Published in final edited form as:

Fetal Diagn Ther. 2016 ; 39(1): 28–39. doi:10.1159/000431321.

Intermediate diastolic velocity as a parameter of cardiac dysfunction in growth-restricted fetuses

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Abstract

Objective—To evaluate the intermediate intracardiac diastolic velocities in fetuses with growth restriction.

Methods—Doppler waveforms of the two atrioventricular valves were obtained. Peak velocities of the E (early) and A (atrial) components, and the lowest intermediate velocity (IDV) between them, were measured in 400 normally grown and in 100 growth-restricted fetuses. The prevalence of abnormal IDV, E/IDV, and A/IDV ratios in fetuses presenting with perinatal death or acidemia at birth (pH < 7.1) was estimated.

Results—IDV was significantly lower and E/IDV ratios significantly higher in the two ventricles of growth-restricted fetuses with reduced diastolic velocities in the umbilical artery ($p < 0.05$). In 13 fetuses presenting with perinatal death or acidemia at birth, 11 (85%) had either an E/IDV or A/IDV ratio >95th percentile, whereas five (38%) showed absent or reversed atrial velocities in the ductus venosus (DV-ARAV) ($p < 0.04$). Fetuses without DV-ARAV but with elevated E/IDV ratios in either ventricle were nearly seven-fold more likely to have perinatal demise or acidemia at birth (OR 6.9; 95% CI, 1.4–34) than those with E/IDV ratios <95th percentile.

Conclusion—The E/IDV and A/IDV ratios in the two cardiac ventricles might provide information about the risk of perinatal demise or acidemia in growth-restricted fetuses.

Keywords

small-for-gestational-age fetus; absent/reversed end-diastolic velocities of the umbilical artery; perinatal death; acidemia at birth; E/A ratio; ductus venosus

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Introduction

Chronic hypoxia can affect fetal growth and fetal cardiac function^{1–13}. Growth-restricted fetuses initiate a hemodynamic process of adaptation to maintain blood and oxygen supply to key organs such as the brain and heart^{14,15}. However, if the hypoxic insult is continuous and severe, the fetus might show a progressive reduction in the diastolic velocities of the umbilical artery^{16–19}. Absent or reversed end-diastolic (ARED) velocities in the umbilical artery are considered a sign of severe fetal deterioration and in some centers as an indication for delivery^{20–24}. In instances for which the decision has to be delayed due to early gestational age, fetal surveillance is carried out by fetal heart rate monitoring^{25,26}, fetal biophysical profile^{27–30}, and Doppler examination^{28,31–35}, for which a critically abnormal waveform in the ductus venosus (absent or reversed atrial velocities) constitutes a manifestation of cardiovascular compromise, and delivery is strongly recommended^{25,26,36–38}. Turan et al.³⁹ and Figueras et al.⁴⁰ reported that when this Doppler finding is observed, the fetus is severely compromised, and survival for more than one week is unlikely. Waiting until the ductus venosus becomes severely affected can also increase perinatal morbidity and mortality, as not all fetuses presenting with fetal death will show a critically abnormal ductus venosus^{41–43}.

The evaluation of fetal cardiac function can provide clinically useful information either by allowing expectant management for a relatively stable fetus or by showing signs of progressive fetal deterioration warranting delivery^{41,44–46}. Fetal cardiac function has been studied by means of: 1) cardiac output and stroke volume calculations^{47–49}, 2) M-mode measurements (shortening and ejection fractions, and displacement of the tricuspid and mitral valves)^{50–53}, 3) Doppler velocities and ratios^{54–56}, 4) systolic and diastolic time-periods^{57–61}, and 5) myocardial tissue velocities and speckle tracking techniques^{62–68}. However, either due to a wide range of normal physiological variations, or to technical constraints, their clinical application has been limited⁶⁹. Most of these techniques evaluate the systolic phase of the cardiac cycle, whereas only a few diastolic parameters have been studied^{70–72}. The cardiac diastole can be divided into four periods: 1) isovolumetric relaxation time, 2) active relaxation (E component of the E/A waveform), which corresponds to the time when the myocardial sarcoplasm re-uptakes calcium after ventricular contraction, 3) diastasis, or the time period between the end of active relaxation (E peak velocity) and the beginning of the atrial contraction, and 4) atrial contraction (A wave)^{73–78}. The relationship between the peak diastolic velocities (E/A ratio) is the most used parameter applied for fetal cardiac diastolic evaluation⁵⁶. Diastasis has not previously been studied in fetuses; we have called the lowest velocity of this period as the “intermediate diastolic velocity” (IDV). The IDV represents the passive resistance when blood enters the ventricle not propelled by the negative ventricular pressure of the active relaxation phase, or by the atrial contraction⁷⁵. In normal fetuses, the E peak velocity and the IDV increase toward the end of pregnancy, becoming similar to the A peak velocity^{71,79}. This increment of the IDV might be a manifestation of reduced ventricular stiffness and increased compliance⁸⁰. On the contrary, in severely affected growth-restricted fetuses, the difference between the E and A peaks is more noticeable due to the reduction of the IDV. A low IDV may be related to increased ventricular resistance associated with chronic hypoxia^{81,82}. The aim of this study was to

evaluate the IDV and its relationship with the E and A peak velocities during cardiac diastole in growth-restricted fetuses at different stages of hemodynamic deterioration.

Methods

Study Design & Participants

This longitudinal study was conducted at the Center for Advanced Obstetrical Care and Research of the Perinatology Research Branch of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), National Institutes of Health, Wayne State University, and Hutzel Women's Hospital, Detroit Michigan. All patients provided written informed consent and were enrolled in research protocols approved by the Human Investigation Committee of Wayne State University and the Institutional Review Board of the NICHD. For this analysis, intracardiac blood velocities were evaluated in 400 normally grown fetuses from women with uncomplicated pregnancies at 20–40 weeks of gestation and in 100 fetuses presenting with growth restriction at different stages of hemodynamic deterioration characterized according to the umbilical artery Doppler waveform. Three dichorionic twin pregnancies with one of the twins with an EFW < 10th percentile were also evaluated. Monochorionic twin pregnancies or fetuses with congenital or chromosomal anomalies were not included in the study. One examination per fetus was analyzed; in growth-restricted fetuses, the examination performed at the time of diagnosis, or at admission before steroid treatment, was evaluated.

Ultrasound Examination

Ultrasound and Doppler evaluations were performed using General Electric (GE) Vivid 9 or GE Voluson E8 (GE Healthcare, Milwaukee, WI, USA) ultrasound equipment with 2- to 5-MHz or 4- to 6-MHz probes. In normally grown fetuses, gestational age was confirmed prior to 11 weeks by the crown-rump length measurement; no complications were documented during pregnancy; delivery occurred between 37 and 42 weeks of gestation; and birth weight was normal⁸³. Estimated fetal weight was calculated using the Hadlock formula⁸⁴. For growth-restricted fetuses, gestational age was estimated in accordance with the earliest ultrasound scan.

Doppler evaluation was performed in the umbilical artery, middle cerebral artery, and ductus venosus⁸⁵. Recordings were obtained in the absence of maternal or fetal movement with an angle of insonation as close as possible to 0° and with a high-pass wall filter of 60 MHz. Three to five consecutive and regular waveforms were obtained and the pulsatility index (PI) was calculated⁸⁶. A PI value ≥ 2 SD for gestational age was considered abnormal⁸⁷.

Clinical Definitions

Normal fetal growth was defined as estimated fetal weight within the 10th and 90th percentiles for gestational age⁸⁸ and normal umbilical artery PI. Fetal growth restriction (FGR) was defined as the estimated fetal weight below the 10th percentile for gestational age^{89,90}. Regarding stages of hemodynamic deterioration, growth-restricted fetuses were classified according to the umbilical artery PI as follows: Stage 1, umbilical artery PI < 2 SD

(n=56); Stage 2, umbilical artery PI ≥ 2 SD with diastolic blood velocities still present (n=20); and Stage 3, ARED velocities (n=24).

Cardiac examination

The fetal heart was evaluated in a cross-sectional plane of the thorax in an apical projection at the level of the four-chamber view. The Doppler sample gate was placed below either the mitral valve or the tricuspid valve, maintaining an angle of insonation as close as possible to 0° in relation to the blood entering the ventricles. Three to five good-quality waveforms were obtained and the following velocities measured: E (early), A (late or atrial), and IDV. IDV was defined as the lowest velocity in the middle of the E and A components of the atrioventricular Doppler waveform (Figure 1). The following ratios were calculated: E/A, E/IDV, and A/IDV in each ventricle. The fetal heart rate and the deceleration time of the E wave were registered in all cases.

Outcome

Severe adverse perinatal outcome was defined as a fetal death after 20 weeks of gestation or neonatal death within 28 days after birth⁹¹ or as an umbilical cord pH ≤ 7.1 ⁹².

Statistical analysis

Locally weighted linear quantile regression models were used to estimate percentiles of IDV, E/IDV, and A/IDV in the two cardiac ventricles as a function of gestational age. A total of 20 models from 20 through 40 weeks of gestation were fit to estimate IDV, E/IDV, and A/IDV quantiles. Each model used the entirety of the data (i.e., measurements across all gestational ages), yet different weights were used for each measurement in each model. The weights for each measurement in the dataset were determined using a Gaussian distribution, so that they decreased exponentially as a function of the distance between the gestational age of each measurement and the gestational age for which the percentiles were being estimated. The resulting locally estimated percentiles were then smoothed using a 5th-degree polynomial function of gestational age to allow interpolation of the percentiles at any desired value of gestational age. The quantreg package under the *R* statistical environment was used to fit these quantile regression models^{93–95}.

To evaluate differences among FGR stages, Doppler parameters and individual cardiac diastolic values were converted into multiples of the expected median estimated as a function of gestational age (MoMs), and differences among and within groups were assessed using the Kruskal-Wallis and Mann-Whitney U tests with correction for multiple comparisons based on pairwise rankings. The prevalence of altered cardiac parameters in fetuses presenting with adverse outcomes, such as perinatal demise and acidemia at birth, was calculated. Proportions were compared using the Chi-square, McNemar, or Fisher's exact test, as appropriate. A p value of <0.05 was considered significant. Agreement was evaluated in 20 normal fetuses according to the method proposed by Bland & Altman^{96,97}. Analyses were performed using SPSS® 19 (IBM Corp., Armonk, New York, USA) and Med Calc® 9.0.1.0 (MedCalc Software bvba, Ostend, Belgium) statistical software.

Results

Descriptive characteristics of the studied groups are presented in Table 1. No differences in ethnicity, maternal age, number of pregnancies, and parity were observed among the groups. Women with growth-restricted fetuses and reduced diastolic velocities in the umbilical artery (FGR stages 2 and 3) were more frequently smokers, had a higher prevalence of preeclampsia, presented with earlier gestational age at delivery, had lower birth weights, and had a higher prevalence of perinatal death and acidemia than women with fetuses at FGR stage 1. The fetal heart rate was similar in all FGR stages. The umbilical artery PI was higher, and the middle cerebral artery PI lower in FGR stage 3 as compared to FGR stage 1. Inter-observer agreement showed a mean difference of 0.1 cm/s in the measurement of the IDV (95% limits of agreement -2.8 to 3.1 cm/s).

Table 2 displays the median and interquartile range MoMs of cardiac function parameters in each of the FGR stages. No differences in the E peak velocity, A peak velocity, E/A ratios, and E deceleration time measured in each ventricle were observed among the FGR stages after correction for multiple comparisons ($p=0.06$ to 0.10). The IDV was significantly lower, and the E/IDV and A/IDV ratios were significantly higher in both ventricles of fetuses at FGR stages 2 and 3 as compared to fetuses at FGR stage 1 ($p<0.05$).

Figure 2 shows the IDV values of the left and right ventricles from all growth-restricted fetuses plotted against normal reference ranges throughout gestation. The prevalence of abnormal IDV in both ventricles increased significantly with increasing FGR stage (Cochran-Armitage Trend Test, $p<0.0001$). The IDV measured in the left ventricle was abnormal ($<10^{\text{th}}$ percentile) for 5%, 62%, and 75% of fetuses at FGR stages 1, 2, and 3, respectively, whereas the IDV measured in the right ventricle was abnormal for 4%, 29%, and 42% of fetuses at FGR stages 1, 2, and 3, respectively.

Figures 3 and 4 show the E/IDV and A/IDV ratios of the left and right ventricles, respectively, obtained from all growth-restricted fetuses and from the subset of fetuses with adverse perinatal outcomes, each plotted against normal reference values. Fewer than 5% of fetuses at FGR stage 1 had abnormal ($>95^{\text{th}}$ percentile) E/IDV and A/IDV ratios, whereas 5% and 29% of those at FGR stage 2, and 21% and 50% of those at stage 3, had E/IDV and A/IDV ratios $>95^{\text{th}}$ percentile, respectively (Table 3).

Absent or reversed atrial blood velocities in the ductus venosus were observed in seven fetuses, six at FGR stage 3 ($6/24=25\%$) and one at FGR stage 2 ($1/20=5\%$); five ($5/7$, 71%) had perinatal death or acidemia at birth. The incidence of perinatal death or acidemia among all growth-restricted fetuses presenting with abnormal ratios was: left E/IDV $6/20$ (30%), left A/IDV $5/16$ (31%), right E/IDV $5/13$ (38%), and right A/IDV $2/7$ (29%). When only fetuses at stage 3 ($n=24$) were considered, 11 had elevated left E/IDV ratios, and of these, five (45%) presented with perinatal death or acidemia at birth. Ten fetuses at FGR stage 3 had elevated right E/IDV ratios, and of these, four (40%) had perinatal death or acidemia.

Table 4 presents the MoMs of the cardiac and Doppler parameters for the 13 fetuses who had acidemia at birth ($n=7$) or perinatal death ($n=6$: 4 fetal deaths and 2 neonatal deaths).

Eleven (85%) of these fetuses had at least one abnormal E/IDV or A/IDV ratio, whereas only five (38%) had reversed atrial blood velocities in the ductus venosus and four (30%) had an abnormal right E/A ratio.

E/IDV ratios contributed significant information about the increased risk of acidemia or perinatal death; the association remained statistically significant after adjustment for gestational age at examination (left E/IDV: OR 6.1; 95% CI, 1.9–19; right E/IDV: OR 9.8; 95% CI, 1.4–68).

Among fetuses without absent or reversed atrial velocities in the ductus venosus, those who had E/IDV ratios >95th percentile in either ventricle were nearly seven-fold more likely to present perinatal demise or acidemia at birth (OR 6.8; 95% CI, 1.5–31) than those who did not. This association remained statistically significant after adjustment for either gestational age at examination (OR 6.9; 95% CI, 1.4–34), or abnormal E/A ratios in either ventricle (OR 9.1; 95% CI, 1.8–45).

Discussion

Principal findings

1) Growth-restricted fetuses with reduced diastolic velocities in the umbilical artery had lower IDV and higher E/IDV and A/IDV ratios than those with a normal umbilical artery PI; 2) 11 of 13 fetuses with acidemia at birth or perinatal demise had increased E/IDV ratios (>95th percentile), whereas five had absent or reversed atrial velocities in the ductus venosus, and four had abnormal E/A ratios; and 3) among growth-restricted fetuses without absent or reversed atrial velocities in the ductus venosus, those who had elevated E/IDV ratios in either ventricle were seven-fold more likely to have perinatal demise or acidemia at birth than those with diastolic ratios between the 10th and 95th percentiles.

Intermediate diastolic velocity in growth-restricted fetuses

The IDV constitutes the lowest amount of blood passing at the end of the diastasis period and is associated with the pressure-volume relationship of the ventricle^{75,98}. According to our results in normal pregnancies, the IDV increases as a function of gestational age, becoming similar to the E and A peak velocities near term. The IDV represents the transitional phase between the active and passive periods of ventricular relaxation that can be altered by ventricular wall thickness^{99–101}, elastic properties of the myocardium¹⁰⁰, and hypoxia^{6,12}. It is possible that chronic hypoxia affects the IDV and the E and A peak velocities differently, thus affecting the ratios. The isolated estimation of IDV showed differences among the various FGR stages, but the E/IDV ratios proved to be more significantly associated with adverse perinatal outcomes. The reduction in IDV might be associated with a prolonged deceleration time of the E wave; however, we could not document significant differences in the E deceleration time among the groups.

Clinical value of the intermediate diastolic velocity in growth-restricted fetuses

Growth-restricted fetuses with a normal umbilical artery PI showed no severe perinatal complications, and most of them had IDV values and E/IDV and A/IDV ratios within the

normal range. In these fetuses, the evaluation of the cardiac diastolic function most probably will not provide significant information to change the clinical management. In growth-restricted fetuses with abnormal diastolic velocities in the umbilical artery, the prevalence of perinatal complications and of abnormal diastolic cardiac parameters was significantly elevated. In these fetuses, the identification of abnormal E/IDV and A/IDV ratios might help in selecting those at a higher risk of adverse outcome, even before reaching an abnormal ductus venosus waveform. Brodzski et al.¹⁰² reported that preterm growth-restricted newborns delivered in the presence of ARED velocities in the umbilical artery showed similar perinatal morbidity and long-term complications than preterm newborns with normal birth weight. The authors suggested that active delivery in the presence of ARED velocities in the umbilical artery might be preferable to expectant management and worsening of the fetal condition. Delivering growth-restricted fetuses in the presence of ARED velocities in the umbilical artery can be performed after 34 weeks of gestation¹⁰³. In earlier gestations, prolongation of pregnancy might be necessary to reduce the risk of respiratory complications¹⁰⁴. In these pregnancies, fetal surveillance is usually performed by monitoring for signs of acute fetal deterioration such as reduced fetal heart rate variability or absent/reversed atrial velocities in the ductus venosus^{25,40,105–108}. Identification of the optimal time of delivery in these fetuses is an enormous challenge. The results of the present study suggest that fetal cardiac diastolic parameters (IDV, and E/IDV and A/IDV ratios) might provide additional information on the process of cardiovascular deterioration in addition to the standard Doppler evaluation in growth-restricted fetuses.

Previous studies on the diastolic cardiac function in growth-restricted fetuses

The contribution of the fetal cardiac diastolic evaluation in growth-restricted fetuses has been previously suggested by Rizzo et al.¹⁰⁹, who showed a reduction of the E/A ratios and reported that the right ventricle was more severely affected than the left ventricle. Gardiner et al.⁴ also reported an increment in the E/A ratio only in the right ventricle, and Makikallio et al.¹¹⁰ showed an increment in the left E/A ratio in growth-restricted fetuses presenting with retrograde flow in the aortic isthmus. Conversely, Hecher et al.¹¹¹ did not find differences in the E/A ratios between complicated growth-restricted fetuses presenting with an abnormal heart rate trace, severe preeclampsia, or fetal death, when compared to uncompromised growth-restricted fetuses. Tsyvian et al.¹¹² showed no significant differences in the E/A ratios between growth-restricted and normally grown fetuses. No consistent data on the value of the E/A ratios in FGR can be found. In our study, E/A ratios were similar between growth-restricted and normally grown fetuses; however, E/IDV and A/IDV ratios showed significant differences between growth-restricted fetuses with and without reduced diastolic velocities in the umbilical artery.

Strengths and weaknesses

Strengths—Normal values of diastolic parameters throughout gestation were constructed using quantile regression analysis in a large group of normally grown fetuses. The proposed anatomical plane for evaluation of the cardiac diastolic parameters can be easily obtained. Classification of growth-restricted fetuses according to diastolic changes in the umbilical artery allows a clear definition of the risk groups independent of gestational age. Good inter-observer agreement for measuring the IDV was documented.

Weaknesses—More fetuses presenting with perinatal death or acidemia at birth are still necessary to estimate the value of cardiac diastolic parameters in the clinical management of severely affected growth-restricted fetuses.

Conclusion

The IDV can provide information on the diastolic cardiac function in growth-restricted fetuses. The prevalence of elevated E/IDV and A/IDV ratios in either cardiac ventricle was higher in fetuses with ARED velocities in the umbilical artery and in fetuses presenting with perinatal death or acidemia at birth.

Acknowledgments

This research was supported, in part, by the Perinatology Research Branch, Division of Intramural Research, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services (NICHD/NIH/DHHS), and, in part, with Federal funds from NICHD/NIH/DHHS under Contract No. HHSN275201300006C. ALT was supported by the Perinatal Initiative of the Wayne State University School of Medicine (WSUSOM), and the Department of Obstetrics and Gynecology of the WSUSOM. The ultrasound experience and technical support of senior Registered Diagnostic Medical Sonographers (RDMS) Catherine Ducharme and Denise Haggerty are gratefully acknowledged.

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Figure 1.

Atrioventricular Doppler waveform of the right ventricle at 26 weeks of gestation showing the early (E), atrial (A), and intermediate diastolic velocities (IDV); a) a normally grown fetus, b) a growth-restricted fetus with reversed diastolic velocities in the umbilical artery. In the growth-restricted fetus, the IDV is lower, and the difference with the E peak velocity (E/IDV ratio) is higher than in the normally grown fetus.

Figure 2.

Intermediate diastolic velocity (IDV) values obtained in the two cardiac ventricles from 100 growth-restricted fetuses plotted against reference ranges calculated from 400 normal fetuses at 20–40 weeks of gestation; solid lines represent the 10th and 95th percentiles. (Stage 1 estimated fetal weight (EFW) <10th percentile and umbilical artery pulsatility index (UA-PI) <2SD; Stage 2 EFW <10th percentile and UA-PI $\geq$ 2 SD with positive diastolic velocities; and Stage 3 EFW <10th percentile and ARED velocities in the umbilical artery).

Figure 3.

Left ventricle E/IDV (upper panels) and A/IDV (lower panels) ratios from 100 growth-restricted fetuses (estimated fetal weight <10th percentile) plotted against normal reference values; solid lines represent the 10th and 95th percentiles. Left panels include all growth-restricted fetuses at different stages of hemodynamic deterioration (stage 1 umbilical artery pulsatility index (PI) <2 SD; stage 2 umbilical artery PI ≥ 2 SD with positive diastolic velocities; and stage 3 ARED velocities in the umbilical artery); right panels show fetuses presenting with perinatal death or acidemia at birth.

Figure 4.

Right ventricle E/IDV (upper panels) and A/IDV (lower panels) ratios from 100 growth-restricted fetuses [estimated fetal weight <10th percentile] plotted against normal reference values; solid lines represent the 10th and 95th percentiles. Left panels include all growth-restricted fetuses at different stages of hemodynamic deterioration (stage 1 umbilical artery pulsatility index (PI) <2 SD; stage 2 umbilical artery PI ≥ 2 SD with positive diastolic velocities; and stage 3 ARED velocities in the umbilical artery); right panels show fetuses presenting with perinatal death or acidemia at birth.

Table 1

Clinical characteristics of the patients

	Normally grown n=400	FGR Stage 1 n=56	FGR Stage 2 n=20	FGR Stage 3 n=24
Maternal age (years)	24 (16–40)	23 (19–36)	26 (19–40)	24 (20–40)
Gravida	1 (1–7)	2 (1–13)	1 (1–8)	2 (1–7)
Parity	0 (0–7)	0 (0–9)	0 (0–5)	0 (0–4)
African-American, %	95	94.6	90	91.6
Gestational age at examination (weeks)	20–40	33 (25–39)	31 (25–36)	27 (21–34)
Smokers	25 (6.7%)	3 (5%)	4 (20%)	6 (25%)*
Preeclampsia (n, %)	0	4 (7%)	11 (55%)	13 (54%)*
Gestational age at delivery (weeks)	39 (37–41)	39 (28–41)	33 (27–36)	28 (21–35)*
Birth weight (grams)	3476 ± 643	2589 ± 604	1259 ± 362	850 ± 487*
Fetal heart rate (bpm)	144 (118–164)	139 (122–158)	143 (125–159)	143 (117–157)
Umbilical artery PI, MoM	0.21	1.32	1.71 [#]	2.38 [#]
Middle cerebral artery PI (MoM)	0.17	1.03	0.77 [#]	0.67 [#]
Ductus venosus PI, MoM	0.20	1.00	1.11	1.71
Perinatal death	0	0	0	6 (25)*
Acidemia	0	0	2 (10)	5 (21)

Data are presented as median (range), mean ± SD, and n (%), unless otherwise shown.

FGR: fetal growth restriction (estimated fetal weight <10th percentile): stage 1 FGR and umbilical artery PI <2 SD; stage 2 FGR and umbilical artery PI >2 SD with positive diastolic velocities; and Stage 3 FGR <10th percentile and ARED velocities in the umbilical artery.

* p < 0.05 versus normally grown fetuses.

[#] p < 0.05 versus FGR stage 1.

Table 2

Median (inter-quartile range) MoM cardiac parameter values from the left and right ventricles of fetuses with growth restriction

	Stage 1 n=56		Stage 2 n=20		Stage 3 n=24	
	Left	Right	Left	Right	Left	Right
E velocity	0.98 (0.87–1.05)	0.98 (0.90–1.07)	0.85 (0.68–0.95)	0.83 (0.73–0.93)	0.83 (0.71–1.06)	0.8 (0.75–0.90)
A velocity	0.99 (0.88–1.08)	0.96 (0.91–1.09)	0.80 (0.70–0.92)	0.81 (0.72–0.87)	0.79 (0.66–0.93)	0.80 (0.67–0.90)
E/A	0.98 (0.92–1.06)	0.98 (0.93–1.07)	1.04 (0.94–1.12)	1.06 (0.92–1.12)	1.08 (0.91–1.19)	1.04 (0.96–1.17)
DT (E wave)	1.00 (0.83–1.18)	0.96 (0.7–1.25)	0.98 (0.72–1.20)	1.10 (0.74–1.24)	1.22 (0.95–1.50)	1.25 (0.98–1.57)
IDV	0.99 (0.88–1.10)	1.34 (1.16–1.52)	0.66* (0.53–0.79)	1.08* (0.93–1.16)	0.59* (0.46–0.70)	0.93* (0.76–1.15)
E/IDV ratio	1.00 (0.90–1.09)	0.99 (0.95–1.12)	1.21* (0.99–1.59)	1.08* (0.97–1.24)	1.43* (1.23–1.76)	1.28* (1.17–1.51)
A/IDV ratio	0.99 (0.89–1.10)	0.99 (0.92–1.11)	1.16* (1.03–1.36)	1.07* (0.95–1.19)	1.41* (1.22–1.57)	1.21* (1.04–1.36)

A: atrial; ARED: absent or reversed umbilical artery end-diastolic velocities; DT: deceleration time; E: early; FGR: fetal growth restriction; IDV, intermediate diastolic flow; MoM, multiple of expected median for gestational age; PI: pulsatility index.

FGR: (estimated fetal weight < 10th percentile); stage 1 FGR and umbilical artery PI < 2 SD; stage 2 FGR and umbilical artery PI 2 SD with positive diastolic velocities; and stage 3 FGR < 10th percentile and ARED velocities in the umbilical artery.

* p < 0.05 versus FGR stage 1 with correction for multiple comparisons.

Table 3

Percentage of abnormal diastolic parameters and ratios () 95th percentile or 10th percentile) at different stages of fetal growth restriction and among fetuses with severe adverse outcomes

	Fetal Growth Restriction				
	Overall	Stage 1	Stage 2	Stage 3	Severe Outcome
RV IDV	17.8	3.6	28.6	41.7	38.5
LV IDV	33.7	5.4	61.9	75	76.9
RV E/IDV	12.9	1.8	9.5	41.7	38.5
LV E/IDV	19.8	5.4	28.6	45.8	46.2
RV A/IDV	6.9	1.8	4.8	20.8	15.4
LV A/IDV	15.8	0	19.1	50	38.5
RV E/A	7.9	5.4	9.5	12.5	23.1
LV E/A	6.9	1.8	9.5	16.7	15.4
RV E	3	3.6	4.8	0	0
LV E	4	3.6	4.8	4.2	7.7
RV A	3	5.4	0	0	0
LV A	4	3.6	4.8	4.2	7.7

Stage 1 FGR and umbilical artery PI <2 SD; stage 2 FGR and umbilical artery PI SD with positive diastolic velocities; and stage 3 FGR < 10th percentile and ARED velocities in the umbilical artery.
A: peak atrial velocity; ARED: absent or reversed end-diastolic velocities; E: peak early velocity; FGR: fetal growth restriction; IDV: intermediate diastolic velocity; LV: left ventricle; PI: pulsatility index; RV: right ventricle.

Diastolic ratios (MoMs) of the left and right ventricles and ductus venosus in fetuses with growth-restriction presenting with perinatal death or acidemia at birth (pH 7.1)

Table 4

Fetus No.	Stage	GA at scan	DV reversed atrial	Outcome	LV E/A	RV E/A	LV E/IDV	RV E/IDV	RV A/IDV
Fetus 1	3	29.0	No	Perinatal death	1.13	1.35	1.59	1.36	1.25 0.91
Fetus 2	3	21.0	Yes	Perinatal death	0.67	1.49	0.89	1.32	1.58 1.03
Fetus 3	3	21.3	Yes	Perinatal death	1.39	1.44	2.08	1.49	1.64 1.12
Fetus 4	3	22.0	No	Perinatal death	1.07	0.95	2.00	1.86	1.36 1.43
Fetus 5	3	25.6	Yes	Perinatal death	1.88	1.18	1.44	0.75	1.00 0.86
Fetus 6	3	26.5	No	Perinatal death	1.12	0.93	1.02	0.89	1.19 1.27
Fetus 7	3	24	No	Acidemia	0.78	1.10	0.99	1.26	1.36 1.24
Fetus 8	3	24.6	No	Acidemia	0.95	0.92	1.17	1.22	1.20 1.30
Fetus 9	3	25.5	Yes	Acidemia	1.08	1.05	1.34	1.22	1.17 1.11
Fetus 10	3	32.0	Yes	Acidemia	0.87	1.16	1.73	1.92	1.35 1.14
Fetus 11	2	33.0	No	Acidemia	1.09	0.89	2.64	2.34	1.24 1.38
Fetus 12	2	33.1	No	Acidemia	0.96	1.18	1.42	1.42	1.22 1.02
Fetus 13	3	24.0	No	Acidemia	1.24	0.97	2.08	1.66	1.53 1.57
Prevalence	(n, %)		5 (38%)		3 (23%)	4 (30%)	9 (69%)	8 (61%)	7 (54%) 3 (23%)

Abnormal ratios: 95th percentile for gestational age, indicated in bold.

A, atrial peak velocity; DV, ductus venosus; E, early peak velocity; GA, gestational age; IDV, intermediate diastolic velocity; LV, left ventricle; RV, right ventricle.