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Reflections

Flour fortification with folic acid to reduce risk of Spina Bifida

EDUCATION

AUTHOR

Niha Marian Hussain
University of Birmingham

Sanjeev Chaand Sharma
University of Birmingham

Address for Correspondence:

Niha Marian Hussain
University of Birmingham School of Medicine
Edgbaston
Birmingham B15 2TT
United Kingdom

Email: NMH801@student.bham.ac.uk

ORCID ID: 0000-0002-7579-9182 (NH)

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Summary:

Spina bifida is the most common neural tube defect (NTD) and is caused by an interaction of genetic and environmental factors. The congenital condition results from the failure of closure of the caudal neural tube and can led to a variety of complications. Current prevention and management interventions include taking folic acid supplements and undergoing operation before or after birth. The compulsory fortification of flour with folic acid has been successful in countries such as the USA, where studies have found that the prevalence of spina bifida declined by 31% since fortification was introduced. Despite the evidence to support the legislation, there are many concerns regarding folic acid fortification. These include certain ethical considerations regarding the feelings of those already living with NTDs as well as a potentially increased risk of cancer due to excess folic acid in the diet.

Relevance:

The British Government has recently announced plans to discuss the mandatory fortification of flour with folic acid. This is in response to the establishment of a causal link between NTDs such as spina bifida and low folic acid levels in mothers during the embryonic stage of pregnancy. Evidence suggests that a diet containing folic acid reduces the risk of spina bifida in offspring by up to 70%.

Take Home Messages:

Further research is needed to explore the long-term effects of increased folic acid in the diet; however, it appears as though the evidence for the mandatory fortification of flour with regards to a significant reduction in the risk of developing NTDs such as spina bifida outweigh potential risks.

In November 2018, the British Government announced plans to consult on the mandatory fortification of flour with folic acid in a bid to reduce the incidence of neural tube defects (NTDs). The causal link between NTDs (such as spina bifida and anencephaly) and low folic acid levels in pregnant women was established in 1991 through trials conducted by the U.S. Department of Health and Human Services. (1) 26 years of subsequent pressure from independent scientists, charities and the Scientific Advisory Committee on Nutrition forced the government to discuss the introduction of this new regulation. The fortification of flour with folic acid is generally thought to be beneficial by the medical community, including The Royal College of Obstetricians and Gynaecologists. (2)

Between 1991 to 2012, the prevalence of pregnancy complicated by NTDs in the UK was 1.28 (95% CI 1.24 to 1.31) per 1000 total births, whereas NTD live births was only 0.20 per 1000 live births. However, there is evidence to suggest that had fortification been implemented at the level adopted by other countries (such as the USA) between 1998 to 2012, there would have been an estimated 21% reduction in the prevalence of NTDs in the UK. (3) Despite the evidence in favour of fortification, potential concerns have been raised, which has delayed the process of implementing the public health measure. This paper aims to provide a background on spina bifida before discussing the advantages and disadvantages of fortifying flour with folic acid.

NTDs are a spectrum of disorders characterised by the abnormal development of the brain or spinal cord. Spina bifida is the most common NTD. The term spina bifida is derived from Latin for 'split spine' and the earliest known cases were two mummified newborns found in King Tutankhamen's tomb. (4) Spina bifida is a multifactorial condition, caused by both genetic and environmental factors. (5) One of the genes most commonly associated with spina bifida is the MTHFR gene, which codes for an enzyme involved in processing folic acid, which is needed convert homocysteine to methionine. (6) It is thought that the failure to convert homocysteine leads to NTDs. Other risk factors include maternal diabetes, obesity (7) and exposure to teratogenic medications, such as the antiepileptic sodium valproate. (8)

Spina bifida results from the failure of closure of the caudal neural tube. In normal embryology, neural tube closure occurs from the 23rd (rostrally) to the 27th (caudally) day after fertilization. (9) However, in spina bifida the vertebrae and membranes surrounding the spinal cord at the lumbosacral region fail to fuse.

There are three classifications of spina bifida: occulta, meningocele and myelomeningocele. Spina bifida occulta, known as 'hidden' spina bifida, is the mildest and most common form. It is believed that up to 10% of the British population have spina bifida occulta. (10) Formal diagnosis is through plain film radiograph, though newborns often have a visible indication above the spinal defect such as an abnormal tuft of hair, dimpling or a birthmark. (11) There are no consequences of spina bifida occulta and so no treatment is required. In meningocele, the meninges herniate through the vertebral opening, forming a fluid-filled sac. This cyst does not contain the spinal cord, so nerve damage is unlikely but when it does occur, patients often experience bowel incontinence as the only resulting symptom. (12) The most severe form of spina bifida is myelomeningocele, in which both the meninges and spinal cord herniate through a gap in the vertebral arch. This results in a variety of complications such as lower limb motor and sensory dysfunction, urinary and bowel incontinence, orthopaedic deformities, hydrocephalus and Chiari II malformation (a downward displacement of cerebellar tonsils through the foramen magnum). (10, 12) Figure 1 summarises the three types of spina bifida.

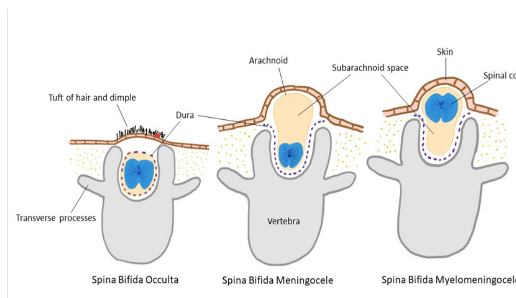

Figure 1: The three types of spina bifida

Spina bifida meningocele and myelomeningocele are surgically treated either by intrauterine repair surgery, or surgery within the first few days after birth. The herniated meningeal sac is excised and in myelomeningocele, the spinal cord is returned to the spinal canal, before the surrounding dura mater is closed over the defect. (13) Surgical correction is required to prevent neurological infections as well as injury to the exposed spinal cord and nerves.

Folic acid is required for haematopoiesis, DNA synthesis and neural development. (14) In a bid to reduce the risk of spina bifida, expectant mothers are currently advised to take folic acid supplements. Daily recommendations for folic acid are usually 200µg for anyone over the age of 11 years, but 300µg plus a 400µg supplement of folic acid during the first 12 weeks of pregnancy for expectant mothers. (15) Evidence suggests that taking these supplements reduces the risk of a mother giving birth to a child with spina bifida by up to 70%. (16)

Without supplementation, folic acid can only be obtained via the consumption of natural folic acid-containing foods (such as legumes, asparagus, eggs, potatoes, brussel sprouts and baked beans). (17) Large portions of these foods would be needed to reach a daily intake of 400μg, which is often too difficult for many women to achieve. Moreover, adequate folic acid levels are most important during the embryonic stage of pregnancy (as this is when the neural tube develops), which is also when many women do not yet know that they are pregnant. Fortification could boost folic acid levels during the first trimester of pregnancy in the bodies of those most at risk from deficiency and therefore at risk of having a child with a NTD. (18) Women at risk include those from lower socio-economic groups, younger mothers and those with unplanned pregnancies.

Food fortification has previously been implemented in the UK. Under the UK Bread and Flour Regulations 1998, industry is currently required to add iron, calcium, thiamine and niacin to all wheat flour and white bread in a bid to reduce deficiencies. (19) Moreover, the compulsory fortification of flour with folic acid has been successful in countries such as Chile and the Unites States. Since introduced in 1998, a US study reported that within two years, the prevalence of spina bifida declined by 31% and the incidence of anencephaly by 16%, exemplifying the benefits. (20)

To summarise, the main advantage of fortifying flour is that the move would reduce the prevalence of folic acid deficiency. This would therefore reduce the incidence of folic acid-dependent conditions such as NTDs. Despite this advantage, there are several concerns, which have contributed to the UK government's delay in employing the change. The fortification of flour is essentially a public health intervention, which means that its implementation is likely to achieve outcomes at a population level but is also likely to fail to meet the immediate needs of individuals. Not all women consume the same levels of folic acid, so fortification may not be fully effective and could even result in some consuming too much folic acid in their diets. Long term consequences of a high intake (>1000μg per day) manifest as abdominal cramps, diarrhoea, irritability, nausea and skin reactions. (21) One could argue that the government should focus on providing health advice and treatment tailored to individual needs to avoid such consequences whilst still preventing a woman's pregnancy being complicated by a NTD, rather than via a non-specific public health measure.

There are also ethical considerations that the government will have to address when trying to eradicate NTDs; patients who suffer a significant disability due to a NTD may feel ashamed and unwanted by society and would rather the government concentrate on managing the needs of existing people affected by NTDs more effectively. Since folic acid is only one of the contributing factors to the development of spina bifida, fortification will not completely eradicate the disease. (22) Therefore, one could argue that it could be more cost effective to spend on improving the current treatment accessed by those suffering with spina bifida, whilst also increasing awareness and reducing the discrimination faced by those living with NTDs, in order to improve the quality of their lives.

Another concern with such a large-scale public intervention is the lack of population-based evidence regarding the long-term effects of increased folic acid intake. The US was the first country to introduce mandatory folic acid fortification in 1998, (16) before which there are no national records lasting over 20 years about the impact of folic acid consumption on the population. Further research is needed to assess the long-term effects of folic acid. Furthermore, high folic acid diets are thought to be associated with an increased risk of cancer. A meta-analysis of 19 studies found an increased risk of cancer overall (RR 1.07, 95% CI 1.00 to 1.14) in subjects taking ≥0.4 mg folic acid supplements per day. The risk of prostate cancer was significantly raised (RR 1.24, 95% CI 1.03 to 1.49). (23) Since the daily folic acid recommendations for most of the public are 0.2mg per day, yet the study observed increased cancer incidence from double that amount, it is possible that there may be a link between cancer and high folic acid intake.

Finally, there are worries that a high intake of folic acid from fortified food could mask macrocytic anaemia which is an important diagnostic sign of vitamin B12 deficiency. (24) As well as haematopoiesis, B12 is essential in brain and nervous function, and therefore deficiency can lead to neurological disturbances such as Alzheimer's disease. (25)

Currently, the government have only announced their plans to begin formal talks for mandatory fortification of flour with folic acid. Discussions regarding how this will be implemented, when and how the move will be regulated are yet to take place but are soon expected due to pressure from several MPs, independent researchers and NHS advisory bodies. (26) Moreover, further research is needed to explore the long-term effects of increased folic acid in the diet, especially its potential link to cancer. However, for now, it appears that the evidence for the mandatory fortification of flour leading to a significant reduction in the risk of developing NTDs outweigh the potential risks. Therefore, medical students and clinicians alike should continue to educate and advise the public about folic acid's health benefits, especially for expectant mothers.

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