Author's response to reviews

Title: Maternal Carotid Remodeling and Increased Carotid Arterial Stiffness in Normal Late-Gestational Pregnancy as Assessed by Radio-Frequency Ultrasound Technique

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Author's response to reviews: see over
Response to Reviewer 1

First, we would like to thank you very much for your helpful comments on our manuscript. We believe this manuscript would improve greatly in consideration of your constructive comments. Second, we would like to apologize that all the data we presented in this manuscript was from the right common carotid artery, not the left. We have replaced the left with right in the whole manuscript. We feel so sorry for making this mistake… The following are our point-to-point responses to your comments. Please check. If there is anything else that we need to do, please let us know. Thank you very much.

Comment 1
This is an interesting study which in my opinion deserves publication, however several problems needs to be addressed.

Response 1
Thank you for your comment. We really appreciate it. We will try our best to answer all the questions you addressed.

Comment 2
In “Introduction” Authors cited previous articles were arterial stiffness (segmental) was estimated by pulse wave velocity (PVW) estimated by transit time and the distance. Than the sentence follows “…Till now, The carotid arterial stiffness parameter, PWV, has not been evaluated in normal pregnant women…” This is completely difficult to understand. As far as I know MyLab ultrasound equipped with arterial stiffness packages allow to estimate local carotid stiffness which is expressed by several parameters also by LOCAL PWV. I do not think that it need to be stressed in Introduction. Nevertheless it need to be rewritten.

Response 2
Thank you for your comment. We totally agree with you. It has been rewritten in the revision in the Introduction section, lines 14-16. Unnecessary sentences have been deleted.

Comment 3
Another sentence from the “Introduction” - “Recently, high resolution ultrasound acquisitions based on radio frequency signal gives the opportunity to assess precisely the regional arterial wall properties 8, which is called automatic QAS (Quality Arterial Stiffness) and QIMT (Quality Intima-Medial Thickness) technique.” In my opinion QAS and QIMT are not “technique” but a names of commercial packages included in Esoate ultrasounds.

Response 3
Yes. We totally agree with you. We have rewritten this sentence and changed
“technique” to “packages” on the first page of introduction, the last second line.

Comment 4
Second-Authors adjusted data for several variables however in Statistical Analysis I could not find a method for data adjustment nor any explanation which and why particular variables were chosen in the first place.
Response 4
Thank you for noticing these points. We have added them in the Statistical Analysis section on page 8, lines 1-4.

Comment 5
Third – in Results Authors should first show unadjusted results than (stating why?) adjusted results. In section 2 of Results “…As expected, RI and PI of LCCA were..” What is RI and PI and why we expected it to be decreased?
Response 5
Thank you for your comments. We have rewritten this and showed the unadjusted results first and then the adjusted results. We have deleted the word “As expected” in section 2 of Results. RI and PI are the abbreviations of resistance index and pulsatility index. We feel very sorry that we forgot to give the full spelling of these two words. They have been added to the Method section on page 8, lines 1-3.

Comment 6
I strongly encourage Authors to seek assistance with the English expression in their manuscript. In my opinion it would need to be considerably improved.
Response 6
Thank you for your suggestion. We have asked an English teacher from our university and she helped us to check the whole expressions of the manuscript.

Comment 7
Level of interest: An article whose findings are important to those with closely related research interests.
Response 7
Thank you for your comment. We are greatly encouraged and we really appreciate your kind comment.

Comment 8
Quality of written English: Not suitable for publication unless extensively edited.
Response 8
Thank you for your comment. We have had an English teacher from our university for help to edit it.
Comment 9
Statistical review: Yes, and I have assessed the statistics in my report.
Response 9
Yes. The related questions have been addressed in previous responses.
Response to Reviewer 2
First, we would like to thank you very much for your helpful comments on our manuscript. We believe this manuscript would improve greatly in consideration of your constructive comments.
Second, we would like to apologize that all the data we presented in this manuscript was from the right common carotid artery, not the left. We have replaced the left with right in the whole manuscript. We feel so sorry for making this mistake…
The following are our point-to-point responses to your comments. Please check. If there is anything else that we need to do, please let us know. Thank you very much.

Comment 1
Table 1 indicates that pregnant women were tested at 32 ± 5 weeks gestation. This is a broad range, and it is either known or likely that many of the outcome measures are affected by gestational age. Have the authors determine whether gestational age is univariately associated with any of the outcome measures, and considered adjusting for this in statistical models as appropriate?
Response 1
Thank you for noticing these points. We have deleted the pregnant subjects who were less than 28 weeks gestation. We totally agree with you that many of the outcome measures are affected by gestational age, however, what we want to observe in this study is the difference of the carotid morphological and arterial stiffness between pregnant women and non-pregnant age-matched women.

Comment 2
The authors should provide more information on subject selection and characteristics to help readers determine whether the pregnant and non-pregnant groups are comparable, and whether known confounds have been addressed. For instance, menstrual cycle phase may influence some of the parameters measured. Do the authors have data on menstrual cycle phase in the non-pregnant controls, and do they know how many were using hormonal contraception? The methods states that all women were recruited from an antenatal clinic. Were non-pregnant women trying to conceive, or did they have fertility problems? The BMI differences are larger than might be expected. Might the authors have self reported pre-pregnancy weight, to allow for calculation of pre-conception BMI? Was the study limited to lifetime non-smokers, or did it include pregnant women who may have stopped smoking shortly before conception or in early pregnancy? Were non-pregnant women also nulliparas, or did this group include parous women?
Response 2
Thank you very much for your comments. These are really important points. Thank you for your reminding. Yes. We have asked each subjects of the menstrual cycle phase (28-30 days). None of the included non-pregnant controls were taking any medicine during the study. Only the pregnant women were from the antenatal clinic. The non-pregnant controls were from the outpatient department coming for physical examination and volunteered for this study. We are very sorry for this mistake and it has been corrected in the revision.

It is a pity that we don’t have self reported pre-pregnancy weight to allow for calculation of pre-conception BMI. The study was limited to lifetime non-smokers. All the non-pregnant women have not got married and do not have the history of conception.

Comment 3
Were subjects asked to avoid caffeine or alcohol the night before the test?
Response 3
Yes, they were.

Comment 4
Pregnancy outcome in the pregnant women should be reported. The methods suggest that pregnancies were uncomplicated at the time of testing. Did any women later develop gestational hypertension, preeclampsia, preterm birth, or other complications with potential cardiovascular consequences?
Response 4
Thank you for your comments. These are very important points. Non of these pregnancies develop any complications in the current study group. This has been added in the revision on the last page of the Results, lines 11-20.

Comment 5
Table 2: The authors present numerous models, each adjusted for a single variable. The presentation of results would be more effective if the authors presented 1 or 2 multivariate models, and incorporated adjustment for all known potential confounding variables into each model. For instance, the authors state that PWV, an index of vascular stiffness, is significantly increased in pregnancy, and that this difference persists after individual adjustments for BMI, heart rate and carotid pressures. What the reader wants to know is whether this difference in PWV reflects a true change in vascular stiffness, or is a reflection of the combined influences of BMI, HR, and carotid pressures on PWV.
Response 5
Thank you for your suggestions. We re-performed the statistics and found the differences in the arterial stiffness parameters did not persist after adjusting for all known potential confounding variables in one time, indicating that these
differences were a reflection of the combined influences of BMI, HR, and carotid pressures on these parameters. This has been stated in the results and discussion.

**Comment 6**
Figure 1: Is this data pregnant women only, or pooled pregnant and non-pregnant women? It may be helpful to show relationships in pregnant and non-pregnant women separately to determine whether the slope of the regression line and strength of the relationship is similar in the two groups. If included on the same figure, pregnant and non-pregnant women should be indicated by different symbols.

**Response 6**
Thank you for your suggestion. The data in the original Figure 1 was pooled pregnant and non-pregnant women. As you suggested, the pregnant and non-pregnant women have been presented in different figures in the revision. Please see the new Figure 1 and Figure 2. Thank you.

**Comment 7**
The authors performed testing in the supine position. Position (supine vs. left lateral dicubitus) has a substantial impact on cardiovascular parameters in late gestation, as uterine compression of the inferior vena cava can reduce return of blood to the heart. The authors should address this in their discussion.

**Response 7**
Thank you for your reminding. We totally agree with you. We addressed this issue on the last page of Discussion, lines 5-8.

**Comment 8**
In the results, subheadings would be more helpful than numbers to orient the reader as to the location of key information.

**Response 8**
Thank you for your suggestion. We have added the subheading to the results.