North Clin Istanb 2024;11(1):60–65
doi: 10.14744/nci.2023.03342

Original Article PEDIATRICS

The effect of maternal weight on neonatal cardiac functions following diabetic and non-diabetic pregnancies

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ABSTRACT

OBJECTIVE: We aimed to study myocardial functions of infants appropriate and large for gestational age (IDM-AGA, IDM-LGA) of diabetic mothers (IDM) and AGA and LGA infants of non-diabetic mothers comparatively.

METHODS: Newborns were assessed between 24 and 72 h. M-Mode, pulsed wave, and tissue Doppler echocardiography were performed.

RESULTS: A negative correlation was found between shortening fraction and maternal weight at delivery in the LGA group (p=0.009, r=-0.58). E/Early diastolic (E') ratio and deceleration time were increased in IDM-AGA than AGA group (p=0.02, p=0.02). There was a negative correlation between maternal blood glucose and E/A ratio (p=0.015 r=-0.63), a positive correlation between maternal blood glucose and mitral A, late diastolic (A') wave in IDM-AGA (p=0.014 r=0.63, p=0.016 r=0.62). Maternal weight gain during pregnancy was in correlation with measured and tei index in IDM-AGA group (p=0.008 r=0.72). Maternal age, pre-pregnancy weight, and weight at delivery and mitral E were higher in IDM-LGA group than IDM-AGA (p=0.03, p=0.01, p=0.003, p=0.012).

CONCLUSION: We found that maternal weight has a negative effect on myocardial function in LGA newborns. Diastolic functions were found impaired in IDM-AGA infants and in infants of mothers with high blood glucose. Maternal weight gain during pregnancy has a negative effect on myocardial functions.

Keywords: AGA; echocardiography; infant of diabetic mother; myocardial functions; LGA.

Cite this article as: *Erolu E, Sahin O, Bilgin L, Karacan M, Akalin F. The effect of maternal weight on neonatal cardiac functions following diabetic and non-diabetic pregnancies. North Clin Istanb 2024;11(1):60–65.*

Infants of diabetic mothers (IDM) are more likely to have congenital malformations, hypoglycemia, hypomagnesemia, increased frequency of admission to neonatal intensive care unit, macrosomia, and shoulder dystocia [1, 2]. The incidence of congenital heart disease (CHD) is increased in IDM [3, 4]. The increased risk was attributed to the teratogenic effect of diabetes mellitus (DM). However, in the absence of CHD, alterations in systolic and diastolic myocardial functions were also found in IDM [5–7]. Transient myocardial hypertrophy is common in IDM even if DM is well controlled during pregnancy [8, 9]. While some studies concluded that diastolic dysfunction in IDMs is related to impaired relaxation of hypertrophic myocardium, other studies proved that diastolic dysfunction is not related to myocardial hypertrophy [2, 10].

Received: August 27, 2022 *Revised:* February 02, 2023 *Accepted:* July 15, 2023 *Online:* January 26, 2024

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Obese women with high body mass index (BMI) are more likely to have newborns large for gestational age than women with normal weight. Furthermore, obese women are more likely to have children with CHD than normal weight women [11, 12]. Coexistence of obesity and DM is common. However, it is found that maternal obesity still remained as a risk factor for CHD when the effect of gestational or pregestational DM was excluded from the study [13]. In the knowledge of the maternal obesity is a risk factor for CHD, our curiosity was about cardiac functions in non-IDM macrosomic infants in the absence of CHD.

In this study, we investigated systolic and diastolic functions and diameters of cardiac chambers of newborns appropriate for the gestational age of diabetic mothers (IDM-AGA) and large for the gestational age of diabetic mothers (IDM-LGA) neonates in comparison with term appropriate for gestational age (AGA) and term large for gestational age (LGA).

Highlight key points

- Higher maternal blood glucose level and higher maternal weight causes impairment on myocardial functions in infant of diabetic mother.
- Maternal weight gain during pregnancy has also negative effects on myocardial function in LGA newborns of non-diabetic mothers.

MATERIALS AND METHODS

The study patients were the newborns born at the Umraniye Training and Research Hospital between September 2018 and March 2019. Term 24 LGA, 20 AGA, 32 IDM (15 IDM-LGA, 17 IDM-AGA) were included postnatally between 24 and 72 h. Pregnancy week was accepted as term delivery between 37^{0-7} and 40^{6-7}. Birth weight percentile (according to Lubchenco intrauterine growth curve) between 10 and 90^{th} percentile was termed as AGA; birth weight above 90^{th} percentile was defined as LGA. All newborns were stable hemodynamically and did not have genetic, systemic, or CHD. Birth weight, length, gender, age in hours, and gestation week were recorded.

Pre-pregnancy maternal weight and weight at delivery, maternal height, systolic and diastolic blood pressure, and blood glucose at the third trimester were recorded. BMI was calculated according to formula; pre-pregnancy weight in kilograms/height in meters^2.

Echocardiography was performed using Philips Affiniti 50C (release 2.0.2 3000 minuteman road and over, MA 01810 USA) echocardiography machine and 12–8 Mhz transducer in all subjects by a single pediatric cardiologist. The interventricular septum (IVSd), left ventricular end-systolic and end-diastolic diameters (LVDd), left ventricular posterior wall thickness (LVPwd), aortic diameter (AoD), left atrial diameter (LAD) were measured by M-Mod echocardiography. Four patients who had IVsd z score above 2 were excluded from the study in order not to affect myocardial functions. Mitral inflow parameters; peak mitral inflow Doppler early filling velocity (E), late filling velocity (A), deceleration time (DT), isovolumetric relaxation time (IVRT) were obtained by pulsed Doppler echocardiography from the lateral mitral annulus. Tissue Doppler echocardiography was performed by pulsed wave Doppler at the lateral mitral valve annulus. E', late diastolic (A') velocities, isovolumetric contraction time (IVCT), IVRT, ejection time (ET) were measured and Tei index (MPI) was calculated according to formula (IVCT+IVRT)/ET. All measurements were averaged after three consecutive cardiac cycles. E/E' and E/A ratios were calculated. All patients gave written and oral consent forms. The study was approved by the local ethics committee of Umraniye Training and Research Hospital with 54132726-000-14119 protocol number, dated June 22, 2018. The study protocol complies with the ethical guidelines of the 1975 Declaration of Helsinki.

Statistical Analysis

Statistical analysis was undertaken using IBM SPSS 22 for Windows (version 10.0). Echocardiographic measurements were compared using the Student's t-tests and correlation analysis was performed using Pearson correlation analysis. $P<0.05$ was considered significant.

RESULTS

There were no differences in terms of age, gender, or gestational week between patient groups (Table 1). A correlation was found between the patients' weight and echocardiographic parameters. These were left ventricular diastolic diameter (p=0.001, r: 0.43), LAD (p=0.001, r: 0.44), and AoD (p=0.001, r: 0.41) and there were weaker correlations between some other

Table 1. Neonatal and maternal characteristics

	LGA	IDM-LGA	p	AGA	IDM-AGA	p	*p	†p
Characteristics of study patients								
Weight (kg)	4214±285	4081±531	0.09	3634±292	3319±130	0.52	0.01	0.001
Height (cm)	39.2±1.4	38.5±1.4	0.17	38.4±1.5	40±0.97	0.46	056	0.001
Gender M (%)	62.5	60	0.54	60	58.8	0.54	0.36	0.39
Age (hours)	31.7±7.7	34.5±15.5	0.80	33.1±18.1	30.5±6.5	0.11	0.06	0.13
Gestational week	39.2±1.4	38.5±1.4	0.059	38.9±1.5	38.9±1.3	0.14	0.07	0.28
Maternal features								
Age	31.5±5.2	35.2±4.5	0.90	30.1±4.5	28.6±7	0.003	0.03	0.035
Body mass index	27.2±5.2	32.3±5.9	0.08	29.1±5.7	23±2.6	0.001	0.08	0.09
Pre-pregnancy weight (kg)	79.6±13	85.2±11.5	0.19	75.6±16.7	59.8±8.3	0.001	0.017	0.018
Weight at delivery (kg)	86.6±13	96.7±15.5	0.16	85±17.5	69.6±7.2	0.001	0.003	0.004
Blood glucose (mg/dl)	85.7±11.9	103±27.7	0.023	123±31	99±63	0.12	0.053	0.103

LGA: Large for gestational age; IDM: Infant of diabetic mother; AGA: Appropriate for gestational age; *: Comparison of IDM-LGA and IDM-AGA; †: Comparison of LGA and AGA.

echocardiographic parameters and weight like IVSD thickness (p=0.018, r: 0.26), mitral E (p=0.007, r: 0.30), and shortening fraction (SF) (p=0.037, r: 0.23).

The results of echocardiographic comparisons between patients grouped according to birth weight percentiles and whether the mother is diabetic or not.

LGA versus AGA

In the LGA group, maternal age, pre-pregnancy, and maternal weight at delivery were significantly higher than the AGA group (p=0.03, p=0.018, p=0.004) (Table 1). Echocardiographic parameters, LVDd (19.3±2.2 mm vs. 17.8±1.5 mm, p=0.001), LVDs (12±2.6 vs. 10.6±1.9 mm, p=0.031), AoD (9.2±0.9 vs. 8.5±0.8 mm, p=0.002), and LAD (11.4±1.2 vs. 10.5±1.07 mm, p=0.002) were higher in LGA group than AGA group (Table 2).

In LGA newborns, a negative correlation was found between the maternal weight at delivery and SF (p=0.009, r: −0.58).

IDM-LGA versus LGA

In the IDM-LGA group, maternal blood glucose was higher than the LGA group (p=0.023)

IDM-AGA versus AGA

In the IDM-AGA group, maternal age, pre-pregnancy, BMI, and weight at delivery were higher than the AGA group (p=0.003, p=0.001, p=0.001, and p=0.001).

In the IDM-AGA group, echocardiography revealed that the E/E' ratio (9.04±1.6 vs. 7.7±1.7) and DT (73.4±28.3 vs. 62.5±13.3) was increased compared to the AGA group (p=0.02, p=0.02).

There was a negative correlation between maternal blood glucose and E/A ratio (p=0.015 r=−0.63) and a positive correlation between maternal blood glucose and mitral A, tissue Doppler A wave in IDM-AGA (p=0.014 r=0.063, p=0.016 r=0.062).

Maternal weight gain during pregnancy was in correlation with MPI in IDM-AGA group (p=0.008 r=0.72)

IDM-LGA versus IDM-AGA

Maternal age, pre-pregnancy, and weight at delivery were higher in IDM-LGA group than IDM-AGA (p=0.03, p=0.01, p=0.003).

LVDd, LVDs, and LAD were higher in the IDM-LGA group than IDM-AGA group (p=0.003, p=0.009, p=0.036).

Mitral E was lower in IDM-AGA than IDM-LGA (p=0.012).

LVDs and IVSd/LVPwd were correlated with maternal blood glucose in IDM-LGA (p=0.009, r=0.80, p=0.038 r=0.69).

TABLE 2. Echocardiographic features of newborns

	LGA	IDM-LGA	p	IDM-AGA	AGA	p	*p	†p
M-MOD Echocardiography								
IVSd (mm)	4.6±0.8	4.7±0.9	0.27	4.2±0.8	4.6±0.7	0.29	0.17	0.54
LVDd (mm)	19.3±2.2	20.6±2.3	0.47	17.8±2.3	17.8±1.50	0.35	0.003	0.001
LVDs (mm)	12±2.6	13±1.4	0.33	10.9±1.9	10.6±1.9	0.36	0.009	0.031
LVPwd (mm)	2.8±0.4	±0.2	0.36	2.7±0.3	2.7±0.4	0.37	0.88	0.99
IVSd/LVPwd	1.69±0.47	1.58±0.30	0.82	1.54±0.27	1.65±0.26	0.72	0.83	0.99
EF%	70.2±12	66.8±5	0.53	1.54±0.27	1.65±0.26	0.72	0.83	0.65
KF%	40.8±8.7	34.7±3.8	0.07	38.8±11.8	37.6±5.2	0.55	0.22	0.52
AoD (mm)	9.2±0.9	8.9±1.04	0.27	8.5±0.9	8.5±0.8	0.19	0.11	0.002
LAD (mm)	11.4±1.2	10.9±1.4	0.39	10.1±1.4	10.5±1.07	0.29	0.036	0.002
Pulsed wave doppler echocardiography								
MitralE (cm/s)	56±10	59±9	0.20	50±7	55±9	0.34	0.012	0.53
MitralA (cm/s)	54±10	53±5	0.28	51±11	58±10	0.34	0.32	0.36
E/A	1.05±0.2	1.1±0.1	0.48	0.96±0.2	0.97±0.20	0.83	0.45	0.11
DT(s)	72±20	70±37	0.73	73.4±28.3	62.5±13.3	0.02	0.16	0.73
IVRT(s)	54.2±10	52±10	0.63	50±6.5	55±9	0.14	0.44	0.32
Tissue doppler echocardiography								
Mitral E'	7.5±1.8	6.7±1.2	0.42	6.2±1.2	6.6±0.9	0.39	0.46	0.02
Mitral A'	7.1±1.9	6.7±0.9	0.33	6.2±1.2	6.6±0.9	0.21	0.07	0.62
E/E'	7±2	8±2	0.51	9.04±1.6	7.7±1.7	0.023	0.30	0.11
MPI	0.52±0.14	0.51±0.10	0.73	0.54±0.11	0.49±0.10	0.69	0.75	0.37

LGA: Large for gestational age; IDM: Infant of diabetic mother; AGA: Appropriate for gestational age; *: Comparison of IDM-LGA and IDM-AGA; †: Comparison of LGA and AGA; IVSd: Interventricular septal diameter; LVDd: Left ventricular diastolic diameter; LVDs: Left ventricular systolic diameter; LVPwd: Left ventricular posterior wall diameter; EF: Ejection fraction; SF: Shortening fraction; AoD: Aortic diameter; LAD: Left atrium diameter; Mitra E: Peak early transmitral doppler flow velocity; Mitral A: Peak atral transmitral Doppler flow velocity; DT: Desceleration time; IVRT: Isovelometric relaxation time; Mitral E': Mitral E with tissue Doppler from the lateral mitral annulus; Mitral A': Mitral A with tissue Doppler from lateral mitral annulus; MPI: Myocardial performance index; LGA: Large for gestational age; IDM: Infant of diabetic mother.

DISCUSSION

Infants large for gestational age are under risk of DM, obesity, early onset of cardiovascular problems, and cancer in their future lives [14]. Maternal obesity, being overweight in pre-pregnancy period, excessive weight gain in pregnancy are contributing factors of giving birth for LGA [15]. Consistent with these findings, we found that maternal age, pre-pregnancy weight, and high weight at delivery of mothers are risk factors for having LGA newborns. Kim et al. [16] found the prevalence of LGA 13.5% among mothers having a pregnancy with excess weight gain, 12.6% among obese mothers, and 17.3% IDM while 5.7% among normal weight women.

The determination of the correlation between the diastolic diameter of left ventricle, the diameter of the left atrium, AoD and birth weight shows the size of cardiac chambers is related to somatic size. Although SF in our study population was not out of the normal range, the weak correlation between SF and birth weight is a new finding.

We found that increased maternal weight at delivery has a negative effect on SF of the left ventricle in LGA newborns. The inverse relationship between maternal weight and SF in the LGA group suggests that obesity-related inflammation and other metabolic processes may affect the myocardial functions. Increases in cardiac biomarkers such as cardiotrophin-1 (which has a hypertrophic effect on myoctyes and titin also shows impaired elastic and mechanical properties of myocardium) were found in the cord blood of LGA infants [17]. Furthermore, decreased anti-oxidative capacity and increased oxidative stress were found in macrosomic newborns [18].

Similar to the LGA-AGA comparison, higher maternal age, pre-pregnancy, and maternal weight at delivery were found in IDM-AGA than AGA newborns. We showed that gaining weight during pregnancy impairs myocardial performance index which shows global ventricular functions in IDM-AGA. Furthermore, diastolic dysfunction was prominent in IDM-AGA group. Impairment in diastolic functions in IDMs was shown previously. However, the reason is controversy [6, 19]. While myocardial hypertrophy can cause impaired relaxation and altered diastolic filling, it was shown that diastolic dysfunction does not depend on the myocardial hypertrophy [2]. Diastolic dysfunction found in IDM-AGA patients cannot be attributed to septal hypertrophy in our study because the septum thickness of IDM group was not different from the control group. None of the patients' IVSd z score was above 2. Maternal glucose level was found to be in inverse relation with diastolic functions in our study. We thought that maternal high blood glucose levels caused diastolic dysfunction through inflammatory processes. In offsprings of diabetic rat mothers, neonatal heart contained high levels of reactive oxygen species and advanced glycation end products according to neonatal hearts in offsprings of non-diabetic rats. Furthermore, in hearts of the IDM rats, tumor necrosis factor-α, nuclear factor-κB, and interleukin 6 mRNA were higher than in the hearts of offspring of non-diabetic rats [20].

In our study, an increase in systolic and diastolic left ventricular dimensions and an increase in left atrium diameter in diabetic LGA and non-diabetic LGA were determined according to their controls. This indicates that ventricular dimensions correlate with macrosomia due to increased transfer of glucose, amino acids, free fatty acids, and the enhancement of fetal growth and ventricular dimensions. Increased cardiac mass was determined in newborns of diabetic mothers [21]. The association found in our study between IVSd/LVPwd and maternal blood glucose level supports this finding.

Conclusion

In this study, diastolic functions were found to be worse in IDM-AGA infants compared to the control and it was shown that the high blood glucose level and the high maternal weight had a negative effect on myocardial functions. In LGA newborns, maternal weight also has a negative effect on systolic function. Left ventricular dimensions and wall thickness are related to macrosomia.

Ethics Committee Approval: The Umraniye Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 22.06.2018, number: 54132726-000-14119).

Authorship Contributions: Concept – EE, FA; Design – EE, MK; Supervision – LB, MK; Materials – OS, LB; Data collection and/or processing – OS; Analysis and/or interpretation – OS; Literature review – EE, FA; Writing – EE; Critical review – MK, LB, FA.

Conflict of Interest: No conflict of interest was declared by the authors.

Use of AI for Writing Assistance: Not declared.

Financial Disclosure: The authors declared that this study has received no financial support.

Peer-review: Externally peer-reviewed.

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