OBSTETRICS

Assessment of ventricular contractility in fetuses with an estimated fetal weight less than the tenth centile

Greggory R. DeVore, MD; Diane L. Gumina, MS; John C. Hobbins, MD

OBJECTIVE: To determine whether abnormal global, transverse, and longitudinal ventricular contractility of the heart in fetuses with an estimated fetal weight <10th centile is present, irrespective of Doppler studies of the umbilical artery and cerebroplacental ratio.

STUDY DESIGN: This was a retrospective study of 50 fetuses with an estimated fetal weight <10th centile that were classified based on Doppler results from the pulsatility indices of the umbilical artery and middle cerebral artery, and the calculated cerebroplacental ratio (pulsatility indices of the umbilical artery/middle cerebral artery). Right and left ventricular measurements were categorized into 3 groups: (1) global ventricular contractility (fractional area change), (2) transverse ventricular contractility (24-segment transverse fractional shortening), and (3) basal−apical longitudinal contractility (longitudinal strain, longitudinal displacement fractional shortening, and basal lateral and septal wall annular plane systolic excursion). Z scores for the above measurements were computed for fetuses with an estimated fetal weight <10th centile using the mean and standard deviation derived from normal controls. Ventricular contractility measurements were considered abnormal if their Z score values were <5th centile (z score <−1.65) or >95th centile (Z score >1.65), depending on the specific ventricular measurement.

RESULTS: The average gestational age at the time of the examination was 32 weeks 4 days (standard deviation 3 weeks 4 days). None of the 50 study fetuses demonstrated absent or reverse flow of the umbilical artery Doppler waveform. Eighty-eight percent (44/50) of fetuses had one or more abnormal measurements of cardiac contractility of 1 or both ventricles. Analysis of right ventricular contractility demonstrated 78% (39/50) to have 1 or more abnormal measurements, which were grouped as follows: global contractility 38% (19/50), transverse contractility 66% (33/50); and longitudinal contractility 48% (24/50). Analysis of left ventricular contractility demonstrated 1 or more abnormal measurements in 58% (29/50) that were grouped as follows: global contractility 38% (19/50); transverse contractility 40% (20/50); and longitudinal contractility 40% (20/50). Of the 50 study fetuses, 25 had normal pulsatility index of the umbilical artery and cerebroplacental ratios, 80% of whom had 1 or more abnormalities of right ventricular contractility and 56% of whom had 1 or more abnormalities of left ventricular contractility. Abnormal ventricular contractility for these fetuses was present in all 3 groups of measurements; global, transverse, and longitudinal. Those with an isolated abnormal pulsatility index of the umbilical artery (n=11) had abnormalities of transverse contractility of the right ventricular and global contractility in the left ventricle. When an isolated cerebroplacental ratio abnormality was present, the right ventricle demonstrated abnormal global, transverse, and longitudinal contractility, with the left ventricle only demonstrating abnormalities in transverse contractility. When both the pulsatility index of the umbilical artery and cerebroplacental ratio were abnormal (3/50), transverse and longitudinal contractility measurements were abnormal for both ventricles, as well as abnormal global contractility of the left ventricle.

CONCLUSIONS: High rates of abnormal ventricular contractility were present in fetuses with an estimated fetal weight <10th centile, irrespective of the Doppler findings of the pulsatility index of the umbilical artery, and/or cerebroplacental ratio. Abnormalities of ventricular contractility were more prevalent in transverse measurements than global or longitudinal measurements. Abnormal transverse contractility was more common in the right than the left ventricle. Fetuses with estimated fetal weight less than the 10th centile may be considered to undergo assessment of ventricular contractility, even when Doppler measurements of the pulsatility index of the umbilical artery, and cerebroplacental ratio are normal.

Key words: cerebroplacental ratio, fetal growth restriction, fetal heart, fractional area change, intrauterine growth restriction, middle cerebral artery Doppler, small for gestational age, speckle tracking, strain, umbilical artery Doppler

Fetuses with an estimated fetal weight (EFW) <10th centile may be at increased risk for neonatal and long-term cardiovascular and noncardiovascular outcomes, depending on associated findings.[1−6] Investigators have used various growth curves,[7−13] examined sequential growth rates,[14,15] evaluated the placenta for pathologic changes,[16,17] and measured Doppler waveforms of the ductus venosus pulsatility index, pulsatility indices of the umbilical artery (UAPI) and middle cerebral artery (MCAPI), and the calculated cerebroplacental ratio (CPR), to further differentiate risk assessment for these fetuses.[18−23] In addition to evaluating fetal somatic growth and peripheral vessel blood flow, previous studies have examined various components of cardiac diastolic and systolic function using M-mode and pulsed Doppler ultrasound.[3,4,24−27]

Most studies involving assessment of cardiac function have reported differences in mean values between control and small for gestational age (SGA), as well as those with fetal growth restriction (FGR) but have not established thresholds (ie, <5th centile or >95th centile) for classification of such findings when an at-risk fetus is examined.[3,4,24] Recently, depending on the software used for analysis, M-mode and pulsed Doppler ultrasound measurements have primarily focused on basal−apical longitudinal contractility of the ventricles, with little attention to global and transverse

Cite this article as: 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;221:498.e1-22.

0002-9378/$36.00

https://doi.org/10.1016/j.ajog.2019.05.042

AJOG at a Glance

Why was this study conducted?

This study was conducted to determine whether abnormal global, transverse, and longitudinal contractility of the right and left ventricles of the heart were present in fetuses with an estimated fetal weight less than the 10th centile.

Key findings

Irrespective of whether the Doppler changes of the umbilical artery pulsatility index and the cerebroplacental ratio were normal or abnormal, there was a significantly greater prevalence of abnormal right and left ventricular contractility in fetuses with an estimated fetal weight <10th centile when compared to controls.

What does this add to what is known?

This study demonstrated abnormal ventricular contractility, which has not been previously reported in fetuses with an estimated fetal weight less than the tenth percentile.

contractility.[24,25,27] The reason for this has been the result of the necessity to the orient the 4-chamber view with the apex at 12 or 6 o'clock so that M-mode and pulsed Doppler analysis could record movement of the ventricular walls parallel to the ultrasound beam for maximal accuracy.

The purpose of this study was to simultaneously measure global, transverse, and longitudinal contractility of the right ventricle (RV) and left ventricle (LV) using speckle tracking analysis of the 4-chamber view, which is independent of the position of the fetal heart in utero, in fetuses with an EFW <10th centile.[28–33] The advantages of speckle tracking software is that it automatically tracks the movement and position of the ventricular endocardium during systole and diastole and provides the following benefits: (1) multiple cardiovascular measurements of ventricular contractility are simultaneously computed from 1 analysis[28–33]; (2) the analysis, which only requires a digital clip of the 4-chamber view, takes less than 4 minutes to perform; (3) the measurements are not dependent on the apex of the heart to be at 12 or 6 o'clock, as is required for some M-mode and all pulsed Doppler measurements of ventricular function; (4) equations for the mean and standard deviation (SD) derived from normal fetuses (20–40 weeks of gestation) are available that can be used to compute Z scores and their corresponding centiles for all cardiac measurements for an at-risk fetus; and (5) the analysis is now available for clinical investigation.

Materials and Methods

Study group: fetuses with an estimated fetal weight <10th centile

This was a retrospective study of 50 patients from 25 to 37 weeks of gestation from the University of Colorado outpatient center whose fetuses had an EFW <10th centile and were examined serially during the third trimester of pregnancy. All patients signed a consent form to participate in the study, which was approved by the Colorado Multiple Institutional Review Board (IRB number 14-1360, date of approval Mar. 16, 2018). The last ultrasound examination before delivery was used for the analysis. The EFW was calculated using the Hadlock equation, which included measurements of the biparietal diameter, head circumference, abdominal circumference, and femur length.[34] Exclusion criteria included a maternal age <18 years and any fetus with genetic or structural anomalies. The UAPI and MCAPI were measured, followed by computation of the CPR.[22,35]

Doppler measurements of the umbilical artery and the CPR in the study group

Using data from a previous study, we used the mean and SD values to compute the Z scores and centiles for the UAPI and CPR for the study group (Equations 1 and 2).[35]

Equation (1)

$$\text{Z score} = (\text{Measurement}_{\text{EFW}<10\text{th}}) - \text{Mean}_{\text{control group}} / \text{SD}_{\text{control group}}$$

Equation (2)

$$\text{Z} - \text{score centile} = \text{Normsdist}(\text{Z Score Value})$$

Because multiple thresholds have been reported for UAPI and CPR,[22] the current study used a CPR <10th centile and UAPI >90th centile to identify at-risk fetuses.

Ultrasound image acquisition of the 4-chamber view in fetuses with an EFW <10th centile

Two-dimensional images of the 4-chamber view were obtained using the Voluson E10 system (GE Healthcare, Milwaukee, WI). Images were optimized to enhance the borders between the blood pool and endocardium and were not dependent on the position of the apex of the heart to be at 12 or 6 o'clock. Three- to ten-second cine clips of the 4-chamber view were stored as Digital Imaging and Communications in Medicine (DICOM) files and exported to an offline cloud database. The DICOM images subsequently were downloaded for offline analysis by one of the authors (G.R.D.), The DICOM image frame rate was equivalent to the frame rate acquisition at the time of the examination.

TABLE 1
Right and left ventricular measurements and equations derived from speckle tracking analysis

Ventricular measurements	Equations	Abnormal values	Previously published intraobserver variability[36-39]
Right and left global contractility			
Fractional area change (Figure 1, B)[38]	{[(end-diastolic area − end systolic area)/end-diastolic area] × 100}	<5th centile	0.93 to 0.93 to 0.94
Right and left transverse contractility			
24-segment transverse fractional shortening (Figure 1, C)[37]	{[(end-diastolic width − end-systolic width)/end-diastolic width] × 100}	<5th centile	0.82 to 0.97
Right and left longitudinal contractility			
Longitudinal strain (Figure 1, D) [36]	{[(end-systolic endocardial length − end-diastolic endocardial length)/end-diastolic endocardial length] × 100} (Figure 1, C)	>95th centile	0.93 to 0.94
Longitudinal displacement fractional shortening (Figure 1, E)[36]	{[(mid-chamber end-diastolic length − mid chamber end-systolic length)/mid chamber end-diastolic length] − 100} (Figure 1, D)	<5th centile	0.93 to 0.94
Basal lateral and septal wall annular plane systolic excursion (Figure 1, F)[39]	(end-diastolic length − end-systolic length) (Figure 1, E)	<5th centile	0.97

DeVore et al. Assessment of ventricular contractility in fetuses with an estimated fetal weight less than the tenth centile. Am J Obstet Gynecol 2019.

Analysis of the RV and LV using speckle-tracking software in fetuses with an EFW <10th centile

Two-dimensional images of the 4-chamber view stored in the DICOM format were imported into an offline cardiac software program for analysis (2D Cardiac Performance) developed by TomTec Imaging Systems, Gmbh (Munich, Germany). As previously described, an M-mode derived from the 2-dimensional image of the 4-chamber view was used to identify a single cardiac cycle (end-diastole, end-systole, end-diastole) used for speckle tracking analysis.[28] Following selection of 1 cardiac cycle, the automated software was activated to detect the endocardial border for each ventricle at end-systole and end-diastole.[28] Once the analysis for each ventricle was completed, the data containing the pixel coordinates for the location of the end-systolic and end-diastolic endocardial pixels were exported to an American Standard Code for Information Interchange text file. The text file was imported into an Excel spreadsheet (Microsoft, Redmond, WA) that had been programed to compute the right and left ventricular measurements listed in Table 1[36−39] and illustrated in Figure 1.

Control population

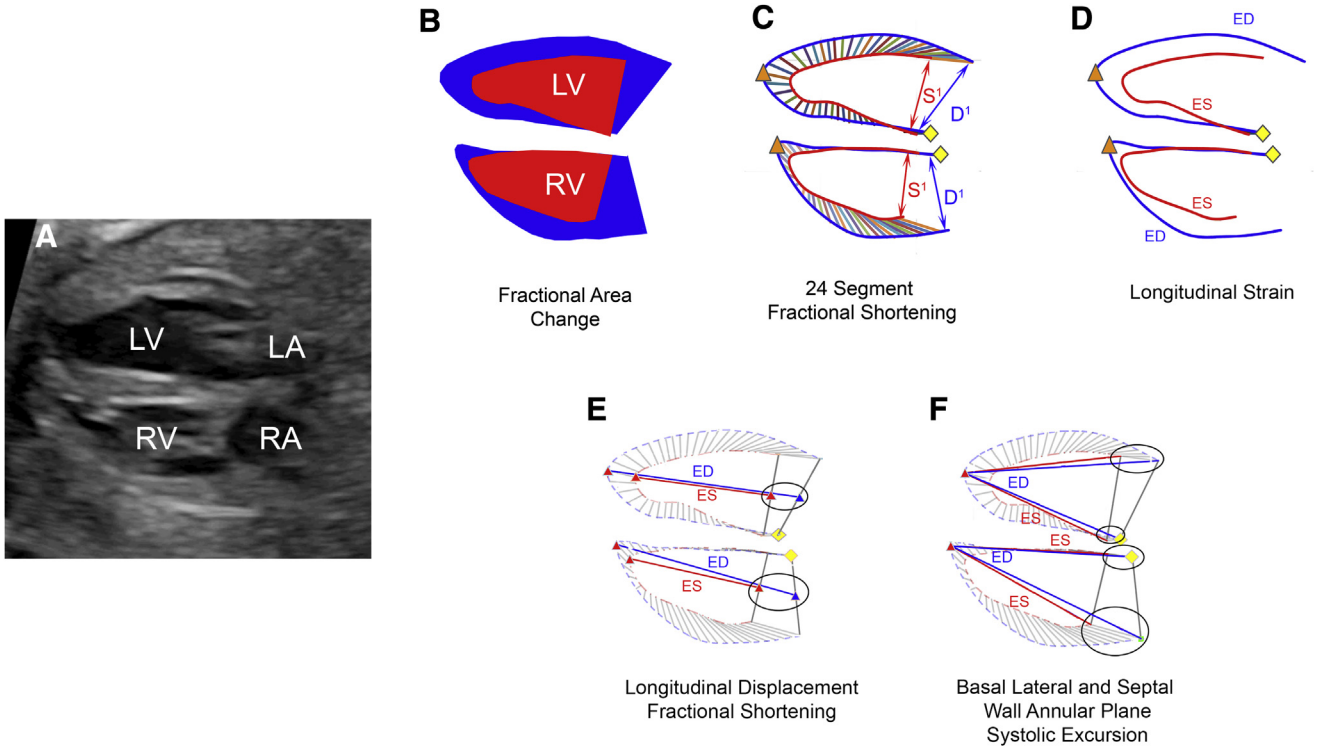
The control population consisted of 200 fetuses examined between 20 and 40 weeks of gestation. The mean and SD values, derived from previous studies of these fetuses,[30−33] were used to compute the Z scores for the following measurements (Table 1) from the RVs and LVs in fetuses with an EFW <10th centile: (1) fractional area change (FAC), (2) 24-segment transverse fractional shortening, (3) longitudinal strain, (4) longitudinal displacement fractional shortening, and (5) basal lateral and septal wall annular plane systolic excursion. The following measurements from the control group were independent of changes in fetal weight from 20 to 40 weeks of gestation: 24-segment transverse fractional shortening, longitudinal strain, and longitudinal displacement fractional shortening. The following measurements were correlated with the estimated fetal weight: FAC, basal lateral wall annular plane systolic excursion, and basal septal wall annular plane systolic excursion.

Statistical analysis

For each of the cardiac measurements described in Table 1, the Z score and corresponding centile values were classified as to whether they were <5th centile (Z score <−1.65) or >95th centile (Z score >1.65). The number of study fetuses that had values <5th or >95th centiles, depending on the measurement, were used to compute the odds ratio and *P* value (NCSS 12, Kaysville, UT) when compared with the expected number (5%) from the control population. A *P* value <.05 was considered significant.

Once the number of fetuses with abnormal measurements of cardiac contractility was identified, they were stratified by the results of the UAPI and CPR. The χ^2 analysis with Yates correction factor was used to determine whether there were significant differences in the number of fetuses with abnormal cardiac measurements (Table 1) between those with a normal vs abnormal UAPI and/or CPR.

FIGURE 1
Graphical display of measurements of ventricular contractility derived from speckle tracking analysis



A, Four-chamber view from which the graphic display of measurements were computed. **B,** Fractional area change. **C,** 24-segment fractional shortening. **D,** Longitudinal strain. **E,** Longitudinal displacement fractional shortening. **F,** Basal lateral and septal wall annular plane systolic excursion.

D', diastolic length of segment 1; *ED*, end-diastolic length; *ES*, end-systolic length; *LA*, left atrium; *LV*, left ventricle; *RA*, right atrium; *RV*, right ventricle; *S'*, systolic length for segment 1.

DeVore et al. Assessment of ventricular contractility in fetuses with an estimated fetal weight less than the tenth centiles. Am J Obstet Gynecol 2019.

Intraobserver and interobserver variability

The intraobserver and interobserver variability have been reported previously for each of the cardiac contractility measurements described in this study.[29–33] Therefore, this analysis was not repeated since the same examiner (G.R.D.) performed all of the measurements for the control and study fetuses. The intraobserver variability for G.R.D. from previous studies is listed in Table 1.

Results

Demographics of the control group

The demographics have been described previously.[29–33] To summarize, the control fetuses demonstrated normal growth for gestational age, determined from first- or second-trimester dating examinations. The fetuses were studied between 20 and 40 weeks of gestation. Fetuses with fetal malformations were excluded from the study as well as fetuses with maternal risk factors that could alter fetal growth.

Demographics of study fetuses with an EFW <10 centile

The ethnicity of the 50 fetuses with an EFW <10th centile was white 82%, Hispanic 6%, black 4%, Asian 2%, and mixed race 6%. The average maternal age was 28.5 (SD 0.71) years. Twenty-four percent of the patients smoked, 32% had other preexisting health issues, 4% had hypertensive disorders of pregnancy, 4% had a TORCH infection (ie, Toxoplasmosis, Other [syphilis, varicella-zoster, parvovirus B19], Rubella, Cytomegalovirus, and Herpes infections), and none had gestational diabetes. The average gestational age at the time of the examination was 32 weeks 4 days (SD 3 weeks 4 days). None of the 50 study fetuses demonstrated absent or reverse diastolic flow of the umbilical artery Doppler waveform.

Distribution of RV and LV measurements classified by the UAPI and CPR

All fetuses, irrespective of the UAPI and CPR (N = 50)

When both ventricles had abnormal contractility findings, all measurements (14%–24%) were significantly different than controls except for the 24-segment fractional shortening of the mid-ventricle segments (9–16) for both ventricles (Table 2). The percent of fetuses with significantly abnormal contractility measurements ranged between 30% and 50% for the RV and 20% and 36% for the LV.

Figure 2 is a tabular representation of the findings for the RVs and LVs grouped by categories of ventricular

TABLE 2
Percent and number of fetuses with an estimated fetal weight <10th centile that had abnormal values for right and left ventricular measurements, irrespective of the Doppler values for the umbilical artery pulsatility index and the cerebroplacental ratio

Measurements	Both ventricles % (N)	Right ventricle % (N)	Left ventricle % (N)
Global contractility			
Fractional area change <5th centile	16% (8)	38% (19)	36% (18)
	OR, 3.6	OR, 11.6	OR, 11.6
	95% CI, 1.3–9.7	95% CI, 4.9–27.4	95% CI, 4.9–27.4
	$P<.01$[a]	$P<.0001$[a]	$P<.0001$[a]
Total global contractility abnormality	24% (8)	38% (19)	38% (19)
24-segment transverse contractility			
Base-segments 1–8 <5th centile	24% (12)	34% (17)	30% (15)
	OR, 6	OR, 5.17	OR, 8.14
	95% CI, 2.4–14.8	95% CI, 4.2–23.2	95% CI, 3.4–19.6
	$P<.0001$[a]	$P<.001$[a]	$P<.0001$[a]
Mid-segments 9–16 <5th centile	12% (6)	30% (15)	22% (11)
	OR, 2.6	OR, 8.14	OR, 5.35
	95% CI, 0.89–7.5	95% CI, 3.38–1958	95% CI, 2.1–13.5
	$P>.05$	$P<.001$[a]	$P=.001$[a]
Apical-segments 17–24, <5th centile	20% (10)	50% (25)	32% (16)
	OR, 4.75	OR,19	OR, 8.9
	95% CI, 1.85–12.16	95% CI, 8.2–44.2	95% CI, 3.7–21.3
	$P=.001$[a]	$P<.001$[a]	$P<.0001$[a]
Total any transverse contractility abnormality	36% (18)[b]	66% (33)[b]	40% (20)
Longitudinal contractility			
Longitudinal strain >95th centile	18% (9)	30% (15)	30% (15)
	OR, 4.2	OR, 8.14	OR, 8.14
	95% CI, 1.6–10.9	95% CI, 3.38–19.58	95% CI, 3.38–19.58
	$P<.01$[a]	$P<.0001$[a]	$P<.0001$[a]
Longitudinal displacement fractional shortening <5th centile	14% (7)	34% (17)	24% (12)
	OR, 3.1	OR, 5.17	OR, 6
	95% CI, 1.1–8.6	95% CI, 4.2–23.2	95% CI, 2.4–14.8
	$P<.05$[a]	$P<.001$[a]	$P<.0001$[a]
Basal-apical lateral wall annular plane systolic excursion <5th centile	22% (11)	34% (17)	26% (13)
	OR, 5.35	OR, 5.17	OR, 6.67
	95% CI, 2.1–13.5	95% CI, 4.2–23.2	95% CI, 2.72–16.35
	$P=.001$[a]	$P<.0001$[a]	$P<.0001$[a]

DeVore et al. Assessment of ventricular contractility in fetuses with an estimated fetal weight less than the tenth centile. Am J Obstet Gynecol 2019. *(continued)*

contractility. Eighty-six percent of fetuses had 1 or more abnormal measurements of cardiac contractility. Fourteen percent had normal cardiac findings for both ventricles. Twenty-two percent had normal contractility of only the RV. Conversely, 42% had normal contractility of only the LV. Analysis of RV contractility demonstrated 78% had 1 or more abnormal measurements. The most frequent abnormality occurred in the transverse contractility group (66%), followed by abnormalities of longitudinal (48%) and global contractility (38%).

TABLE 2
Percent and number of fetuses with an estimated fetal weight <10th centile that had abnormal values for right and left ventricular measurements, irrespective of the Doppler values for the umbilical artery pulsatility index and the cerebroplacental ratio *(continued)*

Measurements	Both ventricles % (N)	Right ventricle % (N)	Left ventricle % (N)
Basal-apical septal wall annular plane systolic excursion <5th centile	16% (8)	32% (16)	20% (10)
	OR, 3.6	OR, 8.9	OR, 4.75
	95% CI, 1.3–9.7	CI, 3.7–21.3	95% CI, 1.85–12.16
	$P<.01$[a]	$P<.0001$[a]	$P=.001$[a]
Total any longitudinal contractility abnormality	34% (17)	48% (24)	40% (20)

CI, confidence interval; *OR*, odds ratio.

[a] The percent and number of fetuses with measurements that were significantly more frequently abnormal than the control group; [b] Significant difference ($P<.05$) between the right ventricle and left ventricle.

DeVore et al. Assessment of ventricular contractility in fetuses with an estimated fetal weight less than the tenth centile. Am J Obstet Gynecol 2019.

Analysis of LV contractility demonstrated 58% had 1 or more abnormal measurements. The most frequent abnormality occurred in the transverse and longitudinal contractility groups (40%), followed by global (38%) contractility. Comparing measurements between the ventricles demonstrated more fetuses had 1 or more abnormalities of transverse contractility of the RV (66%) than the LV (40%), $P<.05$). There were no significant differences between the ventricles for global or longitudinal contractility.

Normal UAPI and CPR (N = 25)

Fifty percent (N=25) of the study fetuses had a normal UAPI and CPR (Table 3). Global FAC was significantly more frequently abnormal in the study fetuses than the control group for both the RV (40%) and LV (40%). Abnormal transverse contractility was significantly more frequent for all 24 segments of the RV (28%–52%) and for the mid- and apical segments of the LV (24%–32%). There was a significant difference for 1 or more abnormal measurements of transverse contractility for the RV (68%) than the LV (36%), $P<.05$. All 4 measurements of longitudinal contractility were abnormal for the RV (28%–32%) and in 3 of the 4 measurements for the LV (24%–32%). There was no significant difference between number of fetuses with abnormal longitudinal measurements between the RV and LV. When global, transverse, and longitudinal contractility measurements were combined, fetuses with an EFW <10th and a normal UAPI and CPR had a greater incidence of abnormal contractility of the RV (80%) than the LV (56%), but the difference was not statistically significant (Figure 2). As a group, 84% of fetuses had 1 or more abnormalities of global, transverse, and longitudinal contractility of 1 or both ventricles (Figure 2).

Abnormal UAPI centile with a normal CPR (N = 11)

Eleven fetuses were in this group (Table 3). Global contractility was significantly more frequent (36%) for both the RV and LV when compared with controls. Abnormalities of the 24-segment RV basal (36%) and apical (36%) transverse fractional shortening were significantly more frequent in the study group than the control fetuses. The RV demonstrated only 1 abnormality of longitudinal contractility, whereas the other measurements of longitudinal contractility were not significantly increased for the RV and LV (Table 3). There were no significant differences between number of abnormal global, transverse, or longitudinal contractility measurements between the RV and LV in the study fetuses (Table 3). When we evaluated the combination of all global, longitudinal, and transverse measurements, 64% of fetuses had 1 or more abnormalities of the RV and 45% for the LV (Figure 2). As a group, 82% of fetuses had 1 or more abnormalities of global, transverse, and longitudinal contractility of 1 or both ventricles (Figure 2).

Abnormal CPR with a normal UAPI (N = 11)

Eleven fetuses were in this group (Table 3). Abnormal global contractility was significantly more frequent (45%) in these fetuses than the control group for the RV, but not the LV (Table 3). Transverse contractility was significantly more frequent for the RV in the study than the control fetuses for the basal (36%) and apical (55%) segments, as well as the LV basal segments (45%) (Table 3). The RV demonstrated only 2 abnormalities of longitudinal contractility, whereas the other measurements of longitudinal contractility were not significantly increased for the RV and LV (Table 3). There were no significant differences between number of abnormal global, transverse, or longitudinal contractility measurements between the RV and LV in the study fetuses (Table 3). When we evaluated the combination of all

FIGURE 2
Display of all 50 participants indicating results from speckle tracking analysis

Number in Group	Abnormal UAPI >90th Centile	Abnormal CPR <10th Centile	NORMAL RV AND LV	NORMAL RV	NORMAL LV	Any Abnormality of Either One or Both Ventricles	Any Abnormality of RV Contractility	Any Abnormality of LV Contractility	Abnormal RV Global Contractility	Abnormal LV Global Contractility	Abnormal RV Transverse Contractility	Abnormal LV Transverse Contractility	Abnormal RV Longitudinal Contractility	Abnormal LV Longitudinal Contractility
1						1	1	1	1	1	1		1	1
2						2	2	2			2		2	2
3					NORMAL LV	3	3		2		3			
4						4	4	3		2	4	1		3
5						5	5	4		3		2	3	4
6						6	6	5	3		5	3	4	5
7					NORMAL LV	7	7				6			
8						8	8	6	4	4	7	4	5	6
9					NORMAL LV	9	9				8			
10					NORMAL LV	10	10		5		9			
11						11	11	7		5	10		6	
12						12	12	8		6	11	5	7	7
13						13	13	9	6	7	12	6	8	8
14						14	14	10	7					
15			NORMAL BOTH	NORMAL RV	NORMAL LV									
16			NORMAL BOTH	NORMAL RV	NORMAL LV									
17						15	15	11	8	8	13	7	9	9
18			NORMAL BOTH	NORMAL RV	NORMAL LV									
19					NORMAL LV	16	16						10	
20					NORMAL LV	17	17				14			
21					NORMAL LV	18	18		9		15			
22			NORMAL BOTH	NORMAL RV	NORMAL LV									
23						19	19	12		9	16	8		
24						20	20	13	10	10	17	9	11	
25				NORMAL RV		21		14						
		Total	4	5	11	21	20	14	10	10	17	9	11	9
		Percent	16%	20%	44%	84%	80%	56%	40%	40%	68%	36%	44%	36%

Number in Group	Abnormal UAPI >90th Centile	Abnormal CPR <10th Centile	Both Ventricles Normal	RV Normal	LV Normal	Any Abnormality of Either One or Both Ventricles	Any Abnormality of RV Contractility	Any Abnormality of LV Contractility	Abnormal RV Global Contractility	Abnormal LV Global Contractility	Abnormal RV Transverse Contractility	Abnormal LV Transverse Contractility	Abnormal RV Longitudinal Contractility	Abnormal LV Longitudinal Contractility
1	1					1	1	1	1		1	1	1	
2	2				NORMAL LV	2	2		2		2		2	
3	3				NORMAL LV	3	3		3				3	
4	4					4	4	2		1	3	2		1
5	5					5	5	3		2	4	3	4	2
6	6			NORMAL RV		6		4		3				3
7	7		NORMAL BOTH	NORMAL RV	NORMAL LV									
8	8			NORMAL RV	NORMAL LV	7								
9	9				NORMAL LV	8	6				5			
10	10		NORMAL BOTH	NORMAL RV	NORMAL LV									
11	11					9	7	5	4	4	6	4	5	4
		Total	2	4	6	9	7	5	4	4	6	4	5	4
		Percent	18%	36%	55%	82%	64%	45%	36%	36%	55%	36%	45%	36%

Number in Group	Abnormal UAPI >90th Centile	Abnormal CPR <10th Centile	Both Ventricles Normal	Normal RV Only	Normal LV Only	Any Abnormality of Either One or Both Ventricles	Any Abnormality of RV Contractility	Any Abnormality of LV Contractility	Abnormal RV Global Contractility	Abnormal LV Global Contractility	Abnormal RV Transverse Contractility	Abnormal LV Transverse Contractility	Abnormal RV Longitudinal Contractility	Abnormal LV Longitudinal Contractility
1		1				1	1	1			1	1	1	1
2		2		NORMAL RV		2		2				2		
3		3			NORMAL LV	3	2		1		2			
4		4				4	3	3	2	1	3	3	2	2
5		5	NORMAL BOTH	NORMAL RV	NORMAL LV									
6		6				5	4	4		2	4	4	3	3
7		7				6	5	5			5			
8		8				7	6	6	3	3			4	4
9		9				8	7	7			6	5		
10		10			NORMAL LV	9	8		4					
11		11			NORMAL LV	10	9		5		7		5	
		Total	1	2	4	10	9	7	5	3	7	5	5	4
		Percent	9%	18%	36%	91%	82%	64%	45%	27%	64%	45%	45%	36%

Number in Group	Abnormal UAPI >90th Centile	Abnormal CPR <10th Centile	Both Ventricles Normal	Normal RV Only	Normal LV Only	Any Abnormality of Either One or Both Ventricles	Any Abnormality of RV Contractility	Any Abnormality of LV Contractility	Abnormal RV Global Contractility	Abnormal LV Global Contractility	Abnormal RV Transverse Contractility	Abnormal LV Transverse Contractility	Abnormal RV Longitudinal Contractility	Abnormal LV Longitudinal Contractility
2	1	1				1	1	1		1	1	1	1	1
3	2	2				2	2	2		2	2	2	2	2
2	3	3				3	3	3			3		3	3
		Total	0	0	0	3	3	3	0	2	3	2	3	3
		Percent	0%	0%	0%	100%	100%	100%	0	67%	100%	67%	100%	100%

		Total All	7	11	21	43	39	29	19	19	33	20	24	20
		Percent All	14%	22%	42%	86%	78%	58%	38%	38%	66%	40%	48%	40%

The *gray rows* represent fetuses with abnormal measurements. The *white rows* represent fetuses with normal measurements. The *blue rows* represent fetuses in which all measurements were normal for either ventricle. The *green rows* represent fetuses in which all measurements were normal for both ventricles.

CPR, cerebroplacental ratio; *LV*, left ventricle; *RV*, right ventricle; *UAPI*, umbilical artery pulsatility index.

DeVore et al. Assessment of ventricular contractility in fetuses with an estimated fetal weight less than the tenth centiles. Am J Obstet Gynecol 2019.

TABLE 3

Percent and number of fetuses with an estimated fetal weight <10th centile that had abnormal values for right and left ventricular measurements based on Doppler values for the umbilical artery pulsatility index and the cerebroplacental ratio

Measurements	Right ventricle normal umbilical artery pulsatility index and normal cerebroplacental ratio N=25	Left ventricle normal umbilical artery pulsatility index and normal cerebroplacental ratio N=25	Right ventricle isolated abnormal umbilical artery pulsatility index >90% N=11	Left Ventricle isolated abnormal umbilical artery pulsatility index >90% N=11	Right ventricle isolated abnormal cerebroplacental ratio <10% N=11	Left ventricle isolated abnormal cerebroplacental ratio <10% N=11	Right ventricle abnormal umbilical artery pulsatility index >90% and abnormal cerebroplacental ratio < 10% N=3	Left ventricle abnormal umbilical artery pulsatility index >90% and abnormal cerebroplacental ratio < 10% N=3
Global contractility								
Fractional area change <5th centile	40% (10)	40% (10)	36% (N=4)	36% (N=4)	45% (N=5)	27% (N=3)	0 (0%)	67% (N=2)
	OR, 6	OR, 6	OR, 5.1	OR, 5.1	OR, 7.5	OR, 3.4		OR, 18
	95% CI, 2.4–15	95% CI, 2.4–15	95% CI, 1.4–19	95% CI, 1.4–19	95% CI, 2–27	95% CI, 0.8–14		95% CI, 1.6–207
	P<.0001[a]	*P*<.0001[a]	*P*=.01[a]	*P*=.01[a]	*P*=.002[a]	*P*=.08		*P*=.02[a]
Total global contractility abnormality	40% (10)	40% (10)	36% (4)	36% (4)	45% (5)	27% (3)	0 (0%)	67% (2)
24-segment contractility								
Base-segments 1–8 <5th centile	28% (N=7)	20% (N=5)	36% (N=4)	18% (N=2)	36% (N=4)	45% (5)	67% (N=2)	67% (N=2)
	OR, 3.5	OR, 2.2	OR, 5.1	OR, 2	OR, 5.1	OR, 7.5:	OR, 18	OR, 18
	95% CI, 1.3–9.3	95% CI, 0.76–6.6	95% CI, 1.4–19	95% CI, 0.4–9.9	95% CI, 1.4–19	95% CI, 2–26	95% CI, 1.6–207	95% CI, 1.6–207
	P=.01[a]	*P*=.14	*P*=.01[a]	*P*=.4	*P*=.01[a]	*P*<.002[a]	*P*=.02[a]	*P*=.02[a]
Mid-segments 9–16 <5th centile	36% (N=9)	24% (N=6)	9% (N=1)	9% (N=1)	27% (N=3)	27% (N=3)	0 (0%)	33% (N=1)
	OR, 5	OR, 2.8	OR, 0.9	OR, 0.9	OR, 3.4	OR, 3.4		OR, 4.5
	95% CI, 2–13	95% CI, 1–7.9	95% CI, 0.1–7.4	95% CI, 0.1–7.4	95% CI, 0.8–14	95% CI, 0.8–14		95% CI, 0.4–51
	P<.0001[a]	*P*<.05[a]	*P*=.9	*P*=.9	*P*=.08	*P*=.08		*P*=.22
Apical-segments 17–24 <5th centile	52% (N=13)	32% (N=8)	36% (N=4)	18% (N=2)	55% (N=6)	27% (N=3)	67% (N=2)	67% (N=2)
	OR, 9.7	OR, 4.2	OR, 5.1	OR, 2	OR, 1.8	OR, 3.4	OR, 18	OR, 18
	90% CI, 4–24	95% CI 1.6–11	95% CI, 1.4–19	95% CI, 0.4–9.9	95% CI, 3–39	95% CI, 0.8–14	95% CI, 1.6–207	95% CI, 1.6–207
	P<.0001[a]	*P*=.003[a]	*P*=.01[a]	*P*=.4	*P*<.001[a]	*P*=.08	*P*=.02[a]	*P*=.02[a]

DeVore et al. Assessment of ventricular contractility in fetuses with an estimated fetal weight less than the tenth centile. Am J Obstet Gynecol 2019.

(continued)

TABLE 3

Percent and number of fetuses with an estimated fetal weight <10th centile that had abnormal values for right and left ventricular measurements based on Doppler values for the umbilical artery pulsatility index and the cerebroplacental ratio *(continued)*

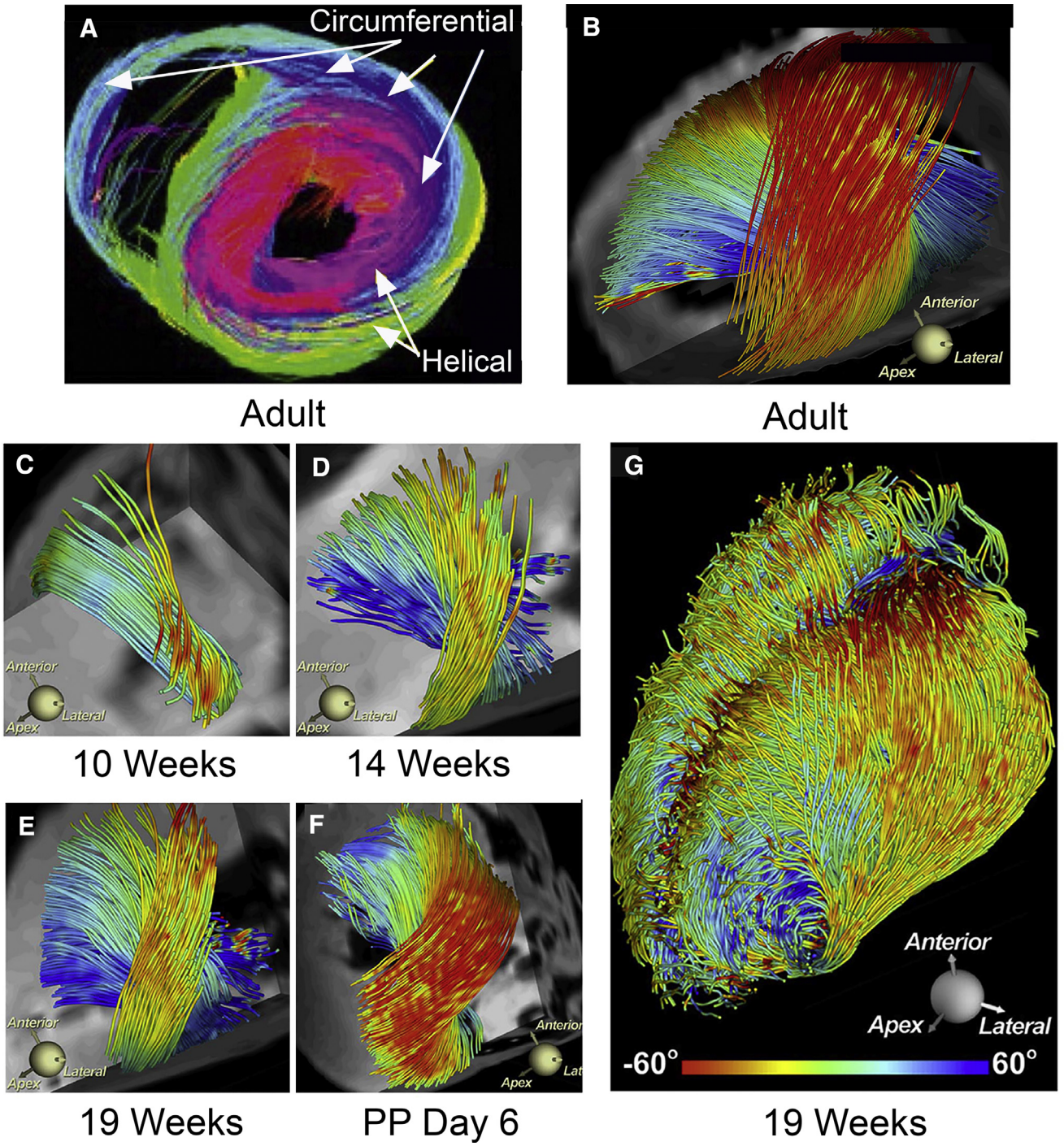
Measurements	Right ventricle normal umbilical artery pulsatility index and normal cerebroplacental ratio N=25	Left ventricle normal umbilical artery pulsatility index and normal cerebroplacental ratio N=25	Right ventricle isolated abnormal umbilical artery pulsatility index >90% N=11	Left Ventricle isolated abnormal umbilical artery pulsatility index >90% N=11	Right ventricle isolated abnormal cerebroplacental ratio <10% N=11	Left ventricle isolated abnormal cerebroplacental ratio <10% N=11	Right ventricle abnormal umbilical artery pulsatility index >90% and abnormal cerebroplacental ratio < 10% N=3	Left ventricle abnormal umbilical artery pulsatility index >90% and abnormal cerebroplacental ratio < 10% N=3
Total any transverse contractility abnormality	68% (17)[b]	36% (9)[b]	55% (6)	36% (4)	64% (7)	45% (5)	100% (3)	67% (2)
Longitudinal contractility								
Longitudinal strain (>95th centile)	32% (N=8)	32% (N=8)	27% (N=3)	27% (N=3)	27% (N=3)	27% (N=3)	67% (N=2)	33% (N=1)
	OR, 4.2	OR, 4.2	OR, 3.4	OR, 3.4	OR, 3.4	OR, 3.4	OR, 18	OR, 4.5
	95% CI, 1.6–11	95% CI, 1.6–11	95% CI, 0.8–14	95% CI, 0.8–14	95% CI, 0.8–14	95% CI, 0.8–14	95% CI, 1.6–207	95% CI, 0.4–51
	P=.003[a]	*P*=.003[a]	*P*=.08	*P*=.08	*P*=.08	*P*=.08	*P*=.02[a]	*P*=.22
Basal-apical displacement fractional shortening <5th centile	28% (N=7)	24% (N=6)	36% (4)	18% (N=2)	45% (5)	18% (N=2)	33% (N=1)	67% (N=2)
	OR, 3.5	OR, 2.8	OR, 5.1	OR, 2	OR, 7.5	OR, 2	OR, 4.5	OR, 18
	95% CI, 1.3–9.3	95% CI, 1–7.9	95% CI, 1.4–19	95% CI, 0.4–9.9	95% CI, 2–26	95% CI, 0.4–9.9	95% CI, 0.4–51	95% CI, 1.6–207
	P=.01[a]	*P*<.05[a]	*P*<.02[a]	*P*=.4	*P*<.002[a]	*P*=.4	*P*=.22	*P*=.02[a]
Basal-apical lateral wall annular plane systolic excursion <5th centile	28% (N=7)	24% (N=6)	27% (N=3)	9% (N=1)	36% (N=4)	27% (N=3)	100% (3)	100% (3)
	OR, 3.5	OR, 2.8	OR, 3.4	OR, 0.9	OR, 5.1	OR, 3.4	OR, 61	OR, 61
	95% CI, 1.3–9.3	95% CI, 1–7.9	95% CI, 0.8–14	95% CI, 0.1–7.4	95% CI, 1.4–19	95% CI, 0.8–14	95% CI, 3–1235	95% CI, 3–1235
	P=.01[a]	*P*<.05[a]	*P*=.08	*P*=.9	*P*=.01[a]	*P*=.08	*P*<.01[a]	*P*<.01[a]
Basal-apical septal wall annular plane systolic excursion <5th centile	32% (N=8)	12% (3)	27% (N=3)	18% (N=2)	27% (N=3)	18% (N=2)	100% (3)	100% (3)
	OR, 4.2	OR, 1.2	OR, 3.4	OR, 2	OR, 3.4	OR, 2	OR, 61	OR, 61
	95% CI, 1.6–11	95% CI, 0.3–4.4	95% CI, 0.8–14	95% CI, 0.4–9.9	95% CI, 0.8–14	95% CI, 0.4–9.9	95% CI, 3–1235	95% CI, 3–1235
	P=.003[a]	*P*=.07	*P*=.08	*P*=.4	*P*=.08	*P*=.4	*P*<.01[a]	*P*<.01[a]
Total any longitudinal contractility abnormality	44% (11)	36% (9)	45% (5)	36% (4)	45% (5)	36% (4)	100% (3)	100% (3)

CI, confidence interval; *OR*, odds ratio.

[a] The percent and number of fetuses with measurements that were significantly more frequently abnormal than the control group; [b] Significant difference (*P*<.05) between the right ventricle and left ventricle.

DeVore et al. Assessment of ventricular contractility in fetuses with an estimated fetal weight less than the tenth centile. Am J Obstet Gynecol 2019.

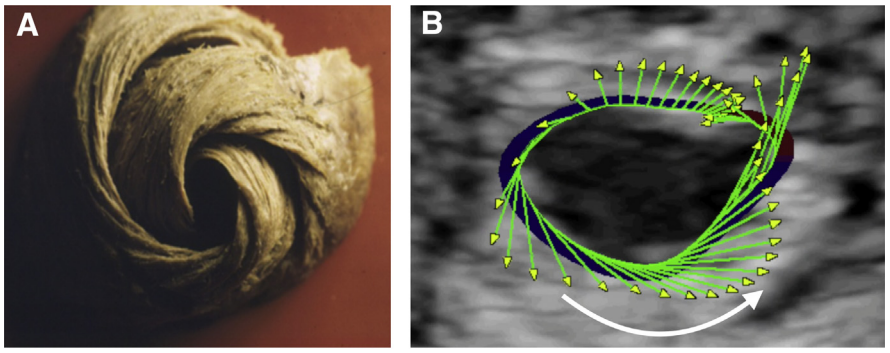
FIGURE 3
Human myocardial fibrillogenesis in the adult and fetal hearts



A, The short axis helical right-handed helix (*red*) and the left-handed helix (*green/yellow*). The circumferential fibers (*blue*) have no helix formation. **B,** The left lateral wall in the adult, with similar color interpretation as in (**A**). **C,** The left lateral wall of a 10-week fetus that has the beginning of helical formation. **D and E,** The evolution of helical and circumferential fibers from 14 to 19 weeks of gestation. **F,** A more-developed fiber orientation at 6 days post-delivery (PD). **G,** The entire heart at 19 weeks. Used with permission.[47,48]

DeVore et al. Assessment of ventricular contractility in fetuses with an estimated fetal weight less than the tenth centiles. Am J Obstet Gynecol 2019.

FIGURE 4
Apical view of the heart muscle



A, Clockwise and counterclockwise spiral formation. Used with permission.[49] **B,** The movement of the individual vectors of the apical myocardium in a counterclockwise rotation of the left ventricle during systole. Used with permission.[47]

DeVore et al. Assessment of ventricular contractility in fetuses with an estimated fetal weight less than the tenth centiles. Am J Obstet Gynecol 2019.

global, longitudinal, and transverse measurements, 82% of fetuses had 1 or more abnormalities of the RV and 64% for the LV (Figure 2). As a group, 91% of fetuses had 1 or more abnormalities of global, transverse, and longitudinal contractility of 1 or both ventricles (Figure 2).

Combined abnormal UAPI and abnormal CPR (N = 3)

Three fetuses were in this group (Table 3). The LV demonstrated a statistically greater incidence of abnormalities of global, transverse, and longitudinal contractility in study fetuses (67%−100%) than controls. The RV only demonstrated significant differences for transverse and longitudinal contractility (67%−100%) when compared with controls. When we evaluated all global, longitudinal, and transverse measurements, 100% of fetuses had one or more abnormalities of the RV and/or LV (Figure 2).

Comparison of measurements of ventricular contractility between fetuses with a normal vs abnormal UAPI and/or and CPR

There were no significant differences between the number of study fetuses with a normal UAPI and normal CPR for any of the individual contractility measurements of the RV and LV when compared with fetuses with an isolated abnormal UAPI, an isolated abnormal CPR, or with both an abnormal UAPI and CPR (Appendix, Supplemental Tables 1 and 2).

Discussion

Principal findings

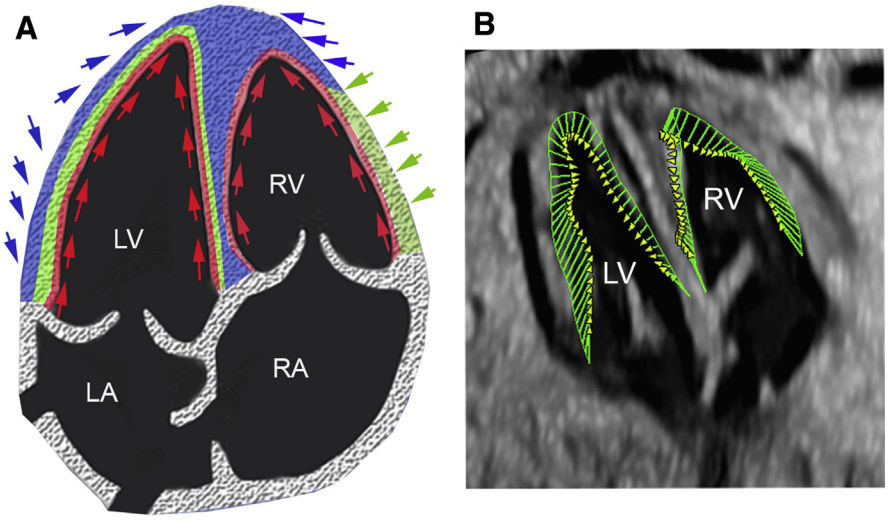
First, there was a significant increase in the number of fetuses with an EFW <10th centile, irrespective of the UAPI and CPR, who demonstrated abnormal right (78%) and left (58%) global, transverse, and longitudinal contractility when compared with the control population. Second, abnormal RV transverse contractility measurements were significantly more frequent than LV measurements for the entire group of 50 fetuses (66% vs 40%) as well as those fetuses with a normal UAPI and CPR (68% vs 36%). Finally, when we compared fetuses with an EFW <10th centile with a normal UAPI and MCA with those with an isolated abnormal UAPI, isolated abnormal CPR, and both abnormal UAPI and MCA, there were no significant differences in the number of fetuses with abnormal ventricular contractility for global, transverse, or longitudinal measurements.

Study design—perspective

Classification of study fetuses based on the number of fetuses with abnormal cardiac contractility measurements <5th or >95th centiles

When we compared measurements of cardiac function between control and study groups, previous investigators have reported the mean and SD of the measurement values for each group and determined whether there was a significant difference between the 2 groups. However, data regarding the number of study fetuses having abnormal findings have not been reported.[40−42] Although previous studies have provided important, foundational insights as to which cardiac measurements were abnormal between study and control groups, the current study took a different approach. We were interested in how many fetuses with an EFW <10th centile had abnormal measurements of ventricular contractility by deriving the number and percent of fetuses whose contractility measurements were outside (<5th or >95th centiles) of the normal distribution, as determined by computing the Z score and corresponding centile using the mean and SD from previously reported control fetuses.[29−33] The reasons for using this approach are 3-fold: (1) outlying measurements in a study group may result in mean values that are skewed as well as values for the SD; (2) investigators who may consider duplicating a particular study to see whether the results are similar before implementing a specific test in patient care may desire to know the percent of study fetuses with abnormal values, instead of just the corresponding *P* value derived from the analysis of the mean and SD values for the study and control groups; and (3) after we determined the percent of study subjects who had abnormal values, the clinician may or may not elect to use the findings in clinical practice, even though the *P* value between the control and study groups is significant.

FIGURE 5
Four-chamber view of myocardial muscle orientation in the fetal heart



Longitudinal **Helical** **Circumferential**

A, The location of the longitudinal, obliquely oriented helical, and circumferential fibers. The circumferential fibers are present along the right and left ventricular free walls as well as the left side of the interventricular septum. **B,** Vector analysis of illustrating the direction and velocity of myocardial segments during systole. The right lateral wall demonstrates longitudinal movement along 2/3 of the wall, with oblique movement of the apical portion of the wall. The left ventricle demonstrates longitudinal movement of the upper 1/3 of the lateral wall, with circumferential movement of the lateral mid and apical sections of the wall. The septal wall demonstrates movement resulting from circumferential and oblique-helical fibers during systole.

LA, left atrium; *LV*, left ventricle; *RA*, right atrium; *RV*, right ventricle.

DeVore et al. Assessment of ventricular contractility in fetuses with an estimated fetal weight less than the tenth centiles. Am J Obstet Gynecol 2019.

Understanding ventricular morphology of the ventricles

To understand ventricular contractility measurements used in this study, it is important to review the orientation of the muscle fibers that comprise the ventricles of the heart.[44,45] In 2013 Mekkaoui et al[46] scanned intact cadaver hearts with diffusion magnetic resonance imaging tractography to identify the fiber orientation of the myocardium. They compared the adult heart with the hearts of fetuses at 10 weeks, 14 weeks, 19 weeks, and a newborn 6 days following birth. They identified 3 fiber orientations in the adult heart; 2 opposing helical tracts that ran from the base to the apex of the left ventricular lateral wall, and a non-helical circumferential tract (Figure 3, A and B).[46–48] The fiber orientation, similar to the adult heart, was not present at 10 weeks of gestation (Figure 3, C) but evolved to an adult orientation by 19 weeks (Figure 3, D, E, G).[46] However, the density of fibers did not approach that of the adult heart until after the postnatal period (Figure 3, F).[46] The helical structure of the ventricles recently was reviewed by Buckberg et al,[36,37] who affirmed the findings of Torrent-Guasp, who hypothesized that the heart demonstrated 2 interconnected muscle bands; a basal loop with transverse fibers surrounding the LV and RV, and an apical loop, composed of a right- and left-handed helix that crossed each other at a 60-degree angle, forming an apical vortex (Figure 4).[47,49] A video has been posted online by Buckberg et al that demonstrates Torrent-Guasp's unraveling of the heart illustrating the aforementioned anatomy (http://www.mdpi.com/2308-3425/5/2/33/s1).[36] The purpose of the right- and left-handed helix is to provide opposite contraction forces from the base and apex for each ventricle that results in ejecting and filling of blood from each chamber, similar to wringing and unwringing of a dishrag.

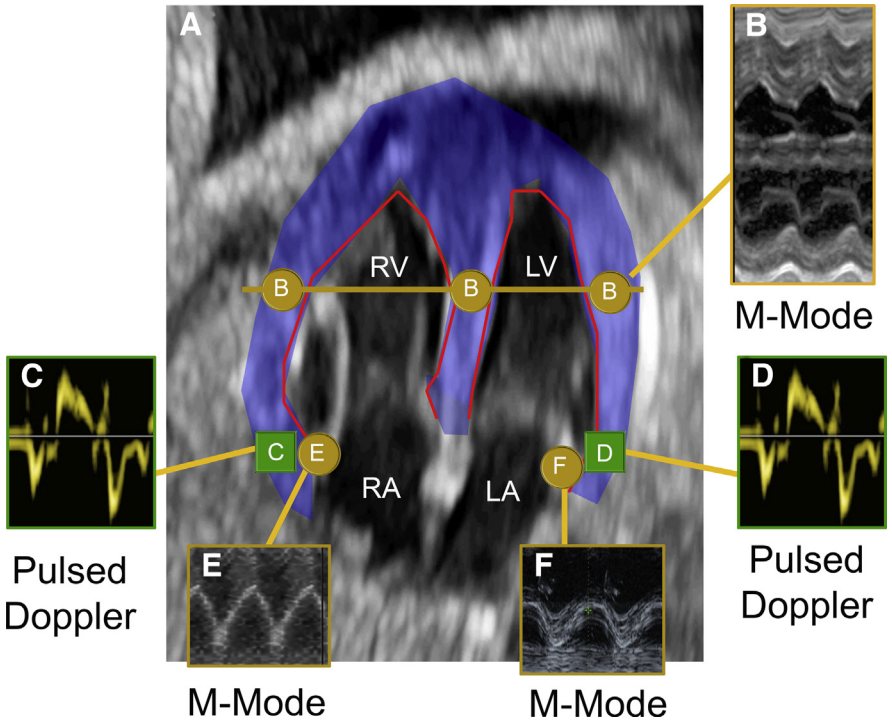
Similar to the apex of the heart, the septum has oblique, opposing helical muscles, resulting in coiling and shortening of the muscles, as is observed in the ventricular walls (Figures 3, 4, and 5).[47,48] In addition, the left lateral ventricular wall and left ventricular septum have circumferential fibers that contribute to contraction of the myocardium toward the center of the LV chamber during systole (Figure 5). Therefore, as the result of myocardial fiber and muscle orientation, the interventricular septum is committed primarily to the LV. Studies of the RV have suggested that longitudinal shortening from the base to the apex of the chamber develops from coiling and shortening of the apical helix, with little contribution from the lateral wall longitudinal and circumferential fibers (Figures 4 and 5).[48,50] In adults and experimental animals, it has been demonstrated that RV heart failure does not occur after elimination of free wall muscle function. However, heart failure occurs when septal ischemia is present.[36,38,39,47,48,50,51]

As the result of the aforementioned muscle orientations that form the components of ventricular contractility, 3 contraction patterns can be identified from the 4-chamber view using speckle tracking analysis; (1) shortening of the base of the ventricles toward the apex (longitudinal contractility); (2) movement of the ventricular walls toward the center of each chamber (transverse contractility); and (3) interaction of muscle groups resulting in a decrease in chamber size during ventricular systole (global contractility).[36,48,50]

Imaging modalities used to measure ventricular contractility

Previous studies evaluating ventricular systolic function have used, in various combinations, M-mode,[24,52–60] pulsed Doppler,[27,61] and 2-dimensional

FIGURE 6
M-mode and pulsed Doppler measurements of longitudinal and transverse contractility



A, Four-chamber view with the apex at 12 o'clock. **B,** The plane of acquisition for the M-mode to measure transverse contractility of the right and left ventricles. **C and D,** Placement of the pulsed Doppler sample volume at the base of the RV and LV walls to record tissue Doppler displacement for computation of longitudinal contractility. **E and F,** Placement of the M-mode cursor to record annular plane systolic excursion of the tricuspid (TAPSE) and mitral (MAPSE) annulus used to evaluate longitudinal contractility.

LA, left atrium; *LV*, left ventricle; *MAPSE*, mitral annular plane systolic excursion; *RA*, right atrium; *RV*, right ventricle; *TAPSE*, tricuspid annular plane systolic excursion.

DeVore et al. Assessment of ventricular contractility in fetuses with an estimated fetal weight less than the tenth centiles. Am J Obstet Gynecol 2019.

images of the 4-chamber view (Figure 6).[39,49,63–68] M-mode has been used to measure movement of the annulus at the base of the right and left ventricles towards the apex, referred to as tricuspid or mitral annular plane systolic excursion. This has been accomplished by placing an M-mode cursor perpendicular to the annuli, located at the base of each ventricle, when the ventricular apex was at 6 or 12 o'clock (Figure 6).[24,58–60] In addition, transverse contractility has been measured by placing the M-mode perpendicular to the interventricular septum and walls, in the mid-chamber, to measure fractional shortening (Figure 6).[52,54–57] Pulsed-wave tissue Doppler has been used to measure systolic peak velocity of the ventricular and septal walls (Figure 6).[27,61] In addition, RV and LV cardiac outputs have been computed from the aortic and pulmonary artery Doppler waveforms.[69–72] Two-dimensional images of the end-diastolic and end-systolic areas of the RV and LV have been used to compute the FAC and longitudinal strain.[61–68,73] Therefore, to measure components of global contractility, transverse contractility, and longitudinal contractility, multiple imaging modalities have been used in previous studies.[11,12,27–30] Several of these measurements require the examiner to orient the ventricular chambers so that the apex is either parallel (tissue Doppler, tricuspid annular plane systolic excursion, mitral annular plane systolic excursion) to the ultrasound beam or perpendicular to the ultrasound beam (transverse M-mode fractional shortening), whereas measurements of FAC and longitudinal strain are not dependent on orientation of the chambers to the ultrasound beam.

To obtain a comprehensive evaluation of ventricular contractility using the aforementioned diagnostic tools may be problematic, depending on the orientation of the fetus during the examination. However, using speckle tracking analysis, as described in this study, allows the examiner to make 2 measurements from each ventricle for the software to compute all of the measurements listed in Table 1 and illustrated in Figure 1. To accomplish this takes less than 4 minutes using proprietary or commercially available software designed for this purpose.

Clinical implications

Evaluation of fetal ventricular contractility in fetuses with a normal UAPI and CPR

Six national societies from the United States, United Kingdom, New Zealand, Canada, Ireland, and France have published varying definitions for intrauterine FGR.[74–79] Although all have included an estimated fetal weight <10th centile as a universal component, there are disparate opinions regarding the role of Doppler ultrasound of the umbilical and middle cerebral arteries as well as the CPR.[74–79] In 2016, a Delphi analysis by an international panel of 45 experts classified fetuses with an EFW <10 centile as follows: (1) SGA: EFW >3rd centile to 10th centile with normal UAPI and CPR; (2) FGR: fetuses with an EFW <3rd centile with normal Doppler measurements of the UAPI and CPR, and (3) FGR: fetuses with an EFW>3rd centile but <10th centile with an abnormality of either the UAPI and/or CPR.[80] Although the ACOG definition of FGR would include all 50 of the study fetuses since it does not discriminate between SGA and FGR fetuses using the

UAPI or CPR, the consensus from the Delphi study would have identified 50% of the study fetuses as SGA and 50% having FGR. When Doppler results of the UAPI and CPR are normal, clinicians may conclude that these fetuses are "constitutionally small" and not at risk for adverse outcome.[81,82] However, the results from the speckle tracking analysis of ventricular function would suggest that these fetuses have a significantly increased incidence of abnormal RV (80%) and LV (56%) ventricular contractility, even though the UAPI and CPR were normal. Girsen et al[83] examined 14 fetuses in which the EFW was <10th centile and the UAPI and UAPI/MCAPI ratio (group 1) were normal. They obtained cord blood measurements of N-terminal fragments of A (atrial)- and B (ventricular)-type natriuretic peptide, which are the breakdown products of A- and B-type natriuretic peptides that are synthesized in response to cardiac volume and pressure overload, resulting in an increase in salt and water excretion, enhanced capillary permeability, and relaxation of vascular smooth muscles.[83] In group I fetuses, they found no significant difference in cardiac systolic function studies (combined RV and LV cardiac output, RV and LV cardiac output, RV and LV fractional shortening, RV and LV ejection forces, and LV myocardial performance index) and B (ventricular)-type natriuretic peptide when compared with control fetuses.[84] However, although the measured values were not significantly different between the controls and Group I fetuses, 31% of group I fetuses had B (ventricular)-type natriuretic peptides values >95th centile.[83] Although A (atrial)-type natriuretic peptide values were significantly different between control and Group I fetuses, the authors did not provide the percent of fetuses with abnormal values for Group I fetuses. Girsen et al[84] also reported similar findings when measuring erythropoietin levels in a similar cohort of fetuses with growth restriction and normal UAPI in which abnormally elevated erythropoietin levels were present in 44% of fetuses, all of whom had normal diastolic and systolic Doppler cardiac function studies. Although the ventricular function measurements used by Girsen et al did not demonstrate differences between Group I (normal UAPI and UA/MCA) and their control fetuses, our study demonstrated a significant difference in ventricular contractility measurements for both the RV and LV for similarly classified fetuses (EFW <10th centile and normal UAPI and CPR).

In a study by Perez-Cruz et al[41] in which they examined global, RV, and LV function in fetuses with an EFW <10th centile and normal Doppler of the UAPI and CPR, they used M-mode, conventional Doppler, and tissue Doppler ultrasound and found significant differences between control and study fetuses. However, to estimate the number of fetuses with abnormal findings when only the mean and SDs are provided between a control and study groups, DeVore et al recently reported deriving these values by a modification of the z-score equation.[76] Because Perez-Cruz et al only reported the mean and SD between the control and study fetuses, the aforementioned analysis using the modified Z-score equation described by DeVore et al was used, which estimated the percent of fetuses with abnormal systolic function to range between 13% and 24% for the LV and 16% and 20% for the RV (Appendix, Supplemental Table 3).[43] Significantly abnormal RV (80%) and LV (56%) function in the current study using speckle tracking analysis was greater than the aforementioned estimates reported in the study by Perez-Cruz et al.[41]

Recently, Crispi et al[85] examined the placentas of fetuses with an EFW <10th centile that were classified as SGA (normal UAPI and CPR) and FGR (abnormal UAPI and/or CPR) using apoptotic markers. They reported accelerated placental aging that included reduced telomerase activity and subsequent telomere shortening associated with active cell senescence.[85] They concluded that accelerated placental aging occurred in both groups of fetuses, supporting a common pathophysiology. They challenged the concept of fetuses with an EFW <10th centile with normal UAPI and CPR as being only "constitutionally small" and suggested they had similar pathologic placentas as those fetuses with FGR.[85]

Evaluation of fetal ventricular contractility in fetuses with an abnormal UAPI and normal CPR

Crispi et al[60] examined 4 biochemical markers (B [ventricular]-type natriuretic peptide, heart fatty acid binding protein, troponin, and high sensitivity C-reactive protein) that have been associated with myocardial cell damage in adults and applied them to fetuses with FGR that were classified according to the UAPI waveform.[26] Stage 1 fetuses were defined as having an abnormal UAPI in the presence of forward flow above the baseline during diastole.[26] They compared the cord blood biochemical markers with echocardiographic measurements (modified myocardial performance and its 3 components—isovolumic contraction time [ICT], ejection time, and isovolumic relaxation time) recorded from the LV and the combined cardiac outputs (CCO) from the RV and LV between controls and study fetuses.[26] Stage 1 fetuses demonstrated no abnormal systolic function echocardiographic measurements (ICT, CCO). Only B-type natriuretic peptide of the biochemical markers was abnormal in these fetuses. In a similar cohort of fetuses with an isolated abnormal UAPI, our results demonstrated significant abnormal values for global, transverse, and longitudinal contractility for both ventricles. Therefore, our findings would suggest that the diagnostic tools derived from speckle tracking analysis may be more sensitive for identifying abnormal systolic function in stage 1 fetuses since none of the systolic function measurements (ICT, ejection time, CCO) reported by Crispi et al were abnormal in this group, even though B-type natriuretic peptide was abnormal.

Evaluation of fetuses with an abnormal CPR <10th centile and normal UA PI < 90th centile

The CPR represents a relationship between the umbilical artery and middle cerebral artery blood flow. When abnormal growth occurs after 32 weeks of gestation, an abnormal CPR may be detected and is often the result of increased blood flow to the fetal brain in the presence of a normal UAPI.[22,86] An abnormal CPR has been reported to be associated with adverse outcome that includes stillbirth, acidosis, neonatal morbidity, and operative obstetrical delivery as the result of intrapartum fetal distress.[2,82,86] Eleven of the 14 fetuses with an abnormal CPR had a normal UAPI. Although some clinicians have embraced the CPR as a diagnostic tool for detecting fetuses at risk for adverse fetal and neonatal outcomes, concern has been raised by some investigators that its performance as an isolated screening tool is limited.[77,79,86] One reason is the varied thresholds that have been suggested for identification of an abnormal value.[22,86] When the CPR is abnormal, identification of cardiac dysfunction may be important to further understand the pathophysiology of changes in cerebral blood flow. In the current study, the only significant abnormality of LV contractility when an isolated abnormal CPR was present was a greater rate of abnormal basal transverse shortening (45%). However, RV global, transverse, and longitudinal contractility were abnormal, with 82% of fetuses having some form of abnormal RV function. In a study of the same cohort of fetuses, Hobbins[87] reported that the RV end-diastolic area was abnormally increased in 45% of these fetuses, with the LV area only increased in 9%. A dilated RV could result in alterations in LV filling, resulting in decreased LV cardiac contractility and associated cardiac output.

Evaluation of fetuses with an abnormal CPR <10th centile and abnormal UAPI >90th centile

Although this combination of findings only occurred in 3 fetuses, 67%−100% had abnormal transverse and longitudinal contractility of both ventricles. However, only the LV demonstrated decreased global contractility, whereas abnormal RV global contractility did not occur in any of the 3 fetuses. Since the number of fetuses studied was small, the only conclusions that can be considered is that cardiac contractility was abnormal for both ventricles, similar to what was observed in the fetuses making up the remainder of the study group.

Patterns of abnormal global, transverse, and longitudinal contractility in fetuses with an EFW <10th centile

When examining transverse contractility, we found the RV was more abnormal than the LV in fetuses with an EFW <10th centile, irrespective of the UAPI and CPR findings and in fetuses with a normal UAPI and normal CPR. The reason for the decreased contractility of the RV may be because it is the systemic ventricle, pumping blood to the body and placenta and therefore working against a higher resistance than the LV. The measurements resulting in a greater resistance may be the result of an enlarged RV, which results in an abnormal sphericity index, as has been previously reported by our group in fetuses with an estimated fetal weight less than the 10th centile.[88] When the RV is enlarged, this results in decreased transverse contractility because of a larger end-diastolic dimension that, when the fractional shortening is computed, results in a lower value for a given systolic displacement of the walls.

Research implications

Previous studies measured biochemical markers suggestive of myocardial dysfunction in fetuses with an EFW <10th centile with a normal UAPI and normal CPR and found that cardiac measurements using pulsed Doppler and M-mode ultrasound were variable, some being normal and others abnormal.[83,84] Since speckle tracking analysis of ventricular contractility, as described in the current study, may identify more fetuses who have been classified as SGA (normal UAPI and normal CPR) as having ventricular dysfunction when compared with using M-mode, conventional and tissue Doppler evaluation of ventricular function, future studies should be undertaken to determine whether there is evidence of biochemical changes in A- and B-type natriuretic peptide as well as erythropoietin cord blood levels in these fetuses who demonstrate abnormal ventricular function defined by speckle tracking criteria described in the current study. If present, this would further underscore the potential of speckle tracking analysis to be a more sensitive indicator of abnormal ventricular contractility than previously used fetal diagnostic tests of ventricular function.[41,83,84] In addition, evaluation of neonatal ventricular function using the same speckle tracking analysis used in the current study should be undertaken to determine whether changes in global, longitudinal, and transverse contractility persist postnatally.

Strengths and limitations

The strengths of this study are (1) demonstration of a single analytic tool using speckle tracking to evaluate ventricular contractility that results in detailed evaluation of global, transverse, and longitudinal contractility of the ventricles; (2) demonstration of ventricular systolic dysfunction in fetuses with an EFW <10th centile who had a normal UAPI and CPR; and (3) identification of different ventricular function profiles, depending on the presence or absence of abnormal UAPI and/or CPR. The limitation of the study is that postnatal evaluation of the heart has not been completed at the time of this writing, as this cohort of fetuses is part of an ongoing study in which follow-up data are being collected and analyzed. Another limitation is that speckle tracking analysis, as described in this study, is only available on one ultrasound machine used routinely for fetal assessment by noncardiologists.

Conclusions

Abnormal ventricular contractility was present in fetuses with an EFW <10th centile, irrespective of the UAPI and

CPR. For both the RV and LV, abnormalities of ventricular contractility were more prevalent in transverse measurements, than global and longitudinal measurements. In addition, the RV demonstrated a greater incidence of abnormal contractility measurements than the LV. Fetuses with an EFW <10th centile may be considered to undergo assessment of ventricular contractility, irrespective of the Doppler findings of the UAPI, and CPR. ■

Acknowledgments

We acknowledge Allison Gillen, RDMS, for obtaining images of the 4-chamber view used in this study.

References

1. Rodriguez-Lopez M, Cruz-Lemini M, Valenzuela-Alcaraz B, et al. Descriptive analysis of different phenotypes of cardiac remodeling in fetal growth restriction. Ultrasound Obstet Gynecol 2017;50:207–14.

2. Crispi F, Miranda J, Gratacos E. Long-term cardiovascular consequences of fetal growth restriction: biology, clinical implications, and opportunities for prevention of adult disease. Am J Obstet Gynecol 2018;218:S869–79.

3. Cruz-Lemini M, Crispi F, Valenzuela-Alcaraz B, et al. A fetal cardiovascular score to predict infant hypertension and arterial remodeling in intrauterine growth restriction. Am J Obstet Gynecol 2014;210:552 e1–52 e22.

4. Cruz-Lemini M, Crispi F, Valenzuela-Alcaraz B, et al. Fetal cardiovascular remodeling persists at 6 months of life in infants with intrauterine growth restriction. Ultrasound Obstet Gynecol 2016;48:349–56.

5. Eriksson JG, Kajantie E, Thornburg K, Osmond C. Prenatal and maternal characteristics and later risk for coronary heart disease among women. Eur J Prevent Cardiol 2016;23:385–90.

6. Mierzynski R, Dluski D, Darmochwal-Kolarz D, et al. Intra-uterine growth retardation as a risk factor of postnatal metabolic disorders. Curr Pharmaceut Biotechnol 2016;17:587–96.

7. Grantz KL, Hediger ML, Liu D, Buck Louis GM. Fetal growth standards: the NICHD fetal growth study approach in context with INTERGROWTH-21st and the World Health Organization Multicentre Growth Reference Study. Am J Obstet Gynecol 2018;218:S641–55.e28.

8. Papageorghiou AT, Kennedy SH, Salomon LJ, et al. The INTERGROWTH-21(st) fetal growth standards: toward the global integration of pregnancy and pediatric care. Am J Obstet Gynecol 2018;218:S630–40.

9. Sovio U, Smith GCS. The effect of customization and use of a fetal growth standard on the association between birthweight percentiles and adverse perinatal outcome. Am J Obstet Gynecol 2018;218:S738–44.

10. Villar J, Cheikh Ismail L, Staines Urias E, et al. The satisfactory growth and development at 2 years of age of the INTERGROWTH-21 Fetal Growth Standards cohort support appropriateness for constructing international standards. Am J Obstet Gynecol 2018;218:S841–54.e2.

11. Kiserud T, Piaggio G, Carroli G, et al. The World Health Organization Fetal Growth Charts: a multinational longitudinal study of ultrasound biometric measurements and estimated fetal weight. PLoS Med 2017;14:e1002220.

12. Blue NR, Beddow ME, Savabi M, Katukuri VR, Chao CR. Comparing the Hadlock fetal growth standard to the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development racial/ethnic standard for the prediction of neonatal morbidity and small for gestational age. Am J Obstet Gynecol 2018;219:474.e1–12.

13. Gaccioli F, Aye I, Sovio U, Charnock-Jones DS, Smith GCS. Screening for fetal growth restriction using fetal biometry combined with maternal biomarkers. Am J Obstet Gynecol 2018;218:S725–37.

14. Tarca AL, Hernandez-Andrade E, Ahn H, et al. Single and serial fetal biometry to detect preterm and term small- and large-for-gestational-age neonates: a longitudinal cohort study. PLoS One 2016;11:e0164161.

15. Hiersch L, Melamed N. Fetal growth velocity and body proportion in the assessment of growth. Am J Obstet Gynecol 2018;218:S700–11.e1.

16. Burton GJ, Jauniaux E. Pathophysiology of placental-derived fetal growth restriction. Am J Obstet Gynecol 2018;218:S745–61.

17. Sultana Z, Maiti K, Dedman L, Smith R. Is there a role for placental senescence in the genesis of obstetric complications and fetal growth restriction? Am J Obstet Gynecol 2018;218:S762–73.

18. Turan OM, Turan S, Sanapo L, Rosenbloom JI, Baschat AA. Semiquantitative classification of ductus venosus blood flow patterns. Ultrasound Obstet Gynecol 2014;43:508–14.

19. Wada N, Tachibana D, Kurihara Y, et al. Alterations in time intervals of ductus venosus and atrioventricular flow velocity waveforms in growth-restricted fetuses. Ultrasound Obstet Gynecol 2015;46:221–6.

20. Bahlmann F, Al Naimi A, Ossendorf M, Schmidt-Fittschen M, Willruth A. Hematological changes in severe early onset growth-restricted fetuses with absent and reversed end-diastolic flow in the umbilical artery. J Perinat Med 2017;45:367–73.

21. Caradeux J, Martinez-Portilla RJ, Basuki TR, Kiserud T, Figueras F. Risk of fetal death in growth-restricted fetuses with umbilical and/or ductus venosus absent or reversed end-diastolic velocities before 34 weeks of gestation: a systematic review and meta-analysis. Am J Obstet Gynecol 2018;218:S774–82.e21.

22. DeVore GR. The importance of the cerebroplacental ratio in the evaluation of fetal well-being in SGA and AGA fetuses. Am J Obstet Gynecol 2015;213:5–15.

23. Berkley E, Chauhan SP, Abuhamad A. Doppler assessment of the fetus with intrauterine growth restriction. Am J Obstet Gynecol 2012;206:300–8.

24. Cruz-Lemini M, Crispi F, Valenzuela-Alcaraz B, et al. Value of annular M-mode displacement vs tissue Doppler velocities to assess cardiac function in intrauterine growth restriction. Ultrasound Obstet Gynecol 2013;42:175–81.

25. Comas M, Crispi F, Cruz-Martinez R, Martinez JM, Figueras F, Gratacos E. Usefulness of myocardial tissue Doppler vs conventional echocardiography in the evaluation of cardiac dysfunction in early-onset intrauterine growth restriction. Am J Obstet Gynecol 2010;203:45.e1–7.

26. Crispi F, Hernandez-Andrade E, Pelsers MM, et al. Cardiac dysfunction and cell damage across clinical stages of severity in growth-restricted fetuses. Am J Obstet Gynecol 2008;199:254.e1–8.

27. Comas M, Crispi F, Gomez O, Puerto B, Figueras F, Gratacos E. Gestational age- and estimated fetal weight-adjusted reference ranges for myocardial tissue Doppler indices at 24-41 weeks' gestation. Ultrasound Obstet Gynecol 2011;37:57–64.

28. DeVore GR, 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;35:1765–81.

29. DeVore GR, Klas B, Satou G, Sklansky M. Evaluation of fetal left ventricular size and function using speckle-tracking and the Simpson rule. J Ultrasound Med 2019;38:1209–21.

30. DeVore GR, Klas B, Satou G, Sklansky M. Speckle tracking of the basal lateral and septal wall annular plane systolic excursion of the right and left ventricles of the fetal heart. J Ultrasound Med 2019;38:1309–18.

31. DeVore GR, Klas B, Satou G, Sklansky M. Longitudinal annular systolic displacement compared to global strain in normal fetal hearts and those with cardiac abnormalities. J Ultrasound Med 2018;37:1159–71.

32. DeVore GR, Klas B, Satou G, Sklansky M. Twenty-four segment transverse ventricular fractional shortening: a new technique to evaluate fetal cardiac function. J Ultrasound Med 2018;37:1129–41.

33. DeVore GR, Klas B, Satou G, Sklansky M. Quantitative evaluation of the fetal right and left ventricular fractional area change using speckle tracking technology. Ultrasound Obstet Gynecol 2019;53:219–28.

34. Hadlock FP, Harrist RB, Sharman RS, Deter RL, Park SK. Estimation of fetal weight with the use of head, body, and femur measurements—a prospective study. Am J Obstet Gynecol 1985;151:333–7.

35. Ebbing C, Rasmussen S, Kiserud T. Middle cerebral artery blood flow velocities and pulsatility index and the cerebroplacental pulsatility ratio: longitudinal reference ranges and terms for serial measurements. Ultrasound Obstet Gynecol 2007;30:287–96.
36. Buckberg GD, Nanda NC, Nguyen C, Kocica MJ. What is the heart? Anatomy, function, pathophysiology, and misconceptions. J Cardiovasc Dev Dis 2018;5.
37. Torrent-Guasp F, Buckberg GD, Clemente C, Cox JL, Coghlan HC, Gharib M. The structure and function of the helical heart and its buttress wrapping. I. The normal macroscopic structure of the heart. Semin Thorac Cardiovasc Surg 2001;13:301–19.
38. Goldstein JA, Tweddell JS, Barzilai B, Yagi Y, Jaffe AS, Cox JL. Importance of left ventricular function and systolic ventricular interaction to right ventricular performance during acute right heart ischemia. J Am Coll Cardiol 1992;19:704–11.
39. Hoffman D, Sisto D, Frater RW, Nikolic SD. Left-to-right ventricular interaction with a noncontracting right ventricle. J Thorac Cardiovasc Surg 1994;107:1496–502.
40. DeVore GR. Computing the Z score and centiles for cross-sectional analysis: a practical approach. J Ultrasound Med 2017;36:459–73.
41. Perez-Cruz M, Cruz-Lemini M, Fernandez MT, et al. Fetal cardiac function in late-onset intrauterine growth restriction vs small-for-gestational age, as defined by estimated fetal weight, cerebroplacental ratio and uterine artery Doppler. Ultrasound Obstet Gynecol 2015;46:465–71.
42. Valenzuela-Alcaraz B, Crispi F, Bijnens B, et al. Assisted reproductive technologies are associated with cardiovascular remodeling in utero that persists postnatally. Circulation 2013;128:1442–50.
43. DeVore GR, Cuneo BF, Satou G, Sklansky M. How to determine the percent of study subjects below the 5th or above the 95th centiles of the control group when only the mean and standard deviations are provided. Ultrasound Obstet Gynecol 2019;54:139–41.
44. Buckberg GD, Hoffman JI, Coghlan HC, Nanda NC. Ventricular structure-function relations in health and disease: Part I. The normal heart. Eur J cardiothorac Surg 2015;47:587–601.
45. Buckberg GD. Basic science review: the helix and the heart. J Thorac Cardiovasc Surg 2002;124:863–83.
46. Mekkaoui C, Porayette P, Jackowski MP, et al. Diffusion MRI tractography of the developing human fetal heart. PLoS One 2013;8:e72795.
47. Cox JL, Bardy GH, Damiano RJ Jr, et al. Right ventricular isolation procedures for nonischemic ventricular tachycardia. J Thorac Cardiovasc Surg 1985;90:212–24.
48. Buckberg GD. The ventricular septum: the lion of right ventricular function, and its impact on right ventricular restoration. Eur J Cardiothorac Surg 2006;29(Suppl 1):S272–8.
49. Di Salvo G, Russo MG, Paladini D, et al. Two-dimensional strain to assess regional left and right ventricular longitudinal function in 100 normal foetuses. Eur J Echocardiogr 2008;9:754–6.
50. Buckberg G, Hoffman JI. Right ventricular architecture responsible for mechanical performance: unifying role of ventricular septum. J Thorac Cardiovasc Surg 2014;148:3166–71.e1-4.
51. Kagan A. Dynamic responses of the right ventricle following extensive damage by cauterization. Circulation 1952;5:816–23.
52. Arduini D, Rizzo G, Pennestri F, Romanini C. Modulation of echocardiographic parameters by fetal behaviour. Prenat Diagn 1987;7:179–87.
53. DeVore GR, Siassi B, Platt LD. Fetal echocardiography. IV. M-mode assessment of ventricular size and contractility during the second and third trimesters of pregnancy in the normal fetus. Am J Obstet Gynecol 1984;150:981–8.
54. Sorensen KE, Borlum KG. Fetal heart function in response to short-term maternal exercise. Br J Obstet Gynaecol 1986;93:310–3.
55. Sorensen KE, Borlum KG. Acute effects of maternal smoking on human fetal heart function. Acta Obstet Gynecol Scand 1987;66:217–20.
56. St John Sutton MG, Gewitz MH, Shah B, et al. Quantitative assessment of growth and function of the cardiac chambers in the normal human fetus: a prospective longitudinal echocardiographic study. Circulation 1984;69:645–54.
57. Wladimiroff JW, McGhie JS. M-mode ultrasonic assessment of fetal cardiovascular dynamics. Br J Obstet Gynaecol 1981;88:1241–5.
58. Mao YK, Zhao BW, Wang B. Z-score reference ranges for angular M-mode displacement at 22-40 weeks' gestation. Fetal Diagn Ther 2017;41:115–26.
59. Messing B, Gilboa Y, Lipschuetz M, Valsky DV, Cohen SM, Yagel S. Fetal tricuspid annular plane systolic excursion (f-TAPSE): evaluation of fetal right heart systolic function with conventional M-mode ultrasound and spatiotemporal image correlation (STIC) M-mode. Ultrasound Obstet Gynecol 2013;42:182–8.
60. Tedesco GD, de Souza Bezerra M, Barros FSB, et al. Fetal heart function by tricuspid annular plane systolic excursion and ventricular shortening fraction using STIC M-mode: reference ranges and validation. Am J Perinatol 2017;34:1354–61.
61. Comas M, Crispi F, Cruz-Martinez R, Figueras F, Gratacos E. Tissue Doppler echocardiographic markers of cardiac dysfunction in small-for-gestational age fetuses. Am J Obstet Gynecol 2011;205:57 e1–6.
62. Barker PC, Houle H, Li JS, Miller S, Herlong JR, Camitta MG. Global longitudinal cardiac strain and strain rate for assessment of fetal cardiac function: novel experience with velocity vector imaging. Echocardiography 2009;26:28–36.
63. Brooks PA, Khoo NS, Hornberger LK. Systolic and diastolic function of the fetal single left ventricle. J Am Soc Echocardiogr 2014;27:972–7.
64. Fan X, Zhou Q, Zeng S, et al. Impaired fetal myocardial deformation in intrahepatic cholestasis of pregnancy. J Ultrasound Med 2014;33:1171–7.
65. Ishii T, McElhinney DB, Harrild DM, et al. Circumferential and longitudinal ventricular strain in the normal human fetus. J Am Soc Echocardiogr 2012;25:105–11.
66. Kapusta L, Mainzer G, Weiner Z, et al. 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;25:1333–41.
67. Matsui H, Germanakis I, Kulinskaya E, Gardiner HM. Temporal and spatial performance of vector velocity imaging in the human fetal heart. Ultrasound Obstet Gynecol 2011;37:150–7.
68. Van Mieghem T, Giusca S, DeKoninck P, et al. Prospective assessment of fetal cardiac function with speckle tracking in healthy fetuses and recipient fetuses of twin-to-twin transfusion syndrome. J Am Soc Echocardiogr 2010;23:301–8.
69. Kiserud T, Ebbing C, Kessler J, Rasmussen S. Fetal cardiac output, distribution to the placenta and impact of placental compromise. Ultrasound Obstet Gynecol 2006;28:126–36.
70. Rizzo G, Arduini D. Fetal cardiac function in intrauterine growth retardation. Am J Obstet Gynecol 1991;165:876–82.
71. Lee JY, Kim YL, Jeong JE, Ahn JW. Prediction of pregnancy complication occurrence using fetal cardiac output assessments made by ultrasonography at 20 to 24 weeks of gestation. Obstet Gynecol Sci 2017;60:336–42.
72. De Smedt MC, Visser GH, Meijboom EJ. Fetal cardiac output estimated by Doppler echocardiography during mid- and late gestation. Am J Cardiol 1987;60:338–42.
73. Goldinfeld M, Weiner E, Peleg D, Shalev E, Ben-Ami M. Evaluation of fetal cardiac contractility by two-dimensional ultrasonography. Prenat Diagn 2004;24:799–803.
74. ACOG Practice bulletin no. 134: fetal growth restriction. Obstet Gynecol 2013;121:1122–33.
75. Royal College of Obstetricians and Gynecologists. The invetigation and management of the small-for-gestaional age fetus. Green top guideline no. 31. 2013. London: Royal College of Obstetricians and Gynecologists; 2013.
76. Lausman A, Kingdom J. Intrauterine growth restriction: screening, diagnosis, and management. J Obstet Gynaecol Can 2013;35:741–8.
77. New Zealand Maternal Fetal Medicine Network, ed. Guidelines for the managemnt of

suspected small for gestational age singleton pregnancies and infants after 34 weeks' gestation. Auckland, New Zealand: New Zealand Maternal Fetal Medicine Network; 2014.
78. Vayssiere C, Sentilhes L, Ego A, et al. Fetal growth restriction and intra-uterine growth restriction: guidelines for clinical practice from the French College of Gynaecologists and Obstetricians. Eur J Obstet Gynecol Reprod Biol 2015;193:10–8.
79. Fetal growth restriction-recognition, diagnosis managment. Clinical practice guideline no. 29. 2017. Version 1.1. Dublin: Institute of Obstetricians and Gynecologists Royal College of Physicians of Ireland; 2017.
80. Gordijn SJ, Beune IM, Thilaganathan B, et al. Consensus definition of fetal growth restriction: a Delphi procedure. Ultrasound Obstet Gynecol 2016;48:333–9.
81. McCowan LM, Figueras F, Anderson NH. Evidence-based national guidelines for the management of suspected fetal growth restriction: comparison, consensus, and controversy. Am J Obstet Gynecol 2018;218:S855–68.
82. Figueras F, Caradeux J, Crispi F, Eixarch E, Peguero A, Gratacos E. Diagnosis and surveillance of late-onset fetal growth restriction. Am J Obstet Gynecol 2018;218:S790–802.e1.
83. Girsen A, Ala-Kopsala M, Makikallio K, Vuolteenaho O, Rasanen J. Cardiovascular hemodynamics and umbilical artery N-terminal peptide of proB-type natriuretic peptide in human fetuses with growth restriction. Ultrasound Obstet Gynecol 2007;29:296–303.
84. Girsen A, Makikallio K, Hiilesmaa V, Hamalainen E, Teramo K, Rasanen J. The relationship between human fetal cardiovascular hemodynamics and serum erythropoietin levels in growth-restricted fetuses. Am J Obstet Gynecol 2007;196:467.e1–6.
85. Crispi F, Paules C, Dantas A, et al. Premature placental aging in term small for gestational age and fetal growth restriction. Am J Obstet Gynecol 2019;220:s145.
86. Kumar S, Figueras F, Ganzevoort W, Turner J, McCowan L. Using cerebroplacental ratio in non-SGA fetuses to predict adverse perinatal outcome: caution is required. Ultrasound Obstet Gynecol 2018;52:427–9.
87. Hobbins JC, Gumina DL, Zaretsky M, Driver C, Wilcox A, DeVore GR. Size and shape of the four-chamber view of the fetal heart in fetuses with an estimated fetal weight less than the tenth centile. Am J Obstet Gynecol 2019;221:495.e1–9.
88. DeVore GR, Zaretsky M, Gumina DL, Hobbins JC. Right and left ventricular 24-segment sphericity index is abnorml in small-for-gestational-age fetuses. Ultrasound Obstet Gynecol 2018;52:243–9.

Author and article information

From the Division of Maternal—Fetal Medicine, Department of Obstetrics and Gynecology, David Geffen School of Medicine at UCLA, Los Angeles, CA (Dr DeVore); Fetal Diagnostic Centers, Pasadena, Tarzana, and Lancaster, CA (Dr DeVore); and Department of Obstetrics and Gynecology, University of Colorado School of Medicine, Denver, CO (Ms Gumina and Dr Hobbins).

Received Feb. 18, 2019; revised May 22, 2019; accepted May 24, 2019.

The authors report no conflict of interest.

Funded by Perelman Family Foundation, New York City, NY.

Corresponding author: Greggory R. DeVore, MD. grdevore@gmail.com

SUPPLEMENTAL TABLE 1

Right ventricular comparison between study fetuses with a normal UAPI and CPR and fetuses with abnormal UAPI and/or CPR

Measurements	Right ventricle normal UAPI and normal CPR N=25	Right ventricle isolated abnormal UAPI 90% N=11	Significant differences between normal and abnormal UAPIAPI	Right ventricle isolated abnormal CPR <10% N=11	Significant differences between normal and abnormal CPR	Right ventricle abnormal UAPI and abnormal CPR N=3	Significant differences between normal UAPI and normal CPR and abnormal UAPI and abnormal CPR
Global contractility							
Fractional area change <5th centile	40% (10)	36% (N=4)	NS	45% (N=5)	NS	0% (N=0)	NS
24-segment contractility							
Base-segments 1–8 <5th centile	28% (N=7)	36% (N=4)	NS	36% (N=3)	NS	67% (N=2)	NS
Mid-segments 9–16 <5th centile	36% (N=9)	9% (N=1)	NS	27% (N=3)	NS	0 (0%)	NS
Apical-segments 17–24 <5th centile	52% (N=13)	36% (N=4)	NS	55% (N=6)	NS	67% (N=2)	NS
Longitudinal contractility							
Longitudinal strain (>95th centile)	32% (N=8)	27% (N=3)	BA	27% (N=3)	NS	67% (N=2)	NS
Basal-apical displacement fractional shortening <5th centile	28% (N=7)	36% (N=4)	NS	45% (N=5)	NS	33% (N=1)	NS
Basal-apical lateral wall annular plane systolic excursion <5th centile	28% (N=7)	27% (N=3)	NS	36% (N=4)	NS	100% (N=3)	NS
Basal-apical septal wall annular plane systolic excursion <5th centile	32% (N=6)	27% (N=2)	NS	27% (N=3)	NS	100% (N=3)	NS
Any abnormal measurement	80% (20)	64% (N=7)	NS	82% (N=9)	NS	100% (N=3)	NS

CPR, cerebroplacental ratio; *NS*, not significant; *UAPI*, umbilical artery pulsatility index.

DeVore et al. Assessment of ventricular contractility in fetuses with an estimated fetal weight less than the tenth centile. Am J Obstet Gynecol 2019.

SUPPLEMENTAL TABLE 2

Left ventricular comparison between study fetuses with a normal UAPI and CPR and fetuses with abnormal UAPI and/or CPR

Measurements	Left ventricle normal UAPI and normal CPR N=25	Left ventricle isolated abnormal UAPI >90% N=11	Significant differences between normal and abnormal UAPI	Left ventricle isolated abnormal CPR 10% N=11	Significant differences between normal and abnormal CPR	Left ventricle abnormal UAPI and abnormal CPR N=3	Significant differences between normal UAPI and normal CPR and abnormal UAPI and abnormal CPR
Global contractility							
Fractional area change <5th centile	40% (N=10)	36% (N=4)	NS	27% (N=3)	NS	67% (N=2)	NS
24-segment contractility							
Base-segments 1–8 <5th centile	20% (N=5)	18% (N=2)	NS	45% (N=5)	NS	67% (N=2)	NS
Mid-segments 9–16 <5th centile	24% (N=6)	9% (N=1)	NS	27% (N=3)	NS	33% (N=1)	NS
Apical-segments 17–24 <5th centile	32% (N=8)	18% (N=2)	NS	27% (N=3)	NS	67% (N=2)	NS
Longitudinal contractility							
Longitudinal strain (>95th centile)	32% (N=8)	27% (N=3)	BA	27% (N=3)	BA	33% (N=1)	NS
Basal-apical displacement fractional shortening <5th centile	24% (N=6)	18% (N=2)	NS	18% (N=2)	NS	67% (N=2)	NS
Basal-apical lateral wall annular plane systolic excursion <5th centile	24% (N=6)	9% (N=1)	NS	27% (N=3)	NS	100% (N=3)	NS
Basal-apical septal wall annular plane systolic excursion <5th centile	12% (N=3)	18% (N=2)	NS	18% (N=2)	NS	100% (N=3)	NS
Any abnormal measurement	56% (N=14)	45% (N=5)	NS	64% (N=7)	NS	100% (N=3)	NS

CPR, cerebroplacental ratio; *NS*, not significant; *UAPI*, umbilical artery pulsatility index.

DeVore et al. Assessment of ventricular contractility in fetuses with an estimated fetal weight less than the tenth centile. Am J Obstet Gynecol 2019.

SUPPLEMENTAL TABLE 3

Computation of the percent of SGA fetuses with significantly abnormal systolic function measurements using an analysis reported by DeVore et al[1] for data from Perez-Cruz (2015) Table 2[2]

Systolic function measurements	Control mean	Control standard deviation	SGA, mean	SGA, standard deviation	Percent of fetuses with values <5th centile	Percent of fetuses with values >95th centile
Left ventricular systolic function						
MAPSE, mm	6	1	5.3	0.9	15%	
Left S' tissue Doppler, cm/s	7.1	0.9	6.4	0.8	16%	
Left ejection time conventional Doppler, ms	170	10	163	11	19%	
Left ejection time tissue Doppler, ms	175	16	167	16	13%	
Left isovolumic contraction time conventional Doppler, ms	30	5	34	6		24%
Left isovolumic contraction time tissue Doppler, ms	38	7	41	9		17%
Right ventricular systolic function						
Tricuspid annular plane systolic excursion, mm	8.2	1.1	7.4	1.2	20%	
Right S' tissue Doppler, cm/s	8.1	1.2	7.4	1.3	16%	
Right isovolumic contraction tissue Doppler, ms	38	7	41	9		17%

MAPSE, mitral annular plane systolic excursion; *SGA*, small for gestational age.

DeVore et al. Assessment of ventricular contractility in fetuses with an estimated fetal weight less than the tenth centile. Am J Obstet Gynecol 2019.

References

1. DeVore GR, Cuneo BF, Satou G, Sklansky M. How to determine the percent of study subjects below the 5th or above the 95th centiles of the control group when only the mean and standard deviations are provided. Ultrasound Obstet Gnecol 2019;54:139–41.

2. Perez-Cruz M, Cruz-Lemini M, Fernandez MT, et al. Fetal cardiac function in late-onset intrauterine growth restriction vs small-for-gestational age, as defined by estimated fetal weight, cerebroplacental ratio and uterine artery Doppler. Ultrasound Obstet Gnecol 2015;46:465–71.