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Review Article

Mandatory Folic Acid Food Fortification to Prevent Neural Tube Defects: The Pro or Con Debate

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Abstract: Neural tube defects are the second most common congenital anomaly. Among the known risk factors, low levels of folic acid rank first as responsible for the majority of cases recorded worldwide. In 1986, the mandatory folic acid food fortification in the U.S.A. led to dramatic reduction of disease incidence, while for many people it was considered as one of the most successful interventions in the history of public health promotion. Despite the satisfactory results from all countries that adopted similar policies, a significant number of countries, including the EU, preferred alternative ways to address it, considering the very limited safety data for such an intervention. Today, after 20 years of mandatory fortification from a sufficiently representative sample (1/3 of the planet), the necessity to apply this at global level should probably be reviewed, since until now no correlation with unfavourable impacts has been demonstrated. *Objective* of the present review was to assess the necessity of mandatory folic acid food fortification in the context of congenital neural tube defects (NTDs) prevention. *Material – Method*: an extensive search in the electronic database PubMed was performed. Animal or in vivo studies and articles were excluded, due to the inability to draw conclusions that is frequently observed, as well as the strong suspicion of failure to respond to clinical data. Furthermore, part of the studies was derived from searches to the References of the articles of the aforementioned database. *Conclusions:* the decision of mandatory folic acid food fortification should be determined by specific factors as: disease prevalence, rates of planned pregnancies, efficiency of existing measures to decrease significantly the overall disease's incidence and the folate level in the general population.

Keywords: Neural Tube Defects, Spina Bifida, Anencephaly, Folic Acid Food Fortification, Folic Acid and Carcinogenicity

1. Introduction

Folic acid (B9) belongs to the class of water-soluble B vitamins. It is present as a natural ingredient in many foods (such as citrus fruits and vegetables) but also in microorganisms.

It was first discovered in 1931 (Wills & Mehta) as a factor that could correct megaloblastic anaemia of pregnant women in India (Will's factor). Ten years later (Mitchell et al) it was isolated from spinach leaves ("folic" derives from the Latin folium meaning "leaf"). These researchers also demonstrated that the same substance was also a growth factor for the development of certain bacterial species (Str. faecalis).

During the following years, a synthetic form of the vitamin was produced (folic acid-FA) as well as folate antagonists, with antitumour and antimicrobial activity.

It should be mentioned that folic acid is more potent than folate, since it is a chemically more stable molecule (DFE: 1 μg folate = 0.6 μg folic acid).

From 1950 till present, the significant biological activity of folic acid is a concern. Metabolic biochemical processes for which it is an essential co-factor are briefly the following: nucleic acids' synthesis, DNA repair processes and gene expression (through methylation reactions). [1]

The presence of folic acid in inadequate quantities is particularly harmful during the initial stages of embryogenesis. Low levels of folate both during pregnancy and during the pre-conception period are related to the occurrence of severe neural tube defects, which constitute the second most common congenital defect. It is an abnormal development of the central nervous system, leading to developmental brain defects known as anencephaly (a condition incompatible with life), or various types of anatomical malformation of the spinal cord and spinal column (spina bifida) and, depending on its type, significant degree of disability. The annual incidence of the disease is estimated to 320,000 cases worldwide, of which 4,500 cases concern the European Union countries. [2-3]

2. Experience with Mandatory Fortification

In the beginning of the '90s, following the publication of studies [4-5] highlighting the significant role of FA administration during pregnancy in reducing NTDs occurrence, both the Disease Control and Prevention Centre (CDC) and the National Health Agency (USPHS) in the U.S.A. recommended that all women of childbearing potential should take folic acid in a dose of 400 μg/day. Due to poor response to the proposed recommendations, the FDA (1998) approved the fortification of cereals with folic acid, setting the grounds for an intervention (mandatory fortification) that is currently considered by many people one of the most remarkable in the world history of public health promotion. Even after the first year, a significant reduction (by 35%) of NTDs prevalence was recorded, [6] with similar results in other countries adopting similar policies, too. Representative results are the areas of S. Canada, with prevalence reduction by 83%, Costa Rica (58%), Chile (48.9%) and Argentina (49.7%). [7-15]

Today, America's example is followed by another 81 countries (FFI, 2015) with significant rates in disease prevention, especially for countries with high prevalence during the pre-fortification period. [6] Table 1 summarises the percentage reduction of disease prevalence (per 1.000 births) following the implementation of mandatory fortification. [9-17]

Table 1. *Percentage reduction of disease prevalence (per 1.000 births) following the implementation of mandatory fortification.*

COUNTRY	BMF[1]	AMF[2]	% PREVALENCE REDUCTION
USA			
Honein 2001	3.78	3.1	18
Simmoms 2004	10.9	8.2	24.5
Chen 2008	8.52	7.20	15.5
Collins 2011	13.4	9.7	27.6
CANADA			
Ray 2002	11.3	5.8	48
De Wals 2003	16.9	8.6	49.1
Liu 2004	4.36	0.96	78
COSTA RICA			
Chen 2004	9.7	6.3	35
Barboza 2011	12	5.1	58
Barboza-Argüello 2014	9.8	4.8	51
S. ARABIA			
Safdar 2007	1.9	0.76	61.8
Seidahmed 2014	1.46	0.81	44.5
CHILE			
Hertampf 2004	17	10.1	40.5
Nazer	17.03	9.29	44
Lopez-Camelo 2010	19.8	10.1	48.9
Cortés 2012	17.1	8.6	50
S. AFRICA			
Sayed 2008	14.1	9.8	30.5
BRAZIL			
Pacheco 2009	7.2	5.1	29.2
Lopez-Camelo 2010	31.4	24.3	22.6
ARGENTINA			
Lopez-Camelo 2010	24.5	12.3	49.7
IRAN			
Abdollahi 2011	31.6	21.9	31
JORDAN			
Amarin 2010	1.85	0.95	49.6

[1]BMF: before mandatory fortification.
[2]AMF: after mandatory fortification.

The following can be concluded from all the studies conducted during the last 20 years in these countries:

1. Folic acid's role in NTDs prevention is indisputable and proven, as long as adequate levels are ensured at least 4 weeks before foetus conception. [3, 18-19]

2. Overall disease incidence may be reduced to a threshold (~5 cases/100.000) above which no further reduction is expected, as it relates to cases of different pathogenesis. [6]

3. Among countries with mandatory fortification, the greatest benefit is expected in those that have: high incidence, high percentage of unplanned pregnancies and low levels of folate in the general population. [21]

4. It is not possible to predetermine the exact impact with relative accuracy, since it is subject to multifactorial interactions. Genetic factors are considered of crucial importance, in which, for example, the reduced response of American women of Spanish origin was attributed (common genetic polymorphism). [6, 20]

5. The possible adverse effects on population sub-groups (such as children, the elderly, cancer patients) are still under study, and the multiannual research so far has led to no indisputable or specific conclusions.

3. Non-mandatory Fortification Policies

Today, many countries, including the EU countries, are reluctant to adopt mandatory fortification policies, mainly due to the incomplete data regarding the safety of the general population and its subpopulations to their potential exposure to high FA levels. Therefore, firstly due to the incomplete data, but also due to the European Food Safety Association (EFSA) report [22] most European countries preferred to implement educational and informative programmes, which motivated women of childbearing potential to take folic acid 400 μg on a daily basis, either through increased dietary intake or through supplements. At the same time, voluntary food fortification is

free until today in almost all EU countries (excluding Sweden, where it is prohibited, and Denmark and Norway, where approval is required); however, the maximum quantity of added vitamin is not defined or specified. [3, 23]

The most reliable data for European reality are found in the database of the European Surveillance of Congenital Anomalies (EUROCAT); however they do not actually allow a satisfactory "mapping" of EU countries, since only some countries participate, and many of those with a really small percentage. For example, Denmark, Germany and Switzerland participate with data for a percentage lower than <10% of total cases, while there is no participation at all from countries with high disease prevalence, such as Lithuania and Romania.

Table 2. *Coverage percentage of European population in EUROCAT database.*

COUNTRY	ARCHIVES NUMBER	% OF ALL CASES (per country)
AUSTRIA	1	14.2
BELGIUM	2	26.1
BULGARY	1	15
CROATIAN	1	12
DENMARK	1	8.7
FINLAND	1	100
FRANCE	4	20.6
GERMANY	2	2.9
HUNGARY	1	100
IRELAND	3	57.8
ITALY	5	31.2
MALTA	1	100
NETHERLANDS	1	10.2
NORWAY	1	100
POLAND	1	54.3
PORTUGAL	1	15.9
SPAIN	4	34.3
SWEDEN	1	100
SWITZERLAND	1	9.9
UN. KINGDOM	8	35.2

EUROCAT 2005.
* FFI NTDs data.

Table 3. *European countries not included in EUROSTAT database.*

COUNTRY	NDTs PREVALENCE
LITHUANIA	20
CYPRUS	11,8
CZECH REPUBLIC	17
ESTONIA	10
GREECE	15
LATVIA	10
LUXEMBOURG	10
SLOVAKIA	4
SLOVENIA	10
LITHUANIA	20

FFI NDTs database 2015.

EUROCAT data concern only 28% of the total number of European cases, and the heterogeneity among countries in terms of data recording, methodology, screening and folate adequacy measurement, makes general conclusions almost impossible. Nevertheless, it is evident that, contrary to the decade 1998-2008, during the last decade some of those have managed to: a) achieve better compliance of women of child-bearing potential to the recommendations for prevention to receive folic acid 400 μg on a daily basis for at least one month prior to pregnancy, and b) satisfactory folic acid levels in the general population. [3, 23, 24]

The fact that the reduced number of anencephaly cases is not accompanied by a reduction of spina bifida prevalence raises a strong suspicion that NTDs prevalence reduction recorded in Europe relates either to the increased number of stillborn children or, more likely, to the increased proportion of interrupted pregnancies. [3] Figure 1

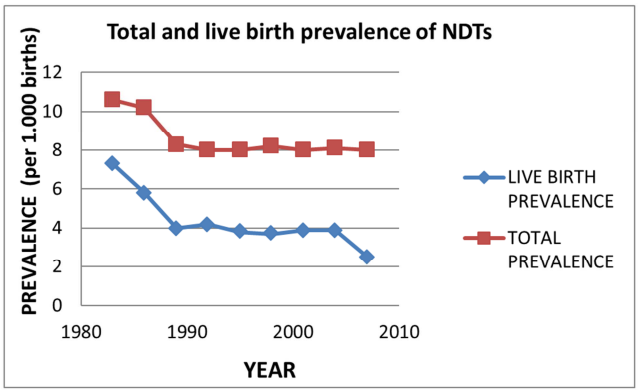

Figure 1. *The overall unchanged prevalence is accompanied with decrease of live birth prevalence in Europe, maybe due to increased proportion of interrupted pregnancies*[3].

At the same time, the declining trend in almost all European countries from 1992 onwards, is attributable to some degree to the liberalisation of food fortification with folic acid, and less on information programmes implemented in some of these countries. The latter finding is particularly disappointing, but probably expected, since such policies have been proven to be inadequate over time. [7, 24, 25]

Therefore, it is estimated that in Europe the overall incidence of the disease has shown no substantial change over the last 25 years, excluding only Ireland and England, which showed extremely high NTDs percentages during the previous years (and still have higher percentages as compared to Europe's average), while no progress has been achieved in terms of primary disease prevention. [3, 24]

Indeed, during the last years, a continuous increase of bibliographic data is observed regarding the failure of many countries, including Ireland, [26] New Zeland, [27] Switzerland, [28] and Denmark [29, 30] in achieving the recommended folic acid intake by women of childbearing potential.

4. Valid Considerations

In those countries where food fortification is mandatory for years, such as America, particularly increased levels of FA were found in the blood of mainly children below the age of 5 years and older people above 60 years old.

According to the existing directives, high FA concentrations

in both children and the elderly suggest that they probably receive larger amounts of folate that the maximum allowed for their age. [10, 45, 46] The potential epigenetic activity of such high concentrations is still under study, but until today it has not been associated with harmful effects, [11, 43, 45] excluding the cases of B_{12} deprivation, the diagnosis of which may theoretically be delayed in cases of high FA doses administration, with significant clinical consequences. However, it should be highlighted that in such cases, the actual problem is B_{12} deprivation (which should probably be examined more frequently) and not the excess of folate. [2, 11]

It is obvious that probably, certain sensitive groups of the general population were overly exposed to high FA doses, for many years in fact, which could probably lead to corrective actions from the countries, while at the same time other information about the safety of fortification are coming up, which is of utmost importance indeed (huge sample of "sensitive population" – multiannual exposure – long follow-up) for scientific data.

At this point it should be mentioned that the Medical Institute of Food and Nutrition (IOM) has set the maximum tolerable limit for synthetic vitamin intake to 1000 μg/day (1998). This was determined taking into account case reports published many years earlier (1947-1960). According to those, the dose of 5 grams had a negative impact, since the correction of anaemia of patients with vitamin B_{12} deficiency, which causes peripheral neuropathy, led to delayed diagnosis of anaemia and development of neurological signs. IOM, having no other data available and with the only objective to avoid "covering up" anaemia due to B_{12} deficiency, set the IUL at 1000 μ/g which were then used as a reference to determine IUL for children and adolescents. Considering that these hypotheses do not seem to be confirmed [44] it is possible to understand that a potential modification of the limits would differentiate fundamentally the assessment of results.

The association between FA and carcinogenicity has justifiably concerned the scientific community significantly, since medications-folic acid antagonists are until today considered as first-line treatment for many types of cancer. At the same time it is known that a diet rich in fibres, fruits and vegetables reduces the risk of cancer. Therefore, according to all studies, a contradiction seems to exist, that folic acid - through methylation reactions - has a dual role of promotion and prevention of carcinogenesis. Based on newer data from the molecular biology of cancer cells, the above mentioned contradictory action of FA may be considered differently, and the dual role of FA may be explained to some extent, given that methylation sites are typically modified in tumour cells, thus favouring different type of epigenetic effects. [31-33] Figure 2.

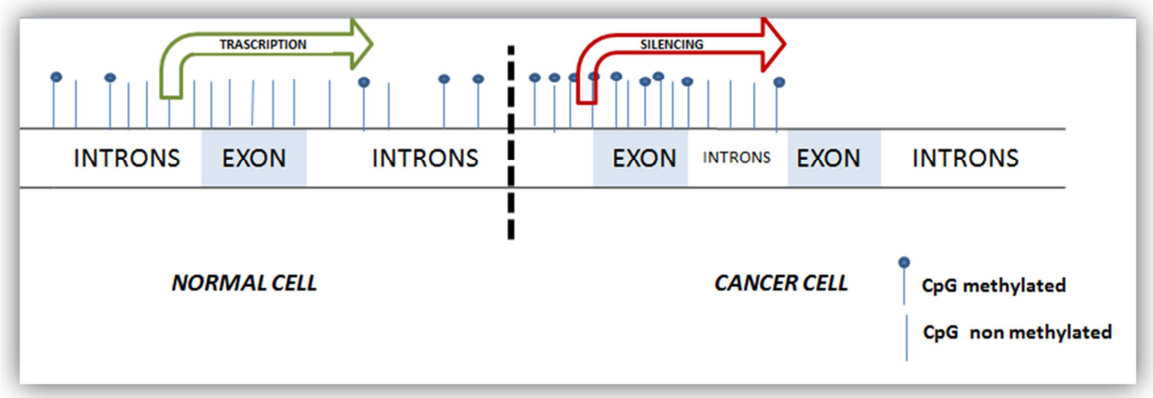

Figure 2. *CpG methylation patterns in normal and tumor human cell. Methylation of CpG dinucleotides in the bulk of the genome where CpG density is low stabilize the genoma. In contrast tumor cells present hypomethylation of CpG dinucleotides in the bulk of the genome and hypermethylation of CpG islands in gene promoter regions (that should normally be unmethylated).*

A typical example is the case of the large intestine - one of the most common sites where malignancies are identified worldwide - where high levels of folic acid seem to reduce the risk of malignancy, but also to accelerate the development of an existing lesion. A very large number of studies conclude in conflicting findings, demonstrating the protective role both in primary [34-36] and in secondary prevention, [37] but also a negative effect, mainly expressed as an increased development of established precancerous or cancerous processes. [36, 38, 39] However, it should be mentioned that most of them, mainly due to methodological constraints, ultimately only serve in enhancing or "weakening" hypotheses, without being able to come to a conclusion.

Alongside, the mandatory fortification, implemented for about twenty years in America, may be considered as a type of "ideal epidemiological study" in which a large population sample is exposed to a potentially harmful or beneficial agent for a long time. Therefore, the conclusions of recent meta-analyses that there is no correlation between folic acid and carcinogenesis cannot be ignored. [40-42]

Despite the fact that the epigenetic action of FA through methylation reactions is indisputable, the effect on gene expression is not anticipated, as it relates to the time and duration of exposure, age, genetic material and tissues integrity. [6, 32]

In conclusion, therefore, the exposure of the general population to increased FA levels is much more complex than we initially thought, and research in this field should continue in this direction.

5. Commentary

The prevention of individual diseases seems to be the solution for those diseases that concern the scientific community at present due to the extremely high morbidity and/or mortality, such as diabetes mellitus, cardiovascular disease and malignancies. Although prevention is a common solution for the majority of diseases, it is not achieved at a satisfactory level, either due to the required complicated or uneconomic procedures, or due to the unknown complex disease mechanisms, which do not allow the development of effective diagnostic algorithms. Therefore, refusal to administer a vitamin, which is proven to be a cornerstone in the prevention of a very serious disease, such as spina bifida or anencephaly, should be based on specific and conclusive data.

Over time, the questions, theories or results of scientific research, which has progressed considerably, are not the only benchmark for deciding on the promotion of public health, which has socioeconomic, political and ethical implications.

The role of social responsibility cannot be restricted to the high availability of a variety of products or medication or information leaflets, especially when these are proven to be ineffective. The role of social responsibility is to identify effective management strategies for cases like folate sufficiency, where the rational or ideal option is not feasible.

For instance, supplemental iron administration during pregnancy for anaemia prevention was based on the results of relevant epidemiologic studies, while the growing theories concerning iron's unfavourable action, mainly through redox reactions, [42, 47-49] will probably modify the proposed recommendations only when they are proven real or significant.

In recent years, the controversy surrounding the mandatory food fortification with folic acid is an ideal opportunity to re-evaluate social responsibility, not only towards the implementation of a policy, but also towards the non-implementation of an intervention.

Today it is estimated that in the USA, due to food fortification (cereals, corn derivatives, and rice), the disease is prevented in 1326 cases annually, with no proven unfavourable effect on the general population. [4] Apart from the significant saving of financial resources (>500 million dollars/year) for many people it was also considered as one of the most successful interventions in the history of public health promotion. [6]

It is obvious that many countries, initially due to the above mentioned concerns, and while waiting for new data regarding safety, preferred alternative ways to manage the problem, aiming to increase folic acid intake mainly by the target population.

However, just before the completion of 20 years since the implementation of mandatory fortification by a sufficiently representative sample (1/3 of the planet), the initial concerns of the other countries should probably be reconsidered, and fears should not turn into phobias. It is really important to understand the importance of the problem as a whole, taking due account that the reported prevalence concerns only part of the total cases, because of the increased number of interrupted pregnancies and high stillbirth. [3] This means that in a hypothetical scenario of a 10-fold incidence of anencephaly, NDTs incidence rates would remain stable.

6. Conclusions

Folic acid food fortification is not a good example of "one model fits all" policy.

The necessity and implementation of the measure in the different Member States, should be determined on the basis of decisive parameters, such as: serum levels of folate in the general population, prevalence of the disease and the effectiveness of the measures already taken.

Seems quite obvious that in countries where disease's prevalence is really close to the achievable prevalence limit, food fortification with folic acid is not expected to add any benefit for congenital neural tube defects. Besides, mandatory food fortification cannot considered essential in countries where: a) the rates of planned pregnancies are particularly high, since in these cases it is possible to ensure satisfactory levels of folate 4 weeks before foetus conception (e.g. Netherlands) and b) the existing measures of fortification and state care have led to significant reduction of overall disease incidence (e.g Ireland).

On the other hand, countries with particularly high disease prevalence or low levels of folate in the general population are expected to have the most significant benefit from mandatory food fortification under study.

The latter category includes the majority of European countries, which seem to insist on "targeted" policies of non-mandatory fortification, although their insufficiency has been demonstrated over time.

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