinone, is the principal from of vitamin K in plants and vegetable oils ***(Corrigan, 1981)***. Most commercial formulas in the United States contain > 50 $\mu g/L$ of vitamin K_1. In contrast, the vitamin K content of human milk varies widely, but is generally < 20 $\mu g/L$ and often < 5 $\mu g/L$ ***(Haroon et al, 1982)***.

Vitamin K_1 absorption from the diet occurs in the small intestine and requires the presence of bile acids ***(Corrigan, 1981)***. Animal studies suggest that vitamin K_1 is absorbed across the intestinal mucosa by energy-dependent transport ***(Hollander, 1981)***.

The intestinal flora synthesize vitamin K in the form of fat-soluble menaquinone or vitamin K_2 ***(Bentley and Meganathan, 1982)***. Bacteria differ widely in this ability: *Bacteroides fragilis* and some strains of *Escherichia coli* are efficient producers of vitamin K, whereas some lactobacilli and pseudomonas organisms are incapable of its synthesis ***(Bentley and Meganathan, 1982)***.