Author's response to reviews

Title: Placental Vascularization Alterations in Hypertensive Disorders Complicating Pregnancy (HDCP) and Small for Gestational Age with HDCP Using Three-Dimensional Power Doppler in a Prospective Case Control Study

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Author's response to reviews: see over
Dear Editor Mr. Jason Pepito,

We would like to thank you for giving us a chance to revise the manuscript, and also thank the reviewers for providing us with constructive suggestions which would help us both in English and in depth to improve the quality of the manuscript. Here we submit the revised manuscript with the ID “1753048901175846”, and the title “Placental Vascularization Alterations in Hypertensive Disorders Complicating Pregnancy (HDCP) and Small for Gestational Age with HDCP Using Three-Dimensional Power Doppler in a Prospective Case Control Study”. The major modifications are in the Discussion of the manuscript, which are according to the reviewers’ suggestions. And the modified or newly added sentences are highlighted. Efforts were also made to correct the mistakes and improve the English of the manuscript.

Yours sincerely,
Ting Yuan

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The point-by-point responses to the two reviewers’ comments are below.
Reviewer 1

Introduction: No comments

Response

Thanks very much.

Methods

1. (1) The proposed classification for Hypertensive disorders is not usual. NHBPEP classification recently reviewed by ACOG should be used. In this case, pre-eclampsia (PE) is recognized as a multi-systemic progressive disorder, and therefore, terms such as minimal or mild preeclampsia should be discouraged.

(2) Additionally, according to ACOG, proteinuria is not a necessary element to characterize PE. This is acknowledged in the latest Williams obstetrics edition (the authors used the former edition as reference). Please comment on that.

Response

(1) Thanks very much for the important suggestion. We now obtain the latest 24th edition Williams Obstetrics and update the concept of preeclampsia syndrome and its classification. The classification of the subgroup of HDCP is now modified in the Method (Page 6, line 109-119), Table 2 and Figures 2-5
according to it. Meanwhile, we have contrasted the two editions of Williams Obstetrics and gone through clinical datasets of all the patients for the final accurate diagnosis, there is now no changes of constitutions and numbers of case group.

(2) We totally accept the opinion about “proteinuria is not a necessary element to characterize PE”, and it has been addressed in the method (Page 6, line 119-121). The reference [12] has been modified.

2. At “Manual mode was set, and the vascular area of the placenta was encircled manually by rotating 30 degrees, six times” it is possible to infer that the authors used the manual mode (VOCAL) to encircle the whole placenta vascularization. Was the whole placenta vascularity assessed? After acquiring the 3D-PD dataset, wasn’t only the spheres the regions of interest? Please clarify this issue.

Response

We firstly apologize for this unclear description and thanks for the reminding.

In consideration of the whole placental blood perfusion varied from region to region, we chose five different sampling sites, including one central, two peripheral at opposite sides and one between the central site and each peripheral site. In other
words, we chose these five spherical sampling volumes in each placenta, the volumes were kept constant. For each spherical sampling volume, the VOCAL mode was activated using a 30 degree rotation angle and the manual setting. The vascular indices were then acquired from five sampling volumes for each placenta, and the average of VI, FI and VFI of the five spherical volumes were used for the final statistical analysis. Therefore, each 3DPD dataset was for the sphere region of interest. We have clarified the description in the method (Page 8, line 163-166 and Page 9, line 180-183).

3. Why use S/D ratio as impedance index? S/D is not commonly assessed, since Pulsatility index (or in some cases the Resistance index) provides a more complete information and it is used as a standard index of flow impedance worldwide.

Response

Thank you very much for the question. First of all, we truly acknowledge the opinion about the value of PI from the reviewer. For the continuous wave Doppler, pulse Doppler, color flow are utilized to measure peak systolic velocity (PSV), end diastolic velocity (EDV), PI, RI and S/D ratio. Among all those parameters, PI is the most important index for normal pregnancy outcome
In the current manuscript, the major subjects we investigated were women with hypertensive disorders complicating pregnancy (HDCP) and HDCP complicating SGA. The reason we used S/D ratio of umbilical artery was based on some results of researches, which provided associations between S/D ratio and placental blood flow and SGA or fetal growth restriction (FGR). Hypertensive disorders are characterized by the higher placental blood flow impedance and intraplacental insufficiency. The sonographic measurement of S/D ratio is an estimate of placental impedance to blood flow, and it can identify placentas with increased vascular impedance [4]. An abnormally high S/D ratio reflects increasing impedance to blood flow within the placenta [5, 6]. So we mainly included S/D ratio and investigated the correlations between S/D ratio with placental vascularization (Table 1-3). Some researchers found that fetuses with elevated S/D ratio showed significantly adverse outcomes, such as lower birth weight, more preterm deliveries, neonatal intensive care unit (NICU) admissions and longer stay in the NICU. For SGA infants, poor perinatal outcome was significantly increased in infants with abnormal S/D ratio. Furthermore, S/D ratio was a significant independent
factor for prediction of poor perinatal outcomes in SGA [4, 7]. It can be inferred that the measurement of S/D ratio of umbilical artery was useful for SGA and its perinatal outcomes. So in table 4, we analyzed the placental vascularizations and S/D ratio of umbilical artery in SGA, in order to confirm these previous results or provide more informations. This question from the reviewer is a good suggestion for us and we will try to assess the value of PI in the related fields. Thank you very much again.

Furthermore, we still analyzed PI according to table 1 to table 4. The value of PI was significantly increased in hypertensive group (P<0.001). There was also significant difference among normotensive group and the subgroups of hypertensive group (P<0.001). There was no significant correlation between the value of PI and the placental 3DPD indices in normotensive group. However, a significant correlation was found between PI and VI in hypertensive population (P=0.003), but the correlation coefficient was low (r=-0.256). The value of PI was also increased in SGA group compared with not-SGA in hypertensive population (P<0.001). Therefore, the results of analysis of PI were similar with S/D ratio. And we are not sure whether we have to add this part to the manuscript or replace of S/D or remain unchanged. Thank you very much.
Results
The greatest strength of the present study was the correlation between placental perfusion and severity of the hypertension disorder.

Response
Thanks a lot. This point is one of the major objectives of the study.

Discussion
The reviewer provided the main adjust about “Limitations of 3DPD quantification” that should be addressed in this paper.

Response
Thanks a lot and we totally acknowledge there has been some limitations of 3DPD quantification although we performed this study using this technique. We have read the related references and addressed the limitations in the Discussion of the manuscript (Page 20 line 403 to Page 21 line 423). We will perform further researches using the alternative methods the reviewer suggested. Thanks very much again. All the references suggested by the reviewer are all cited in this manuscript. And the orders of these references in the current manuscript are given below.
References provided by the reviewer:

1. Nastri CO, Ferriani RA, Raine-Fenning N, Martins WP. Endometrial scratching performed in the non-transfer cycle and outcome of assisted reproduction: a randomized controlled trial. Ultrasound Obstet Gynecol 2013;42:375-82.\[40\] (the order in the revised manuscript)


5. Welsh AW, Hou M, Meriki N, Martins WP. Spatiotemporal image
correlation-derived volumetric Doppler impedance indices from spherical samples of the placenta: intraobserver reliability and correlation with conventional umbilical artery Doppler indices. Ultrasound Obstet Gynecol 2012;40:431-6. ———[44]


Reviewer 2

General comments

This paper is a little bit interesting, and may have new information
for readers of the BMC Pregnancy & Childbirth. However, I think that some major revisions are needed to accept this manuscript for the BMC Pregnancy & Childbirth. My big concern is very insufficient reference papers. Authors should cite more important reference papers.

**Response**

First of all, thank you very much for your interest in the research we did and we’re grateful for the opportunity for the revision.

**Specific comments**

1. (1) How about the reproducibility of 3D power Doppler vascular index measurements? There is a significant variability for placental 3D power Doppler vascular index values among previous studies.

   (2) Authors should show intra-observer agreements with Bland-Altman’s procedure and intra-class correlation coefficients. Authors should address the variability of 3D power Doppler vascular index measurements in more detail.


Response

First of all, we appreciate much for this comment from the reviewer, the researchers who apply 3DPD cannot avoid this problem. We totally accept the modification.

(1) With respect to the reproducibility of placental 3DPD vascular indices, we have read the related references including those the reviewer suggested and addressed this part in the Discussion of the manuscript (Page 18, line 373 to Page 19, line 398).

(2) Just as the reviewer pointed, there is a significant variability for placental 3D power Doppler vascular index values among previous studies. We have been realizing this problem and are aware of avoiding the confounding factors in the procedure of measurements. The only one observer and analyzer for 3DPD imaging acquisitions, measurements and analyses was Ting Yuan, who is a doctoral student and is familiar with the procedures of 3DPD measurements. As what we have addressed in the manuscript, the method was according to the previous study and the machine settings were standard. During the ultrasound examination, the operator was blind to subjects. Each subject was explored for twice consecutively over the same placental area using
3DPD during one ultrasound examination and images were stored in the hard disc, then Ting Yuan analyzed the images by VOCAL for twice per subject. Totally 30 subjects in normal pregnancies were for the intra-observer variability calculation. In the whole process, we have tried our best to reduce the variability.

Here are the details of intra-observer agreements with the Bland-Altman procedure [8] and intra-class correlation coefficients (Table 1 and Figure 1.A-C). The mean percentage difference and 95% limits of intra-observer agreements for VI, FI and VFI were -1.90 (-19.81, 15.92)%, -3.21 (-43.42, 36.91)% and -4.90 (-66.78, 56.83)%, respectively. The difference between the mean difference and zero was not significant for each 3D power Doppler vascularity index. Intra-class correlation coefficients and its 95% confidence interval for VI, FI and VFI were 0.933 (0.87, 0.97), 0.905 (0.81, 0.95) and 0.930 (0.87 to 0.96), respectively (P values were all less than 0.001). Therefore, placental VI and VFI revealed higher reliability than FI in the current study. We're not sure whether we have to add this part to the manuscript. Thank you.
Table 1. Intra-class correlation coefficient and intra-observer agreement for placental vascularity indices

<table>
<thead>
<tr>
<th>Index†</th>
<th>Mean</th>
<th>95% CI</th>
<th>Limits of agreement</th>
<th>ICC</th>
<th>95% CI of ICC</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VI</td>
<td>-1.90</td>
<td>-5.12 to 1.51</td>
<td>-19.81 to 15.92</td>
<td>0.933</td>
<td>0.87 to 0.97</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FI</td>
<td>-3.21</td>
<td>-11.23 to 5.11</td>
<td>-43.42 to 36.91</td>
<td>0.905</td>
<td>0.81 to 0.95</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VFI</td>
<td>-4.90</td>
<td>-16.50 to 7.48</td>
<td>-66.78 to 56.83</td>
<td>0.930</td>
<td>0.87 to 0.96</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

†VI=vascularization index, FI=flow index, VFI=vascularization flow index, CI=confidence interval, ICC=intra-class correlation coefficient
Figure 1 (A-C). Bland-Altman graphs of placental vascular indices acquired by
only one observer measuring twice. The differences were represented as the difference of the parameter/the average of the parameter(%) in the vertical axis. The average of the parameter was presented in the horizontal axis. The upper and lower lines represented the limited of agreement (mean of difference $\pm$ 1.96 standard deviation). The blue line in the middle area represented mean of difference. VI=vascularization index, FI=flow index, VFI=vascularization flow index.

2. References are really insufficient. Authors should cite more important reference papers as below.

   e.g.

   #1 Hata T, et al. Placenta 2011;32:105-115. \[31\] (the order in the revised manuscript)


   #4 Tuuli MG, et al. Placenta 2010;31:192-196. \[39\]

   #5 Noguchi J, et al. Arch Gynecol Obstet 2015;292:75-79. \[28\]


Response

First of all, we apologize for the insufficient references and are grateful for the kindness and patience of the reviewer. All the references suggested by the reviewer and some other related references we have read carefully and cited them in this manuscript. The orders of these references in the current manuscript are given above.

3. Image quality of Figure 1 is poor. There is also no spherical ROI in Figure 1.

Response

Sorry for the poor quality of figure. We provide the new figure of placental 3DPD imaging with ROI. And the figure legend is also modified.

4. We could not know where is a significant difference among groups in Figs. 2-5.

Response

Thanks very much for the suggestions for modifying Figs. 2-5. Based on the results of the Kruskal–Wallis test for the
four groups, the Steel-Dwass test, a post-hoc non-parametric multiple comparisons procedure, is used to test for between-group differences. Figs. 2-5 are modified, this statistical procedure has been added to the Method (Page 10, line 199 and line 208-209) and the results from this procedure are also added to the Result of the manuscript (Page 12, line 242-244). The figure legend is also modified.

5. Quality of written English: Needs some language corrections before being published.

Response

Before the first submitting, we have already made the language corrections, and now the final manuscript has been modified and revised by Scholarly Editing Assistant one more time.

Thanks very much for you and your valuable comments!
References


