Reviewer's report

Title: Reference values for fetal tissue velocity imaging and a new approach to evaluate fetal myocardial function

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Reviewer: Helena M Gardiner

Reviewer's report:

Major compulsory revisions
1 The authors use unusual descriptive terms and these should be altered or their use explained earlier in the manuscript as the paper is difficult to understand in its present form.

I suggest using septum, left ventricular free wall instead of inferoseptum and anterolateral walls

move the paragraph commencing “Atrial contraction begins....” from the Methods section (as it is not a method) to the introduction section as this will clarify why the authors have used the terms pre- and post ejection phases instead of IVRT and IVCT. The latter also requires clarification in the abstract.

2 The introduction infers that little has been published on tissue Doppler and speckle tracking in the fetal heart. The authors should move the references to these techniques into the introduction and précis their use to explain why the method they are proposing may be an improvement to the existing literature.

3 I do not believe that speckle tracking enables such low frame rates (<80 frames/s) – this is not referenced and is not correct. Frame rates of >160 frames/s were obtained in published studies (Matsui et al. Ultrasound Obstet Gynecol 2011; 37: 150–157)

4 Estimation of gestational age is very late. Most studies use the first trimester estimate. Why is this not used here? By the time the fetus is about 16-18 weeks, the error in the measurement of gestational age is approaching +/- 2 weeks and is not suitable data to generate normative curves.

5 The number of fetuses enrolled is just adequate but given concerns about accuracy of dating, caution should be exercised

6 The description of performance of the echocardiogram as well as the morphology is unusual. The terminology suggests it is written by an adult cardiologist. The authors should ask a fetal cardiologist to assist in the preparation of the manuscript as it is odd to state the transducer was placed “perpendicular to the apex” when it is on the maternal abdomen. It is more important to state that the four chamber view should include a whole rib to ensure its quality.

7 The median frame rates are given without ranges – these should be included

8 The methods state the ROI was placed “ABOVE the AV plane”. This is not the
case in Figure 2 where the ROI lies in the Ventricular walls and septum – which would be considered BELOW the plane if one looks at the heart morphologically (as is the paediatric and fetal convention unlike that of adult cardiology practice)

9 The differences – both in terminology and interpretation - between electrical and mechanical timing intervals should be stated in the introduction to clarify the methods and interpretation of this study.

10 Statistical methods:
I do not think it is conventional to use the median if the results are not showing statistical significance. The authors should assess normality of the data and use means and SD or 95% CI and medians (ranges) if not.

The authors state the multiple regression analysis showed a combination of HR and gestational age enhanced the correlations. These 2 variables are very co-dependent - has this been accounted for in the model and analysis? The gestational changes shown in figure 4 are presented as linear. Are the authors sure of this? Most variables show a parabolic path – particularly reflecting the wider spread of data in later gestation. The points seem to suggest this may be the case.

I advise a statistical review of the data.

11 The comparison of the CSD at different gestational ages (Figure 3) should include the site the measurements were made.

12 I do not think the presentation of the data is satisfactory in Table 2 (see point 10)

13. Explain why the velocity may be biphasic in the pre and post-ejection periods

14 “higher maturation rate” is not strictly accurate - do the authors mean rate of change with gestational age?

15 “This corresponded to...” – the e'/a’ ratio is a calculation and not a measured observation. Therefore an increase in e will result in an increase in e'/a’

16 I cannot understand why the authors have combined the measurements of the septum and left free wall in the fetus. While adult cardiology assumes the septum is part of the LV functionally, this is unlikely to be true in the fetus as right heart dominance alters the motion and function of the ventricular septum. The left and right free walls and septum should be considered separately

17 The authors introduce the concept of lactate into the discussion. This is largely irrelevant in this study. The authors have not presented data here to substantiate their claims and the aims of the study are simply to describe normative data. They should remove the latter part of the discussion as well as reference to the post ejection phase and lactate sensitivity. They have described findings in normal healthy pregnancies and I cannot see that lactate enters the discussion.

18 The authors do not discuss how their data compare with previous normative ranges such as those by Chan LY, Fok WY, Wong JT, Yu CM, Leung TN, Lau TK. Reference charts of

19 The increase in values over gestation differs between ventricles and septum in this study. They compare this with previous reports that did not show this between—ventricle difference using pulsed wave Doppler and a statistical method using methods suitable for non-normally distributed data and accounting for outliers—the median absolute relative differences (MARD) or median absolute differences (MAD). I suggest the authors take statistical advice on their data specifically as we described the following in reference 15 that is cited:

“Results (not reproduced here) showed that changes of a number of fetal cardiac parameters with gestational age were different in the second and third trimester. The data also contained a number of outliers. Therefore, piecewise linear robust regressions were fitted with the slope changing after 30 weeks of gestation (MM robust regression procedure {SPLUS Robust library}). We felt that due to a significant proportion of outliers robustness of results was more important than efficiency, and used 75% efficiency setting. These regressions provided better fit than standard linear or quadratic regressions. The 95% reference ranges can be found as predicted values plus–minus 1.96 standard errors and regression coefficients and standard errors are provided in Table 1.”

20 I cannot interpret the comments that increased HR reduces the ability to measure the e' wave accurately: is this because of summation? This requires further explanation.

21 What does “amplitudes of the myocardial velocity curve” mean?

22 Maturational changes in the Tei Index: the current method cannot detect an difference in this index that has been reported by the group in Sydney who demonstrated age-related change in the Tei index.


This information should be incorporated into the paper and the limitations of the proposed method acknowledged accordingly.

Minor Comments:
1 there are some spelling errors – “ejected into the SYSTEMIC circulation” not systematic
2 the difficulties in understanding some phrases are outline in the major section as they impair understanding of the manuscript and are important

Level of interest: An article whose findings are important to those with closely related research interests

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

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**
I declare I have no competing interests