

# 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 1



Last year a friend of mine was thinking about trying for a baby and asked me what I thought about folic acid supplements. Although I'm not a midwife, working at MIDIRS means that, rightly or wrongly, I'm often asked for advice from friends about pregnancy and childbirth. Personally, I had taken – religiously – a well-known brand of multivitamins throughout my pregnancy. My friend's question made me realise that at no point during my own pregnancy had I considered whether I needed to take vitamins or not, I just did it because my general opinion on supplements was '*well, they can't do any harm!*'

This conversation triggered a number of questions about folic acid supplements during pregnancy, such as: how much folic acid is enough, and how much is too much; are there any side effects; is it possible to obtain sufficient folate from diet alone; aren't we all eating fortified foods now anyway; and what **exactly** is folic acid preventing...? A well informed woman with access to the right information could find answers to the above questions without being a midwife, but what sort of questions would be important to a practising midwife, and what does the evidence **really** show about this area?



I happened to be the nearest midwife and, as a big fan of thinking critically about the value of interventions, I soon became very engaged in this conversation. In fact, I have been asked similar questions by women in the past and a few years ago I happened upon some research relating to the possible side effects of folic acid and wrote briefly about it (Wickham 2007, 2008) with a plan to look in more depth at the literature at some point. Tasha's questions and the literature searching and research that they sparked grew into an ongoing conversation between the two of us, so, rather than amalgamate our thoughts into one shared voice, we decided to try something new. This article is more akin to the actual conversations that we have been having, as well as more reflective of the fact that – as we have been highlighting in recent issues of *Essentially MIDIRS* – information journeys are never as straightforward as finished linear articles suggest, but often involve meandering off on tangents, spiralling into unexplored corners and thinking about concepts and related ideas before being able to answer the question at hand.



So as I began to research the use of folic acid supplements during pregnancy, the complexity of the topic was revealed. My pile of studies grew and grew (and grew) as I uncovered research trials, correspondence, and reports dating back to the 1960s, along with more recent government guidance and position statements from the relevant professional bodies. Before I knew it my paper mound had successfully reached 12 weeks' gestation, so I felt it was time my highlighted, dog-eared and scribbled-on surrogate baby had a booking visit with the professionals. The midwife I saw carefully listened and examined my paper mound and after a while pronounced that, not only was there an article in there, but that I was having triplets!



As I palpated the literature, it quickly became apparent from my experience of looking at the research relating to other birth-related interventions such as anti-D, vitamin K and the management of placental birth, that Tasha would not find straightforward answers to her questions. As with some of the above examples, exploration of the evolution of knowledge and thinking in these areas can give us fascinating insights into all manner of issues relating to knowledge and power and teach us about the complexities of this thing we call evidence-based practice as well as (hopefully) providing information that we can then offer to women (see Murphy-Lawless (2012) and Wickham (2012) for more discussion on this).



So this article, part one of three, tells the first part of the story of our investigation into folic acid supplements during pregnancy. Parts two and three will be published in the November and December 2012 editions of *Essentially MIDIRS*. This first article gives some background information about folate, folic acid and the recommendations around this, and looks at the initial research and debate into this area, which culminated in the publication of the trial on which many of these recommendations were originally based.

# Evolution of the Theses

## Folate and folic acid

Firstly, it is important to remember the distinction between folate and folic acid. In the consumer literature and online, the terms are often used interchangeably when they are in fact quite different.

*'Folic acid is a type of B vitamin. It is the man-made (synthetic) form of folate that is found in supplements and added to fortified foods'* (MedlinePlus 2011). Folate is present in a wide variety of foods, from lentils to asparagus, but is particularly present in dark leafy green vegetables, and the term folate is derived from the Latin for leaf, *folium*.

Although there is a variety of different abbreviations used in the research literature, for reference purposes there are 1000 micrograms ( $\mu\text{g}$ , ug or mcg) in 1 milligram (mg). For consistency and readability, I will be using  $\mu\text{g}$  throughout these articles to refer

to the amount of folic acid, even if the original study in question used a different abbreviation.

## Current recommendations and evidence

There is a clear consensus amongst the major UK bodies (see Fig 1), based on individual studies and systematic reviews, that folic acid is effective. These organisations all advocate taking folic acid supplements before and during pregnancy to reduce the risk of neural tube defects.

The US Centers for Disease Control and Prevention recommends that all women of childbearing age consume 400 $\mu\text{g}$  of folic acid daily. The UK's National Institute of Health and Clinical Excellence (NICE), and its Department of Health, advises folic acid supplementation at a dose of 400 $\mu\text{g}$  per day before conception and up to 12 weeks of gestation.



It might already be obvious to many readers, but I think it would be useful to note at this point that folic acid is a prophylactic intervention, and explain what this means. Unlike some interventions, which are used as treatment when a woman or baby has a specific condition, a prophylactic intervention is something that people do or take in order to prevent something happening. It's like putting on a seatbelt when you get into a car; you have no idea whether your car is going to bump into something today, but you want to be safe if it does. Unlike with a seatbelt, though, if you take a prophylactic intervention like folic acid, you never have any idea whether or not you (or your baby) would have had a problem without it (which is one reason why we need to research this at a population, rather than individual, level). Some

kinds of prophylaxis are recommended universally – that is for all women – and some are recommended selectively, for particular groups. The fact that folic acid is a prophylactic intervention rather than a treatment means that, when we come to look at the question of effectiveness, we will need to think about concepts such as relative risk, but we'll return to that at the appropriate time!

### Fig 1: Clear consensus

The most recent Cochrane review into the effect of folic acid supplementation during pregnancy (De-Regil *et al* 2010) found that: *'Folic acid, alone or in combination with vitamins and minerals, prevents NTDs but does not have a clear effect on other birth defects'* (2010:2).

The UK's Scientific Advisory Committee on Nutrition (SACN) – a panel of independent experts who provide advice to the Food Standards Agency, the Department of Health, and other government bodies – says: *'Clear, strong evidence from randomised controlled trials (RCTs), has shown large benefits of folic acid supplementation in reducing the risk of pregnancies affected by NTDs'* (SACN 2006:i).

The UK's Royal College of Obstetricians and Gynaecologists (RCOG), citing the MRC study (1991) and Czeizel & Dudas (1992), states that: *'The effect of periconceptual folic acid on reducing the incidence of both occurrence and recurrence of NTDs has been confirmed in quality randomised controlled trials'* (Fraser & Fisk 2003:1).

The National Institute for Health and Clinical Excellence (NICE) recommends that: *'Pregnant women (and those intending to become pregnant) should be informed that dietary supplementation with folic acid, before conception and up to 12 weeks of gestation, reduces the risk of having a baby with neural tube defects (anencephaly, spina bifida)'* (NICE 2008:84).

As evidence for their recommendations, NICE, SACN and RCOG have cited the same large randomised controlled trial (MRC 1991), and this study was also one of five trials examined in the Cochrane

systematic review (De-Regil *et al* 2010). We'll now take a closer look at some of the developments which eventually led to this key piece of research...

## Marmite, spinach and the historical context of folic acid

The history of scientific discovery in relation to folate and folic acid could begin from a number of points, but a good start is with Lucy Wills, a medical researcher who carried out pioneering work in the late 1920s into macrocytic anaemia in pregnant textile workers in what was then known as Bombay, India (Hoffbrand & Weir 2001). This anaemia was most prevalent in poorer women whose diets were deficient in protein, fruit and vegetables, and, after establishing that yeast prevented macrocytic anaemia in animal studies, Wills began to successfully treat the women with Marmite (Hoffbrand & Weir 2001). In 1941, folic acid was successfully isolated from spinach by Mitchell *et al* (1941) and these and many other research studies and papers published over the next few decades contributed to an exciting and growing field of discovery in relation to what were termed deficiency diseases.

An influential paper by Bryan Hibbard in 1964 gives us a good indication of the state of knowledge at this time and the context of the next stage of research. It is important to note that, as was normal at the time, statements are unreferenced and arguments appear to rely on pathophysiological speculation rather than the evidence that would be the standard today:

*'The formation and development of every human cell is dependent on an adequate supply of folic acid. Folic acid governs the synthesis of the precursors of DNA ... It follows that the body's requirements for folic acid are related to the amount of cellular reproduction occurring at any particular time. During pregnancy the rate of tissue growth increases enormously'* (Hibbard 1964:529).

As Hoffbrand & Weir (2001) note in their history of this area, folic acid therapy had been found to enhance tumour growth. Initial suspicion that there might be a relationship between folic acid and NTDs came from instances where women who had received anti-folate chemotherapy gave birth to babies with NTDs. While studies in mice did not show a link between folate deficiency and NTDs though, Hibbard (1964), who also worked with poorer women – this time in Liverpool, England – showed that there was an association between folate deficiency and NTDs. His research was followed by more work in Liverpool by Smithells *et al* (1971, 1980, 1983) and small retrospective (Laurence *et al* 1980) and prospective (Laurence *et al* 1981) studies in South Wales, all of which continued to confirm this link.

However, this confirmation was not universal. Mills *et al* (1989) carried out research in the USA and found no protective effect, although their research was retrospective and relied on women's recall of vitamins taken. A number of the researchers involved in these studies had begun to debate the relative merits of their own and each others' work and, as can be seen in the title of Wald &

Polani's (1984) paper which discussed the need for a randomised controlled trial, the results of the much larger and more ambitious study which was being carried out under the auspices of the UK's Medical Research Council were eagerly anticipated.

## The MRC Vitamin Study Research Group

In July 1983 the Medical Research Council (MRC) Vitamin Study Research Group launched a large randomised controlled prevention trial to determine whether supplementation with folic acid or a mixture of seven other vitamins around the time of conception could prevent neural tube defects. During the eight years in which it continued, the study included 1817 women, of whom 735 were from the UK and 1082 were women from centres outside the UK; mainly Hungary but also Israel, Australia, Canada, Russia and France. All of the women had had a previous NTD-affected pregnancy and were randomly allocated to one of four groups – to take folic acid, other vitamins, neither, or both. The study was published in *The Lancet* and found that '*...1195 [women] had a completed pregnancy in which the fetus or infant was known to have or not have a neural tube defect; 27 of these had a known neural tube defect, 6 in the folic acid groups and 21 in the two other groups, a 72% protective effect (relative risk 0.28, 95% confidence interval 0.12-0.71). The other vitamins showed no significant protective effect (relative risk 0.80, 95% CI 0.32-1.72). There was no demonstrable harm from the folic acid supplementation, though the ability of the study to detect rare or slight adverse effects was limited'* (MRC 1991:131). In fact, the study itself had ended when evidence of the protective effects of folic acid emerged and the researchers considered that it would be unethical to continue to withhold folic acid from women at high risk of having a baby with neural tube defects.

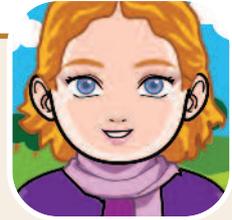
A huge swathe of correspondence, most of which appeared in subsequent editions of *The Lancet*, followed the publication of the MRC study. This kind of correspondence – especially in the days before the internet when much of it would be published in a later edition of the journal that had published the original study, and thus remain easily available decades later to someone with access to a good medical reference library – can be invaluable. This is not to deny the value of modern web-based comments and 'rapid responses' but print text cannot be altered and the researcher who has the means and energy to hunt down such correspondence can gain great insight into the thinking and practice context of the time, the limitations of the research itself and, sometimes, any apparent discrepancies between the results of a study and the later implementation of these in the form of recommendations, practices and/or treatments. Such correspondence – together with our own thinking and that of others – can help us to debate the finer details of the topic, so we'll start by being really clear about what the MRC (1991) study, and those that followed, actually found in relation to efficacy.

# Evolution of the Theses



Hang on, but how do you define efficacy?

Well, one way of putting it simply is this: does, and how well does, the intervention work, and in whom? We also need to consider whether the research was good enough to answer those questions, and it is always important to think about the wider context when investigating efficacy, but we will explore this in later articles, so let's stay with the main question: **does it work?**



Hmmm, how well does folic acid work? OK, well, as far as I can see, the research I looked at concluded that folic acid supplementation worked very well at preventing neural tube defects during pregnancy, and the statistics seem to support that view.

Yes, and maybe it would be useful to quickly define relative risk as I mentioned earlier, because that is part of the question about how well it works. In this instance, this type of statistic allows us to compare the risk of having a baby with an NTD depending on whether or not one takes folic acid. As statistics go, it is a relatively easy one to calculate and understand, but two important things to remember are that:

- (1) This is about risk in population, not individuals. So taking folic acid (or anything else, for that matter) is no guarantee for anyone.
- (2) Relative risk tells us nothing about absolute risk. So women who take folic acid are, on the basis of these results, less likely to have a baby with an NTD than women who don't take folic acid, but it is also important to know what the risk would have been to begin with. If the absolute risk of something is (say) one in ten million to begin with, then something that creates a small reduction in relative risk isn't nearly as impressive than if the absolute risk is one in five. But how about we look at the actual numbers in our next article, when we look at the meta-analysis which has arguably more reliable data to work with...



But in terms of in whom folic acid would work best - the MRC study included women who had already had an NTD affected pregnancy which seems important because I take it that this doesn't tell us about women who haven't had an NTD affected pregnancy. For reasons still unknown, NTDs are more common in the British Isles (particularly northern and western areas, which include Liverpool and South Wales, where much of the early research took place) than in continental Europe. One correspondent to *The Lancet* pointed out that as the large groups used in the UK arm of the MRC study were in Glasgow and Cardiff, this created a bias towards women who were already at a higher risk of NTDs.

Yes, so this could mean that although general folic acid supplementation may be suitable for these geographical populations, it may be too broad to apply to the rest of the UK (Stone 1991:379). So that might be something to look at more closely.

It is worth noting that, near the end of their paper, and following a lengthy discussion where they acknowledged that questions regarding safety, dosage and route of action (among other issues) remained, the authors stated that,

*'It is less clear whether all women planning a pregnancy should take folic acid supplements. The case rests upon questions of safety and cost. In any event, community-wide prevention may be difficult to achieve by providing supplements to everyone and consideration should be given to extending the fortification of staple foods with folic acid'* (MRC 1991:146).



The quotation above demonstrates that the MRC study authors understood that we didn't know whether all women would benefit, but almost in the same breath they are already talking about extending fortification. When we add this to the fact that some of the women in the MRC trial didn't want to be randomised because they had become aware that folic acid had a protective effect, we can see that, metaphorically speaking, the folic acid train had pretty much left the station — even before we had full knowledge about whether it would be beneficial for everyone. Questions also remained about dosage and side effects. We will explore the later research and debate to see if it helps answer these questions in parts two and three of this article.

## Conclusion

This article, part one of three, has taken us from the treatment of macrocytic anaemia with Marmite in the 1920s, to the isolation of folic acid in 1941, the origins of folic acid supplementation in the 1960s and 1970s, and right through to the publication of a trial in 1991 which seems to have been the tipping point for folic acid supplementation. A body of correspondence and research – including a Cochrane review last updated in 2010 – followed the MRC 1991 study, and we'll continue the investigation and look further at the issues surrounding the dosage of folic acid in part two, which will be published in the November 2012 edition of *Essentially MIDIRS*.

## References

De-Regil LM, Fernandez-Gaxiola AC, Dowswell T *et al* (2010). Effects and safety of periconceptual folate supplementation for preventing birth defects. *Cochrane Database of Systematic Reviews*, Issue 10.

Fraser RB, Fisk NM (2003). *Periconceptual folic acid and food fortification in the prevention of neural tube defects*. London: Royal College of Obstetricians and Gynaecologists.

Hibbard BM (1964). The role of folic acid in pregnancy. with particular reference to anaemia, abortion and abortion. *BJOG: An International Journal of Obstetrics & Gynaecology (formerly The Journal of Obstetrics and Gynaecology of the British Commonwealth)* 71(4):529-42.

Hoffbrand AV, Weir DG (2001). The history of folic acid. *British Journal of Haematology* 113(3):579-89.

Laurence KM, James N, Miller M *et al* (1980). Increased risk of recurrence of pregnancies complicated by fetal neural tube defects in mothers receiving poor diets, and possible benefit of dietary counselling. *BMJ* 281(6255):1592-4.

Laurence KM, James N, Miller MH *et al* (1981). Double-blind randomised controlled trial of folate treatment before conception to prevent recurrence of neural-tube defects. *BMJ* 282(6275):1509-11.

Medline Plus (2011). *Folic acid in diet*. <https://www.nlm.nih.gov/medlineplus/ency/article/002408.htm> [Accessed 29 August 2012].

Mills JL, Rhoads GG, Simpson JL *et al* (1989). The absence of a relation between the periconceptual use of vitamins and neural-tube defects. National Institute of Child Health and Human Development Neural Tube Defects Study Group. *New England Journal of Medicine* 321(7):430-5.

Mitchell HK, Snell EE, Williams RJ (1941). The concentration of folic acid. *Journal of the American Chemical Society* 63(8):2284.

MRC Vitamin Study Research Group (1991). Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. *The Lancet* 338(8760):131-7.

Murphy-Lawless J (2012). Midwifery and obstetric knowledge: thinking deeply about birth. *Essentially MIDIRS* 3(8):17-21.

National Institute for Health and Clinical Excellence (2008). *Antenatal care: routine care for the healthy pregnant woman*. London: NICE.

SACN (2006). *Folate and disease prevention*. London: TSO.

Smithells RW (1971). The prevention of congenital abnormalities. *Midwives Chronicle* 84:152-5.

Smithells RW, Sheppard S, Schorah CJ *et al* (1980). Possible prevention of neural-tube defects by periconceptual vitamin supplementation. *The Lancet* 1(8164):339-40.

Smithells RW, Nevin NC, Seller MJ *et al* (1983). Further experience of vitamin supplementation for prevention of neural tube defect recurrences. *The Lancet* 1(8332):1027-31.

Stone DH (1991). Folic acid to prevent neural tube defects [Correspondence]. *The Lancet* 338(8763):379.

Wald NJ, Polani PE (1984). Neural-tube defects and vitamins: the need for a randomized clinical trial. *BJOG: An International Journal of Obstetrics and Gynaecology* 91(6):516-23.

Wickham S (2007). Folic acid: is there a problem? *Practising Midwife* 10(4):35.

Wickham S (2008). Folic acid: the plot thickens. *Practising Midwife* 11(7):39-40.

Wickham S (2012). Whose views count? *Essentially MIDIRS* 3(8):50-1.



## 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.