European Journal of Nutrition & Food Safety
5(4): 242-249, 2015, Article no.EJNFS.2015.021
ISSN: 2347-5641

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Developing the Right Public Health Strategies for Folic Acid and Reduction of Risk of Neural Tube Defects (NTDs) in the United Kingdom

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

Article Information

DOI: 10.9734/EJNFS/2015/18093

Policy Article

Received 2nd April 2015
Accepted 5th June 2015
Published 13th June 2015

ABSTRACT

The UK urgently needs a public health strategy for NTD reduction, which could include the use of food supplements, food fortification or a combination of both. An updated nutritional benefit-risk analysis is needed to inform population-based and/or targeted public health policies for folic acid intake and reduction of risk of neural tube defects. Policymakers should be cautious about the long-term exposure of the population as a whole to additional folic acid, especially potential adverse effects on the nervous system and brain function in older people, and higher levels of intake during infancy and childhood. The European-wide authorised health claim for folic acid food supplements and reduced risk of NTDs could transform the communication of the health benefits for women of childbearing age. Vitamin B_{12} deficiency may be an independent risk factor for NTDs, in which case dietary interventions with folic acid combined with vitamin B_{12} need to be considered.

Keywords: Public health; folic acid; neural tube defects; mandatory fortification; food supplements.

1. INTRODUCTION

NTDs remain one of the commonest categories of birth defects worldwide, affecting an average of one in every 1000 established pregnancies [1,2]. Clinical severity of NTDs varies greatly, and both genetic and non-genetic factors are implicated in the causes of NTDs, with up to 70% of the variance in NTD prevalence attributable to genetic factors [2,3].

In the 1970s, Smithells et al. [4] noted that mothers who were pregnant with foetuses with NTDs had reduced serum concentrations of

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several vitamins (folate, riboflavin and vitamin C). In due course, further definitive research, including a randomised, double-blind trial, showed that folic acid is a significant factor for the prevention of NTDs [5,6,7]. The Medical Research Council (MRC) trial [5] showed that preconceptional supplementation significantly reduced NTD-affected pregnancies by about 70%, and the trial led to the recommendation that all women planning a pregnancy should consume 0.4 mg folic acid per day, and that women at high risk of having a baby with an NTD should receive 4–5 mg/day.

Since the early 1990s, many national authorities have considered how best to introduce primary preventive measures. These dietary interventions include educational campaigns to encourage greater consumption of folate-rich foods, the targeted use of food supplements for women of childbearing age and mandatory fortification of bread and flour with folic acid.

2. RECOMMENDATIONS FOR MANDATORY FORTIFICATION OF BREAD AND FLOUR

In 2006, the Scientific Advisory Committee on Nutrition (SACN) estimated that there are about 700–900 NTD-affected pregnancies per year in the United Kingdom (UK), and its report [8] recommended that mandatory fortification of flour with folic acid would improve the folate status of women most at risk of pregnancies affected by NTDs. However, the committee recognised that mandatory fortification of flour together with the current practice of voluntary fortification of foods with folic acid and general use of food supplements would increase the numbers in the population with total intakes above the Guidance Level (GL)[1]/Tolerable Upper Intake Level[2] (UL) of 1 mg/day based on three scientific risk assessments [9,10,11]. The SACN recommended that mandatory fortification should only be introduced in the UK if it is accompanied by controls on voluntary fortification, guidance on supplements use, measures for careful monitoring of emerging evidence on the effects of long-term exposure to folic acid intakes above the GL/UL per day, and a review of the evidence on benefits and risks. In 2009, the SACN reiterated its recommendations [12], and it also considered the evidence on folic acid and colorectal cancer risk. The working group concluded that there was no evidence to show that supplemental folic acid increases either the risk or the progression of cancer [13,14]. The advice for mandatory fortification of flour with folic acid and estimates of the dietary exposures of different groups in the population at various levels of fortification was published originally by the UK Committee on Medical Aspects of Food Policy [15].

3. THE TARGETED USE OF FOLIC ACID SUPPLEMENTS

Several national authorities have tried to promote the targeted use of folic acid supplements rather than increasing intake of the vitamin for the whole population through mandatory fortification. There are problems with this type of intervention. The neural tube is fully developed 22–28 days after conception, but many women are not aware they are pregnant until after this time. Recommendations for women planning a pregnancy to take folic acid supplements had little impact on the number of babies born with NTDs. Smith et al. [16] advocated that the best policy approach is to focus initially the use of food supplements for those women aiming to become pregnant and to provide education in support of the use of folic acid at and around the time of conception. Smith and Lucock [17] proposed serious consideration of folic acid supplementation trials in workplace nutrition programmes by occupational health professionals. Bearing in mind the international and national public health efforts of the World Health Organisation (WHO) to raise awareness of healthy dietary and lifestyle practices [18], WHO recommendations for daily folic acid supplementation in pregnant women [19] and the recent UK National Institute for Health and Care Excellence (NICE) recommendations to increase vitamin D supplement use among at-risk groups for maternal and child nutrition [20], it would seem that a comprehensive primary health care approach could focus more on women of childbearing age and include stronger and more effective communications to increase awareness of the need for folic acid supplementation.

[1] The EVM Safe Upper Level (SUL) and Guidance Level (GL) refer to the doses of vitamins and minerals used for supplementation that susceptible individuals can take daily on a lifelong basis without medical supervision. The SUL represents an intake that can be consumed daily over a lifetime without significant risk to health on the basis of available evidence. GLs give an approximate indication of levels that would not be expected to cause adverse effects, but have been derived from limited data and are less secure than SULs [10].

[2] UL is defined as the maximum level of chronic daily intake of a nutrient from all sources judged to be unlikely to pose a risk of adverse health effects to humans [11].

4. FOLIC ACID HEALTH CLAIM FOR REDUCED RISK OF NTDs

The European Regulation (EC) 1924/2006 on nutrition and health claims [21] ensures that claims on foods and food supplements can be properly justified and scientifically substantiated. The law set out their conditions of use, established a system for their scientific evaluation by the European Food Safety Authority (EFSA) and created a European register of authorised claims. Health claims and reduction of disease risk claims can be made for a food category, a food or one of its constituents based on an assessment of the totality of the available data and weighing of the evidence. A reduction of disease risk claim falls under Article 14 of the regulation and is defined as any health claim that states, suggests or implies that the consumption of a food category, a food or one of its constituents significantly reduces a risk factor in the development of human disease. Applicants for health claims must follow the procedures set out in the regulation [21] and in the implementing rules [22], which include submission to EFSA of a comprehensive dossier of the scientific evidence, a proposal for the wording of the claim and specific conditions for its use.

The EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) considered an application and concluded that a cause and effect relationship had been established between increasing maternal folate status by supplemental folate intake and a reduced risk of NTDs [23]. Following this positive EFSA scientific opinion, the European Commission and member states authorised the health claim for folic acid supplementation to reduce risk of NTDs [24]. The new claim was published on 28th October 2014. The regulation entered into force on the twentieth day following that of its publication.

The authorisation of the health claim for folic acid supplementation to reduce the risk of NTDs such as spina bifida and anencephaly will undoubtedly help support public health efforts to educate and inform women of childbearing age. The health claim is: “Supplemental folic acid intake increases maternal folate status. Low maternal folate status is a risk factor in the development of neural tube defects in the developing foetus.” The conditions of use are: “The claim may be used only for food supplements which provide at least 400 µg of folic acid per daily portion”, and “Information shall be provided to the consumer to the effect that the target population is women of childbearing age and the beneficial effect is obtained with a supplemental folic acid daily intake of 400 µg for at least one month before and up to three months after conception“ [24].

There is now clearly a need to assess the future use and potential impact of the European-wide health claim for folic acid and reduced risk of NTDs for food supplements, which could help transform the communication of the health benefits for women of childbearing age.

5. ANALYSIS OF NUTRITIONAL BENEFITS AND RISKS

Researchers and policymakers are aware of the need to make informed decisions based on scientific assessment of the balance between positive and negative influences of folate on human health [25,26,27]. Benefit-risk approaches, such as the European-funded project BRAFO (Benefit Risk Analysis of Foods), can assist in decision making at different intake scenarios by assessing qualitative and quantitative comparisons of beneficial and adverse effects. The BRAFO stepwise benefit-risk methodology was applied in a case study reported by Verhagen et al. [28]. This paper summarises the most relevant health effects of folic acid/folate, the quality of the scientific evidence and the population groups affected. Such a benefit-risk approach helps inform the health policy decisions about increasing micronutrient intakes by gaining insight into the magnitude of the risks involved at both ends of the intake spectrum and making choices about their acceptability. In the case of folic acid, risk managers must weigh up the effects of neurological disorders in elderly persons (and strict vegetarians, who may have suboptimal intakes of vitamin B_{12} or be deficient) versus the benefits in other well-defined population groups [28,29,30]. In the Netherlands, the risk managers at the Ministry of Health decided their strategy for prevention of NTDs to be the education of the target group of young females to take folic acid in the form of a food supplement [28].

The forms and bioavailabilities of folic acid in fortified foods and food supplements, as well as the possibility of a lifetime’s exposure where mandatory fortification is considered, raise important questions about the influences on population health. Smith et al. [16] highlighted the key issue of the potential for unknown adverse effects of long-term population exposure

to excess folate/folic acid. The authors suggested that national authorities should be cautious and encourage further research to ascertain the potential detrimental and positive effects caused by long-term, higher intakes of folic acid. Only then can authorities develop the right strategies for the population as a whole.

The SACN has estimated that up to 162 NTD pregnancies per year might be prevented by mandatory fortification of flour at a level of 0.3 mg folic acid/100 g [8]. This translates into about one third to three quarters of a million people being exposed to additional folic acid for every NTD prevented [16]. Of particular interest is the fact that before the mandatory fortification of grains in the USA, the average consumption of folic acid was estimated to be 0.25 mg/day and the fortification programme is estimated to have added 0.1 mg/day, leaving 61% of women of childbearing age still below the recommended level [31]. Those women who achieved the recommended levels of intake were those who consumed food supplements [31]. In addition, Smith et al. [16] cite intake data indicating 43% of children in the USA below five years are consuming double the proposed upper limit of intake for that age group following mandatory fortification. Of this group, 10% exceeded the adult upper limit. Clearly, major questions need to be addressed about the effects of folic acid at this level of intake during infancy and childhood, and more importantly, what the effects are of long-term exposure over a lifetime.

An area of critical importance is the role of folates/folic acid, vitamin B_{12} and homocysteine in brain metabolism and function at all ages, especially in relation to nervous system development, mood, ageing, cognitive function and dementia [32,33]. The metabolism of folic acid/folate and the metabolism of vitamin B_{12} are intimately linked, such that deficiency of either vitamin leads to an identical megaloblastic anaemia. Both folates and vitamin B_{12} deficiency have fundamental roles in central nervous system functions at all ages, as well as in tissue growth, differentiation and repair. Major concerns are that folic acid, in the presence of vitamin B_{12} deficiency, may be harmful to the nervous system and lead to adverse haematological effects, particularly in the elderly. Advocates of national mandatory folic acid fortification policies aimed at reducing the incidence of NTDs in vulnerable pregnancies therefore need to re-evaluate the longer-term implications for brain function and the nervous system, especially in elderly people [34]. In addition, vitamin B_{12} deficiency may be an independent risk factor for NTDs [35], in which case dietary interventions with folic acid combined with vitamin B_{12} need to be considered.

6. MAKING THE RIGHT PUBLIC HEALTH DECISION

The public health policy decision on mandatory fortification of flour and bread in the UK has been deferred for well over a decade [8,12,15]. On 20th March 2015, Public Health England published the results of the National Diet and Nutrition Survey Rolling Programme (NDNS RP) on blood folate status [36]. Two measures of blood folate were reported: serum total folate, which reflects recent dietary intake, and red blood cell (RBC) folate, which reflects longer-term body stores and is generally considered to be the better measure of long-term status. Results were compared with the World Health Organisation (WHO) thresholds of 10 nmol/L for serum total folate and 340 nmol/L for RBC folate in order to indicate risk of biochemical folate deficiency. The mean serum total folate concentration for women of childbearing age in the UK as a whole was 19.2 nmol/L for those aged 16–24 years and 20.3 nmol/L for those aged 25–34 years and those aged 35–49 years. There were no statistically significant differences in the mean concentrations between age groups. The proportion of women of childbearing age who had a serum total folate concentration below the WHO threshold was 22.1% for those aged 16–24 years, 17.7% for those aged 25–34 years and 13.1% for those aged 35 to 49 years [36].

The mean RBC folate concentration for women of childbearing age in the UK as a whole was 552 nmol/L for those aged 16–24 years, 611 nmol/L for those aged 25–34 years and 647 nmol/L for those aged 35–49 years. The proportion of women who had a RBC folate concentration below the WHO threshold was 15.6% for those aged 16–24 years and 10.1% for those aged 35–49 years.

Key findings are that, for women of childbearing age (16–49 years) in the UK as a whole, 11.3% and 16.5%, respectively, had RBC folate and serum total folate concentrations below the WHO threshold. Public Health England notes that low folate status of women of childbearing age is a particular health concern, and that increased folic acid intake through supplementation has been shown to reduce the risk of NTDs such as spina bifida if taken in the peri-conceptional period.

Women planning pregnancy are therefore advised to take a 400 µg folic acid supplement daily until the 12th week of pregnancy [36]. Interestingly, for children in the 4–10 year age group, 1.6% of boys and 5.9% of girls had a RBC folate and a serum total folate concentration below the WHO thresholds, which again raises concerns that increased levels of folic acid from fortification is non-specific and must be safe for all segments of the population.

In an examination of selected national policies towards mandatory folic acid fortification in six countries—Australia, China, Finland, Ireland, UK and the USA—Lawrence et al. [37] concluded that policy should be determined by taking into account the national circumstances and the assessments by national authorities of potential benefits and risks. The selected countries have diverse policy positions on mandatory folic acid fortification depending on, for example, differences in NTD rates, evidence of inadequate folate reserves and folate deficiency among the population, political and moral circumstances, and the need for comprehensive surveillance systems to measure both the effectiveness and the safety of the intervention. For example, Ireland has traditionally operated a liberal policy of voluntary fortification and supplement use, but until recently very little was known about how these practices affected population intakes and status of folate and vitamin B_{12}. Hopkins et al. [38] found that food supplement use, but not fortification, was associated with significantly higher folate and B_{12} dietary intakes and biomarker status relative to non-consumers in Irish adults. Of concern is the finding that two thirds of young women had suboptimal RBC folate levels for protection against NTDs, and among non-consumers of folic acid, only 16% attained optimal RBC folate levels. The relationship between folic acid and health is an ongoing dynamic policy topic in several countries, including the UK. Clearly, as the evidence base continues to evolve, national authorities will need to review the potential benefits and risks for mandatory folic acid fortification and/or the targeted use of folic acid supplements.

7. CONCLUSIONS

Although there is a consensus that folic acid supplementation lowers risk for birth defects, the highly complex and critical biological importance of folic acid-related molecular nutrition makes it a difficult micronutrient to deploy as a simple intervention at a population level. Folic acid has too many biochemical spheres of influence to predict effects in a generalised way. In addition, several gene variants and other nutrients are interactive factors. Indeed, the new epigenetic evidence and the research on the functional role of polymorphism in the aetiology of NTDs and other adverse conditions in older people suggest that there is a need for a more personalised approach to preventive nutrition [39].

Lucock and Yates [40] concluded that it is hardly surprising that the scientific community does not have a true consensus view on whether mandatory fortification is an appropriate population measure. Mandatory fortification of flour and bread would shift nutrient intakes for the whole population that consumes such fortified foods, and not just for the target population. The growing concern is that increasing folate/folic acid in an entire population may be unwise for a significant number of people. The metabolic relationship between folic acid and vitamin B_{12} in relation to neuropsychiatric syndromes and neuropathology, including depression, cognitive decline and Alzheimer's disease in older people, certainly needs a full scientific benefit–risk assessment. Although inadequate vitamin B_{12} status is thought to be limited to the ageing population, it has been found with a relatively high prevalence in women of reproductive age with restricted consumption of animal-based food, an increasingly popular dietary trend, and in pregnant women, who are more likely to be deficient than non-pregnant women. Vitamin B_{12} deficiency may impair folate metabolism, and hence improving vitamin B_{12} status in women of childbearing age would also contribute to a reduction of NTDs [41]. Suboptimal intakes of nutrients tend to be multiple and interrelated. The implementation of preventive public health strategies based on fortification and/or supplementation needs to take into account reduction of risk of NTDs by folic acid and vitamin B_{12} [42,43].

In addition to the scientific challenges highlighted, there are several technical, food labelling and trade policy issues that will need to be addressed if mandatory fortification goes ahead in the UK, including ascertaining the latest policy decisions in other EU countries. The nutritional considerations include assessment of the overages of folic acid needed to counter the inevitable losses due to the baking processes and subsequent shelf-lives of bread and other products, consideration of whether widespread

fortification of all flour-containing products is appropriate, bearing in mind the health issues related to overweight and obesity (i.e. for products high in energy, salt, sugars and fat), an update on the extent to which voluntary additions of folic acid to food products have developed over the last decade and an assessment of the number of people who may not benefit from mandatory fortification of bread and flour because they avoid these products for reasons of weight loss, healthy weight maintenance, food allergy/intolerances or because of food preferences. Clearly, any changes in food fortification policy for micronutrients such as folic acid must be considered within the context of the impact they will have on all segments of the population, and of food technology and safety applications and their limitations [44].

In conclusion, there are still many scientific, technical, legal and consumer behaviour questions that need to be addressed before embracing either a population-based policy of mandatory fortification of bread and flour, a targeted use of folic acid-containing food supplements for women of childbearing age, or a combination of both.

COMPETING INTERESTS

The author is managing director of a specialist consultancy in nutrition and food science, providing advice to the food and food supplements industries, trade associations and government departments, nationally and internationally. The author was a member of the UK Department of Health Committee on Medical Aspects of Food and Nutrition Policy that reported on folic acid and the prevention of disease in 2000.

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