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Prevention of Vitamin K Deficiency Bleeding in Breastfed Infants: Lessons From the Dutch and Danish Biliary Atresia Registries

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What’s Known on This Subject

Intramuscular vitamin K prophylaxis at birth efficaciously prevents vitamin K deficiency bleeding in infancy but increasingly encounters parental refusal. We investigated whether frequent oral prophylaxis prevents vitamin K deficiency bleeding by assessing its prevalence in infants with still-unrecognized cholestatic liver disease.

What This Study Adds

In breastfed infants with cholestatic liver disease, weekly oral (1-mg) vitamin K prophylaxis and intramuscular prophylaxis effectively prevented vitamin K deficiency bleeding. In contrast, daily oral prophylaxis (25 μg) was associated with frequent (>90%) and severe vitamin K deficiency bleeding.

OBJECTIVE. Newborns routinely receive vitamin K to prevent vitamin K deficiency bleeding. The efficacy of oral vitamin K administration may be compromised in infants with unrecognized cholestasis. We aimed to compare the risk of vitamin K deficiency bleeding under different prophylactic regimens in infants with biliary atresia.

PATIENTS AND METHODS. From Dutch and Danish national biliary atresia registries, we retrieved infants who were either breastfed and received 1 mg of oral vitamin K at birth followed by 25 μg of daily vitamin K prophylaxis (Netherlands, 1991–2003), 2 mg of oral vitamin K at birth followed by 1 mg of weekly oral prophylaxis (Denmark, 1994 to May 2000), or 2 mg of intramuscular prophylaxis at birth (Denmark, June 2000–2005) or were fed by formula. We determined the absolute and relative risk of severe vitamin K deficiency and vitamin K deficiency bleeding on diagnosis in breastfed infants on each prophylactic regimen and in formula-fed infants.

RESULTS. Vitamin K deficiency bleeding was noted in 25 of 30 of breastfed infants on 25 μg of daily oral prophylaxis, in 1 of 13 on 1 mg of weekly oral prophylaxis, in 1 of 10 receiving 2 mg of intramuscular prophylaxis at birth, and in 1 of 98 formula-fed infants (P < .001). The relative risk of a bleeding in breastfed compared with formula-fed infants was 77.5 for 25 μg of daily oral prophylaxis, 7.2 for 1 mg of weekly oral prophylaxis, and 9.3 for 2 mg of intramuscular prophylaxis at birth.

CONCLUSIONS. A daily dose of 25 μg of vitamin K fails to prevent bleedings in apparently healthy infants with unrecognized cholestasis because of biliary atresia. One milligram of weekly oral prophylaxis offers significantly higher protection to these infants and is of similar efficacy as 2 mg of intramuscular prophylaxis at birth. Our data underline the fact that event analysis in specific populations at risk can help to evaluate and improve nationwide prophylactic regimens.

Vitamin K is essential for effective coagulation, and a deficiency may result in spontaneous life-threatening hemorrhages.1 As a consequence of the short half-life of vitamin K compared with other vitamins, newborns can become deficient within days in case of inadequate intake. A bleeding because of vitamin K deficiency (VKD) shortly after birth is known as hemorrhagic disease of the newborn, or classical VKD bleeding (VKDB). A bleeding after the first week of life is called “late VKDB.”2 Approximately 50% of infants with late VKDB present with an intracranial hemorrhage.3–5 Breastfeeding is recognized as a major risk factor for both forms of VKD bleedings.4,6,7 This is presumably because of a lower vitamin K intake in breastfed infants: whereas human milk contains 1 to 2 μg/L, most infant formulas are...
artificially fortified and contain ~50 μg/L. A variety of prophylactic regimens have been introduced to prevent VKDB in breastfed infants.7–10 A single intramuscular dose of vitamin K at birth is considered most efficacious, reducing the incidence of classical, as well as late, VKDB to < 0.2 per 100,000, although recent evidence suggests that effectiveness may be hampered by a higher risk of omission of prophylaxis.10–12 Oral administration of vitamin K at birth prevents classical VKDB but fails to prevent late VKDB, even when administered in very high dosages.13 Based on these observations, breastfed infants on oral prophylaxis receive additional doses of vitamin K in the first months of life.12 This strategy has substantially reduced the incidence of late VKDB.12–14 However, prophylactic failures have continued to occur, mostly in infants who later proved to have a cholestatic liver disease.3,9,15–18

Cholestatic infants are especially sensitive to suboptimal vitamin K availability, because the absence of intestinal bile greatly reduces the absorption of vitamin K and other fat-soluble vitamins.19,20 The repeated occurrence of prophylactic failures in infants with unrecognized cholestatic liver disease warrants careful evaluation of the efficacy of vitamin K prophylactic regimens in these infants. National registries for biliary atresia provide a unique opportunity to quantitate the efficacy of vitamin K prophylaxis in a well-defined and homogeneous population of cholestatic infants. These registries allow us to determine the absolute risk of VKDB in breastfed infants under different prophylactic regimens. Moreover, these risks can be weighed against the risk in formula-fed infants. We performed a retrospective cohort study in Dutch and Danish infants with biliary atresia to compare the efficacy of frequent (daily or weekly) oral vitamin K prophylaxis with intramuscular (IM) vitamin K prophylaxis at birth.

METHODS

Study Population

Data from Dutch biliary atresia patients born between 1991 and 2003 were obtained from the Netherlands Study Group for Biliary Atresia Registry, a joint effort of the Dutch Society for Pediatrics and the Dutch Society for Pediatric Surgery. Dutch biliary atresia patients born between 1994 and 2005 were retrieved from the University Hospital of Copenhagen (Rigs Hospital) Department of Pediatric Surgery. The Rigs Hospital is the Danish national referral center for patients with suspected biliary atresia and for Kasai hepatopancreatostomy.

Routine vitamin K prophylaxis aims to prevent VKDB in apparently healthy term infants. Infants with a gestational age of < 37 weeks or a birth weight of < 2,000 g were excluded, because these infants routinely receive additional vitamin K prophylaxis. Patients hospitalized from birth until diagnosis were also excluded, because they may have received additional vitamin supplements, as well as other diets. Late VKDB has been defined to occur after the first week of life and before the age of 6 months.3 Accordingly, infants were excluded if cholesta-
If a PT\textsubscript{control} was not determined by the laboratory, it was defined as the mean of the provided reference range.

VKD was defined as a PR of $>1.5$ in combination with a normal thrombocyte count. A PR above this threshold is rare in healthy infants after the first week of life\cite{22,23}. Significant PR elevations in otherwise healthy biliary atresia infants are unlikely to be because of other causes\cite{24}. A PR of $>4$ was designated as “severe” VKD. VKDB was defined as bruising, bleeding, or intracranial hemorrhage in combination with a PR of $>4$ in any infant between 8 days and 6 months of age and normalizing after administration of vitamin K\cite{2}. The number of bleedings and their locations were noted.

**Statistical Analysis**

We performed a 2-way analysis of variance of clinical and biochemical parameters with a normal distribution pattern to test for statistical differences between groups. Kruskal-Wallis analysis was used for those parameters with a nonnormal distribution. In case statistical significant differences were found, a Bonferroni test for multiple comparisons or a Mann-Whitney U test was used for posthoc analysis, respectively. Fisher’s exact test was performed to determine statistical significance between groups in case of dichotomous parameters. The relative risks (RRs) and 95% confidence intervals (CIs) for VKDB and biochemical levels of VKD were calculated.

We performed conditional logistic regression analysis to assess potential confounding. First, all of the clinical and biochemical parameters were considered as possible confounders and included, 1 by 1, as covariates. Risk factors that changed the odds ratio (OR) by $>10\%$ were added to a model and were maintained in the final model if they induced a change of $>10\%$ in that model. SPSS 12.01 (SPSS Inc, Chicago, IL) was used for all of the analyses.

**RESULTS**

Between January 1991 and December 2003, 139 biliary atresia patients were included into the Netherlands Study Group of Biliary Atresia Registry (Table 1). Seventeen of these infants did not meet the inclusion criteria; 9 had stayed in a hospital from birth until diagnosis, 7 were born outside of the Netherlands, and 1 was excluded because of prematurity. Thirty (25\%) of the remaining 122 infants were exclusively breastfed, and 88 (72\%) were formula fed. In 4 infants, the type of feeding was not documented. In total, 63\% of all of the infants received any amount of breastfeeding, which is similar to the 51\% to 63\% of infants using breastfeeding at the age of 6 weeks in the Netherlands from 1991 to 2003, as known from epidemiologic data (www.cbs.nl/statline).

A total of 46 patients born between January 1994 and December 2005 were reported to the Danish Biliary Atresia Registry. Nine infants were excluded; 6 had stayed in a hospital from birth until diagnosis and 3 were excluded because of prematurity. In addition, 5 infants born before June 2000 were excluded because vitamin K was administered IM after a complicated delivery. Twenty three of the remaining 32 infants (77\%) were breastfed, of which 13 were born before June 2000.

**Clinical Characteristics**

Infants from both countries were categorized according to the type of prophylaxis that they received. Table 2 summarizes the clinical characteristics in breastfed infants on frequent (daily or weekly) oral or IM prophylaxis and the combined group of formula-fed infants. Overall, breastfed infants had a slightly, but significantly, higher birth weight than formula-fed infants. Cholestasis was found $\sim$14 days earlier in Dutch breastfed infants compared with formula-fed infants ($P < .001$). The age at diagnosis correlated significantly with parameters of cholestatic liver disease.
TABLE 2  Comparison of Characteristics for Each Type of Prophylaxis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>25 μg Daily Oral (n = 30)</th>
<th>1 mg Weekly Oral (n = 13)</th>
<th>2 mg IM at Birth (n = 10)</th>
<th>Formula Fed (n = 93)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender, n (%)</td>
<td>10 (33)</td>
<td>7 (54)</td>
<td>6 (60)</td>
<td>49 (53)</td>
<td>.260</td>
</tr>
<tr>
<td>Birth weight, mean ± SD, g</td>
<td>3351 ± 404</td>
<td>3517 ± 347</td>
<td>3304 ± 525</td>
<td>3115 ± 629</td>
<td>.050</td>
</tr>
<tr>
<td>Age at diagnosis, median (IQR)</td>
<td>35 (28–43)</td>
<td>46 (26–59)</td>
<td>54 (16–70)</td>
<td>49 (38–61)</td>
<td>.001</td>
</tr>
<tr>
<td>Weight at diagnosis, mean ± SD, g</td>
<td>3959 ± 423</td>
<td>4531 ± 922</td>
<td>4576 ± 1186</td>
<td>4150 ± 945</td>
<td>.080</td>
</tr>
<tr>
<td>Bilirubin total, μmol/L</td>
<td>147 (104–202)</td>
<td>153 (97–289)</td>
<td>197 (140–304)</td>
<td>178 (122–257)</td>
<td>.080</td>
</tr>
<tr>
<td>Bilirubin direct, μmol/L</td>
<td>98 (71–135)</td>
<td>124 (85–193)</td>
<td>135 (82–182)</td>
<td>127 (93–176)</td>
<td>.130</td>
</tr>
<tr>
<td>Bilirubin indirect, μmol/L</td>
<td>41 (27–76)</td>
<td>193 (152–233)</td>
<td>181 (125–237)</td>
<td>154 (125–180)</td>
<td>.090</td>
</tr>
<tr>
<td>ASAT, median (IQR), U/L</td>
<td>144 (94–235)</td>
<td>131 (103–154)</td>
<td>86 (63–150)</td>
<td>104 (84–133)</td>
<td>.420</td>
</tr>
<tr>
<td>ALAT, median (IQR), U/L</td>
<td>88 (66–135)</td>
<td>52 (34–111)</td>
<td>49 (43–88)</td>
<td>37 (25–62)</td>
<td>.080</td>
</tr>
</tbody>
</table>

Data show infants with biliary atresia. All of the infants in the first 3 columns were exclusively breastfed. ASAT indicates aspartate aminotransferase; ALAT, Alanine aminotransferase.

a P-value was determined by using Fisher’s exact test.

b Data cannot be computed.

c P-value was determined by using ANOVA.

d Data was determined by using Kruskal-Wallis test.

VKD in Breastfed Infants

VKD was evident in all (30 of 30) Dutch breastfed infants with biliary atresia (Table 3). VKD was severe in 29 of 30 (96%), and this was associated with a VKDB in 25 of 30 (83%). Fifteen infants (50%) had multiple bleedings. An intracranial hemorrhage was diagnosed in 13 of 30 (43%) Dutch breastfed infants. In contrast, VKDB occurred in only 1 of the Danish infants after weekly oral prophylaxis (1 of 13 [8%]); each infant had only 1 bleeding. Five of these 13 infants also had an intracranial hemorrhage, present in 5 of 13 (39%) of the Danish breastfed infants on weekly oral prophylaxis and in 3 of 10 (30%) of the infants on IM prophylaxis at birth.

Efficacy of Vitamin K Prophylaxis in Breastfed Infants: Comparison With Formula Feeding

We compared the risk of (severe) VKD and VKDB in breastfed infants receiving frequent oral or IM prophylaxis with the risk in formula-fed infants (Table 4). Only 1 of the 93 formula-fed infants had a VKDB. Dutch breastfed infants were poorly protected against VKDB compared with formula-fed infants, with a relative risk for a VKDB of 77.5 (95% CI: 11.0–548.0). Similar results were obtained when only Dutch formula-fed infants were used for comparison (RR: 73.3; 95% CI: 10.4–518.0). For Danish breastfed infants, a relative risk for a VKDB of 93 was observed (95% CI: 28.7–307.1). Logistic regression revealed that female gender was a risk factor for VKDB in breastfed versus formula-fed infants and an adjusted OR of 93 (95% CI: 28.7–307.1).

DISCUSSION

Our data show that the Dutch vitamin K prophylactic regimen does not protect breastfed infants with biliary atresia. More than 80% of these infants had developed a VKDB at the time that cholestasis was diagnosed. The clinical significance of this is illustrated by the fact that 43% of breastfed infants with biliary atresia presented with a VKDB (OR: 4.1; 95% CI: 1.5–11.3). However, female gender was not significantly associated with (severe) VKD.

TABLE 3  Risk of VKD in Breastfed Infants With Biliary Atresia Under Different Prophylactic Regimens

<table>
<thead>
<tr>
<th>Variable</th>
<th>25 μg Daily Oral, n/N (%)</th>
<th>1 mg Weekly Oral, n/N (%)</th>
<th>2 mg IM at Birth, n/N (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily Versus Weekly Oral</td>
<td>RR 95% CI RR 95% CI</td>
<td>Daily Oral Versus IM at Birth</td>
<td>RR 95% CI RR 95% CI</td>
<td></td>
</tr>
<tr>
<td>VKD</td>
<td>30/30 (100)</td>
<td>5/13 (39)</td>
<td>3/10 (30)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Severe VKD</td>
<td>29/30 (97)</td>
<td>3/13 (23)</td>
<td>2/10 (20)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>VKDB</td>
<td>25/30 (83)</td>
<td>1/13 (8)</td>
<td>1/10 (10)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>13/30 (43)</td>
<td>0/13 (0)</td>
<td>0/10 (0)</td>
<td>.001</td>
</tr>
</tbody>
</table>

P was determined by using Fisher’s exact test.

a VKD was defined by a normal thrombocyte count and PR of >1.5, severe VKD by a PR of >4.

b Data cannot be computed. P = 1.0 for all of the comparisons between weekly oral and IM prophylaxis.
with an intracranial hemorrhage. The risk of VKDB in Dutch breastfed infants with biliary atresia was 8 to 10 times higher than in breastfed infants on either weekly oral prophylaxis or IM prophylaxis at birth and ~80 times higher than in formula-fed infants.

The design of the present study was set out to minimize the risk of bias. To reduce selection bias, we focused on infants with biliary atresia, a rarely missed diagnosis for which national registries are available. The incidence of biliary atresia in the Netherlands and Denmark, calculated from our present study, was 1:21 321 and 1:17 329, respectively. These incidences are in close agreement with the earlier reported incidence of 1:20 000.25 Theoretically, the high overall risk of VKDB in this study could be attributed to a higher detection rate of mild cases. However, the observed fraction of infants with VKDB presenting with an intracranial hemorrhage was in line with previous data,3,5 which makes this option unlikely. We excluded infants who might have received additional vitamin K, such as preterm infants, to reduce the risk of misclassification. Although some clinical parameters differed significantly between groups, these parameters did not significantly influence the risk of VKDB in breastfed infants on conditional logistic regression analysis.

Our definition of a VKD was based on an elevated PR in the absence of thrombocytopenia, parallel to the case definition of VKDB. Although this definition largely excludes diffuse intravascular coagulation, it does not exclude other causes of PR elevation and may, therefore, give rise to misclassification. However, we do not consider this a major concern in the context of infants with biliary atresia, a condition characterized by poor vitamin K absorption. Moreover, liver dysfunction in biliary atresia is unlikely to cause a PR of >1.5 during the first months of life.24 Similarly, a "physiologic" PR of >1.5 is rare after the first week of life.22,23 We also analyzed the data using a higher cutoff value of the PR (>2), but the results were essentially identical (Table 4).

The observed failure of the current Dutch regimen to protect breastfed biliary atresia infants contrasts with surveillance data obtained after introduction of this regimen.12 These surveillance data indicate that daily oral vitamin K prophylaxis was of similar efficacy as IM prophylaxis. This conclusion was supported by the observation that Dutch breastfed infants had adequate vitamin K levels throughout the first 3 months of life and that their coagulation parameters remained within normal limits.26 However, these studies focused on healthy infants and did not address the efficacy of vitamin K prophylaxis in conditions with poor absorption of vitamin K, such as those observed in cholestatic infants. This approach may give rise to equivocal results: recent surveillance data obtained after introduction of this prophylactic regimen seem to contradict the previous findings, with a reported incidence of 3:100 000.27 Five of 6 reported failures had an unrecognized cholestatic liver disease.

Reliable information on the efficacy of prophylactic regimens in high-risk infants is of increasing importance, because these infants now represent the vast majority of prophylactic failures.1,2,15 The method presented here, comparison of well-delineated and homogeneous risk populations, may be very helpful in this respect. In contrast to nationwide surveillance studies, which are sensitive to underreporting,1,12 it seems to be a reliable method to detect prophylactic failures. The presently applied method not only allows us to determine the number of failures but also to calculate the failure rate, because clinical information can be obtained from all of the infants within such a

### Table 4

<table>
<thead>
<tr>
<th>Variable</th>
<th>VKDb</th>
<th>Severe VKD</th>
<th>VKDB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>95% CI</td>
<td>RR</td>
</tr>
<tr>
<td>Formula fed (n = 93)</td>
<td>1.0</td>
<td>NA</td>
<td>1.0</td>
</tr>
<tr>
<td>Breastfed +2 mg IM at birth (n = 10)</td>
<td>4.7</td>
<td>1.4–15.8</td>
<td>18.6</td>
</tr>
<tr>
<td>Breastfed +1 mg weekly oral (n = 13)</td>
<td>6.0</td>
<td>2.1–16.8</td>
<td>21.5</td>
</tr>
<tr>
<td>Breastfed +25 μg daily oral (n = 30)</td>
<td>15.5</td>
<td>7.2–33.6</td>
<td>89.9</td>
</tr>
</tbody>
</table>

NA indicates not applicable. VKDB was defined by a normal thrombocyte count and a PR of >1.5, severe VKD by a PR of >3.

P values as determined by using Fisher’s exact test were .04 for VKD, .02 for severe VKD, and .19 for VKDB.

P values were <0.001 for all of the comparisons.

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**FIGURE 1**

Age at presentation in Dutch and Danish infants with biliary atresia. Infants with VKDB presented significantly earlier than those without VKDB (34 vs 50 days; \( P < .001 \)). There was a significant interaction with feeding type (\( R = 0.669; P < .001 \)). Twenty-seven (96%) of the 28 infants with VKDB and 26 (14%) of the 118 infants without VKDB were breastfed (\( P < .001 \)).
population. It also enables a comparison of failure rates between different subpopulations, such as breastfed infants. Moreover, the availability of biochemical parameters can be used to establish the risk of a “near miss,” (eg, a severe VKD diagnosed before a bleeding could develop).

Most importantly, as presently shown, this strategy allows the detection of differences between regimens in their ability to protect high-risk populations, which remained undetected using surveillance studies.

Comparison of the 2 oral regimens indicates that 1-mg weekly prophylaxis is more effective than 25-μg daily prophylaxis. The most likely explanation for this observation is the dosage; the cumulative dose per week was ~5 times higher in the weekly regimen (1.00 mg vs 0.18 mg for weekly and daily oral prophylaxis, respectively). It has been hypothesized that a high dosing frequency may require a relatively low dose of vitamin K to obtain good efficacy.28 However, our present data do not support the hypothesis that a daily dose of 25 μg is sufficient.

This study firmly establishes the efficacy of formula feeding in preventing VKDB in infants with unrecognized cholestasis. Formula feeding is even more effective than IM prophylaxis, the “gold standard,” to prevent VKDB. The mechanism underlying the preventive efficacy of formula feeding remains unclear. The vitamin K content of formula offers an insufficient explanation, because the average estimated daily intake of vitamin K in formula in our cohort (based on a daily formula intake of 150 mL/kg) is 25 to 50 μg, similar to the dose prescribed in the Dutch prophylactic regimen. A higher production of vitamin K by colonic bacteria in formula-fed infants might play a role.23 However, even a mixed-micellar vitamin K formulation, containing bile acids, is poorly absorbed in infants with biliary atresia.29

Logistic regression revealed that female gender was a risk factor for VKDB. Although both genders were at a similar risk to present with a (severe) biochemical VKD, female infants were at a significantly higher risk of developing a VKDB. This result has not been reported previously, and the meaning of this finding is presently unknown.

**CONCLUSIONS**

We quantified the efficacy of frequent oral vitamin K prophylactic regimens in a cohort of Dutch and Danish biliary atresia infants. Our data clearly indicate that the current Dutch prophylaxis of 25 μg of daily oral vitamin K is insufficient to protect exclusively breastfed infants with biliary atresia from VKDB. Effective oral prophylaxis is feasible, as shown by the efficacy of a weekly oral dose of 1 mg of vitamin K in protecting these infants. Based on these data, the current Dutch prophylactic regimen is presently being reevaluated. We feel that nationwide prophylaxis should be tailored to protect those individuals who are at the highest risk to develop an adverse event. An event analysis in high-risk populations, as a means of “postmarketing” surveillance, could help to achieve this objective.

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