Determinants of Cobalamin Status in Newborns

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ABSTRACT. Objective. Cobalamin deficiency accompanied by bone marrow dysfunction and impaired central nervous system development has been reported in infants who were born to mothers with low cobalamin intake. We investigated the relation between cobalamin status in newborns and in their healthy mothers who consumed an omnivorous diet.

Methods. Serum cobalamin and the functional markers plasma methylmalonic acid (MMA) and total homocysteine (tHcy) were determined in 173 newborns and their mothers. Forty-five children and mothers were re-investigated after 6 weeks.

Results. At birth, median (interquartile range) serum cobalamin levels were 245 (175–323) pmol/L in the mothers and 314 (238–468) pmol/L in the newborns. In the neonates, serum cobalamin, but not folate, was inversely associated with MMA and tHcy. Among maternal factors, low serum cobalamin was the strongest predictor of impaired cobalamin function (defined as low cobalamin, high tHcy, or high MMA levels) in the newborns. After 6 weeks, the maternal cobalamin levels had increased (to 421 [271–502] pmol/L), whereas the newborn levels had declined (to 230 [158–287] pmol/L). In the same interval, the infants had a marked increase in plasma MMA (from 421 [271–502] pmol/L) and MMA (from 0.29 [0.24–0.38] to 0.81 [0.37–1.68] pmol/L). At 6 weeks, parity was a strong predictor of cobalamin status in the infant.

Conclusion. The cobalamin status in the neonatal period is strongly associated with maternal cobalamin status and parity. A reduction in serum cobalamin and an increase in metabolite levels are consistent with impaired cobalamin function in a significant portion of the infants who were born to healthy, nonvegetarian mothers. Pediatrics 2001;108:624–630; newborn, infant, cobalamin, folate, homocysteine, methylmalonic acid.

ABBR EV IATIONS. MMA, methylmalonic acid; tHcy, total homocysteine; OR, odds ratio.

There are several reports on cobalamin deficiency in children of mothers who are strict vegetarians.1,2 The propensity of infants who are born to mothers with low cobalamin intake to become deficient1,3 suggests that cobalamin status during infancy is critically dependent on fetal cobalamin accumulation and, thereby, maternal cobalamin status in pregnancy. In infancy, impaired cobalamin function leads to dysfunction of the central nervous system.4,5 Severe clinical symptoms and neurologic deterioration have been documented in infants with nutritional cobalamin deficiency.6,7 In children from macrobiotic families, metabolic signs of persistent cobalamin deficiency were observed even in adolescence after consumption of animal products since the age of 6 years.8 Although these adolescents seemingly were in good health, clear evidence of impaired cognitive performance was demonstrated.9 This emphasizes the importance of cobalamin status for central nervous system development and shows that even moderate deficiency in children may be harmful.6,10

During the past decade, it was documented that impaired cobalamin status may exist with normal serum cobalamin and without the classical sign of megaloblastosis or neuropathy.11 This concept is based on studies that measure plasma levels of the metabolites methylmalonic acid (MMA) and total homocysteine (tHcy), which serve as markers of cobalamin function in tissues. Cobalamin functions as a cofactor in the enzymes methylmalonyl coenzyme A mutase and methionine synthase, and impaired catalytic activity of these enzymes causes accumulation of MMA and tHcy, respectively. MMA is a relatively specific indicator of cobalamin function, whereas increased tHcy is observed in a variety of conditions, including folate deficiency.12,13

In the present study, we assessed the cobalamin status in newborns and their mothers, at birth and after 6 weeks, by measuring serum cobalamin and the functional markers plasma MMA and tHcy. The aim was to investigate whether maternal factors influenced the cobalamin status of the newborns.

METHODS

Participants

The participants were recruited from among 186 consecutive births, both vaginal and caesarean, of healthy, nonpremature (>35 weeks) newborns, registered at the Department of Obstetrics and Gynecology at Haukeland University Hospital in Bergen, Norway, in the period from 1996 to 1997. Pregnancies that were complicated with diabetes or Rh-incompatibility and mothers who were on regular drug treatment were excluded (a total of 13 mother–newborn pairs). All mothers reported that they consumed an omnivorous diet. A total of 169 mothers and 173 newborns were enrolled in the study; this included 2 sets of twins. All participants were invited for a second investigation after 6 weeks, and 43 mothers with a total of 45 infants chose to do so. The protocol was approved by the local ethics committee, and written informed consent was obtained from the mothers.
**TABLE 2.** Characteristics of the Newborns and Mothers at Birth

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborns (n = 173)*</td>
<td>40 (39–41)</td>
</tr>
<tr>
<td>Birth weight (g) [median (25–75%)]</td>
<td>3700 (3350–4000)</td>
</tr>
<tr>
<td>Small for gestational age [%]</td>
<td>13 (8)</td>
</tr>
<tr>
<td>Caesarean section [%]</td>
<td>31 (18)</td>
</tr>
<tr>
<td>Mothers (n = 169)</td>
<td>45 (27)</td>
</tr>
<tr>
<td>Age (y) [median (25–75%)]</td>
<td>29.0 (26–34)</td>
</tr>
<tr>
<td>Parity</td>
<td>62 (37)</td>
</tr>
<tr>
<td>Intake of vitamin supplements</td>
<td>107 (63)</td>
</tr>
<tr>
<td>Daily [%]</td>
<td>31 (18)</td>
</tr>
</tbody>
</table>

* Includes 2 sets of twins.

**Data Collection**

The gestational age was based on information of the last menstrual date, early ultrasound determination, and a pediatric examination of the newborn at day 1. Data on diet and intake of vitamin supplements during pregnancy were obtained through an interview with the mother at the time of her newborn’s birth. Information on current and former pregnancies was obtained by interview at the time of the newborn’s birth and checked against the data registered by the Medical Birth Register of Norway.

Intake of vitamin supplements was categorized as daily, 2 to 3 times a week, and never. Parity was categorized as, para 0 (no other children), para 1 (1 other child), and para 2+ (2 or more other children).

**Blood Sampling and Storage**

Venous blood samples from the mother and the infant were collected at day 4 (96–108 hours) after birth and after 6 weeks. The samples used for tHcy determination were placed immediately in whole-blood folate (nmol/L) MMA levels in infants at 6 weeks were confirmed with a method based on capillary electrophoresis with laser-induced fluorescence detection.20

Plasma tHcy was determined by liquid chromatography–mass spectrometry–mass spectrometry. Deuterated homocysteine was added as internal standard, and the sample was treated with dithioerythritol, followed by acid precipitation. The supernatant was analyzed by reversed-phase chromatography. The between-day coefficient of variation is approximately 5%. High (>1 μmol/L) MMA levels in infants at 6 weeks were confirmed with a method based on capillary electrophoresis with laser-induced fluorescence detection.20

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**Biochemical Analyses**

The plasma levels of MMA were assayed using a gas chromatography–mass spectrometry method based on ethylchlorformate derivatization.20 The between-day coefficient of variation of this method is approximately 5%. High (>1 μmol/L) MMA levels in infants at 6 weeks were confirmed with a method based on capillary electrophoresis with laser-induced fluorescence detection.20

**RESULTS**

**Statistical Analysis**

Results are presented as median value and interquartile range. Medians were compared by Wilcoxon signed rank test and Mann-Whitney U test. Correlation was assessed by Spearman correlation coefficients.

To assess the simultaneous relations between the various predictors of serum cobalamin, plasma tHcy, and plasma MMA in the infant at birth and after 6 weeks, multiple linear regression models were used. The dependent variable was infant serum cobalamin, plasma tHcy, or plasma MMA. The independent variables were represented in the model as indicator variables denoting membership in 1 of 3 categories for maternal serum cobalamin, plasma tHcy, plasma MMA (tertiles), vitamin intake, and parity. Each regression coefficient estimated the difference in cobalamin, tHcy, or MMA between the reference category and the other categories for each variable.

Logistic regression was used to assess influence of maternal blood indices on cobalamin status in the newborns at birth. The outcomes were low cobalamin (lower quartile), high plasma tHcy (upper quartile), or high plasma MMA (upper quartile).

Two-sided P values <0.05 were considered statistically significant. The SPSS statistical package (version 6.1.1; SPSS, Inc, Chicago, IL) was used for all statistical analyses.

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(63%), the number of other children ranged from 1 to 10, with a mean of 1.7 children per mother. Thirty-six percent of the mothers used vitamin supplements during pregnancy (daily or 2–3 times a week; Table 1), and 74% of the supplements taken contained cobalamin alone or in combination with folate.

At 6 weeks, the majority of the infants (74%) were breastfed exclusively, 24% received a combination of breast milk and formula, and 1 child was formula fed exclusively. The 43 mothers who were examined at 6 weeks did not differ from the whole study population with respect to parity and use of vitamin supplements.

Blood Indices

Concentrations of vitamins and metabolites in newborns and their mothers at birth and after 6 weeks are presented in Table 2. At birth, the median serum cobalamin level was 28% higher in the newborns than in the mothers (Table 2). Fourteen (8%) of 173 newborns and 25 (15%) of 169 mothers had cobalamin levels below the reference range of 150 pmol/L. These newborns with low cobalamin levels had significantly higher median plasma tHcy (8.41 vs 6.18 μmol/L; P = .002) and MMA levels (0.52 vs 0.29 μmol/L; P < .001) compared with newborns with serum cobalamin levels above 150 pmol/L.

We compared the vitamin and metabolite concentrations at birth in the subset of 45 newborns who were investigated at 6 weeks with those of the newborns who did not return for a second investigation (Table 2). Only serum folate was significantly different (P = .02) between the 2 groups.

During the first 6 weeks after birth, the median cobalamin concentrations decreased in the infants and increased in the mothers (Table 2). After 6 weeks, 8 (18%) of 45 infants had serum cobalamin levels below 150 pmol/L, whereas all of the mothers had cobalamin levels above 200 pmol/L.

In the neonates, whole-blood folate was reduced during the first 6 weeks, serum folate was stable, and plasma tHcy levels and in particular MMA increased significantly (Table 2). MMA increased markedly (≥1 μmol/L) in approximately 30% of the infants, moderately (0.1–1 μmol/L) in 30%, and was essentially stable in the remaining infants.

In the infants, the decrease in serum cobalamin and the increase in plasma MMA and tHcy during the first 6 weeks were observed across the whole range of the respective metabolites (Fig 1).

Simple Correlations

We determined the univariate relations between vitamins, tHcy, and MMA in neonates and their mothers at birth and at 6 weeks. The results at birth are shown in Table 3.

At birth, there was a strong association between maternal and newborn cobalamin status, as indicated by high correlation coefficients of newborn serum cobalamin (Fig 2), plasma tHcy, and plasma MMA versus maternal cobalamin, tHcy, and MMA levels (Table 3). In neonates at birth, cobalamin status seemed to be the main determinant of tHcy. This is evident from a strong, inverse association between serum cobalamin and both tHcy and MMA (Fig 3), which contrasts to no significant association between tHcy and serum or whole-blood folate (Table 3).

In the 45 infants who were investigated after 6 weeks, there was still a strong inverse relation between serum cobalamin and plasma tHcy (r = −0.42, P = .005). The association between serum cobalamin and plasma MMA was no longer observed (r = −0.05, P = .7). There was, however, a significant association between values at birth and at 6 weeks for cobalamin (r = 0.58, P < .001), tHcy (r = 0.33, P = .03), and MMA (r = 0.35, P = .02), which is in
agreement with the data presented in Fig 1. Also at 6 weeks, plasma tHcy was not significantly related to serum ($r = 0.04$, $P = 0.8$) or whole-blood folate ($r = -0.24$, $P = 0.1$).

Maternal Determinants of Cobalamin Status in the Newborn

At birth, the strongest predictor by multiple linear regression of newborn cobalamin, tHcy, and MMA levels was maternal serum cobalamin levels and, to a lesser degree, maternal tHcy, MMA, and parity (Table 4). Using logistic regression, we assessed the influence of maternal indicators of cobalamin status on low levels of serum cobalamin (lower quartile: <238 pmol/L) and high levels of plasma tHcy (upper quartile: >7.48 μmol/L) and MMA (upper quartile: >0.38 μmol/L) in the newborns (Table 5). A low maternal cobalamin level (lower tertile: <201 pmol/L) was the strongest predictor of low cobalamin (odds ratio [OR]: 7.5), high tHcy (OR: 11.8), and high MMA (OR: 5.2) levels in the newborns.

At 6 weeks, parity was a strong predictor of cobalamin status in the infant, as determined by serum
All but 1 of the infants with very high MMA levels (1.5 μmol/L; n = 12) were born to parous mothers (Fig 4).

DISCUSSION

In the present study, we demonstrated that maternal cobalamin status predicts cobalamin status in newborns at birth. During the first 6 weeks of life, there is a considerable decrease in the infant’s serum cobalamin level. This is accompanied by a marked increase in functional tissue markers of cobalamin status, plasma tHcy, and plasma MMA. Parity was a strong predictor of cobalamin indicators in the child at 6 weeks.

Cobalamin and Metabolite Levels

In the newborns, the serum cobalamin level was high at birth and decreased during the first 6 weeks (Table 2). These observations confirm published data.21–23 The opposite pattern was found in the mothers; their cobalamin concentrations were low at birth and increased during the 6 weeks (Table 2). Similar observations have been made by others.24–27

In newborns at birth, cobalamin status seems to be the main determinant of tHcy, because tHcy was strongly associated with serum cobalamin, but not with serum or whole-blood folate (Fig 2, Table 3). Similar data were published from a Swiss study on 123 neonates, demonstrating that serum cobalamin was the strongest predictor of tHcy, but there was also a significant association between tHcy and blood folate.28 In contrast, we found only a weak and nonsignificant relation between tHcy and folate (Table 3).

The extensive changes in the levels and associations between cobalamin and metabolites during the neonatal period potentially are of great clinical importance. The reduction in serum cobalamin and the increase in tHcy and MMA may reflect efficient utilization of cobalamin in the growing organism, combined with marginal body stores and an inadequate supply. The high MMA levels and attenuation of the MMA–cobalamin relation at 6 weeks combined with only a moderate increase in tHcy may reflect redistribution of tissue cobalamin in favor of the methionine synthase reaction. Such a mechanism may be necessary to provide sufficient cellular folate and methionine to support cell growth. Another possibility is that the high MMA at 6 weeks cannot be

**TABLE 4.** Maternal Factors at Birth as Determinants of Serum Cobalamin, Plasma tHcy and Plasma MMA in Infants at Birth (n = 173) and at 6 Weeks (n = 45)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Infant Serum Cobalamin (pmol/L)</th>
<th>Infant Plasma tHcy (μmol/L)</th>
<th>Infant Plasma MMA (μmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Birth</td>
<td>6 Weeks</td>
<td>Birth</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>P</td>
<td>B</td>
</tr>
<tr>
<td>Maternal cobalamin*</td>
<td>93</td>
<td>.001</td>
<td>18</td>
</tr>
<tr>
<td>Maternal tHcy*</td>
<td>−47</td>
<td>.005</td>
<td>15</td>
</tr>
<tr>
<td>Maternal MMA*</td>
<td>−38</td>
<td>.02</td>
<td>0.7</td>
</tr>
<tr>
<td>Vitamin supplements†</td>
<td>15</td>
<td>.36</td>
<td>32</td>
</tr>
<tr>
<td>Parity‡</td>
<td>−42</td>
<td>.03</td>
<td>−36</td>
</tr>
</tbody>
</table>

Multiple linear regression; the model contains maternal age, gestational age, and sex in addition to the parameters listed in the table.

* Tertiles.
† Never, 2–3/week, daily.
‡ Para 0, Para 1, Para 2+.

**TABLE 5.** OR for Low Serum Cobalamin, High Plasma tHcy, or High Plasma MMA in Newborns at Birth According to Indicators of Maternal Cobalamin Status*

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>Newborn Serum Cobalamin &lt;238 pmol/L†</th>
<th>Newborn Plasma tHcy &gt;7.48 μmol/L‡</th>
<th>Newborn Plasma MMA &gt;0.38 μmol/L‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal serum cobalamin (vs tertile 3; &gt;293 pmol/L)</td>
<td>201–293</td>
<td>1.7 (0.6–5.2)</td>
<td>2.3 (0.7–7.9)</td>
</tr>
<tr>
<td>&lt;201</td>
<td>7.5 (2.7–20.5)</td>
<td>11.8 (3.8–37.4)</td>
<td>5.2 (1.9–13.9)</td>
</tr>
<tr>
<td>P trend</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Maternal tHcy (vs tertile 1; &lt;7.18 μmol/L)</td>
<td>7.18–9.14</td>
<td>5.4 (1.9–15.9)</td>
<td>3.6 (1.4–9.6)</td>
</tr>
<tr>
<td>&gt;9.14</td>
<td>5.0 (1.7–14.6)</td>
<td>2.8 (1.0–7.4)</td>
<td>1.9 (0.8–4.7)</td>
</tr>
<tr>
<td>P trend</td>
<td>.05</td>
<td>.06</td>
<td>.17</td>
</tr>
<tr>
<td>Maternal MMA (vs tertile 1; &lt;0.14 μmol/L)</td>
<td>0.14–0.19</td>
<td>1.4 (0.6–3.6)</td>
<td>2.2 (0.9–5.2)</td>
</tr>
<tr>
<td>&gt;0.19</td>
<td>2.9 (1.2–7.1)</td>
<td>1.9 (0.8–4.7)</td>
<td>4.9 (1.9–13.2)</td>
</tr>
<tr>
<td>P trend</td>
<td>.02</td>
<td>.16</td>
<td>.001</td>
</tr>
</tbody>
</table>

* Adjusted for maternal age, gestational age, and sex by logistic regression. CI indicates confidence interval.
† Lower quartile (quartile 1).
‡ Upper quartile (quartile 4).

Cobalamin, plasma tHcy, and plasma MMA (Table 4). All but 1 of the infants with very high MMA levels >1.5 μmol/L (n = 12) were born to parous mothers (Fig 4).
accounted for totally by low cobalamin-dependent methylmalonic coenzyme A mutase, and additional mechanisms may be involved (eg, propionate production by the intestinal flora29 or liver immaturity30). Intervention studies to investigate the cobalamin responsiveness of the methylmalonic acidemia may provide an answer to this question. Finally, when screening for, diagnosing, and following up the inborn error of methylmalonic aciduria, the common methylmalonic acidemia reported here, as well as benign methylmalonic aciduria30,31 should be taken into account.

Possible Clinical Implications

We observed no relation between serum cobalamin or metabolite levels and hematologic parameters in the newborns (data not shown), suggesting that the impaired cobalamin function causes no hematologic changes. However, neurologic damage may precede any signs of megaloblastosis.11 The high incidence of elevated tHcy and MMA suggests that impaired cobalamin function may be common in the neonatal period. Considering the important role for cobalamin in central nervous system development, this observation is alarming.

Maternal Predictors of Cobalamin Status in the Newborn

The present study demonstrated that maternal cobalamin status is an important determinant of cobalamin status in newborns. This conclusion gains solid support from the observation at birth in 173 mother–newborn pairs, in whom all 3 markers of maternal cobalamin status (serum cobalamin, plasma MMA, and plasma tHcy) predict low serum cobalamin, high plasma MMA, and high plasma tHcy in the newborns (Tables 4 and 5). There are previous reports on a positive relation between cobalamin in maternal serum and in cord blood,32 but the present data extend this knowledge by demonstrating that this relation is not limited to the circulating cobalamin pool but most likely also involves deeper tissue compartments of cobalamin, as determined by tHcy and MMA levels (Table 4).

At 6 weeks, parity becomes a strong predictor of cobalamin tissue function in the infants. Notably, at this time a methylmalonic acidemia (MMA >1 μmol/L) develops in approximately one third of the infants. The mechanism behind the strong, negative effect of parity on cobalamin marker plasma MMA in neonates is not apparent, but may suggest insufficient placental cobalamin transfer to the fetus in parous women as a result of their lower cobalamin stores.33

CONCLUSION

We found that measures of maternal circulating and tissue cobalamin and parity are strong determinants of cobalamin status in the infant. The maternal factors predicted low serum cobalamin and high plasma MMA or tHcy, which are markers of impaired cobalamin function. Notably, we studied consecutive pregnancies in healthy, well-nourished mothers who consumed an omnivorous, nonvegetarian diet, and even in this population we found biochemical evidence of cobalamin deficiency, particularly in infants who were born to parous mothers. Our data suggest that the prevalence of impaired cobalamin status in the neonatal period may be underestimated and should motivate intervention studies with cobalamin in pregnancy and in newborns.

ACKNOWLEDGMENTS

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AMERICANIZATION OF THE WORLD

...Fast food is the one form of American culture that foreign consumers literally consume. By eating like Americans, people all over the world are beginning to look more like Americans, at least in one respect. The United States now has the highest obesity rate of any industrialized nation in the world. More than half of all American adults and about one-quarter of all American children are now obese or overweight.


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