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 manuscript “Folic acid supplementation, dietary folate intake during pregnancy and risk for spontaneous preterm delivery: a prospective observational cohort study” (MS: 1189894813131909) for publication in BMC Pregnancy and Childbirth.

We especially want to thank Andrew E. Czeizel for reviewing this paper, as he was a reviewer also of the original paper we had to retract earlier this year. It is an honour to be reviewed by a research pioneer of folic acid supplementation in pregnancy. Changes to the manuscript 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:

Reviewer's report: I appreciate the quality of your paper but I have three comments:
1. The Hungarian case control surveillance study showed the control mothers had a lower rate of preterm birth mainly after the use of folic acid after the third trimester, however this study was ended after the second trimester and it is not commented.

We have added a more detailed discussion to the differences in study design in the corresponding paragraph on page 18, lines 21 ff:

However, results are conflicting as summarized in the review by Mantovani et al. [1]. A protective effect of folic acid supplementation was supported by a modest reduction in the PTD rate after the introduction of folate fortification of foods [2]. Some recent observational studies have found that folic acid supplementation reduces the risk of PTD [3-5]. In some cases, this association was found for preconceptional folic acid supplementation for 1 year or longer [4] or third-trimester folic acid supplementation [5], raising questions about extended supplementation schemes compared to the NTD prevention scheme. Folic acid supplementation more than a 1 year before becoming pregnant is not registered in MoBa, but data for the earliest interval (26–9 weeks before conception) suggest an adverse effect of longtime folic acid supplementation on the risk of spontaneous PTD. Though third trimester folic acid supplementation is registered in MoBa, we chose to not include third trimester supplementation as the early PTDs already have occurred at different time points during this period, so that we were not able to retrace the findings by Czeizel et al. [5].
2. There is a prevalent rumor that folic acid can increase the birth weight, it would have been good if the authors logged birth weight also.

The aim with this manuscript was to re-publish our folate paper that had to be retracted (MS: 5131435619198082) without any other major changes so that readers will be able to find the same paper with correct data again.

We agree, though, that studying the association between folate and birth weight would have been another interesting topic to examine. Birth weight is indeed registered in the MoBa study and there is a publication by several of our co-authors including birth weight as outcome [40]. However, we did not have approval by the MoBa board to include birth weight as an outcome into this project.

3. There is an error in page nineteen, authors are right that the Hungarian RCT did not find any effect of folic acid for birth outcomes, it is important to stress that this intervention trial supplied folic acid until the twelfth week of gestation and this time folic acid and multivitamins were used rarely. Also the erroneously state that 8000 mcg [6] of folic acid was used per day; this is not the case it was only 800 mcg. High doses were used in the previous study. [22]

We apologize for giving the wrong dosage of folic acid supplementation in your paper from 1994. The error has been corrected, page 19, lines 16 ff:

However, the Hungarian RCT, one of the biggest performed so far, did not find any effect of a high dosage of 800 µg/d of periconceptional folic acid supplementation on PTD [6].