Author's response to reviews

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

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To The Editorial Team  
*BMC Pregnancy & Childbirth*

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Dear Editors,

Thank you for considering our paper “Folic Acid Supplementation, Dietary Folate Intake during Pregnancy and Risk for Spontaneous Preterm Delivery: A Prospective Observational Cohort Study” (MS: 5131435619198082) for publication in BMC Pregnancy and Childbirth.

We want to thank Andrew E. Czeizel and Bridget S. Mosley for their valuable comments on our manuscript. All changes have been highlighted in the revised paper and a detailed response to all comments follows below.

Yours sincerely,

Verena Sengpiel, on behalf of all authors

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Reviewer 1, Andrew E. Czeizel:

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.

As we excluded all known risk pregnancies due to maternal disease, pregnancy complications or fetal malformations, the preterm delivery rate in our study population is much lower than in the general Norwegian population: 2.5% for spontaneous preterm delivery, 3.4% for overall preterm delivery. We clarified this point at page 14 line 8:

Thus the PTD rate in our study population is 3.4%, approximately half of the PTD rate in the general Norwegian population as we excluded all risk-pregnancies due to maternal disease, pregnancy-complications or fetal malformation.

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 delivery “giant babies”.

The association between folic acid supplementation and maternal folate status with birth weight and the risk of having a baby small for gestational age has been studied in MoBa. No significant associations with these pregnancy outcomes were found: Nilsen et al: Infant birth size is not associated with maternal intake and status of folate during the second trimester in Norwegian pregnant women. The Journal of nutrition 2010, 140:572-579. The study included 2934 singleton pregnancies in 2002-2003.

Birth weight and having a baby small or large for gestational age were not included in the study plan for this paper and we did not apply to the MoBa board for permission regarding birth weight related pregnancy outcomes. But we agree that it would be interesting to go on and study folate variables and birth weight outcomes in a bigger study sample like this.
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).

We fully agree that confounding with some unknown maternal factor might be the reason for the association between early onset of folic acid supplementation and overall as well as early spontaneous preterm delivery. All women with a known disease or pregnancy complication, implying increased risk for preterm delivery, have been excluded from the study though. We adjusted for known risk factors such as smoking. We refer to the issue of confounding once more in the paragraph on early start of folic acid supplementation, page 19 line 17: Of course, women who choose to start early with folic acid supplementation might be distinguished by some other characteristic that could be the causal link to spontaneous preterm delivery so that we cannot exclude confounding.

Studying the association of folate variables and birth weight might give further information how to interpret the association of early start of folic acid supplementation and spontaneous preterm delivery. However, as written above, birth weight as outcome was not part of this study.

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.

We agree and tried to stress the context for interpreting our data throughout the discussion and conclusion – we studied a low-risk population with overall low intake of food-folate and supplemental folic acid, e.g. page 18 line 1:

One of the most obvious explanations for these conflicting results could be the dosage of folic acid. While most of the studies finding an association with gestational length or PTD were based on comparably high doses of folic acid (≥5000 µg/d [1-3], ≥2500 µg/d [2,4] and ≥500 µg/d [5-7]), very few women in our study population consumed as much as 5000 µg/d of supplemental folic acid, while only 9% consumed >500 µg/d and 15% consumed >400 µg/d. However, the Hungarian RCT, one of the biggest performed so far, did not find any effect of a high dosage of 8000 µg/d of folic acid supplementation on PTD [8]. Unfortunately, the folic acid dosage was not indicated in all of the studies [9,10].

Conclusion, page 22, line 3:
The amount of dietary folate and supplemental folic acid intake in 65,668 uncomplicated singleton pregnancies from the Norwegian Mother and Child Cohort Study was not associated with a risk of spontaneous PTD, at least not at the relatively low intake levels of dietary folate (median 155 µg/d corrected for bio-availability, uncorrected 258 µg/d) and supplemental folic acid (median 400 µg/d) in this healthy study population.
Reviewer 2, Bridget S. Mosley:

Comments:

Overall, this is a well designed analysis using appropriate data to address this research question. These results can be added to a body of literature showing inconsistent results evaluating the relationship between folic acid and prematurity.

I would recommend that an additional statement be added in the discussion regarding the uniqueness of population being evaluated. With so many adverse conditions being excluded from the analysis, this study population was a relatively healthy group of women. If folic acid truly does have any protective effect on the risk of prematurity, it may very well be most effective for the group of women that were excluded from this analysis.

We fully agree that when interpreting our results, it is very important to keep in mind that our study population is a highly selected population and stressed this in several paragraphs throughout the discussion:

Discussion, page 17 line 3:
In this large prospective national birth cohort study, we did not find any statistically significant association between the amount of folate intake from the diet or supplements and spontaneous PTD in uncomplicated pregnancies.

Discussion, page 17 line 7:
When interpreting the results, the selection of the study population has to be kept in mind: all known risk-pregnancies due to maternal disease, pregnancy complications or fetal malformation have been excluded from the analysis. There might be an association between the amount of folate intake from diet or supplements and spontaneous PTD in those pregnancies excluded.
Conclusion, page 22 line 3:
The amount of dietary folate and supplemental folic acid intake in uncomplicated 65,668 singleton pregnancies from the Norwegian Mother and Child Cohort Study was not associated with a risk of spontaneous PTD, at least not at the relatively low intake levels of dietary folate (median 155 µg/d corrected for bio-availability, uncorrected 258 µg/d) and supplemental folic acid (median 400 µg/d) in this healthy study population.