Cardiology in the Young

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Impact of overweight and obesity in the fetal cardiac function parameters in the second and third trimesters of pregnancy

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Abstract

Objective: To assess the impact of overweight and obesity in the second and third trimesters of pregnancy on fetal cardiac function parameters. *Methods:* We performed a prospective cohort study of 374 singleton pregnant women between 20w0d and 36w6d divided into three groups: 154 controls (body mass index - BMI < 25 kg/m^2), 140 overweight (BMI 25–30 kg/m^2) and 80 obese (BMI ≥ 30 kg/m^2). Fetal left ventricular (LV) modified myocardial performance index (Mod-MPI) was calculated according to the following formula: (isovolumetric contraction time + isovolumetric relaxation time)/ejection time. Spectral tissue Doppler was used to determine LV and right ventricular (RV) myocardial performance index (MPI'), peak myocardial velocity during systole (S'), early diastole (E'), and late diastole (A'). *Results:* We found significant differences between the groups in maternal age ($p < 0.001$), maternal weight ($p < 0.001$), BMI ($p < 0.001$), number of pregnancies ($p < 0.001$), parity ($p < 0.001$), gestational age ($p = 0.013$), and estimated fetal weight ($p = 0.003$). Overweight pregnant women had higher LV Mod-MPI (0.046 versus 0.044 seconds, $p = 0.009$) and LV MPI' (0.50 versus 0.47 seconds, $p < 0.001$) than the control group. Obese pregnant women had higher RV E' than control (6.82 versus 6.33 cm/sec, $p = 0.008$) and overweight (6.82 versus 6.46 cm/sec, $p = 0.047$) groups. There were no differences in 5-min APGAR score < 7, neonatal intensive care unit admission, hypoglycemia and hyperglobulinemia between the groups. *Conclusions:* We observed fetal myocardial dysfunction in overweight and obese pregnant women with higher LV Mod-MPI, LV MPI' and RV E' compared to fetuses from normal weight pregnant women.

Obesity is on the rise worldwide and is a major global health problem. In 2017, more than 4 million people died as a result of obesity, according to the World Health Organization (WHO). Currently, the increased prevalence of this problem has reached endemic proportions (> 1 billion adults worldwide). Obesity affects most body systems, leading to diabetes, systemic arterial hypertension, and even cancer, necessitating the planning of health policies focused on early prevention, such as good nutrition and breastfeeding.[1] In this scenario, epidemiologic and experimental studies have demonstrated the association between adverse in utero conditions and long-term cardiovascular programming, such as maternal obesity and fetal cardiovascular programming.[2–6]

The "fetal origin" hypothesis, originally proposed by Baker, was based on a model of fetuses of malnourished mothers who became adults more susceptible to diabetes, dyslipidemia, and cardiovascular disease.[7,8] Subsequently, other studies have described the relationship between fetal heart program and long-term adverse effects cardiovascular disease.[9,10] Animal studies showed the relationship between maternal obesity and fetal myocardial fibrosis, which was associated with signaling pathways and collagen accumulation.[11–13] Accordingly, human studies on the effects of maternal obesity on fetal myocardial function have been published.[14,15]

In this context, the alarming worldwide increase in obesity and its complications such as diabetes and cardiovascular disease, including the risk of myocardial damage in utero with a predisposition to cardiovascular disease earlier in adult life, should draw attention to studies in this area. Therefore, our aims in this study are to assess the impact of overweight and obesity in

the second and third trimesters of pregnancy on fetal cardiac function parameters using spectral and tissue Doppler to determine left ventricular (LV) and right ventricular (RV) myocardial performance index (MPI') and peak myocardial velocities.

Materials and methods

This was a prospective cohort study between November 2015 and October 2017, which evaluated modified myocardial performance index (MPI) and peak myocardial velocities during systole and diastole in fetuses from obese and overweight mothers and in controls (fetuses from mothers with body mass index - BMI 20-25 kg/m^2). Data (n = 374) were collected from 20 to 36 + 6 weeks and divided into three groups: 154 fetuses from normal weight women (BMI 20-25 kg/m^2), 140 fetuses from overweight pregnant women (BMI 25-30 kg/m^2), and 80 fetuses from obese women (BMI ≥ 30 kg/m^2).

Pregnant women undergoing routine ultrasound examinations at the Obstetrics Departments of the Federal University of São Paulo (UNIFESP) and the University of Uberaba (UNIUBE) were randomly selected. This study was approved by the Ethics Committee of UNIFESP and UNIUBE (CAE: 87111116.4.0000.5505), and the patients signed the informed consent form.

The inclusion criteria were as follows: singleton pregnancies unaffected by comorbidities such as diabetes mellitus, systemic arterial hypertension, erythematosus systemic lupus, nephropathies, and pneumopathies), fetuses with adequate estimated weight for gestational age (GA), known GA based on the last menstrual period and confirmed by first trimester ultrasound, fetuses with adequate quality of the cardiac ultrasound image and without structural cardiac and/or extracardiac anomalies.

All women enrolled in this study were examined only once with the ultrasound and echocardiography devices Voluson E6 and E8 (General Electric Medical System, Zipf, Austria) with a 3.0–5.0 MHz convex probe. Obstetric ultrasound was performed in all pregnant women to assess fetal morphology, amniotic fluid volume, and fetal biometry. Fetal cardiac structural assessment was performed according to congenital heart disease screening.[16] Fetal cardiac function was then assessed with emphasis on calculation of modified (Mod)-MPI, MPI', and peak velocities of E', A', and S' waves using pulsed and tissue Doppler.

Pulsed Doppler was also used to assess LV MPI, and the Doppler sample was placed on the lateral wall of the ascending aorta, below the aortic valve, and just above the mitral valve in the 4-chamber view of the fetal heart with a sample volume size of 4 mm. Tissue Doppler was used to assess peak velocities: A', E' and S' of both ventricles and to obtain LV and RV myocardial performance index (MPI'). The tissue Doppler sample was placed at the junction between the ventricular walls (RV and LV) at the level of the atrioventricular valve (RV: tricuspid/LV: mitral) in the 4-chamber view. The spectral and tissue Doppler sample size was between 2 and 4 mm. The ultrasound equipment was programmed as follows: spectral Doppler with a scan speed of 5 cm/s, a gain of -10 dB and a wall motion filter (WMF) of 210 Hz for the GE Voluson system with an insonation angle < 20°.[17] For tissue Doppler, the Doppler sweep speed was set to 5 cm/sec and a low PRF and WMF (210 Hz) were used to avoid high frequency Doppler signals. The insonation angle between the ultrasound beam and the ventricular wall was < 30° and no correction angle was applied.[18,19]

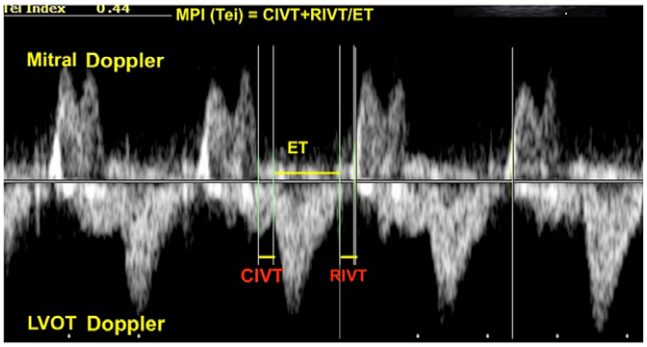

Figure 1. Modified myocardial performance index (Mod-MPI) of the left ventricle measured through the opening clicks of the aortic and atrioventricular valves. [isovolumetric contraction time (ICT) + isovolumetric relaxation time (IRT)] / ejection time (ET).

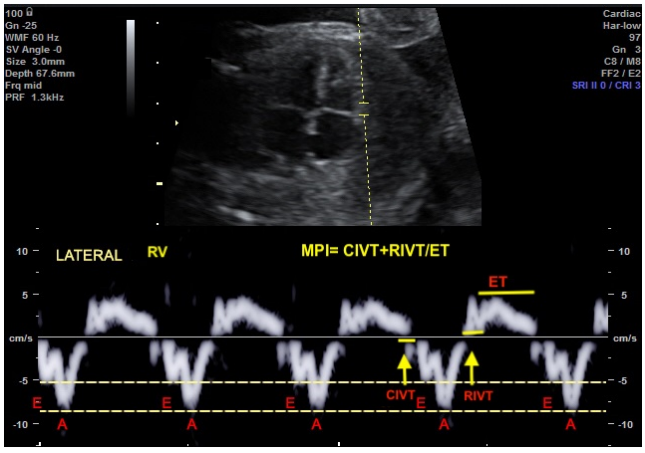

Figure 2. Myocardial tissue Doppler velocities and myocardial performance index obtained by spectral tissue Doppler (MPI') of the right ventricle. E' wave (early diastolic annular peak velocity), A' wave (late-diastolic annular peak velocity) and S' wave (systolic annular peak velocity).

Three consecutive heartbeats were obtained to calculate MPI and MPI' by pulsed Doppler and tissue Doppler, respectively, using atrioventricular and ventriculoatrial (VA) valve clicks. The periods of the cardiac cycles were measured as follows: (1) ICT- from the beginning of the closing click of the atrioventricular valve to the beginning of the opening click of the VA valve; (2) IRT- from the beginning of the closing click of the VA valve to the beginning of the opening click of the atrioventricular valve; (3) ET was calculated from the beginning of the opening click of the VA valve to the beginning of the closing click of this valve.[20–23] MPI and MPI' were calculated using the following formula: [isovolumetric contraction time (ICT) + isovolumetric relaxation time (IRT)] / ejection time (ET) (Figs. 1 and 2).

The G*Power 3.1 program was used to calculate the sample size.[24] To evaluate the effect of maternal fetal weight on fetal cardiac function parameters, a minimum of 269 participants should be included to achieve an effect size of 0.25, power of 80%, and significance level < 0.05.

Data were transferred to an Excel 2010 spreadsheet (Microsoft Corp., Redmond, WA, USA) and analyzed using PASW version 20.0 (SPSS Inc., Chicago, IL, USA). The following data were collected from the patients: maternal age, ethnicity, mode of

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Table 1. Maternal clinical characteristics and postnatal outcomes.

	Controls			Overweight			Obese			
	N	Mean	SD	N	Mean	SD	N	Mean	SD	p-value
Age (years)	154	26.2 [A,B]	7.3	140	28.6	6.7	80	29.8	6.7	< 0.001 [†]
Weight (kg)	154	59.1 [A,B]	6.9	140	77.1[C]	5.9	103	84.7	12.1	< 0,001 [†]
BMI (kg/m²)	154	22.5 [A,B]	1.9	140	27.3 [C]	1.4	80	32.9	3.0	< 0.001 [†]
Number of pregnancies	154	1.8 [A,B]	1.2	140	2.4 [C]	1.6	80	2.7	1.4	< 0.001 [†]
Parity	154	0.5 [A,B]	0.8	140	1.0 [C]	1.4	80	1.2	1.2	< 0.001 [†]
GA at ultrasound (weeks)	154	26.5 [A,B]	4.9	140	27.8	4.9	80	28.3	5.0	0.013 [†]
EFW (grams)	154	1086 [A,B]	708.2	140	1280	780	80	1408	801.8	0.003 [†]
GA at delivery (weeks)	124	38.6	1.42	119	38.9	1.59	69	38.6	1.65	0.091 [†]
Birth weight (grams)	124	3113 [A,B]	425.2	119	3303	432.5	69	3338	464.3	< 0.001 [†]
	n	**N**	**%**	**n**	**N**	**%**	**n**	**N**	**%**	
Ethnicity										0.201 [i]
White	90	154	58.4	70	140	50	39	80	48.7	
Black	16	154	10.4	28	140	20	16	80	20	
Asiatic	2	154	1.3	3	140	2.2	0	80	0	
Mixed	46	154	29.9	39	140	27.8	25	80	31.3	
Type of delivery										0.263 [i]
Vaginal	51	124	41,1	49	119	41.2	22	69	31.9	
Cesarean section	73	124	58.9	70	119	58.8	46	69	66.6	
Forceps	0	124	0	0	119	0	1	69	1.5	
Adverse neonatal outcome										
5[th] min Apgar score < 7	2	124	1.6	0	119	0	1	69	1.5	0.391 [i]
NICU	5	124	4	5	119	4.2	2	69	2.9	0.443 [i]
Hypoglycemia	2	124	1.6	2	119	1.7	3	69	3.3	0.409 [i]
Hyperglobulinemia	2	124	1.6	0	119	0	0	69	0	0.217 [i]

A = controls vsversus overweight; B = controls versus obese; C = overweight versus obese; EFW = estimated fetal weight; GA = gestational age; min = minutes; N = total of participants included in the respective group; n = real number of participants; NICU = neonatal intensive care unit.
[†]ANOVA.
[i]Chi square. $p < 0.05$.

delivery, maternal weight, BMI, number of previous pregnancies, parity, gestational age at ultrasound, estimated fetal weight (EFW), fetal heart rate (FHR), gestational age at delivery, birth weight, adverse neonatal outcome [5-min APGAR score < 7, need for neonatal intensive care unit (NICU), hypoglycemia, and hyperglobulinemia]. Spectral Doppler was used to obtain LV Mod-MPI and the corresponding three-time intervals: ICT, ET, and IRT. Tissue Doppler was used to obtain the E' wave (early diastolic annular peak velocity), A' wave (late diastolic annular peak velocity), S' wave (systolic annular peak velocity), left, right, and septal MPI' and corresponding time intervals: ICT', IRT', and ET'.

Quantitative variables were first tested for normality (Kolmogorov-Smirmov). Continuous variables were expressed as mean and standard deviation. Categorical variables were expressed in percentages. The analysis of variance (ANOVA) test was used to compare maternal clinical characteristics among the three groups. The general linear model (GLM), with gestational age at ultrasound as a covariate, was used to compare fetal cardiac function parameters among the three groups. The Tukey post-hoc test was used for pairwise comparisons. A p-value < 0.05 was considered statistically significant differences.

Results

The maternal clinical characteristics and postnatal outcomes of the study population are shown in Table 1.

In the overweight group, age (28.6 versus 26.2 years, $p = 0.008$), weight (77.1 versus 59.1 kg, $p < 0.001$), BMI (27.3 versus 22.5 kg/m^2, $p < 0.001$), number of pregnancies (2.4 versus 1.8, $p < 0.001$), parity (1.0 versus 0.5, $p < 0.001$), gestational age at ultrasound (27.8 versus 26.5 weeks, $p = 0.021$), EFW (1280 versus 1086 grams, $p = 0.013$), and birth weight (3303 versus 3113 grams, $p < 0.001$) were higher than controls. In the obese group, age (29.8 versus 26.2 years, $p < 0.001$), weight (84.7 versus 59.1 kg, $p < 0.001$), BMI (32.9 versus 22.5 kg/m^2, $p < 0.001$), number of pregnancies (2.7 versus 1.8, $p < 0.001$), parity (1.2 versus 0.5, $p < 0.001$), gestational age at ultrasound (28.3 versus 26.5 weeks, $p = 0.018$), EFW (1408 versus 1086 grams, $p = 0.003$), and birth weight (3338 versus 3113 grams, $p < 0.001$) were higher than controls. The obese group had weight (84.7 versus 77.1 kg, $p < 0.001$), BMI (32.9 versus 27.3 kg/m^2, $p < 0.001$), number of pregnancies (2.7 versus 2.4, $p = 0.025$) and parity (1.2 versus 1.0, $p = 0.018$) higher than the overweight group. There were no significant associations between groups and ethnicity

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Table 2. Right ventricle and left ventricle fetal cardiac function parameters in controls, overweight and obese pregnant women.

	Controls			Overweight			Obese			
	N	Mean	SD	N	Mean	SD	N	Mean	SD	p-value
LV ICT (s)	154	0.032	0.0058	140	0.034	0.0055	80	0.032	0.0062	0.070 †
LV IRT (s)	154	0.042	0.0055	140	0.043	0.0057	80	0.043	0.0053	0.592 †
LV ET (s)	154	0.168	0.0098	140	0.166	0.0092	80	0.166	0.010	0.369 †
LV Mod-MPI	154	0.44 A	0.060	140	0.46	0.056	80	0.45	0.060	0.032 †
RV E' (cm/s)	154	6.33 B	2.11	140	6.46 C	2.05	80	6.82	1.86	0.040 †
RV A' (cm/s)	154	9.79	2.03	140	9.76	2.02	80	9.95	1.7	0.408 †
RV S' (cm/s)	154	6.29	1.41	140	6.43	1.58	80	6.59	1.68	0.486 †
RV ICT' (s)	154	0.037	0.0065	140	0.038	0.0061	80	0.038	0.007	0.298 †
RV IRT' (s)	154	0.042	0.007	140	0.043	0.0060	80	0.041	0.0058	0.308 †
RV ET' (s)	154	0.174	0.011	140	0.172	0.011	80	0.176	0.012	0.080 †
RV MPI'	154	0.46	0.069	140	0.47	0.065	80	0.46	0.072	0.108 †
LV E' (cm/s)	154	5.15	1.55	140	5.39	1.55	80	5.59	1.36	0.098 †
LV A' (cm/s)	154	7.94	2.02	140	7.89	2.05	80	8.33	1.84	0.132 †
LV S' (cm/s)	154	5.40	1.31	140	5.47	1.37	80	5.76	1.26	0.100 †
LV ICT' (s)	154	0.036	0.059	140	0.037	0.0061	80	0.036	0.0064	0.265 †
LV IRT' (s)	154	0.045	0.0062	140	0.047	0.0060	80	0.046	0.0059	0.091 †
LV ET' (s)	154	0.173	0.012	140	0.170	0.011	80	0.170	0.012	0.073 †
LV MPI'	154	0.47 A	0.067	140	0.50	0.067	80	0.48	0.070	0.004 †

A' = peak velocity during the active filling phase using tissue Doppler; A: controls versus overweight; *B* = controls versus obese; *C* = overweight versus obese; E' = velocity peak during the passive filling phase using tissue Doppler; ET = ejection time using spectral Doppler; ICT = isovolumetric contraction time using spectral Doppler; IRT = isovolumetric relaxation time using spectral Doppler; LV = left ventricle; Mod-MPI = modified myocardial performance index using spectral Doppler; MPI' = myocardial performance index using tissue Doppler; N = total of participants included in the respective group; RV = right ventricle; S' = velocity peak during systole using tissue Doppler; SD = standard deviation.
†General linear Model (GLM) using gestational age at ultrasound examination as covariate. Tukey post-hoc test, $p < 0.05$.

($p = 0.201$), mode of delivery ($p = 0.263$), 5th min APGAR score < 7 ($p = 0.391$), need for NICU ($p = 0.443$), hypoglycemia ($p = 0.409$) and hyperglobulinemia ($p = 0.217$) (Table 1).

There were significant group effects on LV Mod-MPI ($p = 0.0320$), RV E' ($p = 0.040$), and LV MPI' ($p = 0.004$). The overweight group showed higher LV Mod-MPI (0.46 versus 0.44, $p = 0.009$) and LV MPI' (0.50 versus 0.47, $p < 0.001$) than the controls. Obese group showed higher RV E' (6.82 versus 6.33 cm/sec, $p = 0.008$) than controls. Obese group showed higher RV E' (6.82 versus 6.46 cm/sec, $p = 0.047$) than overweight group (Table 2).

Discussion

Maternal obesity during pregnancy is associated with other comorbidities (systemic arterial hypertension, diabetes mellitus, dyslipidemia) that may contribute to adverse perinatal outcomes and increase cardiovascular risk in the offspring. Classically, several studies have shown the association between maternal diabetes and fetal myocardial hypertrophy, which may lead to diastolic dysfunction due to reduction in LV distensibility and alteration of left atrial dynamics.[25–27] Currently, some studies in humans have demonstrated that maternal obesity is also associated with myocardial hypertrophy and cardiac dysfunction in utero, but research on long-term follow-up of their offspring is lacking.[14,15] Similar to other studies, we used Doppler echocardiographic parameters to evaluate cardiac function in fetuses of obese mothers (BMI $\geq$ 30 kg/m^2). However, none of them included a group of fetuses from overweight pregnant women (BMI 25–30 kg/m^2) as in our study, which is an important differential aspect of the current research. Furthermore, we should consider that in these studies, sometimes overweight women (BMI 25–30 kg/m^2) were included in the control group.[28] In this setting, we emphasize that in our research, LV Doppler parameters were also altered in fetuses of overweight and obese women compared with controls.

In a recent systematic review and meta-analysis that included thirteen studies, six of which included fetal data, den Harink et al[28] demonstrated lower biventricular longitudinal global strain (LGS) and LV E' and A' waves in fetuses of obese mothers compared to controls. Although LGS can detect systolic cardiac dysfunction at earlier stages, some limitations of this technique should be considered in fetuses, such as small hearts and inadequate visualization of the ventricular endocardial border in some conditions such as obese pregnant women due to maternal abdominal subcutaneous adipose tissue.[20,29,30] In the current study, we evaluated fetal cardiac function by focusing on Doppler measurements and did not collect strain data. Regarding Doppler findings, we observed differences between fetuses from obese women and controls, reflecting LV diastolic dysfunction. Therefore, our results were similar to some studies in human fetuses that support the hypothesis of cardiac fibrosis with consequent reduction in ventricular compliance, as found in experimental studies in fetuses of obese animals.[11,12,14,15]

Alis et al[31] published a study on reference ranges of MPI according to GA and concluded that BMI did not affect MPI, which may reflect a low-risk population (fetuses of non-obese

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mothers). However, in our study, LV MPI and LV MPI' (using spectral and tissue Doppler) were altered in fetuses from mothers with elevated BMI compared with those from mothers with normal BMI. In fact, to the best of our knowledge, no previous studies have been published on fetal MPI and maternal obesity/overweight, which is a difference of the current study.

Regarding the maternal population, the studies that included women with diabetes mellitus and/or arterial hypertensive disorders provided few details concerning the characteristics of groups of these maternal diseases.[28,32] In our study, pregnant women with diabetes mellitus and/or arterial hypertensive disorders were excluded. Except for BMI, other characteristics of our maternal population, such as parity and maternal age, were different in the maternal population of cases compared with controls. Otherwise, Ece et al[14] did not observe any differences between the maternal population of the two studied groups (elevated and normal BMI).

There was also lack of data on long-term follow-up of obese and overweight mothers. This was a limitation of our study, in which fetal and neonatal data were collected with no significant differences in neonatal outcomes between groups.[33,34] Nevertheless, functional cardiac changes in human fetuses and animal studies support the hypothesis that increased maternal BMI is associated with increased long-term cardiovascular risk in their offspring. Furthermore, we evaluated the fetal cardiac function focusing on Doppler measurements and consequently there was lack of assessment of fetal cardiac function using two-dimensional echocardiographic functional parameters such as strain.

In conclusion, we observed fetal myocardial dysfunction in overweight and obese pregnant women with higher LV MPI and LV MPI' compared to fetuses of normal weight pregnant women.

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Competing interests. None.

Ethical statements. This study was approved by the Ethics Committee of UNIFESP and UNIUBE (CAE: 87111116.4.0000.5505), and the patients signed the informed consent form.

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