Neural tube defects and periconceptional folic acid

Rezan A. Kadir, Demetrios L. Economides

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The cause of neural tube defects (NTDs) is multifactorial. The possibility that folic acid played a role was first reported in 1964.[1] Several clinical trials subsequently showed that the risk of recurrence and first occurrence of these abnormalities was decreased by periconceptional folic acid supplementation,[2–5] On the basis of these findings, supplementation of 400 μg folic acid was recommended in 1992 by the Expert Advisory Group in the United Kingdom[6] and by the US Department of Health and Human Services[7] for women in the general population while trying to conceive.

Although periconceptional folic acid supplementation has been shown to be effective in randomized controlled trials, at the population level it has not been associated with any reduction in the incidence of NTDs in Western countries.[8,9] Several factors may be responsible for this observed disparity. Supplementation may not be taken at the right time. The neural tube closure occurs on days 22–28 after ovulation. Since more than 40% of pregnancies are unplanned, most of these women are unaware of being pregnant as early as 22–28 days after ovulation. In addition, the proportion of women found to have started taking folic acid supplements before conception increased from 0.8%–6.7% before 1994 to only 1%–30.6% after 1994 in the various countries studied by Rosano and coauthors.[9] It is also possible that folic acid supplements are not taken by women at highest risk of NTDs (e.g., socially disadvantaged women). Therefore, there was a campaign to increase awareness among health care professionals and the mass media for the use of folic acid before conception. A mass media campaign in the Netherlands led to an increase in preconceptional folic acid use,[10] but 25.8% of women surveyed still chose not to take the supplements even though they were aware of the beneficial effects. The main reason given was a dislike of taking drugs during pregnancy, and 63.6% said that they would prefer to take folic acid in food rather than as a tablet.

Over the last few years, there have also been increasing calls for food fortification with folic acid. This approach would provide a more effective means of ensuring an adequate intake by women in high-risk groups, especially immigrant women, to whom communicating the importance of supplementation may be difficult. However, critics of such policies argued that food fortification may be associated with the masking of macrocytic anemia, which would allow irreversible neurological damage to progress in some people at high risk of vitamin B_{12} deficiency (e.g., elderly people). The other potential risks are interference with folate antagonistic drugs (mainly anticonvulsants), zinc malabsorption and hypersensitivity reactions. Their argument was also based on the lack of firm evidence to support the benefits of food fortification. Many have called for a trial of the efficacy and safety of the intervention before introducing such a policy.

In this issue, 2 groups report on the effect of the Canadian policy for folic acid fortification on the incidence of NTDs. Vidia Persad and coauthors[11] showed a reduction of 54% in the total incidence (live births, stillbirths and terminated pregnancies) of open NTDs after 3 years of food fortification in Nova Scotia (see page 241). Enza Gucciardi and coauthors[12] reported a reduction of 50% in the birth incidence (live births and stillbirths) of NTDs in Ontario from 1986 to 1999, with most of the decrease occurring after 1995 (see page 237); they also report a significant reduction after 1995 in the incidence of terminated pregnancies affected by NTDs, which resulted in a decrease in the ratio of NTD-affected births to therapeutic abortions from 3:1 in 1986 to 1:1 in 1999. They explain that the reduction after 1995 in the total incidence of NTDs is consistent with the expansion in the late 1990s in initiatives to promote folic acid use before conception among women of childbearing age and the 1998 policy to fortify flour and pasta. These data are also compatible with the success experienced in the United States with folic acid fortification, which was associated with a reduction of 19% in the birth incidence of NTDs.[13]

Folic acid supplementation may have additional benefits. There is an increasing recognition that abnormalities in folic acid metabolism may be a cause for miscarriage and the development of a number of congenital abnormalities, including orofacial cleft anomalies and urinary tract anomalies.[5] It has also been suggested that folic acid supplementation given before conception may be associated with an increase in birth weight and a slight decrease in the incidence of preterm labour and small-for-gestational-age babies.[14]

The concerns about the safety of food fortification for people at risk of vitamin B_{12} deficiency are overexaggerated and not substantiated. The interference with antiepileptic medications is unlikely with the level of fortification required to increase the average daily folic acid intake by 400 μg. Folic acid supplementation of 4 mg is recommended and given to women taking these medications in pregnancy without major concern of their epileptic control. In addition, there is increasing evidence of potential benefits of folic acid fortification for adults: it prevents folate deficiency anemia, and it is associated with population-wide reductions in plasma homocystine concentrations and, at least theoretically, should

lead to a reduction in deaths from cardiovascular disease.

Given the available evidence, the fortification of foods with folic acid is justifiable. It is an effective and inexpensive way to ensure adequate folate levels in all prospective mothers and maximizes the effect of folic acid in preventing NTDs. Finally, the advantage of avoiding or minimizing the number of pregnancy terminations in the second trimester because of these anomalies should not be underestimated.

Drs. Kadir and Economides are with the Department of Obstetrics and Gynaecology, Royal Free Hospital School of Medicine, London, England.

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Correspondence to: *Dr. Demetrios L. Economides, Department of Obstetric and Gynaecology, Royal Free Hospital School of Medicine, Pond St., London, England NW3 2QG; fax 44 207 472-6154; demetrios.economides@rfh.nthames.nhs.uk*

Gene patents and the standard of care

Richard Gold, Timothy A. Caulfield, Peter N. Ray

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Although many have debated the ethics of patenting human genes over the past 2 decades, recent controversies surrounding the effect of gene patents on genetic tests for breast and ovarian cancer have brought that debate to a head.[1] In the absence of changes in Canada's patent laws, physicians will face a variety of legal and ethical dilemmas regarding the ordering of appropriate genetic tests for their patients.

A DNA sequence patent provides its holder with a great deal of power to control how anyone — including a physician and his or her patient — uses the "patented" sequence. Since all genetic tests require the reproduction of the patient's target gene, gene patents can create a number of access problems. First, the patent permits patent holders to charge a premium for access to the service. Second, patent holders can require that physicians wishing to order genetic tests for their patients have the test done by the patent holder or one of its licensees. The patent holder may impose additional conditions, such as the requirement that the test be conducted at a specific location. In the case of the *BRCA1* and *BRCA2* genes, a mutation of which increases a woman's predisposition to breast and ovarian cancer, Myriad Genetics, the patent holder, requires anyone wishing genetic testing to send their sample to Myriad in Salt Lake City to be analyzed by a method determined by Myriad at a cost of about US$2500. A comparable test provided by Genetic Diagnostic Laboratories in Ontario, licensed by the Ontario Ministry of Health and Long-Term Care, costs Can$1150.

These limitations pose several problems for physicians. First, the implied or real threats of patent infringement may delay or block the development, validation and implementation of diagnostic tests by Canadian laboratories.[2–4] Second, the method mandated by the patent holder for conducting the test may not be the most appropriate for the patient. Third, the high price charged by patent holders for genetic tests may cause provincial health care systems to refuse to insure these tests. A recent report issued by the Ontario Ministry of Health and Long-Term Care concluded that genetic tests will increase the cost burden on the health care system, at least in the short term.[5] Fourth, the high costs of tests not covered by provincial health insurance plans may render these tests unaffordable and thus unavailable to many patients. Fifth, sending patient samples out of Canada to a company not subject to Canadian laws and regulations may cause ethical concerns over quality control and confidentiality.

It is the availability of tests that perhaps is of greatest con-