



**Paper for discussion: CMACE/RCOG Joint Guideline on the management of women with obesity in pregnancy: recommendation on high dose folic acid supplements.**

**Agenda Item: 5**

Please see paper attached.

## **Folic acid supplementation of women with obesity in pregnancy**

### **Background**

1. In March 2010, the Royal College of Obstetricians and Gynecologists (RCOG) and the Centre for Maternal and Child Enquiries (CMACE) published a joint guideline on Management of Women with Obesity in Pregnancy (see Annex 1). This guideline includes a recommendation for nutritional supplements for women with obesity that wish to become pregnant (page four of Annex 1):

*“Women with a BMI  $\geq 30$  wishing to become pregnant should be advised to take 5mg folic acid supplementation daily, starting at least one month before conception and continuing during the first trimester of pregnancy.”*

2. The Department of Health does not currently make any specific recommendations on folic acid supplementation for obese women wishing to become pregnant. To prevent neural tube defects (NTDs) all women are advised to take a 400 $\mu$ g folic acid supplement when trying to become pregnant, continuing until the end of the first trimester of pregnancy. To prevent recurrence of NTDs in the offspring of men or women with spina bifida themselves or women with a previous pregnancy affected by NTD, folic acid supplements of 5mg/day are recommended (Department of Health, 1992)<sup>1</sup>.
3. Any recommendations specific to obese women of childbearing age affect a significant proportion of the population: 25% of adult women in England are obese (Health Survey for England, 2008). The prevalence of obesity in pregnancy has risen from 9-10% in the early 1990s to 16-19% in the 2000s<sup>23</sup>.

### **Scientific evidence**

4. RCOG/CMACE has indicated that their recommendation is based on evidence from a meta-analysis of 12 observational studies (Rasmussen *et al.*, 2008) and an analysis of two US cross-sectional surveys (Mojtabai, 2004). The meta-analysis included eight case control studies and four cohort studies and found an association between maternal obesity and risk of NTDs [unadjusted odds ratios for an NTD-affected pregnancy were 1.22 (95% CI 0.99-1.49), 1.70 (95% CI 1.34-2.15) and 3.11 (95% CI 1.75-5.46) for women defined as overweight, obese and severely obese respectively]. The analysis of US cross-sectional surveys found a statistically significant association

<sup>1</sup> Department of Health (2002) Folic acid and the prevention of neural tube defects. Report from an Expert Advisory Group.

<sup>2</sup> Heslehurst N, Ells LJ, Simpson H *et al.* (2007) Trends in maternal obesity incidence rates, demographic predictors, and health inequalities in 36,821 women over a 15-year period. *BJOG: An International Journal of Obstetrics and Gynaecology* 114(2): 187-94.

<sup>3</sup> Kanagalingam MG, Forouhi NG, Greer IA *et al.* (2005) Changes in booking body mass index over a decade: retrospective analysis from a Glasgow Maternity Hospital. *BJOG: An International Journal of Obstetrics and Gynaecology* 112(10): 1431-3.

between maternal obesity and lower serum folate levels and serum/red blood cell folate ratio after controlling for several factors including folate intake from food and supplementation. These papers are available in Annex 2.

5. Using data from a formula proposed by Wald *et al.* (2001)<sup>4</sup>, Mojtabai (2004) calculated that obese women (BMI >30) would require an additional 350µg of folic acid to achieve the same serum folate level as women in the underweight category (BMI <20). The survey data used by Mojtabai (2004) for this analysis was from the US, where all women are advised to take 400µg folic acid supplement when trying to become pregnant and cereal grains are subject to mandatory folate fortification.
6. A preliminary search of the literature by the secretariat has not identified any further studies that have investigated the impact of folic acid supplementation in obese pregnant women on NTD risk.
7. Comments from Dr Robert Fraser, who is unable to attend the meeting, are available in Annex 3.
8. **The Committee is asked to note the RCOG/CMACE recommendation and to consider whether to undertake a risk assessment of the evidence on folic acid requirements of obese women who wish to become pregnant.**

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<sup>4</sup> Wald NJ, Law MR, Morris JK et al. (2001) Quantifying the effect of folic acid. *Lancet* 358: 2069-2073.

## Annex 1

### CMACE/RCOG Joint Guideline on Management of Women with Obesity in Pregnancy

Full report available at: <http://www.rcog.org.uk/womens-health/clinical-guidance/management-women-obesity-pregnancy>

#### Extract on folic acid supplementation

*What nutritional supplements should be recommended to women with obesity who wish to become pregnant?*

**Women with a BMI  $\geq$  30 wishing to become pregnant should be advised to take 5mg folic acid supplementation daily, starting at least one month before conception and continuing during the first trimester of pregnancy.**

**B**

In the general maternity population, maternal folate deficiency is associated with fetal congenital malformations, and periconceptional use of folic acid supplementation reduces the risk of the first occurrence, as well as the recurrence, of NTDs (relative risk (RR) 0.28, 95% confidence interval (CI) 0.13–0.58). In women at high risk of fetal NTD (due to previous pregnancy with NTD), a randomised double-blind prevention trial has shown that a higher dose of folic acid supplementation (4mg/day) reduces the risk of a subsequent NTD-affected pregnancy by 72% (RR 0.28, 95% CI 0.12–0.71).

Evidence level 1++

Women with a raised BMI are at increased risk of NTD, with a meta-analysis of 12 observational cohort studies reporting an odds ratio (OR) of 1.22 (95% CI 0.99–1.49), 1.70 (95% CI 1.34–2.15) and 3.11 (95% CI 1.75–5.46) for women defined as overweight, obese and severely obese, respectively, compared with healthy-weight women.

Evidence level 2++

There is evidence from cross-sectional data that, compared to women with a BMI  $<$ 27, women with a BMI  $\geq$ 27 are less likely to use nutritional supplements and less likely to receive folate through their diet. However, compared to women with a BMI  $<$ 27, women with a BMI  $\geq$ 27 have lower serum folate levels even after controlling for folate intake.

Evidence level 2+

The findings from the studies above suggest that obese women should receive higher doses of folate supplementation in order to minimise the increased risk of fetal NTDs.

## **Annex 2**

### **Evidence cited by RCOG/CMACE**

Rasmussen SA, Chu SY, Kim, SY *et al.* (2008) Maternal obesity and risk of neural tube defects. *American Journal of Obstetrics and Gynecology* 198(6): 611-619.

Mojtabai R. (2004) Body mass index and serum folate in childbearing age women. *European Journal of Epidemiology* 19(11): 1029.

### **Annex 3**

#### **Comment for SMCN of SACN on the CEMACE/RCOG Joint Guideline on the Management of Women with Obesity in Pregnancy: Recommendation on High Dose Folic Acid Supplements**

I am aware of this report from March 2010 although I was not a member of the Group nor was I invited to comment on their Guideline. With regard to their recommendation paragraph 4.2 “Women with a BMI >30 wishing to become pregnant should be advised 5mg of folic acid supplementation daily, starting at least one month before conception and continuing during the first trimester of pregnancy”, I was surprised to see such a strong recommendation based on relatively poor evidence. It did give me a sense of déjà vu however since we had very similar discussions about the dose of folic acid to be recommended to women with diabetes when I chaired the NICE Guideline Development Group “Diabetes in Pregnancy”. The Diabetes Guideline (page 10) also recommends the higher folic acid dose (5mg/day) despite in my opinion the absence of any supporting evidence. On this particular recommendation I was outvoted by members of the Committee as there was a feeling that it would be unnecessarily confusing if our Guideline made a different recommendation to the earlier publication from CEMACH “Pregnancy in Women with Type 1 and Type 2 Diabetes in 2002/2003”.

This preamble is of importance because the most likely explanation of the apparent increase in NTD in obese women is an independent effect of periconceptional hyperglycaemia, an aetiology for NTD which as far as we know is not modified by folic acid supplementation or serum levels.

The first paper of interest in this matter is a publication by Ray JG and colleagues, American Journal of Obstetrics and Gynecology 2005; 105: 261-5 “Greater maternal weight and the ongoing risk of neural tube defects after folic acid flour fortification”. This paper reported an adjusted odds ratio for NTD of 1.2 (95% CI 1.1-1.3) per 10 KG incremental rise in maternal weight. The background rate of detected NTDs was 0.6/1000. This paper is included in the meta-analysis of Rasmussen and colleagues. Ray and colleagues reported that the higher risk of NTD with increased maternal weight was not significantly modified in the US by the introduction of folic acid flour fortification. The paper from Mojtabai from the European Journal of Epidemiology again from the US is particularly interesting because their data allowed them to observe that women in higher BMI categories were less likely to take nutritional supplements and that they had lower intakes of folate from food or folic acid from food or from supplements than normal weight women. Despite this the mean red cell folate in the obese category at 176.5 ng/ml (168.1 to 184.9) was not significantly different from the red cell folate level in the normal weight group at 184.8 ng/ml (176.2 – 193.3) in pregnant women in the US National Health and Nutrition Examination Survey (NHANES).

Scott and colleagues in Dublin (Daly S et al. Minimum effective dose of folic acid for food fortification to prevent neural tube defects Lancet 1997; 350: 1666-9) suggested that fortification or supplementation should aim to reach a red cell folate concentration in excess of 400 ng/ml and that supplementation with only 100 µg of folic acid per day resulted in median post treatment concentrations of 375 ng/ml.

It appears then that despite supplementation and fortification in the US the red cell folate levels appear to be suboptimal for the prevention of NTD but if red cell folate is accepted as reflecting folate stores obesity is not having a significant independent effect here.

In the discussion of their meta-analysis by Rasmussen and colleagues they recognised the importance of undiagnosed diabetes. I would extend this to subclinical hyperglycaemia in the obese as the most likely unquantified confounding factor in the meta-analysis.

In conclusion the evidence for an increasing risk of NTD with maternal obesity is established but the ability of an increased dose of folates in diet or folic acid supplementation to modify this risk is far from established. The somewhat simplistic recommendation of the CMACE/RCOG joint Guideline for a higher dose of folic acid supplementation in the obese unfortunately opens up women to the risk that in the event of them having conceived a child handicapped by an NTD, it might be suggested to them that this outcome resulted from their failure to take a higher supplementation dose, when no good evidence from prospective controlled clinical trials exists to support that conclusion.

Robert Fraser  
24 August 2010