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Article

Fetal heart function among diabetic Vs non diabetic mothers. A novel experience.

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Abstract. *Background:* Diabetes mellitus affects not only the structure of the fetal heart but also the function. The aim of this study was to evaluate the impact of Pregestational and gestational diabetes mellitus (DM) on fetal cardiac systolic and global function. *Methods:* 120 pregnant women enrolled between 28 and 36 + 6 weeks of gestation were assessed and divided into three groups: 40 Pregestational DM type II, 40 gestational DM and 40 non diabetics (controls). The right ventricle (RV), left ventricle (LV) systolic function and global function were assessed. The LV systolic function was assessed by the ejection fraction and the mitral annular plane systolic excursion (MAPSE) using M mode and the s' wave by tissue Doppler. The RV systolic function was assessed by tricuspid annular plane systolic excursion (TAPSE) using M mode and the s' wave by tissue Doppler. The global function was measured by Doppler using the myocardial performance index (MPI). *Results:* Fetuses of Pregestational DM type II mothers showed significantly lower LV EF (67% Vs. 69 %, p =0.007), MAPSE(5.39mm Vs 7.02 mm, p<0.001) and lower both lateral and septal LV s' (p=0.009, p = 0.038) than controls while fetuses of gestational DM mothers showed significantly lower EF (65 % Vs 69%, p<0.001), MAPSE (5.49mm Vs 7.02 mm, p<0.001) and lower septal LV s' (5.05 mm Vs 5.70 mm ,p=0.003) than controls. Fetuses of both Pregestational and gestational DM mothers showed

significantly lower RV TAPSE (p=0.033 and p<0.001). Fetuses of both Pregestational and gestational DM mothers showed significantly higher MPI than controls (p<0.001and p<0.001). *Conclusion:* Pregestational and gestational DM affect the fetal heart. M mode, Doppler and Tissue Doppler methods are useful to detect systolic and global cardiac dysfunction.

Keywords: Fetal cardiac systolic function, M- mode, tissue Doppler, s' wave.

Introduction

Maternal DM is one of the evolving diseases nowadays affecting fetal growth and development. Early gestation uncontrolled diabetes mellitus causes defects in cardiogenesis where the occurrence of malformations is five times higher.(1) Diabetes in pregnancy is either Pregestational or gestational. Both structure and function of the fetal heart are affected by maternal diabetes with affection of the fetal placental circulation from the first trimester till the perinatal period as hyperglycemia affects all stages of cardiac development including cardiogenesis, placental development and fetal circulation. The relationship between hemoglobin A1c (HbA1c) and fetal cardiac function has been found to be inverse so that when HbA1c increases the fetal cardiac function decreases.(2, 3)

Fetal echocardiography have been used at first to recognize structural anomalies, however its utilization in fetal cardiac function assessment has emerged and became of robust importance. Two-dimensional (2D) echocardiography, M mode, Doppler and tissue Doppler imaging (TDI) are used to evaluate fetal heart function. TDI has the privilege of being less dependent on loading conditions so it is more accurate for evaluation of cardiac function and can detect subclinical fetal cardiac dysfunction.(4)

Systolic, diastolic and global cardiac function are all parts of cardiac function. In an effort to objectively assess cardiac function ,many criteria have been proposed.(5)

The objective of this study was to assess the systolic and global function of fetuses of diabetic and non-diabetic mothers and explore the impact of Pregestational and gestational DM on the fetal cardiac systolic and global function. The hypothesis is that non-conventional cardiac functional abnormalities may be present and detectable in fetuses of diabetic mothers.

Materials and Methods

This study was carried out on 120 fetuses which were divided into 40 Pregestational DM type II , 40 gestational DM and 40 fetuses of non-diabetic mothers (controls) attending both Alexandria and Tanta Fetal clinics for fetal Echocardiography starting from 28 weeks of gestation.

Fetuses with the following criteria were excluded: Fetal arrhythmia, multiple gestations, and chronic maternal disease other than diabetes mellitus, fetal growth restriction and extra cardiac structural anomalies

All patients were subjected to:

1. History taking including: maternal age, gestational age, gravidity, parity, associated disorders, drugs intake and evidence of glycemic control by HbA1c which was considered significant if >6.5%.
2. All fetuses verifying the inclusion criteria were scanned by fetal echocardiography using Samsung HS30 ultrasound system with the curvilinear C 2-5 probe at Alexandria university hospital and GE Vivid E9 Ultrasound System, with the curvilinear C 4 probe at Tanta university hospital using standard fetal software for analysis
3. The ultrasound examination was carried on the mother being in a supine position, gel was applied to the skin of the abdomen and a basic obstetric scan was done followed by a fetal heart scan.
4. Both fetuses of cases and control group underwent complete 2D fetal echocardiography via the segmental sequential anatomic approach as the following and compared to each other:

1. Left ventricle systolic function:

- **Ejection fraction by M-mode using** Teichholz formula.(6)
- **MAPSE in mm by M mode** in the 4-chamber view of the fetal heart (apical or basal). (5, 7)
- **Lateral and septal systolic annular peak velocity (s' wave) in cm / sec by TDI** in 4-chamber view (apical or basal).(8, 9)

2. Right ventricle systolic function:

- **TAPSE in mm by M mode** in the 4-chamber view of the fetal heart (apical or basal).[(10)]
- **Lateral and septal systolic annular peak velocity (s' wave) in cm / sec By TDI** was measured in the four-chamber view of the fetal heart (apical or basal view).(8, 11)

3. Global function:

- MPI was calculated according to the following parameters: isovolumetric contraction time (ICT), isovolumetric relaxation time (IRT), and ejection time (ET) using the MPI formula ICT + IRT/ET.(12-15)

Statistical analysis of the data

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Categorical data were represented as no. and percentages. Chi-square test was applied to compare between groups. For continuous data, they were tested for normality by the Shapiro-Wilk test. Quantitative data were expressed as min., max., mean, SD and median for normally distributed quantitative variables One way ANOVA test was used for comparing the three groups and Post Hoc test (Tukey) for pairwise comparison while Student t-test was used to compare two groups. On the other hand for not normally distributed quantitative variables Kruskal Wallis test was used to compare three groups and Post Hoc test (Dunn's for multiple comparisons test) for pairwise comparison. Significance of the obtained results was judged at the 5% level.

Results

Demographics and patients' characteristics:

This study was done on fetuses of 40 Pregestational DM type II and 40 gestational DM mothers then compared with 40 fetuses of non-diabetic mothers.

There was no statistical significant difference between the three groups regarding the maternal age, gravidity, parity and fetal gestational age.

Regarding the HbA1c, there was a statistically significant difference between Pre-gestational and gestational diabetic mothers ($p < 0.001$).

Fetal echocardiography

For the left ventricle systolic function:

Regarding the LV EF, there was a statistically significant difference between fetuses of Pregestational diabetic and non-diabetic mothers ($p_2=0.007$) moreover, there is a statistically significant difference between fetuses of gestational diabetic mothers and non-diabetic mothers ($p_3<0.001$).

Regarding the MAPSE, There was a statistically significant difference between fetuses of Pregestational diabetic and non-diabetic mothers ($p_2<0.001$).There was also a

statistically significant difference between fetuses of gestational diabetic and non-diabetic mothers (p_3<0.001).

Regarding the lateral s' wave by TDI, There was a statistically significant difference between fetuses of Pre-gestational diabetic and non-diabetic mothers (p2=0.009).

While For septal s' wave by TDI, there was a statistically significant difference between fetuses of Pre-gestational diabetic and non-diabetic mothers (p_2=0.038), Also there was a statistically significant difference between fetuses of gestational diabetic and non-diabetic mothers (p_3=0.003).

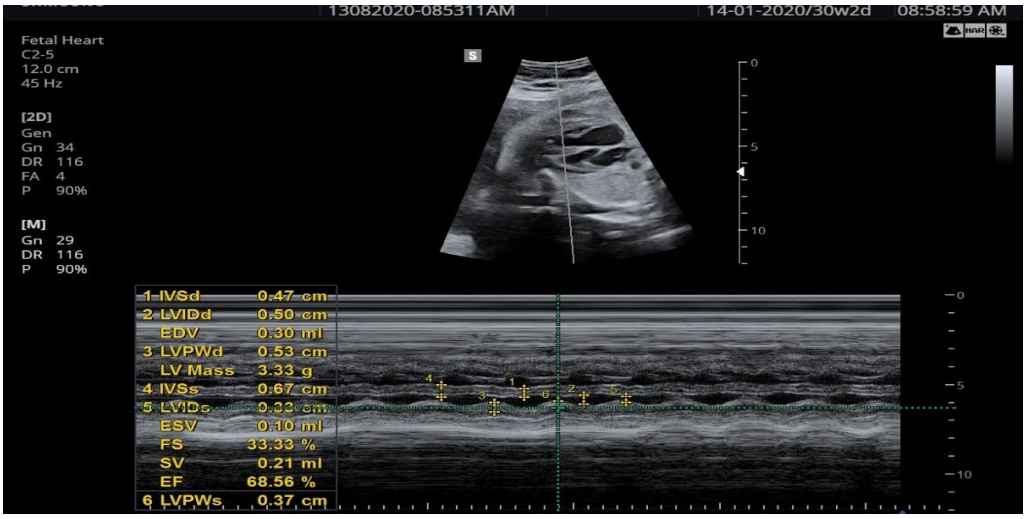

Figure 1: left ventricular ejection fraction in 30 weeks fetus in apical transverse view.

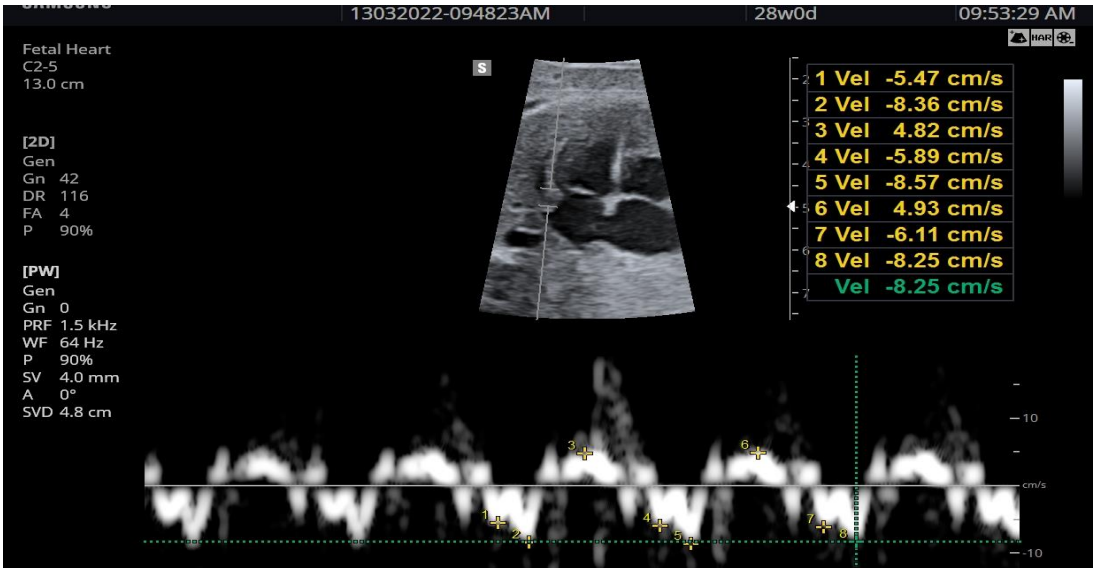

Figure 2: Lateral mitral valve parameters reflecting the systolic (s') function of the left ventricle in apical 4 chamber view by tissue Doppler imaging in 28 weeks fetus where s'=4.87 cm/sec.

For the right ventricle systolic function

Regarding TAPSE, there was a statistically significant difference between fetuses of Pregestational diabetic and non-diabetic mothers (p_2=0.033) moreover, there was also a statistically significant difference between fetuses of gestational diabetic and non-diabetic mothers (p_3<0.001).

Regarding the lateral s' wave and septal s' wave, there was no statistically significant difference between the three groups.

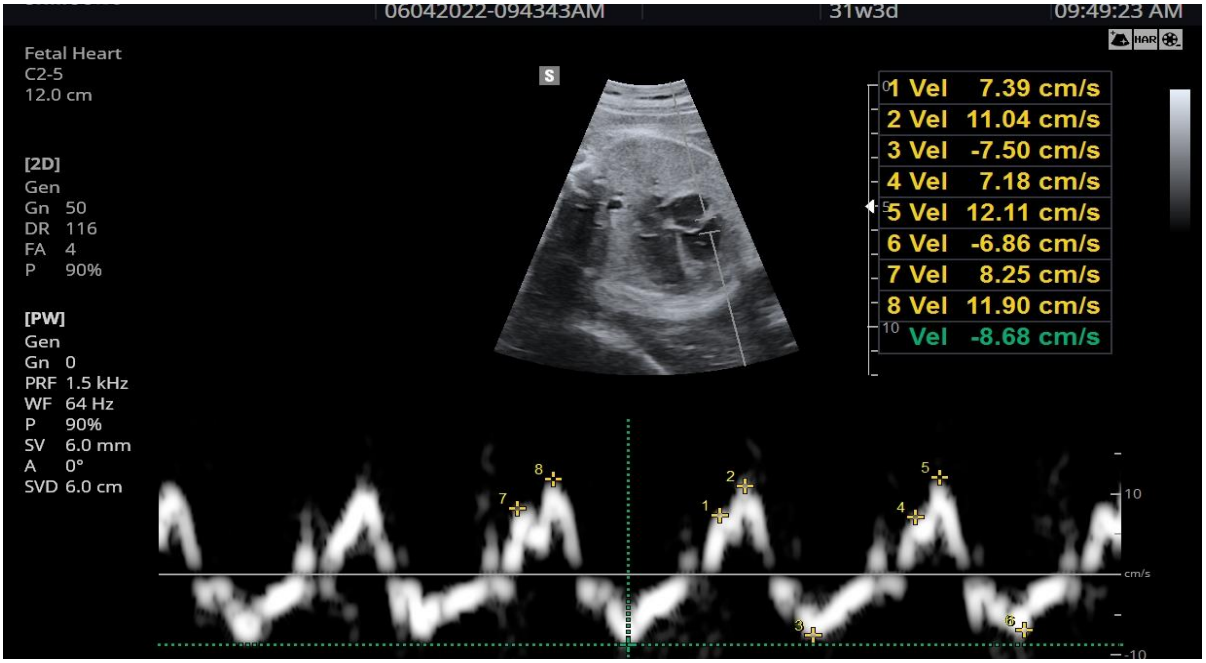

Figure 3: Lateral tricuspid valve parameters in basal 4 chamber view reflecting the systolic (s') function of the right ventricle by tissue Doppler imaging in 31 weeks fetus where s'=7.68 cm/sec

For the global function

Regarding MPI, There was a statistically significant difference between fetuses of Pregestational diabetic and non-diabetic mothers (p_2<0.001). Also there is a statistically significant difference between fetuses of gestational diabetic and non-diabetic mother (p3<0.001).

Table (1): Comparison between the three studied groups according to demographic data

	Group 1 (n = 40)	Group 2 (n = 40)	Group 3 (n = 40)	Test of Sig.	p
Age (/years)					
Mean ± SD.	28.9 ± 6.25	29.2 ± 6.05	31.23 ± 6.72	F=	0.209
Median (Min. – Max.)	29.5 (18 – 40)	29.5 (16 – 41)	31.5 (16 – 42)	1.588	
Gravidity					
Primi gravida	6 (15%)	12 (30%)	17 (42.5%)	χ^2=	0.025*
Multi gravida	34 (85%)	28 (70%)	23 (57.5%)	7.341*	
Mean ± SD.	2.55 ± 1.08	2.35 ± 1.10	2.03 ± 1.07	H=	0.101
Median (Min. – Max.)	2.5 (1 – 6)	2.5 (1 – 5)	2 (1 – 4)	4.590	
Parity	**(n = 34)**	**(n = 28)**	**(n = 23)**		
Primi Parous	14 (41.2%)	8 (28.6%)	10 (43.5%)	χ^2=	0.473
Multi Parous	20 (58.8%)	20 (71.4%)	13 (56.5%)	1.496	
Mean ± SD.	1.82 ± 0.94	1.93 ± 0.77	1.78 ± 0.80	H=	0.659
Median (Min. – Max.)	2 (1 – 5)	2 (1 – 4)	2 (1 – 3)	0.835	
Gestational age (wks -days.)					
Mean ± SD.	32.05 ± 2.84	33.03 ± 2.03	32.75 ± 2.55	H=	0.274
Median (Min. – Max.)	32 (28 – 36)	33 (29 – 36)	33 (28 – 36)	2.588	
HbA1c (%)					
Mean ± SD.	7.79 ± 0.69	5.05 ± 0.64	–	t=	<0.001*
Median (Min. – Max.)	7.8 (6.5 – 9.6)	5.15 (4. – 6.5)	–	18.399*	

SD: **Standard deviation;** F: **F for One way ANOVA test**; H: H for **Kruskal Wallis test;** χ^2: **Chi square test; t: Student t-test;** p: p value for comparing between the three studied groups; *: Statistically significant at $p \leq 0.05$

Group 1: With Pre-gestational type 2 diabetes mellitus; Group 2: With gestational diabetes mellitus; Group 3: Normal pregnant females

Table (2): Comparison between the three studied groups according to different measurements

	Group 1(n = 40)	Group 2(n = 40)	Group 3(n = 40)	Test of Sig. (p)	Sig. bet. grps.
EF (%)					p_1=0.332,
Mean ± SD.	67.09 ± 7.17	65.49 ± 5.70	69.17 ± 6.01	H=14.324*	p_2=0.007*,
Median (Min. – Max.)	63.68[b] (60 – 88)	64.05[b] (59 – 86)	66.8[a] (61.6 – 85.8)	p=0.001*	p_3<0.001*
MAPSE(mm)					p_1=0.961,
Mean ± SD.	5.39[b] ± 1.36	5.49[b] ± 1.32	7.02[a] ± 2.14	F=12.292*	p_2<0.001*,
Median (Min. – Max.)	5.30 (3.20 – 8.40)	5.25 (3.20 – 9.60)	6.30 (4.18 – 13.0)	p<0.001*	p_3<0.001*
TAPSE (mm)					p_1=0.361,
Mean ± SD.	6.08[b] ± 2.38	5.40[b] ± 2.01	7.34[a] ± 2.23	F=7.880*	p_2=0.033*,
Median (Min. – Max.)	5.90 (2.34 – 11.70)	5.20 (2.12 – 11.0)	6.89 (3.60 – 12.40)	p=0.001*	p_3<0.001*
MV Lateral s' (cm/sec)					p_1=0.142,
Mean ± SD.	5.59 ± 1.82	5.62 ± 0.96	6.12 ± 1.49	H=6.858*	p_2=0.009*,
Median (Min. – Max.)	5.22[b] (3.07 – 12.0)	5.60[ab] (3.12 – 9.44)	5.82[a] (2.82 –10.78)	p=0.032*	p_3=0.252
MV Septal s' (cm/sec)					p_1=0.362,
Mean ± SD.	5.27 ± 1.27	5.05 ± 1.05	5.70 ± 1.33	H=9.392*	p_2=0.038*,
Median (Min. – Max.)	5[b] (3.12 – 9.87)	4.94[b] (3.01 – 8.77)	5.39[a] (2.65 – 9.23)	p=0.009*	p_3=0.003*
TV Lateral s' (cm/sec)					
Mean ± SD.	7.08[a] ± 1.94	6.60[a] ± 0.79	7.08[a] ± 1.25	F=1.562	–
Median (Min. – Max.)	6.79 (4.7 – 14.6)	6.36 (5.2 – 9.15)	6.89 (4.46 – 11.2)	p=0.214	
TV Septal s' (cm/sec)					
Mean ± SD.	5.99[a] ± 1.34	5.81[a] ± 0.76	6.11[a] ± 1.03	F=0.807	–
Median (Min. – Max.)	5.84 (4.10 – 12.12)	5.80 (4.00 – 8.06)	6.07 (4.20 – 9.57)	p=0.449	
MPI					p_1=0.347,
Mean ± SD.	0.49 ± 0.10	0.47 ± 0.10	0.40 ± 0.03	H=54.870*	p_2<0.001*,
Median (Min. – Max.)	0.46[a] (0.34 – 0.88)	0.44[a] (0.41 – 0.89)	0.41[b] (0.31 – 0.48)	p<0.001*	p_3<0.001*

SD: **Standard deviation; F**: **F for One way ANOVA test**, Pairwise comparison bet. each 2 groups was done using **Post Hoc Test (Tukey);** H: H for **Kruskal Wallis test,** Pairwise comparison bet. each 2 groups was done using **Post Hoc Test (Dunn's for multiple comparisons test);** p: p value for comparing between the three studied groups; p_0: p value for comparing between **Lateral** and **Septal;** p_1: p value for comparing between **Group 1** and **Group 2;** p_2: p value for comparing between **Group 1** and **Group 3;** p_3: p value for comparing between **Group 2** and **Group 3;** *: Statistically significant at $p \leq 0.05$; Means/Medians with **Common letters** are not significant (i.e. **Different letters** are significant)

Group 1: With Pre-gestational type 2 diabetes mellitus; Group 2: With gestational diabetes mellitus;

Group 3: Normal pregnant females

Discussion

Diabetes mellitus is one of the outgrowing metabolic diseases among pregnant females nowadays, it is either Pregestational or gestational. DM is common among pregnant females, so it is very important to assess its effect on the function of the fetal heart. (1, 16, 17)

In our current study there was no statistical significant difference between the three groups regarding the maternal age which similar to the results of Peixoto AB et al.(18), Ran H et al.(19), Aguilera J et al.(20) and Hou Q et al.(21) studies.

Regarding gravidity and parity, there was no statistical significant difference between the three groups which goes along with Dervisoglu P et al.(22) and Peixoto AB et al.(18) studies.

The gestational age of the 3 groups ranged from 28 weeks to 36 weeks of gestation which is similar to Dervisoglu P et al.(22) study and Ran H et al. (19) study showing no statistically significant difference between the three groups.

Regarding HbA1c level, in our study there was a statistically significant difference between the fetuses of Pre-gestational diabetic and the gestational diabetic mothers ($p < 0.001$) which is similar to Dervisoglu P et al. (22) study.

Regarding the ejection fraction , our study showed a statistically significant difference between fetuses of Pregestational diabetic and non-diabetic mothers ($p_2 = 0.007$) moreover, there is a statistically significant difference between fetuses of gestational diabetic and non-diabetic mothers ($p_3 < 0.001$) similar to Aguilera J et al. (20) study, where the ejection fraction is significantly lower among fetuses of both Pregestational and gestational diabetic mothers which is unlike Dervisoglu P et al.(22) study who showed no statistically significant difference between the three groups. There was no statistically significant difference between fetuses of Pregestational diabetic and gestational diabetic mothers.

Regarding the MAPSE, Bravo-Valenzuela N et al.(23) study showed similar significant results to our study that showed a statistically significant difference between fetuses of Pregestational diabetic and non-diabetic mothers ($p_2 < 0.001$) but this does not go in agreement with Lee-Tannock A et al.(10) study that showed no statistically significant difference between them .There is also a statistically significant difference between fetuses of gestational diabetic and non-diabetic mothers ($p_3 < 0.001$). However there was no statistically significant difference between fetuses of pre gestational diabetic and gestational diabetic mothers.

Regarding the mean mitral s' wave by TDI ,our study showed a statistically significant difference between fetuses of Pre-gestational diabetic and non-diabetic mothers ($p_2 = 0.009$) which agrees with Bayoumy S et al.(24) study but unlike

Dervisoglu P et al.(22) study that showed no statistically significant difference between them. A statistically significant difference between fetuses of gestational diabetic and non-diabetic mothers (p2=0.003) was found which is similar to Balli S et al.(25) study but not in agreement with Dervisoglu P et al.(22) study that showed no statistically significant difference between them. There was no statistically significant difference between fetuses of Pregestational and gestational diabetes mothers similar to Dervisoglu P et al.(22) study.

Regarding TAPSE, similar to Bravo-Valenzuela N et al.(23) and Bayoumy S et al.(24) studies there was a statistically significant difference between fetuses of Pregestational diabetic and non-diabetic mothers (p_2=0.033) but unlike Lee-Tannock A et al.(10) study that showed no statistically significant difference between them. Moreover, there is a statistically significant difference between fetuses of gestational diabetic and non-diabetic mothers (p_3<0.001) while there is no statistically significant difference between fetuses of Pregestational diabetic and gestational diabetic mothers

For mean tricuspid s' wave by TDI, our study showed no statistically significant difference between the three groups which is similar to Dervisoglu P et al.(22) study that showed no statistically significant difference between fetuses of Pregestational diabetic and non-diabetic mothers but not in agreement with Bayoumy S et al .(24) study that showed a statistically significant difference between fetuses of Pregestational diabetic and non-diabetic mothers and also unlike Balli S et al.(25) study that showed a statistically significant difference between fetuses of gestational diabetic and non-diabetic mothers

Regarding the MPI, our study showed a statistically significant difference between fetuses of Pregestational diabetic and non-diabetic mother which has similar significant results to Sanhal CY et al.(26) study. Also there was a statistically significant difference between fetuses of gestational diabetic and non-diabetic mother (p3<0.001) which is in agreement with Sanhal CY et al.(26) Balli S et al.(25) and Bhorat I et al.(27) studies .There was no statistically significant difference between fetuses of Pregestational and gestational diabetes mothers which is similar to Sanhal CY et al. (26) study.

To conclude, this study showed that DM either Pregestational or gestational has a statistically significant effect on systolic and global function of the fetal heart and good control of diabetes is mandatory.

Strengths and limitations of the study

Strengths

To the best of our knowledge, this study is one of few studies conducted in Egypt to study the effect of diabetes on systolic and global function on fetal heart. It is a

prospective study that included 120 pregnant females which is a good number of patients to be studied in relation to other studies done that was done in 2 centers, It included multiple variables to assess systolic and global function of the heart, It included both left and right ventricles assessment and it compared between Pregestational, gestational and non-diabetic mothers regarding multiples parameters while other studies compared between only 2 groups.

Limitations:
The difference between type 1 and type 2 Pregestational diabetes fetuses was not studied and weather the type of Pregestational diabetes affects the fetal heart needs further study, If the treatment for DM as well as the glycemic control can modify the fetal cardiac function was not explained in our study, younger fetal gestational age needs to be studied to explore effect of diabetes on younger gestational age and there is lack of postnatal follow up.

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No funds were received for this project.

Ethics approval and consent to participate

This study was approved by the ethics committee of the Faculty of Medicine, Alexandria University, Egypt and the ethics committee approval number was 0201388. The IRB number is 00012098 and the FWA number is 00018699.All participants provided written consent.

Conflicts of interest

The authors declare no conflicts of interest.

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