



Evolution of the Theses



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\'thē-səs:

“an idea or proposition for consideration, especially one to be discussed, explored or investigated...”

Folic acid supplementation before and during pregnancy: Part 3

This is the third part of an article exploring the evolution of our knowledge in relation to the recommendation that women should take folic acid before and during pregnancy in order to reduce their risk of having a baby with neural tube defects (NTDs). The first part of this article was published in the October edition of *Essentially MIDIRS* and explored the early

history of folic acid supplementation and the MRC (1991) trial, which is widely accepted to be the study that proved the efficacy of folic acid. The second part was published in the November edition of *Essentially MIDIRS* and examined a Cochrane review (De-Regil *et al* 2010) of folic acid supplementation, and considered some of the questions that exist in relation to dosage, timing and side effects. This final part of the article explores some of the wider questions around dietary folic acid, food fortification programmes, and the way that these areas raise issues related to individual choice.





As we have previously discussed, the MRC (1991) study showed that folic acid supplementation is effective at preventing NTDs and most countries recommend that women who are pregnant or planning a pregnancy should take folic acid supplements. However, unlike some other prophylactic interventions, this is a difficult recommendation to implement. Firstly, it relies on women knowing about and choosing to take folic acid *before* they become pregnant, and this necessitates a degree of family planning that is not universally possible. Then, we need to ask whether it is reasonable and desirable for all women who might possibly become pregnant to take folic acid supplements, as some women could then be taking folic acid for years, and what about any side effects? It is unsurprising that women may question this, and this series arose because women were asking us about whether they should take supplements — some women, quite reasonably, wanted to know whether they could just ensure that their diet contained lots of folate instead. A few governments have responded to these issues and the knowledge that folic acid supplementation significantly reduces the risk of NTDs by introducing mandatory fortification of foods, which is seen as a welcome and sensible move by some, and as unreasonable population medication by others.



The data we uncovered during our research were rather confusing. Using data collected during a dietary and nutritional survey of British adults in 1990, Scott *et al* (1991:505) stated that the normal daily median intake of dietary folate for British women was 209µg. This is well below the recommended daily intake of 400µg, but we must not forget that the dose of 400µg was relatively arbitrarily chosen and smaller dosages may still be effective. However, NICE argue, citing Daly *et al* 1995, that increasing dietary intake of foods that are naturally high in folates has **not** been found to be effective in achieving beneficial levels of red cell folate (NICE 2008). Yet this directly contrasts with the conclusions of Ahrens *et al* (2011) who found that '*...the folate-associated benefit on spina bifida risk was found with increasing amounts of dietary folic acid consumed, regardless of folic acid supplementation level*' (2011:731). Could there have been developments between 1995 and 2011 in the assessment of dietary folate which caused researchers' conclusions to change?

The US Centers for Disease Control and Prevention (CDC) has a whole section devoted to folic acid during pregnancy, and an interesting frequently asked questions page. Their advice on the critical window (around 3-4 weeks' gestation) for taking folic acid to prevent neural tube defects seems clearer than the UK government advice for women, but they also go on to provide slightly contradictory advice on the best way to ensure women have enough folic acid within their system. The CDC argue that: '*We cannot be sure that eating folate would have the same benefits as getting 400 micrograms of man-made (synthetic) folic acid. Women who can get pregnant should consume 400 micrograms of synthetic folic acid in addition to the natural food folate from a varied diet*' (CDC 2011). They then point out that '*when taking supplements, more is not better*' but advise women to take a supplement **and** eat a diet rich in folate — which seems a bit belt and braces.

The fact that rates of NTDs differ geographically does raise the question of whether diet – and/or other sociodemographic and lifestyle-related factors – may play a part. Following publication of the MRC (1991) study, a correspondent from the Kochi Medical School in Japan wrote in to compare the exceedingly low rate of NTDs in Japan (0.4-0.6 per 1000 births) with Western countries, and pointed out that their own research had shown that '*...more than 140µg folic acid daily could be absorbed from cooked rice alone*' (Taguchi 1991:506). Taguchi argued that the low levels of NTDs in the Japanese population is due to the higher proportion of fresh vegetables, fish and rice in the average diet — resulting in a dietary folic acid intake far above the daily requirements. Entertainingly (although bearing in mind that British culinary habits have come a long way since the 1970s), Taguchi also recalls from a year spent in the UK a lack of vegetables and a tendency to overcook the few that were eaten in boiling water! He argues that this dietary characteristic is likely to result in suboptimum folate intake, and this opinion was supported by the UK's Department of Health (DH). In a consumer leaflet published in 2004, the DH advised women not to rely on diet alone to obtain sufficient amounts of folate, as they state (although erroneously using the term folic acid when they mean folate): '*Folic acid is also destroyed when food is cooked, especially if vegetables are boiled for a long time*' (DH 2004).

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Unhelpfully, we have very little knowledge on the diets of women in the original research studies, and we must also bear in mind that – as Tasha mentioned above – the diets of women in those studies may not be similar to the diets of women living in the same areas today. If the women in those studies had very low levels of dietary folate intake, then the effect of supplements may appear greater than it would in a population of women who had a better diet to begin with.



Other factors may also play a part. For instance, when referring to research published in the 1960s and 1970s, Davis (1991:506) queried how many women in the MRC study had been taking oral contraceptives and how long before conception did they stop taking the contraceptive? Davis cited previous research which found that levels of serum and red cell folate were significantly lower in women who had been taking oral contraceptives, and argued that on a normal diet without supplements it may take some time for the body to restore its folate pool.



This might mean that folic acid is important for women who have taken oral contraceptives but not for those who do/have not. This is interesting in relation to the recent study by Holzgreve *et al* (2012) which suggested that, as more than half of all women use the contraceptive pill at some point before getting pregnant, oral contraceptives '*are an ideal vehicle to increase not only the awareness for periconceptional folate application, but they can also help to bridge the gap between the recognition of a pregnancy and closure of the neural tube which is before day 26*' (2012:1529). Folic acid-containing oral contraceptives are now available.

One vital piece of the jigsaw that could help us find an answer to this question relates to knowing why folic acid works to prevent NTDs. Despite there being a consensus that '*the main function of folate is as coenzyme in one-carbon transfer during the methylation cycle, a process essential for the syntheses of nucleic acids, which form part of DNA and the neurotransmitters*' (De Regil *et al* 2010), we do not know quite as much about why folic acid works as that statement might imply.



Following the MRC (1991) study, Holzgreve *et al* (1991) corresponded with *The Lancet* to describe how they tested fetal blood for folate concentrations and compared this to the folate concentration of women with an NTD-affected pregnancy. They found that the folate concentrations of the pregnant women were all normal, and concluded that in their study there was no relation between NTDs and low folate values in fetal blood. Holzgreve *et al* called for further research into the role of micronutrients and argued that there is no easy explanation for the protective effect of folic acid. Fifteen years later, other researchers have emphasised that the exact mechanism by which folic acid prevents neural tube defects is still largely unknown (Blom *et al* 2006) and research in the areas of human genetics, cell biology and epidemiology is still ongoing.



Food fortification

Despite the fact that national bodies stress that increasing dietary folate intake is insufficient and urge women to take supplements, many countries have introduced food fortification programmes. These may be voluntary or mandatory. In May 2002, the UK Foods Standards Agency (FSA) decided against recommending mandatory folic acid fortification in the UK. This was in direct contrast with the position of the Royal College of Obstetricians and Gynaecologists (RCOG), who in 2003 re-issued their statement advocating the introduction of folic acid fortification:

'... there is no evidence of harm from folic acid fortification, and the evidence of likely benefit is strong' (Fraser & Fisk 2003:6).

The UK's Scientific Advisory Committee on Nutrition (SACN), a panel of independent experts who provide advice to the Department of Health and other government departments, has recommended that folic acid fortification of flour will further reduce the risk of neural tube defects by an estimated 11-18% (SACN 2006). However, they have pointed out in their opinion paper that whilst some people in the UK, such as the elderly and women of reproductive age, have low folate intakes, others are very close to or exceed the recommended maximum intake of 1000µg per day. The SACN suggest that this is due to higher consumption of fat spreads and cereals which are already fortified with folic acid (SACN 2006:ii). Despite this, the SACN have recommended mandatory fortification of flour with folic acid as the most effective way of reducing the number of women in the UK with an NTD-affected pregnancy.

In their opinion paper (Fraser & Fisk 2003), the RCOG seem to be suggesting that women who will benefit most from fortification are those from a lower socio-economic background with poor diets. Other research into the reasons why some women do not take supplements also found that the same group of women are least likely to benefit from public health advice and, therefore, are most likely to benefit from mandatory fortification (Barbour *et al* 2012).

'As many women do not plan a pregnancy, in particular those at nutritional risk because of poor dietary habits and/or socio-economic status, the only reasonable approach to maintaining adequate periconceptional levels of folic acid would appear to be through food fortification' (Fraser & Fisk 2003:1).

However, despite its pro-fortification stance, the RCOG opinion paper does go on to set out the four major objections to food fortification:

- Freedom of choice
- Risk of masked B12 deficiency in the elderly
- Inappropriate mass medication
- Potential increased likelihood of twins.

De-Regil *et al* (2010) acknowledged that all the studies included in their Cochrane review took place before mandatory food fortification occurred. Now that food fortification is in place in countries such as the US, Canada and Australia, shouldn't we be advising women to take extra folic acid depending on how much fortified food they already consume **and** depending on which country they live in and the amount of food fortification that already takes place? For example, in the US flour is fortified with folic acid which means there is 50µg of folate per 100g of '*bread, whole-wheat, commercially prepared*', which is equivalent to 14µg per slice of bread (USDA 2012). Indeed, since the US began fortification in 1998, some research has shown that typical folic acid consumption is almost twice as high as was originally predicted (Choumenkovitch *et al* 2002, Quinlivan & Gregory 2003). Perhaps women in the US need to be cautious of taking the maximum supplement of folic acid during pregnancy, particularly if they also eat four slices of bread a day, as they could then be receiving 1.5 times the recommended 400µg daily dosage of folate during pregnancy.

In New Zealand, it has been proposed to fortify all yeast-leavened, non-organic bread to a level of 135µg per 100g (Mallard *et al* 2012:2) which is significantly more than is shown in the US nutrient food tables. However, the same research from NZ also argues that – as bread consumption has declined since the previous dietary modelling took place – the level of fortification needs to be increased to obtain the same benefit. The UK's consumer website, NHS Choices, has stated that: '*If you are taking folic acid supplements, it is important not to take too much because this could be harmful. Taking 1mg (1,000 micrograms) or less a day of folic acid supplements is unlikely to cause any harm*' (NHS Choices 2011). According to the Food Standards Agency website, health ministers in the UK are still currently considering whether to approve mandatory food fortification with folic acid — as they have been for nearly a decade now. Within the current economic climate, and considering the bigger problems facing the UK's National Health Service, it seems sensible to suggest that the question of fortification has been put on the back burner.

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So does it all go back to the same message? Providing woman-centred care would solve a number of these problems — assessing a woman's likely intake of fortified food, her individual risk of NTD, and her level of current supplementation, would allow midwives to offer advice on the most suitable level of supplements (or not, as the case may be) for women during pregnancy.



That would be lovely, and it is certainly true of a number of other areas, but I'm not so sure that is the whole answer in this case. As we have gone through the literature – which is vast and conflicting – the thing that has struck me the most is that so much of it is speculative. We have found papers that raise some fascinating questions, yet so few of these questions can be answered by research that passes the standard set by bodies such as the Cochrane Collaboration. Even if we put aside the notion that randomised controlled trials are the only way forward and look at other kinds of studies, it is next to impossible to find data that can help answer the questions that we have raised.

As a midwife, I'm not sure that I am much further forward in being able to offer information to a woman that can truly help her make decisions in this area. I can tell her that folic acid supplementation is effective in the populations of women studied (who she may or may not be similar to) and that it greatly reduced their risk of having a baby with an NTD, which I am sure she will see as a good thing. I need to tell her about the possible side effects, which we discussed last time, but I can't give her a great deal of certainty in relation to these, and I also can't really tell her why folic acid makes a difference, although of course we could have a conversation about methylation if that would interest her, and I can squeeze that in amidst everything else we discuss at booking. Of course, assuming that I am seeing her at booking, I will have to tell her that folic acid supplementation is all a bit moot, because she should have been taking it for several weeks already. The early gestational window for folic acid has always been a big part of the problem, and a recent review of the research in this area (Jägerstad 2012) dismisses some of the concerns about side effects and presents data showing that fortification programmes do make a difference to the rates of NTDs, so I understand why governments and other bodies undertake campaigns and fortification programmes, but this inevitably reduces choice, not just for women but for their families and communities.

Conclusion

With apologies to any readers who were hoping that the first article in this series might conclude with a definitive answer, the area of folic acid is another which highlights the complexity of the choices that women need to make, not to mention the intricacies of the information that midwives need to engage with in order to effectively 'be' with women as they make those decisions. One thing that is very apparent upon reading through the literature on folic acid supplementation is that so many different viewpoints exist in relation to nutrition, the value of supplements, what constitutes a healthy diet and so on. There is also a vast chasm of difference in the health and well-being of women who have the means and access to what is considered a really healthy diet on the one hand, and those who live in poverty resulting in a poor diet on the other. It may not be politically correct but it is also probably not inaccurate to say that fortification seeks to target the lowest common nutritional denominator. Yet what is the most ethical approach in a world where women who have less easy access to healthy food (or to information about what food is healthy) may

also have less easy access to those forums in which issues such as folic acid fortification are debated? This is a huge area and there is no simple or universal answer but we are increasingly seeing challenges to long-established views on diet and nutrition, and it may be that as more people become interested, other, more fruitful threads emerge within the debate. The most appropriate conclusion to draw from this article may not be a conclusion relating to the value of one or the other approaches towards folic acid supplementation and/or fortification *per se*, but more of a recommendation that, in the face of continued uncertainty, we retain the '*openness and fluency*' that Jo Murphy-Lawless (2012:22) recently described.

Our experience of undertaking this first investigation has further cemented our shared belief that there is huge value in revisiting the research from which current beliefs, practices and recommendations originated. As recently noted (Wickham 2012), and despite the emphasis that is placed on currency (in some quarters), we can learn all manner of things from this kind of retrospective investigation. In this case, we gained knowledge about the baseline assumptions which were made more than two

decades ago and which still influence practice today – for example the way in which the dose of folic acid was determined by the initial studies – and also gained insight into the reasons that research, practice, recommendations and guidelines may have taken the direction that they did. We are big fans of modern technology, new apps and connecting via social media and have written these articles while literally on opposite sides of the world, using all kinds of technology. Yet even as we zipped electronic versions of articles to each other across continents and oceans, we were continually reminded that we wouldn't have even be able to access those articles if not for the institutions that have taken care of this body of knowledge in a physical sense. We are left with a greater respect, perhaps especially because of our access to technology, of the importance of physical libraries and archives as repositories and guardians of information, not just for our own research but for that of future women, midwives and editorial teams who might want to take another look at how knowledge grew, but from their own perspective. We look forward to monitoring the debate, seeing the publication of future research and reading the thoughts of others as this particular thesis continues to evolve, and we are eagerly beginning our next investigation which we look forward to bringing you in a few months' time.

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