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Full length article

Folic acid fortification of flour to prevent neural tube defects in Europe – A position statement by the European Board and college of obstetrics and gynaecology (EBCOG)

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ABSTRACT

Neural tube defects are disabling birth defects developing during the very early stages of conception. Children born with spina bifida face significant physical, psychological and social consequences. They may have bowel and urinary dysfunction, and no lower limb muscle control, resulting in lifelong wheelchair use. There is robust evidence that periconceptual folic acid supplementation prevents neural tube defects, when compared with no intervention. However, approximately 40% pregnancies in Europe are unplanned, and women may therefore not be taking prophylactic folic acid at the time of conception. There is evidence that low dose folic acid consumption via flour fortification provides further benefits in prevention of neural tube defects.

Key Points

- There is high quality evidence that periconceptual folic acid supplementation and fortification are associated with a reduction in the incidence of neural tube defects in offspring.
- Folic acid fortification results in an average consumption of 0.15 mg of folic acid per day and this dose is not associated with any health risks [1,2].
- Flour fortification with folic acid is a safe and cost-effective way of protecting the majority of populations, as well as those most vulnerable against folic acid deficiency.
- Over 80 countries started fortifying their flour with folic acid and have seen a subsequent decline in the prevalence of neural tube defects.
- Mandatory flour fortification should be adopted by all European governments.

Neural tube defects in Europe

Neural tube defects (NTDs), including myelomeningocele (spina bifida) and anencephaly, arise due to a failure of the neural tube to close during embryonic development [3]. Over 4,500 pregnancies per year are affected by NTDs in the European Union (EU) [4]. The average prevalence of NTDs for EU countries is 0.91 per 1,000, based on EUROCAT registry data [5], and this has not decreased in the last 3 decades [6].

Up to 91 % of pregnancies affected by anencephaly and 66 % of

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pregnancies affected by spina bifida in European countries are electively terminated, resulting in an abortion [7]. Children born with spina bifida face significant physical, psychological and social consequences. They may have bowel and urinary dysfunction, and have no lower limb muscle control, resulting in lifelong wheelchair use. Many require long-term medical support and may experience limited employment opportunities, as well as social isolation [8].

Current advice about periconceptual folic acid

Women are unlikely to achieve the circulating levels of folate needed to prevent NTDs (red blood cell folate > 906 nmol/L) through a healthy diet alone [9], and since 1991 it has been known that folic acid (FA) supplementation prevents NTDs [10]. Approximately-two thirds of cases of NTDs are preventable with adequate FA supplementation [3]. Current public health advice in most European countries is for women to take 400 mcg of FA for at least 4 weeks prior to pregnancy and during the first trimester, in order to prevent NTDs [9]. However, approximately 40 % of pregnancies in Europe are unplanned [11], so the proportion of women taking the required amount of FA to prevent NTDs is closer to between 10 and 35 % [6].

Supplementation versus fortification

Clearly, the advice for all women to supplement FA is insufficient to prevent NTDs. Food fortification using FA is a much more efficient approach and many countries have already observed great success with such measures. The United States of America (USA) and Canada made FA fortification of flour mandatory in 1998. Canada saw a decrease in NTD prevalence from 1.58 per 1,000 to 0.86 per 1,000 within 4 years of the introduction of mandatory FA fortification [12]. The reduction in prevalence of spina bifida and anencephaly in USA decreased from 0.76 per 1,000 to 0.56 per 1,000 in the first year of mandatory flour fortification [13]. Chile saw a 50 % reduction in NTD incidence over a 10 year period following their introduction of mandatory wheat flour FA fortification in 2000 [14]. The UK adopted a decision to introduce mandatory flour fortification with FA in October 2021, which was modelled to prevent approximately 200 cases of NTD per year [15]. It was estimated that over 2,000 cases of NTD could have been prevented if the UK had introduced FA flour fortification in 1998 [16].

Safety of folic acid fortification

Flour fortified with FA is a safe public health measure. FA is the synthetic form of folate, which is a water-soluble B vitamin (B_9) and excess folate or FA are excreted in the urine [17]. The Institute of Medicine in the USA found no evidence of harmful effects from FA, in relation to reproduction, and development or risk of cancer [18]. It concluded that FA supplementation is a safe intervention [18]. The Scientific Advisory Committee on Nutrition (SACN) in the UK published a report in 2017 with an update on FA in which they examined the evidence in relation to potential adverse effects of FA fortification [19]. They concluded that whilst there are some uncertainties in relation to FA and cancer risk, the methylenetetrahydrofolatereductase (MTHFR) genetic studies suggest higher folate concentrations reduce overall cancer risk [19]. SACN recommended mandatory fortification, alongside restrictions on voluntary dietary fortification with folic acid and clear guidance on the use of FA supplements to ensure no increase in the number of people with intakes above the recommended daily amount.

Other benefits of folate fortification

Continued FA supplementation throughout the second and third trimesters of pregnancy has been shown to improve childhood development and cognition. In the only randomised controlled trial evaluating FA supplementation during the second and third trimesters (FASSTT Offspring trial), mothers received 400 mcg/day of FA or placebo from 14 weeks until the end of pregnancy [20]. A follow up study of children born to mothers receiving FA showed significantly higher cognitive scores at 3 and 7 years [21].

Another benefit of FA fortification for the general population is the reduction in anaemia secondary to folate deficiency. The USA saw a reduction (8.4 % to 0.4 %) in this entity, in people aged over 65 since they introduced mandatory FA fortification [22]. Deficiency in either FA or vitamin B_{12} causes macrocytic, megaloblastic anaemia; folate will resolve the anaemia, however only replacement of B_{12} will prevent neuropathy and spinal cord degeneration. Early concerns that FA fortification would 'mask' B_{12} deficiency in patients with pernicious anaemia arose mainly from studies carried out in the 1950′s, before individual assays for folate and B_{12} were available [17]. Furthermore, B_{12} deficiency does not always present with a macrocytic anaemia, thus clinicians need to test B_{12} serum levels if a patient presents with neurological symptoms. The 2017 SACN report on FA found that FA intakes up to 1 mg/d were not associated with neurological impairment in older people with low vitamin B12 status and that B12 deficiency prevalence did not increase in the USA following mandatory FA fortification [19].

Cost-effectiveness

A systematic review of 13 studies found that mandatory flour fortification with FA was a cost-effective measure. The cost-benefit analysis showed that for each monetary unit spent in the program, there would be a return of 17.5 monetary units [23].

Call to action

EBCOG urges European governments to consider the compelling evidence to make flour fortification with folic acid mandatory.

Approval

This review was peer reviewed by Professor Charles Ventura-Savona, Professor Basil Tarlatzis, Professor Diogo Ayres-de-Campos and Dr Hajra Khattak.

The paper was approved by the Executive Board of the EBCOG on 24th September 2022.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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