

FOLIC ACID SUPPLEMENTATION DURING PREGNANCY MAY REDUCE RISK OF DOWN'S SYNDROME, IN ADDITION TO NEURAL TUBE DEFECTS

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It has been established for some time that folic acid supplementation during pregnancy is associated with a 48% lower risk of having a child with a neural tube defect (e.g., spina bifida, anencephaly). A recent study in *The Lancet* [2003; 361(9366):1331-5] has now shown that folic acid supplementation is also associated with reduced risk of Down's syndrome. Researchers compared medical data from approximately 490 families at high risk of NTD with data from 516 families at high risk of Down's syndrome, and discovered that Down's syndrome was much more prevalent in pregnancies among at-high-risk families of NTD. The evidence suggested that mothers of children with Down's syndrome experience an abnormal metabolism of folate and methyl as well as mutations in their folate gene. These traits are also seen in infants affected by neural tube defects.

Folate (folic acid, a B-vitamin) is unique in nature in that it contains a methyl group (CH₃), which it donates to homocysteine to permit its enzymatic conversion to methionine. Once formed within the cells of the body, methionine (a methyl-containing amino acid) extracts the adenosine ring from adenosine triphosphate (ATP) and becomes S-adenosyl methionine. S-adenosyl methionine is then able to donate its methyl group (which was originally derived from folate) to many biochemical reactions, including the synthesis of DNA bases. Thus, DNA synthesis requires a constant and adequate supply of folate each day of our lives. During pregnancy, the rapid cell division rate of the fetus demands an even greater supply of folic acid, and if the demand is not met, DNA-defects occur, which most often manifest as neural tube defects. Evidence from *The Lancet* study suggests that the same may be true for Down's syndrome. To complicate matters, some individuals have an inborn error of folate or methyl metabolism, in that they show a defect in the enzyme that converts homocysteine to methionine, and thus produce insufficient amounts of S-adenosyl methionine. However, studies show that these individuals can significantly improve the conversion of homocysteine to methionine if they are provided with higher supplementation levels of folic acid (which is the coenzyme for this reaction), in many cases. Thus, mothers who are identified as high-risk for NTD usually express this type of folate or methyl defect and therefore, are prescribed higher supplemental levels of folic acid. *The Lancet* study has provided evidence that these same women are also at higher risk for Down's syndrome, indicating that higher folic acid supplementation may be of great importance in reducing the risk of both NTD and Down's syndrome.

The researchers conclude that because of the links in the development of the two complications, folate supplementation before conception has the potential to reduce NTD and Down's syndrome during pregnancy. Most women would benefit from 400 mcg of folic acid supplementation prior to conception (most multiple vitamins contain this amount) and 800 mcg during pregnancy (the amount contained in prenatal vitamins). Women with folate or methyl metabolism problems require additional amounts of supplemental folic acid, which should be prescribed by their attending physician or specialist, who can best monitor the appropriate biomarkers.

Reference: NNFA Supplement (April 28, 2003)