

## RESEARCH

# Depressed left and right ventricular cardiac output in fetuses of diabetic mothers

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## Abstract

**Introduction:** We compared right and left ventricular cardiac output (RVCO and LVCO) in fetuses of diabetic mothers (FDM) with a large normal cohort.

**Methods:** We prospectively enrolled 264 normal fetuses and 30 FDM. Fetal CO parameters such as semilunar valve velocity time integrals (AVVTI, PVVTI), ventricular outflow diameters (LVOTD, RVOTD) and stroke volumes (AVSV, PVSV) were measured, and LVCO and RVCO were calculated. These were normalized using non-linear regression to estimated fetal weight (EFW) to provide means and standard deviations. Among FDMs, mean Z scores and 95% confidence limits (CL) were calculated and compared to zero.

**Results:** LVCO, RVCO and parameters they were calculated from, increased predictably and non-linearly with increasing EFW. In FDM, LVCO was depressed (mean Z  $-1.679$ , 95% CL  $-2.404$ ,  $-0.955$ ,  $P < 0.001$ ), and AVVTI, LVOTD and AVSV were significantly lower than normal. Similarly, RVCO (mean Z  $-1.119$ , CL  $-1.839$ ,  $-0.400$ ,  $P = 0.003$ ), RVOTD (mean  $-2.085$ , CL  $-3.077$ ,  $-1.093$ ,  $P < 0.001$ ) and PVSV (mean  $-1.184$ , CL  $-1.921$ ,  $-0.446$ ,  $P = 0.003$ ) were lower than normal, however, PVVTI was not different (mean Z  $0.078$ , CL  $-0.552$ ,  $+0.707$ ,  $P = 0.803$ ).

**Conclusion:** Normal biventricular stroke volumes and outputs follow a non-linear regression with EFW. FDM have significantly lower right and left heart stroke volumes and outputs for weight than do normal fetuses.

## Key Words

- ▶ fetus
- ▶ cardiac output
- ▶ Z scores
- ▶ diabetes mellitus

## Introduction

Fetal circulation is unique by virtue of its parallel systemic and pulmonary circuits. The right ventricle is known to be the dominant ventricle with prominence into late gestation (1). The fetal heart normally operates at the upper limit of the Frank Starling curve and accommodates increased venous return with a significant increase in right atrial pressure and a limited cardiac reserve (2). Fetal heart failure, therefore, commonly presents with hydrops. Semi-quantitative methods have been developed to aid in the

evaluation of the hydropic fetus, identify causes and possibly treat fetal heart failure (3). Direct estimation of right and left fetal cardiac output (CO) may enhance the evaluation of fetal heart failure. Therefore, measurement of fetal CO is potentially useful in the assessment of fetal wellbeing.

Fetuses of diabetic mothers (FDM) may have a reversible hypertrophic cardiomyopathy (4). Hypertrophic changes in the newborn heart due to maternal diabetes are well described, but the potential effects of these

myocardial changes on prenatal CO have not been investigated previously. A previous publication from our group reported subclinical myocardial strain abnormalities in FDM even without evidence of hypertrophy (5). These cardiovascular abnormalities might be expected to affect fetal CO. The objectives of this study were: (1) to develop normative fetal stroke volume (SV) and CO Z scores in mid and late gestation and (2) compare cardiac outputs in FDM against the normative fetal cardiac outputs with the goal of evaluating cardiovascular adaptations that occur in FDM.

## Methods

### Patients

This was a cross-sectional investigation involving 294 pregnant women, including 264 normal fetuses and 30 FDM. The study was approved by the Institutional Review Boards of the two participating institutions and conducted between June 2012 and May 2015. Informed consent was obtained from all pregnant women recruited in the study. Inclusion criteria for all normal fetuses recruited at the primary institution included: gestational age (GA) 15–39 weeks, maternal age 18 years or older, maternal body mass index (BMI) 25.0–29.9, intact membranes, no history of medical, surgical or obstetric complications and absence of labor. Fetuses with congenital, chromosomal anomalies and arrhythmias at the time of examination were excluded from the study. Gestational age (GA) was determined by the last menstrual period and confirmed at a first-trimester ultrasound scan. Mothers in FDM group were diagnosed with diabetes mellitus using American Diabetes Association diagnostic criteria (6).

### Fetal ultrasound acquisition

All mothers underwent detailed fetal echocardiography according to published guidelines and a common protocol at both institutions (7, 8). All images were obtained with a Vivid E9 ultrasound system (GE Medical Systems, Milwaukee, WI, USA) utilizing a C2–9MHz broad-band transducer. Each patient was examined at least once for the study by three sonographers. Images were optimized for gain, compression, depth and sector width and acquired at frame rates of 80–100 frames per second. Demographic data were collected, including GA, fetal biparietal diameter (BPD), fetal head circumference (HC), fetal abdominal circumference (AC), fetal femur length (FL), estimated fetal weight (EFW) and date of the study.

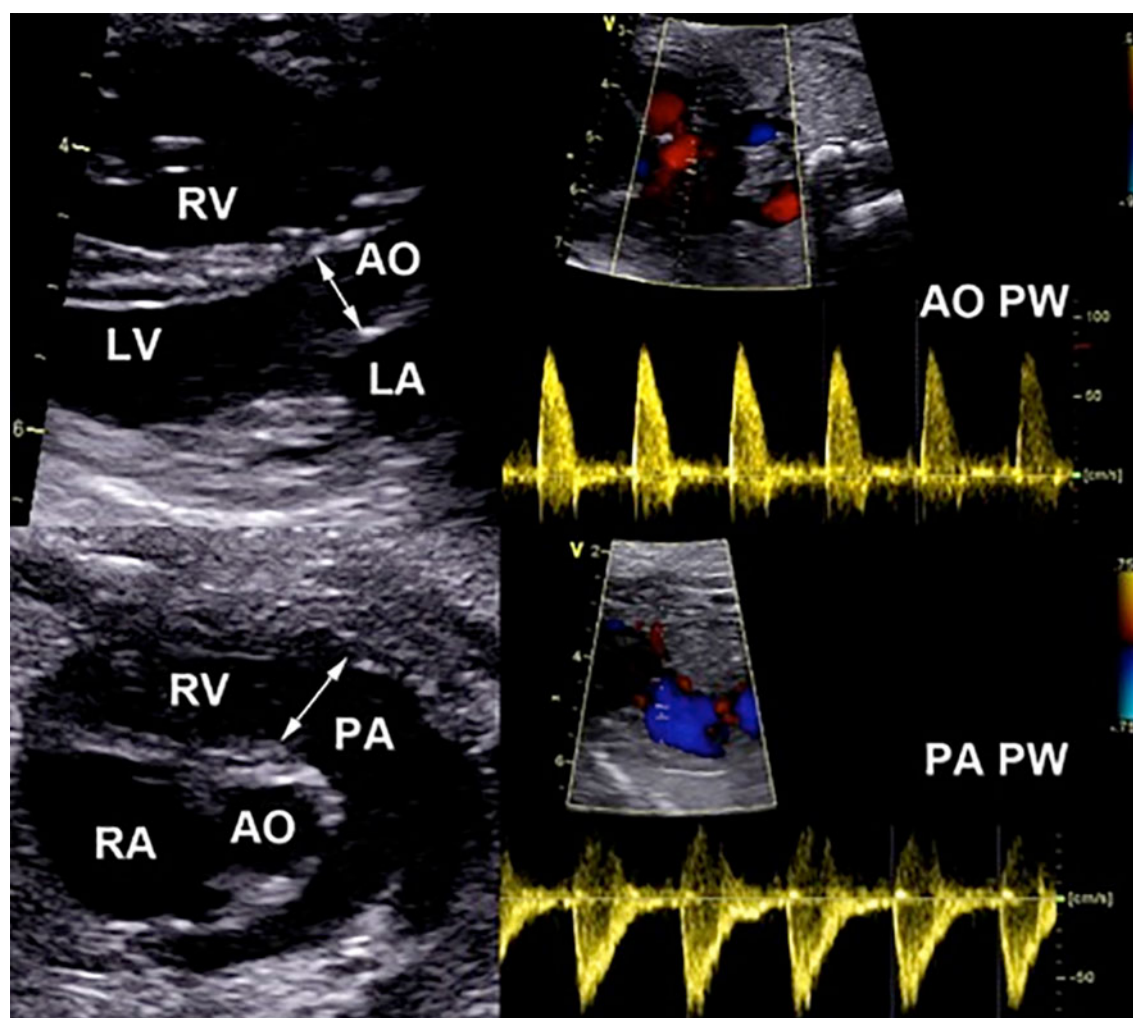
The intraluminal diameter (one inner edge to other inner edge method) of left ventricular outflow tract (LVOTD) was measured in the long axis view of the left heart during maximum expansion in systole (9). The diameters of the right ventricular outflow tract (inner diameter during maximum expansion in systole) (RVOTD) were obtained from the transverse scan of the fetal thorax during systole with insonation perpendicular to the long axis (10) (Fig. 1). Pulse wave Doppler velocity waveforms of the LVOT were obtained from the 5-chamber view. Pulse wave Doppler velocity waveforms of the RVOT were obtained from the short axis of the fetal heart (sagittal scan of the fetus). All Doppler recordings were obtained at an insonation angle <10° to flow (11). Angle correction was not used. Doppler tracings were recorded with the sample volume positioned just proximal to the valve in the center of the vessel (11, 12). The sample volume was set at 1–3 mm; the high-pass filter at 100–200 Hz. At least 5 consecutive uniform Doppler velocity waveforms with the highest velocities and narrow band of frequencies ('clean' signal) were recorded and analyzed. The aortic and pulmonary valve velocity time integrals (AVVTI, PVVTI) were traced on EchoPAC, version 13 (GE Medical Systems) using standard measurement tools by a single research sonographer (MC) (Fig. 1). The following equations were used for stroke volume (SV) and CO calculations:

$$\begin{aligned} \text{SV} &= \text{cross section area of VOT} * \text{VOT VTI} \\ &= (\pi * \text{VOTD}^2 / 4) * \text{VOT VTI} \end{aligned}$$

$$\text{CO} = \text{SV} * \text{HR}$$

### Statistical analysis

All values are expressed as mean ± standard deviation (s.d.) for normally distributed data. The best-fit model for the mean and with the lowest standard deviation was derived using the fractional polynomial to determine a relationship between a variable and EFW. Non-linear regression models to estimate the mean values for the flow parameters and anatomic dimensions were generated based on EFW using the Gompertz growth function  $y = q_1 * \exp[-\exp(q_2 * \text{EFW})]$ . Standard deviations of the flow parameters and anatomic dimensions about their EFW-based means were calculated within EFW quintiles. When standard deviations were noted to vary linearly with EFW, linear regression models to predict standard deviation from EFW were derived. Z scores could then be calculated as (observed value - predicted mean / predicted standard deviation). For ease of use,



**Figure 1**

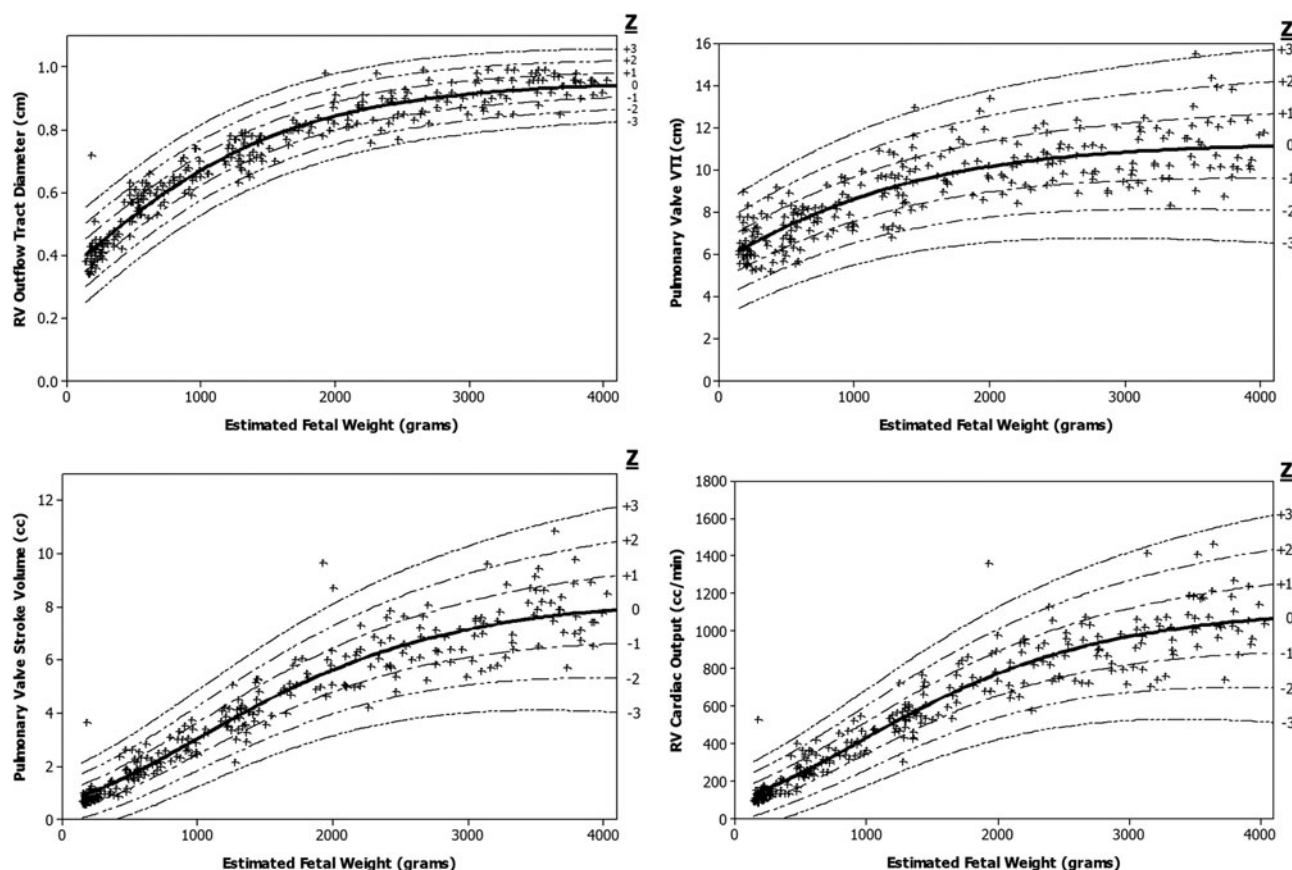
Left ventricular outflow tract diameter measured in fetal cardiac long axis and right ventricular outflow tract diameter is measured in fetal transverse short axis. Velocity time integrals are derived from pulse wave Doppler waveforms obtained parallel to the outflow tracts. AO, aorta; AO PW, aortic valve pulse wave Doppler; LA, left atrium; LV, left ventricle; PA, pulmonary artery; PA PW, pulmonary valve pulse wave Doppler; RA, right atrium; RV, right ventricle.

graphs of parameter value vs EFW showing mean and iso-Z lines were plotted. Echocardiographically derived left and right ventricular outflow tract diameters, velocity time integrals, SVs and COs for FDM were converted to Z scores by comparison with normative data gathered in this study. The FDM Z scores were compared to zero using non-paired two-tailed *t*-test. To assess if these parameters tended to approach or diverge from normal as pregnancy advanced, these z scores were evaluated as a function of EFW using linear regression. Intraclass correlation coefficients were calculated to test measurement variability. A *P* value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS, version 17.0 (IBM).

## Results

### Normative data

The mean GA of the normal fetuses was  $28.1 \pm 1.3$  (16.0–39.7) weeks. The mean EFW (g) for all normal fetuses was  $1610 \pm 1201$ . There was a non-linear exponential increase in fetal biventricular outflow tract diameters, outflow time velocity integrals, SVs and COs with increasing fetal weight (Figs 2 and 3). The prediction intervals were not constant with EFW; normal values were much tighter at lower EFW. The sigmoid Gompertz model reflected well the non-linear associations of normal fetal biventricular outflow tract diameters, outflow time velocity integrals, SVs and COs with EFW (Table 1).



**Figure 2**

Plots of fetal RV outflow tract diameter, pulmonary valve VTI, pulmonary valve stroke volume (cc) and right ventricular cardiac output (cc/min) vs EFW with mean and iso-Z lines. EFW, estimated fetal weight; RV, right ventricle; VTI, velocity time integral.

### Cardiac output in FDM

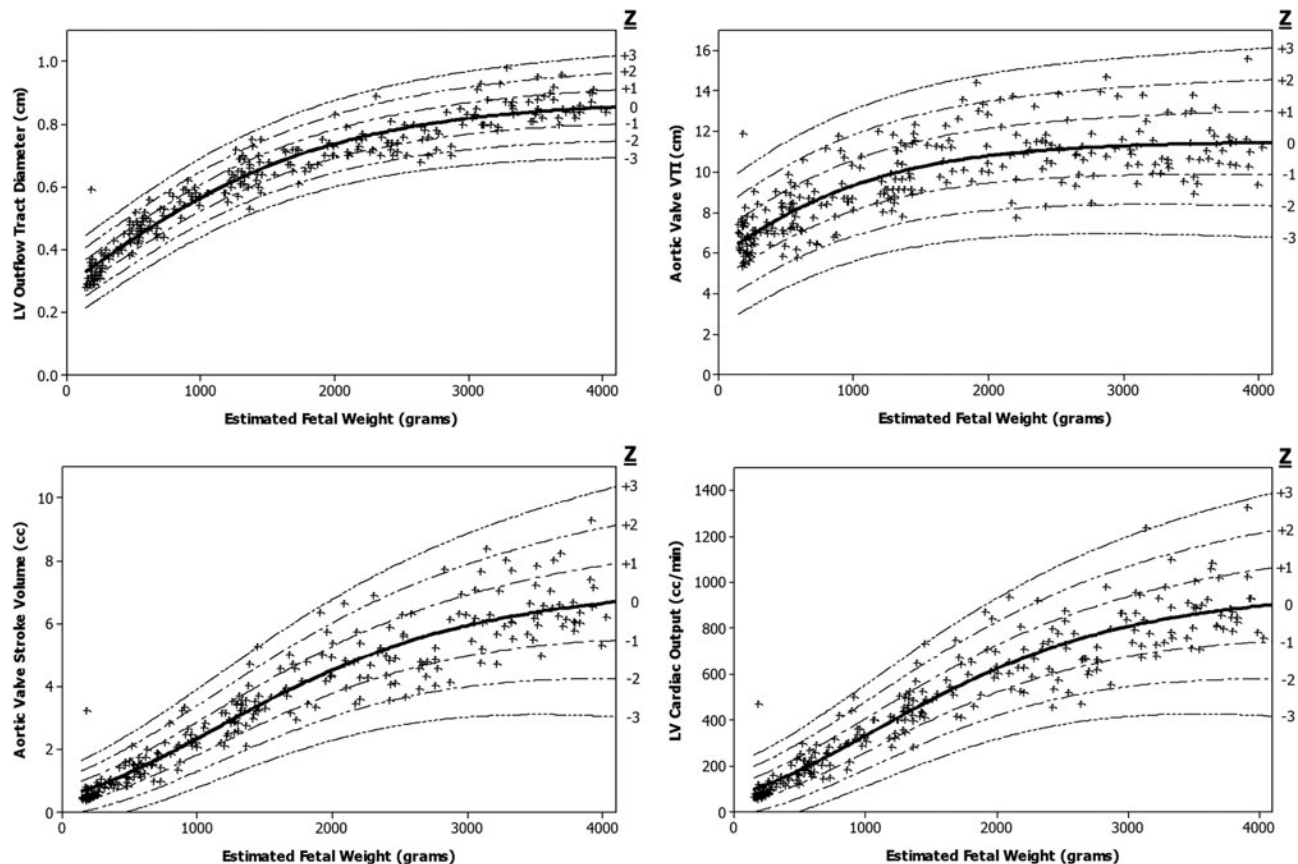
The mean GA of the FDM group was  $25.3 \pm 4.6$  weeks, and the mean EFW of the FDM was  $1014.4 \pm 687.6$  g. The mean maternal hemoglobin A1c in the FDM group was  $6.4 \pm 1.2$  mg/dL. Of the 30 FDM, 12 had pregestational DM controlled on insulin, 5 had pregestational DM controlled by oral hypoglycemic agents, 4 had gestational DM controlled by insulin, 1 had gestational DM controlled by oral hypoglycemic agent and 8 were managed with diet alone. In FDM, as gestation progressed and EFW increased, the normalized right and left ventricular cardiac outputs decreased and the outflow tract diameters and the time velocity integrals diverged from normal, on both the right and left ventricular sides. In FDM, LVCO was depressed (mean  $Z -1.679$ , 95% CL  $-2.404, -0.955$ ,  $P < 0.001$ ). AVVTI (mean  $-0.985$ , CL  $-1.630, -0.340$ ,  $P = 0.004$ ), LVOTD (mean  $-2.340$ , CL  $-3.281, -1.398$ ,  $P < 0.001$ ) and AVSV (mean  $-1.725$ , CL  $-2.461, -0.989$ ,  $P < 0.001$ ) were all significantly lower than normal. Similarly, in FDM, RVCO (mean  $Z = -1.119$ , CL  $-1.839, -0.400$ ,  $P = 0.003$ ), RVOTD (mean  $-2.085$ , CL  $-3.077$ ,

$-1.093$ ,  $P < 0.001$ ) and PVSV (mean  $-1.184$ , CL  $-1.921, -0.446$ ,  $P = 0.003$ ) were lower than normal; however, PVVTI in FDM was not different from normal (mean  $Z 0.078$ , CL  $-0.552, +0.707$ ,  $P = 0.803$ ). Intraclass correlation coefficients with 95% CIs showed excellent agreement for both intra- and inter-observer comparisons (Table 2).

### Discussion

We have presented SV and CO reference regressions with standard deviations for the RV and LV in the normal fetus through mid and late gestation. There are limited published fetal CO normative data from which  $Z$  scores may be derived for quantification, reporting and follow-up by the fetal cardiologist (13, 14, 15). Non-normalized measurements of cardiac dimensions or flow in the growing fetus are not expected to be as meaningful as  $Z$  scores. EFW-corrected CO's are especially relevant for the practicing fetal cardiologist because there are limited valid surrogates for accurate assessment of fetal cardiac function.





**Figure 3**

Plots of fetal LV outflow tract diameter, aortic valve VTI, aortic valve stroke volume (cc), and left ventricular cardiac output (cc/min) vs EFW with mean and iso-Z lines. EFW, estimated fetal weight; LV, left ventricle; VTI, velocity time integral.

### Homogeneity of normalized data

Reference ranges for fetal CO data have been published previously (13, 14, 15). Mielke and coworkers reported fetal SV and CO reference medians and percentiles in 244 fetuses from 13- to 40-week gestation (14). Percentiles are not commonly used in clinical echocardiography practice. Non-parametric reference ranges are also not

recommended in pediatric echocardiography because of the large volume of data required to estimate percentiles reliably (16, 17). The fetal CO data reported by Mielke and coworkers are slightly lower than in the present report. The higher strata of GAs appear to be underrepresented in the Mielke report.

**Table 1** Fetal cardiac flow patterns in the normal fetuses.

Parameter	$q_1 _1$	$q_2 _2$	s.d. function
AVVTI	11.5114	-0.379311	$1.15 + 0.0001 \cdot \text{EFW}$
LVOTD	0.876253	0.106024	$0.03794 + 0.000004 \cdot \text{EFW}$
AVSV	7.20064	0.992382	$0.2964 + 0.000226 \cdot \text{EFW}$
LVCO	965.039	0.950097	$45.72 + 0.02838 \cdot \text{EFW}$
PVVTI	11.3067	-0.366837	$0.8858 + 0.000158 \cdot \text{EFW}$
RVOTD	0.954928	0.000802885	$0.05094 - 0.000003 \cdot \text{EFW}$
PVSV	8.34744	0.943745	$0.3844 + 0.000221 \cdot \text{EFW}$
RVCO	1124.29	0.896793	$53.53 + 0.03203 \cdot \text{EFW}$

' $q_1$ ' and ' $q_2$ ' refer to the coefficients of the Gompertz growth model relating parameter ( $y$ ) to EFW:  $y = q_1 \cdot \exp(-\exp(q_2 \cdot \text{EFW}))$ . 's.d. function' is the linear relation of the standard deviation about the mean parameter value and EFW.

AVSV, aortic valve stroke volume; AVVTI, aortic valve velocity time integral; LVCO, left ventricle cardiac output; LVOTD, left ventricle outflow tract diameter; PVSV, pulmonary valve stroke volume; PVVTI, pulmonary valve velocity time integral; RVCO, right ventricle cardiac output; RVOTD, right ventricle outflow tract diameter.

**Table 2** ICC and 95% CI.

Measurement	Intraobserver		Interobserver	
	ICC	95% CI	ICC	95% CI
AV VTI	0.9750	0.9674–0.9780	0.9675	0.9488–0.9750
LVOT diameter	0.9689	0.9523–0.9756	0.9534	0.9341–0.9694
PV VTI	0.9676	0.9590–0.9751	0.9532	0.9382–0.9733
RVOT diameter	0.9634	0.9586–0.9734	0.9465	0.9237–0.9626

Vimpeli and coworkers reported reference ranges for fetal SV and CO from 11- to 20-week gestation (13), with CO results similar to ours. The present study provides a more comprehensive (including the third trimester) normalization. De Smedt and coworkers reported normal fetal CO data in 28 fetuses from 15 weeks to parturition (15); however, the study was limited by small sample size and differences in methodology, where fetal CO was calculated using mitral and tricuspid inflow velocities, unlike our study that used outflow tract measurements.

### Cardiovascular adaptations in fetuses of diabetic mothers

We observed decreased SV and CO for RV and LV in FDM compared to normal fetuses. This is in contrast to the report of Lisowski who found higher right and left ventricular fetal CO in early pregnancy, but no significant differences at late gestation when mother's DM was well controlled (18). The differing observations could be related to the important differences between the studies; they excluded type II and poorly controlled type I mothers in the 17 patients studied. They used the mitral and tricuspid valve VTI for CO calculation and compared against historical controls. Pilania and coworkers suggest that CO is higher in FDM, but did not adjust the CO for EFW (19). In a previous study, we have reported decreased systolic strain parameters and lower ejection fraction in FDM (5); this observation is consistent with the lower CO parameters observed in the present study. Depression of CO in FDM is more striking as EFW increases. The data presented here, showing depression of CO and progressive divergence of both outflow tract diameters and time velocity integrals from normal, are most easily interpreted as a consequence of diastolic dysfunction in FDM. Evidence for diastolic dysfunction has been shown in infants of diabetic mothers. The inference that diastolic dysfunction is the primary cause of our CO observations is strong, but unproven.

The hypertrophic myocardial changes seen in infants of diabetic mothers are well documented and described. But as stated previously, our group has reported evidence of myocardial strain abnormalities even in infants without ventricular hypertrophy (5). The embryogenic effects of maternal hyperglycemia and fetal hyperinsulinemia on the molecular myocardial makeup are still unclear (20). One might postulate that infants of pregestational diabetics may demonstrate a greater change in CO, as compared to infants of gestational diabetics, if the embryogenic effects are indeed the cause. This study did not separate out these two groups, but further research may be warranted to determine which babies might be at higher risk for poor myocardial performance.

Others have evaluated birth weight and placental weight associations in gestational DM and found significant associations between maternal hemoglobin A1C, history of glucose intolerance and higher placental weight in FDM pregnancies (21). Increased angiogenesis, with increased capillary leakiness have been described in the type 1 diabetic human placenta and may be related to increased levels of placental vascular endothelial growth factor (22). It has been suggested that there is increased blood flow to the placenta in FDM. In a study evaluating MCA Doppler velocities in gestational DM, no significant differences were found in MCA Doppler velocities (23). In our study, the EFW in the FDM pregnancies were not significantly different than their GA-matched normal controls. It is likely that there is redistribution of the fetal blood volume and cardiac output to the diabetic placenta resulting in a net decrease in fetal LV and RV CO. We did not evaluate fetal placental and umbilical blood flows in this study. Further focused evaluation of the fetal cardiovascular adaptations is needed to elucidate the pathophysiological mechanisms.

### Limitations

CO calculation is based on accurate reproducible measurements of the LVOTD, RVOTD and VTI.

All echocardiograms were performed according to a standardized protocol at both institutions; however, measurements in routine clinical practice may demonstrate more variability. Others have normalized LVOTD and RVOTD to femur length (9, 24); differences in normalization could account for minor discrepancies. Finally, heart rate variability will alter CO calculations. Fetuses included in this database had no evidence for tachy or bradyarrhythmias at initial screening.

## Conclusions

The fetal CO Z score database developed in this study is robust and comprehensive and could be valuable in clinical evaluation and follow-up of fetuses in pathological states. We have demonstrated depressed biventricular CO in FDM. Altered placental blood flow and ventricular compliance changes may contribute to the production of this alteration. The prognostic significance of this finding is yet to be determined.

### Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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