Taking action on prevention of NTDs

Reinforcing the message about starting folic acid before pregnancy is critical, even in women using contraception, write Eimer O'Malley and Michael Turner

NEURAL TUBE DEFECTS (NTDs) are a group of congenital malformations associated with the failure of closure of the neural tube, which is normally complete by day 28 of embryonic development. They include anencephaly, encephalocele and spina bifida. They are the second most common major congenital anomaly and in contrast with other congenital anomalies, primary prevention of NTDs is possible with folic acid (FA). NTDs affect approximately one in 1,000 pregnancies in Europe.[1,2] However, the burden of illness with NTDs is high in Ireland compared with other European countries because we have a consistently high fertility rate and twice as many babies with spina bifida are live-born with lifelong consequences.[1]

It is estimated that two-thirds of NTDs are preventable by folic acid supplementation. The other third are associated with factors such as poor glycaemic control in the first trimester, hyperthermia, maternal obesity, aneuploidy or genetic disorders.[3]

In 1991-1992, two landmark randomised controlled trials reported that folic acid supplementation commenced before pregnancy prevented the occurrence and recurrence of NTDs.[4,5] Since 1993, therefore, national recommendations in Ireland and other countries advised women to start 400µg orally before pregnancy and to continue for the first trimester.[6] Women considered at higher risk of NTDs (for example, women with diabetes mellitus, obesity at the first antenatal visit, a previous pregnancy complicated by a NTD, a family history of NTDs, inflammatory bowel disease, women taking certain antiepileptic medications or folate antagonists) were advised to start 5mg folic acid per day oral dosage, which requires a prescription from a doctor.[7] The American College of Obstetricians and Gynecologists in a recently updated clinical guideline advised that higher dose folic acid is required at least three months pre pregnancy to bring about a 70% risk reduction in high-risk cases.[3,8]

However, since 1993 the prevalence of NTDs in Ireland has not fallen and may have even increased *(see Figure 1)*. A comprehensive national audit of 225,998 total births in the Republic of Ireland found the overall rate of neural tube defects was 1.04/1,000 births with no improvement in trends since the guidelines on supplementation were first published.[9] This has been confirmed again by a similar audit of births nationally in 2012-2015.[9] Furthermore, data from the EUROCAT registries have shown no improvement in NTD prevalence rates in the UK or Europe over the past 25 years.[10]

The supplementation strategy for the primary prevention of NTDs has, to date, not succeeded. There are a number of possible reasons. Half of pregnancies worldwide, including Ireland, are unplanned.[11] Among women, especially immigrant or educationally disadvantaged groups, there is a lack of knowledge that to prevent NTDs, FA should be commenced before pregnancy.[12]

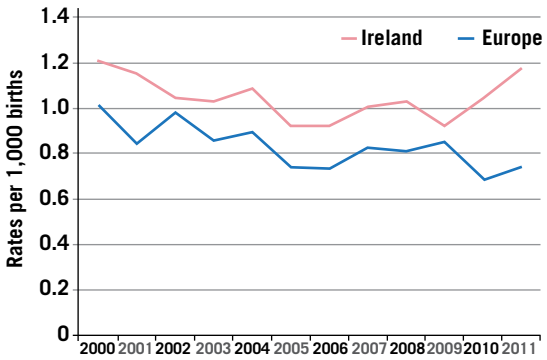
The Safefood report released in December 2017 entitled *The folate status of pregnant women in the Republic of Ireland; the current position*, reported on a survey of 564 women in early pregnancy. Of the 331 women who did not take FA pre-pregnancy, 76.4% stated that they did not expect to get pregnant and 35.0% did not know that they needed to take folic acid before becoming pregnant.[12,13]

In a prospective observational study from the UCD Centre for Human Reproduction, it was shown that most women who start folic acid during pregnancy do not commence supplementation until their pregnancy test is positive.[14] Of the 245 women who commenced it after their last menstrual period, 84% commenced it more than four weeks after their last menstrual period, which coincides with neural tube closure.[14]

In the recent Safefood report, dietary folate intake in women (n = 392) presenting for antenatal care was inadequate, with a median total intake of 235.2µg.[13] The WHO recommends a daily intake of folate for pregnant women of 600µg to sustain cellular development, which is rarely met even by a woman taking a healthy folate-rich diet.[15]

The Safefood report found 98.2% of women are taking

Figure 1: NTD per 1,000 births in Ireland and Europe 2000-2011[9]



Note: Europe rate excludes UK and Ireland.

Rates for 2000-2004 are Irish EUROCAT registry data rates (62% national coverage); 2009-11 rates are from a study by McDonnell et al.[9] Rates from 2005-2006 are from the previous FSAI study, rates for years 2007-2008 are estimated. Data on Europe rates from EUROCAT network

FA supplementation at the time of the first antenatal visit, which is high compared to previous national surveys and shows the willingness of women to comply. Less than half (42.8%) of the women, however, commenced folic supplementation before pregnancy and only 24.9% were taking it for more than 12 weeks beforehand. At the time of presentation for the first visit, therefore, the opportunity to prevent NTDs had often been lost. Of the women who commenced folic acid four to eight weeks before conception, 78.4% achieved the red blood cell (RBC) folate level of > 906nmol/L (measured at the first antenatal visit) compared to just 53.3% of those who commenced FA four to eight weeks after conception[13] (906nmol/L is considered the optimal RBC folate level threshold above which there is a risk reduction of NTDs to < 8/10,000 live births).[16]

The inconsistent public information on folic acid supplementation, with guidelines both nationally and internationally differing, may be another factor here. A review of 20 European national guidelines on the use of folic supplementation found that only four of the 20 advised that women commence it preconceptually while none made any recommendation on when to stop during pregnancy.[17]

It is also notable that voluntary fortification of food with folic acid is decreasing in Ireland. A Dublin study found that of the 346 products fortified with folic acid in 2004, only 152 (45%) were fortified in 2014.[18] As the process is voluntary, food manufacturers do not have to inform the Food Safety Authority of Ireland (FSAI) of changes to its levels in products. Despite recommendations in reports from the FSAI in 2006 and 2016, mandatory fortification has not been implemented in Ireland or indeed through the European Union. Given the mobility of food and food ingredients across national borders, implementation of mandatory fortification is challenging and is likely to be more so post-Brexit.

What needs to happen in primary care?

In light of recent evidence from the Safefood reports and epidemiological data, the national guidelines we believe need to be updated with inclusion of the following key messages:

- All women who could possibly become pregnant in the near future, whether intentionally or not, should take FA 400µg orally daily, which is inexpensive and available over the counter
- Women who are planning a pregnancy should start FA at least six weeks before trying to conceive to achieve optimal maternal RBC folate associated with the prevention of NTDs
- All women who are at high risk of NTDs and who could possibly become pregnant in the near future, whether intentionally or not, should be taking FA 5mg orally daily (which requires a prescription from their doctor).
- All women should continue FA at the same pre-pregnancy dose for the first trimester.

The World Health Organization (WHO) recommends that women require 600µg folate daily for pregnancy and 500µg for lactation but the recent Safefood report found that only 2.6% of Irish women presenting for antenatal care are achieving adequate dietary folate.[13] Therefore, women should continue to take 400µg daily for the rest of their pregnancy to promote foetal development and prevent maternal anaemia.[19]

There is a key role for the GP in the education of women of child-bearing age regarding folic supplementation. This is highlighted by a survey of pregnant women who were taking it at the time of their first visit to the hospital. Of the 563 women, 63.1% cited their family doctor as their source of advice about folic acid compared to just 3.6% citing their obstetrician. Furthermore, of the 251 women who took it pre-pregnancy, 55.0% named their family doctor as their source of advice on use compared to just 4.8% citing their obstetrician.[12] The time-point in the pregnancy when the woman usually meets the obstetrician is after neural tube closure, which is too late for effective intervention.

Thus, the need for GPs to keep reinforcing the message about starting FA before pregnancy is critical, even in women using contraception. In those women who require the higher 5mg dose of folic acid, it is important to ensure these women are given repeat prescriptions. Another cohort of women that needs special consideration are those who are undergoing investigation or treatment for infertility, many of whom are also obese due to polycystic ovarian syndrome.

Based on the dietary inadequacies reported in Irish women in the Safefood report and the WHO recommendations on the role of folate in the prevention of anaemia and in fetomaternal cellular development, it is advisable to continue folic acid supplementation throughout the second and third trimester. Women should continue to follow national guidelines for healthy eating during pregnancy but they need to be informed that healthy eating alone is unlikely to prevent NTDs.

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References on request