

# Evaluation of fetal cardiac function in maternal gestational diabetes mellitus by speckle tracking echocardiography

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## Research Article

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# Abstract

The aim of this study was to assess the cardiac function in fetuses of mothers with gestational diabetes mellitus (GDM) by using fetalHQ, a quantitative analysis software for the assessment of fetal cardiac function based on speckle tracking echocardiography. In this prospective cross-sectional study, 49 fetuses exposed to GDM and 50 normal fetuses were enrolled and fetal echocardiography were performed and analyzed. In the GDM group, left ventricular ( $24 \pm 4$  vs.  $28 \pm 4$ ,  $p < 0.001$ ) and right ventricular global longitudinal strain ( $23 \pm 4$  vs.  $26 \pm 4$ ,  $p = 0.002$ ) and right ventricular free wall strain ( $26 \pm 6$  vs.  $29 \pm 5$ ,  $p = 0.006$ ) were significantly lower compared with the control group, whereas there was no significant difference in global spherical index ( $1.2 \pm 0.1$  vs.  $1.2 \pm 0.1$ ,  $p = 0.425$ ). Additionally, 24-segment transverse fraction shortening of the right ventricle was more impaired than the left and the segments with reduced fraction shortening were mainly located in the mid and apical sections of the right ventricle, and mid section of the left ventricle. In conclusion, fetuses exposed to GDM may have cardiac dysfunction before the onset of cardiac morphologic abnormalities, and the right ventricle is more vulnerable than the left during fetal development.

## Introduction

Gestational diabetes mellitus (GDM) is the most common metabolic disease that occurs during pregnancy, affecting 9.3–25.5% of pregnant women [1]. Previous studies have shown that GDM adversely affects the structure and function of the fetal heart and fetal cardiac dysfunction may occur even the fetal heart is structurally normal [2, 3].

Fetal echocardiography is the most commonly used method to evaluate and monitor fetal cardiac function at present because of its noninvasiveness, low cost and radiation free to mother and fetus. M-mode echocardiography is a simple and effective method for the assessment of fetal cardiac function by calculating the fractional shortening (FS), but it has limitations. It has been testified that the endocardial wall of the ventricle in the systolic period does not move vertically, but tangentially to the center of the chamber, so FS calculated by traditional M-mode echocardiography does not represent the systolic displacement at the same endocardial segment [4]. Hence, the results of studies on left ventricular FS calculated by M-mode echocardiography between GDM fetuses and normal fetuses need to be further evaluated or validated [5–7]. Strain imaging, which is based on the principle of two-dimensional speckle tracking, is an emerging noninvasive ultrasonic technique for quantitative analysis of cardiac deformation, and has been widely used in pediatric and adult cardiology. Since there have been many studies on the effects of GDM in fetal cardiac deformation, no consensus has yet been reached. The results of different studies were controversial, which might be caused by diverse ultrasound equipment and the different diagnostic criteria used for GDM [8–11]. According to Miranda et al. [7], peak right ventricular global longitudinal systolic strain was lower in fetuses of mothers with GDM or pregestational diabetes than control by using proprietary special speckle tracking software (EchoPAC) but there was no difference in strain values for the left ventricle. By contrast, Patey et al. [9] found GDM fetuses had significantly higher values of left and right ventricular longitudinal, circumferential and radial strain by

using the same software. Rolf, et al. [10] and Wang et al. [11] showed that maternal GDM would impair the left and right ventricular segmental longitudinal strain in fetuses (software: QLab, AFI, respectively). Obviously, these studies have some limitations. These softwares used for assessing cardiac deformation in the aforementioned studies were originally developed for adult hearts and were more prone to errors due to the small fetal heart size and fast heart rates when applied to assess fetal heart function [10]. A special quantitative analysis software called fetalHQ for the assessment of fetal cardiac function is now commercially available. The principle of fetalHQ is also based on speckle tracking and strain values can be calculated by tracking the endocardium motion. Meanwhile, the ventricular endocardium is divided into 49 points which starts from the insertion of the atrioventricular valve on the lateral wall and traces down to the apex and goes up to the insertion of the atrioventricular valve on the interventricular septum, which results in 24 transverse segments defined as 2 points opposite each other. Thus, 24-segment transverse ventricular FS can be calculated [4]. It overcomes the limitation of traditional M-mode echocardiography for the measurement of FS by using speckle tracking technique to track the systolic displacement of the same endocardial segment. The objective of this study is to evaluate the cardiac function in fetuses exposed to GDM by using fetalHQ.

## Materials And Methods

### Study population

In this prospective cross-sectional study, we recruited 75 pregnant women with GDM (GDM group) and 50 normal pregnant women (control group) between 20 and 40 weeks gestation from July 2020 to January 2021. All subjects were single pregnancies and had completed fetal systemic ultrasound examination prior to fetal echocardiography. Exclusion criteria for both groups were maternal type 2 diabetes mellitus, chronic inflammatory disease, thyroid disease, hypertension, kidney disease, fetal cardiac or extracardiac malformation, fetal arrhythmia, fetal growth restriction and fetal chromosomal abnormality. Referral reasons for control group included advanced age, adverse pregnancy history, family history of congenital heart disease and intracardiac echogenic focus. GDM was diagnosed if one or more of the following criteria was met: fasting plasma glucose  $\geq 5.11$  mmol/L, 1h plasma glucose  $\geq 9.99$  mmol/L, and 2h plasma glucose  $\geq 8.49$  mmol/L with a 75-g oral glucose

tolerance test. Finally, 26 cases were ruled out (4 fetuses with congenital heart defects, 8 GDM pregnant women complicated with thyroid disease, and 14 with poor image quality) and 49 pregnant women with GDM and 50 normal pregnant women were included in this study.

The study protocol was approved by the Medical Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (TJ-IRB20210312) and informed consent was obtained from each participant before their enrollment in the study.

### Maternal characteristics

Clinical characteristics, including maternal age, date of last menstruation, gestational age (calculated by the last menstrual period), number of pregnancies, parity, and medical past history, laboratory test results, and medical treatment were collected from electronic medical records. After recording the present clinical characteristics, all subjects underwent standard fetal echocardiography and myocardial strain assessment.

### **Fetal echocardiography**

Fetal echocardiography was performed on Voluson E10 ultrasound machine (GE Healthcare, Tiefenbach, Austria) equipped with either an EM6C or RM6C transducer. First, a comprehensive fetal echocardiographic examination was carried out to rule out congenital heart defects according to the recommendations of the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) [12]. Then, the image was optimized to make the borders between the blood pool and endocardium clear and the standard four-chamber view was acquired as saved as a 3-second loop with frame rate of 72-85 Hz with minimized maternal respiration and fetal movement interferences.

### **Fetal cardiac function analysis**

Cardiac function analysis was performed using the machine build-in software fetalHQ which was activated by pressing *Ventricular Shape and Contractility* in the fetalHQ menu. Fetal cardiac end-diastolic and end-systolic time were determined from the M-mode tracing of the tricuspid annulus. On the end-systolic image of four-chamber view, the septal and lateral atrioventricular valve insertion points and the apex were identified for the selected right or left ventricle. The machine build-in automated tracking algorithm outlined the endocardium in successive frames throughout the cardiac cycle. After the tracking quality was verified (with subsequent manual adjustment of the region of interest if necessary), endocardial motion was analyzed by speckle tracking to calculate the global longitudinal strain (GLS) of the left and right ventricles and strain of right ventricular free wall (Figure 1). In the meantime, the following parameters were calculated through fetalHQ: fractional area change (%) = [(end diastolic area - end systolic area) / end diastolic area] \* 100; FS (%) = [(end diastolic transverse length - end systolic transverse length) / end diastolic transverse length] \* 100. In addition, global sphericity index (GSI) was calculated with the widest transverse length (orthogonal to the longest length from the epicardial borders at the widest part of the four-chamber view) divided by the longest length (from the epicardial border of the posterior mid atrial wall to the apical epicardial border of the ventricles). Left and right ventricular sphericity index (SI) were calculated with the end-diastolic widest transverse length divided by the basal-apical length of the right or left ventricle. Since the left and right ventricles were divided into 24 transverse segments for the calculation of FS, segments 1-8, 9-16 and 17-24 were subsequently defined as basal, mid and apical sections, respectively.

### **Statistical analysis**

Data were analyzed with SPSS 19.0 (IBM, Armonk, NY, USA). Continuous data were tested for normality (Shapiro Wilk test). Normally distributed data were expressed as mean  $\pm$  standard deviation and non-

normally distributed data were expressed as median and interquartile interval. For comparison between groups, independent T test was performed for normally distributed data and non-parametric test was performed for non-normally distributed data. All statistical tests were two tailed, and  $p$  value  $<0.05$  was considered statistically significant.

## Results

### Maternal characteristics

The maternal clinical characteristics was summarized in Table 1. There were no significant differences in the parity and gestational age at examination between the two groups, whereas the age ( $p = 0.008$ ) and gravidity ( $p = 0.01$ ) of the pregnant women with GDM were higher than those of the control group (Table 1).

Table 1  
Maternal Characteristics and Fetal Cardiac Function

	Control group (n = 50)	GDM group (n = 49)	p Value
Maternal Characteristics			
Age, yrs	30 ± 4	32 ± 5	<b>0.008</b>
Gestational age, wk	27.0 ± 3.1	28.1 ± 3.1	0.08
Gravidity	2 [1–2]	2 [1–4]	<b>0.01</b>
Parity	0 [0–1]	0 [0–1]	0.578
Fetal cardiac function			
LV GLS, %	28 ± 4	24 ± 4	<b>&lt; 0.001</b>
RV GLS, %	26 ± 4	23 ± 4	<b>0.002</b>
RV free wall strain, %	29 ± 5	26 ± 6	<b>0.006</b>
LV FAC, %	49 ± 5	45 ± 7	<b>&lt; 0.001</b>
RV FAC, %	41 [37–45]	36 [33–43]	<b>0.001</b>
LV EF, %	63 ± 6	59 ± 8	<b>0.002</b>
LV SV, ml	0.7 [0.5-1.0]	0.7 [0.6-1.0]	0.662
LV CO, ml/min	101 [75–137]	107 [86–133]	0.597
GSI	1.2 ± 0.1	1.2 ± 0.1	0.425
LV SI	2.0 ± 0.3	2.0 ± 0.3	0.453
RV SI	1.6 ± 0.2	1.5 ± 0.2	0.256

Defined significance level are marked in bold.

Values are expressed as mean ± standard deviation or median [interquartile range].

GDM = gestational diabetes mellitus; LV = left ventricle; RV = right ventricle; GLS = global longitudinal strain; FAC = fractional area change; EF = ejection fraction; SV = stroke volume; CO = cardiac output; GSI = global spherical index; SI = spherical index.

## Fetal Cardiac Function Parameters

The fetal cardiac features in GDM group and control group were shown in Table 1. Left and right ventricular GLS and right ventricular free wall strain were significantly lower in GDM group than those in control group (all  $p < 0.01$ ) (Fig. 1). Meanwhile, left ventricular ejection fraction and left and right

ventricular fractional area change were significantly lower in GDM fetuses than control (all  $p < 0.01$ ). There were no significant differences in left ventricular stroke volume and cardiac output between two groups. Additionally, there were no significant differences in GSI and left and right ventricular SI, either.

The results of fetal 24-segment transverse FS in GDM group and control group were shown in Table 2. Obviously, transverse FS in some segments of the left and right ventricle reduced in the GDM group when compared with the control and right ventricle was more impaired than the left. The segments with reduced FS were mainly located in the mid section of the left ventricle, and mid and apical sections of the right ventricle.

Table 2

Comparison of 24-segment transverse fractional shortening between control group and the GDM group

		Control group (n = 50)	GDM group (n = 49)	p Value
LV-basal	FS-1, %	11 [3–16]	11 [3–16]	0.867
	FS-2, %	13 ± 9	13 ± 9	0.815
	FS-3, %	16 ± 7	16 ± 8	0.956
	FS-4, %	18 ± 7	18 ± 8	0.719
	FS-5, %	21 ± 7	20 ± 7	0.51
	FS-6, %	23 ± 7	22 ± 7	0.339
	FS-7, %	26 ± 7	24 ± 7	0.217
	FS-8, %	28 ± 7	26 ± 7	0.14
LV-mid	FS-9, %	30 ± 7	28 ± 8	0.093
	FS-10, %	32 ± 7	30 ± 8	0.063
	FS-11, %	34 ± 7	31 ± 8	<b>0.047</b>
	FS-12, %	35 ± 8	32 ± 8	<b>0.043</b>
	FS-13, %	37 ± 8	33 ± 8	0.053
	FS-14, %	40 [33–45]	35 [30–38]	<b>0.036</b>
	FS-15, %	40 [34–47]	37 [31–42]	0.077
	FS-16, %	42 [34–48]	39 [32–44]	0.17
LV-apical	FS-17, %	44 [35–49]	41 [34–46]	0.305
	FS-18, %	44 [37–50]	41 [35–49]	0.389
	FS-19, %	45 [36–49]	42 [35–49]	0.475
	FS-20, %	45 [37–49]	42 [35–49]	0.437
	FS-21, %	46 [37–50]	42 [34–49]	0.433
	FS-22, %	45 [36–51]	43 [31–49]	0.437

Defined significance level are marked in bold.

Values are expressed as mean ± standard deviation or median [interquartile range].

GDM = gestational diabetes mellitus; LV = left ventricle; RV = right ventricle; FS = fractional shortening; The number represents the corresponding segment and segments 1–8, 9–16, 17–24 represent the basal, mid and apical sections, respectively.

		Control group (n = 50)	GDM group (n = 49)	p Value
	FS-23, %	46 [36–51]	43 [30–50]	0.441
	FS-24, %	46 [35–51]	44 [30–50]	0.475
RV-basal	FS-1, %	16 ± 10	11 ± 12	0.05
	FS-2, %	17 ± 9	13 ± 11	<b>0.041</b>
	FS-3, %	17 [12–22]	14 [7–22]	0.073
	FS-4, %	18 [13–24]	15 [10–24]	0.069
	FS-5, %	20 [15–25]	16 [12–24]	0.059
	FS-6, %	20 [16–25]	18 [13–25]	0.11
	FS-7, %	21 [17–25]	19 [14–25]	0.143
	FS-8, %	21 [18–25]	20 [14–26]	0.18
RV-mid	FS-9, %	22 [19–26]	21 [16–26]	0.212
	FS-10, %	22 [20–27]	21 [17–25]	0.157
	FS-11, %	22 [20–27]	21 [17–25]	0.124
	FS-12, %	23 [20–28]	22 [17–25]	0.103
	FS-13, %	23 [19–28]	22 [18–25]	0.051
	FS-14, %	24 [19–30]	21 [18–26]	<b>0.029</b>
	FS-15, %	26 ± 9	21 ± 8	<b>0.006</b>
	FS-16, %	26 ± 9	21 ± 9	<b>0.003</b>
RV-apical	FS-17, %	27 ± 9	20 ± 10	<b>0.001</b>
	FS-18, %	27 ± 9	20 ± 11	<b>0.001</b>
	FS-19, %	27 ± 9	20 ± 12	<b>0.001</b>
	FS-20, %	27 [20–33]	20 [11–32]	<b>0.01</b>
	FS-21, %	26 [21–34]	22 [9–32]	<b>0.038</b>
	FS-22, %	27 [21–33]	22 [7–34]	0.066

Defined significance level are marked in bold.

Values are expressed as mean ± standard deviation or median [interquartile range].

GDM = gestational diabetes mellitus; LV = left ventricle; RV = right ventricle; FS = fractional shortening; The number represents the corresponding segment and segments 1-8, 9-16, 17-24 represent the basal, mid and apical sections, respectively.

	Control group (n = 50)	GDM group (n = 49)	p Value
FS-23, %	26 [21–33]	23 [6–34]	0.096
FS-24, %	26 [21–33]	23 [5–34]	0.124
Defined significance level are marked in bold.			
Values are expressed as mean ± standard deviation or median [interquartile range].			
GDM = gestational diabetes mellitus; LV = left ventricle; RV = right ventricle; FS = fractional shortening; The number represents the corresponding segment and segments 1-8,9–16,17–24 represent the basal, mid and apical sections, respectively.			

## Discussion

In this study, we found that fetuses exposed to GDM had reduced left and right ventricular longitudinal strain and fractional area change when compared with normal fetuses, indicating that maternal GDM impaired fetal cardiac function. Furthermore, we found that transverse FS reduced mainly in mid and apical sections, suggesting that reduced fetal cardiac function was segment dependent.

It is well-known that slight  $\beta$ -cells dysfunction usually exists in pregnant women with GDM, and insulin resistance during pregnancy is usually more serious than those without GDM. As a result, there is a vicious circle, leading to significant increase in blood glucose [13]. Correspondingly, blood glucose will increase in fetus of the mother with GDM, which will have a negative effect on fetal heart.

Ventricular GLS measured by speckle tracking echocardiography is a sensitive parameter for the evaluation of cardiac dysfunction [14]. Our study confirmed that the parameters representing fetal cardiac systolic function, including GLS, right ventricular free wall strain, ejection fraction and fractional area change, significantly reduced in GDM fetuses when compared to the control. Similarly, Aguilera et al. [8] found that GDM fetuses had lower left and right GLS and left ventricular ejection fraction. Yovera et al. [15] found left and right ventricular fractional area change and left ventricular ejection fraction reduced at  $24^{+0} - 32^{+0}$  weeks in the GDM fetuses, although there were no differences in left ventricular fractional area change and ejection fraction at  $32^{+1} - 40^{+1}$  weeks. However, there were no differences between the two groups in GSI and left and right ventricular SI in our study, which was in contrary to the previous findings [8]. This may be explained by the difference in gestational age of GDM fetuses between our study (mean gestational age: 28.1 weeks) and previous study (median gestational age: 36.0 weeks) [8]. Recently, Yovera et al. [15] pointed out that GSI in GDM fetuses reduced at  $32^{+1} - 40^{+1}$  weeks but had no difference from the control at  $24^{+0} - 32^{+0}$  weeks. Combining with our research, it suggests that functional parameters (such as GLS, ejection fraction and fractional area change) are more sensitive than morphological parameters (such as GSI, left and right ventricular SI), and functional abnormalities in GDM fetuses may occur before morphological changes.

Furthermore, compared with previous studies on strain, the value of the left and right ventricular GLS measured in our study is relatively higher. This may be explained in part by the differences of gestational age, frame rate and angle of insonation. Clavero et al. [16] searched the studies measuring GLS and strain rate from inception to October 2019 and summarized that the left and right ventricular strain and strain rate could increase, decrease or remain stable during gestation and values between various studies were not comparable because of different ultrasound systems and algorithms. Semmler et al. [17] reported that angle of insonation and frame rate had influences on GLS. GLS value calculated from low frame rate is higher when compared to high frame rate images; and the larger the angle of insonation, the higher the value of GLS.

In this study, we found that transverse FS reduced mainly in mid and apical sections and more segments were involved in the right ventricle. These findings were in accordance with previous studies. Yovera et al. [15] calculated the mean FS value for the base, mid and apical sections and found that there were more sections with reduced FS in the right ventricle than the left. Our findings support the hypothesis that the dominant part of the fetal heart is the right side and the right ventricle is damaged earlier than the left [18]. It also concordances with the fact that the architecture and orientation of the left ventricular myocardial fibers are more complex compared to the right ventricle, making the left ventricular function less vulnerable to injury [19]. Furthermore, the basal loop surrounding the left and right ventricles is predominantly composed of transverse fibers [20], so the transverse contraction of the basal section may be less impaired than that of the mid and apical.

## Limitations

The limitation of this study is that the proportion of pregnant women with severe GDM who need insulin or hypoglycemic drug therapy in the study is very small, so we did not analyze the relation of cardiac dysfunction to severity of GDM. Additionally, we do not follow up offspring of mother with GDM for further investigating whether hyperglycemic environment in the fetal period has a persistent effect on the child's heart.

## Conclusions

In conclusion, cardiac systolic function of fetuses exposed to GDM is significantly impaired and abnormal cardiac function may occur before morphologic change. Through a comprehensive, noninvasive cardiac segmental functional assessment, we speculate reasonably that the right ventricle is more vulnerable than the left during fetal development and the mid and apical sections tend to be affected earlier than the basal. Furthermore, 24-segment transverse FS might be a sensitive indicator to evaluate cardiac systolic function in fetuses, but it need to be validated in larger studies.

## Declarations

**Authors' contributions** Study concepts and design: HL, YD, PH. Material preparation: PH, LF, YG, XC. data acquisition and interpretation: HL, YD. data collection and statistical analysis: HL, PH. Manuscript preparation: PH. Manuscript editing: YD, HL.

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**Data availability** Datasets are available upon request.

**Conflicts of interest** All authors have no conflicts of interest to disclose.

**Ethics approval** This study was approved by the Medical Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (TJ-IRB20210312).

**Consent to participate** All participants gave their written informed consent.

**Consent for publication** All the authors agree to publish the article.

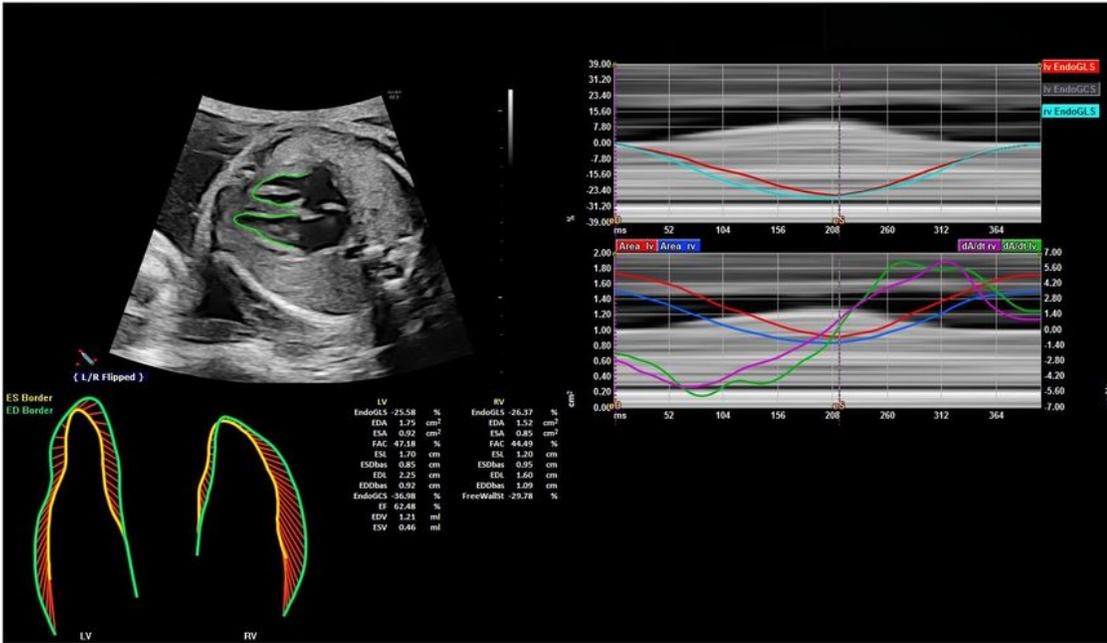
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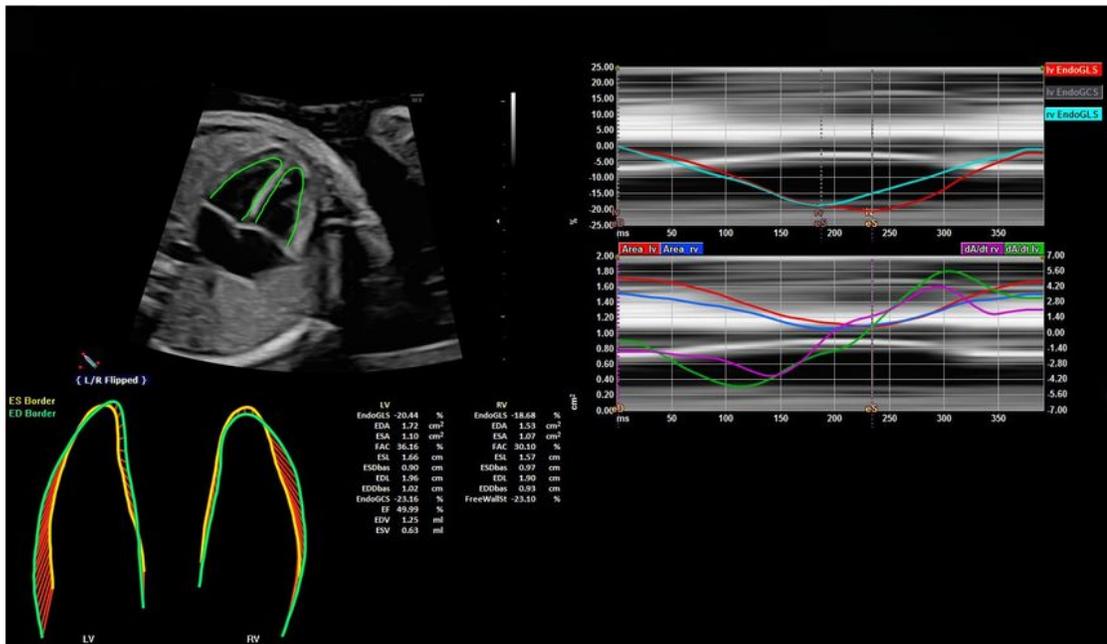
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## Figures



**A**



**B**

**Figure 1**

Myocardial deformation analysis of the left and right ventricle in a normal fetus with gestational age of 26w1d (A) and a GDM fetus with gestational age of 25w4d (B) The top left picture shows the end-systolic four-chamber view and the green curve represents the automatically traced endocardial border. The bottom left shows schematic diagram of left and right ventricular end-systolic and end-diastolic border and specific strain values. The top right picture shows the curve of left and right ventricular global

longitudinal strain in the cardiac cycle. A: left ventricular global longitudinal strain = 25.58%, right ventricular global longitudinal strain = 26.37%, right ventricular free wall strain = 29.78%; B: left ventricular global longitudinal strain = 20.44%, right ventricular global longitudinal strain = 18.68%, right ventricular free wall strain = 23.1%.