Author’s response to reviews

Title: Women born with very low birth weight have similar menstrual cycle pattern, pregnancy rates and hormone profiles compared with women born at term

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Author’s response to reviews:

Dear editor,

Thank for this thorough review. We have tried our best to answer and have made changes according to the suggestions from the reviewers. We appreciate the reviewers the acknowledgment of the hardship to perform a study of this kind.

Below follow a point by point answer to each of the reviewer’s comments.

We are looking forward to receiving a prompt decision regarding the manuscript.

Kind regards on behalf of all the authors,

Gunilla Sydsjö
Reviewer reports:

Robert T Chatterton (Reviewer 1): 1. Abstract: The statement that individuals born with low birth weight have a reduced likelihood to reproduce is not accurate. In the deKeyser population study women born small for gestational age had a statistically increased rate of reproduction in the age 25-27 group. This age is not substantially different from the age range in the present study so the hypothesis of low reproductive efficiency is not reasonable for this study.

Thank you for this remark. Since we performed that study (DeKeyser N, Josefsson A, Bladh M, Carstensen J, Finnstrom O, Sydsjo G) there have been a couple more studies published that have been studying reproductive pattern for men and women born with deviant birth characteristics showing that low birth weight is indeed associated with reduced likelihood to reproduce. Therefore we think this sentence “Individuals born very preterm or with VLBW have a reduced likelihood to reproduce according to population-based register studies.” is adequate as a background statement.

Please see below


2. The authors indicate that at the initial recruitment 27 of 38 VLBW subjects were SGA but not the proportion in the group that actually participated.

Thank you for you noticing this. 19 (79.2%) of the 24 VLBW subjects were born SGA. This has been added to the manuscript.

3. In the study the proportion of VLBW women with children was not different from the control group so results of the hormone measurements cannot be related to low reproductive efficiency. Thank you for this remark. Actually the women are still rather young and their reproductive period is still ongoing. But the positive observation is that the participating women in this limited material are not deviating markedly from the controls in reproductive history and or hormone levels.

4. Table 2 does not show the number of subjects included. Was this 24 in all cases?
Yes, that’s correct. The total number of subjects included was 24 in the VLBW-group and 25 in the control group. Information pertaining to this has been added to the table.

5. Table 3: The age at which samples were obtained should be indicted and information on the day of the last menstrual period. It was not reasonable to conduct a study in which so few of the subjects would be available for hormone testing. As a result of having no information on the menstrual cycle and so few subjects, the power of the test is too low to report.

Please see discussion.

Nanette Santoro (Reviewer 2): The authors have attempted to perform a very difficult study and have provided some new and useful data despite several shortcomings in the approach which diverge from the ideal. The purpose of the manuscript is to describe reproductive health parameters in 27-28 year old women who were born at very low birth weight. The sample size is too small to draw firm conclusions, but as noted above this is an extraordinarily difficult study to complete and therefore any information is welcome about the topic. Nonetheless, there are several clarifications that the authors need to provide to allow a reader to interpret the data.

1. There are two ways to be born at VLBW: either one is born very prematurely or one is severely small for gestational age. It is not clear how many of the women who underwent hormonal assessment were in each category. While the sample size is overall small, it would be helpful to distinguish these two groups because they may have different reproductive parameters.

19 of 24 of the women in the VLBW group was born SGA, and 5 were born <32 gestational weeks and 13 were born in gestational weeks 33-37. Please see added text in the manuscript.

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2. Reproductive hormones drawn at random throughout the menstrual cycle have very limited value for comparison purposes given the very large fluctuations across the menstrual cycle. This should be specifically acknowledged as a limitation of interpretation. AMH levels, on the other hand, vary far less across the menstrual cycle and are a more valid measurement.

We agree that hormone samples drawn at random are of limited values but at least showed that we did not have “outliers” in any group. We have added in the discussion: “Ideally all samples should have been drawn at more than one time point, such as at the time of ovulation and during the mid-luteal phase but that was not possible due to practical reasons and long distance from the hospital for many participants.” Regarding AMH we have also added: “Unfortunately we did not analyse AMH levels in women using oral contraceptives because we omitted all hormonal analyses in these women, but AMH is probably not affected by use of oral contraceptives and could have added some information.”

3. Pages 5-6, lines 143-159 are confusing, as are page 8 lines 180-185. Line 142: The 25 women using hormonal contraception are subtracted from the overall 49? Please be more specific. The 'misunderstanding' alluded to on line 145 is also unclear. Does this mean that the 25 women using hormonal contraception did not have an AMH determination? If so, then please simply say so. Please specify that menstrual cycle data was NOT utilized for women using hormonal contraception.

We have now tried to clarify lines 143-159.

On lines 180-185, the numbers do not seem to add up correctly. Please clarify. If 80 girls were enrolled at both, and 49 participated in follow up, the number two completed questionnaires and the number who completed both questionnaires and hormone determinations should be explicitly derived. How the numbers go from 49 on line 180 to 45 on line 185 seems to be an impossible calculation. Please clarify.

We agree that the paragraph was difficult to understand. The paragraph has been rewritten and is now, hopefully, easier to understand.

4. If p<0.05 is taken as statistically significant, then the systolic blood pressure differences between the two groups bears comment (Table 2).

Yes, it could be mentioned. We have just chosen not to since the material is relatively small and the p-value was 0.047. However, a sentence regarding this finding has been added.