Speckle tracking analysis of the fetal heart in uncomplicated pregnancies and complicated pregnancies: a pilot study using FetalHQ

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Abstract

Background: Strain imaging by speckle tracking echocardiography (STE) is a novel and promising ultrasound technique for a detailed evaluation of fetal cardiac function. It may contribute to the selection of high-risk patients with pregnancy complications affecting fetal hemodynamics and inducing fetal cardiac remodeling, such as maternal diabetes mellitus (DM) and placental pathologies with ensuing fetal growth restriction (FGR). STE is already used in adults and pediatrics, but is still under evaluation in fetal medicine. The aim of this pilot study is to substantiate the feasibility of FetalHQ, a newly developed speckle tracking software, and to determine normal values of fetal strain throughout pregnancy. Also, potential effects of maternal DM and FGR on fetal strain will be studied.
Methods: Fetal STE was performed in uncomplicated pregnancies and pregnancies complicated by maternal DM or FGR. Dynamic cine loop clips of the fetal heart were collected during regular planned ultrasound examinations between 18-40 weeks of gestation. Global longitudinal strain values of the left ventricle (LV) and right ventricle (RV) were measured at each examination using offline software FetalHQ. Intra- and interobserver variability were estimated using intraclass correlation coefficient and Bland-Altman analysis. Linear mixed effect models were used to determine the development of fetal strain throughout gestation and potential effects of maternal DM and FGR on fetal strain. Mean strain values within 18-24 weeks, 25-31 weeks and 32-40 weeks of gestation were compared between study groups using independent-samples T-test and Mann-Whitney U test.
Results: A total of 69 participants (101 clips) with uncomplicated pregnancies, 20 participants (46 clips) with pregnancies complicated by maternal DM and 18 participants (52 clips) with pregnancies complicated by FGR were included. Comparing examinations between observers showed moderate agreement for the LV and poor agreement for the RV, with significant differences in measurements between observers for both ventricles. Comparing repeated measurements of one observer showed good agreement for the LV and moderate agreement for the RV, with significant differences between repeated measurements of the RV only. Analysis of good quality clips only improved agreement between and within observers. Fetal strain in uncomplicated pregnancies showed a significant decrease with advancing pregnancy in both ventricles. No significant differences were observed between fetal strain in uncomplicated pregnancies and fetal strain in pregnancies complicated by maternal DM or FGR.
Conclusion: This pilot study showed that the feasibility of speckle tracking analysis using FetalHQ is currently limited. Reliability and reproducibility of strain analysis should be improved by gaining experience with the analysis and standardizing the operative protocol, such as image acquisitions and angle of insonation, before implementation as a tool to evaluate fetal cardiac function.

Introduction

Speckle tracking echocardiography (STE) is a novel and promising ultrasound technique for comprehensive assessment of the fetal heart. It offers a more detailed evaluation of fetal cardiac function in addition to conventional echocardiography.[1] STE quantifies myocardial contractility directly by measuring deformation of the myocardium based on tracing speckles, which are natural acoustic reflections of the ultrasound beam existing in an unique pattern over the myocardium.[2,3] These patterns enable tracking of the myocardial shape during a heart cycle and measure the magnitude of deformation, expressed as percentage (strain) or velocity (strain rate) of change. Moreover, STE is angle-independent and enables evaluation of cardiac function in three dimensions.[4,5] These unique

characteristics of STE enable accurate assessment of the fetal heart's function and early detection of subclinical cardiac dysfunction.

Several pregnancy complications are known to affect fetal cardiac function by challenging the heart hemodynamically, resulting in cardiac remodeling and a period of subclinical cardiac dysfunction.[6] Pregnancy complications known to challenge the fetal heart are maternal diabetes mellitus (DM) and placental pathologies with ensuing fetal growth restriction (FGR). In case of maternal DM, the hyperglycemic intrauterine environment is associated with both teratogenic effects on the fetal heart and cardiac remodeling.[7,8] Fetal hyperinsulinism and insulin-like growth factors cause the cardiomyocytes to grow by hypertrophy as well as by hyperplasia, resulting in myocardial hypertrophy and cardiomegaly.[9] This remodeling pattern leads to stiffness of the myocardium, which may affect deformation of the fetal heart and induce cardiac dysfunction. Both pregnancies complicated by pregestational DM1 or DM2 and pregnancies with gestational DM were found to induce cardiac remodeling.[9,10] Moreover, in pregnancies complicated by FGR, placental insufficiency is associated with chronic pressure and volume overload of the ventricles, to which the fetal heart responds by adaptive cardiac remodeling.[11] Time and duration of exposure to pathologic conditions during pregnancy are key factors to the type of cardiac remodeling. Accordingly, different patterns of cardiac remodeling are found depending on timing of diagnosis of FGR.[7,12] Late-onset FGR results in a more globular or elongated shape of the ventricles and subtle cardiac dysfunction, whereas early-onset FGR results in a hypertrophic myocardium and cardiomegaly to preserve sufficient contractility and a notable decrease in longitudinal function. Because of the risk of subclinical cardiac dysfunction due to cardiac remodeling, pregnancies complicated by maternal DM or FGR may benefit from a comprehensive cardiac assessment by STE to select high-risk pregnancies and improve monitoring and clinical management.

STE is well-validated and widely used in adults and clinical experience is increasing in pediatric cardiology.[13–15] In fetal medicine, this technique is still under evaluation and requires additional validation in the fetal heart. In a systematic review, studies on the normal development of fetal strain throughout pregnancy showed contradictory results and considerable heterogeneity.[16] In order to implement fetal STE in clinical practice, reference values of fetal strain throughout gestation are mandated. FetalHQ is a newly developed offline ultrasound software for speckle tracking that is derived from adult and pediatric echocardiographic principles. Therefore, the aim is to perform a pilot study on the feasibility of FetalHQ for the functional assessment of the fetal heart and to determine normal values of strain in healthy fetuses throughout pregnancy. Furthermore, the effect of pregnancy complications maternal DM and FGR on fetal strain will be studied.

Methods

Study population

A prospective longitudinal observational study was performed on the fetal heart in uncomplicated pregnancies, pregnancies complicated by maternal DM and pregnancies complicated by FGR. Ultrasound images were obtained during regular planned ultrasound examinations between 18-40 weeks of gestation from January to December 2021 at the obstetric ultrasound outpatient clinic in the Wilhemina Children's Hospital in Utrecht, the Netherlands. Uncomplicated pregnancies were defined as non-anomalous singleton pregnancies of mothers aged >18 years, with normal fetal cardiac morphology and sinus rhythm. Pregnancies with congenital malformations, chromosomal abnormalities, cardiac failure or fetal arrhythmia, maternal hypertensive disorders, maternal DM, FGR or other conditions with possible effects on fetal hemodynamics, such as endocrinological disorders or chronic maternal illness, were excluded from this group. Maternal DM was defined as pregestational DM1 or DM2 or gestational glucose intolerance existing in both current and previous pregnancies diagnosed following current international guidelines. Pregnancies with gestational glucose intolerance without a history of gestational diabetes were excluded. Other exclusion criteria were similar as described above. FGR was defined as abdominal circumference or estimated fetal weight below the

10th centile. Exclusion criteria were similar as described above. All participants provided a written informed consent.

Fetal echocardiography and strain analysis

Ultrasound images were collected by experienced sonographers using a GE Voluson E10 ultrasound system equipped with a 5.0-MHz high-frequency transducer. A 2D grayscale dynamic cine loop clip of a four-chamber view of the fetal heart was obtained. Image acquisitions such as gain, depth and sector width were optimized. Clips were stored in Digital Imaging and Communications in Medicine format and analyzed at a later time point. The clips were rated based on quality (good/moderate/poor), of which an example is shown in *figure 1*. Within each dynamic clip, a single cardiac cycle was selected in advance by one observer, in which all measurements were performed, in order to standardize examinations. The clips were analyzed using offline software FetalHQ (GE Healthcare). The length and width of the fetal heart were measured in end-diastole to determine the global size and shape of the fetal heart. A single cardiac cycle was selected by anatomical M-mode tracing of the right atrioventricular valve motion. End-diastole and end-systole were defined by complete closure of the atrioventricular valve. Both left ventricle (LV) and right ventricle (RV) were analyzed from the same clip and during the same examination. Three points were selected to mark the endocardial border of each ventricle separately: 1) septal wall insertion of the valve, 2) free wall insertion of the valve and 3) apex. The software automatically displays a proposed trace line along the endocardial border and could be modified by adjusting anchor points or individual dots as needed to optimize alignment with the endocardium. After confirmation of the tracing, the software generates a graphical display representing the movement between end-diastole and end-systole and the corresponding global longitudinal strain values. This pilot study was limited to measurements of global longitudinal strain. Strain measurements in the circumferential and radial dimensions and segmental strain fall out of the scope of this pilot study. It must be underlined that data are presented as negative strain values, since the myocardium shortens in the longitudinal dimension during systole.[4] When deformation of the ventricles becomes less, this translates into less negative values or an positive absolute difference. However, in terms of strain it implies a decrease and is reported as such.

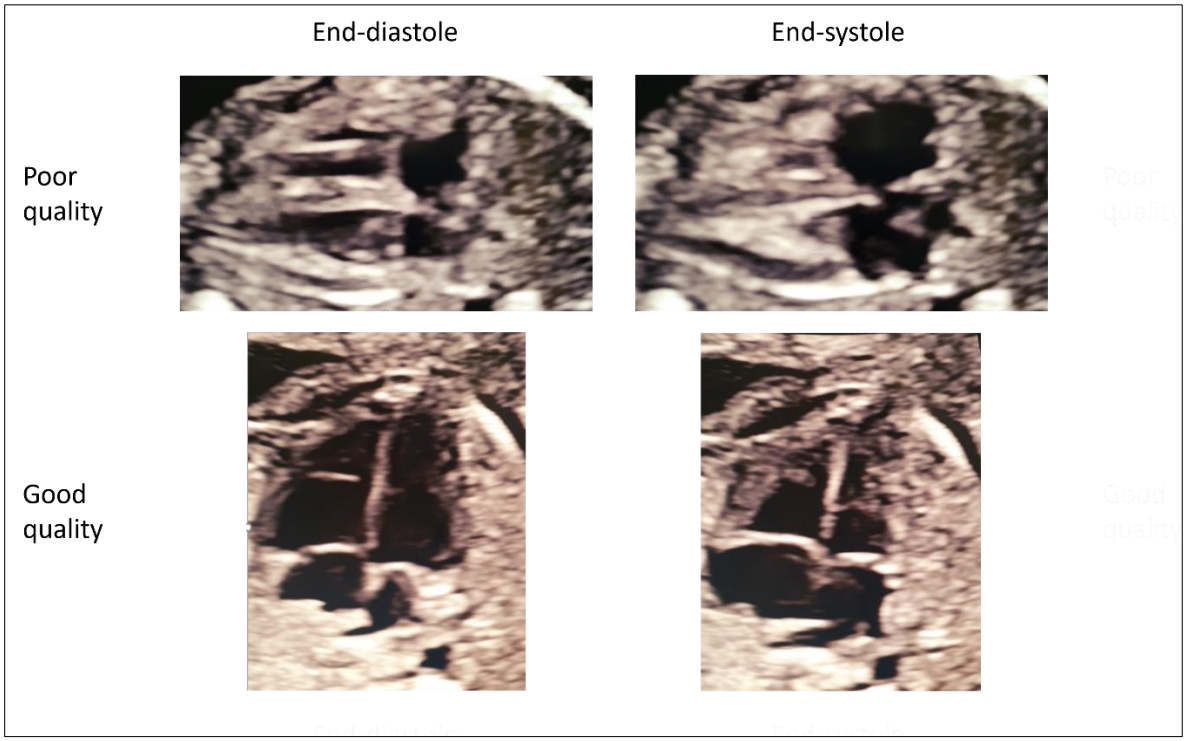

Figure 1: Quality of cine loop clips. *Images showing an example of poor quality clips (top) in end-diastole and end-systole and good quality clips (bottom) in end-diastole and end-systole.*

Feasibility and reproducibility

To determine the feasibility of FetalHQ and the reproducibility of measurements using FetalHQ, inter- and intraobserver variability were measured. All clips were analyzed by one observer and intraobserver variability was assessed by analyzing a subset of clips a second time at an interval of ≥1 week. A randomly selected subset of clips was analyzed by a second observer to assess interobserver variability. The observers were blinded to each's others measurements. Inter- and intraobserver variability were measured by calculating intraclass correlation coefficient (ICC) and Bland-Altman analysis.

Statistical analysis

Statistical analysis was performed using IBM® SPSS® Statistics software version 26. For all analyses, normality of the data distribution was determined using a Shapiro-Wilk test. To compare continuous variables of study characteristics between study groups, a one-way ANOVA with post-hoc Tukey HSD test was used for normally distributed data and a Kruskal Wallis test with Bonferroni correction was used for non-normally distributed data. To determine the inter- and intraobserver variability, the ICC was measured using a two-way mixed model, with a randomly selected set of clips analyzed by fixed observers, and absolute agreement. ICC values were defined as poor (<0.50), moderate (0.50-0.75), good (0.75-0.90) or excellent (>0.90) agreement according to a guideline published in 2016.[17] A Bland-Altman analysis was used to evaluate limits of agreement.[18] The mean difference, standard deviation and limits of agreement (*mean difference ± 1,96 x SD*) were calculated. A one-sample t-test was used to evaluate if mean differences between or within observers were statistically significant. Linear regression analysis was used to estimate potential systematic bias of measurements between or within observers. The development of fetal strain throughout pregnancy was analyzed using a linear mixed effects model for repeated measurements, which takes the longitudinal follow-up of a subgroup of participants and potential missing data into account. The model was estimated with the restricted maximum likelihood method. Using this model, linearity of the relationship between gestational age and fetal strain was assumed. The null hypothesis that the slope of the average line equals zero was tested, meaning no significant change of fetal strain over time. The upper and lower 95% prediction limits were represented. To compare fetal strain values in uncomplicated pregnancies to fetal strain values in pregnancies complicated by maternal DM or FGR, the slopes of the average lines of each study group were compared using a linear mixed effects model. Also, mean strain values were calculated for measurements within three different gestational age intervals: 18-24 weeks, 25-31 weeks and 32-40 weeks of gestation. Within these intervals, mean fetal strain in uncomplicated pregnancies was compared to mean strain in pregnancies complicated by maternal DM or FGR using an independent-samples T-test for normally distributed data and a Mann-Whitney U test for non-normally distributed data. A p-value of <0,05 was considered statistically significant in all analyses.

Results

Study characteristics

A flowchart showing the inclusion process of participants is shown in *figure 2*. A total of 110 participants were recruited in this study. Two participants were excluded because of missing data and one participant was excluded due to the development of gestational DM after inclusion, which was defined as an exclusion criterium. One hundred and seven participants met the inclusion criteria and were included for strain analysis, of which 69 participants with uncomplicated pregnancies, 20 participants with pregnancies complicated by maternal DM and 18 participants with pregnancies complicated by FGR. A total of 231 cine loop clips were obtained from these pregnancies, of which 32 clips were excluded because of very poor quality or an interval of <2 weeks between consecutive clips obtained from the same participant. A residual of 199 clips (101 uncomplicated, 46 maternal DM, 52 FGR) were analyzed and data was extracted for analysis.

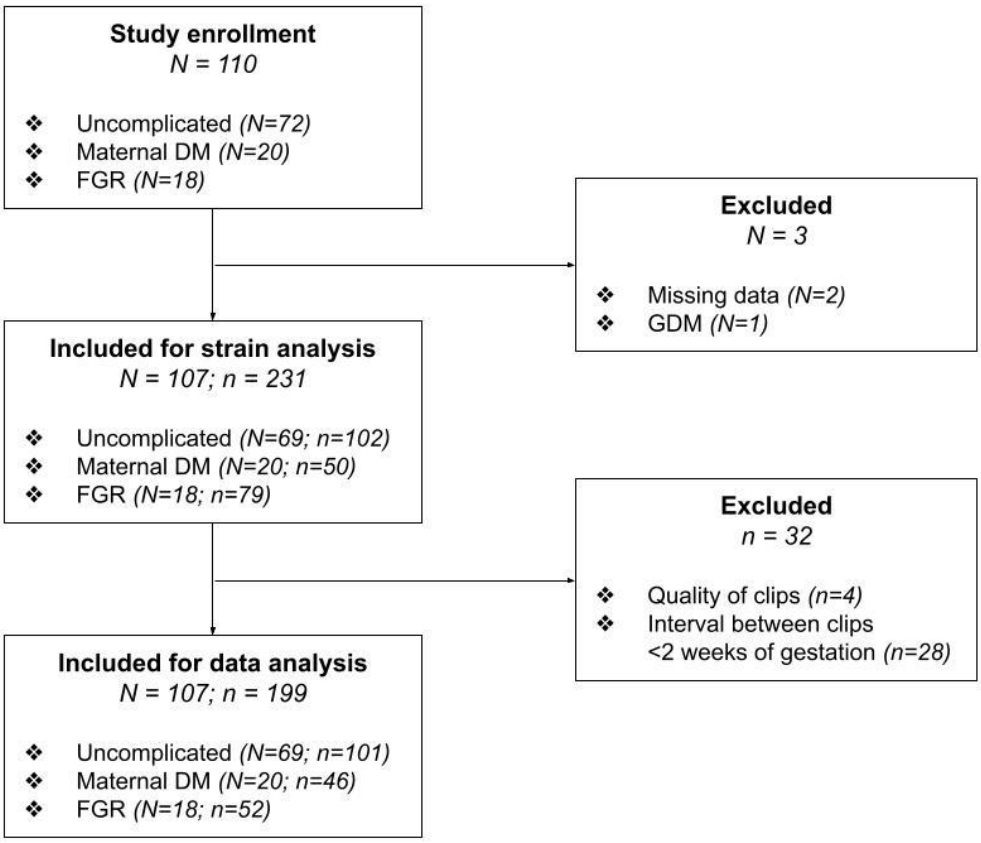

Figure 2: Flowchart. *The diagram shows the flow of enrollment of participants to inclusion of cine loop clips for data analysis. N=number of participants, n=number of cine loop clips. (G)DM=(gestational) diabetes mellitus. FGR=fetal growth restriction.*

Demographics of participants and ultrasound characteristics are shown in *table 1*. Several differences in continuous variables were observed between the study groups. The age of participants with pregnancies complicated by FGR was significantly lower than the age of participants with uncomplicated pregnancies (p=0,006) or pregnancies complicated by maternal DM (p=0,002). Median body mass index (BMI) of participants with pregnancies complicated by maternal DM was significantly higher than BMI of participants with uncomplicated pregnancies (p=0,0002) and, although not significant, almost reached statistical difference compared to participants with pregnancies complicated by FGR (p=0,089). Median gravidity and parity of participants with pregnancies complicated by FGR were significantly lower than in participants with uncomplicated pregnancies (p=0,001 and p=0,006, respectively) and pregnancies complicated by maternal DM (p=0,002 and p=0,002, respectively).

Longitudinal follow-up of participants was performed in 18 participants with uncomplicated pregnancies, 12 participants with pregnancies complicated by maternal DM and 13 participants with pregnancies complicated by FGR. Median frame rate and fetal heart rate of the obtained cine loop clips did not differ statistically between the study groups.

Table 1: Study characteristics.

Maternal characteristics	Uncomplicated (N=69)	Maternal DM (N=20)	FGR (N=18)	All (N=107)
Maternal age *(years)*	33 (20-43)[c]	34 (28-43)[c]	29 (21-40)[ab]	32 (20-43)
Body mass index *(kg/m²)*	22.7 (17.3-37.5)[b]	29.3 (19.9-41.5)[a]	24.0 (18.9-42.3)	23.5 (17.3-42.3)
Gravida *(n)*	3 (1-8)[c]	3 (1-5)[c]	1 (1-5)[ab]	3 (1-8)
Para *(n)*	1 (0-6)[c]	1 (0-3)[c]	0 (0-3)[ab]	1 (0-6)
Primipara *(%)*	24.6	10	66.7	29
>1 ultrasound/participant	18/69	12/20	13/18	43/107
Ultrasound characteristics	*(n=101)*	*(n=46)*	*(n=52)*	*(n=199)*
Frame rate (frames/second)	64 (28-99)	61 (20-115)	64 (23-96)	64 (20-115)
Fetal heart rate (bpm)	144 (125-167)	143 (128-185)	145 (123-168)	144 (123-185)

Continuous data are presented as median (range). [a]=significantly different from 'uncomplicated'. [b]=significantly different from 'maternal DM'. [c]=significantly different from 'FGR'. P<0,05 was considered statistically significant. DM=diabetes mellitus. FGR=fetal growth restriction. Bpm=beats per minute. N=number of participants. n=number of cine loop clips.

Feasibility and reproducibility

To substantiate the feasibility of speckle tracking analysis using FetalHQ, the variability in fetal strain measurements between and within observers was quantified. Results of ICC calculations and Bland-Altman analysis are shown in *table 2* and *figure 3.* A randomly selected subset of 53 clips was analyzed by two different observers to calculate the interobserver variability, of which 29 clips were rated as good quality and analyzed separately as well. For LV strain, moderate agreement was reached between observers according to the ICC. Bland-Altman analysis showed that differences between observers significantly differed from zero, but no systematic bias was identified. Similar results were found in the analysis of good quality clips only. For RV strain, poor agreement was reached between observers according to the ICC. Bland-Altman analysis showed that differences between observers significantly differed from zero, and significant systematic bias was identified. The results slightly improved in the analysis of good quality clips only, but still reached poor agreement between observers.

Table 2: Inter- and intraobserver variability.

	Number of clips (n)	ICC (95% confidence interval)	Mean difference	Standard deviation	Difference between observers (p)	95% limits of agreement	Systematic bias (p)
Interobserver							
LV strain	53	0,685 (0,369 – 0,832)	-3,23	5,71	0,0001	-14,42; 7,97	0,374
RV strain	53	0,112 (-0,255 – 0,411)	-7,31	9,58	<0,0001	-26,09; 11,47	0,015
LV strain	29*	0,634 (0,136 – 0,837)	-3,79	5,49	0,001	-14,55; 6,97	0,263
RV strain	29*	0,401 (-0,140 – 0,702)	-4,69	7,76	0,003	-19,90; 10,52	0,004
Intraobserver							
LV strain	22	0,809 (0,547 – 0,920)	-1,29	3,50	0,097	-8,15; 5,57	0,108
RV strain	22	0,584 (0,061 – 0,822)	-1,92	4,21	0,044	-10,17; 6,33	0,045
LV strain	20*	0,831 (0,583 – 0,933)	-1,00	3,54	0,222	-7,94; 5,94	0,114
RV strain	20*	0,654 (0,166 – 0,860)	-1,43	4,07	0,133	-9,41; 6,55	0,063

**=cine loop clips rated as good quality only. LV=left ventricle. RV=right ventricle. ICC=intraclass correlation coefficient. P<0,05 was considered statistically significant.*

A randomly selected subset of 22 clips was analyzed twice by one observer to calculate the intraobserver variability, of which 20 clips were rated as good quality and analyzed separately as well. For LV strain, good agreement was reached between the measurements according to the ICC. Bland-Altman analysis showed that differences between repeated measurements by one observer were close

to significance (p=0,097), and no systematic bias was identified. These results improved in the analysis of good quality clips only. For RV strain, moderate agreement was reached for repeated measurements by a one observer according to the ICC. Bland-Altman analysis showed that both difference between repeated measurements and systematic bias reached significance. These results slightly improved in the analysis of good quality clips only. The ICC showed moderate agreement, but the difference between repeated measurements was not statistically significant and no systematic bias was identified, although close to significance.

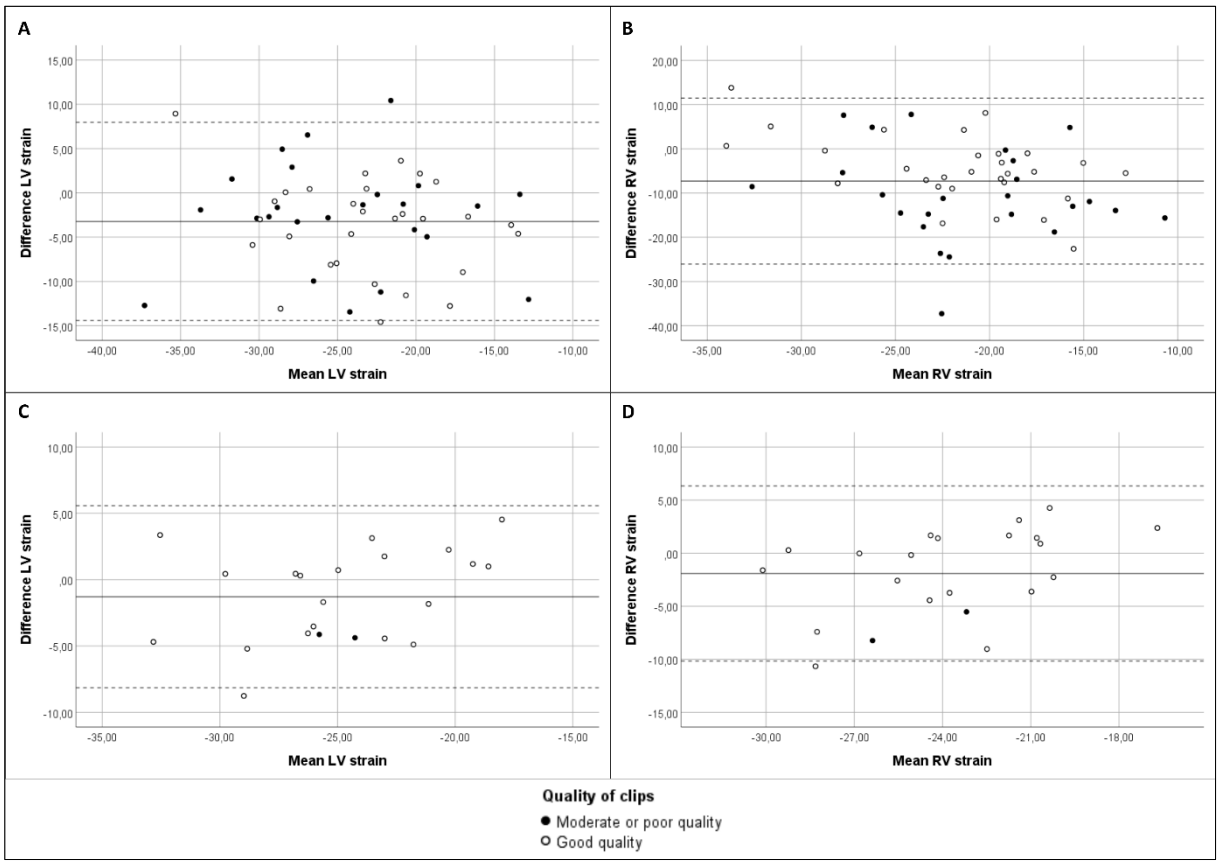

Figure 3: Agreement between and within observers. *Bland-Altman plots showing (A) the interobserver agreement of the left ventricle and (B) right ventricle and (C) the intraobserver agreement of the left ventricle and (D) right ventricle. LV=left ventricle. RV=right ventricle.*

Development of fetal strain throughout pregnancy

To investigate the development of fetal strain over time, strain values were collected in uncomplicated pregnancies at different time points throughout pregnancy. *Figure 4* shows fetal strain values of both LV and RV with advancing pregnancy, the average line calculated by a linear mixed effect model for repeated measurements and the 95% prediction limit. A total of 101 clips of 69 participants were used in this analysis, of which 18 participants visited for more than one ultrasound examination. Based on these data, strain values become less negative over time, meaning that there is a significant decrease of fetal strain with advancing pregnancy in both LV (p=0,033) and RV (p=0,026).

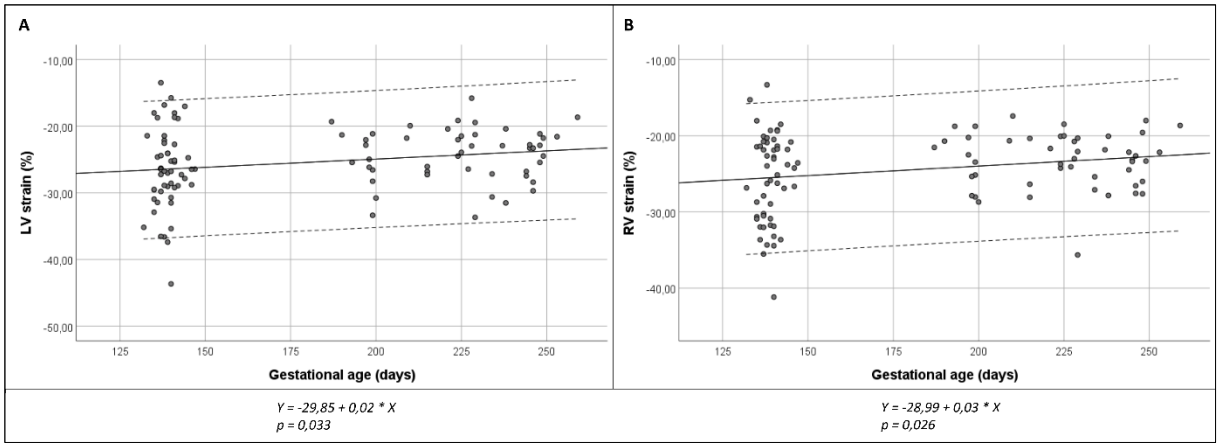

Figure 3: Development of fetal strain throughout pregnancy. *Dot plots showing strain values in uncomplicated pregnancies of (A) the left ventricle and (B) the right ventricle with advancing pregnancy. The average line calculated by a linear mixed effect model for repeated measurements and the 95% prediction limits are shown. LV=left ventricle. RV=right ventricle.*

Fetal strain in pregnancies complicated by maternal DM or FGR

Strain values of fetuses in uncomplicated pregnancies were compared to strain values of fetuses in pregnancies complicated by maternal DM or FGR to study potential effects of these pregnancy complications on fetal strain. Using a linear mixed effects model, slopes of the average lines of each study group were compared. No significant differences in slope were found between uncomplicated pregnancies and pregnancies complicated by maternal DM (LV: p=0,310, RV: p=0,253) or pregnancies complicated by FGR (LV: p=0,311, RV: p=0,894). Moreover, mean strain values of the study groups were compared within three different gestational age intervals, of which results are shown in *figure 5*. Within the interval of 18-24 weeks of gestation, the number of included clips were 53 clips of uncomplicated pregnancies, 11 clips of DM pregnancies and 5 clips of FGR pregnancies. Within the interval of 25-31 weeks of gestation, the number of included clips were 18 clips of uncomplicated pregnancies, 16 clips of DM pregnancies and 26 clips of FGR pregnancies. Within the interval of 32-40 weeks of gestation, the number of included clips were 30 clips of uncomplicated pregnancies, 19 clips of DM pregnancies and 21 clips of FGR pregnancies. No significant differences were observed in mean strain of fetuses in uncomplicated pregnancies compared to fetuses in pregnancies complicated by maternal DM within 18-24 weeks (LV: p=0,581, RV: p=0,803), 25-31 weeks (LV: p=0,878, RV: p=0,986) or 32-40 weeks (LV: p=0,268, RV: p=0,498) of gestation. Similarly, no significant differences were observed in mean strain of fetuses in uncomplicated pregnancies compared to fetuses in pregnancies complicated by FGR within 18-24 weeks (LV: p=0,984, RV: p=0,551), 25-31 weeks (LV: p=0,819, RV: p=0,877) or 32-40 weeks (LV: p=0,494, RV: p=0,871) of gestation.

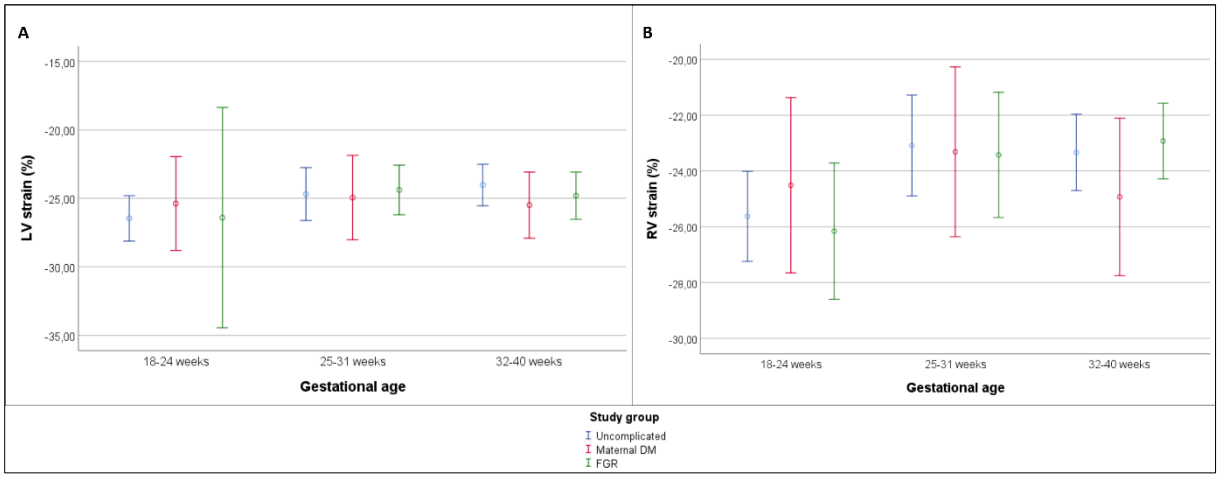

Figure 5: Comparison of fetal strain in uncomplicated pregnancies and pregnancies complicated by maternal DM or FGR. *Error bars showing the mean + 95% confidence intervals of (A) left ventricle strain and (B) right ventricle strain of study groups within three different gestational age intervals. LV=left ventricle. RV=right ventricle.*

Discussion

The objectives of this pilot study were to substantiate the feasibility of FetalHQ in the functional assessment of the fetal heart, to determine normal strain values and the development throughout pregnancy and to study potential effects of maternal DM or FGR on fetal strain. Using FetalHQ, the current findings showed that reproducibility of fetal strain values is limited between observers, especially in the analysis of the RV, and reproducibility was moderate-good for repeated intraobserver measurements. A significant decrease in fetal strain was observed with advancing pregnancy in both ventricles. No significant effect of pregnancy complications maternal DM or FGR on fetal strain was observed.

In order to implement functional cardiac assessment by FetalHQ in clinical practice, good agreement between repeated measurements of fetal strain within and between observers is mandated. In 2021, Huntley and colleagues published a comparable study on the evaluation of reproducibility and agreement of several cardiac shape and deformation parameters using FetalHQ.[19] They reported a similar ICC for LV strain and an higher ICC for RV strain, although still showing moderate agreement between observers for RV strain. According to their Bland-Altman analysis, the differences between observers were close to significance (LV: p=0,08, RV: p=0,09), where our results showed highly significant differences, and they did not observe any systematic bias for RV strain. Compared to our results on intraobserver variability, they found a slightly lower ICC values on LV and RV strain, but less systematic bias. Several other studies have been performed on fetal strain with various offline speckle tracking software packages, in which agreement between and within observers was analyzed. Variable findings were reported, with mostly good agreement between observers, but low to moderate agreement was reported as well.[20–26] Overall, studies on feasibility and reproducibility of fetal strain demonstrate the difficulty of measuring dynamic deformation parameters.
There are several factors that may contribute to the difficulties in fetal strain analysis. Firstly, image acquisitions have a great impact on the reliability of strain analysis. Considering the small size, high heart rate and 3D structure of the fetal heart, using higher frame rates improves tracking of speckle patterns and results in different strain values compared to lower frame rates.[2,27] Frame rates of >80-110 frames per second are recommended to maximize the accuracy of strain analysis.[28] In our study, a median of 64 frames per second was obtained, varying from 20 to 115 frames per second, which might contribute to the variability in our analysis. Also, image quality and angle of insonation may be potential contributors. As shown in our results, analysis of good quality clips only improved the inter- and intraobserver variability. Though, differing image quality represents everyday-practice in which optimal quality is not always achievable. Moreover, a study of Semmler et al. showed that different strain values were obtained depending on the angle of insonation, despite the assumption of STE being

an angle-independent ultrasound method.[29] Significant differences in fetal strain values were found between apex up/down, apex oblique and apex perpendicular. These findings were in line with our experience during strain analysis, suggesting that difficulty in analysis may also depend on angle of insonation.
Other contributors to error or bias between observers are the selection of a cardiac cycle and manual adjustments of the endocardial trace line. Patey et al. compared repeated measurements in the same frame to measurements repeated in a different frame.[30] A good-excellent ICC was calculated for repeated measurements in the same frame, which was decreased to moderate-good ICC for repeated measurements in different frames. Moreover, the software displays a proposed trace line that could be manually adjusted to adequately align the endocardium. These manual adjustments are needed to obtain reliable measurements.[19] However, we noticed that small changes in the trace line highly effect the acquired strain values. This means that the technique still entails a significant subjective part that is human determined. Therefore, not only sufficient image quality, evident valve insertions and high contrast between blood and endocardial border are required, but also clear and uniform measure instructions are compulsory for adequate and reliable strain analysis. Accordingly, our study and other studies on feasibility and reproducibility of fetal strain showed higher agreement between and within observers in the LV compared to the RV.[19,21,25,26] Anatomical structures located in the RV, such as the moderator band, may hamper the delineation process of the endocardium, resulting in less reliable strain values and higher observer variability. Moreover, we noticed that acquired practice of an observer refined its ability to reduce variability between measurements, indicating a learning-curve. Therefore, the first examinations performed by an observer are less accurate than following measurements, but still were included in our data analysis. In order to improve reliability and reproducibility using FetalHQ, observers should be sufficiently practiced for analysis and agree on an operative protocol, in which image acquisitions and angle of insonation are standardized.

Many studies aimed to establish normal values of fetal strain in order to be able to explore the effects of pregnancy complications on fetal cardiac deformation.[16] However, these studies showed a broad range of values that may account for normal strain in healthy fetuses, with decreasing or stable fetal strain throughout these pregnancies. Most of these studies used a cross-sectional study design and there is a lack of universal methods in the use of fetal STE, which hampers interpretation of the results. Van Oostrum et al. recently performed a large longitudinal study on fetal strain of 124 fetuses in uncomplicated pregnancies.[31] In accordance with our findings, their study found a gradual decrease, or less negative values, of fetal strain in both LV and RV throughout pregnancy. Decreasing fetal strain throughout pregnancy might be explained by the increasing loading conditions of the ventricles with advancing pregnancy as a result of increasing placental resistance and growing attribution of the pulmonary circulation.[32,33] As the preload and afterload of the ventricles increase with advancing pregnancy, fetal cardiac deformation might decrease due to the enhanced systolic wall stress.[34,35]
As described above, it is hypothesized that both maternal DM and FGR cause a decrease of fetal strain as a result of cardiac remodeling. Ten studies investigated the effect of maternal DM on fetal strain, of which 7/10 reported significantly lower fetal strain compared to uncomplicated pregnancies.[36–45] Three studies investigated the effect of FGR on fetal strain. Two studies did not observe a significant difference in fetal strain, while one study observed abnormal ventricular contractility as a result of FGR.[46–48] However, this effect was more pronounced in transverse contractility than in global or longitudinal contractility and more common in the RV. In contrast, no significant effect of maternal DM or FGR was found in our study.
It must be mentioned that interpretation of findings on normal fetal strain throughout pregnancy and the effect of pregnancy complications in this pilot study should take into account the significant variability in measurements between observers. Although measurements of one observer showing good agreement for LV and moderate agreement for RV were used for these analyses, strain analysis using FetalHQ should be optimized in order to formulate conclusions on normal fetal strain and the effect of pregnancy complications.

This study is strengthened by a longitudinal follow-up of a number of participants in all study groups, which is preferable for the examination of gestational development of fetal strain. Also, measurements between and within observers were standardized by the selection of a single cardiac cycle in advance by one observer, in which all measurements were performed. Limitations of the study were the suboptimal image quality and frame rates, and variable angles of insonation used in the ultrasound clips. Also, the inclusions were inconsistent in gestational age at which an ultrasound examination was performed, and only a small number of participants were included in this pilot study.

In conclusion, this pilot study showed that the feasibility of speckle tracking analysis using FetalHQ is currently limited. Reliability and reproducibility of strain analysis should be improved by gaining experience with the analysis and standardizing the operative protocol, such as image acquisitions and angle of insonation, before implementation as a tool to evaluate fetal cardiac function.

Acknowledgments

We would like to thank the sonographers of the obstetric ultrasound outpatient clinic in the Wilhemina Children's Hospital at Utrecht for their contribution in patient enrollment and the collection of ultrasound clips. Also, we would like to thank Peter Zuithoff of the Julius Center for Health Sciences and Primary Care at Utrecht for his assistance in statistical analysis.

References

1. Dandel M, Lehmkuhl H, Knosalla C, Suramelashvili N, Hetzer R. Strain and strain rate imaging by echocardiography - basic concepts and clinical applicability. Curr Cardiol Rev. 2009 Apr 30;5(2):133–48.
2. DeVore G, Polanco B, Satou G, Sklansky M. Two-Dimensional Speckle Tracking of the Fetal Heart: A Practical Step-by-Step Approach for the Fetal Sonologist. J Ultrasound Med. 2016 Aug 1;35(8):1765–81.
3. Bansal M, Kasliwal R. How do I do it? Speckle-tracking echocardiography. Indian Heart J. 2013;65(1):117–23.
4. Visentin S, Palermo C, Camerin M, Daliento L, Muraru D, Cosmi E, Badano L. Echocardiographic Techniques of Deformation Imaging in the Evaluation of Maternal Cardiovascular System in Patients with Complicated Pregnancies. Biomed Res Int. 2017;2017.
5. Biswas M, Sudhakar S, Nanda N, Buckberg G, Pradhan M, Roomi A, Gorissen W, Houle H. Two- and three-dimensional speckle tracking echocardiography: clinical applications and future directions. Echocardiography. 2013 Jan;30(1):88–105.
6. Van Mieghem T, Hodges R, Jaeggi E, Ryan G. Functional echocardiography in the fetus with non-cardiac disease. Prenat Diagn. 2014 Jan;34(1):23–32.
7. Crispi F, Sepúlveda-Martínez Á, Crovetto F, Gómez O, Bijnens B, Gratacós E. Main Patterns of Fetal Cardiac Remodeling. Fetal Diagn Ther. 2020 May 1;47(5):337–44.
8. Lisowski L, Verheijen P, Copel J, Kleinman C, Wassink S, Visser G, Meijboom E. Congenital heart disease in pregnancies complicated by maternal diabetes mellitus. An international clinical collaboration, literature review, and meta-analysis. Herz. 2010 Jan;35(1):19–26.
9. Ullmo S, Vial Y, Di Bernardo S, Roth-Kleiner M, Mivelaz Y, Sekarski N, Ruiz J, Meijboom E. Pathologic ventricular hypertrophy in the offspring of diabetic mothers: a retrospective study. Eur Heart J. 2007 Jun;28(11):1319–25.
10. Garg S, Sharma P, Sharma D, Behera V, Durairaj M, Dhall A. Use of fetal echocardiography for characterization of fetal cardiac structure in women with normal pregnancies and gestational diabetes mellitus. J Ultrasound Med. 2014 Aug 1;33(8):1365–9.
11. Crispi F, Bijnens B, Figueras F, Bartrons J, Eixarch E, Le Noble F, Ahmed A, Gratacós E. Fetal growth restriction results in remodeled and less efficient hearts in children. Circulation. 2010 Jun 8;121(22):2427–36.
12. Rodríguez-López M, Cruz-Lemini M, Valenzuela-Alcaraz B, Garcia-Otero L, Sitges M, Bijnens B,

Gratacós E, Crispi F. Descriptive analysis of different phenotypes of cardiac remodeling in fetal growth restriction. Ultrasound Obstet Gynecol. 2017 Aug 1;50(2):207–14.
13. Nabeshima Y, Seo Y, Takeuchi M. A review of current trends in three-dimensional analysis of left ventricular myocardial strain. Cardiovasc Ultrasound. 2020 Jun 26;18(1).
14. Smiseth O, Torp H, Opdahl A, Haugaa K, Urheim S. Myocardial strain imaging: how useful is it in clinical decision making? Eur Heart J. 2016 Apr 14;37(15):1196-1207b.
15. Slieker M, Fackoury C, Slorach C, Hui W, Friedberg M, Fan C, Manlhiot C, Dillenburg R, Kantor P, Mital S, Liu P, Nathan P, Mertens L. Echocardiographic Assessment of Cardiac Function in Pediatric Survivors of Anthracycline-Treated Childhood Cancer. Circ Cardiovasc Imaging. 2019 Dec 1;12(12).
16. van Oostrum NHM, de Vet CM, van der Woude DAA, Kemps HMC, Oei SG, van Laar JOEH. Fetal strain and strain rate during pregnancy measured with speckle tracking echocardiography: A systematic review. Eur J Obstet Gynecol Reprod Biol. 2020 Jul 1;250:178–87.
17. Koo TK, Li MY. A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. J Chiropr Med. 2016 Jun 1;15(2):155.
18. Bland JM, Altman DG. Applying the right statistics: analyses of measurement studies. Ultrasound Obstet Gynecol. 2003 Jul 1;22(1):85–93.
19. Huntley ES, Hernandez-Andrade E, Soto E, Devore G, Sibai BM. Novel Speckle Tracking Analysis Showed Excellent Reproducibility for Size and Shape of the Fetal Heart and Good Reproducibility for Strain and Fractional Shortening. Fetal Diagn Ther. 2021 Sep 1;48(7):541–50.
20. Biancardi M, de Sa R. Behavior of fetal longitudinal myocardial fibers assessed by speckle tracking to obtain strain and strain rate values for low-risk pregnancies. J Perinat Med. 2020 Feb 1;48(2):144–52.
21. Chelliah A, Dham N, Frank L, Donofrio M, Krishnan A. Myocardial strain can be measured from first trimester fetal echocardiography using velocity vector imaging. Prenat Diagn. 2016 May 1;36(5):483–8.
22. Enzensberger C, Achterberg F, Degenhardt J, Wolter A, Graupner O, Herrmann J, Axt-Fliedner R. Feasibility and Reproducibility of Two-Dimensional Wall Motion Tracking (WMT) in Fetal Echocardiography. Ultrasound Int open. 2017 Feb 1;3(1):E26–33.
23. Erickson C, Levy P, Craft M, Li L, Danford D, Kutty S. Maturational patterns in right ventricular strain mechanics from the fetus to the young infant. Early Hum Dev. 2019 Feb 1;129:23–32.
24. Kapusta L, Mainzer G, Weiner Z, Deutsch L, Khoury A, Haddad S, Lorber A. Second trimester ultrasound: reference values for two-dimensional speckle tracking-derived longitudinal strain, strain rate and time to peak deformation of the fetal heart. J Am Soc Echocardiogr. 2012 Dec;25(12):1333–41.
25. Kapusta L, Mainzer G, Weiner Z, Deutsch L, Khoury A, Haddad S, Lorber A. Changes in fetal left and right ventricular strain mechanics during normal pregnancy. J Am Soc Echocardiogr. 2013 Oct;26(10):1193–200.
26. Kim S, Miyakoshi K, Kadohira I, Tanaka M, Minegishi K, Matsumoto T, Yoshimura Y. Comparison of the right and left ventricular performance during the fetal development using velocity vector imaging. Early Hum Dev. 2013 Sep;89(9):675–81.
27. Enzensberger C, Rostock L, Graupner O, Götte M, Wolter A, Vorisek C, Herrmann J, Axt-Fliedner R. Wall motion tracking in fetal echocardiography-Application of low and high frame rates for strain analysis. Echocardiography. 2019 Feb 1;36(2):386–93.
28. D'hooge J, Bijnens B, Jamal F, Pislaru C, Pislaru S, Thoen J, Suetens P, Van de Werf F, Angermann C, Rademakers F, Herregods M, Sutherland G. High frame rate myocardial integrated backscatter. Does this change our understanding of this acoustic parameter? Eur J Echocardiogr. 2000 Mar;1(1):32–41.
29. Semmler J, Day TG, Georgiopoulos G, Garcia-Gonzalez C, Aguilera J, Vigneswaran T V., Zidere V, Miller OI, Sharland G, Charakida M, Simpson JM. Fetal Speckle-Tracking: Impact of Angle of Insonation and Frame Rate on Global Longitudinal Strain. J Am Soc Echocardiogr. 2020 Sep 1;33(9):1141-1146.e2.

30. Patey O, Gatzoulis M, Thilaganathan B, Carvalho J. Perinatal Changes in Fetal Ventricular Geometry, Myocardial Performance, and Cardiac Function in Normal Term Pregnancies. J Am Soc Echocardiogr. 2017 May 1;30(5):485-492.e5.
31. Oostrum NHM, Vet CM, Clur SB, Woude DAA, Heuvel ER, Oei SG, Laar JOEH. Fetal myocardial deformation measured with 2D-STE: longitudinal prospective cohort study in 124 healthy fetuses. Ultrasound Obstet Gynecol. 2021 Sep 24;
32. Gardiner H. Response of the fetal heart to changes in load: from hyperplasia to heart failure. Heart. 2005 Jul;91(7):871–3.
33. Kiserud T. Physiology of the fetal circulation. Semin Fetal Neonatal Med. 2005;10(6):493–503.
34. Donal E, Bergerot C, Thibault H, Ernande L, Loufoua J, Augeul L, Ovize M, Derumeaux G. Influence of afterload on left ventricular radial and longitudinal systolic functions: a two-dimensional strain imaging study. Eur J Echocardiogr. 2009 Dec;10(8):914–21.
35. Burns A, La Gerche A, D'hooge J, MacIsaac A, Dior D. Left ventricular strain and strain rate: characterization of the effect of load in human subjects. Eur J Echocardiogr. 2010;11(3):283–9.
36. Aguilera J, Semmler J, Anzoategui S, Zhang H, Nicolaides K, Charakida M. Cardiac function in gestational diabetes mellitus: A longitudinal study from fetal life to infancy. BJOG. 2021 Jan 1;128(2):272–9.
37. Kulkarni A, Li L, Craft M, Nanda M, Lorenzo J, Danford D, Kutty S. Fetal myocardial deformation in maternal diabetes mellitus and obesity. Ultrasound Obstet Gynecol. 2017 May 1;49(5):630–6.
38. Lee-Tannock A, Hay K, Gooi A, Kumar S. Longitudinal assessment of ventricular strain, tricuspid and mitral annular plane systolic excursion (TAPSE and MAPSE) in fetuses from pregnancies complicated by diabetes mellitus. Eur J Obstet Gynecol Reprod Biol. 2021 Jan 1;256:364–71.
39. Liu F, Liu S, Ma Z, Zhan X, Tao G, Cheng L, Song X. Assessment of left ventricular systolic function in fetuses without myocardial hypertrophy of gestational diabetes mellitus mothers using velocity vector imaging. J Obstet Gynaecol. 2012 Apr;32(3):252–6.
40. Miranda J, Cerqueira R, Ramalho C, Areias J, Henriques-Coelho T. Fetal Cardiac Function in Maternal Diabetes: A Conventional and Speckle-Tracking Echocardiographic Study. J Am Soc Echocardiogr. 2018 Mar 1;31(3):333–41.
41. Patey O, Carvalho J, Thilaganathan B. Perinatal changes in fetal cardiac geometry and function in diabetic pregnancy at term. Ultrasound Obstet Gynecol. 2019 Nov 1;54(5):634–42.
42. Song Y, Yin H, Wang W, Zou Y, Liu D, Zhang G, Ji X. Evaluation of fetal cardiac functions in the setting of maternal diabetes: Application of the global spherical index, global strain and fractional area change by the speckle tracking technique. Eur J Obstet Gynecol Reprod Biol. 2021 Sep 1;264:162–7.
43. Wang H, Xu Y, Fu J, Huang L. Evaluation of the regional ventricular systolic function by two-dimensional strain echocardiography in gestational diabetes mellitus (GDM) fetuses with good glycemic control. J Matern Fetal Neonatal Med. 2015 Dec 12;28(18):2150–4.
44. Wang X, Lian Y, Wang X, Tian M. Study of Regional Left Ventricular Longitudinal Function in Fetuses with Gestational Diabetes Mellitus by Velocity Vector Imaging. Echocardiography. 2016 Aug 1;33(8):1228–33.
45. Wang D, Liu C, Liu X, Zhang Y, Wang Y. Evaluation of prenatal changes in fetal cardiac morphology and function in maternal diabetes mellitus using a novel fetal speckle-tracking analysis: a prospective cohort study. Cardiovasc Ultrasound. 2021 Dec 1;19(1).
46. Crispi F, Bijnens B, Sepulveda-Swatson E, Cruz-Lemini M, Rojas-Benavente J, Gonzalez-Tendero A, Garcia-Posada R, Rodriguez-Lopez M, Demicheva E, Sitges M, Gratacós E. Postsystolic shortening by myocardial deformation imaging as a sign of cardiac adaptation to pressure overload in fetal growth restriction. Circ Cardiovasc Imaging. 2014 Sep 1;7(5):781–7.
47. Dahlbäck C, Gudmundsson S. Increased pulsatility in the fetal ductus venosus is not related to altered cardiac strain in high-risk pregnancies. J Matern Fetal Neonatal Med. 2016 Apr 17;29(8):1328–33.
48. DeVore GR, Gumina DL, Hobbins JC. Assessment of ventricular contractility in fetuses with an

estimated fetal weight less than the tenth centile. Am J Obstet Gynecol. 2019 Nov 1;221(5):498.e1-498.e22.