Folate Status during Pregnancy in Women Is Improved by Long-term High Vegetable Intake Compared with the Average Western Diet

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ABSTRACT The effect of increasing dietary folate on folate status during pregnancy is controversial. The aim of this study was to compare folate intake and folate status during pregnancy of women with high long-term vegetable intake and those eating an average Western diet. In a prospective study that included 109 participants, pregnant women adhering to a predominant vegetarian diet with high vegetable intake for 8 ± 0.5 y with subgroups of ovo-lacto vegetarians (n = 27) and low meat eaters (n = 43) and women eating an average Western diet (control group, n = 39) were compared with regard to dietary intake and plasma and red blood cell (RBC) folate concentrations during wk 9–12, 20–22 and 36–38 of gestation. Plasma and RBC folate concentrations were highest in ovo-lacto vegetarians, followed by low meat eaters and lowest in the controls. Ovo-lacto vegetarians and low meat eaters showed a lower risk for folate deficiency, with RBC folate concentrations of <320 nmol/L resulting in odds ratios of 0.10 (95% confidence interval, 0.01–0.56) and 0.52 (95% confidence interval, 0.20–1.34), respectively. In ovo-lacto vegetarians, the RBC folate concentration was positively related to the intake of vitamin B-12 (r = 0.51, P < 0.0001). The results of the study suggest that long-term high vegetable intake favorably affects plasma folate as well as RBC folate concentrations throughout pregnancy and reduces the risk of folate deficiency if an adequate vitamin B-12 supply is ensured. J. Nutr. 131: 733–739, 2001.

KEY WORDS: folic acid • vitamin B-12 • nutritional status • pregnancy • plant-based diet • vegetarianism • humans

Folate deficiency during pregnancy has been implicated as an important factor contributing to the occurrence and recurrence of neural tube defects, low birth weight, preterm birth, delayed maturation of the nervous system, growth retardation and megaloblastic anemia (1–9). In the case of low folate body stores, the increased folate requirements during pregnancy rapidly lead to folate deficiency. Although folate supplementation has been recommended before conception and throughout pregnancy (3,10–13) compliance with this recommendation has remained poor (14,15). To optimize folate status of the general population, a high consumption of vegetables and fruits is considered important, and therefore this advice has been included in many nutritional guidelines (16–18). Even so, the effect of dietary folate is unclear (19,20) and little is known about the bioavailability of folate from different types of diets (21). We examined the protective effect of a predominant vegetarian diet characterized by the preference of foods of plant origin, high consumption of raw food and whole grain products and low consumption of refined products (22–24) on the folate status in pregnant women. The aim of the study was to compare the folate intake and status of pregnant women practicing a plant-based diet in a long term with subjects consuming an average Western diet.

MATERIALS AND METHODS

Study design. This study was designed as a prospective study with pregnant volunteers enrolling throughout pregnancy (Fig. 1). Participants entered the study at any stage of pregnancy and were followed until delivery. Information on dietary intake and blood samples were collected in each trimester of pregnancy (wk 9–12, 20–22 and 36–38 of gestation, i.e., postmenstruation). The study was approved by the Ethics Committee of the Division of Human Medicine, University of Giessen, Germany. Informed consent was obtained from all participants.

Selection of subjects and selection instruments. Pregnant women of each trimester of pregnancy responding to announcements in health magazines and to study information handed out by their gynecologists were recruited for this study from 1995 to 1997. Of 249 responding women, 203 received a questionnaire asking about their nutritional behavior, food consumption (semi-quantitative food frequency list, considering the usual dietary intake before pregnancy), anthropometric and sociodemographic data, use of oral contraceptives, parity, smoking and sport habits as well as prevalent diseases; 22 women were not interested in further participation and 24 women were excluded from further study participation (1 was pregnant with twins, 9 were taking multivitamin and mineral supplements and 14 lived >200 km from the study site). Of the 249 women, 201 women completed and returned the questionnaire (self-classification...
of responders: 120 adhered to a predominantly vegetarian diet, 74 consumed an average Western diet and 7 consumed other diets). The food frequency list was used to assign subjects into diet groups by a priori defined selection criteria. In all, 109 women remained in the study (Fig. 1).

Women consuming a predominantly vegetarian diet were characterized by a high consumption of unheated vegetables (>100 g/d), preference of whole grain products (ratio of refined grain products to whole grain products of <0.95) and limited meat consumption (<300 g meat/wk, <105 g meat products/wk). Selected predominantly vegetarians should not have changed their diet substantially for ≥3 y and were divided into low meat eaters and ovo-lacto vegetarians (who completely omitted meat and meat products from their diet). For comparison, women practicing an average Western diet (control group) were selected who did not follow any special diet and who corresponded with the average German population as defined in the results of the German National Consumption Study (25). This diet consisted mainly of refined grain products (ratio of refined grain products to whole grain products of >1.05) and of >300 g meat and 105 g meat products per wk and <100 g unheated vegetables per d.

Due to pregnancy-related and organizational reasons of 109 participants, only 60 were assessed three times throughout pregnancy. One ovo-lacto vegetarian and one low-meat eater after the first trimester and one ovo-lacto vegetarian after the second trimester dropped out of the study after a miscarriage. After the second trimester, seven ovo-lacto vegetarians, nine low meat eaters and five women of the average Western diet group were not assessed because of relocation or birth of the child before the last blood sampling date.

**Blood sampling and analyses.** After overnight fasting, venous blood was drawn into trace element-free Vacutainers and Vacutainers containing EDTA. Plasma was separated from red blood cells (RBC) within 2 h after blood sampling and stored at ~4–7°C. RBC folate was preserved by adding 0.4 g ascorbate/L solution. Both plasma and RBC folate concentrations were determined with a chemiluminescent competitive protein binding assay (ACS Folate Assay; Ciba Corning Diagnostics GmbH, Fernwald, Germany). The coefficient of variation was 7.9% for serum folate and 3.9% for RBC folate analysis. Serum vitamin B-12 concentrations were analyzed by ACS cobalamin assay (Abbott Diagnostics Division, Maidenhead, Berks, U.K.) that incorporates microparticles coated with porcine intrinsic factor to bind cobalamin. The coefficient of variation was 4.2%. Serum zinc concentrations were analyzed with atomic absorp-

**FIGURE 1** Study design. RBC indicates red blood cells.

**RESULTS**

**Characteristics of study population.** Predominantly vegetarians and the average Western diet group did not differ with regard to age or parity (Table 1). They differed significantly in BMI, use of oral contraceptives in the year before pregnancy and serum vitamin B-12 concentrations. Marginal differences were observed in smoking habits. However, neither BMI, the use of oral contraceptives nor smoking habits were found to be related to plasma or RBC folate concentrations during pregnancy. Ovo-lacto vegetarians had consumed a plant-based diet as derived from the German Food Code and Nutrition Data Base BLS II.2 (27). Folate and cobalamin concentrations in multivitamin-fortified juices were taken from producer’s data. With regard to the different bioavailability of natural folate in different foods, intake was calculated as free folate equivalents (FFE = monoglutamate + 0.2 × polyglutamate conjugates) as derived from the German Food Code and Nutrition Data Base. The used database does not allow the calculation of dietary folate equivalents for foods enriched with folate (Institute of Medicine 1998). Folate intake was adjusted for total energy intake by using nutrient density (amount of nutrient/10 MJ) because individual differences in total energy intake produce variations in folate intake unrelated to dietary composition due to its positive correlation of most nutrients with total energy intake (28, 29).

**Statistical analyses.** For all analyses, SPSS 8.0 (SPSS, Chicago, IL) and SAS 8.0 (SAS Institute, Cary, NC) were used. Food consumption and dietary folate intake are presented as median values with 25th and 75th percentiles and were compared by the Mann-Whitney U test. The body mass index (BMI) was calculated as pre gravid weight (kg)/height (m²). To normalize distribution of plasma folate and serum vitamin B-12, the data were log-transformed. Mean blood values are presented as arithmetic means ± SEM; plasma folate concentrations are presented as geometric means and SEM. Folate deficiency was defined as RBC folate concentration of <320 nmol/L (29).

The folate status of the dietary groups was compared by using generalized estimating equations (GEE). GEE models allow an appropriate analysis of longitudinal data with repeated measurements and missing values; for all models, a dependent working correlation matrix was chosen with simultaneous adjustment for age, BMI, parity, smoking habits, use of oral contraceptives, vitamin B-12 status and supplemental folate. The risk of folate deficiency was computed by a logistic GEE regression analysis; odds ratios and 95% confidence intervals are provided. All two-way interactions were tested, but no interactions with P < 0.15 were found.

**REFERENCES**

1. Abbreviations used: BMI, body mass index; EAR, estimated average requirement; FFE, free folate equivalent; GEE, generalized estimating equations; RBC, red blood cells.
for 8.7 ± 0.8 y, and low meat eaters had consumed their diet for 7.5 ± 0.7 y.

**Dietary intake.** Although ovo-lacto vegetarians and low meat eaters ate similar amounts of vegetables, fruits and grain products, they differed significantly with respect to consumption of meat and fish, potatoes and legumes and soy products (Table 2). They also tended to differ in the consumption of raw food.

Women eating a predominantly vegetarian diet consumed more whole grain products, vegetables, legumes, soy products and fruits and less meat, fish and eggs than the average Western diet group. In addition, they consumed more raw food. Consequently, the dietary groups differed in folate intake in all trimesters of pregnancy (Table 3). Differences in FFE (P < 0.0001) were more evident than in total folate (P = 0.022) throughout pregnancy. Folate intake was highest in ovo-lacto vegetarians, followed by low meat eaters and lowest in the average Western diet group. Changes in folate intake during pregnancy were not significant within any dietary group. With the exclusion of supplemental folate, the estimated average requirement (EAR, 520 μg DFE/d) as proposed by the Institute of Medicine (20) was met by 13% of ovo-lacto vegetarians, 9% of low meat eaters and 5% of the average Western diet group throughout pregnancy. With the inclusion of supplemental folate, the EAR was met by 33% of ovo-lacto vegetarians and low meat eaters and 36% of the average Western diet group. EAR for vitamin B-12 (2.2 μg/d) was met by 60% of ovo-lacto vegetarians, 93.6% of low meat eaters and all women of the average Western diet group throughout pregnancy.

**Plasma folate.** Mean plasma and RBC folate concentrations of nonsupplemented participants are shown in Figure 2. The GEE analyses showed significant differences in plasma folate concentrations between dietary groups (P < 0.0001).
folate between ovo-lacto vegetarians, low-meat eaters and the average Western diet group after control for the effects of serum vitamin B-12, supplemental folate and other potentially confounding variables (Table 4). Ovo-lacto vegetarians and low meat eaters did not differ significantly.

GEE models reveal a positive relation between plasma folate and energy-adjusted folate intake calculated as FFE (β-coefficient ± se of folate intake (μg FFE/MJ) = 0.0065 ± 0.0022, P = 0.0037, simultaneously adjusted for supplemental folate and serum vitamin B-12). There was no significant relation to unadjusted data. Serum vitamin B-12 as well as folate derived from supplements and multivitamin fortified juices appeared to be the strongest predictors of plasma folate (Table 4), followed by the consumption of raw food and green leafy vegetables (β-coefficient ± se of raw food consumption (g/d) = 0.0001 ± 0.00001, P = 0.042, and of green leafy vegetables (g/d) = 0.0005 ± 0.0003, P = 0.060, simultaneously adjusted for supplemental folate, folate from multivitamin fortified juices and serum vitamin B-12). All other food groups were removed from the model. Total consumption of any other food group was not correlated with plasma folate concentrations. In addition, the amount of folate derived from consumed raw food was related to the change in plasma folate throughout pregnancy (r = 0.252, P = 0.043).

**RBC folate.** RBC folate concentrations were highest in ovo-lacto vegetarians, followed by low meat eaters and lowest in the average Western diet group (Fig. 2). The GEE model of RBC folate showed differences between ovo-lacto vegetarians versus the average Western diet group but not between low meat eaters versus the average Western diet group after control for the effects of serum vitamin B-12, folate intake from multivitamin fortified juices, supplemental folate and other covariates (Table 4). Ovo-lacto vegetarians and low meat eaters also differed significantly. Potentially confounding variables of folate status that are discussed in the literature (30), such as serum zinc and ferritin, were not found to be significant. In all diet groups, RBC folate concentrations rose after the first trimester and were strongest in ovo-lacto vegetarians (Fig. 2). In ovo-lacto vegetarians, a relationship between vitamin B-12 intake and RBC folate (r = 0.510; P = 0.001) was observed, but no such relationship was found in the other dietary groups.

In the GEE model, RBC folate was positively related to plasma folate (dependent variable: plasma folate, β-coefficient ± se of RBC folate = 0.0004 ± 0.0001, P < 0.0001). There was no significant relation observed between RBC folate and RBC folate intake. The folate derived from supplements appeared to be the strongest predictors of RBC folate, followed by serum vitamin B-12 as well as the folate derived from multivitamin fortified juices (Table 4). All other food groups dropped out from the model. Total consumption of any food group had no effect on neither RBC folate concentrations nor changes throughout pregnancy.

**Occurrence of folate deficiency.** Plasma folate concentrations of <6.8 nmol/L were not found in any women of this study. Throughout the pregnancy, the occurrence of folate deficiency defined as RBC folate concentrations of <320 nmol/L in nonsupplemented participants was lower in predominantly vegetarians (13.8%) than in the average Western diet group (29.0%); deficiency occurred in 7.5% of ovo-lacto vegetarians and in 17.4% of low meat eaters. In the first trimester of pregnancy, folate deficiency was observed in 15.4% of ovo-lacto vegetarians, 30.0% of low meat eaters and 30.0% of the average Western diet group. In the second trimester of pregnancy, folate deficiency was observed in 6.3% of ovo-lacto vegetarians, 17.2% of low meat eaters and 25.0% of the average Western diet group. In the third trimester of pregnancy, folate deficiency was observed in none of ovo-lacto vegetarians, in 5.0% of low meat eaters and 33.3% of the average Western diet group. In ovo-lacto vegetarians, RBC folate concentrations below 320 nmol/L occurred in only one subject, meeting the EAR for vitamin B-12 (2.2 μg/d) and did not occur in subjects with an intake of vitamin B-12 higher than 3 μg/d. After excluding women with serum vitamin B-12 concentrations of <120 nmol/L as a determinant of a functional folate deficiency, participants with folate deficiency showed significantly lower folate intake (P = 0.022) than did women without folate deficiency after adjustment for total energy intake. Of supplemented women, none of ovo-lacto vegetarians, 14.3% of low meat eaters and 4.9% of the average Western diet group were folate deficient.

The odds ratios (95% confidence interval) for the risk of folate deficiency, as a result of a logistic GEE model, were lower for ovo-lacto vegetarians and low meat eaters compared with the average Western diet group (Table 4).

**DISCUSSION**

The folate requirement increases substantially during pregnancy due to the increase of cell multiplication. An inadequate folate intake rapidly leads to low maternal and fetal plasma concentrations and RBC folate concentrations that are associated with complications such as the occurrence of neural tube defects (9,31). There is a lack of information concerning
dietary folate intake during pregnancy and concerning the effect of higher dietary folate intake on the folate status, because the effect of food-derived folate is often compared with the effect of supplemental folate (19). Although nutrition guidelines (10,11,16–18) recommend a high consumption of folate-rich foods to optimize folate status, there is no information on the effect of long-term high vegetable intake on folate status during pregnancy. To our knowledge, there are no data on the effect of food-derived folate from different diets at different time points of pregnancy.

The present study suggests that long-term high consumption of vegetables leads to an improvement in folate status and may reduce the risk of folate deficiency during pregnancy. In addition, in a vegetarian diet the intake of vitamin B-12 has to be focused to improve folate status.

The predominantly vegetarians examined in this study ate a plant-based diet for 8 ± 0.5 years. In 1992, the proportion of persons eating a diet as described above was estimated to be 5–7% (32). They generally consumed large amounts of vegetables and fruits, of which a substantial amount were eaten unheated, leading to a significantly higher folate intake than in the average Western diet group. Nevertheless, the mean food-derived folate intake of all dietary groups was above the mean intake of an average German diet in women of childbearing age (237 μg DFE/d) (33) and the folate intake of ovo-lacto vegetarians and low meat eaters was higher than in other studies (19,34).

The differences between the diets are reflected by the folate status of the women measured as blood parameters. The dietary groups differed significantly in plasma as well as RBC folate concentrations. The highest mean plasma folate concentrations of participants were observed in ovo-lacto vegetarians, followed by low meat eaters. Plasma folate concentrations were significantly affected by the trimester of pregnancy. Decreasing plasma folate concentrations during pregnancy were also observed by Hall et al. (35) and may be explained by hemodilution. There was no significant correlation between the consumption of vegetables, fruits and legumes and any improvement in folate status. However, changes in plasma folate concentrations were correlated with the amount of folate from raw food consumed because folate content of raw food is not diminished by heating.

The RBC folate concentrations are considered to be an indicator of long-term folate status (36,37), a marker for usual folate intake and tissue stores (38). In other studies, RBC folate concentrations were significantly lower in women with pregnancies affected by neural tube defects than in women with normal pregnancies (8,12,39). Daly et al. (9) observed that RBC folate concentrations of <340 nmol/L at wk 15 of gestation were associated with an eightfold greater risk of neural tube defects compared with RBC folate concentrations of ≥906 nmol/L.

In the present study, the risk of folate deficiency defined as RBC folate concentrations below 320 nmol/L (34) was lower for ovo-lacto vegetarians and low meat eaters than for the average Western diet group. In the course of total pregnancy, RBC folate concentrations of <320 nmol/L were observed in fewer ovo-lacto vegetarians and low meat eaters than in the average Western diet group. In the first trimester of pregnancy, RBC folate concentrations of <320 nmol/L was observed only in 15.4% of ovo-lacto vegetarians in contrast to 30.0% of low meat eaters and 30% of the average Western diet group. In the first trimester of pregnancy, RBC folate concentrations were significantly lower in women with pregnancies affected by neural tube defects compared with RBC folate concentrations >340 nmol/L.

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Ek and Magnus (40) observed a significant increase in RBC folate concentrations from early pregnancy to wk 30–33 of gestation; thereafter a decrease was observed. Changes have been attributed to modifications in folate metabolism during pregnancy (40–42). RBC folate accumulates before an increased transfer of folate to the fetus that occurs during the last
weeks of pregnancy (40). In the present study, in all diet groups, RBC folate concentrations rose after the first trimester, with a greatest rise in ovo-lacto vegetarians. Although the average Western diet group members without folate supplementation were consistently folate deficient during all trimesters of pregnancy, ovo-lacto vegetarians mostly were folate deficient in the first trimester of pregnancy, despite little change in folate intake during pregnancy. Only a few ovo-lacto vegetarians in the second trimester and none in the third trimester were folate deficient. No ovo-lacto vegetarian taking supplements were folate deficient. The data suggest a preventive effect for folate deficiency for women eating a predominantly vegetarian diet on a long-term basis. Further studies are needed to investigate the effect on risk reduction of neural tube defects, low birth weight, preterm birth and other pregnancy complications related to folate status.

Self-recruitment of participants may result in selection bias. This problem mostly concerns the average Western diet group, in whom we have to expect more interest in nutritional problems and a more health-conscious diet than in the base population. The high folate intake of the average Western diet group may support the possibility of selection bias in the average Western diet group, but if so, this will not diminish the importance of the study results because the expected differences between predominantly vegetarians and an average Western diet group with lower folate intake may be more substantial than observed in the present study.

Low maternal plasma vitamin B-12 concentrations are considered to be an independent risk factor for neural tube defects (36). Because vitamin B-12 deficiency reduces the uptake of folate by cells, this increases plasma folate and decreases RBC folate concentrations (43–45). High plasma folate concentrations have been reported in macrobiotic children with vitamin B-12 deficiency (46) and in long-term vegans (47). In our study, vitamin B-12 concentrations in serum showed a positive effect on RBC folate concentrations, suggesting the importance of an adequate vitamin B-12 supply during pregnancy for efficient folate utilization. Also, in ovo-lacto vegetarians the RBC folate concentrations were strongly correlated with the dietary intake of vitamin B-12. Folate deficiency was observed in only one ovo-lacto vegetarian meeting the EAR for vitamin B-12 and in no ovo-lacto vegetarian with vitamin B-12 intakes of >3 μg/d. Consumption of a predominantly vegetarian diet on a long-term basis may affect vitamin B-12 deficiency during pregnancy. To increase the efficient use of dietary folate, vegetarian women should ensure that they consume adequate vitamin B-12 by consuming dairy products and, if acceptable, fish. Folate supplements should be combined with vitamin B-12 to minimize the risk of masking a vitamin B-12 deficiency.

In conclusion, the present study shows that long-term high consumption of vegetables is associated with improved folate status and therefore may reduce the risk of folate deficiency during pregnancy. This implies that a predominantly vegetarian diet consumed on a long-term basis with a high dietary folate intake can be considered a useful way to optimize folate status and to reduce, but not eliminate, the risk of folate deficiency during pregnancy. A combination of a folate-rich diet and folate supplements may be recommended as a preventive step.

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LITERATURE CITED


TABLE 4

Multivariate relationships between dietary characteristics and indicators of folate status in pregnant women consuming a predominantly vegetarian diet subdivided into ovo-lacto vegetarians (OLV) and low meat eaters (LME) or an average Western diet (reference group)

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>Plasma folate (nmol/L)</th>
<th>Red blood cell folate (nmol/L)</th>
<th>Folate deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Independent variable</strong></td>
<td>β</td>
<td>SE</td>
<td>P-value</td>
</tr>
<tr>
<td>Intercept</td>
<td>−18.6527</td>
<td>11.8600</td>
<td>0.1158</td>
</tr>
<tr>
<td>Diet group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OLV</td>
<td>7.0856</td>
<td>2.3517</td>
<td>0.0026</td>
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<tr>
<td>LME</td>
<td>4.6005</td>
<td>1.7160</td>
<td>0.0073</td>
</tr>
<tr>
<td>Serum vitamin B-12, pmol/L</td>
<td>17.2135</td>
<td>3.4565</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Supplemental folate, μg/d</td>
<td>0.0215</td>
<td>0.0052</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Folate from multivitamin fortified juices, μg/d</td>
<td>0.0008</td>
<td>0.0004</td>
<td>0.0461</td>
</tr>
</tbody>
</table>

1 Definition of folate deficiency: red blood cell folate <320 nmol/L.
2 Coefficients of generalized estimation equation models, simultaneously adjusted for age, pregravid body mass index, parity, smoking habits and oral contraceptive use before pregnancy.
3 95% confidence interval.
4 Log-transformed variable.


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