Author's response to reviews

Title: Fetal cardiac diameter to biparietal diameter ratio as a predictor of hemoglobin Bart’s disease among fetuses at risk at mid-pregnancy

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Version: 2
Date: 8 March 2014

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March 8, 2014

Dear The editor in-chief BMC Pregnancy and Childbirth

Enclosed please find our revised manuscript entitled “Fetal cardiac diameter to biparietal diameter ratio as a predictor of hemoglobin Bart’s disease among fetuses at risk at mid-pregnancy” which we are submitting to your journal in the hope that it may be accepted for publication. The revised version of the manuscript has been corrected as suggested by the reviewers as indicated in the response section below, giving a point-by-point response to the concerns, and highlighted in the manuscript. However, we have to apologize for some data we could not provide.

All authors of the original manuscript have read and approved the revised version of this manuscript. All authors agree to all changes.

Words count = 1977 (excluding abstract & references)
Abstract word count: 196

Disclosures: no conflicts of interest to disclose.

Thank you very much for all valuable comments by the reviewers and the editors

With best wishes.
Yours sincerely,

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Response to the Reviewers
Reviewer 1

Major Comments, divided by manuscript section:

Introduction
1. At risk pregnancies should be managed by doctors experienced in this field for scanning, counseling and invasive testing if necessary. Leaving the job to a doctor in general practice is not ideal. Would the authors revise the related text?
Response: We agree with the reviewer. However, in our country the number of experts are very limited while the prevalence of Hb Bart disease is very high, often general practitioners have to do it. So we add the following sentence in the “Introduction”: “Though such a screening should be performed by specialist sonographers, general practitioners often have to do, especially in the rural areas with high prevalence of the disease.”

2. ?CB ratio is more easily measured than CT ratio...? Is there any evidence? Is there a marked difference in getting a good subcostal four chamber view and a view to measure CT ratio?
Response: To the best of our knowledge, no solid evidence demonstrates the difference in difficulty of the two methods. This is the assumptions based on our extensive experience on this kind of screening, together with the fact that thoracic diameter is not measured in routine works but the BPD measurement is routinely done in daily ultrasound. So we tone down the phrase to be “It seems to us that the accurate C/T ratio ……. in the “Introduction”

Methods
3. 2-5 MHz is not optimal for cardiac scan. Would authors mention as a limitation in the Discussion?
Response: We add this limitation in the “Discussion”, at the end of the paragraph regarding a limitation of the study....

4. If an ultrasonographer can show a typical 4-chamber view, it is not too difficult to obtain a optimal view to measure CT ratio. Would the authors include this in the discussion?
Response: In our experience, though typical 4-chamber view could be visualized, the thoracic diameter was not optimal in several cases.
5. 7.5-15 seconds is long enough to cause artifact in measurements. Would the authors include this as in the discussion?

Response: This limitation is added in the “Discussion”, at the end of the paragraph regarding a limitation of the study….

6. The authors wrote: ?Based on previous studies of ultrasound sonomarkers...? Is there any reference?

Response: The reference is now added.

Results

7. What were the reasons for poor quality VDS in 11 cases?

Response: Poor quality because of “obscured cardiac border”. This is now added.

8. What additional time was used to obtain STIC, manipulate the volumes and measure C/B ratio?

Response: We have to apologize that we could not provide the additional time because we did not record during the measurement.

9. Figure 2: There was a lot of overlap in C/B ratio between unaffected and affected pregnancies. Would the authors discuss this point?

Response: Though overlap, black line or medians are markedly distant and all cases in the box plot are above median of the normal group. However, the graph has now been replaced by the scatter plots as suggested by the Reviewer 2.

10. Table 1: Would the authors show (a) the number of fetuses at each gestation, (b) cardiac diameter, (c) biparietal diameter of affected and unaffected pregnancies? This will give clues to whether increased CB ratio was due to large heart or small BPD.

Response: Table 1 has now been updated to include number of fetuses at each gestation, cardiac diameter, biparietal diameter as suggested.

Discussion

11. The authors studied cardiac diameter to BPD (C/B ratio), a new one, to predict Hb Bart’s disease. However, there are some limitations of this C/B ratio.

From the data presented, it seems to me that this C/B ratio does not have advantages over the conventional CT ratio +/- MCA PSV. An increase in C/B ratio can be due to small BPD related to head shape rather than cardiomegaly.

Would the authors discuss this issue?

Response: This study does not compare the effectiveness of C/B ratio with other techniques. We aimed to see whether it has clinical potentials or not. It is preliminary. Regarding that C/B ratio may be increased due to small BPD related head shape variations instead of cardiomegaly, this may be theoretical limit of C/B ratio. We now discuss in “Discussion”, paragraph concerning limitations of this study….. However, in this study the mean BPDs in the affected and unaffected
group are comparable, therefore, this could not affect the conclusion but it may be affect in real practice.

12. The authors wrote: "The main objective of this study was to develop a new simple and effective way to screen fetal Hb Bart’s disease...? However STIC is not a simple technique and not commonly available in general setting. Would the authors discuss this issue?

Response: This has been discussed in “Discussion”, paragraph concerning limitations of this study......

13. Conclusion
A sensitive of 91.5% cannot be considered as highly effective.
STIC itself is not simple, and not practical for widely use. Would the authors revise the conclusion?
Response: We tone down the sentence to be “be effective, though not perfect” and delete the last sentence “The measurement is simple, promising and possibly more practical for widely use.”

Minor
1. Discussion
Does STIC offers more accurate measurement of Cardiac dimension than 2D ultrasonography? Why not study 2D ultrasound measurement first before studying STIC? A retrospective analysis of stored data would give a preliminary answer.
Response: Since we can control the cardiac dimension in three-orthogonal plane as described in the “Methods” resulting more proper plane and previous described (ref 5-7). We have to apologize that we did not separately record cardiac diameter during 2D-examination, but the values of C/T ratio with 2D was recorded. So we could not simply analyse C/B ratio with 2D, while cardio-STIC volumes were acquired and were ready for off-line analysis.

Reviewer 2:
In the manuscript “Fetal cardiac diameter to biparietal diameter ratio as a predictor of hemoglobin Bart’s disease among fetuses at risk at mid-pregnancy,” the authors have observed some cardiac alterations in fetuses with Hb Bart’s hydrops fetus.

Some comment/question to authors are as follows:

1) Figure 2 is better illustrated as scatter plot of individual data of C/B ratio. It looks like there is a big gray zone between normal and affected fetuses.
I wonder this is a rather nonspecific observation that may occur in any fetus under severe hypoxia. Can authors prove this? What is the explanation IF this is a specific finding ONLY in Hb Bart’s hydrops fetus.
Response: Figure 2 is now presented as scatter plot of individual data of C/B as suggested. We agree with the reviewer that this is not specific for only HbBart’s
hydrops, it may be used in other fetal disorders of anemia, but among fetuses at risk of Hb Bart’s (the couples had alpha-thalassemia-1 trait in both of them) once cardiomegaly occur, it strongly suggests and definite diagnosis must be made. Please note that all fetuses in this study had a priori risk of 25%, very high, as a common pattern of autosomal recessive disease.

2) Why don’t the authors show the result of a known parameter: C/T ratio?
Response: Since cardiac diameter yielding C/T ratio in our cases based on 2D, we have records of C/T ratio values but no records of cardiac diameter separately. It might not be appropriate to compare the C/B and C/T ratio derived from different techniques. Additionally, this is the first study focusing on C/B ratio to see if it is possible or not for clinical use. In case it suggests effective, this must be tested with 2D ultrasound in the future study.

3) According to Table 1, I wonder how many subjects in each gestation week that were recruited for the analyses. All suspected fetus? Are they all were followed up from 18 to 21 weeks gestation? IF Yes, then the question arises if in these high risk pregnancies with a known diagnosis of fetal hydrops fetalis (by various criteria) that these pregnancies were continued for the purposes of this study?
Response: The number of subjects in each gestational week is now added in Table 1. All fetuses had definite diagnosis by cord blood analysis, obtained by cordocentesis immediately after ultrasound examination. Each case was examined only once.