Preterm infants who remain exclusively human milk fed post NICU discharge are at high risk of developing vitamin K deficiency in early infancy

HIGH PREVALENCE OF SUBCLINICAL VITAMIN K₁ DEFICIENCY AMONG HUMAN MILK-FED PRETERM INFANTS IN EARLY INFANCY

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BACKGROUND
- Vitamin K (VK) status of preterm infants post-NICU discharge and in early infancy is unknown.
- Exclusive breast milk feeding is often the only factor identifiable in cases of idiopathic VK deficiency bleeding.
- Despite the low VK content of human milk, VK supplements are not routinely given to human milk-fed preterm infants after NICU discharge; in contrast, vitamins A, B, C, D, and E are widely given.

AIM
To examine the VK status of breast milk fed preterm infants nearing discharge and in early infancy.

HYPOTHESIS
In the absence of extra VK supplementation at/after discharge home, preterm babies who remain exclusively or predominantly human milk fed will have a high prevalence of subclinical VK deficiency in early infancy.

METHODS
Design: Prospective, multicentre, observational cohort study with ethics approval.
Included: preterm infants born <33 weeks’ gestation and exclusively or predominantly human milk fed, approaching NICU discharge.
Excluded: infants with cholestasis.
Measures of VK status: serum concentrations of vitamin K₁ (VK₁) and PIVKA-II (Protein Induced by Vitamin K Absence/antagonism of blood clotting factor II; undercarboxylated prothrombin).
Timing of assessment: Samples taken at two time points: ~35 weeks postmenstrual age (PMA) for baseline VK status, and at ~2 months corrected age (CA) (primary outcome).

MAIN RESULTS:
VK status approaching NICU discharge
Of n=45 infants assessed prior to discharge (at median PMA 35+1): only 1/45 (2%) was VK deficient, an exclusively breast fed 23+6 week gestation baby.
VK status in early infancy:
N=37 completed the study, at median CA 8 weeks. By this time only 12/37 (32%) remained exclusively breast milk (BM) fed. Overall by 8 weeks CA, 9/37 (24%) infants had developed VK deficiency (as shown by ↑PIVKA-II).
But of BM-fed infants 8/12 (67%) were VK deficient vs. only 1/25 (4%) FM/mixed feeding babies, p=0.0001 (Figure).

CONCLUSIONS:
- VK concentrations were significantly lower and PIVKA-II concentrations higher in exclusive BM vs FM/mixed fed babies, Table.
- The majority of exclusively breast milk fed babies had evidence of mild vitamin K deficiency by 2-3 months CA.
- Preterm infants who remain exclusively human milk fed post NICU discharge are at a high risk of developing mild vitamin K₁ deficiency in early infancy without additional K₁ supplements.
- Routine post-discharge K₁ supplementation may prevent subclinical K₁ deficiency in breast-fed babies in early infancy.

DEFINITIONS USED FOR ‘SATISFACTORY’ AND ‘DEFICIENCY’ OF VITAMIN K STATUS

Satisfactory VK status: normal PIVKA-II (<50.9 mAU/mL)
VK deficiency: raised PIVKA-II (≥51.0 mAU/mL)

Table: Measures of vitamin K status of preterm infants in early infancy according to mode of feeding.

<table>
<thead>
<tr>
<th></th>
<th>Exclusive breast milk fed, n=12</th>
<th>Formula/mixed fed, n=25</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin K₁</td>
<td>[μg/L]</td>
<td>[μg/L]</td>
<td></td>
</tr>
<tr>
<td>median</td>
<td>0.15 (0.10-0.59)</td>
<td>1.91 (0.16-5.31)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IQR</td>
<td>[0.11-0.24]</td>
<td>[1.29-2.32]</td>
<td></td>
</tr>
<tr>
<td>PIVKA-II</td>
<td>[μg/L]</td>
<td>[μg/L]</td>
<td></td>
</tr>
<tr>
<td>median</td>
<td>80.8 (23.6-496.6)</td>
<td>21.6 (14.1-129.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IQR</td>
<td>[36.2-232.7]</td>
<td>[18.8-25.9]</td>
<td></td>
</tr>
</tbody>
</table>

Data are median (range) [IQR, interquartile range]
*VK₁ reference range: 0.15-1.55 μg/L

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