6

Selective Abortion and Folic Acid Fortification as Contrasting Strategies for Prevention of Congenital Neural Tube Defect

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1. Introduction

Prenatal diagnosis of severe disability and the option of termination of pregnancy (TOP) have been widely available to parents in most countries in the Western world for three decades. This has come to be known as selective abortion. The ethics of this procedure is a large subject that I will not attempt to address in this paper. Some countries have laws that forbid selective abortion unless the mother's life is at risk. Where neural tube defects (NTDs) are concerned, medical opinion might favour TOP in a mother carrying an anencephalic fetus. The anencephalic infant will not normally survive for more an hour after birth but the mother may have a difficult and even life threatening labour because the lack of a fetal head prevents normal labour from progressing. The pregnancy tends to go overdue and vaginal delivery is complicated by shoulder dystocia and can be very difficult and hazardous for the mother. However 60% of women in the world would not be able to access an early TOP for this type of pregnancy due to poverty, religious reasons or anti-abortion legislation. In the republic of Ireland, which has anti-abortion legislation, this situation has encouraged legislators to consider minimising the need for selective abortion by introducing mandatory fortification of flour with folic acid (FA).

1.1 Objections to folic acid fortification of bread, flour and grain

Scientists, oncologists and politicians have urged caution in implementing folic acid fortification of bread, flour and grain. Oncologists were amongst the first to point out that many cancer chemotherapy drugs work by inhibiting folate metabolism and subsequent research showed that giving folic acid can accelerate tumour growth in animal models (Hubner et al., 2007). The arguments for and against fortification depend on the interpretation of data from countries where fortification has already been implemented. In Chile, which has similar anti-abortion legislation to The Republic of Ireland, a ten year policy of fortification has reduced the incidence of NTD births by 40% - from 17/10,000 births to 10.1/10,000 births (Hertrampf et al., 2004). However the UK and Irish governments have held back on fortification and the following issues have caused pause for thought:

1.1.1 There has been a slight increase in colorectal and prostate cancer in middle life in the USA

Mandatory FA fortification has been in force for ten years in the USA and Canada and the incidence of NTD conceptions has dropped 20-40% varying between different regions of North America. However, a slight increase in the incidence of colorectal and prostate cancer was noticed which coincided with the introduction of fortification (Mason et al., 2007).The latest paper from the USA on colorectal cancer since fortification (n=535,000) showed that far from an increased risk, subjects with the highest folate intakes were 30% less likely to develop cancers (Gibson et al., 2011).

1.1.2 Supplementation trials and cancers risk

A trial comparing FA supplementation and low dose aspirin with placebo suggests that giving folic acid 1000 microgram daily increases the risk of middle life cancers, especially colorectal and prostate (Cole et al 2007). This is thought to occur in folate replete populations when an unnaturally high folate status accelerates cell proliferation in early cancers. However, supplementation with folic acid and other B vitamins in folate deficient populations and populations where there is a high incidence of the gene for slow folate metabolism (MTHFR C677T) may decrease the risk of these cancers (Le Marchand et al., 2002; Figueiredo et al., 2011).

1.1.3 Masking of vitamin B12 deficiency

Masking of B12 deficiency by giving folic acid for macrocytic anaemia was a problem in the last century but B12 deficiency is much less likely to go undiagnosed in a modern medical setting. However, there have been warnings that folic acid fortification might have an adverse effect on B12 status and cognitive function in older age groups (Clarke et al., 2004).

1.1.4 Folic acid in not a natural substance

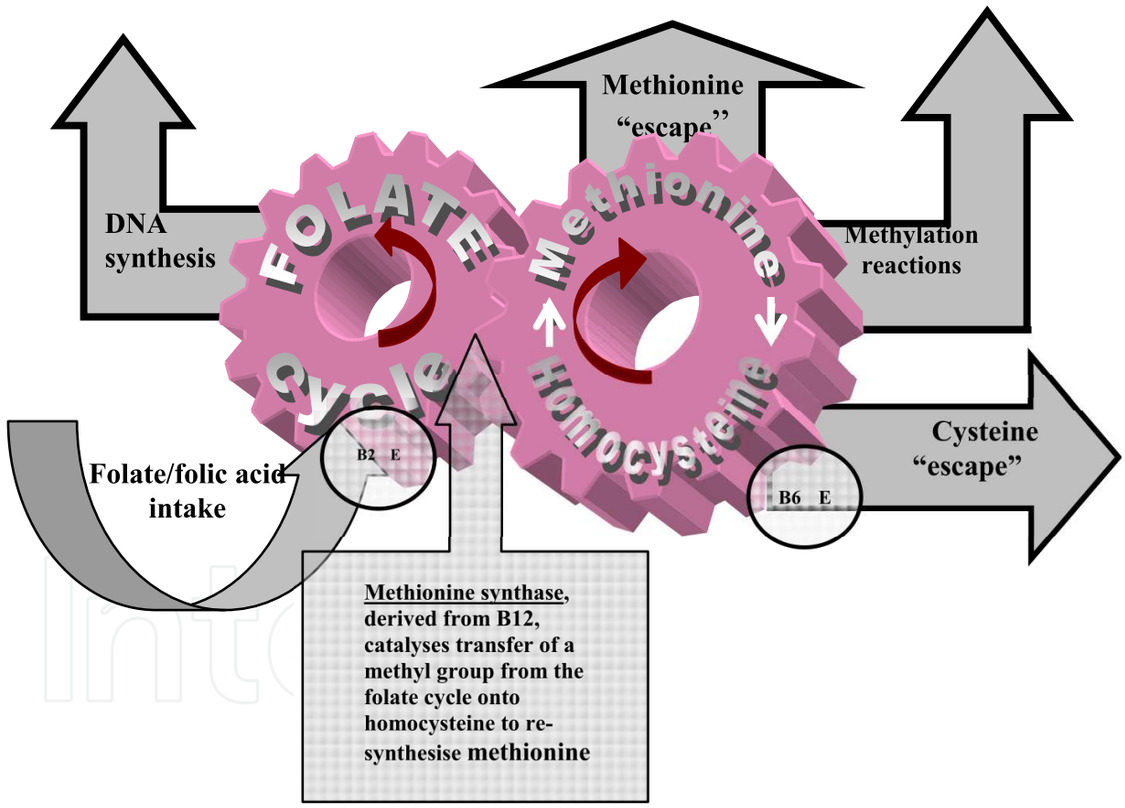
Folates are the natural form of the vitamin and are present in fruit and vegetables whereas FA is a synthetic man made substance. However, folates are labile molecules that break down with storage and heat. Folic acid is a relatively stable synthetic molecule and is quickly metabolised into the folate pathways in small quantities but a high dose may not be metabolised so well. High intake of FA results in a measurable residue of circulating folic acid which could, theoretically, have adverse effects, on the development of the fetal central nervous system for instance (Smith et al., 2008). Research in Ireland has shown that fortification that delivers a dose of 100 microgram daily is safe, in this respect. There was no detectable unmetabolised serum folic acid at this dose (Sweeney et al, 2007).

1.1.5 30% of NTD conceptions will still occur

The precise reason for this is unknown but some genetic combinations may make the development of some NTDs inevitable. However, other B vitamins are involved in the folate-methionine-homocysteine cycle (Figure 1; McNulty et al., 2002). Instability of this cycle and build up of high levels of homocysteine are thought to play a key role in delaying neural tube closure (Rosenquist et al., 2002). Zinc deficiency might also be a factor in some NTDs (Srinivas et al., 2001).

1.2 Benefits from public health measures for prevention of NTDs

In terms of public health benefit, we should also concern ourselves with the efficacy of folic acid fortification compared with the policy in the United Kingdom and other European countries where women are encouraged to take folic acid 400 μg daily starting about six weeks before a planned conception and offered ultrasound screening and the option of TOP if a NTD fetus is diagnosed. Is prevention of NTD conceptions by folic acid fortification a valid alternative? It has the advantage that the 40% of conceptions that are unplanned but not unwanted (Botto et al., 2005; Gipson & Stanelli, 2011) will benefit from this policy whereas the UK policy will only achieve an intake of folic acid sufficient to reduce the risk of NTD conceptions in 60% of subjects at the very most. However, the concordance rate for starting folic acid before conception in planned pregnancies is poor and does not seem to make a significant impact on the incidence of NTD conceptions (Botto et al., 2005). The best concordance data shows only 10-20% of women with both planned pregnancies and starting a folic acid supplement before conception (Rezan et al., 2002).



B2 E denotes an enzyme pathway dependant on vitamin B2
B6 E denotes an enzyme pathway dependant on vitamin B6

Fig. 1. Simplified version of the folate-methionine-homocysteine cycle illustrating the role of vitamins B2 (riboflavin), B6 (pyridoxine) and B12 (cobalamin) in modulating the cycle and directly or indirectly lowering homocysteine burden.

1.3 Objections to policy of pre-conception advice with option of selective abortion

Having listed the objections to fortification, we need to consider the reasons why a policy of advising pre-conception folic acid and ultrasound screening for NTDs in early pregnancy may be considered unsatisfactory. This will always involve a significant number of women being offered TOP as an option when screening shows a NTD fetus.

1.3.1 Pre-conception folic acid concordance has failed

The level of success for starting folic acid before conception is too low to make a measurable impact on the rate of NTD conceptions. Since the neural tube develops before a woman knows she is pregnant, starting folic acid as soon as pregnancy is confirmed will never make a noticeable impact on the incidence of NTD conceptions. According to a survey based on data for England and Wales published by the UK Office for National Statistics (Morris & Wald, 2007) 969 NTD conceptions were recorded in 2004 (801 women had TOPs for NTD but 168 were recorded as going to term with NTD infants). The authors estimate that there are 1,100 NTD conceptions in the whole of the UK (if Scotland and Northern Ireland are included).

1.3.2 Selective abortion is a psychological trauma

The distress to mothers who opt for selective abortion for a NTD conception is a significant issue. A review of the evidence on the impact of selective abortion concludes that women experience a bereavement reaction that is similar to that experienced with a stillbirth (Statham et al., 2000).

1.3.3 Screening misses a significant proportion of NTDs

The data from Morris and Wald indicates that a significant minority of NTDs are missed on ultrasound screening (see 1.2.1) which is approximately 17% of all NTD conceptions. However, another source of error is the pregnancies that spontaneously abort due to NTDs which has been estimated at 600-1200 per year in the UK (UK Department of Health report 2000). In at least half of these aborted foetuses NTD is caused by chromosomal abnormalities so that folate status has no bearing on aetiology or prevention. However, some women with NTD conceptions who spontaneously abort in this way might have benefitted from increased intake of FA before conception and they certainly get no benefit from the policy of selective abortion.

1.4 Assessing the case for folic acid fortification in the UK and Ireland

The success of fortification in Chile and North America is encouraging and the recent data on cancers in these countries has reassured the public health experts that the apparent increased risk of cancers with fortification is either very small or just a statistical aberration. It is particularly significant that the USA and Canada have not wavered from the policy of FA fortification. Ultimately, the question of whether fortification is a cost-effective exercise has to be addressed. This can be estimated by comparing: A/ costs mandatory fortification reimbursed to UK millers by government = government reimbursement to millers for

adding folic acid 140 µg/100mg + cost of government monitoring B/ government savings from mandatory fortification = cost of TOP x drop in number of TOPs done for NTD+ lifetime medical cost of treatment for NTD patients x drop in number of NTD births This can be estimated for the UK from Morris and Wald's data on selective abortion for NTDs and live NTD births who survive infancy and from research carried out in Surrey (Nichols et al 2008a) using data on total folate intake from a women attending local midwives' booking in clinics.

2. Estimation of benefits of UK adopting policy of mandatory folic acid fortification of flour and bread

The research carried out by the author and colleagues at The University of Surrey, UK was used, with data from other sources, to estimate the impact of fortification for the whole nation.

2.1 Two groups of women were investigated

a. Eighteen Surrey women were assessed for dietary folate intake as part of a larger research project (Nichols et al 2008b) which assessed dietary folate intake using weighed food diet diaries. Each subject was given a seven-day diet diary to complete and given the use of battery operated microtonic scales with detailed instructions. Research has demonstrated the weighed seven-day diet diary to be a reasonably accurate tool for measuring nutrient intake in free-living individuals (Day et al., 2001, Nelson et al 1998). The diet diary data was entered into "WinDiets Professional", a computerised database for analysis of nutritional intake (Wise, 1999). The output included an estimate of daily folate intake for each of the 18 subjects. Although this was a small sample, the mean folate intake at 267 µg/day was very similar to the UK national averages from the UK National Diet and Nutritional Survey 2002 (229 µg/day for women aged 19-24 yr, 234 µg/day for women aged 25-34 yr). Therefore the figure of 267 µg/day was assumed to be the approximate dietary intake for group B women and the basis for calculating total folate intake by adding together this presumed dietary folate and folic acid supplementation in the larger sample of Surrey Group B women attending the district midwife booking-in clinic.
b. 200 women were asked to complete questionnaires when they attended midwives' booking in clinics in the catchment area of The Royal Surrey Count Hospital. The response rate was 43.5%. The women were asked to complete the questionnaire and return it to the researchers in a stamped addressed envelope. The questions asked the following:

- whether the pregnancy was planned or unplanned
- whether the pregnancy was natural or an assisted pregnancy
- whether a supplement was started before or after conception
- if before conception, number of weeks taken
- exactly what brand(s) of supplement was used
- age, and age at completion of education

With a good response rate, this sample was thought to be adequate to calculate statistical significance for the different amounts of folic acid in the different over-the-counter supplements and for estimation of total folate intake (TFI).

2.2 Estimation of total folate intake

Owing to the poor availability of dietary folate resulting from loss of folate content in cooking and poor absorption of food folate compared with synthetic folic acid (McKillop et al., 2002; Standing committee on the Scientific Evaluation of Dietary Reference Intakes, Washington DC, 1998), various authorities have recommended a downward adjustment of approximately 50% for dietary folate (Eichholzer et al., 2006) when calculating a combined value for dietary folate/day + FA/day (FAD). Therefore, corrected total folate (TFI) was calculated using the estimated mean dietary intake for all Group B Surrey women (DM) using the formula:

$$\mathrm{TFI} = [(\mathrm{DM}) \div 2] + \mathrm{FADmg/day}$$

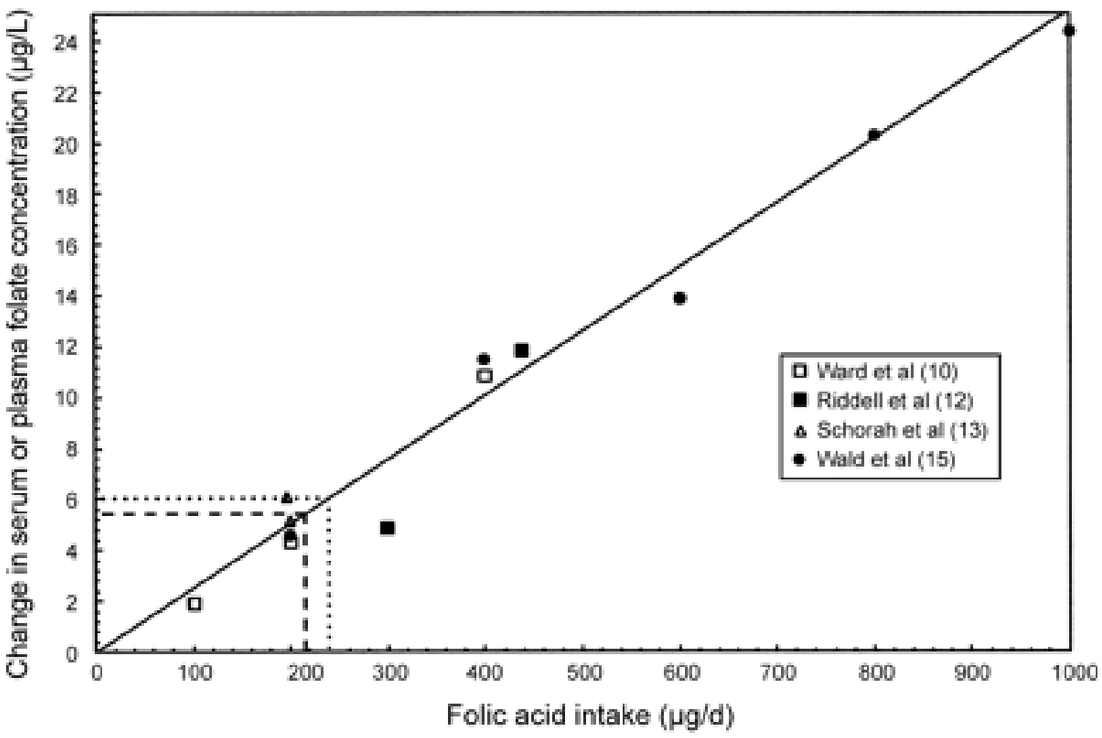


Fig. 2. Relation between controlled folic acid intake and the resulting change in median or adjusted mean serum or plasma folate concentration. Data were derived from intervention studies looking at the effect of longitudinal folic acid supplementation or fortification with known daily amounts of folic acid on median or adjusted mean serum or plasma folate concentrations. The broken and dotted lines represent the change in plasma or serum folate concentration observed by two research groups (Jacques et al., 2000; Lawrence et al, 1999) respectively, in 2 studies examining the effect of the current US folic acid fortification regimen on folate status. $y = 0.0254x + 0.0514$ ($r = 0.984$, $P < 0.0001$).

The predicted average uplift from FA fortification at the level of 140 μg/100gm of flour TFI is 220 μg/day (Eichholzer et al., 2006; Quinlivan & Gregory, 2003). Figure 2 was used to calculate the uplift of folate intake with fortification which was estimated for women in group B using the formula:

$$\text{Estimated TFI after fortification} = [(\text{DM}) \div 2] + \text{FAD} + 220\text{mg / day}$$

Since at least 70% of mothers will achieve a serum folate level that prevents the NTD malformation on an intake of >700 μg/day (Homocysteine Lowering Trialist's Collaboration, 2005; Rosenquist & Finnell 2001) (Figure 1), the data for estimated TFI after fortification was analysed using this standard. 24% (21/87) of women attending the DMCs had unplanned pregnancies and were younger (mean age 29.8 yr, compared with average 33 yr). Numerous surveys suggest that the national average for pregnancies that are unplanned, but not necessarily unwanted, is 40%. However, there were probably a higher proportion of women with unplanned pregnancies among the 113 women who had failed to return a completed questionnaire so that the true figure for Surrey women having unplanned pregnancies may be closer to the 40% national average. Using the above formula, the expected uplift of TFI was estimated for all pregnancies and separately for unplanned pregnancies (Table 1).

	Mean TFI before fortification	Mean TFI after fortification	Increased to >700 μg/day before-after fortification	P values for uplift
All district midwife clinic	497 μg/day (95% Cl 358-635)	717 μg/day (95% Cl 579-855)	21%-55%*	0.01
Unplanned pregnancies	160 μg/day (95% Cl 81-240)	380 μg/day (95% Cl 301-460)	4.8%-4.8%	ns

* 34% improvement in reaching >700 μg/day TFI

Table 1. Estimated total daily folate acid intake - dietary folate + folic acid (TFI) before and after fortification with folic acid 140 μg/100 g of flour as implemented in The USA. P values are given for the difference between number of subjects with an adequate intake of total folate (700 μg/day or more) before and after fortification (from Nichols et al., 2008a).

Only one woman with an unplanned pregnancy had been taking FA 400 μg/day (in a multivitamin tablet), compared with 75% of women with planned pregnancies.

2.3 Estimation of expected number of NTD malformations averted with folic acid fortification for the UK

The estimated number of UK NTD conceptions/year is 1100 (Morris & Wald, 2007). If fortification achieves a national 34% improvement in the number of women attaining the optimal level of daily TFI >700 μg/day for prevention of NTDs (Homocysteine Lowering Trialist's Collaboration), this would result in 374 of these 1100 women/year reaching this standard. In this "high risk" group, achieving optimal TFI should protect 62-94% (Berry et al, 1999) = 232-352 NTD malformations/year averted. Thus approximately 292 infants a year

will be born normal and healthy after fortification that are currently either being diagnosed as NTD and aborted or born with a NTD malformation. An alternative calculation is based on expected rise in serum folate with fortification (Wald et al., 2003). The rise in serum folic acid in group B subjects was estimated from FA intake before and after fortification by reading off expected plasma folate values from Figure 2:

$$\text{Estimated plasma folic acid before fortification} = 12.6\text{mg / L}$$

$$\text{Estimated plasma folic acid after fortification} = 18.4\text{mg / L}$$

$$\text{Estimated change in plasma folic acid} = 5.4\text{mg / L}$$

$$\text{Percentage change} = (5.8 / 12.6)\text{x}100\% = 46\%$$

Doubling serum folate (100% rise) halves the risk of NTD (Berry et al., 1999), therefore a 46% increase would reduce the total number of UK NTD conceptions by 253/year (from 1100 to 847). Therefore from the two methods of calculation a mean value of 273 averted NTD conceptions is assumed, though this may be an underestimate as improving folate intake without reaching the 700 μg/day will prevent the NTD malformation in some cases.

2.4 Estimation of expected cost-benefit balance with folic acid fortification of flour in the UK

Calculations of cost-benefit expected from folic acid fortification will depend on the balance between:

a. The costs of mandatory fortification

= government reimbursement to millers for adding folic acid 140 μg/100mg

and

b. government savings from mandatory fortification

= cost of TOP x drop in number of TOPs done for NTD + average lifetime cost of treatment for NTD patients x drop in number of NTDs births

2.4.1 Cost to the UK government of mandatory folic acid fortification

The national Association of British and Irish Millers estimated in March 2011 that 5600,000 tonnes of wheat are milled to make flour/year in the UK. The cost per ton for fortification in 2011 British Pounds Sterling, estimated from the experience of fortification and monitoring expenses in Chile (Llanos et al., 2007) is £0.13/ton. Therefore the expected cost of fortification for the UK is £728000/year

2.4.2 Cost saving benefits from UK mandatory fortification

Of the 273 averted NTD conceptions averted, 17% (46) will, on past evidence, be NTD births which will be associated with a range of lifetime medical costs and 83% (227) of women will

opt for selective abortion. Although I could not find a UK estimate for average lifetime costs of infants that survive birth with an NTD malformation, there were a range of costs from other countries ranging from £15,400 – 326,000. The median figure was £240,000 (Ouyang et al., 2007). However, this was an estimation of mean average costs for the USA and USA medical expenses are higher than UK prices (even the same drugs cost roughly twice as much) and average per capita health expenditure is 2.2 times higher (Kaiser Family Foundation 2008). I assume here that the same x2.2 difference will apply to lifetime NTD medical costs. Therefore an estimate of mean average lifetime NTD medical costs in the UK = £240,000÷2.2 = £109,091. The UK cost of a therapeutic TOP is £800. Therefore the annual saving from fortification in British pounds is:

$$109{,}091x46 + 800x227 = 5{,}018{,}181 + 181{,}600 = 5{,}199{,}781$$

2.4.3 Estimated cost benefit of UK mandatory fortification

Therefore the estimated annual cost saving of fortification in British pounds is:

$$4{,}471{,}781 - 728{,}000 = 5{,}126{,}981$$

This converts to approximately $7 million. A comparison with the estimated savings for Chile in 2001-2001 of only $2.3 million (Llanos et al., 2007) may be largely because their health services are less able to cope with complex medical problems that arise in children who survive with NTD malformations, early deaths will often occur and this will be associated with lower lifetime costs. The Centre for Disease Control and Prevention, USA gives a much higher estimate of $453 million/year. Apart from the higher US costs and larger population, this estimate includes the loss of earning for parents who stop work to care for a spina bifida child which is not included in my estimate for the UK.

3. Conclusions

The above figures are only an estimate of the cost-benefit of fortification and there are a number of factors that would have to be taken into consideration if fortification was implemented in the UK. It will never completely eliminate the need for selective abortion or the advisability of women who plan their pregnancies to start taking a FA supplement before conception. We estimated (Nichols et al., 2008a) that 45% of women in group B would still fail to achieve optimal total folate intake after fortification. When women attend to see a primary care doctor or nurse for contraceptive advice or review of ongoing contraception, there is an opportunity to raise the importance of pre-conception issues and boost FA concordance whenever there is a possibility of a future planned pregnancy. A comprehensive package of pre-conception care will be even more effective at reducing the risk of NTDs and other congenital malformations as described in section 3.3. The combined effect of fortification and adequate preconception advice, linked to contraceptive advice, could double the number of NTDs averted. This chapter has concentrated on the benefits of FA fortification with respect to averted NTD malformations, but there are other expected benefits and several remaining concerns (Table 2). In particular, there is growing evidence that other fetal malformations are prevented by fortification and FA supplementation has been shown to reduce the risk of intrauterine growth retardation. It is interesting to note

that most of these benefits from improving folate status were predicted by Bryan Hibbard nearly 50 years ago (Hibbard, 1964) and now we have evidence that improving folate status may also prevent childhood cancers (Table 2). Added to this, there is growing evidence that FA fortification may deliver more benefits than side effects amongst elders (Table 2). It is too soon to claim this as a dependable measure of cost benefit from FA fortification but close monitoring of FA intake, blood folate levels and outcomes may help to clarify matters.

3.1 Remaining concerns

After fortification a monitoring protocol should include B12 status in view of the 25-43% incidence of borderline and moderate vitamin B12 deficiency found in three UK elder studies and the suspicion that high folate intake may exacerbate both B12 deficiency and associated cognitive decline (Green & Miller, 2005; Table 2) and the evidence for a role for borderline vitamin B12 deficiency in NTD (Ray JG et al., 2007; Molloy et al., 2009;), other fetal malformations and low birth weight (Table 2). The structure of the UK National Health Service (NHS) should make monitoring of B12 status an eminently achievable objective. Another concern is that high folate intake may reduce the efficacy of anti-folate drugs used in treatment of cancers, rheumatoid arthritis and psoriasis (Smith et al., 2008). This, however, is avoidable if these patients are advised to avoid the fortified bread and their folate status is monitored by blood tests, when appropriate. The issue of unmetabolised FA is unresolved but the North American experience of fortification has been encouraging. The predicted problems relating to unmetabolised FA have failed to materialise in the post-fortification decade. One prediction is that high levels of unmetabolised FA may have an adverse effect on immune function in elders by inhibiting the action of NK cells. This has only been described in one study (Pfeiffer at al., 2004) and there are no reports to suggest that fortification has caused NK cell problems. Lastly, the possibility that high intake of FA may influence gene expression by modifying epigenetic imprinting (Smith et al., 2008) and this has been demonstrated in animal models but there is, as yet, no evidence that this is harmful to humans. Remaining concerns that have to be taken into consideration and answered are summarized in table 2.

	Remaining concerns	**Answers to concerns**
FA fortification and infant health	15% of group B had predicted TFA above 1000 μg/day which might increase unmetabolised FA in circulation and there are purely hypothetical suggestions that this could have adverse affects on fetal development. However, the USA have set this safe upper limit due to relatively slender evidence that masking of vitamin B12 deficiency may start at this level (Standing Committee on the Scientific Evaluation 1998) which is unlikely to apply to pregnant women.	Although the evidence linking TFI with NTDs is strongest, there is also evidence that FA prevents several other major congenital malformations, including congenital heart defects, limb defects, and orofacial clefts (Eichholzer et al., 2006) and fetal trisomy (Eskes et al., 2006), and that inadequate maternal TFI plays a role in intrauterine growth retardation (Relton et al., 2005a; Relton et al., 2005b) and lymphoblastic leukaemia in childhood (Thompson et al., 2001).

	Remaining concerns	**Answers to concerns**
FA fortification and cancers	Research already mentioned has raised the possibility that fortification may increase the incidence of colorectal and prostate cancers. Recent trials failed to confirm this risk (Figueiredo et al., 2011,Gibson et al., 2011). The initial increase in these cancers observed in USA was either very small or a statistical aberration	FA fortification may have been responsible for a drop in the incidence of childhood cancers: neuroblastomas (French et al., 2003) and several other childhood cancers (Preston-Martin et al., 1998; Grupp SG et al., 2010) and even coloectal cancers may be averted in subjects with low folate status (Figueiredo et al., 2011).
Affects of fortification on elders	Although low folate status is known to be a factor in cognitive decline, FA intake greater than 1000 μg/day may exacerbate borderline vitamin B12 deficiency and exacerbate cognitive decline (Morris et al., 2004; Clarke et al., 2004; McCracken et al., 2006; Clarke et al., 2007).	Since fortification was introduced in North America a 5% reduction in stroke related mortality has been observed (Yang et al., 2006; Selhub et al., 2000). A well established association between folate status and cognitive decline was tested in The Netherlands using 800 μg/day, given to subjects with raised serum homocysteine. This showed a significantl slowing of the rate of cognitive decline (Durga et al 2007).
General inad-equacies of FA fortification	FA fortification does nothing for borderline deficiencies in the other B vitamins that are relevant to fetal development and elder health issues and the problem of unmetabolised FA at the suggested level of fortification has not been solved. In the Surrey research (Nichols et al., 2008a) 45% of women still had a sub-optimal FA intake and the USA experience shows that fortification has failed to reduce NTD conceptions in some ethnic groups (Yang et al., 2007).	The established benefits in terms of averting NTD malformations may outweigh any remaining concerns. However, any campaign associated with introduction of fortification should emphasize the need for women to continue to take a pre-conception B vitamin supplement. Public policy on voluntary fortification can be used to control the excessive levels of FA added to some products to minimise the risk of pushing FA intake above 1000 μg/day.

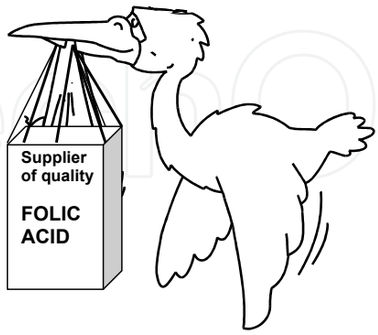
Table 2. Remaining concerns about FA fortification compared with established benefits

3.2 Opportunistic linkage of advice on pre-conception FA to contraception appointments

First, consider if the patient is likely (or most unlikely) to become pregnant in the future. Second, if future pregnancy is a possibility, ask if they expect to "become pregnant" or "start a family" at some time in the near or distant future. Lastly, offer them the brochure (outlined below) that explains the importance of taking pre-conception FA and, where appropriate, advise them to tell their friends (an intelligent young woman will usually want to do this).

Before pregnancy

The government recommends that all women planning to become pregnant should start taking folic acid vitamin tablets from at least six weeks before the planned pregnancy and up to the twelfth week of pregnancy.



Folic acid plays an important role in the early development of the human embryo. For about 35 years medical scientists have claimed that lack of folic acid is a cause of miscarriage, congenital malformations and handicap but only after particularly convincing research in 1991, has the government recommended a daily tablet of folic acid for all women.Women who have had a previous baby with the rare but serious spinal cord defect "spina bifida" should take a relatively high dose of 5 milligrams, but these women are likely to be under the care of their doctor or a specialist for this treatment. All other women should ask at their chemist for the folic acid 0.4 mg tablet, which should be available at any chemist shop Other pre-pregnancy advice which you may or may not be aware of is listed below.

Non-Smoking

Children of smoking parents are more likely to be born with health problems such as baby asthma. Sometimes smoking may cause serious problems for the baby and when babies are born very underweight this will usually be partly due to smoking before pregnancy, not just during pregnancy. But the effects of smoking are unpredictable and most babies born to smoking mothers will appear to be quite normal. Research has shown, however, that these babies never do quite so well in later life as the children of non-smokers.

Alcohol

Both parents should cut back on alcohol before conception. Views differ as to what is a safe limit, but it is probably safest for both of you to cut it out completely

Contraception and smear test

Women should discuss contraception with the family doctor or practice nurse when they start to plan for pregnancy. Some delay may be advisable if you have had a pregnancy in the last year or two, whatever the outcome. Statistics show that a minimum of 15-month gap between children is advisable. This gives the body time to recover fully. Most experts agree that it is best to switch from the contraceptive pill to another form of contraception two or three months before pregnancy. This allows normal hormone balance to be restored and pregnancy is less likely to be troublesome. There is even some evidence that there is an increased risk of miscarriage when women become pregnant immediately after stopping the pill. Normally, smear tests should be done every three years, but if you are planning to become pregnant, an earlier smear test is advisable - i.e. within the year before attempting to conceive.

Diet

Although women need extra folic acid as already described, most of the other vitamins, micro nutrients and body building nutrients that are needed for fertility and good health can be obtained from a really healthy diet with plenty of fresh fruit and vegetables and unprocessed whole foods. Recent evidence suggests that eating fish is also beneficial to the outcome of pregnancy, especially in prevention of premature birth. How healthy is your diet? Everyone thinks his or her diet is "quite good" but most of us are in the "could do better" category. Some men and women will benefit from special help with their diet from a doctor or dietician. Pre-conception supplements (e.g. Pregnacare) are available which contain extra micronutrients, in addition to folic acid. This may be helpful if you feel run down and tired or if you have had problems with pregnancy in the past such as a miscarriage or postnatal depression.

Foods which are better avoided before and during pregnancy are:

- Liver and liver products (contain too much vitamin A)
- Swordfish and other large fish should not be eaten around the time of conception or during pregnancy due to traces of mercury
- Soft ripe cheese, pate and raw eggs can contain harmful bacteria that infect the placenta
- Raw meat including cured meat such as parma ham may be a source of toxoplasma parasite (see next section).
- Too much "junk" food such as sweets, biscuits cakes and fizzy drinks

Lastly, remember that you should build up your strength and bodily resources for pregnancy. If you are underweight you may have trouble conceiving and your baby may be underweight at birth, which is not a good start for a baby. Now is not the time to lose weight.

Infection

Most women will have had a rubella jab at some time, but we now know that it is best to have a blood test to check immunity to rubella, even if you did have the jab at school. Another infection, which very occasionally causes miscarriage or abnormalities, is toxoplasmosis, which is caught mainly from uncooked meat but maybe also from cat faeces. You should, perhaps, avoid contact with sick cats or litter trays whilst you are pregnant. Chickenpox infection during pregnancy also carries a small but significant risk to both mother and baby but if you are sure you have had chickenpox there is nothing to worry

about. Women who think they have never had chickenpox should discuss this with their doctor. Sexually transmitted diseases are a particular problem when you are planning to start a family. Both the man and woman should attend The Genitourinary Clinic if there is any suspicion of infection as lingering infection can cause infertility or miscarriage and can sometimes have a damaging effect on the baby.

Medical problems

If you or your partner has a medical problem such as diabetes or epilepsy you should see your doctor for advice before starting a pregnancy. If either of you are on any regular medication for any condition (including over the counter medications) you should discuss this with a doctor or nurse. If you have a family history of a hereditary disease such as Haemophilia or Muscular Dystrophy you should see your doctor about being referred to see a genetic counsellor at a hospital clinic.

3.3 Implications for future research

Future considerations include the further development of gene testing to determine which subjects need a higher dose of FA before a first conception rather than waiting for a NTD conception before offering such advice and further consideration of advice on preconception supplementation with the other B vitamins and nutrients such as zinc.

Future research therefore should include:

- Establishing a way of linking contraceptive advice to pre-conception advice on FA supplementation, diet and other aspects of preparation for a healthy pregnancy.
- Resolving the issue of a safe upper limit for total combined folate and folic acid intake, currently set at 1000 μg/day.
- Investigating the biochemistry of unmetabolised FA.
- Investigating interactions between folate status and B12 status by monitoring reliable biomarkers for both after fortification and monitoring outcome (NTDs and cognitive decline etc.).
- Further research into gene-nutrient interactions involving B vitamins and both well established genetic variants and candidate genes revealed by genome wide association studies.

A true and accurate cost-benefit analysis for FA fortification can only be completed when this research has been done.

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5. Glossary of acronyms

DM Mean daily dietary folate for group A women (used for group B calculations)

FA Folic acid (also has chemical name pteroylmonoglutamate)

FAD Daily FA intake from supplements

n Number of participants in a research project

NTD Neural tube defect (the developmental fault in the early embryo that causes spina bifida, hydrocephalus and anencephaly)

TFI Total folate intake (a combined value for dietary folates and FA)

TOP Termination of pregnancy

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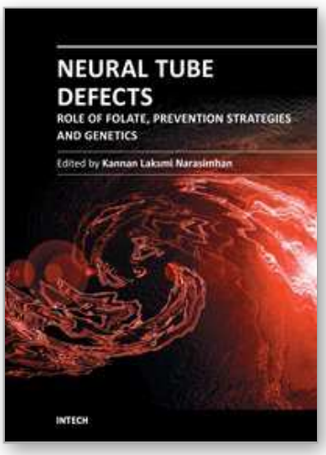

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