Markers of Maternal and Infant Metabolism are Associated with Ventricular Dysfunction in Infants of Obese Women with Type 2 Diabetes

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Abstract

BACKGROUND—To test the hypothesis that infants born to obese women with pregestational type 2 diabetes mellitus (IBDM) have ventricular dysfunction at one month that is associated with markers of maternal lipid and glucose metabolism.

METHODS—In a prospective observational study of IBDM (OB+DM, n=25), echocardiography measures of septal, left (LV) and right ventricular (RV) function and structure were compared at one month of age to infants born to OB mothers without DM (OB, n=24), and non-OB without DM (Lean, n=23). Basal maternal lipid and glucose kinetics and maternal plasma and infant (cord) plasma were collected for hormone and cytokine analyses.

RESULTS—RV, LV, and septal strain measures were lower in the OB+DM infants vs. other groups, without evidence of septal hypertrophy. Maternal hepatic insulin sensitivity, maternal plasma free fatty acid concentration, and cord plasma insulin and leptin most strongly predicted decreased septal strain in the OB+DM infants.

CONCLUSION—IBDM's have reduced septal function at one month in the absence of septal hypertrophy, which is associated with altered maternal and infant lipid and glucose metabolism.

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These findings suggest that maternal obesity and DM may have a prolonged impact on the cardiovascular health of their offspring, despite resolution of cardiac hypertrophy.

Since the mid-1940's, cardiac hypertrophy at birth, particularly in the septum, has been a well-known phenomenon in infants born to women with pre-gestational type 2 diabetes mellitus (IBDM)(1). This hypertrophy is thought to be transient, often resolving in two weeks to six months of age.(1–4) Emerging evidence suggests that ventricular function during gestation and at birth is impaired in IBDM, even in the absence of cardiac hypertrophy.(5, 6) Although unclear from the current literature, early life ventricular abnormalities may predispose these children to develop overt cardiac dysfunction as adults or as other cardiovascular risk factors emerge.

Mechanisms for ventricular contractile abnormalities in IBDM remain obscure. Some data(5, 7, 8), but not all(9), suggest that maternal and infant glycemia is associated with impaired cardiac function. Recent evidence points to a possible relationship between maternal adipose tissue/lipid metabolism and adverse cardiac function in the offspring.(6, 10) Additional findings demonstrate the association of maternal lipid metabolism with elevated infant birth weight in diabetic pregnancy.(11–13) None of these previous studies have separated the effects of maternal obesity and diabetes mellitus on cardiac function in the infants, nor have they examined the predictive value of maternal lipid and glucose metabolism on infant ventricular function. Furthermore, advances in neonatal cardiac imaging permit a more comprehensive assessment of ventricular function in neonates that could not be previously obtained with conventional imaging.(14)

Therefore, the primary objective of this study was to compare left (LV) and right ventricular (RV) function in infants born to three groups: 1) obese women with pre-gestational type 2 diabetes mellitus (OB+DM), 2) obese women without diabetes mellitus (OB), and 3) non-obese women without diabetes mellitus (Lean) with conventional and two-dimensional quantitative echocardiography. The secondary objective was to examine indices of maternal lipid metabolism as predictors of infant ventricular function in this cohort. Our hypothesis was that ventricular functional abnormalities will be greatest in infants born to obese women with DM and would be associated with markers of maternal lipid metabolism.

METHODS

This was a prospective observational study of three groups of women who were receiving prenatal care at the Women's Health Center at Barnes-Jewish Hospital/Washington University School of Medicine in St. Louis between May 2011 and December 2013, and their neonates. Infants were stratified into three separate groups based on maternal body mass index and diabetic status: Infants born to 1) obese women with pre-gestational, type 2 DM, requiring insulin (White Class B or C [OB+DM]), 2) obese women without DM or insulin resistance (no pre-gestational or gestational and normal 50g glucose challenge, [OB]), and 3) non-obese controls without DM (Lean). Obesity was defined as pre-pregnancy body mass index between 30 and 45 kg/m^2. Women with pre-gestational DM were on insulin therapy, and had HbA1C   8 (183 mg/dL, 64 mmol/mol) for greater than 3 months prior to pregnancy as previously described(13). Exclusion criteria for all women included: 1)

multiple gestation pregnancy, 2) inability to provide voluntary informed consent, 3) current self-reported use of illegal drugs (cocaine, methamphetamine, opiates), 4) current smoker who did not consent to cessation, 5) current usage of daily medications by class: corticosteroids, beta-blockers (known to affect lipid metabolism) or anti-psychotics (known to alter insulin resistance and metabolic profiles), and 6) known fetal anomalies. For women without DM, exclusion criteria included: 1) diagnosis or history of gestational diabetes or abnormal 50g glucose challenge between 24 and 28 weeks, 2) pre-pregnancy DM or 3) prior macrosomic (>4000g) infant. This study was approved by the Human Research Protection Office at Washington University School of Medicine (IRB#201012828, NCT#01346527).

Assessment of Cardiac Structure and Function

A transthoracic complete M-mode, two-dimensional (2D) and Doppler echocardiographic examination was performed at one month of age with a commercially available ultrasound imaging system (Vivid 7 and 9; General Electric Medical Systems, Milwaukee, Wisconsin). The timing of the echocardiographic study was carefully selected to occur at one month of age to avoid the early postnatal period of cardiopulmonary instability with a patent ductus arteriosus (PDA) and rapidly decreasing pulmonary vascular resistance. All of the infants were clinically healthy at birth and were discharged home with their mothers. None of the infants in this study had evidence of a PDA or altered pulmonary hemodynamics at one month of age. All the infants were stable in room air at the time of the study. All exams were performed two hours after feedings. One designated pediatric cardiac sonographer, blinded to the maternal and infant clinical and demographic data, and experienced in acquiring images for conventional and 2D speckle tracking echocardiographic (2DSTE) analysis obtained all the echocardiographic images using a transducer (7.5–12 MHz) center-frequency phased array probe and optimized to visualize the myocardial walls.(15) The echocardiographic images were acquired according to the guideline of the American Society of Echocardiography(16) and with a previous validated protocol in decubitus position during restful period without changing the position of the infant or disturbing the hemodynamic condition to minimize heart rate and respiratory variation during the image acquisition.(15, 17)

Cardiac Structure—Relative wall thickness (RWT) and LV mass index (LVMI, Devereux formula) were calculated using M-mode imaging of the LV in the parasternal short-axis view, and LVMI was indexed to height$^{2.7}$ (g/m$^{2.7}$).(16, 18) Using M-mode imaging, interventricular septal wall thickness was measured in the parasternal long axis view at the level of the tip of the mitral valve midway between the apex and the crux of the heart. The RV linear dimensions (inflow at base and mid-cavity, length, and tricuspid valve annulus) were measured from the apical four-chamber view. The RV linear dimensions at the proximal and distal outflow were measured from the parasternal short axis view.

Cardiac Function—Conventional indices of LV function, shortening fraction (SF) and biplane LV ejection fraction (EF), were measured according to the guidelines of the American Society of Echocardiography.(16, 19, 20) Myocardial mechanics were analyzed by the quantification of LV, RV, and septal longitudinal strain (%) and strain rate (%/sec) by 2DSTE, an emerging quantitative echocardiographic technique to characterize ventricular

function in neonates.(14) The strain parameters were acquired using a previously validated image acquisition and data analysis protocols from our laboratory.(15, 17) A frame rate to heart rate ratio (FR/HR) between 0.7 and 0.9 frames/sec per bpm was utilized to optimize myocardial speckle tracking and mechanical event timing.(21) LV global longitudinal strain (LV GLS, %) and systolic, early and late diastolic global longitudinal strain rates (LV GLSRs, GLSRe, and GLSRa, (%/sec) respectively) were calculated by averaging all values of the regional peak longitudinal strain obtained from 17 segments in two-chamber, apical long-axis, and apical four-chamber views.(22) Peak strain was measured as end-systolic strain at the closure of the aortic valve.(23) RV global longitudinal strain (RV GLS,%) was measured from an RV focused apical four-chamber view and calculated by averaging all values of the regional peak longitudinal strain obtained from six segments. LV and RV segmental longitudinal strain (SLS, %) were measured at the apical-, mid-, and basal-ventricular levels in the RV and LV free walls. Septal GLS and GLSRs, GLSRe and GLSRa measures were calculated by averaging all values of the SLS obtained from 9-segments in the two-chamber, apical long-axis, and apical four-chamber views along the septal wall. A lower magnitude of strain (%) and strain rate (%/sec) indicates worse ventricular function. A single observer (PL), who was blinded to the maternal and infant clinical and metabolic values, analyzed the strain imaging using vendor customized commercially available software (EchoPAC; General Electric Medical Systems, Waukesha, WI, version 110.0.x). We have previously demonstrated reliable intra- and inter- observer reproducibility of strain imaging in neonates.(15, 17, 24)

Lipid and Glucose Metabolism Studies

All pregnant women underwent basal lipid and glucose kinetic studies (using stable isotope tracer methodology) and a subset (n=49) also underwent hyperinsulinemic-euglycemic clamp during gestation weeks 32–36 as previously described.(13) Maternal plasma at 32–36 weeks gestation and infant (cord) plasma at birth was collected for hormone and cytokine analyses as previously described.(13)

Statistical Analyses

Normally distributed demographics, plasma metabolite, hormone variables, and echocardiographic variables between groups were examined by one-way analysis of variance (ANOVA) and group differences were compared through post-hoc testing using Tukey honestly significant difference testing. Non-normally distributed variables determined by the Shapiro-Wilk test were examined by chi-square and independent samples Kruskal-Wallis one-way ANOVA. Relationships between outcome variables were examined using univariate (Pearson Product Correlation Coefficient) and standardized linear regression analysis with Bonferroni adjustment for multiple correlations were used to refine the ability to predict LV, RV, and Septal global and regional deformation strain combining multiple metabolic measures. Univariate analysis was utilized to determine the best predictors to enter in the model (significant correlation > 0.4) and then backward step-wise regression was performed. Statistical significance was considered at $p < 0.05$. Due to the lack of data regarding the relationship between maternal and infant lipid and glucose metabolism with postnatal ventricular function, and the exploratory nature of this study, we used data from our previous work in nongravid insulin- resistant and control participants and data from our deformation

studies to estimate sample size, assuming an alpha of 0.05, where 20 subjects per group would provide 99% power to detect 20% differences in echocardiographic measures between groups (13, 24, 25). All statistical analyses were performed using SPSS (IBM, Armonk, NY).

RESULTS

Seventy-nine women were enrolled and studied at 32–36 weeks' gestation. Of the 79 mothers enrolled in the original study,(13) 72 of the neonates returned at one month of age (30 ± 5 days) and received conventional and speckle-tracking echocardiograms between May 2011 and December 2013. Infants were stratified into the three separate groups: 1) OB +DM, n=25, 2) OB, n=24, and 3) Lean, n=23. The infants included were from a previous study reported by our group, but their echocardiographic data was not initially analyzed in the study.(13) There was a statistical difference between the gestational age at birth between the OB+DM (37 ± 2 weeks) and the OB (39 ± 2 weeks) and Lean (39 ± 1 weeks) groups, but after adjusting for birthweight, gender, and postnatal age at the time of echocardiogram univariate correlations did not reveal relationships between the echocardiographic indices and gestational age between the groups. Table 1 displays the demographic, clinical, and metabolic characteristics of the study population.

Assessment of Cardiac Structure and Function

Ventricular Structure—LV mass, LV mass index, relative wall thickness, and interventricular septal wall thickness, were not different between the three groups. RV major dimension was only significantly higher between the OB+DM and the OB groups ($p < 0.05$), (Table 2).

Ventricular Systolic Function—The results of the ventricular functional analyses are provided in Table 2. There were no differences in conventional measures of LV systolic function (EF and SF) among groups. Septal GLS was significantly lower in OB+DM compared to both the OB and Lean ($p < 0.005$ for both). Septal SLS displayed a preserved normal apex to base gradient pattern in all three groups ($p < 0.05$), but SLS at the apex and mid-level of the septum were significantly lower in OB+DM compared to OB and Lean ($p < 0.002$ for both). LV GLS was significantly lower in OB+DM vs. Lean groups ($p < 0.05$). LV SLS also displayed a preserved normal apex to base gradient pattern ($p < 0.05$), but LV SLS was significantly lower at the basal- and mid-ventricular level in OB+DM vs. Lean ($p < 0.05$). RV GLS was significantly lower in OB+DM vs. Lean ($p < 0.05$). RV SLS displayed a preserved normal base to apex gradient pattern ($p < 0.05$) with no differences in values in all three groups. RV and LV systolic strain rate (SRs) patterns were all similar amongst the groups.

Ventricular Diastolic Function—The feasibility of GLSRe and GLSRa was 93%, as seven out of 72 patients had fused early and late strain curves and were excluded from the analysis. LV GLSRe and GLSRa were not different between the groups, however both RV and Septal GLSRe were significantly lower in OB+DM vs., Lean ($p < 0.001$).

Relationships between Maternal Lipid and Glucose Kinetics with Ventricular Deformational Indices

Using univariate analysis in OB and OB+DM women only (n=49), several maternal and infant variables were tested for association with LV, RV, and septal GLS. Variables found to have an association with septal GLS (R 0.40, P<0.05) included maternal age, endogenous glucose production per unit of insulin during the baseline period and during hyperinsulinemia, glucose rate of disappearance during hyperinsulinemia (i.e. insulin sensitivity), suppression of endogenous glucose production with hyperinsulinemia, and plasma free fatty acid concentration during hyperinsulinemia. Infant variables with a correlation with septal SLS (R 0.40, p<0.05) included cord plasma insulin, C-peptide and leptin and infant birth weight. Using these variables in a backward step-wise regression analysis (multicollinearity: tolerance=0.52–0.78, variance inflation factor=1.3–1.9), a model including maternal plasma free fatty acid concentration during hyperinsulinemia, suppression of endogenous glucose production with hyperinsulinemia, infant birth weight and cord plasma insulin and leptin most strongly predicted decreased septal strain in the OB +DM (adjusted R^2=0.62). None of the maternal or infant lipid and glucose metabolism variables were associated with LV or RV strain measures.

DISCUSSION

In this study we utilized an emerging non-invasive echocardiographic modality, deformation imaging by 2DSTE, to quantitatively characterize ventricular performance and assess early-stage disease-related cardiac changes in IBDM at one month of age. The principal and novel finding of this study is that IBDM have reduced septal strain (septal function) in the absence of septal hypertrophy that was associated with alterations in maternal lipid and maternal and infant glucose metabolism. In addition, IBDM had decreased RV and LV deformation values with relatively preserved ventricular structure.

Pregestational diabetes has an effect on early embryonic development that may alter cardiac morphogenesis during gestation and extend to the neonatal period, exposing the IDBM to varying degree of myocardial damage.(5) The high levels of glucose in the maternal blood will cause fetal hyperglycemia through the placenta leading to fetal cardiomyocyte injury directly with excessive apoptosis of myocardial cell.(26) Pregestational type 2 DM is also characterized by hyperlipidemia.(6, 27) As the pregnancy progresses, the excessive availability of lipids and higher maternal free fatty acid concentration might lead to increased fatty acid delivery to the fetus resulting in lipid accumulation within the fetal cardiomyocyte.(6, 26) The fetal heart adapts to the hyperlipidemia by increasing the expression of fatty acid metabolizing proteins, thereby increasing the reliance on fatty acids as energy.(6, 26) This adapting heart is initially able to maintain cardiac output under these conditions. However, the continued exposure of the fetal heart to this metabolic environment eventually leads to apoptosis, fibrosis, and contractile dysfunction.(6) In this study we found that several maternal and infant metabolic variables had associations with decreased septal strain in infants born to obese and diabetic women, including maternal hepatic insulin sensitivity, maternal plasma free fatty acid concentration, and cord blood insulin and leptin.

The complex interaction between excessive glucose and lipid metabolism affects the heart of IBDM in multiple ways, including cardiac malformations, hypertrophic cardiomyopathy (even with good maternal glycemic control), and functional impairment (even in the absence of structural changes).(28) The most common cardiac pathology in IBDM is asymmetrical septal hypertrophy.(28–30) Myocardial mass is thought to increase because of the presence of higher levels of fetal insulin during gestation that can lead to septal wall dysfunction immediately after birth. The septal wall dysfunction can occur in systole, but more commonly presents in diastole.(22) The majority of the IBDM's are asymptomatic despite this dysfunction, and the observed septal wall hypertrophy is typically transient.(1–4) In the current study, septal wall thickness was not different between the three groups at one month of age, but global and segmental longitudinal strain at the apex and mid-level of the septum were significantly lower in OB+DM compared to OB and Lean groups. Diastolic strain rate measures were also decreased in OB+DM compared to OB and Lean groups, with preserved systolic strain rate measures. Wang et al. found similar significantly decreased longitudinal strain in the apical segments of the septum in fetuses of women with DM.(30)

Interventricular septal wall thickening and dysfunction in the IDBM may transiently disrupt the performance of both the LV and RV in the early neonatal period.(31) In this study, LV morphology was not different among groups, but at one month of age both septal and LV global longitudinal strain were lower in OB+DM infants in comparison with Lean infants. Al Biltagi et al. utilized 2DSTE derived LV deformation imaging to assess LV function in IBDM in the immediate postnatal period and found reduced LV longitudinal strain and impaired systolic function, but did not distinguish between pre-gestational type 1 and type 2 DM. Previous studies using tissue Doppler and 2DSTE have observed similar decrease in LV GLS with fetuses of obese and DM mothers.(6, 30) Russel et al. demonstrated that in fetuses of pregestational diabetic mothers altered cardiac function (detected by decreased strain imaging) is evident before cardiac structural changes.(32) Combined with our results, these studies may suggest that altered cardiac function not only precedes cardiac structural changes, but persists from gestation through the early postnatal period, even after the morphological alterations resolve.

The impact of IBDM on LV diastolic function is unclear from the current literature. (5, 31, 33) Weber et al. found normal LV early/late velocity ratio in the fetuses and neonates of well-controlled pregestational diabetic mother.(33) Kozak-Barany et al.(31) and Al-Biltagi et al.(5) found that LV diastolic function was significantly impaired in infants in the first week of age, even in the presence of well-controlled glycemia.(31) In our study LV diastolic function, as measured by early and late strain rate, was preserved at one month of age. Although, there may be a component of LV diastolic dysfunction in the early transitional period that reflects the abnormal myocardial relaxation and slower LV filling, the resolution of morphological abnormalities appears to be followed closely by the normalization of LV diastolic function.

Deformation imaging by 2DSTE has also been shown to have a greater sensitivity for measuring global and regional LV function than conventional echocardiography in neonates. (14) In the first week of age, studies have shown a decrease in SF in infants born to mothers with pre-gestational and gestational DM,(5) while other studies have demonstrated normal

ejections fraction in gestational diabetes.(34) In this study, we found decreased LV global and segmental longitudinal strain with preserved ejection fraction and SF in infants born to OB+DM at one month of age. The clinical significance of these results lie in the notion that advances in neonatal cardiac imaging with 2DSTE now provide the capability to obtain quantitative information that often supersedes the qualitative information from conventional methods; and permit a more comprehensive (regional and global) assessment of LV function in neonates that could not be previously obtained.(14)

Pre-existing maternal diabetes alters both LV and septal performance and potentially complicates RV function as well.(30) There is a paucity of studies(6, 30) that have characterized RV function with deformation imaging by 2DSTE in the fetus of pregestational DM, but none in IBDM. Our study in neonates showed that RV global longitudinal strain and early diastolic strain rate were significantly decreased in the OB+DM infants, which is a similar finding to the reported altered RV deformation values in fetuses of gestational diabetes.(30) There are a few mechanisms that could explain RV dysfunction in IBDM. The pathways that are most responsible for RV remodeling in IBDM likely include insulin resistance, and amplified sympathetic nervous and renin-angiotensin-aldosterone systems.(26, 35–37) The common link between the pathways is the accumulation of collagen in the myocardium and development of myocardial fibrosis, which likely results from prolonged hyperglycemia with advanced glycation end-products and excessive production of oxygen free radicals.(37) These changes may lead to a loss of elasticity with an increase in ventricular stiffness that first causes diastolic dysfunction, then hypertrophy and finally systolic dysfunction.(26, 35) In our study, we observed: 1) diastolic dysfunction, as manifested by decreased RV global longitudinal strain rate at early diastole; 2) slightly altered RV morphology (increased RV major); and 3) subsequent systolic dysfunction seen through decreased RV global longitudinal strain in IBDM.

The strongest potential cause for the deterioration of RV function maybe the "interventricular interaction" achieved through the septum.(35) We demonstrated that the apex-to-base gradient in the RV free wall longitudinal strain was preserved between the three groups, but that RV GLS was significantly decrease in the OB+DM. The RV GLS measurement includes part of the septal wall from the apical four-chamber view, further supporting the significance of this interventricular dependence.(35)

This study has important limitations. There is evidence that the fetus of a mother with pregestational type 2 DM has decreased myocardial deformation in the longitudinal, radial, and circumferential direction, suggesting diffuse pattern of myocardial involvement.(6) In this study we only evaluated longitudinal strain imaging, as the feasibility and reproducibility of radial and circumferential strain has not been well described in neonate, and GLS remains the most reliable quantitative tool of the three to assess ventricular function in infants.(15) We did not assess torsional mechanics at one month of age, but recognize the utility of this emerging speckle tracking modality to assess ventricular mechanics.(5, 34)

We chose to study the neonates at one month of age, rather than at birth, to avoid the early postnatal period of cardiopulmonary instability. Our group has previously developed a

standardized cardiac strain imaging protocol to limit the variability in image acquisition.(15) Although scan-rescan analysis was not performed in this study, one dedicated sonographer, experienced in conventional and quantitative neonatal echocardiography acquired all of the images, further decreasing the variability in image acquisition. Our study was also limited by the small sample size in each group, but 20 neonates was determined to be enough to detect group differences in the outcome variables. Although the current literature does not yet support a link between altered septal function at one month of age and adult ventricular dysfunction, future longitudinal studies are needed to follow a larger cohort with serial echocardiograms from early gestation to birth, through the late neonatal period, and into childhood to further investigate these associations and questions.

CONCLUSION

In conclusion, infants born to obese women with pregestational type 2 DM have reduced interventricular septal wall function at one month of age in the absence of septal hypertrophy, which is associated with altered maternal and infant lipid and glucose metabolism. In addition, LV and RV function are decreased. These findings suggest that maternal obesity and DM may have a prolonged impact on the cardiovascular health of their offspring, despite resolution of cardiac hypertrophy. Aggressive maternal glucose and lipid metabolism management during pregnancy in women with diabetes to modulate infant cardiac dysfunction might be warranted.

Acknowledgments

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Table 1

Maternal and Infant Demographics and Plasma Metabolites

	Lean (n=23)	OB (n=24)	OB+DM (n=25)	F ratio p-value
Maternal Variables				
Age (years)	23 ± 3	25 ± 5	30 ± 6 *†	<0.001
Ethnicity				0.58
African-American	20 (87%)	22 (92%)	19 (76%)	
Caucasian	3 (13%)	2 (8%)	5 (20%)	
Other	0	0	1 (4%)	
Height (cm)	161.3 ± 5.2	164.7 ± 5.7	168.1 ± 9.3 †	<0.01
Weight (kg)	69.9 ± 7.9	112.2 ± 21.3	127.6 ± 21.9 *†	<0.001
Gravida (#)	2 ± 1	3 ± 2	4 ± 3 †	0.05
Prenatal Visits (n, %)				
1–5 visits	(2, 8)	(2, 8)	(1, 4)	
6–10 visits	(13, 57)	(13, 54)	(10, 31)	
>10 visits	(8, 35)	(9, 38)	(14, 56)	
Triglycerides (mg/dL)	145.7 ± 45.2	158.7 ± 56.5	182.2 ± 94.1	0.19
Total Cholesterol (mg/dL)	206.0 ± 33.6	197.8 ± 35.6	178.5 ± 38.4 †	0.03
HDL-Cholesterol (mg/dL)	71.3 ± 17.7‡	57.7 ± 13.6	57.0 ± 15.6	0.003
LDL-Cholesterol (mg/dL)	105.5 ± 30.0	108.4 ± 30.7	86.0 ± 33.5 †	0.03
Leptin (µg/L)	20.5 ± 6.3	49.2 ± 20.3 **	53.9 ± 38.6 *†	<0.001
IL-6 (pg/mL)	2.8 ± 1.0	3.6 ± 1.8	4.1 ± 2.1†	0.03
IGF-1 (ng/mL)	313.8 ± 92.6	280.1 ± 103.8	394.1 ± 190.4 *	0.02
Infant Variables				
Gestational age (weeks)	38 ± 1	39 ± 2	37 ± 2 *†	<0.001
Delivery Mode, Vaginal (%)	15 (65%)	10 (42%)	9 (36%)	0.10
Gender, Female (%)	11 (48%)	12 (50%)	12 (44%)	0.32
Resuscitative Breathing				
Yes/No (%)	(9/91)	(13/87) **	(48/52) *†	0.01

	Lean (n=23)	OB (n=24)	OB+DM (n=25)	F ratio p-value
Birth Weight (grams)	3056 ± 476	3320 ± 375	3591 ± 692 *†	0.004
Birth Length (cm)	50.3 ± 2.6	50.8 ± 2.2	50.6± 2.9	0.73
Ponderal Index	24.1 ± 2.3	25.7 ± 2.2	27.5± 3.5 †	0.01
APGAR-1 min	8 ± 1	7 ± 2	6 ± 3 †	0.005
APGAR-5 min	9 ± 1	9 ± 1	8 ± 2 *†	0.004
Cord Blood				
Glucose (mg/dl)	93.1 ± 27.0	78.9 ± 14.4	86.9 ± 28.3	0.09
Insulin (µU/ml)	11.8 ± 7.4	10.9 ± 6.9	27.8 ± 24.1 *†	<0.001
C-peptide (ng/ml)	0.87 ± 0.54	1.18 ± 0.81	1.83± 1.13 *†	<0.001
HOMA-IR	2.8 ± 2.0	2.2 ± 1.7	6.0± 6.2 *†	0.001
IGF-1 (ng/ml)	61.2 ± 30.2	52.4 ± 19.7	70.5 ± 43.5	0.49
FFA (mEq/L)	0.14 ± 0.10	0.15 ± 0.10	0.16 ± 0.06	0.29
Leptin (µg/L)	11.2 ± 6.9	13.3 ± 9.1 **	30.9 ± 25.1 *†	<0.001
IL-6 (pg/ml)	9.1 ± 10.4	10.0 ± 12.1	10.5 ± 13.2	0.83

Values are means ± SD. OB: Obese, OB+DM: Obese + diabetes mellitus. IGF-1: plasma insulin-like growth factor-1, FFA: plasma free fatty acid, plasma IL—6: interleukin 6. NICU: neonatal intensive care unit. Post hoc analysis:

*
p<0.05, OB+DM vs. OB;

**
p<0.05, OB vs. Lean;

†
p<0.05, OB+DM vs. Lean

Table 2

Neonatal Echocardiographic Parameters

Variable value	Lean (n=23)	Obese (n=24)	Obese + DM (n=28)	F ratio P
HR (bpm)	155± 17 (118–186)	160 ± 17 (133–196)	158 ± 23 (117–226)	0.72
LV structure				
LVM (g)	10.6 ± 3.0 (7.1–20.0)	11.6 ± 3.4 (6.8–19.6)	11.6 ± 2.8 (7.8–19.3)	0.38
LVMI	46.3 ± 11.0 (31.0–80.1)	50.9 ± 13.0 (34.9–78.4)	49.5 ± 11.5 (33.5–80.3)	0.42
RWT (mm)	0.30 ± 0.08 (0.18–0.47)	0.36 ± 0.08 (0.18–0.54)	0.35 ± 0.12 (0.17–0.72)	0.14
LV systolic function				
EF(%)	64 ± 6 (52–71)	64 ± 9 (51–81)	64 ± 7 (56–80)	0.92
SF (%)	34 ± 4 (28–43)	38 ± 5 (30–47)	36 ± 5 (28–45)	0.06
GLS (%)	−19.2 ± 1.5 (−15.7—−21.0)	−18.0 ± 2.1 (−12.5—−21.5)	−17.5 ± 1.9 (−15.0—−20.2) *	0.008
GLSRs (1/sec)	−1.6 ± 0.2 (−1.1—−2.1)	−1.6 ± 0.2 (−1.1—−2.1)	−1.6 ± 0.3 (−1.2—−2.0)	0.77
SLS Base (%)	−19.5 ± 3.0 (−9.5—−23.2)	−16.7 ± 3.4 (−16.0—−28.0) **	−17.9 ± 2.3 (−13.6—−22.4) *	0.01
SLS Mid (%)	−19.2 ± 2.0 (−16.1—−24.0)	−16.6 ± 3.0 (−8.9—−21.4) **	−17.9 ± 2.9 (−9.2—−22.4) *	0.01
SLS Apex (%)	−22.7 ± 2.2 (−16.8—−26.3)	−21.6 ± 3.7 (−14.5—−28.6)	−21.2 ± 3.3 (−12.9—−25.7)	0.23
LV diastolic function				
GLSRe (1/sec)	2.9 ± 0.6 (2.2, 4.5)	2.7 ± 0.7 (1.7, 3.6)	2.5 ± 0.6 (1.7, 3.5)	0.11
GLSRa (1/sec)	2.2 ± 0.7 (0.6, 3.6)	2.1 ± 0.7 (1.3, 3.6)	1.9 ± 0.7 (0.4, 2.9)	0.17
RV structure				
RV length (mm)	3.0 ± 0.2 (2.9, 3.3)	2.9 ± 0.2 (2.7, 3.2)	3.0 ± 0.2 (2.6, 3.4)	0.19
RV major (mm)	1.8 ± 0.2 (1.5, 2.3)	1.8 ± 0.1 (1.6, 2.3)	1.9 ± 0.2 (1.6, 2.3) †	0.04
RV minor (mm)	1.5 ± 0.1 (1.4, 1.9)	1.5 ± 0.1 (1.3, 1.7)	1.5 ± 0.1 (1.3, 1.7)	0.31
RV systolic function				
GLS (%)	−22.1 ± 2.3 (−18.2, −21.0)	−21.4 ± 3.5 (−13.8, −26.8)	−19.5 ± 3.9 (−7.8, −25.8) *	0.03
GLSRs (1/sec)	−2.0 ± 0.3 (−1.7, −2.6)	−2.0 ± 0.3 (−1.2, −2.9)	−1.9 ± 0.4 (−1.4, −2.9)	0.29
SLS Base (%)	−30.3 ± 5.3 (−18.7, −40.5)	−29.2 ± 7.1 (−16.4, −40.3)	−27.4 ± 8.0 (−11.2, −44.4)	0.36
SLS Mid (%)	−27.1 ± 4.6 (−16.1, −35.0)	−25.9 ± 7.1 (−1.9, −35.2)	−24.5 ± 7.7 (−3.2, −38.8)	0.41
SLS Apex (%)	−19.8 ± 6.0 (−9.6, −29.2)	−19.6 ± 6.3 (−6.3, −30.9)	−18.2 ± 6.5 (−5.3, −32.9)	0.61
RV diastolic function				

Variable value	Lean (n=23)	Obese (n=24)	Obese + DM (n=28)	F ratio P
GLSRe (1/sec)	3.1 ± 0.7 (2.2, 4.5)	2.9 ± 0.8 (1.4, 4.5)	2.4 ± 0.7 (1.1, 3.4) *†	0.008
GLSRa (1/sec)	2.5 ± 0.9 (0.3, 3.8)	2.1 ± 0.8 (0.3, 3.5)	2.1 ± 0.8 (0.6, 3.5)	0.12
Septal structure				
SWT (mm)	0.41 ± 0.06 (0.36–0.58)	0.43 ± 0.06 (0.27–0.51)	0.42 ± 0.06 (0.27–0.55)	0.47
Septal systolic function				
GLS (%)	−19.1 ± 1.2 (−16.5, −20.9)	−19.2 ± 2.7 (−18.9, −21.2)	−17.7 ± 2.4 (−13.2, −21.9) *†	0.005
GLSRs (1/sec)	−1.7 ± 0.2 (−1.3, −2.2)	−1.8 ± 0.3 (−1.3, −2.5)	−1.8 ± 0.4 (−1.2, −2.6)	0.65
SLS Apex (%)	−22.5 ± 1.9 (−19.1, −25.5)	−23.0 ± 6.3 (−6.3, −28.6)	−20.6 ± 2.9 (−11.0, −26.2) *†	0.002
SLS Mid (%)	−18.0 ± 1.6 (−15.3, −35.0)	−18.5 ± 1.5 (−15.2, −21.0)	−16.5 ± 2.6 (−8.1, −22.4) *†	0.002
Septal diastolic function				
GLSRe (1/sec)	3.0 ± 0.4 (2.0, 3.7)	2.8 ± 0.6 (1.6, 4.0)	2.2 ± 0.4 (1.3, 3.6) *†	0.004
GLSRa (1/sec)	2.7 ± 0.6 (0.9, 3.3)	2.6 ± 0.5 (0.9, 3.6)	2.6 ± 0.8 (0.8, 3.3)	0.67

Values are mean ± SD. Range provided in parentheses.

Lean, infants born to women without obesity or diabetes; Obese, infants born to women with obesity but not diabetes; Obese + DM: infants born to women with obesity and diabetes,

HR, heart rate; bpm, beats per minute, LV, left ventricle; LVM, left ventricular mass measured by M-mode echocardiography; LVMI, left ventricular mass index;

EF, ejection fraction; SF, shortening fraction; RWT, relative wall thickness; SWT, septal wall thickness

GLS, global longitudinal strain; GLSRs, global longitudinal systolic strain rate; GLSRe, early global longitudinal diastolic strain rate;; GLSRa, late global longitudinal diastolic strain rate

*
p<0.05 OB + DM *vs.* Lean

**
p<0.05 OB *vs.* Lean

†
p<0.05 OB+DM *vs.* OB