Biochemical indexes of the B vitamins in cord serum are predicted by maternal B vitamin status\textsuperscript{1,2}

Rima Obeid, Winfried Munz, Monika Jäger, Werner Schmidt, and Wolfgang Herrmann

ABSTRACT

Background: The concentration of total homocysteine (tHcy) is higher in newborns than in older children. Vitamin B-12 is the major determinant of tHcy in newborns. Maternal status of folate, vitamin B-12, and vitamin B-6 during pregnancy may affect the biochemical markers of these micronutrients in newborns.

Objective: Our objective was to study the relation between concentrations of the metabolites and B vitamins in maternal sera and concentrations in the umbilical venous blood of the corresponding newborns.

Design: We studied healthy pregnant women at the time of labor who were expecting healthy, full-term, appropriate-birth-weight babies. Samples were available from 82 mother-infant pairs.

Results: Concentrations of B vitamins were higher in cord samples than in maternal blood (folate, 2-fold; vitamin B-12, 1.5-fold; and vitamin B-6, 6-fold). Concentrations of cystathionine and methylmalonic acid (MMA) were also higher in the infants than in the mothers (\(\bar{x} \pm SD\): cystathionine, 462 \pm 189 and 343 \pm 143 nmol/L; MMA, 353 \pm 144 and 233 \pm 110 nmol/L). No significant differences in tHcy concentrations were observed between fetal and maternal samples. Concentrations of vitamin B-12 did not differ significantly between mothers of infants from different quartiles of cord MMA. Higher fetal MMA concentrations were related to higher maternal MMA and vitamin B-12 concentrations and lower fetal concentrations of vitamin B-12. Fetal concentrations of cystathionine were predicted by maternal cystathionine, gestational age, fetal vitamin B-6, and fetal tHcy.

Conclusions: Maternal concentrations of the metabolic markers of B vitamins predict values in fetal blood at delivery. Fetal tHcy concentrations were low but were predicted by the vitamin status of the mother. The effect of increasing maternal intake of vitamins B-12 and B-6 during pregnancy on the fetal concentrations of the metabolites should be investigated. Am J Clin Nutr 2005;82:133–9.

KEY WORDS Homocysteine, methylmalonic acid, cystathionine, folate, vitamin B-12

INTRODUCTION

The requirements for B vitamins (folate, vitamin B-12, and vitamin B-6) are exceptionally high during pregnancy as a result of increased maternal metabolic rate and fetal demands (1). Available evidence suggests that maternal nutritional status before and during pregnancy is the main determinant of the nutritional status of the offspring (2, 3). Folate, vitamin B-12, and vitamin B-6 function as cofactors in one-carbon metabolism, DNA synthesis, and numerous methylation reactions. These metabolic pathways are particularly active in developing embryos.

Poor maternal status of B vitamins has been linked to pregnancy complications and poor outcomes (4–8). B vitamins may lower serum concentrations of total homocysteine (tHcy) (3) and may protect against undesirable pregnancy outcomes (7, 9). The metabolism of folate, vitamin B-12, vitamin B-6, and tHcy is interrelated, and the tHcy concentration is a sensitive indicator of the status of the B vitamins. Moreover, the concentration of methylmalonic acid (MMA) becomes specifically elevated in the blood of vitamin B-12-deficient persons (10). Cystathionine is an intermediate product of homocysteine transsulfuration. This compound increases in the case of vitamin B-6 deficiency. The combined use of the metabolic markers (tHcy, MMA, and cystathionine) improves the sensitivity and the specificity of detecting possible disturbances in the remethylation and the transsulfuration pathways (10).

Several studies investigated B vitamin status in pregnant women and their newborns (11–15). Maternal concentrations of tHcy before delivery were strongly related to preconception levels and, more importantly, to tHcy concentrations in umbilical cord blood (3, 11). Folate-supplemented mothers and their newborns had lower concentrations of tHcy at the time of labor than did those who had not taken supplements (3). Studies of neonates (aged 3 d to 6 mo) have shown markedly higher serum concentrations of tHcy and MMA in these infants than in older children (16). Moreover, concentrations of tHcy and MMA were higher in newborns 6 wk after birth than at birth (2). However, most neonates remain virtually asymptomatic. Elevated concentrations of tHcy in neonates are related to higher concentrations of MMA, cystathionine, or methionine (16, 17). In contrast with the case in older children, the metabolic changes were associated with lower concentrations of vitamin B-12 rather than folate (16). Therefore, a transient inadequate vitamin B-12 status and a disturbed transmethylation at this age have been suspected (2, 16, 17). The
reports mentioned above prompted us to examine the concentra-
tion of the metabolites and the corresponding vitamins in umbil-
ical venous blood at birth. The present study was designed to
investigate the relation between the concentration of the metab-
olites and B vitamins in maternal sera and in the venous umbilical
cord sera of the corresponding newborns.

SUBJECTS AND METHODS

Subjects and clinical data

Pregnant women admitted with the onset of confirmed labor
were randomly recruited among consecutive deliveries at the
Department of Obstetrics and Gynecology, University Hospital
of Saarland. Inclusion criteria were being a healthy pregnant
woman aged >17 y and free of chronic diseases or pregnancy
complications and expecting a singleton, full-term (≥37 wk),
healthy infant of appropriate length and weight. Both vaginal
and cesarean births were included. Samples from 82 mothers and
from the venous umbilical cord blood of their newborns were
available at the end of the study.

Gestational age was defined on the basis of information about
the last menstrual period and an ultrasound estimation of the fetus
size. This was then confirmed after birth by a physical examina-
tion of the newborn. Maternal anthropologic measures and data
on smoking, diet, vitamin use during pregnancy, parity, and
gravidity were obtained by interviewing the participants on ad-
mission. Parity was defined as primiparous (no former children)
or multiparous (parity of 1 or ≥2). Clinical characteristics of the
newborns were also documented (weight, length, head circum-
fERENCE, blood gases, and venous and arterial blood pH). The
study was approved by the Medical Ethical Committee of the
University Hospital of Saarland, and all participants gave their
informed consent to participate.

Blood sampling and laboratory analysis

Nonfasting blood samples were obtained from the antecubital
vein of the mothers 1–12 h before birth. Immediately after de-
livery, the cord was clamped at both ends and cut. A blood sample
was collected from the umbilical vein. Maternal and cord blood
samples were collected in tubes without anticoagulant, left to
clot, and centrifuged within 45 min at 2000 × g and 4 °C. Serum
was directly separated and stored at −70 °C until analyzed.

Serum concentrations of tHcy, cystathionine, and MMA were
measured by using gas chromatography–mass spectrometry as
described elsewhere (18). Maternal and cord blood were mea-
sured in the same run. Concentrations of vitamin B-12 and folate
were measured by using a chemiluminescence immunoassay
(ADVIA Centaur System, Bayer, Germany). The serum concen-
tration of vitamin B-6 (pyridoxal-5′-phosphate, or PLP) was de-
termined by HPLC with a fluorescence detector and reagents
from Immundiagnostik (Bensheim, Germany). The reference
values in our laboratory for nonpregnant women (aged 17–42 y)
are as follows: >207 pmol/L for vitamin B-12, >16.8 nmol/L for
folate, and ≥36.1 nmol/L for vitamin B-6 (the 5th percentiles),
<13.0 μmol/L for tHcy, <243 nmol/L for MMA, and <290
nmol/L for cystathionine (the 95th percentiles).

Statistical analysis

The distribution of each continuous variable was assessed by
using the Kolmogorov-Smirnov test. All variables were skewed
and were therefore log-transformed to approach a normal distri-
bution before tests were applied that propose such a distribution
of the data. Data are presented as means or geometric means and
SDs. Means of continuous variables were compared between
mothers and cord sera by using the paired Student’s t test. Intra-
group multiple comparisons were performed by using one-way
analysis of variance (ANOVA). The post hoc Tamhane test was
performed to identify significantly different group means when
the ANOVA test was significant. Multivariable backward re-
gression analyses were conducted to identify significant vari-
ables that predicted changes in the concentrations of the metab-
olites in cord sera. Correlations between different variables were
examined by using Spearman’s test. All tests were two-sided, and
P values < 0.05 were considered to be statistically significant.

RESULTS

The main characteristics of the participating women and their
newborns are shown in Table 1. Concentrations of some bio-
chemical markers in maternal and cord serum samples are shown
in Table 2. Significantly higher concentrations of MMA, folate,
vitamin B-12, and PLP were observed in cord serum samples
than in maternal sera (Table 2). Mean concentrations of folate,
vitamin B-12, and PLP were 2-, 1.5-, and 6-fold higher, respec-
tively, in fetal than in maternal sera. Mean concentrations of
cystathionine were slightly lower in the mothers than in cord
blood samples. No significant differences in the concentrations
of tHcy were found between maternal and cord sera (Table 2).
The interindividual CVs for fetal tHcy, cystathionine, and MMA
were 34%, 40%, and 39%, respectively. The CVs of maternal
concentrations were 27% for Hcy, 38% for cystathionine, and
43% for MMA.

| TABLE 1 |
|----------------|----------------|
| Main characteristics of the mothers and infants | Value |
| Characteristic | Value |
| Mothers (n = 82) | |
| Age (y) | 30 ± 6 |
| Current BMI (kg/m²) | 28.2 ± 4.4 |
| Weight increase during pregnancy (kg) | 12.7 ± 5.0 |
| Vaginal delivery [n (%)] | 56 (68) |
| Smoking [n (%)] | 18 (22) |
| Folate supplementation during pregnancy [n (%)] | 14 (17) |
| Parity [n (%)] | |
| Nulliparous | 36 (44) |
| Parity of 1 | 27 (33) |
| Parity ≥ 2 | 19 (23) |
| Infants (n = 82) | |
| Gestational age (wk) | 39.5 ± 1.1 |
| Boys [n (%)] | 42 (51) |
| Birth weight (g) | 3363 ± 423 |
| Head circumference (cm) | 35 ± 1.8 |
| Venous blood pH | 7.4 ± 0.1 |
| Arterial blood pH | 7.3 ± 0.1 |
| P<sub>CO₂</sub> (mm Hg)<sup>2</sup> | 45.0 ± 9.1 |
| P<sub>O₂</sub> (mm Hg)<sup>2</sup> | 20.2 ± 15.2 |

1 ± SD (all such values).
2 P<sub>CO₂</sub>, partial pressure of carbon dioxide; P<sub>O₂</sub>, partial pressure of oxygen.
Correlations between maternal serum and cord blood markers

TABLE 3

Concentrations of the metabolites and B vitamins in maternal serum and in cord blood samples

<table>
<thead>
<tr>
<th>Serum marker</th>
<th>Mothers (n = 82)</th>
<th>CV%</th>
<th>Cord blood (n = 82)</th>
<th>CV%</th>
<th>Fetal-maternal difference</th>
<th>Fetal/maternal ratio</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>tHcy (μmol/L)</td>
<td>5.62 ± 1.61</td>
<td>27</td>
<td>5.37 ± 1.93</td>
<td>34</td>
<td>−0.12 ± 1.50</td>
<td>0.96 ± 0.30</td>
<td>0.484</td>
</tr>
<tr>
<td>Cystathionine (nmol/L)</td>
<td>343 ± 143</td>
<td>38</td>
<td>462 ± 189</td>
<td>40</td>
<td>214 ± 969</td>
<td>1.35 ± 0.39</td>
<td>0.052</td>
</tr>
<tr>
<td>MMA (nmol/L)</td>
<td>233 ± 110</td>
<td>43</td>
<td>353 ± 144</td>
<td>39</td>
<td>119 ± 122</td>
<td>1.51 ± 0.57</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vitamin B-12 (pmol/L)</td>
<td>172 ± 48</td>
<td>27</td>
<td>248 ± 128</td>
<td>49</td>
<td>86 ± 81</td>
<td>1.44 ± 0.48</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PLP (nmol/L)</td>
<td>13.1 ± 9.4</td>
<td>65</td>
<td>78.0 ± 72.9</td>
<td>78</td>
<td>82.0 ± 67.9</td>
<td>6.04 ± 3.57</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Folate (nmol/L)</td>
<td>27.0 ± 19.6</td>
<td>62</td>
<td>60.9 ± 21.1</td>
<td>34</td>
<td>30.7 ± 15.0</td>
<td>2.23 ± 1.19</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Some important correlations between maternal and cord blood markers are shown in Table 3. Gestational age correlated significantly with the concentration of cystathionine in cord serum (r = −0.33, P = 0.004). This correlation remained significant after adjustment for fetal PLP or maternal cystathionine. Maternal concentrations of MMA and vitamin B-12 did not correlate significantly (r = −0.16, P = 0.148).

Concentrations of B vitamins and their metabolites in cord and maternal sera according to quartiles of MMA in cord serum are shown in Table 4. A higher concentration of cord MMA was associated with higher concentrations of tHcy and cystathionine in cord blood. The mean concentration of fetal vitamin B-12 was significantly higher in infants with lower MMA than in those with higher MMA. Furthermore, mean concentrations of MMA were significantly higher in mothers of infants in the fourth quartile of cord MMA than in mothers of infants in the first MMA quartile. Concentrations of vitamin B-12 did not differ significantly between mothers of infants from different quartiles of cord MMA.

The differences between fetal and maternal MMA (ΔMMA) increased along quartiles of fetal MMA. On the other hand, differences in vitamin B-12 between maternal and cord sera (ΔB-12) were higher in the lowest quartile of cord MMA (Table 4). Concentrations of MMA in cord sera showed a negative and highly significant correlation with ΔB-12 (Figure 1). Backward regression analysis showed that concentrations of MMA in cord sera were predicted by maternal MMA (β = 0.565, P < 0.001), maternal vitamin B-12 (β = 0.379, P = 0.012), and fetal vitamin B-12 (β = −0.362, P = 0.001).

Shown in Figure 2 are the mean (95% CI) concentrations of folate, PLP, tHcy, and cystathionine in maternal and cord sera according to quartiles of tHcy in cord serum. Mothers of infants with higher concentrations of tHcy had lower concentrations of folate and PLP and higher concentrations of tHcy than did mothers of infants with lower concentrations of tHcy. Higher concentrations of tHcy in cord serum were also associated with slightly lower concentrations of cord folate and PLP and higher concentrations of cord cystathionine. However, concentrations of cystathionine were not higher in mothers of infants with higher tHcy. Concentrations of tHcy in cord blood were predicted by maternal tHcy (β = 0.721, P < 0.001), fetal cystathionine (β = 0.259, P = 0.016), and maternal cystathionine (β = −0.239, P = 0.032) in that order.

Shown in Figure 3 are the mean (95% CI) maternal and fetal concentrations of cystathionine, tHcy, folate, and PLP according to concentrations of cystathionine in cord serum. Higher concentrations of cystathionine in cord serum were associated with lower fetal and maternal PLP, higher maternal cystathionine, and higher fetal and maternal tHcy. Regression analysis showed that gestational age (β = −2.881, P = 0.009), maternal cystathionine (β = 0.574, P < 0.001), fetal tHcy (β = 0.234, P = 0.014), and fetal PLP (β = −0.113, P = 0.015) were significant factors that predicted cystathionine concentrations in cord serum.

TABLE 3

Correlations between maternal serum and cord blood markers

<table>
<thead>
<tr>
<th>Maternal markers</th>
<th>Cord blood markers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>tHcy</td>
</tr>
<tr>
<td>Gestational age</td>
<td>−0.13</td>
</tr>
<tr>
<td>tHcy</td>
<td>0.60</td>
</tr>
<tr>
<td>Cystathionine</td>
<td>0.42</td>
</tr>
<tr>
<td>MMA</td>
<td>0.06</td>
</tr>
<tr>
<td>Folate</td>
<td>−0.28</td>
</tr>
<tr>
<td>Vitamin B-12</td>
<td>0.04</td>
</tr>
<tr>
<td>Vitamin B-6</td>
<td>−0.23</td>
</tr>
</tbody>
</table>

* Correlations were assessed by Spearman’s ρ test. tHcy, total homocysteine; MMA, methylmalonic acid.

P < 0.05.
both the correlation coefficient and the difference in vitamin B-12 concentrations between cord and maternal sera (median: 35.5 compared with 22.9 nmol/L; *P* = 0.026). Folate was also slightly higher in infants of supplemented mother than in infants of unsupplemented mothers (median: 73.2 compared with 58.0; *P* = 0.064).

Eighteen mothers who smoked during pregnancy reported having smoked <10 cigarettes daily. Significantly lower serum concentrations of folate were detected in smoking than in nonsmoking mothers (median: 18.4 compared with 30.6 nmol/L; *P* = 0.009). Moreover, lower cord serum concentrations of folate were observed in cord blood samples from newborns of smoking mothers than in samples from newborns of nonsmoking mothers (median: 57.1 compared with 61.0; *P* = 0.039). These findings were not related to folate supplementation during pregnancy because smoking mothers and their infants differed from nonsmoking mothers and their infants when only non-vitamin-users were considered in the analysis.

Neither the type of delivery nor the duration of the vaginal delivery was related to any of the markers investigated in this study (data not shown). No relation between parity and the vitamins (folate, vitamin B-12, and vitamin B-6) at birth were significant implications on the progress and outcome of the pregnancy. Insufficient maternal vitamin B-12 status may affect methylation potential in neonates (19). The current study included a healthy group of pregnant women and their newborn infants. Concentrations of B vitamins and their metabolites showed a relatively wide range of interindividual variations. The most remarkable finding in this study was that markers of the B vitamins (folate, vitamin B-12, and vitamin B-6) at birth were related to maternal markers.

**DISCUSSION**

Maternal vitamin deficiency during pregnancy may have significant implications on the progress and outcome of the pregnancy. Insufficient maternal vitamin B-12 status may affect methylation potential in neonates (19). The current study included a healthy group of pregnant women and their newborn infants. Concentrations of B vitamins and their metabolites showed a relatively wide range of interindividual variations. The most remarkable finding in this study was that markers of the B vitamins (folate, vitamin B-12, and vitamin B-6) at birth were related to maternal markers.

**TABLE 4**

Concentrations of some biochemical markers in cord blood and in maternal serum according to quartile (Q) of methylmalonic acid (MMA) concentrations in cord blood.

| TABLE 4 |
|------------------|--|--|--|--|---|
| **Cord blood markers** | Q1 | Q2 | Q3 | Q4 |
| MMA (nmol/L) | 250 ± 37 | 308 ± 13 | 362 ± 19 | 558 ± 150 |
| Vitamin B-12 (pmol/L) | 298 ± 79 | 281 ± 211 | 232 ± 69 | 194 ± 68 |
| tHcy (µmol/L) | 4.81 ± 1.28 | 5.07 ± 1.94 | 5.44 ± 1.68 | 6.35 ± 2.40 |
| Folate (nmol/L) | 62.4 ± 26.8 | 62.1 ± 19.1 | 61.7 ± 18.1 | 57.1 ± 19.9 |
| Cystathionine (nmol/L) | 426 ± 182 | 378 ± 163 | 488 ± 217 | 588 ± 2030 |

**Maternal markers**

| MMA (nmol/L) | 168 ± 47 | 221 ± 76 | 247 ± 80 | 323 ± 144 |
| Vitamin B-12 (pmol/L) | 179 ± 50 | 181 ± 57 | 169 ± 35 | 159 ± 49 |
| tHcy (µmol/L) | 5.43 ± 1.63 | 5.63 ± 1.40 | 5.63 ± 1.42 | 5.81 ± 1.98 |
| Folate (nmol/L) | 24.9 ± 20.4 | 26.8 ± 14.0 | 26.4 ± 18.0 | 30.6 ± 25.0 |
| Cystathionine (nmol/L) | 358 ± 145 | 330 ± 104 | 361 ± 204 | 324 ± 101 |

**Fetal-maternal difference**

| ∆MMA (nmol/L) | 79 ± 41 | 75 ± 74 | 104 ± 82 | 223 ± 185 |
| ∆B-12 (pmol/L) | 126 ± 66 | 106 ± 112 | 72 ± 67 | 39 ± 46 |
| ∆Hcy (µmol/L) | −0.59 ± 1.65 | −0.31 ± 1.42 | −0.04 ± 1.27 | 0.51 ± 1.53 |
| ∆Folate (nmol/L) | 35.2 ± 19.8 | 31.4 ± 8.7 | 33.2 ± 12.9 | 22.5 ± 13.9 |

* tHcy, total homocysteine; ∆, difference.
* ANOVA.
* Geometric ¯ ± SD.
* Geometrically transformed values.
* *P* < 0.05 (post hoc Tamhane test).

**Other important analyses**

Serum concentrations of all biochemical markers did not differ significantly between cord serum samples from boys and those from girls. Comparable values were also found in mothers of boys and those of girls (data not shown). As would be expected, mothers who reported having taken folate supplementation during pregnancy (n = 14) had significantly higher concentrations of serum folate than did unsupplemented mothers (median: 35.5 compared with 22.9 nmol/L; *P* = 0.026). Folate was also slightly higher in infants of supplemented mother than in infants of unsupplemented mothers (median: 73.2 compared with 58.0; *P* = 0.064).

Eighteen mothers who smoked during pregnancy reported having smoked <10 cigarettes daily. Significantly lower serum concentrations of folate were detected in smoking than in nonsmoking mothers (median: 18.4 compared with 30.6 nmol/L; *P* = 0.009). Moreover, lower cord serum concentrations of folate were observed in cord blood samples from newborns of smoking mothers than in samples from newborns of nonsmoking mothers (median: 57.1 compared with 61.0; *P* = 0.039). These findings were not related to folate supplementation during pregnancy because smoking mothers and their infants differed from nonsmoking mothers and their infants when only non-vitamin-users were considered in the analysis.

Neither the type of delivery nor the duration of the vaginal delivery was related to any of the markers investigated in this study (data not shown). No relation between parity and the vitamins or the metabolites could be confirmed in this study even after omitting the mothers who took folate during pregnancy.

**FIGURE 1.** Scatter plot representing the correlation between concentrations of methylmalonic acid (MMA) in cord serum and the difference in vitamin B-12 concentrations between cord and maternal sera (ΔB-12). The correlation coefficient and *P* value are according to Spearman’s test. Data on both the x and the y axes are anti-log.
Concentration of B vitamins in cord serum in relation to maternal serum

The concentration of B vitamins was considerably higher in fetal serum than in maternal serum (Table 2). A marked decrease in the serum concentration of B vitamins is known to take place during pregnancy (1, 20–25). Loading pregnant women with pyridoxal HCl was followed by a prompt increase in serum concentrations of PLP (24). Most importantly, higher concentrations of PLP were detected in cord serum after vitamin B-6 loading of the mothers than in cord serum from unsupplemented mothers (24). Furthermore, the PLP concentration showed an arterial-venous gradient with higher concentrations in umbilical venous than in arterial serum (26). These findings indicate that vitamin B-6 is readily transformed into its active form and then actively transferred to the fetus.

Data about the transplacental transfer of B vitamins are limited. It was reported that the placenta synthesizes transcobalamin and is rich with transcobalamin receptor (27). Furthermore, vitamin B-12 and folate are efficiently sequestered in the intervillosus space of the placenta (28). The placenta was shown to accumulate vitamin B-12 injected in pregnant animals (29). Therefore, the placenta seems to extract these essential micronutrients from the maternal circulation and redistribute them, probably favoring the fetus (26, 29–32). Rappazzo et al (33) investigated vitamin B-12 content in fetal and adult tissues. Despite high concentrations of vitamin B-12 in fetal serum, the fetal liver contained only 30% of the adult liver vitamin B-12 content calculated as pg vitamin B-12/mg tissue. The authors concluded that the fetus retains most of the vitamin B-12 in the blood and utilizes the available amount for biochemical reactions (33). The wide range of between-subjects CVs for fetal vitamin B-12 (49% in the cord samples compared with 27% in the mothers) also suggests that the transport of maternal vitamin B-12 may be determined by factors other than the concentrations of the vitamin.

Concentration of the metabolites in maternal and cord sera

The concentration of tHcy in cord samples did not differ significantly from that of the mothers (Table 2). Previous studies reported lower tHcy concentrations in cord serum than in maternal serum (3, 11). However, the mean maternal tHcy concentration was lower in our study than in previous ones (3, 11, 19). Additionally, differences in study designs, timing of blood collection, analytic methods, or the groups studied may be responsible for these different findings. As in previous reports (3), the concentration of tHcy in cord and maternal sera was strongly correlated in our study (Table 3). Previous studies showed that concentrations of methionine are much higher in cord than in maternal blood samples (19, 34). On the other hand, fetal concentrations of tHcy seemed to be maintained at low levels, despite the fact that the fetus is likely to be exposed to high concentrations of methionine. The high requirement for methyl groups implies that the transmethylation of methionine is active in developing embryos. Therefore, tHcy can be formed from methionine in the fetus. Moreover, tHcy was lower in the umbilical artery than in the umbilical vein (11). These results strongly suggest that tHcy remethylation to methionine is highly active during prenatal life because tHcy concentrations are relatively low in cord blood. This is probably due to the high fetal...
demand for tetrahydrofolate in DNA synthesis. Cystathionine is also formed as a product of tHcy catabolism (discussed below).

Concentrations of MMA were higher in cord blood than in the mothers or in healthy adults (Table 2; 10, 19). Concentrations of MMA were predicted by cord vitamin B-12 and maternal MMA (Table 2, 3). In addition, the regression analysis showed that higher maternal vitamin B-12 was a predictor of higher fetal MMA. Moreover, lower cord MMA was associated with larger differences between cord blood and maternal concentrations of vitamin B-12, but not with higher maternal concentrations of vitamin B-12 (Figure 1, Tables 3 and 4). These results suggest a rate-limiting step in the transplacental transport of vitamin B-12. Polymorphisms in the transcobalamin gene are one factor that might influence the transport of vitamin B-12 from the placenta to the fetus. Moreover, high serum concentrations of vitamin B-12 in cord blood may be related to a slower uptake of the vitamin, probably because of a lower expression or activity of transcobalamin receptor. A slow rate of MMA elimination from the plasma compartments in the fetus may also be related to higher MMA at birth. Finally, the positive association between fetal concentrations of vitamin B-12 and MMA suggests that the activity (or the expression) of fetal methylmalonyl-CoA mutase may be enhanced by increasing maternal intake of vitamin B-12. The effect of vitamin B-12 supplementation during pregnancy on fetal MMA needs further investigation.

Concentrations of cystathionine were higher in the mothers in the current study than in our reference population of nonpregnant women or in our previous investigations of healthy individuals (10). Because our study included a normal group of pregnant women and their infants, elevated cystathionine is probably physiologic. Elevated cystathionine in addition to low PLP in the third trimester and in fetal blood suggest a slower rate of the transsulfuration pathway. The mean concentration of cystathionine was higher in fetal blood than in the mothers (Table 2). The mean concentration of cystathionine in cord blood from our subjects was comparable with the values in a recent study of Brazilian women (19). High concentrations of cystathionine have also been reported in newborns (aged ≈4 d) (17).

Cystathionase activity is absent in human fetal liver tissues (35) and is dependent on pre- and postnatal age (36, 37). Hepatic transsulfuration activity was reported to be reduced at birth, especially in premature infants (36, 37). Although all newborns in our study were full-term, we observed a significant correlation between gestational age and concentrations of cystathionine in cord serum. Cystathioninuria in premature infants has been shown to improve after vitamin B-6 treatment, which is known to enhance the activity of cystathionase (37). These data indicate that higher cystathionine at birth might be related to incomplete activities of the enzymes that mediate the transsulfuration pathway. Interestingly, markers of the transsulfuration pathway (PLP...
or cystathionine) were significant determinants of fetal Hcy (Table 3). Cysteine was found to be lower in cord serum than in the mothers (19). This implies that homocysteine transferral via cystathionase is a rate-limiting step in the production of cysteine. It would be interesting to investigate the effect of improving maternal vitamin B-6 status on homocysteine transsulfuration in newborns.

In summary, the results of our study show that umbilical cord concentrations of MMA and cystathionine can be predicted by maternal concentrations. Lower cord concentrations of MMA and cystathionine were related to higher vitamin B-12 and vitamin B-6, respectively. The effect of maternal supplementation with vitamin B-12, vitamin B-6, or both during pregnancy on the newborn concentration of the metabolites should be investigated.

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