Reviewer's report

**Title:** Folic Acid Supplementation, Dietary Folate Intake during Pregnancy and Risk for Spontaneous Preterm Delivery: A Prospective Observational Cohort Study

**Version:** 2 **Date:** 21 May 2013

**Reviewer:** Andrew E. Czeizel

**Reviewer's report:**

The aim of the study is important because preterm birth is the major factor of infant mortality and different disabilities. Thus the prevention of preterm birth by the simple and cheap method of folic acid use would be important. However, the results of previous studies were controversial, and authors want to add new data into this debated topic.

The study design and material based on the well-known MoBa are good with excellent statistical analysis of data.

I have only 4 comments.

1. The rate of preterm birth in the Norwegian population is 7%, however, this rate is 2.5% in their sample size (1,628/65,668 = 2.47%), this difference needs explanation.

2. Gestational age and birth weight have obvious correlation. I understand that the outcome of authors was preterm birth, but readers of the paper would be curious as secondary endpoint for gestational age specific birth weight. For example, in Hungary several obstetricians do not recommend pregnant women to use folic acid or folic acid-containing multivitamins during pregnancy because they will deliver “giant babies”.

3. Authors found an increased risk for overall and early spontaneous preterm birth if pregnant women were supplemented more than 8 weeks prior to conception. Obviously preterm birth mainly a maternal variable (in contrast to fetal oriented birth weight), but in general the risk of preterm birth associated with risk factors in the second part of pregnancy.

Thus women in this subgroup may have some special risk factors – if the association is causal – with some maternal factors (e.g. smoking or special diseases)

4. The previous Hungarian population case-control study (cited by the authors) showed an association of high doses (3-9 mg, estimated average 5.6 mg) of folic
acid with lower risk of preterm birth particularly if folic acid was used during the third trimester. On the other hand the Hungarian RCT used a multivitamin containing 0.8 mg of folic acid during the periconceptional period without any effect for birth outcomes, among them preterm birth. To my mind the results of this study are in agreement with the previous Hungarian findings. Low doses of folic acid cannot modify the rate of preterm birth, however, large doses of folic acid may have preterm birth reduction effect, because in the study of authors only 2 women used large doses of folic acid (more than 5 mg), and 575 were supplemented with pharmacological doses of folic acid (between 1-5 mg). Thus a dose-dependent effect cannot be excluded.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

'I declare that I have no competing interests'