OBSTETRICS

Size and shape of the four-chamber view of the fetal heart in fetuses with an estimated fetal weight less than the tenth centile

Check for updates

John C. Hobbins, MD; Diane L. Gumina, MS; Michael V. Zaretsky, MD; Camille Driver, MA; Annabelle Wilcox, BA; Greggory R. DeVore, MD

BACKGROUND: Fetuses with an estimated fetal weight below the 10^{th} centile have an increased risk of adverse perinatal and long-term outcomes as well as increased rates of cardiac dysfunction, which often alters cardiac size and shape of the 4-chamber view and the individual ventricles. As a result, a simple method has emerged to screen for potential cardiac dysfunction in fetuses with estimated fetal weights $<10^{th}$ centile by measuring the size and shape of the 4-chamber view and the size of the ventricles.

OBJECTIVE: To determine the number of fetuses with an abnormal size and shape of the 4-chamber view and size of the ventricles in fetuses with an estimated fetal weight $<10^{th}$ centile.

MATERIALS AND METHODS: This was a retrospective study of 50 fetuses between 25 and 37 weeks of gestation with an estimated fetal weight $<10^{th}$ centile. Data from their last examination were analyzed. From an end-diastolic image of the 4-chamber view, the largest basal—apical length and transverse width were measured from their corresponding epicardial borders. This allowed the 4-chamber view area and global sphericity index (4-chamber view length/4-chamber view width) to be computed. In addition, tracing along the endocardial borders with speckle tracking software enabled measurements of the right and left ventricular chamber areas and the right ventricle/left ventricle area ratios to be computed. Doppler waveform pulsatility indices from the umbilical (umbilical artery pulsatility index) and middle cerebral arteries (middle cerebral artery pulsatility index) were analyzed, and the cerebroplacental ratio (middle cerebral artery pulsatility index/umbilical artery pulsatility index) computed. Umbilical artery pulsatility indices $>90^{th}$ and cerebroplacental ratios $<10^{th}$ centile were considered abnormal. Using data from the control fetuses, the centile for each of the cardiac measurements was categorized by whether it was $<10^{th}$ or $>90^{th}$ centile, depending upon the measurement.

RESULTS: Of the 50 fetuses with estimated fetal weight $<10^{th}$ centile, 50% (n = 25) had a normal umbilical artery pulsatility index and cerebroplacental ratio. These fetuses had significantly more ($P < 0.02$ to <0.0001) abnormalities of the size and shape of the 4-chamber view than controls. In all, 44% had a 4-chamber view area $>90^{th}$ centile, 32% had a 4-chamber view global sphericity index $<10^{th}$ centile, 56% had a 4-chamber view width $>90^{th}$ centile, and 80% had 1 or more abnormalities of size and/or shape. The remaining 50% of fetuses (n = 25) had abnormalities of 1 or both for the umbilical artery pulsatility index and/or cerebroplacental ratio. These fetuses had significantly higher rates of abnormalities ($P < 0.05$ to <0.0001) than controls for the following 4-chamber view measurements: 36% had a 4-chamber view area $>90^{th}$ centile; 28% had a 4-chamber view global sphericity index $<10^{th}$ centile; and 68% had a 4-chamber view width $>90^{th}$ centile. Only those fetuses with an abnormal umbilical artery pulsatility index had significant changes in ventricular size; 56% had a left ventricular area $<10^{th}$ centile; 28% had a right ventricular area $<10^{th}$ centile; 36% had right ventricular/left ventricular area ratio $>90^{th}$ centile. One or more of the above abnormal measurements were present in 92% of the fetuses.

CONCLUSION: Higher rates of abnormalities of cardiac size and shape of the 4-chamber view were found in fetuses with an estimated fetal weight $<10^{th}$ centile, regardless of their umbilical artery pulsatility index and cerebroplacental ratio measurements. Those with a normal umbilical artery pulsatility index and an abnormal cerebroplacental ratio had larger and wider measurements of the 4-chamber view. In addition, the shape of the 4-chamber view was more globular or round than in controls. These fetuses may have an increased risk of perinatal complications and childhood and/or adult cardiovascular disease. Screening tools derived from the 4-chamber view, acting as surrogates for ventricular dysfunction, may identify fetuses who could benefit from further comprehensive testing and future preventive interventions.

Key words: Doppler pulsatility index, cerebroplacental ratio, fetal echocardiography, fetal growth restriction, Glo4CV length sphericity index, intrauterine growth restriction, small for gestational age, umbilical artery pulsatility index

Fetuses with an estimated fetal weight (EFW) below the 10th centile are at risk for adverse outcome such as death, perinatal morbidity, abnormalities of postnatal motor skills, cognition, memory, neuropsychological dysfunctions, hypertension, atherosclerosis, coronary artery disease, stroke, obesity, immune dysfunction, metabolic syndrome, cancer, and a shortened life span.[1–9] The task for the clinician is to identify those fetuses with an EFW $<10^{th}$ centile who are at risk for perinatal and postnatal complications. Prenatal diagnostic approaches have used various growth curves used to define fetal growth restriction (FGR), as well as Doppler measurements of pulsatility indices of the umbilical (umbilical artery pulsatility index [UAPI]) and middle cerebral (cerebral artery pulsatility index [MCAPI]) arteries and the cerebroplacental ratio (CPR).[10–16] Commonly, if the Doppler indices are normal, fetuses with EFWs $>3^{rd}$ centile but $<10^{th}$ centile have been thought to be at lower risk for adverse outcomes in several studies[17–19]. These fetuses have been classified as small for gestational

Cite this article as: Hobbins JC, Gumina DL, Zaretsky MV, et al. 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.

0002-9378/$36.00

https://doi.org/10.1016/j.ajog.2019.06.008

AJOG at a Glance

Why was this study conducted?

This study was designed to evaluate the screening potential of assessing the size and shape of the 4-chamber view and the size of the right and left ventricles as surrogates for cardiac dysfunction in fetuses with estimated fetal weights $<10^{th}$ centile.

Key findings

Fetuses with an EFW $<10^{th}$ centile had an increased area of the 4-chamber view, an abnormal globular shape of the 4-chamber view, and an abnormal size of the ventricles.

What does this add to what is known?

Using these indirect markers for cardiac dysfunction, this study demonstrates that commonly used methods of Doppler surveillance poorly identifies fetuses with an estimated fetal weight $<10^{th}$ centile with an abnormal size and shape of the 4-chamber view and an abnormal size of the right and left ventricles.

age (SGA),[20] signifying that they are "constitutionally" small[21] and therefore may have a "benign condition."[17–19] Those with EFWs $<10^{th}$ centile with any abnormal UAPI or CPR have been defined as having FGR.[10]

Applying diagnostic tools used to evaluate ventricular size and function in pediatric and adult patients, investigators have identified forms of ventricular dysfunction in FGR that have persisted postnatally. In these fetuses, ventricular remodeling alters the primary structure/shape of the heart as an adaptive response to FGR .[4,10,20,22–25] Early studies of the fetal heart have linked FGR to cardiomegaly.[26,27] Recently, Rodriquez-Lopez et al described 3 phenotypes of fetal ventricular remodeling: (1) elongation of the ventricular chambers, (2) a round, or globular shape of the ventricles, and (3) hypertrophic ventricular walls. These phenotypes were associated with an increased area of the 4-chamber view (4CV), ventricular dysfunction, and adverse perinatal outcomes.[28] Unfortunately, assessment of fetal ventricular function requires sophisticated ultrasound imaging techniques (pulsed Doppler, tissue Doppler, M-mode, 4-dimensional virtual organ computer-aided analysis, and speckle tracking) that are not available to all clinicians.[29] Because changes in the overall cardiac size and shape of the 4CV and size of the individual right ventricle (RV) and left ventricle (LV) are features of cardiac dysfunction,[24,28,30,31] the current study addressed whether a simple approach to measure these parameters could identify fetuses with an EFW $<10^{th}$ centile who might be at risk for cardiac dysfunction, irrespective of their UAPI and CPR findings.

Materials and Methods

The purpose of this study was to identify whether there was a significant increase in the number of fetuses with an EFW $<10^{th}$ centile who had an abnormal area and shape of the 4CV as well as abnormal areas of the right and left ventricles, to determine whether these measurements could be used as screening tools for cardiac dysfunction. A total of 50 patients signed a consent form to participate in the study, which was approved by the Colorado Multiple Institutional Review Board (Institutional Review Board Number 14-1360, date of approval March 16, 2018). Exclusion criteria included a maternal age <18 years and any fetus with genetic or structural anomalies. For this study, the last ultrasound examination prior to delivery was used for the analysis. The EFW was computed from measurements of the biparietal diameter, head circumference, abdominal circumference, and femur length using the Hadlock formula.[32,33] All fetuses had EFWs <10th centile on entrance to the study and were serially examined during the third trimester of pregnancy.

Two-dimensional real-time grayscale clips of the fetal heart at the level of the 4CV were obtained at each study visit. To evaluate the size and shape of the 4CV, the end-diastolic image was identified using a technique previously described.[30,31] The 4CV basal—apical length was measured from the base to the apex of the heart, as well as the widest transverse width (Figure 1). From these 2 measurements, the global sphericity index and global area of the 4CV were computed as follows[30,31]:

Equation 1.

$$\text{4-Chamber Global Sphericity Index} = \text{End-Diastolic Basal-Apical Length}/\text{End-Diastolic Transverse Width}$$

Equation 2.

$$\text{4-Chamber Global End-Diastolic Area} = (3.4159 * \text{End-Diastolic Basal Apical Length} * \text{End-Diastolic Transverse Width})/4$$

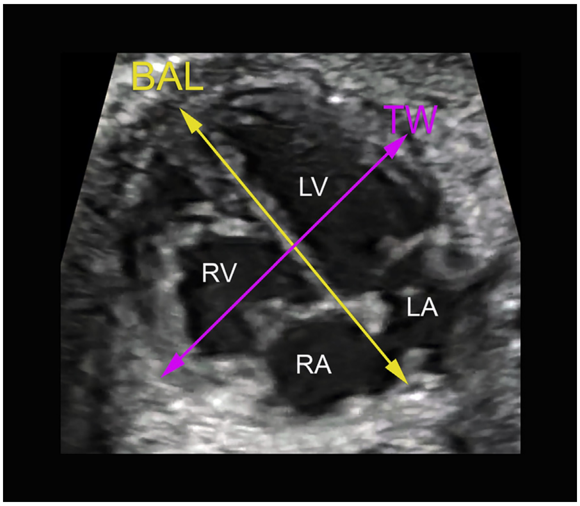
As previously reported, the mean (1.233) and standard deviation (SD) (0.0953) for the 4CV global sphericity index was independent of gestational age.[30]

From the same 4-chamber view clip, speckle tracking software (TomTec Imaging Systems, Munich, Germany) was used to measure the end-diastolic endocardial borders of the RV and LV, as previously described (Figure 2), which allowed computation of the end-diastolic areas of the RV and LV.[31,34,35] From these measurements, the RV/LV area ratio was computed (mean, 0.88; SD, 0.18) which was independent of the EFW. A value $>90^{th}$ centile (1.11) was considered abnormal. Coupled with each cardiac study, the pulsatility indices of the umbilical and middle cerebral arteries were measured, and the CPR was calculated using the following formula[11,36] :

Equation 3.

$$\text{Cerebroplacental Ratio} = \text{Middle Cerebral Artery Pulsatility Index}/\text{Umbilical Artery Pulsatility Index}$$

FIGURE 1
End-diastolic 4-chamber view. The basal-apical length (BAL) is measured from the base of the atrial chambers to the apex of the ventricular chambers



The transverse width (TW) is measured perpendicular to the BALW at the widest portion of the 4-chamber view.

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

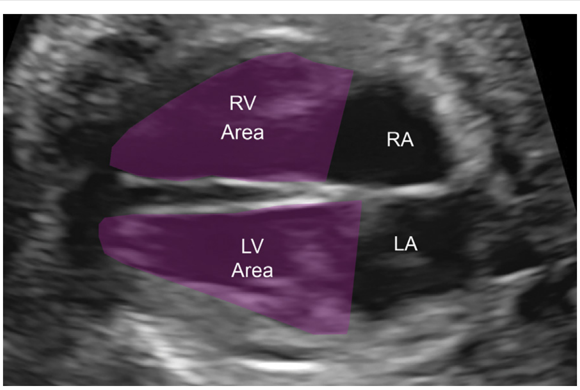
Hobbins et al. Size and Shape of the Four-Chamber View in Fetuses With an Estimated Fetal Weight <10th Centile. Am J Obstet Gynecol 2019.

Using previously published equations, the mean and SD from control fetuses in which the EFW was the independent variable were used to compute the *Z* score and corresponding centile for the 4CV area, 4CV length, 4CV width, LV area, RV area, UAPI, and CPR, as follows.[30,31 37]

$$Equation\ 4.\ Z\text{-}Score = (Measured\ Value_{Study\ Fetuses} - Mean_{Control\ Fetuses}) / Standard\ Deviation_{Control\ Fetuses}$$

$$Equation\ 5.\ \text{Excel Centile Formula} = \text{Normsdist}\ (Z\text{-score value})$$

FIGURE 2
Ventricular end-diastolic measurements



The purple overlay demonstrates the end-diastolic area of the right ventricle (RV) and left ventricle (LV).

LA, left atrium; *RA*, right atrium.

Hobbins et al. Size and Shape of the Four-Chamber View in Fetuses With an Estimated Fetal Weight <10th Centile. Am J Obstet Gynecol 2019.

Measurements of the 4CV global sphericity index, 4CV area, 4CV length, 4CV width, RV area, LV area, RV/LV $_{area}$ ratio, biometry, and Doppler studies were used from the last ultrasound prior to delivery. *Z* scores >1.28 (>90th centile) or ≤1.28 (10th centile) were used to separate study fetuses with an abnormal UAPI and/or CPR as well as measurements of the 4CV (4CV area, 4CV global sphericity index, 4CV length, and 4CV width) and ventricles (RV area, LV area, and the RV/LV area ratio).[30,31,36,37]

The study fetuses were divided into the following 6 groups: (1) all fetuses, irrespective of the UAPI and CPR; (2) those with a normal UAPI and CPR; (3) those with any abnormal UAPI and/or CPR; (4) those with an isolated abnormal UAPI and normal CPR; (5) those with an isolated CPR and normal UAPI; and (6) those with both an abnormal UAPI and CPR. Using measurements from a detailed analysis of global, transverse, and longitudinal ventricular contractility in the same cohort of fetuses, the presence or absence of any form of abnormal ventricular contractility was determined for each of the above 6 groups.[38]

χ^2 Analysis with Yates correction factor (NCSS 12, Kaysville, UT) were used to compute the odds ratio, 95% confidence interval, and *P* value to determine whether there were significant differences between the control and study fetuses for the cardiac measurements described above. The interobserver variability for the 4CV length, 4CV width, 4CV area, and the 4CV global sphericity index was compared between 2 of the authors (D.G. and G.R.D.) for 27 fetuses using the Bland—Altman 2-tailed *t* test. The intraobserver measurements for the above measurements from the 4CV and the RV and LV areas have been previously reported (by G.R.D.) and were not recomputed for the current study.[24 25,39]

Results

Control group

The demographics have been previously described.[30,31] Briefly, the fetuses demonstrated a normal estimated weight for gestational age, determined from first or second trimester dating examinations. The fetuses were studied between 20 and 40 weeks of gestation. Fetuses with congenital malformations were excluded from the study, as well as fetuses with maternal risk factors that could alter fetal growth.[30,31]

Demographics of fetuses with an EFW <10th centile

The maternal ethnicity of the 50 fetuses with an EFW <10th centile was 82% white, 6% Hispanic, 4% black, 2% Asian, and 6% mixed race. The average maternal age was 28.5 years (SD, 0.71). Of the patients, 24% smoked, 32% had other pre-existing health issues, 4% had hypertensive disorders of pregnancy, 4% had a TORCH (ie, *Toxoplasma gondii*, rubella virus, cytomegalovirus [CMV], herpes simplex virus) infection, 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). The fetal sex was 58% female and 42% male. None of the 50 study fetuses demonstrated absent or reverse diastolic flow of the umbilical artery Doppler waveform.

Interobserver measurements of the 4CV end-diastolic length, width, and global sphericity index

The 2-tailed *t* test demonstrated no significant differences between the 2 examiners, as shown by the following results as represented by the mean and standard error of the mean: (1) 4CV length (35.92 ± 0.96 vs 35.17 ± 0.88); (2) 4CV width (41.19 ± 1.30 vs 41.2 ± 1.27); and (3) 4CV global sphericity index (1.14 ± 0.018 vs 1.17 ± 0.10).

Distribution cardiac measurements in fetuses with an EFW <10th centile

Of the fetuses, 50% (n = 25) had a normal UAPI and CPR, and 50% (n = 25) had an abnormal UAPI and/or CPR.

Group I: All fetuses, irrespective of the UAPI and CPR (n = 50)

As a group, the following were significantly more frequent (P = 0.02 to 0.0001) when compared to controls (Table 1): 4CV area >90th centile, 40% (n = 20); 4CV global sphericity index <10th centile, 30% (n = 15); 4CV width >90th centile, 62% (n = 31); LV area <10th centile, 40% (n = 20); RV area<10th centile, 22% (n = 11); and the RV area/LV area ratio >90th centile, 28% (n = 14). In all, 86% (n = 43) of the fetuses had 1 or more of the above abnormal measurements. Of these 43 fetuses, 86% (n = 37) had 1 or more types of abnormal ventricular contractility.

Group 2: Normal UAPI and CPR (n = 25)

As a group, the following were significantly more frequently noted (P = 0.003−0.0001) when compared to controls (Table 1): 4CV area >90th centile, 44% (n = 11); 4CV global sphericity index <10th centile, 32% (n = 8); and 4CV width >90th centile, 56% (n = 14) (Table 1). In all, 80% of the fetuses (n = 20) had 1 or more of the above abnormal measurements. Of these 20 fetuses, 85% (n = 17) had 1 or more types of abnormal ventricular contractility.

Group 3: Any abnormal UAPI and/or CPR (n = 25)

As a group, the following were significantly more frequently found (P = 0.01−0.0001) when compared to controls (Table 1): 4CV area >90th centile, 36%; 4CV global sphericity index <10th centile, 28%; 4CV width >90th centile, 68%; LV area <10th centile, 56%; RV area <10th centile, 28%; and an RV area/LV area ratio >90th centile, 36% (Table 1). In all, 92% (n = 23) had 1 or more of the above abnormalities. Of these 23 fetuses, 87% (n = 20) had 1 or more types of abnormal ventricular contractility.

Group 4: Abnormal UAPI with a normal CPR (n = 11)

As a group, the following were significantly more frequently noted (P = 0.01−0.0001) when compared to controls (Table 1): 4CV global sphericity index <10th centile, 36%; 4CV width >90th centile, 55%; LV area<10th centile, 82%; RV area < 10th centile, 36%; and an RV area/LV area ratio >90th centile, 36% (Table 1). In all, 91% (n = 10) had 1 or more of the above abnormal measurements. Of these 10 fetuses, 80% (n = 8) had 1 or more types of abnormal ventricular contractility.

Group 5: Abnormal CPR with a normal UAPI (n = 11)

As a group, the following were significantly more frequently noted (P = 0.01−0.0001) when compared to controls (Table 1): 4CV area >90th centile 45%; 4CV width >90th centile, 73%; RV area >90th centile, 45%; and RV area/LV area ratio >90th centile, 36% (Table 1). In all, 91% (n = 10) had 1 or more of the above abnormal measurements. Of these 10 fetuses, 90% (n = 9) had 1 or more types of abnormal ventricular contractility.

Group 6: Combined abnormal UAPI and abnormal CPR (n = 3)

As a group the following were significantly more frequently seen (P = 0.02−0.008) when compared to controls (Table 1): 4CV width >90th centile 100%; LV area<10th centile 100%; and RV area <10th centile, 66%. In this small group, 100% had 1 or more of the above abnormal measurements and 1 or more types of abnormal ventricular contractility.

Comment

Principal findings

Our principal findings were as follows: (1) Of the fetuses with EFWs <10th centile and normal UAPI and CPR measurements, 80% had at least 1 measurement of abnormal size and shape of the 4CV. (2) Those with an isolated abnormal UAPI demonstrated the 4CV to be significantly wider and more globular, and to have decreased LV and RV areas. (3) Those with an isolated abnormal CPR had a significantly higher incidence of an increased area and width of the 4CV. In addition, 45% had enlarged RVs, creating a significant discrepancy in the RV/ LV area ratio.

A striking finding involved those with normal UAPI and CPR (Group 2) who had significantly higher rates of abnormalities than controls in the 4CV area, 4CV width, and 4CV global sphericity index. However, ventricular size and RV/LV area ratio were not different from controls. Fetuses with abnormal UAPIs

TABLE 1

Summary of cardiac measurements in fetuses with an estimated fetal weight below the 10th centile, stratified by the results of the umbilical artery pulsatility index and the cerebroplacental ratio

Fetuses <10th centile	4CV Global cardiac area >90th centile	4CV Global sphericity index <10th centile	4CV Global transverse width >90th centile	Left ventricular area <10th centile	Right ventricular area <10th centile	Left ventricular area >90th centile	Right ventricular area >90th centile	Right ventricular area/left ventricular area ratio >90th centile
Group 1. All Study Fetuses, Irrespective of the UAPI and CPR	20/50 (40%) OR, 6 95% CI, 2.8–12.5 $P < 0.0001$[a]	15/50 (30%) OR, 3.6 95% CI, 1.8–8.2 $P = 0.001$[a]	31/50 (62%) OR, 14.7 95% CI, 7–30.6 $P < 0.0001$[a]	20/50 (40%) OR, 6 95% CI, 2.8–12.5 $P < 0.0001$[a]	11/50 (22%) OR, 2.5 95% CI, 1.1–5.7 $P < 0.02$[a]	6/50 (12%) OR, 1.2 95% CI, 0.46–3.2 $P = 0.6$	10/50 (20%) OR, 2.2 95% CI, 0.97–5.1 $P = 0.06$	14/50 (28%) OR, 3.5 95% CI, .1.6–7.5 $P < 0.001$[a]
Fetuses Classified by the UAPI and CPR								
Group 2. Normal UAPI and CPR	11/25 (44%) OR, 7 95% CI, 2.8–17.6 $P < 0.0001$[a]	8/25 (32%) OR, 4.2 95% CI, 1.6–11 $P < 0.003$[a]	14/25 (56%) OR, 11.4 95% CI, 4.6–28.5 $P < 0.0001$[a]	6/25 (24%) OR, 2.8 95% CI, 1–8 $P = 0.05$	4/25 (16%) OR, 1.7 95% CI, 0.53–5.4 $P = 0.3$	5/25 (20%) OR, 2.2 95% CI, 0.76–6.6 $P = 0.14$	5/25 (20%) OR, 2.2 95% CI, 0.76–6.6 $P = 0.14$	5/25 (20%) OR, 2.2 95% CI, 0.76–6.6 $P = 0.14$
Group 3. Fetuses with any Abnormal UAPI and/or CPR	9/25 (36%) OR, 5.0 95% CI, 2–13 $P < 0.001$[a]	7/25 (28%) OR, 1.3–9.3 $P < 0.01$[a]	17/25 (68%) OR, 7.3–49.9 $P < 0.0001$[a]	14/25 (56%) OR, 11.4 95% CI, 4.6–28.5 $P < 0.0001$[a]	7/25 (28%) OR, 3.5 95% CI 1.3–9.4 $P < 0.01$[a]	1/25 (4%) OR, 0.38 95% CI, 0.05–2.9 $P = 0.34$	5/25 (20%) OR, 2.2 95% CI, 0.76–6.6 $P = 0.14$	9/25 (36%) OR, 5.0 95% CI, 2–13 $P < 0.001$[a]
Group 4. Abnormal Doppler UAPI >90th Centile, Normal CPR	3/11 (27%) OR, 3.7 95% CI, 0.8–13.7 $P = 0.08$	4/11 (36%) OR, 5.1 95% CI, 1.4–19.1 $P < 0.01$[a]	6/11 (55%) OR, 10.8 95% CI, 3–38.6 $P < 0.001$[a]	9/11 (82%) OR, 40.5 95% CI, 8.1–200 $P < 0.0001$[a]	4/11 (36%) OR, 5.1 95% CI, 1.4–19.1 $P < 0.01$[a]	0/11 (0%0	0/11 (0%)	4/11 (36%) OR, 5.1 95% CI, 1.4–19.1 $P < 0.01$[a]
Group 5. Abnormal CPR < 10th Centile, Normal UAPI	5/11 (45%) OR, 7.5 95% CI, 2.1–26.8 $P < 0.002$[a]	2/11 (18%) OR, 2 95% CI, 0.4–9.9 $P = 0.4$	8/11 (73%) OR, 24 95% CI, 5,9–97.8 $P < 0.0001$[a]	2/11 (18%) OR, 2 95% CI, 0.4–9.9 $P = 0.4$	1/11 (9%) OR, 0.9 95% CI, 0.1–7.4 $P = 0.92$	1/11 (9%) OR, 0.9 95% CI, 0.1–7.4 $P = 0.92$	5/11 (45%) OR, 7.5 95% CI, 2.1–26.8 $P < 0.002$[a]	4/11 (36%) OR, 5.1 95% CI, 1.4–19.1 $P < 0.01$[a]
Group 6. Both Abnormal UAPI and CPR	1/3 (33%) OR, 4.5 95% CI, 0.39–51 $P = 0.22$	1/3 (33%) OR, 4.5 95% CI, 0.39–51 $P = 0.22$	3/3 (100%) OR, 61 95% CI, 3–1235 $P = 0.007$[a]	3/3 (100%) OR, 61 95% CI, 3–1235 $P = 0.007$[a]	2/3 (66%) OR, 18 95% CI, 1.6–207 $P = 0.02$[a]	0/3 (0%)	0/3 (0%)	1/3 (33%) OR, 4.5 95% CI, 0.39–51 $P = 0.22$

CI, confidence interval; *CPR*, cerebroplacental ratio; *4CV*, 4-chamber view; *OR*, odds ratio; *UAPI*, umbilical artery pulsatility index.

[a] Data in cells with superscript letter "a" represent significant differences in the number of fetuses with abnormal measurements when compared to the control fetuses.

Hobbins et al. Size and Shape of the Four-Chamber View in Fetuses With an Estimated Fetal Weight <10th Centile. Am J Obstet Gynecol 2019.

and normal CPRs (Group 4), while having higher rates of an abnormal 4CV width and 4CV global sphericity index than controls, had significantly smaller ventricles. Because the LV area was more proportionally decreased in size, the RV/LV area ratio was significantly increased. Like those in the other groups, fetuses with abnormal CPRs and normal UAPIs (group 5) demonstrated abnormalities of an increased 4CV area and 4CV width, but the ventricles were affected in a different way. In 45% (n = 5) of cases, the RV was enlarged, creating an increase in RV/LV area ratio for a different reason. The frequent enlargement of the 4CV width, noted in all study groups, undoubtedly was responsible for the increased 4CV area, which was observed in all groups except those with abnormal UAPIs (groups 4 and 6).

Importantly, a separate companion study evaluated the same cohort of patients with EFWs <10th centile for abnormalities of ventricular contractility using speckle tracking technology.[38] Fetuses with abnormal measurements of the 4CV and ventricles in each group had at least 1 abnormality of ventricular contractility. Because these dysfunctional changes occurred in fetuses with a normal UAPI and CPR, abnormalities of size and shape of the 4CV may warrant increased scrutiny despite reassuring Doppler results, especially as these fetuses have been reported to have ventricular dysfunction with postnatal cardiovascular consequences when other cardiovascular imaging modalities have been used.[6,20]

Findings related to other investigations

The above findings now provide some basis for understanding how changes in size and shape of the 4CV, acting as surrogates for cardiac dysfunction, relate to other studies assessing fetal Doppler as an indicator of overall fetal condition and markers of hypoxia at the tissue level in the fetal heart. In FGR, impaired placental perfusion results in varying degrees of oxygen and nutrient deprivation, to which the fetal cardiovascular system adapts at the organ, tissue, and subcellular levels of the heart. One mechanism to maintain cardiac output is to change the size and shape of the 4CV and ventricles.[4,6]

In 2007, Girsen et al evaluated patterns in Doppler wave forms from the umbilical artery and the ductus venosus in fetuses with EFW <10th centile, and demonstrated a progressive increase in adverse perinatal outcome in those with a normal Doppler UAPI (group I), an abnormal UAPI with a normal DV (group II), and those with an abnormal UAPI and abnormal DV (group III).[39] As the Doppler values became incrementally more abnormal (groups I–III), the incidence of an abnormal 5-minute APGAR score increased and umbilical artery blood gases showed lower PO_2 values.[39] The peptide, N-terminal peptide of proA-type natriuretic peptide, a biochemical marker for increased venous pressure and atrial distension, was present in all 3 groups, whereas RV and LV cardiac output, diastolic filling, and ventricular fractional shortening were not significantly different from the control fetuses.[39] In 2008, Crispi et al classified fetuses with an EFW <10th centile and an abnormal UAPI >2 SD above the mean as follows: Stage I, presence of end-diastolic flow of the UA; Stage 2, absence of end-diastolic flow of the UA; and Stage 3, reverse end-diastolic flow of the UA. In addition to computing the RV and LV combined cardiac output, they examined ventricular function by measuring the myocardial performance index with pulsed Doppler echocardiography and examined both diastolic and systolic ventricular function.[40] They also measured biochemical markers that were associated with abnormal cardiac function (B-type natriuretic peptide) and myocardial cell damage (heart fatty acid–binding protein, C-reactive protein, and troponin I).[40] They found abnormal amounts of B-type natriuretic peptide to be present in all 3 stages of an abnormal Doppler UAPI.[40] In addition, perinatal deaths were not associated only with abnormal levels of the biochemical marker of abnormal cardiac function, but also with the markers linked to myocardial cell damage.[40] These 2 studies strongly suggest that fetuses with EFW <10th centile can experience enough hypoxia to release a marker of ventricular dysfunction before abnormal changes in umbilical artery waveforms, markers of cell damage, or even when some abnormal echocardiographic changes are present. Also, although Dopplers of the umbilical arteries do seem to convey information about incremental fetal deterioration, they are not sensitive indicators of hypoxia or early cardiac dysfunction when they are normal.

From the results of our study, coupled with an understanding of fetal cardiac deterioration, we hypothesize that in the early stages of modest hypoxia (normal Doppler UAPI), the lateral walls of the 4CV widen, without major changes in the 4CV length, thus creating a larger, rounder heart capable of maintaining stroke volume.[6] If hypoxia worsens (abnormal UAPI and/or abnormal CPR), the ventricular areas become discrepant in size because the larger RV is dealing with increased resistance in the placental circulation,[41,42] and the pulmonary arteries.[43] The latter change occurs in concert with brain sparing.[44] In the next and last stage of late FGR, the demand of the fetus exceeds the ability of the placenta to function properly because of pathological changes in the villi and other placental structures.[45–47] This may result in decreased end-diastolic flow in the umbilical artery Doppler waveform. The 4CV of these fetuses, although being rounder and wider, generally are of normal size. Yet the fetuses in this study had smaller left ventricles. This results in a mismatch between the size of the 4CV and the inner measurements of the ventricular areas that can be explained by thickening of the myocardium, as has been previously described.[28]

Clinical implications

Managing pregnancies complicated by fetuses with an EFW<10th centile has been challenging. Protocols have used traditional surveillance such as serial biometry, fetal heart rate monitoring, biophysical profiles, and Doppler wave form analysis.[48] Early/severe FGR fetuses show a fairly consistent pattern of deterioration.[49,50] In contrast, late FGR fetuses pursue a much less predictable pathway to morbidity, which may not appear until months or years after birth in the form of postnatal cardiovascular dysfunction,[20,23,28,51,52] abnormal neurological development,[3,53,54] or the metabolic syndrome.[55] Fetuses/infants with late emerging neuro-developmental abnormalities may often have a normal UAPI.[3] Our findings suggest that some cases of cardiac compromise are not predicted by commonly used assessment of the UAPI and the CPR and, therefore, all fetuses with EFWs $<10^{th}$ centile might benefit from sophisticated testing of left and right ventricular function through methods such as myocardial performance indices,[56] tricuspid annular peak systolic excursions, mitral annular peak systolic excursions,[57] ventricular sphericity indices,[30,37] or newer methods of ventricular function using speckle tracking analysis.[34,35,38,58–60] However, these types of evaluations are not currently available for all patients, require special expertise, and are expensive. Cardiac screening of the size and shape of the 4CV and the size of the ventricular chambers could represent a far simpler, intermediate step, to identify those fetuses most in need of heightened surveillance before and after birth. Further studies are required to better clarify the above relationships.

The ultrasound screening techniques described in this study involved the acquisition of a 2-dimensional digital clip of the 4CV. From the derived image at end diastole, the size and shape of the 4CV were assessed by obtaining only 2 measurements: the 4CV width and 4CV length. Although speckle tracking software was used to measure the end-diastolic LV area and RV area, the ventricular areas can be measured by using point-to-point tracking software, available on all current ultrasound machines.[37] Therefore, using common tools, it is possible to measure lengths and areas of the 4CV and the area of the ventricles. The screening described in this study can be readily performed.

Research implications

The question may be posed, "Why are FGR fetuses predisposed to abnormal cardiac contractility?" In animal models, the cardiomyocytes are vulnerable to hypoxia, which can result in shortening of the sarcomeres within these cells, which are important components of cardiac contractility.[61,62] However, when the myocardium has undergone remodeling, often another "hit" is needed to adversely affect contractility of the myocardium. Epigenetics can play a role through hypermethylation of DNA, which exerts an effect on endothelial dysfunction responsible for hypertension in children and cardiovascular and renal disease, metabolic syndrome, and diabetes in children and adults.[23,63,64]

There is some evidence that if cardiac remodeling is identified early, there is a possible opportunity to ameliorate or even to reverse the process. Based on the epigenetic "2 strike" concept, initial remodeling may represent the first "hit," with the heart waiting for the second "hit" to occur sometime later in life. Armed with this information, parents can avoid the second strike after birth for their children through breastfeeding,[65] special diets[65,66] (especially those with a beneficial balance of polyunsaturated/saturated fats),[65] exercise,[67] and avoidance of smoking. Also, preventive actions with vitamins such as folic acid[68] and/ or supplementation with alpha omega fatty acids[66,69] could be initiated.

Strengths and limitations

Two elements of the study design require further clarification. First, there is a lack of uniformity regarding which Doppler thresholds to use in the clinical management of fetuses with an EFW $<10^{th}$ centile.[11] We have chosen a more inclusive cutoff of the 90^{th} and 10^{th} centiles, which would identify more fetuses with an abnormal UAPI and/or CPR. If we had selected the 5^{th} and 95^{th} centiles as our thresholds, 10 fewer cases would have been labeled as being abnormal, 7 of which had at least 1 abnormality of cardiac size and shape. Second, we elected to first identify the number of fetuses with abnormal cardiac measurements using the thresholds of the 10^{th} and 90^{th} centiles (*Z*-score equivalents ≤ 1.28 or >1.28). Following the computation of the cardiac results, the number of fetuses who had cardiac measurements that fell outside this range were computed for analysis of the odds ratio, corresponding confidence intervals, and *P* values. The reason for approaching the analysis in this manner, instead of just comparing Z-score values between the control and study fetuses, was to determine how many study fetuses actually had abnormal cardiac measurements, as defined in our study protocol. In doing so, we believed that this approach had more clinical relevance.[70]

Our study deals mostly with pregnancies complicated by late-onset growth disturbance, with 50% of fetuses having a normal UAPI and CPR. None of our patients with UAPIs $>90^{th}$ centile had absent or reversed diastolic flow in umbilical artery. A larger sample of fetuses $<10^{th}$ centile with more severe Doppler profiles might yield different results. Yet, we believe that the study's strength is that the fetuses with an EFW $<10^{th}$ centile are representative of the more common "real-world" scenario in which they often do not have obvious signs of Doppler deterioration resulting in absent or reversed flow of the umbilical artery.[39,40]

This cross-sectional study did not track sequential changes occurring in the area of the 4CV and ventricles. Longitudinal studies with an expanded database are in progress to determine whether fetuses with an EFW $<10^{th}$ centile demonstrate evolving changes in the size and shape of the 4CV and changes in the RV area and LV area as the UAPI and/or CPR become abnormal.

A limitation of the current study is that we have not correlated our findings with neonatal cardiology and neurological outcomes. However, as studies of the neonatal heart, brain, and cognitive abilities are presently in progress at the University of Colorado in this cohort of fetuses, these correlations will be the focus of further reports from this group in an expanded cohort of fetuses with an EFW $<10^{th}$ centile.

In conclusion, the current study demonstrates that, regardless of normal measurements of the UAPI and CPR, 86% of fetuses with an EFW $<10^{th}$ centile had 1 or more abnormal measurements of the size and/or shape of the 4CV and ventricles. When the UAPI and CPR were abnormal, concomitant abnormalities of the ventricular area were present for the LV (28%, $<10^{th}$ centile) and RV (58%, $>90^{th}$ centile). ■

Acknowledgment

The authors would like to acknowledge Allison Gillen, who contributed by obtaining ultrasound images of the 4-chamber view used in this study.

References

1. Cnattingius S, Haglund B, Kramer MS. Differences in late fetal death rates in association with determinants of small for gestational age fetuses: population based cohort study. BMJ (Clinical research ed) 1998;316:1483–7.

2. Khalil AA, Morales-Rosello J, Elsadigg M, et al. The association between fetal Doppler and admission to neonatal unit at term. Am J Obstet Gynecol 2015;213:57.

3. Eixarch E, Meler E, Iraola A, et al. Neurodevelopmental outcome in 2-year-old infants who were small-for-gestational age term fetuses with cerebral blood flow redistribution. Ultrasound Obst Gynecol 2008;32:894–9.

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

5. Barker DJ, Winter PD, Osmond C, Margetts B, Simmonds SJ. Weight in infancy and death from ischaemic heart disease. Lancet 1989;2:577–80.

6. 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.

7. Madden JV, Flatley CJ, Kumar S. Term small-for-gestational-age infants from low-risk women are at significantly greater risk of adverse neonatal outcomes. Am J Obstet Gynecol 2018;218:525.

8. McEwen EC, Guthridge SL, He VYF, McKenzie JW, Boulton TJ, Smith R. What birthweight percentile is associated with optimal perinatal mortality and childhood education outcomes? Am J Obstet Gynecol 2018;218:S712–24.

9. Malhotra A, Allison BJ, Castillo-Melendez M, Jenkin G, Polglase GR, Miller SL. Neonatal morbidities of fetal growth restriction: pathophysiology and impact. Front Endocrinol 2019;10:55.

10. Gordijn SJ, Beune IM, Thilaganathan B, et al. Consensus definition of fetal growth restriction: a Delphi procedure. Ultrasound Obstet Gynecol 2016;48:333–9.

11. 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.

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

13. 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.

14. Villar J, Papageorghiou AT, Pang R, et al. The likeness of fetal growth and newborn size across non-isolated populations in the INTERGROWTH-21st Project: the Fetal Growth Longitudinal Study and Newborn Cross-Sectional Study. Lancet Diabetes Endocrinol 2014;2:781–92.

15. 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.

16. Clausson B, Gardosi J, Francis A, Cnattingius S. Perinatal outcome in SGA births defined by customised versus population-based birthweight standards. Br J Obstet Gynecol 2001;108:830–4.

17. O'Dwyer V, Burke G, Unterscheider J, et al. Defining the residual risk of adverse perinatal outcome in growth-restricted fetuses with normal umbilical artery blood flow. Am J Obstet Gynecol 2014;211:420.

18. McCowan LM, Figueras F, Anderson NH. Evidence-based national guidelines for the management of suspected fetal growth restriction: comparison, consensus, and controversy. Ame J Obstet Gynecol 2018;218:S855–68.

19. 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.

20. Crispi F, Figueras F, Cruz-Lemini M, Bartrons J, Bijnens B, Gratacos E. Cardiovascular programming in children born small for gestational age and relationship with prenatal signs of severity. Am J Obstet Gynecol 2012;207:121.

21. Ananth CV, Vintzileos AM. Distinguishing pathological from constitutional small for gestational age births in population-based studies. Early Hum Dev 2009;85:653–8.

22. Cohen E, Whatley C, Wong FY, et al. Effects of foetal growth restriction and preterm birth on cardiac morphology and function during infancy. Acta Paediatr 2018;107:450–5.

23. Crispi F, Bijnens B, Figueras F, et al. Fetal growth restriction results in remodeled and less efficient hearts in children. Circulation 2010;121:2427–36.

24. Agata Y, Hiraishi S, Oguchi K, et al. Changes in left ventricular output from fetal to early neonatal life. J Pediatr 1991;119:441–5.

25. Patey O, Carvalho JS, Thilaganathan B. Perinatal changes in cardiac geometry and function in growth restricted fetuses at term. Ultrasound Obstet Gynecol 2019;53:655–62.

26. Veille JC, Hanson R, Sivakoff M, Hoen H, Ben-Ami M. Fetal cardiac size in normal, intrauterine growth retarded, and diabetic pregnancies. Am J Perinatol 1993;10:275–9.

27. DeVore GR. Examination of the fetal heart in the fetus with intrauterine growth retardation using M-mode echocardiography. Semin Perinatol 1988;12:66–79.

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

29. Devore GR. Advanced assessment of fetal cardiac function. In: Kline-Fath B BD, Bahado-Sing R, ed. Fundamental and advanced fetal imaging—ultrasound and MRI, 1st ed. Philadelphia, PA: Wolters Kluwer; 2015. p. 114–64.

30. DeVore GR, Satou G, Sklansky M. Abnormal fetal findings associated with a global sphericity index of the 4-chamber view below the 5th centile. J Ultrasound Med 2017;36:2309–18.

31. DeVore GR, Satou G, Sklansky M. Area of the fetal heart's four-chamber view: a practical screening tool to improve detection of cardiac abnormalities in a low-risk population. Prenatal diagnosis 2017;37:151–5.

32. Hadlock FP, Deter RL, Harrist RB, Park SK. Estimating fetal age: computer-assisted analysis of multiple fetal growth parameters. Radiology 1984;152:497–501.

33. 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.

34. 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.

35. 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.

36. 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.

37. DeVore GR, Klas B, Satou G, Sklansky M. Evaluation of the right and left ventricles: an integrated approach measuring the area, length, and width of the chambers in normal fetuses. Prenatal Diagnosis 2017;37:1203–12.

38. DeVore GR, Gumina D, 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.

39. 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.

40. 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.

41. Parra-Saavedra M, Simeone S, Triunfo S, et al. Correlation between histological signs of placental underperfusion and perinatal morbidity in late-onset small-for-gestational-age fetuses. Ultrasound Obstet Gynecol 2015;45:149–55.

42. Mari G. Arterial blood flow velocity waveforms of the pelvis and lower extremities in normal and growth-retarded fetuses. Am J Obstet Gynecol 1991;165:143–51.

43. Yamamoto Y, Hirose A, Howley L, Savard W, Jain V, Hornberger LK. Parameters of fetal pulmonary vascular health: baseline trends and response to maternal hyperoxia in the second and third trimesters. Ultrasound Obstet Gynecol 2017;50:618–23.

44. Cruz-Martinez R, Figueras F, Oros D, et al. Cerebral blood perfusion and neurobehavioral performance in full-term small-for-gestational-age fetuses. Am J Obstet Gynecol 2009;201:474.

45. Mayhew TM, Wijesekara J, Baker PN, Ong SS. Morphometric evidence that villous development and fetoplacental angiogenesis are compromised by intrauterine growth restriction but not by pre-eclampsia. Placenta 2004;25:829–33.

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

47. 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.

48. ACOG. ACOG practice bulletin no. 134: fetal growth restriction. Obstet Gynecol 2013;121:1122–33.

49. Ferrazzi E, Bozzo M, Rigano S, et al. Temporal sequence of abnormal Doppler changes in the peripheral and central circulatory systems of the severely growth-restricted fetus. Ultrasound Obstet Gynecol 2002;19:140–6.

50. Hecher K, Bilardo CM, Stigter RH, et al. Monitoring of fetuses with intrauterine growth restriction: a longitudinal study. Ultrasound Obstet Gynecol 2001;18:564–70.

51. Barker DJ, Osmond C, Golding J, Kuh D, Wadsworth ME. Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease. BMJ (Clin Res Ed) 1989;298:564–7.

52. Arnott C, Skilton MR, Ruohonen S, et al. Subtle increases in heart size persist into adulthood in growth restricted babies: the Cardiovascular Risk in Young Finns Study. Open Heart 2015;2:e000265.

53. Sanz-Cortes M, Egana-Ugrinovic G, Simoes RV, Vazquez L, Bargallo N, Gratacos E. Association of brain metabolism with sulcation and corpus callosum development assessed by MRI in late-onset small fetuses. Am J Obstet Gynecol 2015;212:804.

54. Lindstrom L, Wikstrom AK, Bergman E, Lundgren M. Born small for gestational age and poor school performance—how small is too small? Horm Res Paediatr 2017;88:215–23.

55. Darendeliler F. IUGR: genetic influences, metabolic problems, environmental associations/triggers, current and future management. Best Practice Res Clin Endocrinol Metabolism 2019 Jan 22:101260. https://doi.org/10.1016/j.beem.2019.01.001. [Epub ahead of print].

56. Henry A, Alphonse J, Tynan D, Welsh AW. Fetal myocardial performance index in assessment and management of small-for-gestational-age fetus: a cohort and nested case-control study. Ultrasound Obstet Gynecol 2018;51:225–35.

57. 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 Gynecology 2013;42:182–8.

58. 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. Journal Ultrasound 2019;38:1309–18.

59. 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.

60. 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.

61. Corstius HB, Zimanyi MA, Maka N, et al. Effect of intrauterine growth restriction on the number of cardiomyocytes in rat hearts. Pediatr Res 2005;57:796–800.

62. Schipke J, Gonzalez-Tendero A, Cornejo L, et al. Experimentally induced intrauterine growth restriction in rabbits leads to differential remodelling of left versus right ventricular myocardial microstructure. Histochem Cell Biol 2017;148:557–67.

63. Sehgal A, Doctor T, Menahem S. Cardiac function and arterial biophysical properties in small for gestational age infants: postnatal manifestations of fetal programming. J Pediatr 2013;163:1296–300.

64. Zanardo V, Fanelli T, Weiner G, et al. Intrauterine growth restriction is associated with persistent aortic wall thickening and glomerular proteinuria during infancy. Kidney Int 2011;80:119–23.

65. Rodriguez-Lopez M, Osorio L, Acosta-Rojas R, et al. Influence of breastfeeding and postnatal nutrition on cardiovascular remodeling induced by fetal growth restriction. Pediatr Res 2016;79:100–6.

66. Skilton MR, Raitakari OT, Celermajer DS. High intake of dietary long-chain omega-3 fatty acids is associated with lower blood pressure in children born with low birth weight: NHANES 2003-2008. Hypertension 2013;61:972–6.

67. 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.

68. Jiang HL, Cao LQ, Chen HY. Blood folic acid, vitamin B12, and homocysteine levels in pregnant women with fetal growth restriction. Genet Mol Res 2016;15.

69. Skilton MR, Pahkala K, Viikari JS, et al. The association of dietary alpha-linolenic acid with blood pressure and subclinical atherosclerosis in people born small for gestational age: the Special Turku Coronary Risk Factor Intervention Project study. J Pediatr 2015;166:1252–7.

70. 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.

Author and article information

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

Received Feb. 18, 2019; revised June 5, 2019; accepted June 7, 2019.

The authors report no conflict of interest.

The research was funded by the Perelman Family Foundation, New York, NY.

Corresponding author: John C. Hobbins, MD. jchobbins@gmail.com