Clinical

Pregnancy and folic acid supplementation

Prof Michael Turner, Director of the University College Dublin Centre for Human Reproduction at the Coombe Women & Infants University Hospital, looks at how long women should take folic acid for and when they should start

Folate is a water-soluble organic compound belonging to the B vitamin group which is, in general, essential for the synthesis of ribonucleic acid (RNA), DNA and other cell components. As pregnancy advances, a woman's folate requirements increase to support foetal organogenesis and cellular growth, as well as supporting maternal cellular development.

Natural folates are found in a variety of foods such as legumes, green leafy vegetables, nuts and certain fruits. However, folates are unstable and loss can occur, for example, with harvesting, cooking and increased temperature.

Folic acid (FA) is the synthetic form and is chemically more stable. As FA is not in the diet naturally, it can only be consumed in supplements or fortified foods. It has the advantage of a higher bioavailability than folate.

In view of the increased requirements during pregnancy, the World Health Organization (WHO) recommends that the daily folate intake in women should be increased from 400µg per day to 600µg during pregnancy and to 500µg during breastfeeding. However, even women on a folate-rich diet rarely achieve these levels.

In the 2017 Safefood Report on the folate status of pregnant women in the Republic of Ireland, the total median dietary intake of folate was only 235.2µg (IQR 143.6). Of the total folate, the median percentage of dietary folate coming from voluntarily fortified food was 10.9 per cent. Reports from Dublin City University have shown that voluntary food fortification with FA by the food industry in Ireland has been declining since 2008 (Kelly *et al*, 2015).

Prof Michael Turner

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Neural tube defects

A good example of the critical role of folate in foetal organogenesis is the prevention of neural tube defects (NTDs), which complicate about one in 1,000 pregnancies in Ireland. They include spina bifida, anencephaly and encephalocele and are the commonest preventable major congenital anomaly. There are about 500 people in Ireland with spina bifida which carries a lifelong burden of illness for them and their families.

Numerous observational studies had linked inadequate folate intakes with an increase in the risk of NTDs. Two randomised controlled trials provided strong evidence that FA supplementation could prevent about two-thirds of, but not all NTDs.

In a multicentre placebo-controlled UK study with four arms, FA reduced the recurrence rate by three-quarters in women who previously had a pregnancy complicated by a NTD (MRC, 1991). The trial involved 1,195 women from 33 centres and the recurrence rate was 3.5 per cent in the non-supplemented group compared with 1 per cent in the group receiving 4mgs FA alone, prior to pregnancy and for the first six weeks of pregnancy.

A Hungarian study of 4,753 women found that 0.8mg of FA daily started at least one month before pregnancy, and continued for the first eight weeks of pregnancy, prevented the first occurrence of a NTD, compared with controls who received only trace element supplementation (0 vs 6, p = 0.02) (Czeizel and Dudas, 1992).

After the two landmark studies were published, governmental bodies worldwide made national recommendations about periconceptual FA supplementation to prevent NTDs. In Ireland, the Department of Health in 1993 recommended that "women likely to become pregnant should take an extra 400µg of FA prior to conception, and during the first 12 weeks of pregnancy".

Low-dose FA supplements are inexpensive and available over-the-counter. It is also recommended that women at increased risk of NTDs, such as women with a previous pregnancy complicated by an NTD, need to take a high-dose prescription-only FA supplement (see table below).

Supplementation strategy

However, the supplementation strategy for the primary prevention of NTDs has so far not worked. A comprehensive national audit found the overall rate of NTDs for 2009-11 was 1.04/1,000 births, which had not improved since the 1993 recommendations were made (McDonnell *et al*, 2015). This audit was repeated in 2012-15 using the same methodology and the rate was 1.05/1,000 births (NS) (McDonnell *et al*, 2018).

A similar lack of success has also been reported by various congenital anomaly registers in the rest of Europe. It is attributable, in part, to a lack of women's knowledge about the purpose of FA supplementation and the fact that one-third of pregnancies are unplanned.

Also, many European guidelines on FA supplementation are outdated and do not reflect evidence from recent studies (Cawley *et al*, 2015).

Compliance predictors

In an observational study of 564 women who attended the Coombe in early pregnancy, the strongest predictors of preconceptual FA supplementation on univariable analysis were higher maternal age, higher education and income, being married, being nulliparous, not smoking, a history of infertility treatment and a planned pregnancy (Cawley *et al*, 2015).

On multivariable analysis, however, both nulliparity and planned pregnancy were the most important predictors of preconceptual FA. It was surprising that multiparous women were less likely to take supplementation.

It may be that a healthy outcome of a first pregnancy may result in complacency in planning a second pregnancy.

In a further observational study at the University College Dublin (UCD) Centre for Human Reproduction of 502 women at the Coombe, compliance with FA supplementation at the time of presentation for antenatal care was high at 98.2 per cent (Cawley *et al*, 2017). However, only 42.8 per cent of women had started FA before they became pregnant and most women did not start until about six weeks gestation when their pregnancy test became positive, which is around the time that the neural tube closes. The commonest brands consumed were the multivitamin Pregnacare (34.3%) and the FA-only Clonfolic (31.5%). Only 6.7 per cent were taking the high-dose 5mg FA daily.

Despite the high level of supplementation at the first antenatal visit (mean 12 weeks gestation), only 67 per cent of women had a red blood cell (RBC) folate above 906nmol/l, which is considered optimal for the prevention of NTDs.

Optimum level

To achieve an optimum level, women need to start FA at least six weeks before conception. This is consistent with recent dose-response studies which found that women need to take 400µg per day for more than 12 weeks to achieve the optimal RBC folate. In particular, in countries like Ireland where FA food fortification is voluntary, baseline folate measurement in the non-pregnant adult population are relatively low, and time is required for supplementation to work.

In the United States (US) where FA food fortification is mandatory, an updated evidence report and systematic review for the Preventive Services Task Force in 2017 concluded that all women planning or capable of pregnancy should take a daily supplement containing 400 to 800µg of FA to reduce their risk of having a pregnancy affected by an NTD (Mitchell, 2017). The commonest dose taken by pregnant women in the US is 800µg.

National guidelines

There has also been uncertainty about when women should stop FA supplementation during pregnancy. Some national guidelines recommend the end of the first trimester, others make no recommendation. However, in a secondary analysis of the UCD Centre study, women who started FA before pregnancy were less likely to become anaemic later in pregnancy or postpartum than women who started FA during pregnancy (O'Malley *et al*, 2018).

This supports the WHO policy of continuing FA supplementation throughout pregnancy which potentially also reduces the need for a blood transfusion following obstetric haemorrhage. It should also help the mother recover quicker after delivery.

Consideration could also be given to women taking 400µg twice a day for the first month after they start so that RBC folate levels are optimised sooner.

If the use of FA supplementation is to be effective in primary prevention of NTDs, national guidelines worldwide need to be updated (Cawley *et al*, 2015).

Firstly, all women who may possibly become pregnant within the next three months, whether intentionally or not, need to take FA 400µg daily and not just women who are planning a pregnancy.

Consideration should be given to taking the low-dose supplement twice a day for the first month, so that RBC folate levels are optimised earlier.

Secondly, women who are planning to become pregnant in the near future should start supplementation at least one month before trying to conceive, so that the FA has had an opportunity to optimise maternal folate levels before neural tube closure.

Thirdly, women at increased risk of NTDs who may possibly become pregnant within the next three months, whether intentionally or not, need to start high-dose 5mg FA supplementation which requires a prescription from a doctor.

Fourthly, all pregnant women (including those who previously took high-dose FA) should continue FA 400µg daily for the duration of pregnancy and during breastfeeding, and not stop at the end of the first trimester.

If the mother is folate-depleted while breastfeeding, breast milk concentrations are maintained but the mother herself becomes further folate depleted (WHO Technical Consultation, 2008).

This may also be disadvantageous if there is a short interpregnancy interval before the next pregnancy.

Apart from public health communications, most women receive their information on FA supplementation from their family doctor. If they wait for advice until they attend for hospital antenatal care, it is too late to prevent a NTD.

It is important that women receive consistent, clear advice based on the latest scientific evidence from all healthcare professionals in primary care as to how they can prevent NTDs. Furthermore, it is in the interest of maternal wellbeing that she continues supplementation throughout pregnancy and while breastfeeding.

References available upon request

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Women at higher risk of a neural tube defect requiring high-dose folic acid
Personal or family history of folate-sensitive congenital anomalies e.g. cleft palate
Family history of NTD in a first- or second-degree relative
Maternal type 1 or 2 diabetes mellitus
Moderate/severe maternal obesity (BMI > 34.9kg/m$^{2)}$
Teratogenic medications e.g. valproic acid, metformin, methotrexate
Gastrointestinal malabsorption conditions e.g. Crohn's, active gluten enteropathy

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