Should Folic Acid Fortification be Mandatory in Israel?

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In this issue of *IMAJ*, the public health services of the Ministry of Health compare the incidence of neural tube defects in Israel before and after the introduction of the guidelines, in 2000, for women to take 0.4 mg of synthetic folic acid daily, particularly during the 3 months preceding conception and in the first trimester of pregnancy [1]. The authors found a marked decline in the rate of spina bifida in the last 3 years: from 4.9 to 2.7 per 10,000 live births among Jews and 9.5 to 6.2 per 10,000 live births among Arabs and Druze.

In 1976, Smithells et al. [2] suggested that folate deficiency may cause NTD because the mothers of infants with NTD had low blood folate levels. Smithells and co-workers [3] also suggested some years later (1983) that folic acid supplementation during the preconception period could potentially reduce the risk of neural tube defects. In 1991, the UK Medical Research Council Vitamin study [4] also supported this hypothesis. These studies prompted many health services all over the world to issue recommendations for women of childbearing age to take daily supplements of folic acid periconceptionally in addition to consuming food with high levels of folate. An important issue was how effective were the recommendations alone, or in combination with campaigns to increase knowledge and use of folic acid supplements periconceptionally among women.

Three public health strategies are proposed to overcome the problem and to insure a maximal response [5]:

- To issue a recommendation for all women of childbearing age to take supplements of folic acid in combination with a healthy diet
- To fortify food with synthetic folic acid on a voluntary basis
- To fortify an essential food on a mandatory basis

National regulations regarding the fortification of food still vary greatly among European Union countries and North America. Fortification of foods was introduced in the United States as early as 1942 when the Food and Drug Administration required that enriched cereal grains contain certain vitamins and minerals. Folic acid was not originally included and was only added to the recommendations in 1992. Voluntary fortification of foods has been practiced for several years in various member states of the EU (UK, Ireland, Spain, Portugal, Switzerland and Austria). In other states fortification is either restricted or not allowed. In Ireland the withdrawal of fortified breakfast cereal for 12 weeks reduced red cell folate concentration in woman dramatically (by 111 nmol/L), suggesting the magnitude of such a policy [6]. In the USA, Canada and Chile, mandatory fortification of flour improved the folate and homocysteine status, and neural tube defect rates fell by 31% to 78% [7].

There is also accumulating evidence, based mostly on case-control studies [8], that folic acid might prevent other major birth defects [8-11] such as congenital heart disease, orofacial clefts, and anomalies of the urinary tract. However, this is still controversial since there are also studies that do not show any significant correlation between folate fortification and the incidence of these birth defects [8].

In 2002, the UK Food Standards Agency decided against the introduction of mandatory folic acid fortification. One reason was the issue of freedom of choice, but interestingly they were also worried about adverse affects, particularly masking the diagnosis of vitamin B12 deficiency by prevention of anemia and precipitation of neurologic complications [12-14]. Other issues that were raised were possible interactions with drugs (the known interaction between phenytoin and folate can potentially cause reduction in seizure threshold by lowering serum phenytoin [15]), hypersensitivity reactions, cancer promotion and increase of twinning rate [12-15].

Vitamin B12 deficiency can affect up to 10–15% of the population over 60 years of age [14]. The U.S. National Institute of Medicine determined that there is suggestive but not conclusive evidence that folic acid, in addition to masking vitamin B12 deficiency, precipitates or exacerbates the neurologic damage of B12 deficiency. Anemia provides an important clue to the diagnosis of a low vitamin B12 concentration, particularly in the elderly, in whom some of the neurologic signs, e.g., confusion, paresthesias, and dementia, are seen in many other conditions. However, Mills and team [14] have shown that the proportion of American patients with low vitamin B12 but without anemia was 39% before fortification and did not increase after fortification (38%). Moreover, vitamin B12 deficiency is now diagnosed not by hematologic data alone, but also by testing for serum B12 levels specifically.

NTD = neural tube defects
EU = European Union
The current study by Zlotogora and colleagues [1] found a significant reduction in the incidence of spina bifida in Israel following the introduction of the new guidelines. The paper also suggests that the awareness, knowledge and practice of consumption of folic acid in pregnant women in Israel continue to increase. It would have been interesting to examine the effect of the guidelines on specific high risk groups such as women with a previously affected child or fetus, women consuming anti-epileptic medication, or women suffering from diabetes or impaired vitamin B12 status.

The final recommendation of the current IMJ study is to implement mandatory food fortification in Israel. For this to take place a careful assessment of the benefits as well as potential negative health effects is vital. This recommendation also means that everybody has to consume fortified products even if they prefer not to. This practice is thus against the public’s freedom of choice. A compromise would be voluntary fortification of certain, labelled food accompanied by a national campaign to increase knowledge and awareness of women and their spouses during the reproductive years. These campaigns should be available to all women in Israel regardless of factors such as language, cultural barriers or illiteracy. Obstetricians, pediatricians and family physicians can play an important role in informing and motivating women. This approach will lead to a further decline in neural tube defects without possible adverse effects and without challenging the freedom of choice.

References

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Heresy is only another word for freedom of thought
Graham Greene (1904-1991), British writer

Capsule

**IgG dual action**

Under normal conditions, immunoglobulin G (IgG) antibodies are anti-inflammatory, yet during infection they can protect the body by recruiting inflammatory cells or pathways. Kaneko et al. show that IgG can alternate between these states by modifying the sialylation of polysaccharides on the non-variable part of the IgG that is responsible for binding and activating receptors on immune cells. These receptors bind sialylated forms of IgG less strongly, which signals the cell to load its surface with inhibitory proteins. However, under situations of immune challenge, the sialic acid residues are lost, which allows IgG to bind more tightly and so turn up inflammatory signaling. By switching activity in this way, IgG antibodies may restrict their pro-inflammatory effects to periods of infection and so limit the potential for inadvertent harm resulting from their activity.

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