

# Evolution of the Theses

Tasha Cooper, Sara Wickham

\ 'thē-səs:

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

## Folic acid supplementation before and during pregnancy: Part 2



In part one of this article, which was published in last month's *Essentially MIDIRS*, we examined the early history of folic acid, considered some of the events leading up to the publication of the MRC 1991 trial, and explored the trial results. The MRC trial indicated that 400µg/day of folic acid was an effective method of reducing the risk of having a baby with a neural tube defect (NTD) in women who had previously given birth to a baby with an NTD. This finding appears to have been considered 'good enough', as it led to the public health recommendations we listed in part one, but, actually, this still leaves questions unanswered. Many questions were raised by correspondence published following the MRC trial, including some on the most appropriate dosage and potential side effects of folic acid, which will be the focus of this article. Some questions may have been answered by later research, and in this article we will also look at the Cochrane review (De-Regil *et al* 2010) in order to determine whether the publication of further trials has helped to clarify some of the issues. De-Regil *et al* (2010:13) found that:

*'Periconceptional folate supplementation (alone, or in combination with other vitamins and minerals) reduces the prevalence of NTDs in comparison with no intervention, placebo or multiple micronutrients without folic acid (risk ratio (RR) 0.28, 95% confidence interval (CI) 0.15 to 0.52).'*



I think the 'good enough' point is a really important one. The figures in the MRC trial (1991) show that folic acid supplementation reduces the risk of NTDs by 72%. I was a midwifery student when the MRC (1991) trial was published, and my earliest memory of folic acid in practice was hearing my mentor advising women to consider taking it, while telling me about the research study that had recently proven its worth. Without wanting to devalue the academic debate or the usefulness of returning to the issues raised in exploring folic acid supplementation, I think it is also important to recall how exciting the finding of the MRC trial was for women and their families, midwives and other caregivers. These results were great news in that they provided real hope that a simple and cost-effective intervention could prevent a very real and horrible problem and many practitioners were keen to embrace and adopt these results into their conversations with women. Of possibly greater concern was how challenging it was going to be to get news of the value of folic acid to the people who really needed to hear it — for it was well understood that folic acid needed to be taken earlier in pregnancy than women tended to see a midwife.

So it is easy to understand how trial findings can change practice and/or recommendations so quickly, even though many questions may still be unanswered. What is often harder is figuring out how we can explore the nuances of the related questions later on. Once something has become accepted as the norm, it is hard to question it without being seen as a crazy radical, and even harder to get funding or ethical approval to research it as no-one wants to suggest taking the 'norm' away from women or babies when we know that, at least from one perspective, it is deemed to be a 'good thing'. This can be seen very clearly if we take a brief look at the relationship between the current Cochrane review and the questions that have been raised.

## The Cochrane review

It is so widely accepted that *'there seems to be sufficient evidence of known benefits of folic acid supplementation on NTDs (Lumley 2001)'* (De-Regil *et al* 2010:5) that De-Regil *et al*, the authors of the latest Cochrane review, are clear that their objectives relate more to whether folic acid can also help prevent other conditions, as well as to concerns that have been raised about dosage, fortification and side effects.

*'In 1991, one randomised controlled trial (RCT) demonstrated that periconceptual folic acid supplementation prevented the recurrence of NTDs (MRC 1991) and in 1992 another RCT showed that a multiple micronutrient supplement containing folic acid prevented the occurrence of NTDs (Czeizel 1992). The latter results were confirmed in a public health campaign among women preparing for marriage conducted between 1993 and 1995 in China after which the risk of neural tube defects among the fetuses or infants of the women who took a folic acid supplement more than 80% of the time decreased by between 40% and 85% (Berry 1999)'* (De-Regil *et al* 2010:3).

Following on from the Lumley *et al* (2001) review, five trials were included in the De-Regil *et al* (2010) review with a total of 6105 women. Of the women included in the trials considered by De-Regil *et al* (2010), 1949 had either a history of neural tube

defects or had had a previous pregnancy affected by NTD, and 4156 women had no history.

We will return to specific elements of the Cochrane findings later, but it is of note that all of the trials used in the review were seen to have problems with potential sources of bias:

- Only three of the five studies provided evidence of appropriate randomisation.
- Although all of the studies were described as double blind, it was unclear to the Cochrane reviewers whether this was actually the case.
- In all of the studies, women were randomised before they became pregnant. While this is an inevitable consequence of studies that are evaluating the pre-conceptual use of an intervention, it does make the results difficult to interpret. The Cochrane reviewers chose to look at the outcomes in relation to the number of women who became pregnant, but where a significant proportion of women did not become pregnant (30% of the women randomised by Czeizel *et al* (1994), for example), the results may not accurately reflect the effects of the folic acid. It is possible that taking folic acid may have had an effect on whether women became pregnant in the first place, or that the women who became pregnant were somehow different from those who didn't.

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The table of 'Characteristics of included studies', which is where Cochrane reviewers detail individual elements of the research papers included, shows a significant degree of uncertainty about potential bias in every study. This is often the case where reviews include older studies, but it does need to be borne in mind when interpreting findings.

## Questions and dissent

Questioning, dissent and debate are always valuable aspects of the evolution of knowledge and understanding in any area. The questions we raised at the end of part one of this article (Cooper & Wickham 2012) were manifold and many researchers wrote to *The Lancet* following publication of the MRC trial in 1991 to express concerns about the conclusions, or raise questions relating to folic acid supplementation. Many of the issues are interlinked but they can be broken down into two main areas, the first of which includes questions concerning efficacy, dosage, route and side effects of folic acid supplementation. We will consider these questions in this article, part two of three, while questions relating to the second main area of concern – dietary folate intake, food fortification, and the more ideological levels of this debate – will be addressed in part three in the December 2012 edition of *Essentially MIDIRS*.

One of the earliest and most prolific correspondents was Richard (Dick) Smithells, a paediatrician, researcher, teacher and, in retirement, bellringer who, according to the Royal College of Physicians (Buckler 2012), was highly respected and in fact won awards for his work into folic acid supplementation. Smithells published a number of studies in the 1970s, 1980s and 1990s, although these studies would not have met the current criteria for inclusion in the Cochrane review (De-Regil *et al* 2010) and, for reasons we have been unable to ascertain, his work does not warrant a mention in the list of excluded studies. Smithells was among the first to raise many of the questions relating to neural tube defects and folic acid supplementation in print (though it should be noted that he was in support of supplementation and was often seeking greater clarity rather than disagreeing with the MRC study findings), and we have used his work here to frame parts of our discussion.

### 1) Is the suggested dosage, route, and form of folic acid intake appropriate, especially for women who have not previously had a baby with an NTD?

#### a) Is 400µg the right dose? How about for 'low-risk' women?

One of the first questions raised in *The Lancet* by Smithells *et al* (1991) related to the choice of dosage in the MRC (1991) study. They argued that a higher dose of 400µg in supplemental tablet form may be appropriate for high-risk women, but that for the general population of women, who they perceived to be at lower risk, a lower dose of 360µg would be a realistic goal via fortification of staple foods. Of the five trials considered by the De-Regil *et al* (2010) Cochrane review, three (Laurence *et al* 1981, MRC 1991, ICMR 2000) allocated women to 4000µg of folic acid per day, and the

other two (Kirke *et al* 1992, Czeizel *et al* 1994) used 360µg and 800µg respectively. Smithells *et al* (1983) had conducted their own study using a daily folic acid dose of 360µg, and, following positive results, a team in Salford Health Authority in northern England began to provide free periconceptional folic acid to women with a history of NTDs in the family and their results were included in another study (Seller 1985), reporting that 360µg was effective. All of this does beg the question of whether an even lower dose might be effective (as well as the question about whether dietary sources of folate could be adequate for 'low-risk' women) but, thus far, smaller doses have not been tested in trials that meet Cochrane standards, and Seller's work is also not mentioned in De-Regil *et al* (2010). This question, however, may be academic; as discussed in a recent *Essentially MIDIRS* editorial (Wickham 2012), once something has been found to be effective, either for the population in general or for a particular sub group, and unless there are serious and widespread concerns about side effects, it is very difficult to carry out research into alternatives.

#### b) Are divided doses better than single doses?

Following publication of the MRC 1991 trial, Smithells *et al* (1991) also argued that divided doses are absorbed and utilised by the body more efficiently than single doses, and that this would also reduce side effects such as nausea. In biochemical terms, Smithells *et al* advised:

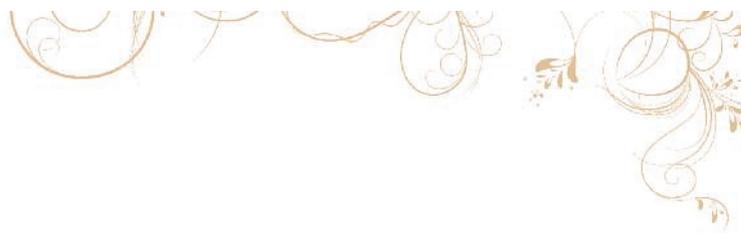
*'100µg/kg body weight of folic acid yields almost twice as much 5-methyl tetrahydrofolate when given in two divided doses rather than as one dose' (1991:380).*

Interestingly, in the instructions for a leading brand of antenatal vitamins in the UK, women are advised to take two of the vitamin tablets per day – across which the recommended daily amount of 400µg of folic acid is divided – thereby providing them with a divided dose.

In the Cochrane review, De-Regil *et al* note that the use of 5-methyl-tetrahydrofolate (5-MTHF) has been proposed as an alternative to folic acid supplementation, stating that four controlled trials using different doses have shown that supplementation with 5-MTHF is at least as effective as folic acid in improving folate status in women of childbearing age (2010:4). De-Regil *et al* (2010) do not mention the issue of divided doses specifically, but the current uncertainty that exists in relation to dosage and periodicity was a key objective of their review:

*'Questions remain about the best dose and periodicity of folic supplementation as there is still a high prevalence of birth defects worldwide. Doses ranging from 360µg (0.36 mg) (Kirke 1992) to 6000µg (6 mg) (Chen 2008) a day have proven to be effective in preventing both occurrence and recurrence of NTDs; this wide response to supplementation may be determined by the baseline blood folate concentrations in each population' (2010:18).*

Unfortunately, they did not find data which would provide definitive answers and concluded that:



*'Improving nutrition surveillance in order to find the appropriate dose and supplementation scheme is crucial to promote a cost-effective public health policy that can reach a larger number of people'* (De-Regil *et al* 2010:18).

### c) Is isolation the answer?

Smithells *et al* (1991:380) proposed that the accompanying vitamins which are often taken with folic acid may also play a role in preventing NTDs and another correspondent to *The Lancet* urged caution against making simplistic recommendations for single supplements, suggesting that nutritional deficits amongst women do not occur in isolation (Crawford 1991:380). While this may be a valid point worthy of further consideration, it is unfortunately also rather too complex an area to be easily researched using Western medicine's favoured tools of the randomised controlled trial, systematic review and meta-analysis. A number of the trials that were considered by De-Regil *et al* (2010) but ultimately rejected (either because of bias, or in this case, a poor fit with the question being asked) had explored multiple supplements and other more complex interventions, but were not able to find enough useful data to add to our knowledge in this area. As Kotaska (2004) has also pointed out, randomised controlled trials are limited in their ability to research complex interventions.

### 2) Does folic acid – especially at the levels recommended – have unwanted side effects?

Researchers have argued that *'Intakes of 1000µg total folic acid plus food folates are without identifiable risk of any known adverse effects'* (Hathcock 1997:434). However, concerns about the risks and side effects of folic acid supplementation – both for the women and babies who are exposed to the direct effects of intake and, where population-level fortification is operational, to the wider population – have existed since the debate began. Some of these concerns relate to specific possible side effects (Mason & McNabb 2000) but commentators have also questioned how much is still unknown (Robinson 1997, McNally 2000).

Scott *et al* (1991), for instance, were among those concerned about the high levels of folic acid used in some of the trials, and another correspondent considered the long-term implications for women taking supplements over several pregnancies (Reynolds 1991:506), emphasising that the risks of such a policy are unknown. Michel Odent commented on the MRC study in the *MIDIRS Midwifery Digest*, concurring with Reynolds' view that excess folate as well as folate deficiency may harm the developing nervous system (Reynolds 1991:505), and adding that *'...folic acid is a neurotoxin and convulsant in laboratory animals'* (Odent 1991). While the wider question of long-term risk remains, later investigation into this area suggested that the amount of folic acid required before seizures are affected – 5000-30,000µg – is far above what would normally constitute an average intake. *'Folic acid doses of 5-30 mg orally have produced some evidence of increased frequency of seizures in epileptics, but there is no evidence of such effects at lower intakes of folic acid'* (Hathcock 1997:432). Eros *et al* (1998) also found that doses less than 1000µg of folic acid did not increase the risk for epileptic

seizures in either women with epilepsy or healthy women, but concerns remain about the effect that fortification may have on people with epilepsy (Murphy *et al* 2000).

Another area of concern is respiratory and allergic conditions. Bekkers *et al* (2011) found no adverse respiratory or allergic outcomes apart from what they describe as a small increased risk of early wheeze. Kieft-de Jong *et al* (2012) showed no association between folic acid supplementation and wheezing, shortness of breath or atopic dermatitis in offspring. However, mothers with a high circulating level of plasma folate were found to be at higher risk of having an infant with atopic dermatitis in the first two years of life. As one of us has previously stated:

*'Supplementation may carry potential downsides as well as significantly reducing the risk of neural tube defects in babies (eg Mitchell et al 2004). Less advantageous consequences of supplementation include an increased likelihood of multiple births (Werler et al 1997, Martin & Park 1999), concerns about the role of folic acid in carcinogenesis (Eichholzer et al 2006) and the possibility that folic acid and vitamin B<sub>12</sub> supplementation may methylate or otherwise affect genes in humans as well as mice (Ainsworth 2006)'* (Wickham 2008:39-40).

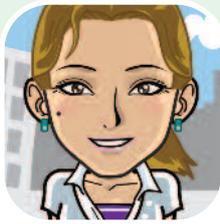
Other recent debates have focused on Cole *et al's* (2007) argument that, although their findings were not statistically significant, an increase in colorectal neoplasias following folic acid supplementation warrants further investigation. Bayston *et al* (2007) disagreed with this; Mason *et al* (2008) responded and the debate continues, albeit sporadically, in both the medical and midwifery literature, with the Cochrane review noting early on that:

*'From the safety perspective, an observational study on the fetal origins of disease has proposed that normal to high maternal folate status coupled with low vitamin B12 status was associated with higher adiposity and insulin resistance in Indian babies (Yajnik 2008) which could probably have a long-term effect in the fetus later in life. Additional potentially undesired effects of folic acid supplementation come from the possible association of the use of multivitamins containing folic acid and an increase in twin pregnancies (Vollset 2005) as well as the ambiguous findings on the effects of folic acid supplementation on colonic lesions (Fife 2009, Jaszewski 2008, Wu 2009)'* (De-Regil *et al* 2010:4).

In relation to the data available from the review itself, the reviewers conclude that:

*'Only one study reported findings on side effects like nausea, vomiting, constipation or diarrhoea (Czeizel et al 1994) and the number of reported cases was very low in both the group of women receiving folic acid with multiple micronutrients and the control group during the pre-pregnancy and pregnancy period'* (De-Regil *et al* 2010:14).

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Hmmm, so even though we found lots of debate, there are hardly any proven side effects of folic acid then?



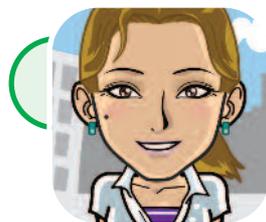
That's a hard one to answer. While some of the suggestions in this area are speculative, it is worth noting that the debate in this area is wide and ongoing; we encountered far more discussion (of variable levels of academic rigour) on potential side effects than we have the space to include here. It is important to reiterate that research does tend to focus on short-term side effects, not least because it is extraordinarily difficult to measure long-term ones, and that the concerns about the effect that folic acid may have on future obesity, multiple pregnancy and colonic lesions are very real.



But the risk of neural tube defects is very real, and is more of a worry than the side effects of folic acid, so surely that means it is better to take folic acid than not?



I guess it boils down to personal ideology. Some women might be happy to take folic acid simply because it is recommended or because they have seen a promotional campaign or have decided to take prenatal vitamins. Some will look more closely at the evidence and they might choose to take it because they know that it reduces the risk of NTDs, whereas others may think, 'well I am low-risk and I don't like taking supplements unless I need to, so I want to see more evidence of safety and/or look at whether there are alternatives.'



And are there any alternatives?



Well that's what we need to consider next, in part three. Many governments have considered and/or implemented food fortification programmes, which means that women (and everyone else) who eat foods like flour, cereal and bread are getting additional folic acid whether they want it or not. This is also partly because not everybody who becomes pregnant has planned to become pregnant, so it removes the need for people to plan ahead. It does also raise some wider questions about choice, which we will return to next time.

## Conclusion

In this article, part two of three, we have explored some of the questions that have been raised since the efficacy of folic acid supplementation was demonstrated, especially as these concern dosage, timing and potential side effects. We also looked at these questions in relation to the findings of the current Cochrane review. As is often the case, the answers are not clear-cut and many issues continue to be unresolved. The other significant debate in this area concerns dietary folic acid, which also raises questions about fortification programmes, and this will be the focus of the final part of this article, in the December 2012 edition of *Essentially MIDIRS*.

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### Tasha Cooper BSc (Hons), MCLIP

joined MIDIRS in 2009 as a Librarian in the Information Department and now works as Assistant Editor of *Essentially MIDIRS*. Her academic background is in information management and she was awarded Chartered Librarian status in March 2011, but she also holds professional qualifications in marketing.



### Sara Wickham

is a midwife, teacher, author and researcher who divides her time between working as the Editor of *Essentially MIDIRS* and as an independent midwifery lecturer and consultant. She has lived and worked in the US and New Zealand as well as the UK and is the author of more than 200 books and articles relating to birth and midwifery.