Periconceptional Vitamin Profiles Are Not Suitable for Identifying Women at Risk for Neural Tube Defects

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ABSTRACT Folic acid and other vitamin deficiencies may play a role in the etiology of neural tube defects. The Medical Research Council Vitamin Study confirmed the beneficial effect of folic acid supplementation on the prevention of neural tube defects. However, the concentrations of vitamins other than folate were not a common feature of any of the former studies. We measured the concentrations of vitamin A, riboflavin, riboflavin-5'-monophosphate, flavine-adenine-dinucleotide, vitamin B-6, vitamin B-12, vitamin C, vitamin E, folate and ferritin in the serum of women who had previously had a child with a neural tube defect and were planning a further pregnancy. Vitamin and folic acid supplements were supplied before conception to 44 high risk women before conception. Eighteen other high risk women not given supplements were the control group. We concluded that vitamin profiles do not form a suitable means for identifying women at risk for neural tube defects before pregnancy. This endorses the hypothesis that the beneficial effect of folic acid supplementation on the prevention of neural tube defects is possibly at least partly due to the fact that it overrides a relative folic acid shortage caused by a metabolic disorder. J. Nutr. 123: 197-203, 1993.

INDEXING KEY WORDS:
• vitamin profiles • humans
• neural tube defects • supplementation

tifying the environmental triggers, which can either be eliminated from the environment or avoided. So far, little can be done to modify the genetic components, but progress is being made in the identification of these components. An inherited folate metabolic disorder (Yates et al. 1987), hyperhomocysteinemia (Steegers-Theunissen et al. 1991) and methionine deficiency in laboratory animals (Coelho and Klein 1990) have been postulated as predisposing factors for the occurrence of neural tube defects.

Nutritional deficiencies might be a trigger for neural tube defects (Hibbard and Smithells 1965, Laurence et al. 1980, Smithells et al. 1983). Deprivation of folate and other vitamins during wk 4 after conception might be a precipitating factor. Experimental animal research has confirmed the need for an adequate folate provision for normal reproductive performance (Mooij et al. 1992b). An increased incidence of folic acid metabolism disarrangement in women who have recently had a child with a neural tube defect is suggested as an etiological factor (Laurence 1985). Folic acid supplementation starting before pregnancy would prevent 72% of neural tube defects in high risk women [MRC Vitamin Study Research Group 1991]. This is consistent with a report by Thiersch (1952), who found an association between neural tube defects and prenatal exposure to the folate antagonists aminopterin and methotrexate. Because folate deficiencies can cause defective DNA synthesis and a reduced rate of cell multiplication, folate has received the most attention as an etiological factor for these malformations, but vitamin B-6 and vitamin B-12 deficiencies might also be factors because they lead to

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a shortage of remethylation enzymes and an increased level of the embryotoxic homocysteine (Brattström 1989, Clarke et al. 1991). Earlier studies showed lower first trimester levels of RBC folate, white cell vitamin C, vitamin B-12 and evidence of riboflavin deficiency (Schorah et al. 1980, Smithells et al. 1976) in mothers with offspring with neutral tube defects.

Therefore, the present study was undertaken to evaluate the vitamin A, riboflavin, vitamin B-6, B-12, C and E concentrations in serum, folate concentrations in serum and RBC and serum ferritin concentrations in women who had already had a child with a neural tube defect and planned a further pregnancy. Vitamin supplements were offered to a group of 68 women at risk for having a pregnancy complicated with a neural tube defect. From this group, 50 women agreed to take the supplements and 18 women did not want to use them. This paper describes the vitamin concentrations in both groups before pregnancy and during the early stages of gestation and the effects of folic acid and multivitamin supplementation. The epidemiological and obstetrical data were also evaluated.

**MATERIALS AND METHODS**

Women who had previously had a child with a neural tube defect participated in the study after giving informed consent. Approval was given first by the ethics committee of the University Hospital. All the women were planning a further pregnancy but were not pregnant at the time of enrollment. They were questioned about their obstetrical history, medication use, social class and general physical condition. We used a questionnaire to collect information on their diets to determine the intakes of the selected vitamins. The women were supplemented with one multivitamin Gravitamon² (Chefaro B. V., Oss, The Netherlands) tablet per day and 5 mg of folic acid (Pharbita B. V., Zaandam, The Netherlands) per day taken orally. Supplementation was started at least 28 d before conception, and the women were asked to use mechanical contraception during this period. Because the time of conception varied after discontinuing mechanical contraception, the duration of supplementation between the first and the second blood samples varied from 50 to 160 d.

Sixty-eight volunteers were recruited for the study. For ethical reasons, it was not allowed to randomize the participants. Vitamin supplements were offered to 50 women, and 18 other women were willing to participate in the study but did not want to use supplements. Six of the women who received supplements were excluded from the study because of inadequate data collection. A total of 62 pregnancies were evaluated.

The blood samples were collected in a vacuum tube from an antecubital vein with the use of a tourniquet. All the samples were taken between 0900 and 1200 h from fasting subjects under similar conditions. Supplementation was given daily until wk 12 of gestation. No special advice was given regarding nutrition. On enrollment, blood samples were taken to assess hemoglobin, hematocrit, blood smear morphology, ferritin, liver function tests and vitamin profiles. The concentrations of vitamin A, total riboflavin activity [i.e., its three constituents: riboflavin, riboflavin-5'-monophosphate (FMN) and flavin-adenine-dinucleotide] and vitamin C were determined using HPLC techniques with fluorescence detection, as previously described (Mooij et al. 1991).

This paper also describes the simultaneous determination and assay characteristics of vitamin B-12 and folic acid, performed with the Dualcount SPB (Solid Phase Boil) Radioassay (Diagnostic Products, Los Angeles, CA) in plasma and, in the case of folic acid, also in RBC. Serum ferritin was determined with the Tandem-E Fer immunoenzymetric assay from Hybritech Europe S.A. (Liége, Belgium) (Mooij et al. 1992a). The determinations of vitamin B-6 (pyridoxal-5'-phosphate) in whole blood were performed with the HPLC techniques as previously described by Steegers-Theunissen et al. (1992). The concentrations of vitamin E (α-tocopherol) in plasma were determined with HPLC techniques with fluorescence detection after modification of the procedures described by Williams (1985). The serum samples were denatured with ethanol, diluted with bidistilled water and centrifuged after the addition of mobile phase (n-hexane-ethanol, 99.5:0.5, v/v). Using an automated sampler (Wisp 710B, Waters, Millipore, Milford, MA) a 20-μL aliquot of the supernatant was injected onto a normal phase guard column (Chrompack) that was in line with a silica column (ChromSep Microsampler Si-3 Normal Phase 100 × 4.6 mm) and equipped with an automatic HPLC liquid solvent pump (Model 590, Waters). The flow rate was 2.0 mL/min and the fluorescence excitation and emission wavelengths for vitamin E were 295 nm and 390 nm, respectively. The determination of vitamin E was linear from 0.40 μmol/L (the detection limit) up to 200 μmol/L. The precision in terms of intra- and inter-assay CV was 2.8% (10 replicate determinations, mean concentration 22.2 μmol/L) and 6.6% (13 simultaneous assay runs, mean concentration 23.7 μmol/L), respectively.

As soon as pregnancy was suspected, a pregnancy test was performed and an ultrasound investigation was used to determine the gestational age. Prenatal

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²Gravitamon contains the following: all-trans-retinol, 300 μg, thiamine, 3 mg, riboflavin, 2 mg, nicotinamide, 10 mg, vitamin B-6, 1 mg, vitamin B-12, 1 μg, rutoside, 10 mg, vitamin C, 50 mg, cholecalciferol, 10 μg, α-tocopherol, 1 mg, calcium carbonate, 500 mg, ferrous equivalent to 16 mg Fe; copper carbonate, 0.1 mg and zinc sulfate, 1 mg.
diagnostics were offered when desired. In wk 6 and 9 of pregnancy, blood samples were taken and treatment compliance was evaluated by counting the number of tablets left. The outcomes of all the completed pregnancies were recorded, including details of any fetal malformation, the sex, birth weight and obstetrical complications. If a miscarriage occurred, the fetus was examined if possible.

Statistics. Comparison of the mean periconceptional vitamin concentrations (t = 0) was performed by Student's two-sample test. Simultaneous comparison of the three mean vitamin concentrations within the two groups was done by the one-way ANOVA. Any changes in the vitamin concentrations between the two groups during pregnancy were tested by Student's one-sample test. The level of significance was 0.05.

RESULTS

Table 1 shows the sample characteristics and the outcome of previous pregnancies in both groups. There were no differences in age, body weight and obstetrical history between the two groups. The percentages of miscarriages in the supplemented and nonsupplemented groups were 25 and 29%, respectively. These percentages were higher than the reported 15% miscarriage rate of recognized pregnancies in the normal population (Boué et al. 1975). The social class distributions of the women in the two groups, based on the Registrar General's classification (Office of Population Censuses and Surveys 1970), were comparable. The percentages of women in classes 4 and 5, the lower social classes, were 16% for the supplementation group and 25% for the women without supplementation.

Table 2 gives the outcome of the pregnancies. Two spontaneous miscarriages occurred in both groups. The miscarriage rate (two cases) was higher in the unsupplemented group (n = 18) than in the supplemented group (n = 44). No abortions were performed on account of an antenatal diagnosis of neural tube defects in the unsupplemented group, whereas one pregnancy was terminated in the supplemented group because of an anencephalic fetus. No chromosomal disorders were found in the fetuses examined after miscarriage. Four children were born with congenital disorders. An anencephalic fetus and a child with congenital heart disease were born to supplemented mothers, whereas a child with a cleft palate and a child with coloboma of the iris were born to the unsupplemented group. One supplemented mother delivered twins. The mean birth weights of

### Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Age</th>
<th>Body weight</th>
<th>Social class 4 &amp; 5</th>
<th>Infertility</th>
<th>Previous pregnancies</th>
<th>Miscarriages</th>
<th>NTD</th>
<th>Intratelline death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supplemented</td>
<td>44</td>
<td>28.3 ± 5.5</td>
<td>61.9 ± 6.6</td>
<td>16</td>
<td>7</td>
<td>92</td>
<td>25</td>
<td>48</td>
<td>15</td>
</tr>
<tr>
<td>Unsupplemented</td>
<td>18</td>
<td>29.1 ± 7.9</td>
<td>60.9 ± 6.2</td>
<td>25</td>
<td>0</td>
<td>41</td>
<td>29</td>
<td>44</td>
<td>7</td>
</tr>
</tbody>
</table>

1Values are means ± SD. NTD = neural tube defect pregnancies.
2Classification based on Registrar General's classification (Office of Population Censuses and Surveys 1970): 1, professional; 2, intermediate occupations; 3, skilled, manual and non-manual; 4, partly skilled; 5, unskilled.

### Table 2

<table>
<thead>
<tr>
<th>Group</th>
<th>Preganacies</th>
<th>Miscarriages</th>
<th>Ectopic pregnancies</th>
<th>Termination of pregnancy</th>
<th>Live births</th>
<th>Congenital malformations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supplemented</td>
<td>44</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>41</td>
<td>2</td>
</tr>
<tr>
<td>Unsupplemented</td>
<td>18</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>16</td>
<td>2</td>
</tr>
</tbody>
</table>

1Pregnancy termination because of an anencephalic fetus.
2One twin birth.
3Anencephalus and congenital heart disease (atrial septal defect).
4Cleft palate and coloboma iridis.
TABLE 3

Blood vitamin concentrations in high risk women with and without supplementation before and during pregnancy

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Supplementation</th>
<th>Preconceptional</th>
<th>6 wk</th>
<th>9 wk</th>
<th>Pregnancy</th>
<th>Groups</th>
<th>$P$ value</th>
<th>Times</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin A, μmol/L</td>
<td></td>
<td></td>
<td>1.68 ± 0.11</td>
<td>1.62 ± 0.11</td>
<td>1.54 ± 0.07</td>
<td>0.38</td>
<td>0.49</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+</td>
<td></td>
<td>1.56 ± 0.09</td>
<td>1.61 ± 0.09</td>
<td>1.46 ± 0.10</td>
<td>0.33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin C, μmol/L</td>
<td></td>
<td></td>
<td>37.0 ± 9.4</td>
<td>50.0 ± 8.0</td>
<td>24.0 ± 7.0</td>
<td>0.30</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+</td>
<td></td>
<td>45.7 ± 3.2</td>
<td>51.4 ± 2.7</td>
<td>52.2 ± 2.1</td>
<td>0.23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total riboflavin,$^2$ nmol/L</td>
<td></td>
<td></td>
<td>264 ± 12.5</td>
<td>263 ± 10.8</td>
<td>264 ± 11.4</td>
<td>0.97</td>
<td>0.83</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+</td>
<td></td>
<td>263 ± 14.3</td>
<td>318 ± 16.8</td>
<td>314 ± 13.4</td>
<td>0.51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Riboflavin, nmol/L</td>
<td></td>
<td></td>
<td>5.58 ± 0.58</td>
<td>6.46 ± 1.07</td>
<td>5.00 ± 0.80</td>
<td>0.31</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+</td>
<td></td>
<td>4.23 ± 1.21</td>
<td>7.84 ± 2.50</td>
<td>9.43 ± 2.49</td>
<td>0.68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAD, nmol/L</td>
<td></td>
<td></td>
<td>225 ± 10.2</td>
<td>222 ± 8.4</td>
<td>225 ± 9.3</td>
<td>0.66</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+</td>
<td></td>
<td>232 ± 12.0</td>
<td>272 ± 13.8</td>
<td>267 ± 9.9</td>
<td>0.20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FMN, nmol/L</td>
<td></td>
<td></td>
<td>33.4 ± 3.0</td>
<td>35.6 ± 2.9</td>
<td>32.7 ± 2.4</td>
<td>0.16</td>
<td>0.30</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+</td>
<td></td>
<td>28.2 ± 1.8</td>
<td>41.3 ± 3.3</td>
<td>36.9 ± 3.2</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin B-6, nmol/L</td>
<td></td>
<td></td>
<td>39.6 ± 3.2</td>
<td>41.2 ± 3.6</td>
<td>47.3 ± 5.4</td>
<td>0.38</td>
<td>0.40</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+</td>
<td></td>
<td>43.3 ± 2.8</td>
<td>55.9 ± 4.9</td>
<td>60.4 ± 4.6</td>
<td>0.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin B-12, pmol/L</td>
<td></td>
<td></td>
<td>352 ± 48.3</td>
<td>302 ± 37.0</td>
<td>277 ± 34.3</td>
<td>0.12</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+</td>
<td></td>
<td>260 ± 31.5</td>
<td>276 ± 39.2</td>
<td>270 ± 40.0</td>
<td>0.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Folate, RBC, nmol/L</td>
<td></td>
<td></td>
<td>519 ± 41.6</td>
<td>515 ± 45.1</td>
<td>492 ± 55.3</td>
<td>0.10</td>
<td>0.82</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+</td>
<td></td>
<td>823 ± 160</td>
<td>1657 ± 147</td>
<td>1776 ± 277</td>
<td>0.008</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Folate, serum, nmol/L</td>
<td></td>
<td></td>
<td>16.2 ± 3.2</td>
<td>19.6 ± 4.2</td>
<td>18.4 ± 3.2</td>
<td>0.53</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+</td>
<td></td>
<td>13.5 ± 2.7</td>
<td>302 ± 85.6</td>
<td>262 ± 66.9</td>
<td>0.004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferritin, μg/L</td>
<td></td>
<td></td>
<td>33.5 ± 7.9</td>
<td>36.2 ± 7.6</td>
<td>29.5 ± 6.5</td>
<td>0.86</td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+</td>
<td></td>
<td>35.6 ± 8.5</td>
<td>46.3 ± 9.4</td>
<td>31.9 ± 6.0</td>
<td>0.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin E, μmol/L</td>
<td></td>
<td></td>
<td>19.0 ± 2.0</td>
<td>15.4 ± 1.2</td>
<td>18.6 ± 1.7</td>
<td>0.79</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+</td>
<td></td>
<td>18.4 ± 1.3</td>
<td>15.3 ± 1.3</td>
<td>17.8 ± 1.4</td>
<td>0.06</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^1$Values are means ± SEM, $n = 44$ for the supplemented group and $n = 18$ for the control (unsupplemented) group. Comparison of base-line concentrations ($t = 0$) was by Student's t test. Comparison of the means within each group by one-way ANOVA. FAD = flavine-adenine dinucleotide, FMN = flavine-mononucleotide.

$^2$The sum of riboflavin, FMN and FAD.

the children were 3245 and 3150 g for supplemented and unsupplemented women, respectively. Instrumental delivery was necessary for 7% of the women in both of the groups.

Table 3 shows the mean vitamin concentrations before pregnancy and at wk 6 and 9 of gestation for both groups. Preconceptional significant differences between the groups at $t = 0$ and within the groups at different testing points are also given. Comparison of the preconceptional mean vitamin concentrations between the groups revealed no significant difference for any of vitamins measured. During early pregnancy, the concentrations of vitamin A, total riboflavin and its three constituents remained unchanged in the unsupplemented women. Concentrations of vitamin B-6, folate in serum and RBC, ferritin and vitamin E did not change either in this group. Vitamin B-12 and vitamin C concentrations decreased significantly in the early pregnancy period. In the women using supplements, the concentrations of vitamins A, C, B-2 total, riboflavin and flavine-adenine-dinucleotide, B-6, B-12, E and ferritin did not change during pregnancy.

Folic acid concentrations both in serum and RBC increased significantly. The mean FMN concentrations also increased significantly during early pregnancy in the supplemented group.

**DISCUSSION**

Our trial was conducted on women in whom a previous pregnancy had been complicated by a neural tube defect and who therefore ran an increased risk of a recurrence. Dietary studies (Laurence et al. 1980, Schorah et al. 1980, Smithells et al. 1976) have provided evidence of an association between the maternal vitamin status and the occurrence of neural tube defects. These studies showed lower serum folate, RBC folate, white cell vitamin C and vitamin B-12 concentrations in the mothers of infants with neural tube defects, but others failed to show this association (Molloy et al. 1985) or found only small differences in RBC folate concentrations between the women with affected and unaffected pregnancies [Hall
1977, Yates et al. 1987). One of the concerns of a therapeutical trial is whether the treatment achieves effective concentrations of the agent at its site of action in the body. With regard to the prevention of neural tube defects, it is impossible to assess the vitamin concentrations in the neural tissue of the fetus. The closest alternative is to measure the vitamin concentrations in maternal blood. No folate or vitamin concentration thresholds have been found below which neural tube disturbances occur.

In the light of previous results, it was not considered ethical to allocate the participating women at random to a supplementation or a nonsupplementation group. The study was therefore not randomized and was not designed for an interventional approach. Instead it was intended to evaluate the vitamin profiles of well-nourished high risk women in the periconceptional period and to investigate the changes in vitamin profiles during supplementation.

The groups were comparable with respect to population characteristics and obstetrical history. Four of the live-born infants had congenital malformations. The pregnancy of one woman who received supplementation was complicated by a neural tube defect (Table 2). The serum vitamin profiles in this case were no different from those measured in the other supplemented women. One child from a supplemented woman was born with a congenital heart abnormality, whereas in the unsupplemented group, one child was born with a cleft palate and one child was born with coloboma of the iris (Table 1).

In the present study, no conclusions can be drawn about the effects of supplementation on the offspring, because of the small numbers. The preconceptional mean base-line concentrations of all the vitamins were similar in both groups, indicating that the vitamin status of the women in both groups were comparable. None of the women had used dietary supplements on a regular basis before the study. Supplement users generally consume a more nutrient-dense diet and are probably in less need of supplementation than other individuals [Kurinji et al. 1986]. The vitamin B-12 and vitamin C concentrations in the women without supplementation decreased significantly during early pregnancy. This is consistent with observations that low levels of maternal vitamin C and vitamin B-12 are associated with pregnancies complicated by neural tube defects [Gardiki-Kouidou and Seller 1988, Schorah et al. 1980, Smithells et al. 1976]. No decreases in the vitamin B-12 and vitamin C concentrations were observed in the women using supplementation, whereas the folate concentrations in serum and RBC increased, as did the mean FMN concentrations. The concentrations of folate in the serum and RBC after supplementation were comparable to those achieved after supplementation in nonpregnant women [Mooij et al. 1991]. Multivitamin supplementation had no effect on the other vitamin concentrations, which is not consistent with the effects of multivitamin supplementation observed in nonpregnant women [Mooij et al. 1991]. This might be attributed to changes in urinary excretion rates of these nutrients or tissue redistribution secondary to pregnancy.

If dietary components are related to neural tube defects, what are the potential mechanisms through which they work, and why have clear vitamin deficiencies seldom been demonstrated? Beneficial effects of folic acid supplementation on the recurrence of neural tube defects have been reported by the Medical Research Council Vitamin Study [MRC Vitamin Study Research Group 1991], but no differences could be demonstrated in the serum folate concentrations between women with neural tube defect recurrences and women with unaffected children. Although the authors suggested that the range of values of blood folate levels among women in most populations might be too narrow to demonstrate any differences, their findings do not contradict the protective effects of folic acid supplementation.

During the critical stages of organogenesis, cell growth is primarily established by cell division. Severe deficiencies of any essential nutrients may result in fetal death, and any minor deficiencies may result in malformations. Folic acid cofactors are needed for the synthesis of nucleic acids and are essential for cell division and growth. Vitamins C, B-6 and B-12 play a role in maintaining folic acid in its reduced form [Davis 1986]. Furthermore, folic acid and vitamin B-12 are involved in the remethylation of homocysteine to methionine, vitamin B-6 serves as a cofactor to the conversion of homocysteine to cystathionine, and both processes lead to reduced levels of the toxic metabolite homocysteine [Ueland and Refsum 1989]. Because nerve tissue is dependent on the methionine synthetase reaction, it may be affected by the absence of folate or vitamin B-12 [Dinn et al. 1980]. Nevertheless, severe vitamin deficiencies are rare in well-nourished women, even in the women whose pregnancies are complicated by a neural tube defect. Seller (1983) hypothesized that rapidly growing tissue is much more sensitive to lower than normal amounts of necessary metabolites than other tissue. Normal vitamin concentrations in affected pregnancies are consistent with observations of a possible embryotoxic effect of an accumulation of plasma homocysteine in pregnancies with a neural tube defect [Steegers-Theunissen et al. 1991]. Supplementation with high doses of vitamin B-6 and folic acid may modify hyperhomocysteinemia that arises from genetic causes and may explain the beneficial effect of folic acid supplementation and the normal serum vitamin concentrations usually observed in women at risk for neural tube defects.

Little information is available about vitamin E concentrations in early pregnancy. Vitamin E may be an
antioxidant of polyunsaturated fatty acids and protect the integrity of the erythrocytes by preventing oxidation of the phospholipids in the cell membrane. Maternal serum vitamin E concentrations rise in the second and third trimester of pregnancy due to an increase in the serum lipid concentration (Jagadeesan and Prema 1980). In this study, supplementation did not have any effect on the serum vitamin E concentrations, which confirmed the observations made by Baker et al. (1975). Vitamin E concentrations are also thought to be controlled by other metabolic processes and are not only a reflection of the vitamin E intake and body stores.

In our groups, the ferritin concentrations were unaffected by pregnancy and were comparable with values in nonpregnant women not using oral contraception (Mooij et al. 1992a), which is indicative of sufficient iron stores at this stage of pregnancy. In the present study, we observed normal preconceptional vitamin profiles in women at risk for neural tube defects. The vitamin status of the women who received multivitamin and folic acid supplementation was mainly affected by preventing any decrease in the vitamin B-12 and C concentrations and by increasing the serum and RBC folate concentrations. These vitamins certainly play an important role in reproductive performance and should therefore be available in sufficient quantities. Health-conscious individuals with an adequate diet are probably capable of maintaining a sufficient vitamin profile before and during pregnancy. The vitamin profiles of the women with offspring affected by a neural tube defect did not demonstrate any acute deficiencies. However, it is possible that a state of chronic malnutrition contributes to these defects rather than an acute deficiency near the time of conception (Slattery and Janerich 1991). Supplementation in these women may override the effects of chronic malnutrition. It is still unclear which women should receive supplementation on the basis of their periconceptional nutritional status. The possibilities of neurotoxic effects of high levels of circulating free folate during embryonic development should be ruled out (Scott et al. 1991). Because vitamin measurements in well-nourished individuals are in general not able to identify women at risk, it may still be possible to identify specific groups at risk for neural tube defects. Therefore, vitamin and folic acid supplementation is recommended for women at risk for neural tube defects, and for women who use folate-antagonists and probably for women with unrecognized malnutrition, malabsorption or increased need to bypass metabolic blocks. However, the appropriate doses still needed to be determined.

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LITERATURE CITED


