Author’s response to reviews

Title: "Reduced fetal growth velocities and the association with neonatal outcomes in appropriate-for-gestational-age neonates: a retrospective cohort study"

Authors:

Manouk Hendrix (manouk.hendrix@mumc.nl; manouk.hendrix@maastrichtuniversity.nl)
Sander van Kuijk (sander.vankuijk@mumc.nl)
Antonio Gavilanes (danilo.gavilanes@mumc.nl)
Desiree Kramer (desiree.kramer@mumc.nl)
Marc Spaanderman (marc.spaanderman@mumc.nl)
Salwan Al-Nasiry (salwan.alnasiry@mumc.nl)

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Manouk Hendrix (manouk.hendrix@mumc.nl)
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Marc Spaanderman (marc.spaanderman@mumc.nl)
Salwan Al-Nasiry (salwan.alnasiry@mumc.nl)

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Reply to reviewer:

This manuscript presents a study of the characteristics of AGA (10th - 80th BW percentiles) subclasses. The subclasses defined were: 1) optimal (BW 50th-80th percentiles) and suboptimal (BW 10th -50th percentiles); 2) with and without perinatal complications; and 3) BW ≥ expected BW and BW< expected BW. Expected BW’s were calculated based on 20 week AC measurement but method not described or referenced. All fetuses had two BPD, HC, AC and FDL measurements, at ~20 wks and ~ 32 wks, and a list of perinatal complications. Growth rates were calculated for the four biometric parameters. The authors found that growth rates were lower in the suboptimal AGA group compared to the optimal AGA group but there were no significant differences in the incidences of perinatal complications. However, the growth rates were significantly lower in the AGA subgroup with perinatal complications compared to the subgroup without. Three perinatal complications were higher in the BW<expected BW subgroup. The authors conclude that growth velocities could play an important role in the detection of mild growth restriction.

Q1/ This is a very well designed investigation with a large sample and a comprehensive data set. The data analysis is appropriate and most of the conclusions are supported by the results obtained. The problems found primarily concerned omissions, which should be readily corrected, although a few concern definitions.

A1/ We sincerely thank the reviewer for the effort taken in reviewing our manuscript and his thorough remarks highlighting certain issues in the manuscript. We would like to respond to his questions and hereby submit a revised manuscript taking into considerations the reviewer’s comments. We would like to apologise for the fact that our remarks and changes are depicted in two different colours which may be disturbing; this is due to the fact that different computers were used during the revision process.

Q2/ In the Introduction, the authors make a number of sweeping statements about growth restriction definitions (2nd and 3rd paragraphs) but provide no data or citations to justify them. The basis for these statements needs to be given. Also, in the last paragraph, the authors introduce 'growth potential ' and make statements about growth velocities being measures of growth potential without citing the work of Deter et al (Am J Obstet Gynecol, 2018; 218(Suppl):S656-S675.) who have studied this subject extensively. Based on their work, growth potential does not change (as stated by the authors) since it depends primarily on genetic factors, but growth can deviate from what would be expected due a large number of factors. This paragraph needs to be re-written.
A2/ We admit that the work of Deter et al. has been inadvertently overlooked, however, the cited article was published after the submission of our manuscript. Nevertheless, their previous work on defining fetal growth potential by using Individual Growth Assessment is highly relevant. These paragraphs in the introduction have been rewritten with citing the work of Deter et al.

Q3/ In the Methods, there are several important omissions.

A/ We admit that this paragraph of the methods was not clear. We have rewritten it.

First, the birth weight evaluations are age-specific so a fetal age is required. The authors provide no information on how fetal age was determined.

A/ The pregnancies were dated (fetal age) according to the formula of Robinson calculated from crown-rump length (CRL) measurement in the first trimester

Second, the authors indicate that the "Hadlock equation" was used for weight estimation but cite a reference containing several weight estimation equations. The specific one used in this study needs to given.

A/ We have specified the used Headlock equation in the text.

Thirdly the authors state that the absolute values of the measurements were used in calculating growth rates but do not indicate why. All measurements are positive so this is not necessary.

A/ We mean by “absolute” values raw values in (in mm/week) as opposed to percentiles. The sentence is adjusted.

Fourthly, the authors state that differences in growth rates in the suboptimal and optimal AGA subgroups were expected but provide no evidence to justify expectation and give no standards for making such evaluations. This sentence should be omitted.

A/ The sentence about the expectation of differences in growth rates is omitted.

Fifthly, the authors indicate that "expected birth weights" were calculated from 20 week AC measurements but do not indicate how this was done or give a justification for such a procedure. Without this information, there is no validity for the results obtained with 'expected birth weights'.

A/ We apologize for the incomplete description. We have explained the method and premise of expected birthweights in the Methods and Results sections. We don’t consider this a standard method to estimate expected birth weight and acknowledge that the method described by Deter et
al. is more valid. However, we wish to include this data as it provides additional clues to the hypothesis of reduced fetal growth potential.

Finally, the authors give a list of conditions that constituted their "composite adverse neonatal outcome" but provide no definitions or citations for these conditions. Without this information, the reader does not know what these terms really mean.

A/We added literature to the composite adverse neonatal outcome.

Q4/In the Results, the authors state that they found a linear relationship between AC velocity and birth weight. However, they do not give the function, do not define (B=0.001) or give the R2 for this regression. This information is needed to evaluate the quality of the regression.

A4/ We have added the function of the linear relationship between AC velocity and birth weight.

Q5/In the Discussion, under Main findings, the authors state that neonates with adverse outcomes had lower growth velocities for "all studied parameters". However, the results presented in Table 4 indicate that the growth velocity difference for FDL was not statistically significant. This error needs to be corrected.

A5/ We have corrected the sentence about the growth velocities.

Q6/Also in this section, the authors conclude that growth velocities may play a role in predicting adverse neonatal outcomes. However, they do not discuss the meaning of finding differences between groups and using such differences to identify individuals at risk for adverse outcomes. As discussed in detail by Pepe et al (Am J Epidemiol, 2004;159:882-890), it is much easier to find differences between groups (particularly with very large sample sizes as in this study) than it is to separate individuals at risk from those that are not, based on the same indicator parameter. The latter depends on the degree of overlap between normal and abnormal groups. As can be seen in Table 4, the ranges of velocities (min-max) for those with and without adverse outcomes overlap considerably. Given the large sample size, these overlaps are not likely to decrease in larger samples. For this reason, it is unlikely that growth velocities as determined by the authors can contribute significantly to the identification of at risk fetuses. This issue needs to be discussed by the authors to give the reader a proper perspective.

A6/ We thank the reviewer for highlighting this issue. We added a paragraph to the limitation section acknowledging the inability of fetal growth velocities to be good predictive tests based on these data. Accordingly, we have also rephrased sentences throughout the manuscript pertaining to prediction of FGR based on our data.
Q7/In the Interpretation section, the authors give a number of different methods for identifying fetuses who fail to maintain their growth trajectories. However, they do not mention Individualized Growth Assessment (Deter et al Am J Obstet Gynecol, 2018; 218(Suppl):S656-S675), which uses empirical measurements of growth velocity to specify 3rd trimester growth trajectories and quantifies departures from these trajectories due to growth pathology. This is the most extensive use of growth trajectories and should be cited.

A7/ We thank the reviewer for this suggestion. The paragraph in the Discussion (as well as the introduction) have been rewritten citing the work of Deter et al.

Q8/The tables and figures are quite self-explanatory but contain p-values for statistical tests that are not indicated in the footnotes. This information should be added so the reader can evaluate the statistical analyses used.

A8/ We have added the p-values in the footnotes.

This is a very good study of an important subject which provides interesting data on a group not extensively studied [those whose birth weights are considered 'normal']. However, the manuscript is deficient in many important respects that could affect the validity of the conclusions made. Re-evaluation of a revised manuscript is recommended.