Multivitamin Supplementation During Pregnancy: Emphasis on Folic Acid and L-Methylfolate

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[Rev Obstet Gynecol. *2011;4(3/4):126-127 doi: 10.3909/riog0165*]

In this Key Opinion Leader interview, co-Medical Editor of *Reviews in Obstetrics & Gynecology* James A. Greenberg speaks with nutritionist Stacey J. Bell about prenatal vitamins.

Dr. Greenberg: Are all prenatal vitamins the same?
Ms. Bell: Most prenatal vitamins are similar in that they contain at least 100% of the daily need for each essential vitamin and mineral. However, differences exist among prenatal vitamins in the form of folic acid, in the amounts of each nutrient, specific nutrients (eg, some contain docosahexaenoic acid [DHA], an omega-3 fatty acid necessary for fetal brain and eye development), and how they are sold (ie, by prescription or over the counter). Prescription prenatal multivitamins may contain higher amounts of iron, with or without a stool softener. A recommended prenatal vitamin should contain at least 100% of the requirement for three key nutrients: folic acid, vitamin B_{12}, and iron. The requirement for each nutrient is increased during pregnancy, and it is nearly impossible to meet these needs through diet alone.

Of these, folic acid is particularly important. Deficiencies of dietary folic acid can lead to abnormalities in the mother (anemia, peripheral neuropathy) and the fetus (congenital abnormalities). Dietary supplementation with folic acid around the time of conception has been known to reduce the risk of neural tube defects (NTDs). Folic acid is also thought to reduce the risk of preterm birth and congenital heart disease. One important difference among prenatal vitamins is the source of folic acid. It may be included as folic acid, or the bioavailable form, L-methylfolate. Having the option to prescribe the bioavailable form of this important nutrient may be advantageous for some pregnant women who are at risk for these aforementioned conditions. Regardless of the folic acid source, it is important for pregnant women to use prenatal vitamins throughout pregnancy, and it is preferable in prepregnancy.

Dr. Greenberg: Is L-methylfolate a better option than folic acid for prenatal care?
Ms. Bell: It may be. Taking the bioavailable form of any nutrient guarantees that adequate amounts are being provided. About 40% to 60% of the population has genetic polymorphisms that impair the conversion of supplemental folic acid to its active form, L-methylfolate.

In vivo, the body converts dietary folic acid to L-methylfolate through a series of enzymatic processes. The final stage is done with the enzyme methyltetrahydrofolate reductase (MTHFR). Those with certain polymorphisms have inadequate MTHFR activity. Based on the high prevalence of these genetic polymorphisms and the importance of assuring that pregnant women get adequate folic acid, supplementation with L-methylfolate may be the best option to avoid blood folate deficiencies. At present, it is not practical

to test every woman to see if they have the relevant polymorphisms. My advice is to prescribe prenatal vitamins containing L-methlyfolate instead of folic acid for women with a family history of NTDs or preterm births. Other women can use prenatal vitamins containing folic acid. However, there is preliminary evidence that L-methylfolate may be useful to prevent postpregnancy anemia.

Dr. Greenberg: Has L-methlyfolate been tested and shown to be bioavailable?

Ms. Bell: It is reasonable to question the safety and efficacy of L-methylfolate, because up until recently, only folic acid was available for prenatal vitamins. The concern is whether the exogenous form of L-methylfolate is truly incorporated and used by the body. If so, L-methylfolate should be able to serve as a methyl donor for DNA and ribonucleic acid (RNA) assembly and to regulate homocysteine metabolism. Increased plasma homocysteine is a risk factor for vascular disease, as well as for adverse pregnancy outcomes. In a study by Lamers and colleagues,[1] healthy women were randomly assigned to consume 400 μg of folic acid, 416 μg of L-methylfolate (the bioequivalent dose of folic acid), and 208 μg of L-methylfolate (half dose). Each group experienced increases in plasma folate and decreases in homocysteine concentrations. The lowest dose of L-methylfolate had a significantly smaller increase in plasma folate compared with the other two groups. These findings suggest that L-methylfolate is bioactive and behaves predictably by increasing plasma levels of folate and decreasing homocysteine.

Dr. Greenberg: Has a prenatal vitamin containing L-methylfolate been compared with one with folic acid during pregnancy?

Ms. Bell: Yes. Bentley and colleagues[2] conducted a retrospective, comparison study of different forms of folic acid in pregnant women. The women either used a prenatal supplement containing L-methylfolate or one with folic acid. Women were followed during pregnancy until term. In contrast with women who used a prenatal product that contained folic acid, those who had L-methylfolate in their prenatal supplement had significantly higher hemoglobin levels at the end of the second trimester ($P < .011$) and at delivery ($P < .001$). Based on this study, it appeared that women benefitted from L-methylfolate in their prenatal vitamin in terms of having a lower incidence of anemia. ■

References

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