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Vitamin K_1 Content of Maternal Milk: Influence of the Stage of Lactation, Lipid Composition, and Vitamin K_1 Supplements Given to the Mother

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ABSTRACT. Using a sensitive electrochemical assay for vitamin K_1 and standardized techniques for breast-milk collection, we studied the vitamin K_1 content of human milk during the first 5 wk of lactation with respect to 1) individual and interindividual differences, 2) the relationship of vitamin K_1 to other lipids, and 3) the influence of oral supplements of vitamin K_1 on breast milk concentrations. Comparison of fore and hind milk from the mothers revealed higher vitamin K_1 concentrations in hindmilks, suggesting that the lipid content influences the vitamin K_1 concentration in maternal milk. Samples of maternal milk from nine mothers collected from day 1 to day 36 of lactation showed significantly higher vitamin K_1 concentrations in colostral milk than in mature milk. For colostral milk there was a significant correlation of vitamin K_1 to cholesterol ($r = 0.62$) but not to total lipid or phospholipid suggesting a role for cholesterol in the secretion of vitamin K_1 into colostral milk. For mature milk correlation coefficients of vitamin K_1 with all lipids were low ($r = 0.29$–0.37) suggesting that at later stages of lactation dietary fluctuations of vitamin K_1 may be a more important determinant of the vitamin K_1 content of breast milk than the lipid composition. To test the influence of diet, mothers were given oral supplements of vitamin K_1. Doses of 0.5–3 mg produced substantial rises in breast milk vitamin K_1 with peak levels between 12 and 24 h. In one mother in whom the milk sampling was standardized, a dose-response relationship was observed: the lowest dose of 100 μg was similar to that which might be ingested in a meal and produced a 2-fold increase in the vitamin K_1 content of breast milk. (*Pediatr Res* 22: 513–517, 1987)

Abbreviations

HDN, hemorrhagic disease of newborn
MK, menaquinone
HPLC, high-performance liquid chromatography
GC, gas chromatography
UV, ultraviolet

Some 40 yr ago Dam *et al.* (1), using a bioassay for vitamin K, found lower levels in maternal milk than in cow's milk and suggested (2) that an insufficient supply of the vitamin in breast-fed infants is a risk factor that may lead to classical HDN with bleeding in the 1st wk of life. This hypothesis was strengthened by the large study of Sutherland *et al.* (3) who found a higher incidence of bleeding in breast-fed babies. More recently a late onset form of HDN has been recognized in which intracranial hemorrhage is common (4). Although the etiology of late onset HDN is probably different from that of classical HDN, it is now well established that the majority of babies who develop late onset HDN are exclusively breast-fed (4). The reasons for this association, however, are unclear. Attempts to find out whether infants with late onset HDN have a purely dietary deficiency due to an inadequate intake of vitamin K_1 have proved inconclusive. In two recent studies, in which random milk samples were analyzed from mothers of affected infants, there was no direct association of the disease with low vitamin K_1 concentrations in the milk (5, 6). This may be due to the fact that random milk samples were not representative of the babies' total dietary intake for vitamin K_1. In a preliminary study, in one mother we found quite wide variations in the same day and from day to day (7). Changes of the lipid composition and dietary factors might account for this variability of the vitamin K_1 content of maternal milk. In the present study we have, therefore, extended these observations to a systematic study of the variability of the vitamin K_1 content of human milk during the first 5 wk of lactation and its relationship to other lipids. Breast milk was collected using carefully standardized techniques.

To find out if dietary fluctuations in vitamin K can influence the vitamin K_1 concentration of maternal milk we have also studied the time course of vitamin K_1 concentrations in human milk when mothers were given varying exogenous doses of vitamin K_1.

MATERIALS AND METHODS

Milk sampling. To assess vitamin K_1 concentrations in fore and hind milk, 10 mothers expressed 10-ml volumes of their milk from the first breast used for feeding (using an electric breast pump) sequentially into a series of test tubes. The first 10 ml of milk were defined as fore milk and the last 10 ml as hind milk.

The variability of the vitamin K_1 and lipid composition of breast milk during the course of lactation was studied by collecting milk samples from nine mothers of full-term infants at days 1, 3, 5, 8, 15, 22, 29, and 36 of lactation. The age of the mothers ranged between 17 and 34 yr, mean 24 yr. For half of the mothers this was their second child. The birth weight of the infants ranged from 2800 to 4370 g, mean 3700 g. Samples were taken at all nursing times throughout the day by complete emptying of both

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breasts using a manually operated breast pump. Each milk specimen was mixed and an aliquot of 5–10 ml was removed for analyses. The remainder of the expression was fed to the infants. No formula feeds were given. The five to six samples obtained on each day were pooled. All milk volumes obtained per collection process were recorded. The data strongly suggest that breasts were almost completely emptied by this procedure. For example milk volumes at day 1 ranged between 15 and 40 ml per collection process. In mature milk more than 100 ml of milk were obtained, respectively.

To assess the influence of oral supplementation on the vitamin K_1 content of breast milk, the mothers were given a vitamin K_1 preparation designed for oral intake (Konakion, Hoffmann LaRoche, Basle, Switzerland). In the first study we followed the time course of vitamin K_1 in maternal milk after giving small oral doses of vitamin K_1 to individual mothers. At their discretion the mothers were asked to collect either fore milk, hind milk, or the whole milk from one breast. In a second study the relationship between the ingested dose and the vitamin K_1 time course in maternal milk was determined in one mother using standardized conditions for the administration of vitamin K_1 and milk collection. The mother took vitamin K_1 with a glass of milk in the evening and there was an interval of at least 5 days between the ingestion of different doses of vitamin K_1. The whole milk content of the first breast of feeding was collected using an electric pump.

Materials. Vitamin K_1 and MK-6 standards were donated by Hoffmann LaRoche. All reagents for vitamin K_1 determination were HPLC grade and purchased from Rathburn Chemicals Ltd., Walkerburn, Scotland. Tocopherol standards were purchased from Eastman Kodak, New York, NY and Supelco, Bellefonte, PA. *O*-Phtaldialdehyde and lipid standards were from Sigma Chemicals, St. Louis, MO. All other chemicals and organic solvents for total lipid, cholesterol, phospholipid, and vitamin E determination were of analytical or HPLC grade and came from Merck, Darmstadt, FRG.

Analysis of vitamin K_1. Hexane Extraction of Vitamin K_1 from Milk. Aliquots of milk (1–2 ml) were extracted with 6 volumes of hexane after addition of 2 volumes of ethanol to precipitate proteins: the ethanol contained an accurately known amount (3–6 ng) of MK-6 as an internal standard. The mixture was vigorously mixed (by hand and vortex mixer) and centrifuged to separate the upper hexane phase from a lower aqueous-ethanoloic phase. The upper hexane layer was transferred and evaporated to dryness under a stream of N_2.

Preliminary Clean-Up Using Sep-Pak Silica Cartridges. Lipid extracts of milk were redissolved in 2 ml of hexane and loaded into a Sep-Pak silica cartridge (Waters Associates, Northwich, England) by means of a glass syringe with a Luer end fitting. The tube containing the lipid was rinsed with another 2 ml of hexane and was loaded onto the cartridge in the same way. The cartridge was eluted with 10 ml of hexane to elute a hydrocarbon fraction (discarded) followed by 10 ml of 3% (v/v) diethylether in hexane to elute a fraction containing vitamin K_1 and the internal standard. The eluate was collected and the solvent was removed under N_2.

Semipreparative Normal-Phase HPLC. Further purification of the lipid extract was carried out by semipreparative HPLC in a column (25 cm × 5 mm, i.d.) of Spherisorb-5 nitrile (5 μm silica chemically bonded with cyano propyl silyl groups from Phase Separations, Clwyd, England) with a mobile phase of 3–6% (v/v) of dichloromethane in hexane and a flow rate of 1 ml/min. Details of the procedures used for the preparation of 50% water-saturated dichloromethane, column equilibration, sample injection, and the collection of the vitamin K_1-containing fraction have been described elsewhere (8, 9).

Analytical Reversed-Phase HPLC. The fraction collected from the semipreparative HPLC stage was evaporated to dryness under N_2, redissolved in ethanol (50–100 μl), and an aliquot was (5–20 μl) analyzed by reversed phase HPLC with dual-electrode electrochemical detection as previously described (10). Quantification of vitamin K_1 was made by reference to the MK-6 internal standard by the method of peak height ratios from a calibration curve carried out on the same day. A typical chromatogram for vitamin K_1 and MK-6 determination is shown in Figure 1. As can be seen from the height of the vitamin K_1 peak, representing 2.7 ng/ml of milk all our reported data ranging from 0.3 to 4.8 ng/ml are well above the detection limit of 0.1 ng/ml when 1 ml of milk is extracted. Figure 1 also shows that under the chromatographic conditions used vitamin K_1 is well separated from MK-6. Menaquinones with longer side chains (*e.g.* MK-7, etc.), due to their more apolar properties, would elute well after MK-6, but were not detected in the milk volumes extracted for analysis.

Characteristics of the Vitamin K_1 Assay. The precision of the vitamin K_1 measurements in a variety of tissues by this method has been established to be in the range of 5–20%. The within-run coefficient of variation of seven replicate analyses of human milk (mean concentration 1.1 ng/ml) was 10%. The effectiveness of the hexane extraction procedure for milk was evaluated by comparing it against an exhaustive lipid extraction procedure with chloroform-methanol (2:1, v/v) by the method of Folch as described previously (11). For duplicate extractions of the same milk sample the hexane method gave values of 4.0 and 4.4 ng/ml compared to values of 4.0 and 4.2 ng/ml by the Folch method. Although the internal standard is a naturally occurring K_2-vitamin, analysis of human milk showed no detectable endogenous MK 6 in the volumes extracted.

Analysis of tocopherols and other milk lipids. Analysis of tocopherols was performed after hexane extraction using reversed phase HPLC and fluorimetric detection. Details have been described elsewhere (12). Total vitamin E was calculated by summation of the chromatographic peaks of α-tocopherol and (β + γ) − tocopherol. The cholesterol content was determined colorimetrically by the phtaldialdehyde method (13). Comparison of

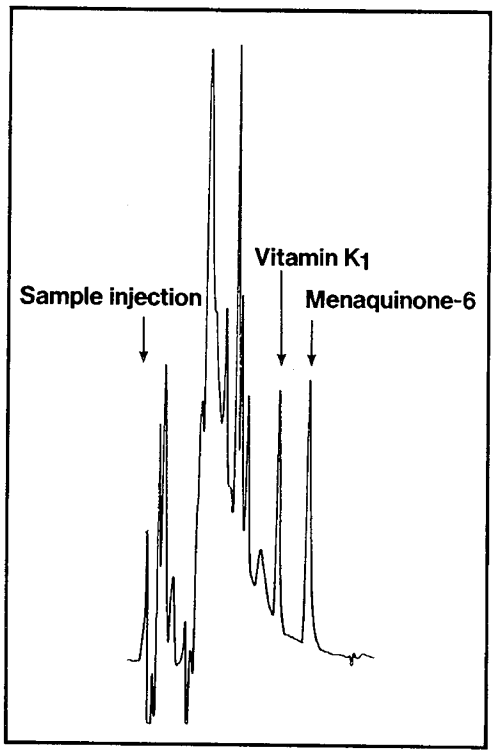

Fig. 1. Vitamin K_1 in maternal milk. The figure is a typical chromatogram. The volume of milk extracted was 1 ml, the amount of internal standard (M-6) added was 3.28 ng, and the vitamin K_1 concentration of the sample was 2.7 ng/ml.

this method with more time consuming methods such as HPLC and GC methods (14, 15) gave similar results. This method was therefore considered to be well suited for routine analysis (15). Total lipids were analyzed gravimetrically after extraction of lipids as described previously (16). Phospholipids were determined as lipid phosphorous (17).

Statistical analysis. Differences between data of fore and hind milk and milk samples from different stages of lactation were evaluated by the paired Wilcoxon test. The Wilcoxon U test was used for comparison of vitamin K_1 levels at different stages of lactation. Appropriate correlation and regression analyses were performed according to Sachs (18).

RESULTS

Vitamin K_1 content of fore and hind milk. The vitamin K_1 concentrations in paired samples of fore and hind milk collected from 10 mothers are shown in Figure 2. In individual mothers the sample of hind milk always had a higher concentration of vitamin K_1 than in the corresponding sample of fore milk ($p < 0.01$; paired Wilcoxon test).

Vitamin K_1 content of human milk during the course of lactation. The variability in the vitamin K_1 content of human milk collected over the first 36 days of lactation was studied in another series of nine mothers in whom milk was collected with the complete expression of both breasts. Individual values for vitamin K_1 concentrations showed considerable variation both within the same mother on different days and between different mothers on the same day. The vitamin K_1 concentration in maternal milk decreased during the first days of lactation and, with a great variability of the individual values, remained relatively constant thereafter (Fig. 3). As there were no significant differences in vitamin K_1 transitional (days 8–15) and mature milk (days 22–36), we treated data as one group. The median concentration of vitamin K_1 in colostral milk (days 1–5) was 1.8 ng/ml and was significantly higher ($p < 0.001$) compared to mature milk (days 8–36) (1.2 ng/ml). The highest median (2.7 ng/ml) was seen on the first day of lactation.

Correlation between vitamin K_1 and other lipids. Vitamin K_1 determinations had been done on human milk samples which had additionally been analyzed for total lipids, cholesterol, phospholipids and vitamin E (12) and therefore we could study the interdependencies of vitamin K_1 with either lipid. For colostral milks regression analysis showed good correlations between vitamin K_1 and cholesterol and between vitamin K_1 and vitamin E whereas no correlations could be found for vitamin K_1 with either total lipids or phospholipids. For mature milks, however, correlation coefficients of vitamin K_1 with total lipids, cholesterol, and vitamin E were consistently low (Table 1).

Time course studies after oral doses of vitamin K_1. The time course of vitamin K_1 in milks from three different mothers after 0.5–3 mg doses of vitamin K_1 is shown in Figure 4. The peak levels in maternal milk were attained between 12 and 24 h after vitamin K_1 ingestion. Even after 48 h vitamin K_1 levels were above the range found in mature milks from nonsupplemented

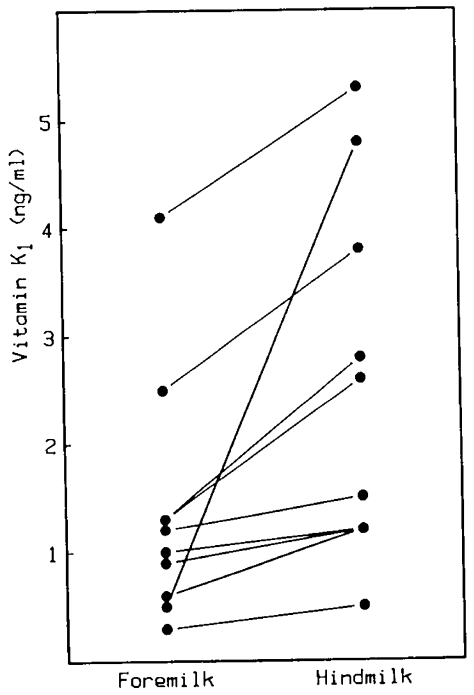

Fig. 2. Vitamin K_1 in maternal milk. Changes during the breast expression are shown; foremilk—first 10 ml and hindmilk—last 10 ml.

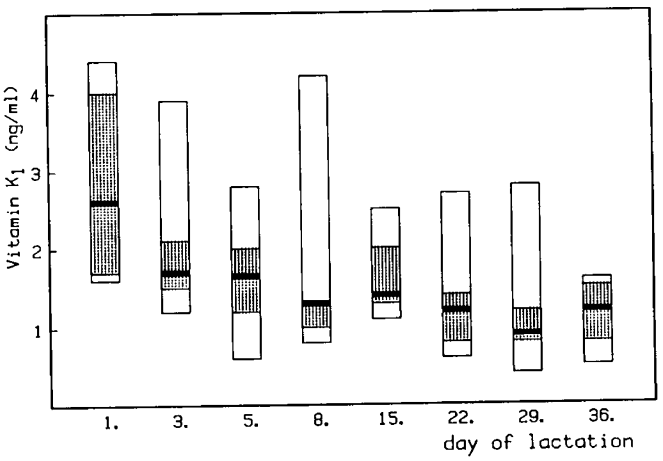

Fig. 3. Vitamin K_1 in maternal milk. Changes during the course of lactation in nine mothers are shown. *Bars*, median (50th percentile); *rectangles*, range for all data, *dotted area*, 25th to 75th percentile.

Table 1. *Correlation between vitamin K_1 and lipid components in maternal milk according to the stage of lactation*

	Days 1–5 ($n = 24$) (r)	Days 8–36 ($n = 43$) (r)
Vitamin K_1/phospholipids	0.20	0.29
Vitamin K_1/total lipids	0.11	0.37
Vitamin K_1/cholesterol	0.62	0.30
Vitamin K_1/vitamin E	0.66	0.29

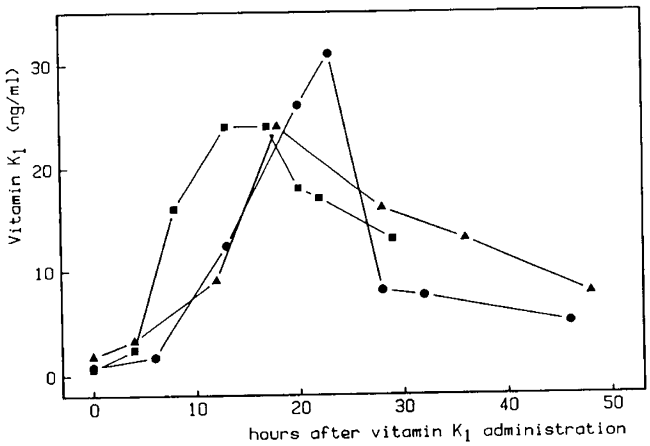

Fig. 4. Vitamin K in maternal milk. Time course after oral supplementation in three different mothers is shown. ■, 3 mg foremilk; ▲, 1 mg hindmilk; ●, 0.5 mg total breast expression.

mothers. For these three mothers in whom the method of vitamin K_1 administration and milk sampling were not standardized, there was no relationship between the ingested dose and the concentrations of vitamin K_1 in the milk. For one mother, however, where techniques were standardized, a clear dose response relationship was observed (Figure 5). In the same mother a dose of 100 μg of vitamin K raised the breast-milk concentrations from 2.5 to 4.9 ng/ml after 16 h; this then declined to 1.9 ng/ml after 24 h.

DISCUSSION

The measurement of the vitamin K content of human milk has proved technically difficult. Early studies using a method based on HPLC with a UV detector showed much lower concentrations than originally suspected by bioassays (11). In the present study we have used a new method based on HPLC with a dual-electrode electrochemical detector to measure vitamin K_1 in milk. This is more sensitive and selective than UV detection and the sample volume analyzed could be reduced to 1–2 ml. The range of values obtained for mature milk, however, was comparable being 0.4–4 ng/ml for the electrochemical method and 1.1–6.5 for the UV method. Motohara *et al.* (6) used HPLC with fluorometric detection and reported normal values for vitamin K_1 in maternal milk similar to ours, but also claimed to detect "vitamin K_2" although this is a generic term for many molecular forms of K_2 vitamins or menaquinones. Subsequent correspondence (7) revealed this "vitamin K_2" to be MK-4, a vitamer that has not previously been detected in animal tissues except by radioisotopic studies after the administration of menadione (19). Preliminary work in our laboratory suggests that vitamin K_1 is the major K vitamer of human milk, although very small amounts of longer sidechain menaquinones (*e.g.* MKs 7 and 8) seem to be present and might be nutritionally relevant. The presence of long-chain menaquinones is not unexpected since these bacterial forms have been previously detected in human livers by HPLC methods (20). MK-4 was not detected in our studies.

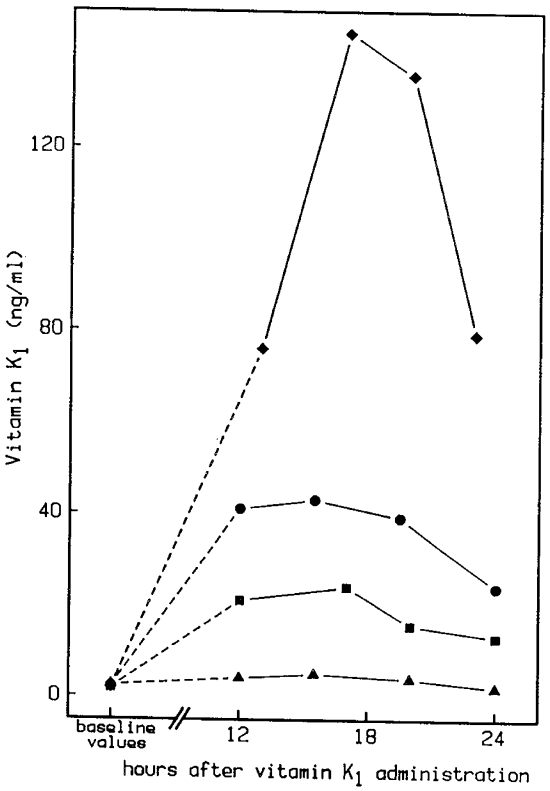

Fig. 5. Vitamin K_1 in maternal milk. Time course after oral supplementation in one mother given different doses of vitamin K_1 is shown. ▲, 0.1 mg; ■, 0.5 mg; ●, 1 mg; ◆, 3 mg.

Inasmuch as vitamin K is fat soluble, its concentration in maternal milk might be expected to be related to the lipid content. The lipid concentration of hindmilk is higher than in fore milk (21), and we were not surprised to find higher vitamin K_1 levels in hind milk. The magnitude of the difference between fore and hind milk varied due to the different volumes (20–100 ml) expressed by individual mothers. However, the vitamin K_1 content in hind milks was higher in all 10 mothers suggesting that lipid composition influences the vitamin K_1 content of maternal milk.

The lipid composition of maternal milk changes during the course of lactation and the most pronounced changes occur in the first week (22). Correlations between vitamin K_1, vitamin E and lipids were therefore analyzed at different stages of lactation. For colostral milks we found an excellent correlation of vitamin K_1 with cholesterol and vitamin E but no correlation with total lipids and phospholipids. These data suggest that at this stage of lactation the secretion of vitamin K_1 into breast milk may be related to the secretion of cholesterol and vitamin E. Based on the results of appropriate regression analyses some of us (23) recently proposed that in early lactation a major proportion of cholesterol is secreted into human milk by a mechanism which is independent of the apical membrane of secretory cells. Further studies revealed good correlations between vitamin E and cholesterol in colostral milk and a poor correlation between vitamin E and other lipids, suggesting that cholesterol is a carrier for vitamin E (12).

The good correlation found between vitamin K_1 and both cholesterol and vitamin E may thus indicate that this mechanism is also the carrier for vitamin K_1. As the correlations lessen during the course of lactation, it seems that the proposed membrane-independent pathway predominates in early lactation only, possibly to meet the nutritional needs of the newborn (12). Such a mechanism that tends to increase the vitamin K_1 concentrations of breast milk in the first few days of life would have undoubted benefits to the newborn, since there are strong reasons to believe that their vitamin K status is precarious. Thus cord blood (24) and liver stores (20) are both low and, when vitamin K is not given at birth, subclinical vitamin K deficiency [as evidenced by the finding of descarboxyprothrombin (PIVKA II) in plasma] is common in entirely breast-fed infants who receive small volumes of maternal milk during the first 4 days of life (25).

In mature milks the correlations of vitamin K_1 to cholesterol, total lipids, and vitamin E were weak. A much closer correlation might have been expected from the fore and hind milk studies. As the precision of the vitamin K_1, vitamin E, and lipid assays was 10% or less, it is unlikely that these weak correlations are due to methodological errors alone.

The only source of vitamin K_1 for man is the diet and dietary fluctuations may become more important determinants of the vitamin K_1 content of breast milk than the lipid composition at later stages of lactation. In a preliminary study in one mother Haroon *et al.* (11) demonstrated a marked increase of the vitamin K_1 levels in maternal milk after a large oral dose (20 mg) of vitamin K_1. In the present study, performed with much smaller doses of vitamin K_1, peak concentrations of vitamin K_1 in maternal milk were seen between 12 and 24 h after vitamin K_1 ingestion. Even a vitamin K_1 dose as low as 100 μg raised the breast milk concentration by more than 2-fold. Much higher amounts of vitamin K_1 may be ingested with a meal rich in green vegetables and milk products (26), although vitamin K_1 is probably less well absorbed from a meal than from a vitamin K_1 preparation. It seems likely therefore that dietary factors might account for minor fluctuations of the maternal milk contents of vitamin K_1.

The dietary intake of vitamin K_1 among lactating women has

not been investigated but might be low because lactating mothers may tend to avoid green vegetables, known to have a high vitamin K_1 content, because they are suspected to cause flatulence in the baby.

The present results might explain why nearly all cases of late onset HDN are seen in breast-fed babies. Our studies suggest that attempts to establish a pathogenic role for low vitamin K_1 concentrations in the milk of babies with late onset HDN will remain inconclusive if only random milk samples are analyzed. Collection of maternal milk samples over a longer period of time might overcome temporary fluctations of vitamin K_1 levels due to dietary factors and lipid composition and might permit a better estimation of the babies' vitamin K supply. These observations also suggest that it might be useful to give lactating mothers vitamin K supplements, as mature maternal milk always contains less vitamin K_1 than cow's milk and most infant formulas (11).

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REFERENCES

1. Dam H, Glavind J, Larsen HE, Plum P 1942 Investigations into the cause of physiological hypoprothrombinemia in newborn children. IV. The vitamin K content of woman's milk and cow's milk. Acta Med Scand 112:210–216
2. Dam H, Dyggve H, Larsen H, Plum P 1952 The relation of vitamin K deficiency to hemorrhagic disease of the newborn. Advan Pediatr 5:129–153
3. Sutherland JM, Glueck HI, Gleser G 1967 Hemorrhagic disease of the newborn: Breast feeding as a necessary factor in the pathogenesis. Am J Dis Child 113:524–530
4. Lane PA, Hathaway WE 1985 Vitamin K in infancy. J Pediatr 106:351–359
5. von Kries R, Sutor A, Pollmann H, Göbel U, Shearer MJ 1984 Vitamin K-Gehalt der Muttermilch bei gestillten Säuglingen mit lebensbedrohlicher Blutungsneigung infolge Vitamin K-Mangels. Monatsschr Kinderheilkd 132:725(abstr)
6. Motohara K, Matskura M, Matsuda I, Iribe K, Ikeda T, Kondo Y, Yonekubo A, Yamamoto Y, Tsuchiya F 1984 Severe vitamin K deficiency in breastfed infants. J Pediatr 105:943–945
7. von Kries R, Göbel U, Shearer MJ, McCarthy PT 1985 Vitamin K deficiency in breastfed infants. J Pediatr 107:650–651
8. Shearer MJ 1983 High-performance liquid chromatography of K vitamins and their antagonists. In: Giddings JC, Grushka E, Cazes T, Brown PR (eds) Advances in Chromatography. Marcel Dekker Inc, New York, pp 243–301
9. Shearer MJ 1986 Assay of K vitamins in tissues by high-performance liquid chromatography with special reference to ultraviolet detection. In: Chytil F, McCormick DM (eds) Methods in Enzymology. Academic Press, Orlando, FL, pp 235–251
10. Hart JP, Shearer MJ, McCarthy PT 1985 Enhanced sensitivity for the determination of endogenous phylloquinone (vitamin K_1) in plasma using high-performance liquid chromatography with dual electrode electrochemical detection. Analyst 110:1181–1184
11. Haroon Y, Shearer MJ, Gunn WG, McEnery G, Barkhan P 1982 The content of phylloquinone (vitamin K_1) in human milk, cow's milk and infant formula determined by high-performance liquid chromatography. J Nutr 112:1105–1117
12. Harzer G, Haug M 1985 Correlation of human milk vitamin E with different lipids. In: Schaub J (ed) Composition and Physiological Properties of Human Milk. Elsevier Publishers, Amsterdam, pp 247–254
13. Bachman KC, Lin J-H, Wilcox CJ 1976 Sensitive colorimetric determination of cholesterol in dairy products. J Assoc Off Anal Chem 59:1146–1149
14. Haug M, Harzer G 1984 Cholesterol and other sterols in human milk. J Pediatr Gastroenterol Nutr 3:816–817
15. Jensen RG, Cholesterol in human milk. In: Goldman A, Atchinson S (eds) Lactation III. The Effects of Human Milk on the Recipient Infant. Plenum Press, New York (in press).
16. Gentner PR, Bauer M, Dieterich I 1981 Separation of major phospholipid classes of milk without previous isolation from total lipid extracts. J Chromatogr 206:200–204
17. Gentner PR, Haasemann A 1979 Phosphorometrie - Eine Methode zur schnellen quantitativen Bestimmung von Phospholipiden nach dünnschichtchromatographischer Trennung. Fette Seifen Anstrichm 81:357–360
18. Sachs L (ed) 1969 Statistische Auswertungsmethoden. Springer-Verlag, Berlin
19. Taggatt VW, Matschiner JT 1969 Metabolism of menadine-6,7-^{3}H in the rat. Biochemistry 8:1141–1146
20. McCarthy PT, Shearer MJ, Gau G, Crampton OE 1986 Vitamin K Content of human livers at different ages. Haemostasis 16 (suppl 5):84(abstr)
21. Harzer G, Haug M 1984 Abhängigkeit der Frauenmilch-lipide von der Dauer der Stillperiode, der Tageszeit, dem Stillvorgang und der mütterlichen Ernährung. Z Ernährungswiss 23:113–125
22. Harzer G, Haug M; Dieterich I, Gentner PR 1983 Changing patterns of human milk lipids in the course of the lactation and during the day. Am J Clin Nutr 37:612–621
23. Harzer G, Bindels JG, Haug M 1985 Korrelationen zwischen dem Triglycerid-, Phospholipid- und Cholesteringehalt in Muttermilch. Ern Umschau 32:224–225
24. Shearer MJ, Rahim S, Barkhan P, Stimmler L 1982 Plasma vitamin K_1 in mothers and their newborn babies. Lancet. 2:460–463
25. von Kries R, Göbel U, Maase B 1985 Vitamin K deficiency in the newborn. Lancet 2:728–729
26. Shearer MJ, Allan V, Harron V, Barkhan P 1979 Nutritional aspects of vitamin K in the human In: Suttie JW (ed) Vitamin K Metabolism and Vitamin K-Dependent Proteins. University Park Press, Baltimore, pp 317–327