New standard for dietary folate intake in pregnant women¹-³

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ABSTRACT The Institute of Medicine Panel for Folate and Other B Vitamins and Choline considered data from population-based and metabolic studies to revise the dietary intake standards for pregnancy. The recommended dietary allowance (RDA) for pregnant women is the average daily dietary intake sufficient to meet the requirements of 97–98% of pregnant women. The RDA is derived from the amount estimated to meet the requirement of half of healthy pregnant women, or the estimated average requirement (EAR). Maintenance of red cell folate was selected as the primary indicator of adequacy of folate status during pregnancy. The dietary folate equivalent (DFE) was used to interpret studies in which folate was provided as a combination of food folate and synthetic folic acid because folic acid is more bioavailable than is food folate. Many population-based studies confirmed that an estimated 10% CV. Data from the metabolic studies support an expansion of the number of maternal red cells and the size of the reproductive organs (3). Folate is actively transferred to the fetus during gestation, as evidenced by the higher concentrations of folate in cord blood relative to those in maternal blood (4). Because of the increased demands that are placed on the supply of folate during pregnancy for the synthesis of DNA and other one-carbon transfer reactions, pregnant women are at a higher risk of developing folate deficiency than are nonpregnant women. When folate intake is inadequate, maternal blood folate concentrations decrease significantly; if inadequate folate intake is sustained during pregnancy, megaloblastic anemia may develop (5). Inadequate folate intake and low serum folate concentrations were associated with poor pregnancy outcomes (6). It is therefore important to ensure adequate folate intake during pregnancy to prevent maternal folate depletion, which would thus allow for adequate fetal supplies for growth and development.

The maintenance of red cell folate, which reflects liver folate concentration and thus tissue stores (7), was selected as the primary indicator of adequate folate status for pregnant women. When red cell folate was not measured, serum folate was evaluated in population-based studies. The EAR and RDA for folate were based on data from a controlled metabolic study (8) and a series of population-based studies in which dietary folate intake was reported (5, 9–15).

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This article provides an overview of the approach taken by the Institute of Medicine Panel for Folate and Other B vitamins to derive the EAR and RDA for folate and does not include an exhaustive review of all data critiqued. Key data from specific research studies that were evaluated and considered to be relevant to folate adequacy for pregnant women are summarized and the congruence of findings among the very different types of protocols is highlighted. The interpretation and application of the EAR and RDA for folate for pregnant women are addressed and key areas of future research are presented.

**DIETARY FOLATE EQUIVALENTS**

To estimate the RDA, the recommended folate intake was expressed as a dietary folate equivalent (DFE) to account for differences in the bioavailability of food folate and synthetic folic acid (1). The DFE is used to convert synthetic folic acid that is added to food to a quantity equivalent to the quantity of naturally occurring food folate.

**Bioavailability of synthetic folic acid**

Synthetic folic acid is ≈100% bioavailable when consumed under fasting conditions on an empty stomach (16). Evidence for the high bioavailability of synthetic folic acid was also provided by Daly et al (17), who found that the concentration of red cell folate increased incrementally in response to graded doses of supplemental folic acid.

**Bioavailability of folic acid consumed with food and in fortified foods**

Pfeiffer et al (18) examined the bioavailability of $^{[13\text{C}]}$ folic acid administered in apple juice with or without a serving of food and found that bioavailability was slightly (∼15%) lower when the folic acid was consumed with food than without food. On the basis of these experimental data, the bioavailability of synthetic folic acid consumed with food is estimated to be 85%.

Cuskelly et al (19) concluded that folic acid in a supplement was equally bioavailable as folic acid in fortified bread and breakfast cereal on the basis of red cell folate responses over a 3-mo period. Pfeiffer et al (18) evaluated the bioavailability of folic acid from cereal-grain foods enriched experimentally with $^{[13\text{C}]}$ folic acid and reported a slight but insignificant difference between the control (water with folic acid) and each of the tested foods (white and whole-wheat bread, pasta, and rice). These 2 studies complement each other and indicate that folic acid in fortified cereal-grain products is highly available and efficacious.

**Bioavailability of endogenous food folate**

Sauberlich et al (20) concluded that the bioavailability of food folate was ≤50% that of synthetic folic acid. In addition, Cuskelly et al (19) showed that food folate is less bioavailable than is the synthetic form.

**Calculation of dietary folate equivalents**

Many controlled studies of folate requirements used a diet with a defined folate content and supplemented with synthetic folic acid. Given that folic acid taken with food is assumed to be 85% bioavailable and food folate to be 50% bioavailable, folic acid taken with food is 1.7 times more available than is folate occurring naturally in foods. Thus, if a mixture of synthetic folic acid (μg) plus food folate (μg) is fed, the DFE is calculated as follows to determine the EAR:

$$\text{DFE} = \text{food folate} + (1.7 \times \text{synthetic folic acid})$$

Expressed differently, 227 nmol (100 μg) food folate is equivalent to 385 nmol (170 μg) synthetic folic acid when consumed via a fortified food.

**INDICATORS OF ADEQUACY**

Red cell folate concentration, which reflects liver folate concentration (7) and is considered to be an indicator of long-term folate status, was selected as the primary indicator of adequacy. Folate is accumulated only by developing reticulocytes (21); because the life span of red cells is ∼120 d, the red cell folate concentration most accurately reflects folate status 2–3 mo before the time of the analysis. However, because red cells are being synthesized and released into the circulation daily, the red cell folate concentration changes over time in response to inadequate folate supplies within the bone marrow. This is especially relevant during pregnancy, when production of red cells increases by ∼33% (22).

When the red cell folate concentration was not measured, serum folate was evaluated with the recognition that hemodilution contributes to a moderate reduction in serum folate concentration during gestation. Homocysteine concentrations do not reflect folate status during pregnancy, possibly because of hormonal changes, hemodilution, or other unknown factors associated with pregnancy (23). Risk reduction for neural tube defects was not considered as a basis for establishing the RDA for pregnant women. A separate recommendation was presented and discussed by the Institute of Medicine (1).

**KEY STUDIES CONSIDERED**

**Controlled metabolic study**

A metabolic study was conducted by Caudill et al (8) in which either of 2 amounts of folate was consumed for 12 wk by pregnant women during the second trimester (14–25 wk of gestation). The folate status of the pregnant women was compared with that of a nonpregnant control group who were consuming the same amounts of folate as the women in the pregnant group for 12 wk. Folate was provided as a combination of 272 nmol (120 μg) dietary folic acid/d and 748 or 1654 nmol (330 or 730 μg) synthetic folic acid/d, consumed with a low-folate diet. The DFEs of the 2 groups were ≈1362 nmol/d [681 μg/d, ie, 120 + (330 × 1.7)] and >2266 nmol (1000 μg/d). Folate status was normal [serum > 7 nmol/L (3 ng/mL) and red cell folate > 300 nmol/L (140 ng/mL)] in all subjects consuming 1362 nmol (600 μg) DFE/d and was not significantly different from that of the nonpregnant group consuming the same amount of folate.

**Population-based studies**

The adequacy of folic acid supplements or folate-fortified foods plus a low-folate diet to maintain normal red cell or serum folate concentrations was assessed in several population-based studies (5,9–15). A series of studies was conducted by Willoughby (5) and Willoughby and Jewell (9,10), involving ∼3500 pregnant women enrolled at 12 wk of gestation and assigned to receive 0, 227, 793, or 1020 nmol (0, 100, 350, or 450 μg) folic acid/d. In addition to the supplements, the subjects consumed low-folate
diets estimated to provide ≈227 nmol (100 μg) folate/d. When supplements containing 227 nmol (100 μg)/d were provided in addition to the low-folate diets, 33% of the group had serum folate concentrations indicating deficiency (<7 nmol/L (3 ng/mL)) and 5% developed megaloblastic anemia (9). In contrast, 681 nmol (300 μg) folic acid/d was sufficient to maintain a mean serum folate concentration that was similar to the mean in healthy non-pregnant women (9) and to prevent megaloblastic anemia (5). Dawson (11) reported similar findings: 340 nmol (150 μg) folic acid/d in addition to a low-folate diet (beginning at 28 wk) resulted in serum folate concentrations of <7 nmol/L (3 ng/mL) in 30% of the group at delivery. Hansen and Rybo (12) reported data that confirmed these findings: 227 nmol (100 μg) folic acid/d plus a low-folate diet was insufficient to prevent serum folate reduction (<4 nmol/L, or 2 ng/mL) in 15% of the group. In contrast, a supplement of 1135 nmol (500 μg) folic acid/d resulted in a mean serum folate concentration of 13 nmol/L (6 ng/mL) at 36–38 wk of gestation. These data support the conclusion that 227–340 nmol (100–150 μg/d) supplemental folic acid plus a low-folate diet was inadequate to maintain normal serum and hematologic indexes, which were the only outcomes measured.

Serum and red cell folate and bone marrow morphology of pregnant women taking 1135 nmol (500 μg) supplemental folic acid/d were compared with those of pregnant women taking a placebo (13). Mean serum and red cell folate concentrations were ≈21 and 870 nmol/L (10 and 400 ng/mL), respectively, in the folic acid–supplemented women at 36 and 38 wk of gestation and post-partum. Bone marrow aspirates at 38 wk were essentially normal. In contrast, a large percentage of the placebo-treated subjects had serum and red cell folate concentrations lower than normal.

Red cell folate concentrations in 103 pregnant women supplemented with 227 nmol (100 μg) folic acid from 25 wk of gestation until delivery were compared with those of 103 unsupplemented pregnant control subjects by Chanarin et al (14). Dietary folate in 111 duplicate 24-h diets was measured and reported to be 1532 nmol (676 μg)/d. Supplementation of the usual diet with 227 nmol (100 μg) folic acid/d resulted in maintenance of red cell folate concentrations throughout pregnancy, whereas a significant reduction in red cell folate was observed in the unsupplemented subjects. The accuracy of the dietary estimates could not be ascertained but the estimates were higher than expected.

The efficacy of maize fortified with folic acid to maintain red cell folate concentrations in pregnant women was evaluated by Colman et al (15). Red cell folate responses in women receiving maize fortified to provide 681, 1135, or 2266 nmol (300, 500, or 1000 μg) folic acid/d was compared with that of a control group. Maize containing 681 nmol (300 μg) folic acid in addition to dietary folate was effective in preventing the progression of folate depletion in the eighth month of pregnancy. McPartlin et al (24) measured the urinary excretion of folate catabolites in pregnant subjects and nonpregnant control subjects as an indicator of folate requirements. These investigators converted the quantity of urinary catabolites to a DFE and estimated the recommended folate intake for second-trimester pregnant women to be 1475 nmol (660 μg/d).

The data from the only diet-controlled metabolic study that has been conducted in pregnant women agree with the findings from the population studies and confirm that a combination of ≈681 nmol (300 μg) synthetic folic acid/d from supplements, fortified food, or both plus ≈227 nmol (≈100 μg) dietary folate/d is sufficient to maintain normal folate status during pregnancy (8). Expressed as a DFE, the consistent finding across the numerous population studies and the controlled metabolic study is that 1362 nmol (600 μg) DFE/d is adequate to maintain normal folate status.

**INTERPRETATION OF RDA AND EAR FOR PREGNANT WOMEN**

The RDA of 1362 nmol DFE/d is the value to be used in guiding healthy pregnant women to achieve adequate folate intake. Differences in the intended application of the new RDAs and the previous RDAs were discussed in the Institute of Medicine report (1). If an individual pregnant woman’s folate intake, on average, meets or exceeds the RDA, it is likely that her folate intake will be adequate. If the pregnant woman’s average folate intake, over time, is less than the RDA, it can be inferred that there is an increased likelihood that the intake will be inadequate. The likelihood increases the greater the decrease in intake below the RDA. The EAR of 1178 nmol (520 μg) DFE/d may be used to estimate the prevalence of inadequate nutrient intake in groups of pregnant women. This is done by estimating the percentage of the pregnant women in the group whose usual folate intakes are less than the EAR (1). It is important to recognize that estimates of folate intake that are based on currently existing nutrient databases significantly underestimate folate intake because of methodologic problems in the analytic assays used to measure food folate (1). In addition, these databases do not include the folic acid that has been added to the food supply as a result of fortification. Therefore, conclusions regarding the EAR for folate should not be based on estimates of folate intake derived from currently available food-composition tables.

**APPLICATION OF DIETARY REFERENCE INTAKES**

To achieve an intake of 1362 nmol DFE/d, a pregnant woman should couple a varied diet that includes folate-dense foods with sources of synthetic folic acid, such as fortified food products. Alternatively, a varied diet could be coupled with a folic acid–containing supplement, such as the widely available nonsuppresion supplements. Prenatal supplements containing 1 mg folic acid/supplement exceed the RDA of folate for pregnant women.

Since January 1998, all enriched cereal-grain products in the United States have contained 317 nmol (140 μg) folic acid/100 g, eg, breads, pastas, noodles, rice, and corn grits (25). Examples of quantities of folic acid contained in average servings are 91 nmol (40 μg) in 2 slices of bread and 136 nmol (60 μg) in 1 cup of prepared pasta or rice. Most commercially available, ready-to-eat breakfast cereals contain 227 nmol (100 μg) folic acid/serving and a small number contain 908 nmol (400 μg) folic acid/serving. To convert the folic acid contained in these products to a DFE, one can assume that 227 nmol folic acid consumed as fortified food is equivalent to 385 nmol (170 μg) DFE.

It is important to educate pregnant women about folate-dense foods that are also concentrated sources of other essential nutrients and are often high in fiber and low in fat. Examples of these folate-dense foods are orange juice, dark-green leafy vegetables, strawberries, and legumes, which all have, on average, ≈170–227 nmol (≈75–100 μg) folate/serving. In calculating the DFE of these foods, the actual quantity is the DFE because it is provided by food folate. For example, 227 nmol folate naturally occurring in food is the same as 227 nmol DFE.
CONCLUSION AND RESEARCH RECOMMENDATIONS

The new DRIs for pregnant women include the RDA of 1362 nmol (600 μg) and the EAR of 1178 nmol (520 μg) DFE daily. The DRIs for folate are expressed in DFEs to account for the higher bioavailability of synthetic folic acid than of food folate. Research priorities for the future include the need to revise the folate nutrient databases because these currently provide underestimates of the folate contents of foods and do not include folic acid in enriched cereal-grain products. In addition, nutrient databases need to present separate quantities for food folate and synthetic folic acid. Research efforts to improve estimates of the bioavailability of folate and folic acid need to continue so that future RDAs can be revised as necessary. More information is needed to characterize folate RDAs by trimester of pregnancy because data are insufficient to address potential gestational differences.

REFERENCES