Author's response to reviews

Title: Fetal growth determines duration of the human pregnancy

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Author's response to reviews: see over
Dear Chief Editor,

Please find attached the revised version of our manuscript “Fetal growth determines duration of the human pregnancy” for publication in BMC Pregnancy and Childbirth.

We are grateful for the constructive comments by the reviewers. Amendments are entered in bold in the manuscript. We have made the requested formatting changes and included “Competing interest”, “Authors contribution” and “Acknowledgement” sections. The responses to reviewers follow in an itemised fashion:

Reviewer 2:

Major Compulsory Revisions:

First of all the women included in the study had menstrual periods between 24 and 32 days (28 ± 4), which means that the difference in gestational length, when calculated from LMP could be as much as 8 days because of differences in menstrual periods. If the women carrying fetuses with the smallest size at the ultrasound examination had menstrual periods of 32 days and those with the largest fetuses had 24 days, this would explain the major part of the differences in duration of pregnancy between the groups. Probably, to control for this possible error the authors included the ultrasound estimation in second trimester (HC) as a confounder. However, I do doubt that the HC could be considered a true confounder as fetal size (HC) is closely associated with LMP, pregnancy length and birth weight. What makes the use of HC as a confounder even more doubtful is the fact that the HC, AC and FL used in the present study all had been estimated from this same population.

- **Response:** Gestational age calculated from LMP for women with a history of regular menstrual periods (28±4 days) was corrected for cycle lengths different from 28 days. This procedure has been included in the methods section of the manuscript. Since we corrected gestational age for cycle length, it is less likely that variation in cycle length explains the difference in duration of pregnancy between the groups.
Controlling for the difference between LMP and ultrasound dating (HC) reduced the effect of fetal size on pregnancy length by around half, but the difference was still significant for AC and FL. Irrespective of whether the difference between LMP and ultrasound dating using HC represents a confounder or not, the effect of fetal size on pregnancy length is strongly present both when dating from LMP and when controlling for HC. We have inserted a comment on this in the conclusion section.

Secondly, the span of the time for ultrasound estimation is rather wide from 10 to 24 gestational weeks. Presumably error measurements might differ between a scan in week 10 and week 24.

- **Response:** Although the measurement error increases with increasing gestational age between 10 and 24 weeks, this does not influence the mean value since the random error has a symmetrical and normal distribution.

To convince the readers that smaller fetuses have longer pregnancies the authors would need to do some revisions. They could include information on mean or median length of menstrual periods for each strata (-2.5 SD to 2.5 SD) and possibly control for the differences. Alternatively limit the study to include only those with 28 day-cycles. They should also control for the time in pregnancy, when the scan was performed.

- **Response:** Since we corrected gestational age for those with menstrual cycle length other than 28 days, we believe that stratification according to cycle length is not needed.

For the biometric measurements, the increasing variation with advancing gestational age is taken care of by using SD-scores.

Minor Essential Revisions:

The title is somewhat misleading. Though the authors point out in the abstract that fetal growth express fetal size in the second trimester such an assumption would be based on all embryos having the same size in early pregnancy, which probably is not true. I believe that to use the term "growth" there should at least be two measurements. A more correct title would therefore be "Fetal size at second trimester determines duration of the human pregnancy."
Response: There are valid arguments for regarding fetal size at the time of ultrasound scanning as a reflection of growth from conception. On the other hand side, we also acknowledge the reviewer’s point that the term growth demands two measurements at different times and have changed the title accordingly.

In the abstract a population of 650 low-risk pregnancies is mentioned, however in the present study only the 541 with spontaneous deliveries are included, which should be stated explicitly in the abstract.

Response: We have re-phrased the Abstract to clarify that only 541 women with spontaneous deliveries were included in the analysis.

The authors state that the obstetric outcome was good, but only gestational length and birth weight are presented. The authors could have included mode of delivery (spontaneous start of delivery is not equivalent with vaginal delivery), APGAR scores and neonatal outcomes in Table 1.

Response: To further show that obstetric outcome was good we included caesarean sections, forceps/vacuum, breech deliveries and Apgar scores to Table 1.

In the Discussion, p 9 "Our results are supported by a recent study --". The ref. for this study is missing.

Response: This reference (20) has now been inserted into the text and the reference list.

Reviewer 3:

Major Compulsory Revisions:

1. This study is predicated on an assumption that women with certain knowledge of their last menstrual period, regular cycle etc. provides a population with sufficient certainty about gestational age to be useful for research purposes. However, the authors have excluded 8 women ‘because the discrepancy between ultrasound and menstrual age was more than 14 days’. This is not discussed further in the paper, but needs justification. Was this pre-specified? Does it challenge the underlying assumption about precision of gestational age assessment? Why 14 days rather than, say, 10 or 7 days?

Response: The present study was part of the larger “Fetal Age and Growth” project, which was designed to establish ultrasound reference ranges for fetal age assessment and growth.
In that protocol we had specified that subjects would be excluded if the discrepancy between ultrasound and menstrual age was more than 14 days. We had similar thoughts to those pointed out by the reviewer, but chose 14 days since there is documentation that such a discrepancy is associated with an increase risk of growth-restriction and adverse outcome. The aim of the present study was to study low-risk pregnancies. We have inserted a paragraph in the Conclusion section to emphasis this point.

2. There is a possible source of bias here which isn’t addressed in the paper and which hinges on what the attending clinicians did with the information provided on second trimester measurements. If they re-calculated gestational age on the basis of second trimester fetal measurements (as is very commonly done), then gestational ages would be advanced for bigger fetuses and reversed for smaller fetuses. Since the authors only included women with ‘spontaneous deliveries’ [I assume that this means spontaneous labours and would potentially include instrumental deliveries and emergency caesarean sections in labour – but this does need clarification] then it is quite likely that bigger fetuses would be more likely to be excluded because of induction of labour for perceived post-term pregnancy. It would be useful to give a breakdown of ALL pregnancies included in the study [like a CONSORT flow chart in randomised trial] rather than only those included in the analysis, to reassure the reader that there was no differential effect.

Response: In a new Table 1 we present a flow chart of the entire study population showing characteristics and outcome of both the spontaneous and the non-spontaneous deliveries. We have accordingly reduced the first paragraph of the Results section. The included women had spontaneous onset of labour. This is clarified in the flow chart. As mentioned by the reviewer, our clinicians used the ultrasound based fetal age assessment for their clinical management. Post-term was regarded as ≥296 days of pregnancy, but induction was not necessarily contemplated unless oligohydramnios or other abnormal findings were present. Rather than the large fetus, we assume therefore that the small fetus, commonly having less amniotic fluid than a large fetus, was at risk of being induced and excluded from the analysis thus reducing the effect of fetal size on pregnancy length. We also believe that the clinicians’ focus on IUGR also affects the “normal” small fetus who
faces a higher risk for intervention during pregnancy than their larger peers, distributing them to the excluded group and thus possibly reducing the effect found in the present study.

It is reassuring that in an initial analysis including all participants, induced or not, caesarean section or not, we still found a strong linear effect of fetal size on length of pregnancy (Table A and B inserted below).

Table A. Means (standard deviations) of head circumference (HC), abdominal circumference (AC), femur length (FL), and pregnancy duration according to deciles of each biometrical measure.

<table>
<thead>
<tr>
<th>Decile</th>
<th>Grouped in deciles of HC</th>
<th>Grouped in deciles of AC</th>
<th>Grouped in deciles of FL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HC, mm</td>
<td>Pregnancy, days</td>
<td>AC, mm</td>
</tr>
<tr>
<td>1</td>
<td>56.2 (6.4)</td>
<td>284.1 ( 8.9)</td>
<td>44.6 (5.2)</td>
</tr>
<tr>
<td>2</td>
<td>76.8 (5.9)</td>
<td>284.3 ( 7.8)</td>
<td>63.4 (5.5)</td>
</tr>
<tr>
<td>3</td>
<td>95.5 (4.5)</td>
<td>284.7 ( 8.5)</td>
<td>80.0 (4.4)</td>
</tr>
<tr>
<td>4</td>
<td>114.2 (6.1)</td>
<td>282.4 (10.1)</td>
<td>97.9 (5.5)</td>
</tr>
<tr>
<td>5</td>
<td>132.6 (3.9)</td>
<td>282.1 ( 9.6)</td>
<td>113.9 (4.0)</td>
</tr>
<tr>
<td>6</td>
<td>147.1 (4.3)</td>
<td>282.7 ( 9.0)</td>
<td>128.5 (4.1)</td>
</tr>
<tr>
<td>7</td>
<td>163.1 (4.6)</td>
<td>281.2 (10.3)</td>
<td>144.7 (5.4)</td>
</tr>
<tr>
<td>8</td>
<td>181.3 (5.9)</td>
<td>283.1 ( 9.8)</td>
<td>160.7 (5.6)</td>
</tr>
<tr>
<td>9</td>
<td>202.0 (6.3)</td>
<td>282.7 ( 8.7)</td>
<td>182.7 (5.8)</td>
</tr>
<tr>
<td>10</td>
<td>221.6 (6.4)</td>
<td>279.2 (10.9)</td>
<td>203.0 (7.0)</td>
</tr>
<tr>
<td>Total</td>
<td>139.0 (51.7)</td>
<td>282.6 ( 9.5)</td>
<td>121.9 (49.4)</td>
</tr>
<tr>
<td>P for linear trend</td>
<td>0.007</td>
<td>0.009</td>
<td>0.011</td>
</tr>
</tbody>
</table>

Table B. The association between pregnancy duration (days) and head circumference (HC), abdominal circumference (AC), and femur length (FL) in multivariable linear regression*.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coeff</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HC, 10 mm</td>
<td>-3.1</td>
<td>-4.0, -2.2</td>
</tr>
<tr>
<td>AC, 10 mm</td>
<td>-2.6</td>
<td>-3.5, -1.8</td>
</tr>
<tr>
<td>FL, 3 mm</td>
<td>-3.1</td>
<td>-4.1, -2.0</td>
</tr>
</tbody>
</table>

* Adjusted for gestational age.
Minor points:

1. P4 para 1 final sentence: it is more accurate to say: reducing the number of inductions of labour for presumed post-term pregnancy.

   *Response*: The text has been corrected according to the reviewer’s suggestion.

2. ‘foetal’ is better spelt ‘fetal’.

   *Response*: Corrected.

3. I wasn’t clear what was meant by ‘when adjusting for the difference between LMP and ultrasound dating’ p7 para 2.

   *Response*: Adjusting for the difference between LMP and ultrasound dating (page 7, para 2) means that this difference is incorporated in the multivariable regression analysis (Table 2). The text has been amended.

4. ‘delivery’ should read ‘labour’ p8 para 2 l 8.

   *Response*: “Delivery” (p8, para 2, l 8) has been changed to “labour”.

5. ‘pregnancies’ should read ‘women’ p8 para 2 l 10.

   *Response*: “Pregnancies” (p8, para 2, l 10) has been changed to “women”.

6. Reference 7 is incorrectly cited.

   *Response*: Now corrected.