

# Functional Assessment of Fetal Heart by Echocardiography in Maternal Diabetes Mellitus

## Abstract

**Background:** Diabetes mellitus constitutes a significant risk for the fetus if present in pregnant woman. Tissue Doppler imaging (TDI) is less dependent on loading conditions, so it is more accurate for assessment of cardiac function and can detect subclinical fetal cardiac dysfunction. The aim of this work was to assess fetal heart functional abnormalities (left ventricular systolic and diastolic function, right ventricular systolic and diastolic function) and their relation to maternal glycemic control.

**Methods:** This prospective case-control study was carried out on 30 diabetic mothers either with pregestational diabetes (PGDM) or gestational diabetes (GDM) and 20 healthy mothers in the third trimester. Patients were subdivided in to two groups: group I: poorly controlled diabetic pregnant mothers (17 cases) and group II: well-controlled diabetic pregnant mothers (13 cases). Patients were subjected to fetal echocardiography (left ventricular systolic and diastolic function assessment, right ventricular systolic and diastolic function assessment).

**Results:** There was significantly higher values regarding fasting blood glucose level, 2 hours post-prandial blood glucose level and HbA1c in poorly controlled patients versus well controlled ( $P$  value  $< 0.001$ ). It was noticed that E' and A' wave velocities of the mitral annulus, MPI and IVRT were significantly higher in fetuses of groups I, II than fetuses of group III ( $P < 0.05$ ). Fetuses of groups I, II showed significantly lower E/E' ratio when compared to fetuses of group III ( $P < 0.05$ ).

**Conclusions:** By using tissue Doppler imaging at around 28 weeks of gestation, it was discovered that the systolic and diastolic function indices measures were different in foetuses of diabetic mothers than in normal foetuses. Despite having well-controlled diabetes, the

echocardiographic results of uncomplicated non-diabetic women's foetuses were significantly different from those of diabetic women's foetuses.

**Keywords:** Fetal Heart, Echocardiography, Maternal Diabetes Mellitus.

UNDER PEER REVIEW

## Introduction:

“Fetal echocardiography is the ultrasonic evaluation of the developing human cardiovascular system prior to birth, non-invasive in nature and can be highly accurate. It is presently the standard method used for detection of the fetal cardiovascular disease”<sup>[1]</sup>.

“Diabetes mellitus constitutes a significant risk for the fetus if present in pregnant woman. The fetal heart is threatened in a double fashion. First at the beginning of gestation, the disease has a teratogenic effect, cardiogenesis is impaired in the correct expression of genes coding for the cardiac development. Second, starts at the end of the second or beginning of the third trimester, the fetus may be affected by **pathological ventricular hypertrophy, commonly referred as ventricular hypertrophy**”<sup>[2]</sup>.

**A number of studies showed that there is a five folds increase** in the risk of congenital heart diseases among diabetic pregnancy with suboptimal glycemic control and such women should be referred for detailed fetal echocardiography<sup>[3]</sup>. “Maternal hyperglycemia results in fetal hyperinsulinemia and asymmetric septal hypertrophy, macrosomia, and hypoglycemia in infants”<sup>[4]</sup>.

“Fortunately, in most cases, cardiac hypertrophy is transient with spontaneous echocardiographic resolution within early months after birth requiring no therapy”<sup>[5]</sup>. “The other most common cardiac malformations **in fetuses of diabetic mothers include the following: coarctation of aorta (CoA), transposition of great arteries (TGA), truncus arteriosus, double outlet right ventricle (DORV), ventricular septal defect (VSD), hypoplastic left heart syndrome (HLHS), and heterotaxy syndrome**”<sup>[6]</sup>.

“Although several articles have documented cardiac malformation and defect in fetuses of diabetic mothers m there is a little information about their systolic and diastolic cardiac function”<sup>[7]</sup>.

“Tissue Doppler imaging (TDI) has the benefit of being less dependent on loading conditions, so it is more accurate for assessment of cardiac function and can detect subclinical fetal cardiac dysfunction”<sup>(9)</sup>. “Fetal echocardiography shows the timing of development of myocardial changes in the fetus of diabetic mother with documentation of increased ventricular septal thickening and ventricular inflow and outflow velocities”<sup>[7]</sup>.

The aim of this work was to assess fetal heart functional abnormalities (left ventricular systolic and diastolic function, right ventricular systolic and diastolic function) and their relation to maternal glycemic control.

### **Methodology:**

This prospective case-control study was carried out on 50 pregnant women, 30 diabetic mothers either with pregestational diabetes (PGDM) or gestational diabetes (GDM) and 20 healthy mothers in the third trimester (from 28th week until birth), in the echocardiography unit, Cardiology department, Tanta University International Educational Hospital during the period from October 2020 to March 2021.

Exclusion criteria were diagnosed cardiac diseases or abnormal echocardiography findings in mothers, presence of fetal structural heart disease, fetal arrhythmia, twin pregnancies, maternal hypertension (pregnancy induced or essential), intrauterine growth retardation (defined as weight for gestation less than 5th percentile<sup>[8]</sup>, polyhydramnios, refusal of the mother to give informed written consent.

Patients were subdivided into group I: poorly controlled diabetic pregnant mothers with either gestational or pregestational diabetes (17 cases) and group II: well-controlled diabetic pregnant mothers with either gestational or pregestational diabetes (13 cases).

All pregnant mothers were subjected to: history taking, physical examination, routine laboratory investigations, fetal echocardiography.

### **Fetal echocardiography:**

A detailed fetal echocardiographic examination was performed using vivid- E9 echocardiographic machine (GE) medical system equipped with M5S probe (frequency 1.7-3.3 MHz) for echocardiography. All fetuses were studied. A full morphological examination of the fetal heart, using five transverse views through the fetal abdomen and thorax was performed at all examinations [9].

**left ventricular systolic function assessment:**

**M-mode:** by obtaining subcostal four-chamber view, which was obtained by imaging the fetal chest in a transverse projection from the anterior chest wall and angling the transducer slightly cephalad. The cursor of the M-mode was angled perpendicular to the ventricular septum at the level of the tips of the mitral valve. End diastolic and end systolic measurements of the ventricles were obtained from the endocardial surface of the ventricular wall to the interventricular septum.

**Ejection fraction:**

Ejection fraction (EF) was measured as end diastolic ventricular internal dimension (EDVID) – end systolic ventricular internal dimension (ESVID)/EDVID

$$EF = \frac{EDVID - ESVID}{EDVID} \cdot [10]$$

Fractional shortening is calculated by the following equation [10]:

$$FS = \frac{LVEDD - LVESD}{LVEDD} \times 100$$

**Tissue Doppler imaging parameters (TDI):**

**S wave:** The study was performed by activating TDI function in the same machine. The gain control and filter were manipulated to get the clearest and less noisy tracing of myocardial velocity. From the spectral tissue Doppler in the lateral portion of the mitral valve ring, the spectral curve obtained shows the systolic movement of the mitral valve ring (Sa) [10].

**Left ventricular diastolic function assessment:**

**Pulsed Doppler velocity across the mitral valve:** By obtaining apical-4-chamber view, flow velocity across mitral valve is examined using pulsed Doppler, the sample volume should be placed between the leaflet tips then peak velocities were obtained, E (early diastolic, rapid filling phase) waves and A (late diastolic, atrial contraction) waves then get measurements of peak E and A waves, E/A ratio was also measured <sup>[10]</sup>.

**Tissue Doppler imaging:** Myocardial tissue velocity is measured in apical 4 chamber view using TDI with sample volume (SV) located at left lateral ventricular wall for mural mitral annulus. Two dominant waves are observed during diastole, namely E` (early diastolic wave) and A` (late diastolic, atrial filling wave), the mean peak value was obtained, then the mean ratio between the peak velocities of E` and A` waves was measured. The ratio between the mitral inflow E wave and tissue derived E` wave of left ventricle (E/E`) also had been calculated.

**Ventricular global function, myocardial performance index (MPI):** Tissue Doppler time intervals were measured from mitral inflow and left ventricular outflow Doppler tracings <sup>[10]</sup>. The interval 'a' from cessation to onset of mitral inflow is equal to the sum of isovolumic contraction time (IVCT), ejection time (ET), and isovolumic relaxation time (IVRT). ET 'b' is derived from the duration of the left ventricular outflow Doppler velocity profile. The sum of ICT and IRT was obtained by subtracting b from a <sup>[10]</sup>.

$$MPI = \frac{(IVCT) + (IVRT)}{(ET)}$$

**Right ventricular systolic function assessment:**

**M-mode, Tricuspid annular plane systolic excursion (TAPSE):** Tricuspid annular plane systolic excursion can be determined in M-mode echocardiography by aligning the lateral tricuspid annulus with the ventricular apex in the apical four-chamber view and measuring the lateral annular displacement <sup>[10]</sup>.

**Tissue Doppler imaging (S wave):** Tricuspid annular excursion is measured in 4 chamber view using TDI with sample volume (SV) located at basal part of right ventricular wall for tricuspid annulus. The velocity S' is read as the highest systolic velocity <sup>[10]</sup>.

**Right ventricular diastolic function:**

**Pulsed Doppler across the tricuspid valve:** By obtaining apical-4-chamber view, flow velocity across tricuspid valve is examined using pulsed Doppler, the sample volume should be placed between the leaflet tips then peak velocities were obtained, E (early diastolic, rapid filling phase) waves and A (late diastolic, atrial contraction) waves then get measurements of peak E and A waves, E/A ratio was also measured <sup>[10]</sup>.

**Statistical analysis**

Statistical analysis was done by SPSS v26 (IBM Inc., Chicago, IL, USA). Quantitative variables were presented as mean and standard deviation (SD) and compared between two groups utilizing Student t-test and for the three groups utilizing One way ANOVA (F) test and Post Hoc test (Tukey) for pairwise comparisons. Kruskal Wallis test was utilized to compare between more than two studied groups for not normally distributed quantitative variables and Post Hoc (Dunn's multiple comparisons test) for pairwise comparisons. Qualitative variables were presented as frequency and percentage (%) and were analysed utilizing the Chi-square or Fisher's Exact correction test. A two tailed P value < 0.05 was considered statistically significant.

**Results:**

Non-significant difference was present between the three groups as regard to the age of the mother or the gestational age (P value > 0.05). Table 1

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

	Diabetic mothers (n = 30)		Control cases (n = 20)	P-value
	Poorly controlled (n = 17)	Well controlled (n = 13)		

Age of mothers (years)	28.88 ± 6.50	28.31 ± 5.86	26.90 ± 7.25	0.651
Gestational age (weeks)	33.0 ± 2.15	33.85 ± 2.34	31.95 ± 2.31	0.067

Data are presented as mean ± SD.

There were significantly higher values regarding fasting blood glucose level, 2 hours post-prandial blood glucose level and HbA1c in poorly controlled patients versus well controlled (P value < 0.001). Table 2

**Table 2: Comparison between the diabetic groups according to the maternal glycemic control**

	Diabetic women (n = 30)		P-value
	Poorly controlled (n = 17)	Well controlled (n = 13)	
HbA1c (%)	7.70 ± 0.94	6.01 ± 0.49	<0.001*
FBG	170.2 ± 44.66	97.38 ± 3.64	<0.001*
2 hrs. PPBG	236.6 ± 48.60	120.6 ± 6.32	<0.001*

Data are presented as mean ± SD, \* significant as P value < 0.05. HbA1c: Glycated hemoglobin, FBG: Fasting blood glucose level. PPBG: Post-prandial blood glucose level.

There was no significant difference in EF measured by M-mode, FS, LVESD, LVEDD, S wave velocity, E/A ratio, E`/A`, Tricuspid E/A, TAPSE, Tricuspid S wave, IVCT and ET between fetuses of the three studied groups. It was noticed that E` and A` wave velocities of the mitral annulus, MPI and IVRT were significantly higher in fetuses of groups I, II than fetuses of group III (P <0.05). Fetuses of groups I, II showed significantly lower E/E` ratio when compared to fetuses of group III (P <0.05). No significant difference was noticed between the groups I and II regarding E` and A` wave velocities at mitral annulus, E/E` ratio, IVRT and MPI. Table 3

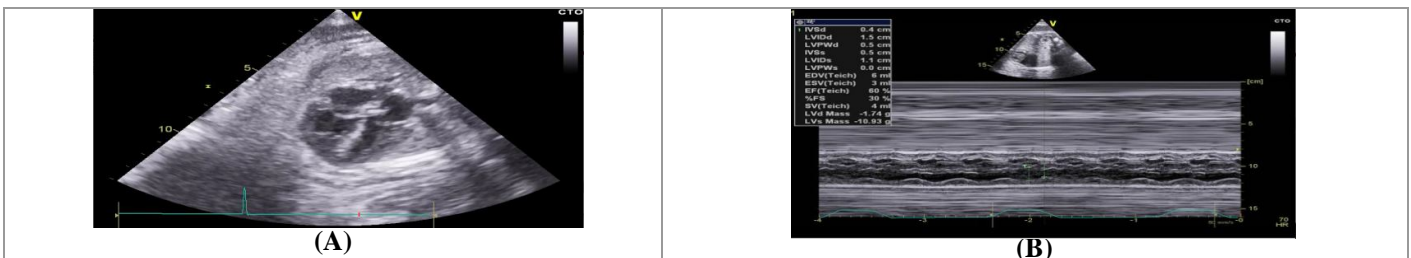
**Table 3: Comparison between the three studied groups according to the ventricular systolic function, left ventricular diastolic function, right ventricular diastolic and systolic function and left ventricular global function**

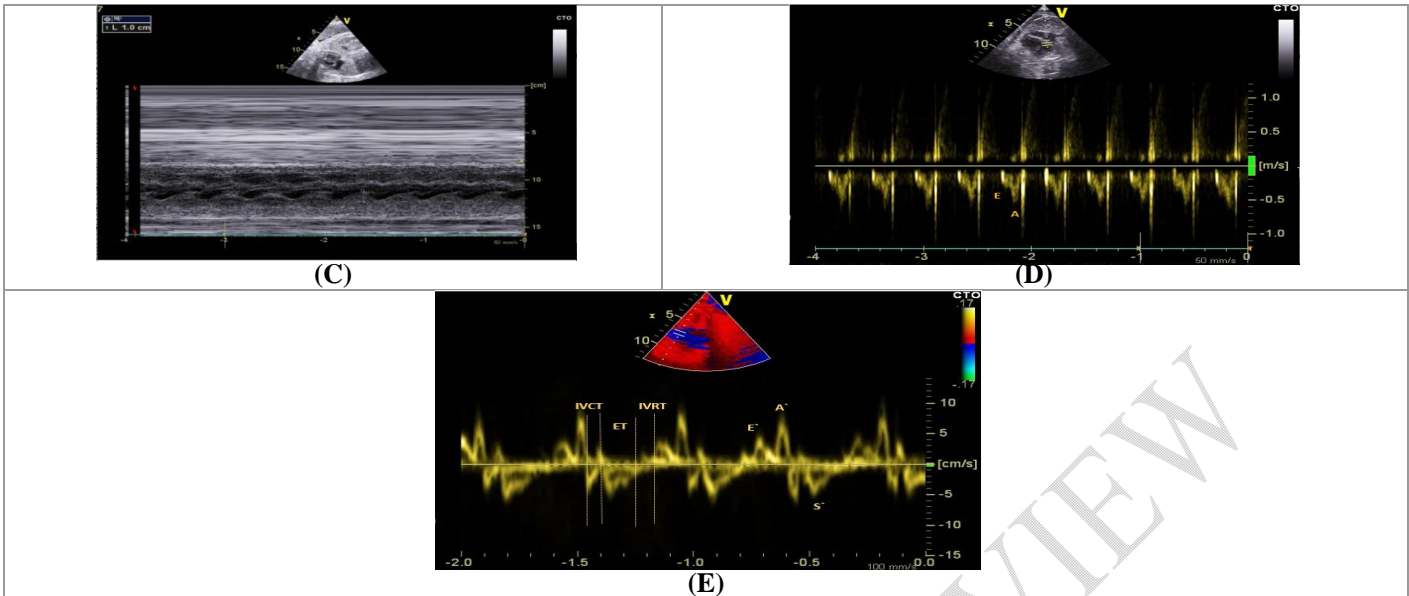
	Ventricular systolic function			P-value
	Diabetic women (n = 30)		Non-diabetic women (n = 20)	
	Poorly controlled (n = 17)	Well controlled (n = 13)		
EF (%)	70.82 ± 9.89	65.85 ± 5.29	66.60 ± 4.83	0.107
LVEDD (cm)	1.20 ± 0.33	1.23 ± 0.23	1.05 ± 0.18	0.106
LVESD (cm)	0.75 ± 0.23	0.84 ± 0.17	0.69 ± 0.12	0.080
FS (%)	36.88 ± 7.92	33.54 ± 5.68	34.60 ± 6.86	0.401
S wave (m/sec)	0.052 ± 0.018	0.058 ± 0.011	0.060 ± 0.008	0.240

Left ventricular diastolic function				
<b>E/A ratio</b>	0.69 ± 0.10	0.69 ± 0.08	0.65 ± 0.10	0.317
<b>E/E`</b>	6.34 ± 1.90	6.49 ± 1.67	8.70 ± 2.33	0.001* p <sub>1</sub> =0.979 p <sub>2</sub> =0.003* p <sub>3</sub> =0.010*
<b>E' (m/sec)</b>	0.067 ± 0.016	0.060 ± 0.011	0.045 ± 0.010	<0.001* p <sub>1</sub> =0.392 p <sub>2</sub> <0.001* p <sub>3</sub> =0.003*
<b>A' (m/sec)</b>	0.085 ± 0.029	0.082 ± 0.010	0.068 ± 0.013	0.017* p <sub>1</sub> =0.789 p <sub>2</sub> =0.018* p <sub>3</sub> =0.014*
<b>E`/A`</b>	0.91 ± 0.45	0.74 ± 0.18	0.68 ± 0.19	0.091
Right ventricular diastolic and systolic function				
<b>Tricuspid E/A</b>	0.69 ± 0.04	0.67 ± 0.04	0.68 ± 0.07	0.618
<b>TAPSE (cm)</b>	0.92 ± 0.20	1.04 ± 0.12	0.92 ± 0.24	0.182
<b>Tricuspid S wave (m/s)</b>	0.63 ± 0.06	0.60 ± 0.05	0.61 ± 0.05	0.505
Left ventricular global function				
<b>IVCT (msec)</b>	34.12 ± 8.10	32.46 ± 4.81	30.80 ± 5.03	0.278
<b>IVRT (msec)</b>	58.46 ± 9.21	54.38 ± 6.96	42.45 ± 6.64	<0.001* p <sub>1</sub> =0.329 p <sub>2</sub> <0.001* p <sub>3</sub> <0.001*
<b>ET (msec)</b>	156.5 ± 65.49	141.4 ± 58.08	173.9 ± 31.06	0.217
<b>MPI</b>	0.77 ± 0.51	0.74 ± 0.34	0.43 ± 0.07	0.008* p <sub>1</sub> =0.964 p <sub>2</sub> =0.013* p <sub>3</sub> =0.044*

Data are presented as mean ± SD, \* significant as P value < 0.05. LVESD: Left ventricular end systolic dimension, LVEDD: Left ventricular end diastolic dimension, EF: Ejection fraction, TAPSE: Tricuspid annular plane systolic excursion, IVCT: Isovolumetric contraction time, IVRT: Isovolumetric relaxation time, ET: Ejection time, MPI: Myocardial performance index, FS: Fractional shortening.

A 24-years old woman presented to our hospital at 30 weeks of her second pregnancy, she was gravida 2, para 1 and abortion 1, complaining from polyuria and dry tongue. She was diagnosed by type 1 diabetes mellitus eleven years ago, not hypertensive, no other past medical history.





**Figure 1: (A) Four-chamber view of the fetal heart, (B) Assessment of left ventricular systolic function and left ventricular dimensions by M-mode. LVESD and LVEDD represent the internal left ventricular dimensions, (C) Assessment of systolic right ventricular function by M-mode (Tricuspid annular plane systolic excursion). It represents the longitudinal function of the right ventricle, (D) Assessment of fetal left ventricular diastolic function by pulsed Doppler velocity across mitral valve. The E wave represents the early diastolic filling, the A wave represents the atrial contraction. The E and A waves represent the diastolic function, (E) Assessment of fetal left ventricular systolic, diastolic and global function by tissue Doppler imaging (TDI). The E` wave represents the early diastolic myocardial velocity, the A` wave represents the late diastolic myocardial velocity and the S` wave represents the peak systolic myocardial velocity. The Ejection time represents the period of ventricular ejection, the IVCT represents the period between the closure of atrioventricular valves and opening of semi-lunar valves and IVRT represents the period between closure of the semi-lunar valves until the opening of the atrioventricular valves.**

## Discussion

“Maternal diabetes is associated with increased risk of fetal morbidity, stillbirth and neonatal morbidity and mortality. Fetal echocardiography has emerged as a great progress for prenatal diagnosis of congenital heart disease that has made the intra-uterine treatment possible as well” [11].

In the present study it was found that there was no significant difference between the three groups regarding to maternal or gestational age. Significant difference between the two

groups of diabetic mothers as regard FBG and 2 hours PPBG was reported. Significant higher levels in poorly controlled **diabetic group versus well controlled group.**

**As regard evaluation of LV systolic** function by M-mode in the current study, it was reported that there was no significant difference in fetal left ventricular EF%, FS% or left ventricular end systolic and diastolic dimensions in fetuses of diabetic mothers compared to non-diabetic mothers. There was no significant difference between fetuses of mothers of poorly controlled diabetes when compared to those of well-controlled diabetic mothers. There was no significant difference between the three groups as regard LV systolic function as assessed by tissue Doppler imaging (lateral mitral annular S wave).

The previous mentioned results **agreed well with Chen C et al. <sup>[12]</sup> study, they found that fetal LV fractional shortening and ejection fraction did not differ among the fetuses of poorly controlled diabetic mothers, fetuses of well controlled diabetic mothers and the control groups.**

**Moreover, Moradian et al. <sup>[7]</sup> also found no significant difference in lateral S wave velocity when comparing ventricular function between fetuses of diabetic mothers and normal mothers by tissue Doppler.**

Gandhi et al. <sup>[13]</sup> didn't agree with our study as they reported increased ventricular diameters and contractility in fetuses of GDM when compared to normal pregnancy.

Regarding fetal diastolic ventricular function assessment, the current study found that there was no significant difference in the mean E/A ratio across mitral and the tricuspid valve inflow in diabetic group versus control group. No significant difference was also reported in mean E/A ratio between the fetuses of poorly controlled diabetic mothers and those of well controlled diabetic mothers.

In the current study, we found that the diastolic velocity of atrial contraction phase (A wave) is higher than the rapid filling phase at the beginning of diastole (E wave) in each case of the three groups (diabetic and non-diabetic).

As regard myocardial diastolic velocities measured by tissue Doppler of ventricular walls, there was significantly higher left ventricular E' and A' in fetuses of diabetic pregnancies (poorly and well-controlled) when compared to fetuses of normal pregnancies, while there was no significant difference regarding the left ventricular E'/A' ratio. As comparison between the fetuses of well-controlled and poorly controlled diabetic mothers, there was higher E' wave velocity in poorly controlled diabetic mothers than well controlled diabetic mothers but it did not reach values.

In the present study, significant lower ratios of (E/E') were observed in the mitral valve flow in fetuses of diabetic mothers (poorly and well controlled) when compared to control cases. Additionally, lower E/E' was reported in fetuses of poorly controlled diabetic mothers compared to well controlled diabetes, yet the difference was not statistically significant.

These data came in agreement with Hate'm et al. <sup>[14]</sup> they found that “myocardial velocities (E' and A' waves) at the level of mitral annulus was significantly higher in fetuses of diabetic mothers than fetuses of normal mothers. They also showed that the E/E' ratio in normal pregnancies was significantly higher than in diabetic ones, demonstrating impaired cardiac function”.

Pilania R et al. <sup>[15]</sup> study didn't agree well with the present study and observed reduced E/A ratio across both mitral and tricuspid valves in diabetics when compared to normal cases. This suggested increased ventricular stiffness at 26-28 and 34-36 weeks of gestation. They postulated that altered metabolic environment and fluctuations in maternal blood sugar levels may be responsible for the impaired diastolic function.

In a study by Nii et al. <sup>[16]</sup> “the E/E` ratio was decreased due to greater rates of increased E` values than E during the course of pregnancy. They concluded that this accelerated increase in E` values is related to increased ventricular compliance. For the estimation of the filling pressure, E/E` becomes useful only after 25 weeks gestation”.

By studying the ventricular global function, in the present study there was significant increase in fetal MPI and IVRT in diabetic group compared to the control group. Although, MPI and IVRT values were higher in **poorly controlled group compared to well controlled diabetics.** **However, no statistically significant** difference was noted.

IVCT and ET values show no significant difference between fetuses of diabetic pregnancies and uncomplicated normal pregnancies. No significant difference between well-controlled and poorly controlled diabetic pregnancies as regard IVCT and ET was also noted.

These results came in agreement with Balli et al. <sup>[17]</sup> in their study who found higher MPI related to significantly higher IVRT **in fetuses of GDM when compared to normal pregnancy,** **while IVCT and ET during pregnancy were similar between the groups.**

**Pilania et al. <sup>[15]</sup> observed increased MPI** at both, 26 - 28 and 34-36 weeks of gestation in diabetics when compared to normal pregnancy.

In contrast, Moghadam E et al. <sup>[11]</sup> in their study did not approve any abnormalities in MPI of the fetuses of gestational diabetic mothers when compared to non-diabetic ones.

By assessment of the right ventricular systolic function in the present study, no significant difference in TAPSE between fetuses of diabetic mothers (controlled and poorly controlled) and non-diabetic ones was reported. Non-significant difference was present also between fetuses of well controlled and poorly controlled diabetic pregnancies.

Tricuspid annular S wave velocity measured by tissue Doppler revealed no significant difference between fetuses of diabetic mothers and healthy pregnancy. Non-significant difference also was present between well and poorly controlled diabetic pregnancies.

This study came in accordance with Aguilera J. et al. <sup>[18]</sup> study, they showed no significant difference in TAPSE between fetuses of diabetic and control groups but fetuses whose mothers were treated with insulin had lower global longitudinal RV systolic function measured by global longitudinal strain compared with that of fetuses in the control group.

Chen C. et al. <sup>[12]</sup> reported that in the period of  $\geq 34$  weeks, the ratios of right to left cardiac output, measured by peak flow velocities and velocity-time integrals of aorta and pulmonary artery in pulsed Doppler pattern, in both DM1 (poorly controlled group) and DM2 (well controlled diabetic group) were smaller than in the control group.

Limitations: The study was a single center study, not all fetuses who were appropriate for the study had good quality of echocardiographic image and was excluded from the study and relatively small number of cases and lack of follow-up period.

### **Conclusions:**

Maternal diabetes cause early subclinical change in fetal cardiac function. Tissue Doppler imaging is a useful, efficient and sensitive tool to study the changes in cardiac structure and function in fetuses. The systolic and diastolic function indices measures were affected in fetuses of diabetic mothers as compared to normal at  $\geq 28$  weeks of gestation by tissue Doppler imaging. Echocardiographic findings were significantly different between fetuses of uncomplicated non-diabetic women compared to fetuses of diabetic pregnancies, even though diabetic status was well controlled.

### **Ethical Approval and Consent**

The study was done after approval from the Ethical Committee of Faculty of Medicine, Tanta University. An informed written consent was obtained from all the subjects of the study.

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