Review Article

Folic Acid – Recommendations and Interventions

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Introduction

Folic acid (FA) is known to play an important role in the prevention of birth defects.[1] Neural tube defects (NTDs) are severe congenital anomalies many of which are considered potentially preventable if mothers take adequate folic acid in the peri-conceptional period i.e. from at least one month before to one month after conception. Folates are required for the normal development and closure of the neural tube in the early stages of embryonic development (neurulation stage embryos). The exact pathogenic mechanisms underlying NTD development are complex and remain to be elucidated.[2-3]

NTDs are reported to occur at an overall prevalence rate of 10.29 per 10,000 births (2011-2015) in European countries.[4] It has been estimated that the lowest achievable rate of non-preventable NTD with folic acid is 5-6 per 10,000 births,[5] hence European countries can potentially half the current occurrence of NTDs if women were to take adequate folic acid in the peri-conception period.

Women's peri-conceptional blood folate levels may be augmented in three main ways: by increasing food folate intake, through FA vitamin supplementation and by fortification of food with folic acid.[6]

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Studies have shown that encouraging increased food folate intake alone is often inadequate to reach the optimal levels required to effectively decrease the incidence of NTDs.[7-8] It has been estimated that to consume the recommended amount of food folate, a person would need to eat an unrealistic quantity of certain food such as: "*23 spears of cooked asparagus or 4 cups of cooked okra or 4 cups of raw spinach or 2 slides of beef liver or 6 cups of orange juice or 4.5 cups of cooked broccoli*.[9] In view of this Health Authorities around the globe have embarked on further public health initiatives directed at improving women's peri-conceptional folate status, these include the issuing of National Guidelines and Recommendations, Health Promotion Campaigns and Mandatory Food Fortification with FA.[10-11]

This review describes the public health recommendations and interventions that have been undertaken in a bid to increase women's preconception folic acid intake and the successes, or otherwise, of the various actions.

National Guidelines and Recommendations

In 1992, both the US and Britain issued recommendations advising women planning pregnancy to take FA supplementation.[12-13] These were followed by similar recommendations in 1993 in a number of countries including Canada, New Zealand, China, South Africa, Ireland, Spain, Norway and the Netherlands.[11] Since then several other countries have issued policies and recommendations related to increasing folate intake and peri-conceptional FA supplementation.[10]

In January 1992, a UK Department of Health Expert Advisory Group released recommendations that all women planning a pregnancy should take 400ug of FA supplement per day and women with a history of NTD should take 4mg of FA preconceptionally and through the first 12 weeks of pregnancy.[13] These recommendations still hold today, with the latest position statement of the Scientific Advisory Committee on Nutrition

(SACN) recommending that even if food fortification is introduced, *"all women who could become pregnant and those with a history of a previous NTD-affected pregnancy should continue to supplement their diet with 400 µg and 5 mg per day of folic acid respectively prior to conception and until the twelfth week of pregnancy"* (Article 17).[14]

Similarly, US guidelines[12] issued in September 1992 advised that "*all women of childbearing age in the United States who are capable of becoming pregnant should consume 0.4 mg of folic acid per day for the purpose of reducing their risk of having a pregnancy affected with spina bifida or other NTDs*". The guidelines continue to state that "*women who have had a prior NTD-affected pregnancy are at high risk of having a subsequent affected pregnancy. When these women are planning to become pregnant, they should consult their physicians for advice.*"[12] as higher doses of FA are merited in such circumstances.

It is recommended that for optimal prevention of NTDs, FA supplementation is to be taken from at least one month prior to conception, as neural tube development starts in the very early embryological stages of development, and should be continued through the first trimester of pregnancy .[15] Such use is reflected in the official policies released by the various countries.

In spite of national recommendations being in place research has shown that women's compliance with FA supplementation remains inadequate,[16-17] indicating that more than just guidelines are needed.

Health Promotion campaigns

Subsequent to national recommendations and guidelines, a number of national and regional health promotion campaigns were developed and aimed at actively increasing women's awareness and knowledge of the benefits of FA and the recommendations for uptake of FA supplementation. The rationale of these campaigns is that greater awareness and knowledge of the association between the correct use of FA and prevention of NTDs would result in improved uptake of FA supplementation in women, with consequent increase in their blood folate levels and decrease in the occurrence of NTDs.[18]

Research has shown that whereas health promotion campaigns can and do significantly increase women's awareness and knowledge of FA supplementation, correct peri-conceptual use does not increase to such an extent, with the observed increase in the rates of preconception supplementation remaining far less than desired.[19] These low rates of preconception supplementation persist even when pregnancy has been planned.[20] More importantly, follow up studies show that the decrease in occurrence of NTDs following such campaigns has not been satisfactory, even in countries where voluntary food fortification is available.[17]

Most studies evaluating the effectiveness of Health Promotion Campaigns conclude that whereas campaigns have been effective in increasing women's awareness and knowledge, there have been disappointing results regarding their effectiveness in increasing preconception consumption of FA.[21]

Chivu *et al* (2007)[22] conducted a systematic literature review identifying studies reporting on the results of health promotion interventions carried out to "*increase awareness, knowledge and folic acid consumption before and during pregnancy*". The authors identified a total of 31 studies meeting their inclusion criteria and they found that "*on average, women's awareness increased from 60% to 72%, knowledge from 21% to 45% and consumption from 14% to 23%"* concluding that in spite of increased awareness women's *"average usage was less than 25%"*.[22] These results were further corroborated by another comprehensive systematic review of the literature conducted by Rofail *et al*[23] in 2012, who conclude that "*these campaigns usually changed the knowledge and behaviour of less than half the target population"* (p.95).[23]

Table 1 gives a summary of the findings of studies, published since 2010, investigating and documenting women's peri-conception FA supplementation.

Table 1: *Women's pre / peri-conception folic acid supplementation*

Country	Authors	Year Published	Study Population / sample	Survey dates	Sample size	Peri-conception use of FA *(%)*
EUROPE						
Denmark	Rasmussen and Clemmensen[44]	2010	Consecutive pregnant women attending a midwife consultation.	Aug 2008	84	*51.2*
Ireland	Delany *et al*[45]	2011	Women attending first antenatal visit at three maternity hospitals in Dublin.	Jul-Sep 2009	297	*36.0**
Netherlands	Zetstra-van der Woude *et al*[46]	2012	Pregnant women attending antenatal visits. Survey carried out in the Northern Netherlands**.**	2009	515	*51.6**
France	Tort *et al*[47]	2013	Nationally representative sample of women giving birth in France	2010	12646	*14.8*
Italy	Lauria *et al*[48]	2014	Sample surveys of delivering women from 3 birthing centres in Italy	2010-12	973	*37.9*
USA and CANADA						
Canada-National	Miller *et al*[49]	2011	Stratified random selection of post-partum women identified through the Canadian Census of Population as having delivered in the three-month period preceding the 2006 Census. Part of Canadian Maternity Experiences Survey.	2006	6421	*57.7*
USA	Hoyo *et al* [50]	2011	Pre-pregnancy & pregnancy-related data on dietary supplementation obtained by interviewing pregnant women at two obstetric-care facilities in Durham County, North Carolina.	2005-08	539	*51*
MIDDLE EAST						
UAE	Al-Hossani *et al*[51]	2010	Pregnant women of UAE nationality in Abu Dhabi Emirate attending 2 main maternal and child health centres.	Not given	277	7.8
Iran	Nosrat *et al*[52]	2012	Convenience purposive sampling of primaparous women registered with Primary Health Care Centres, private gynaecology clinic and the Dezyani Gynaecology and Obstetrics hospital.	Jun-Nov 2008	676	2.0
ASIA						
China	Zeng *et al*[53]	2011	Women attending prenatal or pre-pregnancy care visits in six provinces in Northern China.	Jun-Aug 2008	33025	*8.0**
	Xing *et al*[54]	2012	Pregnant women attending routine antenatal care for the first time in regions of Hefei and Maanshan. Study carried out within the China Anhui Birth Defects and Child Development Cohort study.	Oct 08 – Sep 09	4290	*16.1**
Taiwan	Jou *et al*[55]	2010	Women attending a community hospital in North Taiwan for their first antenatal visit.	Mar–Dec 2008	275	*15.6*
AUSTRALIA						
New South Wales	Wilton and Foureur[56]	2010	Consecutive primagravidae women attending antenatal clinic of a tertiary hospital in Sydney.	Sept 05-Mar 06	295	*23.4**

* Reported percentage stated specifically to include the use of FA at least 4 weeks before until at least 4 weeks after conception. Unmarked rates are those described as 'prenatal' and/or 'perinatal' consumption but full period of FA use not specified.

Health Promotion Campaigns and NTDs

Issuing recommendations and undertaking health promotion campaigns to increase women's peri-conceptional FA knowledge and uptake without reaching the primary intended goal of reducing NTDs could be considered futile. Disappointingly, it has been shown that in spite of extensive health promotion campaigns, the decrease in occurrence of NTDs has not been satisfactory,[24] with several studies reporting only a mild and often insignificant decrease in reduction in NTDs after introducing recommendations and FA campaigns without implementing mandatory food FA fortification.[25-26]

This limited success in reducing potentially preventable NTDs through health promotion campaigns is described in a comprehensive review by Botto *et al* (2005)[17] who investigated the occurrence of NTDs using data from 13 birth registries in Europe that could report on NTD prevalence before and after the issuing of recommendations. The authors found that "*rates of neural tube defects showed no detectable change.... regardless of the recommendations' form, timing, and intended target"* (p.574-575).[17]

A more recent paper by Khoshnood *et al* (2015)[27] highlights that this situation persists and '*recommendations, voluntary fortification, or both have not been effective in decreasing the prevalence of neural tube defects in Europe'*. This contrasts with the decrease of neural tube defects seen in other countries that have introduced mandatory fortification. The authors emphasize that '*voluntary guidance for women isn't working and Europe should seriously consider mandatory fortification'* (p.5).[27]

These findings clearly indicate that more than just recommendations and health promotion campaigns are necessary to achieve the desired prevention of avoidable NTDs.

Mandatory Food Fortification

Confronted with the widely documented limited success of the recommendations and health promotion initiatives to increase women's peri-conceptional uptake of FA to decrease the occurrence of NTDs, researchers have argued that new approaches are needed.[28] Indeed, several prominent public health officials and epidemiologists have advocated strongly in favour of mandatory, widespread staple food (grain) fortification with FA.[29-30]

Concerns regarding the health risks of the widespread use of FA food fortification and the issue of freedom of choice have hindered the implementation of FA food fortification especially in Europe.[31]

The main health concerns related to mandatory food fortification with FA include possible masking of Vitamin B12 deficiency, associations with certain cancers, cognitive decline and autism. However, current research is inconclusive and none of these concerns have been confirmed at the recommended levels of food fortification. The evidence is generally deemed insufficient to impede the consideration of food fortification to decrease NTDs. Further discussion of these health concerns can be found elsewhere.[32-38]

Table 2: *Countries that have introduced mandatory fortification*

Country	Year of implementation of Mandatory Fortification	Level of fortification mandated
USA*	1998	140 µg /100g flour
Canada*	1998	150 µg /100g flour
Costa Rica*	1998	180 µg/100g flour
Chile*	2000	220 µg/100g flour
South Africa*	2003	150 ug/100g flour
Brazil**	2004	150 µg /100g flour
Australia***	2009	2-3 mg/kg flour

*Crider et al, 2011[57]; **Pacheco, 2009[58]; ***FSANZ, 2009[59]

Table 3: *NTD rates pre and post mandatory food fortification (listed by year of fortification)*

Country By Year of mandatory folic acid fortification introduced and level of fortification mandated	Conditions reported	Pre-fortification NTD rate/1,000 (Reference time period)	Post-fortification NTD rate/1000 (Reference time period)	Decline in NTD rate *(%)*
Oman (1996 – 5mg/kg flour)				
(Alasfoor *et al*, 2010)[60]	Spina bifida	**3.06**** (1996)	**2.11** (1997)	***31%***
Canada (1998 - 150ug/100g flour)				
7 Canadian Provinces (De Wals *et al*, 2007)[61]	All NTDs	**1.58*** (1993-1997)	**0.86*** (2000-2002)	***46%***
Newfoundland (Liu *et al*, 2004)[62]	All NTDs	**4.36*** (1991-97)	**0.96*** (1998-01)	***78%***
Nova Scotia (Persad *et al*, 2002)[63]	All NTDS	**2.58*** (1991-97)	**1.17*** (1998-00)	***55%***
Ontario (Ray *et al*, 2002)[64]	Anencephaly and Spina bifida	**1.13*** (Jan 94-Dec 97)	**0.58*** (Jan 98-Mar 00)	***49%***
USA (1998 - 140ug/100g flour)			**-**	**-**
US, California (Chen *et al*, 2008)[65]	Anencephaly and Spina bifida	**0.85**** (1986-96)	**0.72**** (1998-03)	***15%***
US, 8 States (Canfield *et al*, 2005)[66]	Anencephaly	**0.42*** (1995-96)	**0.35*** (1999-00)	***17%***
	Spina Bifida	**0.64*** (1995-96)	**0.41*** (1999-00)	***36%***
United States, CDC (Honein *et al*, 2001)[67]	Anencephaly and Spina bifida	**0.38**** (Oct 95-Dec 96)	**0.31**** (Oct 98-Dec 99)	***19%***
Costa Rica (1998 - 180ug/100g flour)				
(Tascan-Chen *et al*, 2004)[68]	All NTDs	**9.7**** (1996-98)	**6.3**** (1999-00)	***35%***
(Maria Paz Barboza *et al*, 2015)[69]	All NTDs	9.8 (1996-1998)	4.8 (2003-2012)	***51%***
Chile (2000 - 220ug/100g flour)				
(Cortes *et al*, 2012)[70]	All NTDs	**1.71** (1999-2000)	**0.86** (2001-2009)	***51%***
Saudi Arabia (2001 – 1.6mg/kg flour)				
(Safdar *et al*, 2007)[71]	All NTDs	**1.9**** (1997-00)	**0.76**** (2001-2005)	***60%***
Jordan (2002 – 1.5ppm in flour)				
(Amarin *et al*, 2010)[72]	All NTDs	**1.85*** (2000-01)	**0.95*** (2005-06)	***49%***
South Africa (2003 – 1.5mg/kg flour)				
(Sayed *et al*, 2008)[73]	All NTDs	**1.41**** (Jan 03- Jun 04)	**0.98**** (Oct 04 – Jun 05)	***31%***
North Iran (2007 – 150ug/100g flour)				
(Golalipour *et al*, 2014)[74]	All NTDs	**1.78*** (Mar 06- Jun 07)	**0.84*** (Mar 08 – Sep 09)	***53%***
Australia (2009 – 2-3mg/kg flour)				
(Bower *et al*, 2016)[75]	All NTDs	**2.43*** (2007- 2009)	**0.82*** (2010-2014)	***66%***

Implementation of food fortification

Over 50 countries globally have introduced mandatory fortification of grain products with folic acid.[39] Table 2 lists a few of the countries that have introduced fortification and the levels of food fortification they have implemented.

In Europe, although several national recommendations and health promotion campaigns have been undertaken, mandatory food fortification remains unimplemented and, to date, European women rely on peri-conceptional supplementation and voluntary fortification of certain foods. This has been criticised widely as a "*Missed Opportunity*" in introducing effective public health intervention for the primary prevention of severe birth defects.[26]

In 2007, the UK Food Standards Agency (FSA) recommended the *"mandatory fortification of white and brown wheat flour"* (p.19)[40] however, this has not yet been implemented.

Food fortification and NTDs

In countries that have introduced food fortification, red blood cell folate and serum folate levels in the general population have been found to increase, while elevated homocysteine levels, associated with increased risk of cardiovascular disease, have decreased.[41]

Studies have been undertaken in countries that have implemented FA food fortification to evaluate the occurrence of NTDs before and after fortification.[42] These studies, from different regions around the world, report a significant reduction in NTDs immediately following mandatory food fortification. Table 3 gives a summary of studies presenting pre and post-mandatory food fortification and neural tube defect prevalence. The significant decrease in NTDs experienced is unequivocal.

A recent meta-analysis of the global prevalence of spina bifida by folic acid fortification status gives the overall rate of neural tube defects for livebirths, stillbirths and terminations of pregnancy in countries with fortification as 35.22/100,000 births (95% CI 32.18-38.56) while this rate is 52.29/100,000 (95% CI 46.28-59.08) in countries that have not implemented mandatory fortification.[43]

Mandatory food fortification with FA has thus been shown to have effectively reached the primary aim of decreasing the occurrence of potentially preventable NTDs in several diverse countries.

Conclusions

The public health interventions implemented to improve maternal peri-conceptional FA intake vary from minimal recommendations to official policies and health education campaigns through to legislation with mandatory fortification of staple foods. The wide variation in degree of intervention implemented reveals the fact that there is no consensus on the ideal level of public health intervention as regards FA supplementation and food fortification and just how far the state should intervene is controversial.[30,36]

Many countries worldwide have issued official recommendations often accompanied by extensive and expensive health promotion campaigns encouraging women's preconceptional intake of folic acid; these have, however, had limited benefits in the decrease of occurrence of NTDs. This contrasts with the evidence of success in countries that have implemented mandatory food fortification with folic acid.

The policy maker's decision to undertake the implementation or otherwise of any intervention is not to be taken lightly and must be based on well informed, evidence based assessments. Taking no action is also associated with its consequences - those of failing to prevent potentially avoidable major birth defects.

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