Author’s response to reviews

Title: Prenatal screening of fetal ventriculoarterial connections: benefits of 4D technique in fetal heart imaging

Authors:

Yu Wang (wangyu_us@hotmail.com)
Miao Fan (Fanmiao_r@sina.com)
Faiza Siddiqui (fas5130@psu.edu)
Meilian Wang (wangmeilian_m@hotmail.com)
Wei Sun (sunwei_us@hotmail.com)
Xue Sun (731056407@qq.com)
Wenjia Lei (leiwj01@163.com)
Ying Zhang (baogoubei@hotmail.com)

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Author’s response to reviews:

Dear Editor,

We would like to submit our revised manuscript entitled “Prenatal screening of fetal ventriculoarterial connections: benefits of 4D technique in fetal heart imaging” to the Journal of Cardiovascular Ultrasound.

We have addressed the issues raised by each reviewer in the revision and made some changes in the manuscript to ensure that the revision conforms to the journal style. We have provided our responses to the reviewer’s comments and marked the changes made in the original manuscript. Each of the co-author has reviewed and approved of the revision. Please let us know if you have any additional questions. Once again, thank you!
Responses to Reviewer’s Comments

Reviewer #1: In this study Wang and al evaluate retrospectively the accuracy of a new protocol navigation in propose a novel protocol of 4D volume analysis in identification prenatal ventriculoarterial connections congenital defects.

General comments: improving prenatal diagnosis of congenital heart disease is of great interest in pediatric cardiology and even more in gynecologists who perform a prenatal screening of fetal congenital malformations. The protocol proposed by the authors in this study is interesting and maybe, could contribute the increase of the diagnosis accuracy of conotruncual anomalies in the fetus mainly before the 29 GW as detection rate of ventriculoarterial connections in late pregnancy was very poor.

Many comments have to be addressed:

Response: We would like to thank the reviewer for the constructive comments and criticisms.

Question: Major comments: the authors stated that this protocol that consist in navigating the reference point in three orthogonal planes in reconstructed 4D volumes should be easier for a non expert sonographer than multiplanar reformatting of the volumes. To support this it could be interesting to ask the sonographers implied in the study to try to reformat the acquired volumes and compare the time, the difficulties and the diagnosis accuracy in comparison to the novel protocol. In the other side, although is not beyond the aim of the study, what was the diagnosis of 2D fetal echocardiography in those patients?

Response: Thanks a lot for raising a very valid question. In fact, we designed the study to evaluate our proposed protocol for volume analysis and test the feasibility of using it in routine screenings. We think the detection rate by this method is high enough for routine screenings.
However, we did not mean to use only 4D volumes in routine screenings, replacing conventional 2D scans. As far as we know, no obstetric centers in the world only use 4D volumes to make a diagnosis. We fully agree with the reviewers’ point that the detection rate of additional method should be included in the current study. So, we re-designed our study, including data to confirm the value of the 4D method. It is well known that 4D modality could provide additional information helping the 2D diagnosis. Also, it is well accepted that 4D volumes of gray-scale and color are both used when conotruncal anomalies are suspected. When re-performed the study, we excluded some cases in which there is only volumes with gray-scale. Only 101 cases were left for screening sonographers performing analysis. Four methods were used and the detection rate was compared. Method 1, 2D method. One screening sonographer performed the 2D image interpretation. Method 2, 4D-1 modality, another screening sonographer made volume analysis using no exact algorithm. The effect of this method was then compared with 4D-2 method, using our protocol in processing the volumes. Method 3, 4D-2 method, another screening sonographer processed 4D volumes of both gray-scale and color. Navigating the reference point was used when processing the gray-scale volume. Method 4, the combined method. The sonographer made diagnosis using both 2D and 4D data. He made volume analysis after reviewing the 2D images. The results confirmed that including 4D data into 2D screenings, using our proposed protocol to analyze volumes, could improve the detection rate for TGA, TOF, and TCA during the second trimester.

Question: Another concern is about the low detection rate of ventriculoarterial connections in late pregnancy, we agree with authors that It's possible that increased acoustic shadows of the fetal ribs reduced the quality of the 4D acquisition.

Some authors proposed acquisition method score to assess the quality of the volume acquired (checklist of cardiac structures visualized) what do you think about, does this influence you detection rate, and did this improve overtime in you experience?

Response: Another very valid question. We reviewed the literatures the reviewer mentioned and found volume acquisition conditional score system was very useful. Avnet et al. [26] demonstrated that trainees could get high quality volumes under the guidance of this condition scoring system. In fact, we believe that using this scoring system would help the screening sonographers to acquire high-quality volumes. Also, it could improve over time. We made some remarks in the Discussion Section, Paragraph 3. It was described as following:
Uittenbogaard et al. [25] found that some key roles (i.e., fetal movement artifact, ROI setting, acquisition angle, fetal apex position, and fetal shadowing artifact) in volume acquisition may affect the volume quality, and thus proposed an acquisition condition scoring system. A study by Avnet et al. [26] demonstrated that trainees could get high quality volumes under the guidance of this condition scoring system. In fact, we have been performing volume acquisition in our obstetric screenings center since 2012. Screening sonographers were trained in a short-term session to familiarize with the acquisition conditions similar to that proposed by Uittenbogaard et al. [25] and no additional time out of the scheduled 30-min slots was needed to perform volume acquisition for fetus in the second trimester, either for normal or CHD fetuses. A training session including these acquisition conditions may obviously improve over time for the incorporation of STIC in routine screenings. In our experience, a clear 4CV on 2D is essential before commencing acquisition, and a clear image without distortion and shadows in Panel B confirms the quality of the volumes, which is reasonable when the acquisition angle is set to (GW+5)°. Longer acquisition times with smaller angles assure maximal information in a 4D volume, while the acquisition time must decrease when fetal movement is frequent. Parameter settings should be made according to actual situation. However, volumes obtained in late pregnancy were not satisfactory as more shadows may present or useful information may not be included due to the large size of the fetus.

The reviewer mentioned about the low detection rate during the late pregnancy. As a retrospective study, we did not evaluate the acquisition quality as some factors (i.e., fetal movement) were not recorded. We referenced a volume quality scoring system proposed by Goncalves et al. Volumes were scored 1 to 5 based on image quality. Some key roles were taken into consideration while scoring the volumes, such as fetal motion artifact, shadowing artifact, and the sharpness of the image. The results showed that the detection rate was correlated to volume quality. The mean score for volume quality during the second trimester was significantly higher than that during the late pregnancy. Low detection during the late pregnancy may be caused by the poor quality of volumes.

Minor comments:

Method section

Question: Page 6, line 39: Subjects: I suggest population study rather than subject
Response: The “subject” has been changed to “Population study” according to the reviewer’s suggestion.

Question: Page 6, line 48 The sentence “All fetuses complicated with ventricular septal defect (VSD).” is not clear, they were included or excluded from the study

Response: We are sorry for not making a clear description in the original manuscript. In fact, all TOF, TCA fetuses of course had a VSD. We have made corrections in the revised manuscript. It is described as “All TGA fetuses included in the study complicated with VSD”.

Results:

Question: In the Table 2, the success rate of TOF was 31/37 but in the text you state that 6 was diagnosed as VSD and 2 as DORV? What was the misdiagnosis of the 45% of normal fetuses not detected by 4D modality?

Response: We realize that it was not mentioned clearly. When re-performing the study, we checked all the data carefully. For the normal fetuses, if the volume quality is poor, the origin of the great arteries could not be visualized sometimes (i.e. affected by shadows). It was recorded as “Unclear” or “Uncertain” in this condition.

Discussion section:

Question: Page 13 line 34: … we have been performing volume acquisition in cardiac screenings in our center since 2012. Why did you review the fetal echocardiogram since 2010

Response: We used volumes obtained from our echocardiography center, not acquired by screening sonographers. In the Discussion section, Paragraph 3, we mentioned “We have used 4D STIC in fetal echocardiography since 2007 and the 4D technique has shown its value in
helping diagnosis.” and mentioned “In fact, we have been performing volume acquisition in our obstetric screenings center since 2012.”.

Again, thanks a lot for the valuable points raised by the reviewer. We think we learned a great deal from the reviewer’s point, which helped us in improving the current manuscript and would also help in developing better study design in future.

Reviewer #2:
Authors have attempted to describe a method of fetal cardiac assessment during routine ultrasound examination. It is certainly congratulable but I have reservations which I have stated below.

Response: We would like to thank the reviewer for reviewing our manuscript and for the constructive comments and criticisms.

Question: In Background:
Recent published data has shown that the incidence of CHD is higher than authors mentioned 0.6% (0.8-10%) per life birth.

Response: We searched recently published literatures and made corrections about the incidence rate of CHD in the revised manuscript. It was described in background as following: Congenital heart disease (CHD), accounting for about 2.4 to 13.7 per 1000 live births [1], is the most common congenital malformation leading to perinatal morbidity and mortality and is considered the leading cause of death in newborn with congenital anomalies [2,3].
Question: In Methods:
Authors should clarify what they meant by "All fetuses complicated with ventricular septal defect (VSD)" when talking about tetralogy of Fallot and common arterial trunk. Is it not expected to have VSD in these conditions? Double outlet tight ventricle has a very broad spectrum. Hence, clarification is needed which forms of DORV were included in this study.

Response: We apologize for not making clear descriptions in the original manuscript. We stated that “All TGA fetuses included in the study complicated with VSD” in the revised manuscript.

For DORV, it is a complex CHD and have many classifications according to the spatial relationship of the great arteries or the position of VSD to aortic/pulmonary valve. For the spatial relationship, the ascending aorta and the pulmonary artery may lie side by side, or the aorta was on the right-anterior or left-anterior to the pulmonary artery, or the two great arteries were orthogonal to each other, similar to the situation of TOF. For the first three situations, the two great arteries were in parallel and were easy to distinguish from TOF. For the last situation, it was necessary to discern the subaortic conus. We stated the classifications of DORV in the revised manuscript. It was described in Methods, Paragraph 1, as following: For DORV fetuses, parallel great arteries (aorta on the left/left-anterior/right-anterior to the pulmonary artery) were found in 18 cases, while orthogonal great arteries were demonstrated in the other 4 cases.

Question: Maternal age is mentioned, what is the relevance for this study?

Response: It has been deleted in the revised manuscript.

In Data sheet analysis and Discussion:
Question: There is some confusion over the description of anatomy of cardiac lesions in this paragraph: "Morphologically, the difference of DORV from TOF lies in that both a subaortic and subpulmonic muscular conus could be identified in DORV. As the study aimed to propose a 4D modality to rule out fetal CTA anomalies by screening sonographers, the definition of TOF in the study was a large malaligned VSD, overriding of aorta over the VSD (<75%), and stenosis
pulmonary artery. DORV was defined as one complete arterial trunk and at least 75% of the other arterial trunk emerge from the right ventricle. When only one great artery was identified arising from the ventricles, the fetus was suspected as TCA, whether the pulmonary artery arising from the aorta could be visualized or not."

There is not entirely correct definition either for DORV or CTA. If the authors aim for "simplified" approach that it is all meaningless if sonographers have been asked to distinguish normal from abnormal only. Otherwise there should be precise definition of abnormalities used. It is not good enough to call common arterial trunk if no effort to delineate pulmonary artery branches has been shown.

Response: We appreciate the reviewer for raising a very valid question. We agree with the reviewer’s point that “a precise definition” should be used in the study. For DORV, it is really a complex malformation with many types. Distinguishing DORV from TOF remains challenging for sonographers, even experienced echocardiographers. Discerning the subaortic conus is essential to make the diagnosis of DORV. For TCA, precise diagnosis needs clear determination of origination of the pulmonary artery. However, volumes with gray-scale could not help much in displaying this information. This is why we included volumes with color in our protocol (4D-2 modality), when we re-performed the study.

Questions: Results: Authors have described high detection rate using 4D data sheet analysis at second trimester 18-28 weeks and much poorer results in third trimester. There is no clear explanation why as this method should be universal for both gestations.

Response: This is a very valid question. In the revised manuscript, we included a scoring system to quantitatively evaluate volume quality. The results showed that the detection rate was correlated to volume quality. The mean score for volume quality during the second trimester was significantly higher than that during the late pregnancy. Low detection during the late pregnancy may be caused by the poor quality of volumes.

Question: Most important part, comparison with conventional 2D imaging is missing. Authors refer to previously published papers on low detection rate of certain forms of CHD but there is no real prove that STIC method is superior to conventional 2D sweep in this study. Authors mention that STIC is novel method but actually it has been around more than a decade. It has
been proved than additional tool to 2D but not a replacement due to many reasons including fetal movement and poor quality of acquired data sheets which can preclude from remote analysis of the data.

Response: Thanks a lot for the reviewer’s point. We re-designed and re-performed the study to present the value of 4D modality. We want to clarify the point that we never think that 4D could replace 2D in routine screenings. We have published several articles about the value of 4D in the diagnosis of fetal CHDs. Our point is that 4D could provide additional information which could facilitate prenatal diagnosis. We fully agree with the reviewer’s point that 2D data should be included in the study. For the new design, we carried out four methods and made comparisons. Method 1, 2D method. One screening sonographer performed the 2D image interpretation. Method 2, 4D-1 modality, another screening sonographer made volume analysis using no exact algorithm. The effect of this method was then compared with 4D-2 method, using our protocol in processing the volumes. Method 3, 4D-2 method, another screening sonographer processed 4D volumes of both gray-scale and color. Navigating the reference point was used when processing the gray-scale volume. Method 4, the combined method. The sonographer made diagnosis using both 2D and 4D data. Volume analysis was performed after reviewing the 2D images.

In fact, the most significant advantage of 4D over 2D is that 4D contains more information to be used in subsequent diagnosis. For example, when navigating the reference point, the great arteries were gradually revealed with its characteristics (i.e., the bifurcation of the pulmonary artery). For conventional 2D imaging, it is impossible for post-processing and only the original sonographic cuts are stored. If the characteristics of the great arteries are not well recorded, the screening sonographers are unable to make correct diagnosis. It was also one of the reasons for the higher detection rate of 4D-2 modality in evaluating fetal TGA, when compared with the 2D method.

We tried to evaluate if it is useful to include the 4D into routine 2D cardiac screenings. It is the combined method (method 4) in the current study. After reviewing 2D images, the screening sonographers may have a preliminary judgement, thus could process the volumes more precisely. At the same time after reviewing the 4D images, the sonographers can reevaluate the 2D images to determine whether there are some missed details previously. The results showed that the combined method could effectively improve the diagnostic accuracy in TGA, TOF, and TCA during the second trimester, when compared with using the 2D modality alone, which suggested the value of potential incorporation of the 4D STIC technique into routine screenings.
Question: Authors have overlooked published article by Zidere et al. "Three-dimensional fetal echocardiography for prediction of postnatal surgical approach in double outlet right ventricle: a pilot study" which gives a relevant inside of anatomy and difficulties of diagnosis of DORV.

Input of paediatric cardiologist is much needed as well as English language revision.

Response: We read the article recommended by the reviewer. It is an in-depth study in which more information could be obtained from 4D volumes to make not only a preliminary diagnosis, but provide a detailed assessment of intra-cardiac anatomy. A pediatric cardiologist apparently could get more information from the 4D volumes than a screening sonographer. It is difficult for a screening sonographer to understand this complex cardiac malformation in the way a pediatric cardiologist does. The protocol proposed by us may prove to be extremely useful for this diagnosis. However, when re-performing the study, we seek help from a pediatric cardiologist and learned more about cardiac anatomy and embryonic development of DORV, TOF, TGA, and TCA. The better understanding of the anomaly undoubtedly could help the diagnosis, whether 2D or 4D.

In the Discussion Section, Paragraph 8, we made detailed remarks about DORV and added the reference (Published by Zidere et al) the reviewer mentioned.

We also asked a professional proof reading company to make English language revision.

At last, we want to convey our thanks to the reviewers. The advice is professional and would help us in designing better studies in future.