# An Exploration of Health Effects of Folic Acid in Pregnancy Beyond Reducing Neural Tube Defects

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## Abstract

**Objectives:** First, to examine the biological basis of why folic acid may have health effects beyond its proven effect of reducing neural tube defects; and second, to explore current controversial policies of folic acid supplementation and food fortification.

**Methods:** We searched MEDLINE for English-language papers published from 1991 to 2003, using the key words "folic acid" and "folate." The literature search was restricted to human studies. Of 8986 publications identified, 65 were relevant to the objectives of this paper.

**Results:** Analysis of the literature revealed that a major mechanism of folic acid in improving infant health may be related to its effect in correcting maternal folate-homocysteine-methylenetetrahydrofolate reductase metabolic defects. Conversely, exposure to high levels of folic acid may have such adverse health effects as increased risk of neurologic disorders in the general population.

**Conclusions:** Randomized trials or well-designed prospective cohort studies are needed to assess the effects of folic acid on various pregnancy outcomes. To enable an examination of the association between folic acid and rare outcomes, such as a specific category of birth defects and fetal and neonatal deaths, it is necessary to recruit a large number of pregnant women to participate in such studies.

## Résumé

**Objectifs :** (1) Examiner les fondements biologiques pouvant expliquer les raisons pour lesquelles il est possible que l'acide folique puisse avoir des effets sur la santé, au-delà de son efficacité éprouvée pour la réduction des anomalies du tube neural; (2) Explorer les politiques controversées actuelles en matière de supplémentation et d'enrichissement des produits alimentaires à l'acide folique.

**Méthodes :** Des recherches ont été menées dans MEDLINE en vue d'en tirer les articles de langue anglaise portant sur le sujet, publiés entre 1991 et 2003, à l'aide des mots clés « *folic acid* » et « *folate* ». La recherche documentaire a été restreinte aux études sur l'homme. Des 8 986 publications identifiées, 65 se sont avérées pertinentes en ce qui concerne les objectifs du présent article.

**Résultats :** L'analyse de la littérature a révélé qu'il était possible que l'un des principaux mécanismes par lequel l'acide folique améliore la santé des nouveau-nés soit associé à l'effet de cette substance sur le redressement des anomalies du métabolisme du composé folate-homocystéine-méthylènetétrahydrofolate réductase chez la mère. Inversement, il est possible que l'exposition à des taux élevés d'acide folique puisse entraîner des effets indésirables pour la santé, tels qu'un accroissement du risque de présenter des troubles neurologiques, au sein de la population générale.

**Conclusions :** Des essais randomisés ou des études de cohorte bien conçues s'avèrent nécessaires pour évaluer les effets de l'acide folique sur diverses issues de grossesse. Afin de permettre l'examen de l'association entre l'acide folique et les issues rares, telles qu'une catégorie particulière d'anomalies congénitales et de décès fœtaux et néonatals, nous devrons recruter un nombre important de femmes enceintes disposées à participer à ces études.

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**Key Words:** Folic acid, folate, methylenetetrahydrofolate reductase, homocysteine, pregnancy, placentae, birth defects, fetal growth and development, multiple births

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## INTRODUCTION

Randomized controlled trials (RCTs) and community intervention studies have demonstrated that periconceptional folic acid supplementation substantially reduces the risk of neural tube defects in infants.[1–3] A recent Cochrane review concluded that periconceptional folic acid supplementation could reduce the risk of neural tube defects by more than 50%.[4] Policies of folic acid supplementation and food fortification have been recommended and (or) implemented in industrialized countries to prevent neural tube defects.[5–11]

Recent studies have suggested that folic acid may have other beneficial health effects, such as reducing risks of congenital heart disease,[12–14] oral cleft,[15,16] urinary tract abnormalities,[13,17] and limb deficiency.[14] However, exposure to high levels of folic acid has been reported to have adverse effects on rare but important adult neurologic disorders,[18,19] potentially by delaying the diagnosis and

treatment of these conditions.[18,19] In addition, high levels of folic acid have been reported to increase the risk of multiple births, although the observed association tended to be weak and the study results were inconsistent.[20–22]

In this paper, we examined the biological basis of why folic acid may have health effects beyond its effect of reducing neural tube defects, as well as current policies of folic acid supplementation and food fortification.

## METHODS

Using the key words "folic acid" and "folate," we searched MEDLINE for English-language human studies published from 1991 to 2003. Following a review of paper titles and abstracts, the full text of papers that were relevant to our study purpose were read in depth. Because of the heterogeneity in the study designs, outcomes of interest, and outcome ascertainment methods used, no attempt to pool results from different studies by meta-analysis was undertaken. The decision to include papers was made according to the authors' best judgment of the relevance and importance of the studies.

The literature search identified 8986 publications pertaining to folic acid and folate. After careful analysis of the clinical relevance and quality of the original studies, 65 papers were chosen for this review.

### *Function and Metabolism of Folic Acid*

Folic acid, or folate, one of the B vitamins, is a co-enzyme in the production of nucleic acids and protein and is therefore required for cell differentiation, development, and growth.[23] Laboratory investigations have shown that folic acid depletion causes DNA instability in human lymphocytes[24] and increases apoptosis of human cytotrophoblastic cells *in vitro*.[25]

A common missense mutation in the methylenetetrahydrofolate reductase (MTHFR) gene, a C to T substitution at nucleotide 677 (677TT), is responsible for reduced MTHFR activity and associated increased homocysteine concentrations, especially in patients with folic acid depletion.[26] The occurrence of this gene mutation in the general population is greater than 5% in a homozygous state.[26] The MTHFR gene (677TT) mutation was substantially increased in women with recurrent early pregnancy loss,[27] preeclampsia,[28] and placenta vasculopathy.[29] Folic acid deficiency and (or) hyperhomocysteinemia have been observed in patients with atherosclerosis or myocardial infarction [30–33] and in women with various placenta-mediated pregnancy complications, including preeclampsia,[34–36] placental abruption,[37,38] spontaneous abortion,[39] stillbirth,[37,39] and intrauterine growth retardation.[37,39]

Ray and Laskin explored the relation between abnormality in the folate-B12-homocysteine axis and the risk of placenta-mediated diseases and drew parallels to the relation between folate deficiency or hyperhomocysteinemia and the development of atherosclerosis.[40] Endothelial dysfunction is demonstrable within the myometrial arteries of women with preeclampsia, and the incubation of healthy vessels in plasma obtained from women with preeclampsia induces similar endothelial changes.[41] Hyperhomocysteinemia presumably causes vessel endothelial dysfunction, as demonstrated by abnormal brachial artery flow-mediated dilation following methionine loading.[42] Thus young women with folate deficiency or hyperhomocysteinemia may be prone to enthodelial dysfunction, including placental endovasculature.[43,44] Among women with recurrent early pregnancy loss, the chorionic vessel wall diameter was inversely related to fasting maternal plasma homocysteine levels.[45] Together, these data suggest that the origin of placental microvascular disease may arise from a metabolic defect of maternal folate-homocysteine-MTHFR.

### *Pregnancy Benefits of Folic Acid Beyond the Prevention of Neural Tube Defects*

Similarities exist between neural tube defects and other birth defects, such as congenital heart defects and defects in the abdominal wall.[46] These defects, having common embryologic links, are often found to coexist.[46] The neural crest cells, which eventually differentiate into the aorticopulmonary (or conal) septum, have their origin in the same area of the neural ectoderm where neural tube closure occurs.[46] Undifferentiated cells from this area are interchangeable and can express either phenotype.[47] The heart, neural tube, and abdominal wall closure are common sites of birth defects with other known teratogens, such as vitamin A.[48,49]

Epidemiologic studies found that periconceptional multivitamin supplements containing folic acid could reduce the risk of cardiovascular defects,[12,14] oral clefts,[15,16] urinary tract abnormalities,[13,17] and limb reduction.[14] Hernandez-Diaz *et al.* found that, compared with infants whose mothers had no exposure to folic acid antagonists, the relative risks of cardiovascular defects, oral clefts, and urinary tract defects in infants whose mothers were exposed to folic acid antagonists decreased from 2.2- to 3.4-fold.[50] Periconceptional folic acid supplements mitigated against the adverse effect of folic acid antagonists.[50]

### *Potential Adverse Health Effects of Consuming a High Dosage of Folic Acid*

There has been a lot of controversy on the fortification of food with folate. [5,18,19,51–54] Since food fortification is