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Echocardiographic Evaluation of Fetal Cardiac Structure and Function in Pregnant Women with Hyperglycemia

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Abstract: ***Objective: To evaluate differences in various fetal echocardiographic parameters in women with or without hyperglycemia during pregnancy. Material and Methods: We studied fetal cardiac structure and function in 50 uncomplicated singleton pregnancies and in 100pregnancies complicated by hyperglycemia. Maternal glycemic control was deemed adequate in 80 women and inadequate in 20. Fetal echocardiography was done to assess interventricular septal thickness and cardiac function, both systolic [ejection fraction (EF)] and diastolic [using E/A ratio, Ea value and E/Ea ratio]. All these parameters were compared between groups. Results: Fetal cardiac interventricular septal thickness during diastole was increased in hyperglycemicas compared to normal pregnant females (p value<0.05) and it was independent of glycemic control. Fetal cardiac systolic function as indicated by ejection fraction was also increased in hyperglycemic pregnant females (p value<0.05) but it was found to be decreased in uncontrolled diabetic females. Fetal cardiac diastolic dysfunction as indicated by low E/A ratio, low Ea value and increased E/Ea ratio was present in pregnant females with hyperglycemia and it was dependent on glycemic control of the patient (p value<0.05). Conclusion: Fetuses of diabetic mothers have increased incidence of cardiac dysfunction and it was related to control of diabetes.***

Keywords: Fetal echocardiography, cardiac function, hyperglycemia, pregnancy, interventricular septal thickness

1. Introduction

Diabetes is said to be the most common medical complication observed in the pregnancy.[1] Recent study revealed that GDM accounts for around 9-25% of total pregnancies, following the diabetes and condition of obesity incidence in the general population closely. [2] It has been found that in 2016, in the United States around 6% of the total pregnancies were convoluted by gestational diabetes. [3] In accordance with Diabetes in Pregnancy Study Group of India (DIPSI), the diagnosis of GDM is made by a single step test with the use of 75 g of glucose, by using oral glucose tolerance test, not based on intake of the last meal with a value of threshold of blood sugar levels at 2 h being >140 mg/dl. [4]The intrauterine exposure to a high maternal blood glucose level causes a considerable increase in the secretion of insulin in pancreas of fetus, thus causing fetal hyperinsulinemia. This leads to rise in glucose and fat storage thus making the fetus larger in size than the normal, it also raises the oxygen demand, causing hypoxemia. The heart of fetus is one of the main organs being affected by hypoxemia and hyperinsulinemia. [5]GDM also causes an atypical environment, thus affecting the structure and function of heart of fetus. The hypertrophic cardiomyopathy (which is more common during the 3rd trimester mainly affect the Interventricular septum), congenital heart anomalies (Transposition of the Great Arteries (TGA) and Septal defects), effusion of pericardium and Persistent Truncus Arteriosus (PTA) are the main linked cardiac disorders present in fetuses of mothers who are diabetic. The hyperinsulinemia in fetus has been reported as a reason of myocardial hypertrophy in fetus having impaired function of heart, mainly during diastole, being the result of lowered distensibility of left ventricle and alteration in dynamics of left atrium secondary to hypertrophy of myocardium.[6]

The fetal echocardiography is one of the main non-invasive methods used for evaluation of cardiac anomalies of fetus *in utero* and also for assessment of myocardial performance in fetus. The advancement in techniques of high-resolution echocardiography, Doppler (Pulse wave Doppler (PWD) and Tissue Doppler imaging (TDI)) have made the understanding of function of fetal heart better.[7] PW Doppler is used to assess the diastolic flow across the atrioventricular (AV) valve. The E/A ratio is defined to assess the diastolic function of ventricle that is generally influenced by different loading conditions.[8] Various studies have evaluated the utility of TDI, allowing the direct assessment of the longitudinal motion velocity of the mitral and tricuspid annulus. TDI is not dependent upon the loading conditions.[9] The E/Ea ratio is observed to be one of the main echocardiographic parameters which is applied mainly to evaluate the diastolic function of ventricles of fetus. Dual-gate Doppler (DD) method also helps to determine the E/Ea

at the similar heartbeat, thus showing the flow of blood as well as the wave form of TDI in real time. [10]Speckle-tracking echocardiography is emerged recently as a quantitative ultrasound method to evaluate the function of myocardium accurately by assessing the speckle's motion being recognized on regular 2-dimensional sonograms. It also gives the angle-independent, non-Doppler, and objective calculation of deformation of myocardium as well as the systolic and diastolic dynamics of left ventricle. By evaluating the dislocation of the speckles while cardiac cycle, strain and rate of strain is measured quickly offline after a proper acquisition of image.[11] The data in relation to the accuracy, feasibility, and clinical uses of speckle-tracking echocardiography are quickly advancing.

2. Literature Survey

Various studies have been performed demonstrating cardiac dysfunction in fetuses born to diabetic pregnant females. **Mrudhula Tejaswi G et al**[12] studied cardiac changes in fetus of diabetic mothers and non-diabetic controls from 24 gestation weeks till the period of neonates; showing correlation with glycemic control of mother; investigate implications on perinatal or neonatal adverse outcome. A significant hypertrophy of myocardium is observed among fetuses of diabeticmother's vs controls, most rigorous among the poorly controlled diabetics. Changes in structure seen in the neonate. The dysfunction of myocardium cannot be seen in the neonates. Myocardial hypertrophy was a surrogate marker for suboptimal glycemic control, and can be predicted for neonatal morbidities like hyperbilirubinemia, hypoglycemia, long term NICU stays, and fetal persistent cardiac shunts. They revealed a noteworthy correlation between maternal glycemic control and fetal myocardial hypertrophy among GDM pregnancies. There is a link between adverse perinatal events including hypoglycemia and fetal myocardial hypertrophy. Newborns were not seen to have relevant cardiac comorbidities clinically even when there was important septal hypertrophy in utero.

Raafat M et al[13] did fetal cardiac function analysis providing important hemodynamic status information and adaptation of heart to various perinatal complications. The study found that prenatal echocardiographic study needs to be done in fetuses of diabetic mothers because of high congenital heart defects risk and risk of hypertrophic cardiomyopathy onset with cardiac function impairment in fetus at the third trimester.

Ghaderian M et al[14] assessed the studies on changes in functions of heart of fetuses of mothers with diabetes with more focus on hypertrophic cardiomyopathy occurrence. All of the comparative studies assessing the changes in cardiac parameters quantitatively using echocardiography were included for assessment. Fetal echocardiography revealed a lower mitral E/A ratio significantly, decreased tricuspid E/A ratio, increased thickness of interventricular septum, raised myocardial performance index, increased isovolumic time of relaxation, and raised isovolumic contraction time in fetuses of GDM group in comparison to the healthy group. The GDM presence affects the fetal cardiac parameters potentially mainly as hypertrophic cardiomyopathy causing both systolic and diastolic cardiac dysfunction.Similarly **Darwish et al 2022**[15]**, Atiq M et al 2017**[8]**, Sanhal CY et al 2017** [16] found out similar results regarding fetal cardiac structure and systolic and diastolic function relationship with maternal diabetes.

Qingsha Hou et al.[17]conducted a cross sectional study in 2021 in which he found out that there was decreased in mitral E/A ratio in GDM patients. He found out that E/Ea ratio which correspond to ventricular filling pressure was significantly lower in GDM patients as compared to controls independent of glycemic control. He also found out Ea wave increases progressively faster than E-wave, thus E/Ea ratio decreases with an increasing GA and levels out in the early third trimester.

3. Material and Methods

This observational cross-sectional study was conducted between November 2020 and November 2022. It was conducted in the Department of Obstetrics and Gynecology in collaboration with Pediatric Cardiology Unit (PCE-CS) Unit and Rajiv Gandhi Centre for Diabetes and Endocrinology of Jawaharlal Nehru Medical College and Hospital, AMU, Aligarh after taking approval from Institutional Ethics Committee. It included 150 women with singleton pregnancy between 20-40 weeks of gestation presenting to JNMCH in OPD or IPD. Gestational age was measured by First trimester scan (preferably) or LMP (in case scan unavailable). Out of which 100 women were hyperglycemic and 50 were uncomplicated pregnancies. And among 100 hyperglycemic patients, 75 were controlled on treatment and 25 were uncontrolled on treatment (Diet or Insulin).Diagnosis of hyperglycemia in pregnancy, in accordance with Diabetes in Pregnancy Study Group of India (DIPSI), was made by a single step test with the use of 75 g of glucose, by using oral glucose stress test, irrespective of intake of the last meal with threshold of blood glucose levels at 2 h being >140 mg/dl.Criteria For Controlled Diabetes was fasting glucose <95mg/dl ,1 hr. postprandial glucose <140mg/dl,2 hr. postprandial glucose <120mg/dl and HbA1c level <6%. Exclusion criteria for the women were refusalto give informed written consent, women with major structural and chromosomal fetal abnormalities, maternal chronic disease like chronic hypertension on medication, renal disease, liver disease, hematological disease, Connective tissue disorder like SLE, multiple pregnancy, pre-eclampsia and pregnancy conceived by ART. After taking history and examination, all women underwent 2-D conventional fetal echocardiography, Pulse Wave Doppler (PWD), Tissue Doppler Imaging (TDI). Data were acquired and recorded during the course of each scan.

Imaging Protocol

Fetal echocardiography was performed on **GE vivid E95** machine using cardiac probe. Standard M mode, 2D and doppler echocardiography evaluation was performed in all patients.M mode measurements include Interventricular septal thickness, and ejection fraction. Under maternal voluntary suspended respiration without fetal movement or fetal breathing movement interventricular thickness was measured in transverse four chamber view with the cursor perpendicular to the IVS. Measurement was taken in

triplicate at the middle of IVS at end-diastolic phase using cine loop. The average of three measurements was used for analysis. Ejection fraction (EF) was measured as end diastolic ventricular internal dimension (EDVID)–end systolic ventricular internal dimension (ESVID)/EDVID. The transducer ultrasound beam was maintained at an angle $<20^0$to the direction of blood flow.Pulse wave doppler measured diastolic flow across mitral and tricuspid valves. Itmeasured E wave velocity which represent early passive diastolic flow caused by ventricular relaxation, A wave velocity which represent late active ventricular filling caused by atrial contraction during late diastole and E/A ratio. Reduced E/A ratio is hallmark of diastolic dysfunction. Tissue doppler imaging measured the velocity of longitudinal motion of mitral annulus, tricuspid annulus, and basal part of interventricular septum. Ea and Aa wave were measured. Ea WAVE reflect ventricular relaxation (elongation) Ea wave is earliest marker of diastolic dysfunction and decreases with decreasing longitudinal lengthening. **E/Ea ratio** is calculated by dividing peak E wave velocity by peak Ea velocity. Left ventricular end diastolic pressure (LVEDP) can be estimated by this. Diastolic dysfunction leads to larger E/Ea ratio.

4. Statistical Analysis

Data was compiled on IBM SPSS version 26 and it was subjected to statistical analysis with the help of same. Qualitative data was reported as frequency and percentage, while quantitative variables was reported as mean ±standard deviation or median (inter quartile range) according to normalcy of data. Statistical comparison among groups was performed using independent sample t test for quantitative variables. Pearson chi square test was used for qualitative analysis of data. Graphs were made with the help of Microsoft world 2016. $p < 0.05$ was considered to be statistically significant.

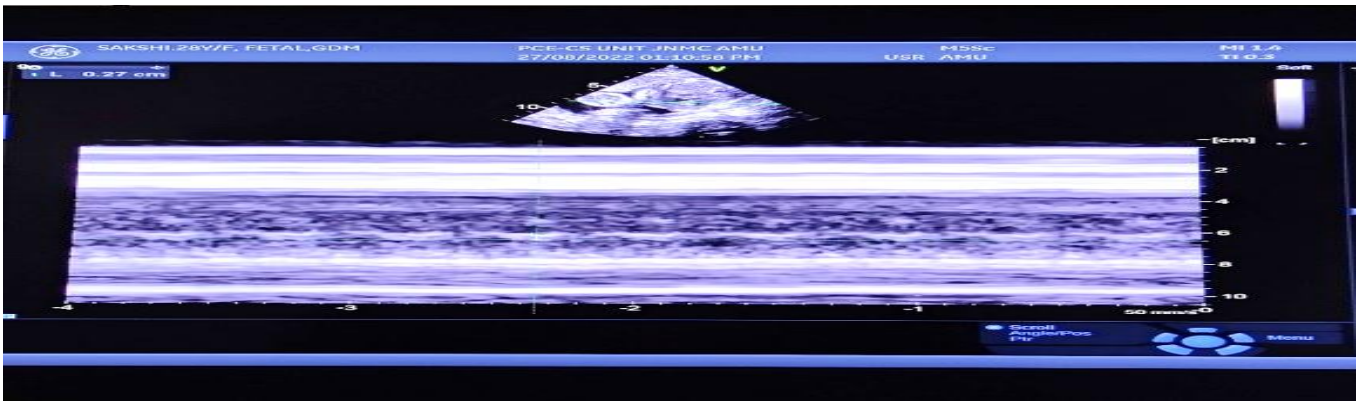

Figure 1: Fetal cardiacIVS thickness on M Mode Imaging

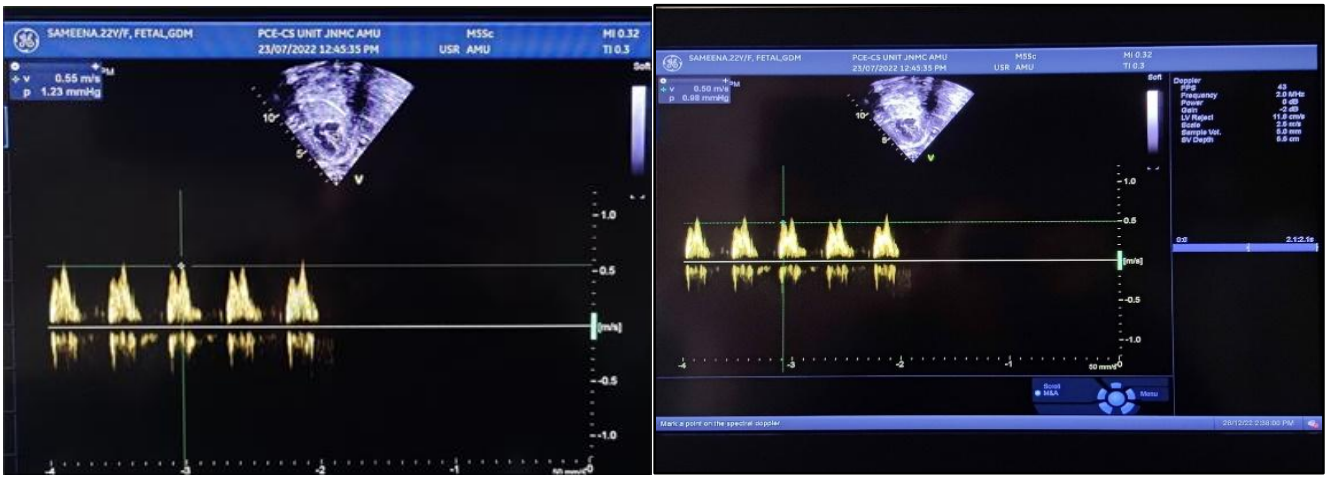

Figure 2: Pulse Wave Doppler Imaging E and A wave velocity

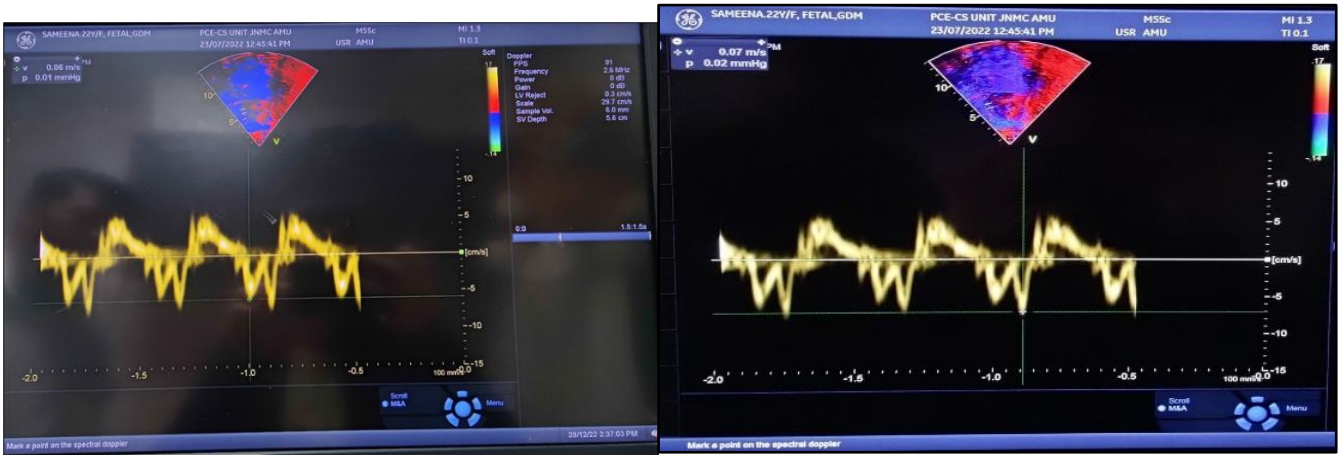

Figure 3: Tissue Wave doppler imaging Ea and Aa velocity

5. Results and Observations

Fetal echocardiography was performed in all the 150 patients and fetal cardiac parameters were recorded as M Mode imaging (IVS thickness, Ejection fraction), Pulse Wave Doppler (Mitral and Tricuspid E velocity, A velocity and E/A ratio) , Tissue Wave Doppler (Mitral and Tricuspid Ea value , Aa value and Ea/Aa ratio), Dual Gate Doppler (Right and left sided E/Ea ratio).These parameters were expressed as Mean ± SD. All these parameters were compared between 2 groups (Normal pregnant females vs pregnant females with hyperglycemia, between controlled and uncontrolled DM on treatment (Diet or Insulin).

Demographic characteristics of my patients

Table 1 shows demographic and obstetric characteristics of patients. Mean maternal age of patients was 25.98 ± 4.31 among normal pregnant females and 27.52 ± 4.29 among hyperglycemics. The mean (±standard deviation) gestational age at the time of examination in fetuses of gestational diabetic mothers was 31.62 ± 3.74 weeks and in fetuses of the control group was 32.7 ± 3.21.Among 150 patients, 100 were having hyperglycemia (GDM or OvertDM) and 50 were normal pregnant females. In 100 diabetic females, 80 have good glycemic control and 20 have diabetes uncontrolled on treatment.

Comparison of fetal echocardiographic variables between groups

Table 2 shows comparison of variables between pregnant females with hyperglycemia with normal pregnant females. Most of the variables are statistically significant. Fetal cardiac structural index measured as interventricular septal thickness during diastole (IVSD) was significantly increased in hyperglycemic pregnant females (0.41 ± 0.06) as compared to normal pregnant females without hyperglycemia (0.29 ± 0.04) (p value 0.001).Fetal cardiac systolic function as indicated by ejection fraction (EF) was significantly increased (P < 0.05) in the presence of hyperglycemia. Fetal diastolic function pulse wave doppler parameter as indicated by E/A ratio was significantly decreased in diabetic pregnant females (p >0.05). Also, other diastolic function parameters, Ea and Ea/Aa ratio, on tissue wave doppler were significantly decreased in diabetic pregnant females as compared to controls (p < 0.05). Low Ea value indicates impaired myocardial relaxation and hence diastolic dysfunction. In addition, another diastolic function parameter E/Ea ratio which is indicator of left ventricular end diastolic pressure was increased in hyperglycemic (9.81 ± 1.71) as compared to controls (9.00 ± 1.97) (p <0.05). This indicates diastolic dysfunction in presence of hyperglycemia.

Variables were also compared between controlled and uncontrolled GDM as shown in **Table 3**. There was no significant difference in IVSD between two groups. But fetal cardiac functional indices, E/A ratio and Ea were significantly lower in pregnancies with uncontrolled DM indicating diastolic dysfunction. E/Ea ratio was also increased in uncontrolled DM patients on right side. Hence fetal cardiac diastolic dysfunction in hyperglycemic pregnant females is dependent on glycemic control of the patient. Ejection fraction which is indicator of fetal cardiac systolic function was decreased in uncontrolled DM group as compared to patients with good glycemic control.

Table 1: Demographic characteristics of groups

Characteristics	Hyperglycemia (Mean ± SD)		p value
	Present (n=100)	Absent (n=50)	
Maternal age	27.52±4.29	25.98±4.31	0.84
Parity	1.40±1.17	1.00±1.10	0.09
BMI	25.97± 3.28	22.77 ± 3.46	0.14
Gestational age at time of fetal echo	31.62 ± 3.74	32.7 ± 3.21	0.30

Table 2: Comparison of Fetal Echocardiographic variables between Hyperglycemic and Normal pregnant females

	Hyperglycemia (Mean±SD)		t value	p value
M MODE	Present (n=100)	Absent (n=50)		
IVS thickness (mm)	0.41 ± 0.06	0.29 ± 0.04	0.011	0.001
EF(%)	59.26 ± 5.55	52.68 ± 5.34	1.81	0.02
Pulse Wave Doppler				
M-E(cm/s)	36.81 ± 7	43.44 ± 9	0.997	0.03
M-A(cm/s)	53.74 ± 8	55.38 ± 8	1.718	**0.07**
M-E/A	0.65 ± 0.09	0.78 ± 0.14	0.110	0.05
T-E(cm/s)	37.50 ± 7	43.76 ± 9	0.178	0.02
T-A(cm/s)	55.08 ± 9	57.18 ± 9	1.88	**0.08**
T-E/A	0.65 ± 0.09	0.76 ± 0.10	0.101	0.05
Tissue Wave Doppler				
LV-Ea(m/s)	0.03 9 ± 0.000	0.049 ± 0.009	0.866	0.01
LV-Aa(m/s)	0.066 ± 0.014	0.060 ± 0.014	1.771	**0.09**
LV-Ea/Aa	0.609 ± 0.10	0.849 ± 0.25	1.610	0.02
RV-Ea(m/s)	0.042 ± 0.003	0.050 ± 0.008	0.990	0.01
RV-Aa(m/s)	0.067 ± 0.01	0.063 ± 0.017	1.718	**0.05**
RV-Ea/Aa	0.653 ± 0.22	0.839 ± 0.28	1.551	0.01
RV-E/Ea	9.30 ± 1.22	9.01 ± 2.49	1.001	**0.05**
LV-E/Ea	9.81 ± 1.71	9.00 ± 1.97	0.810	0.01

Table 3: Comparison of Fetal Echocardiographic variables between Controlled and Uncontrolled GDM patients

	(Mean±SD)		t value	p value
M MODE	Controlled GDM (n=80)	Uncontrolled GDM (n=20)		
IVS thickness (mm)	0.402	0.403	1.66	0.06
EF (%)	57.44 ± 5.80	56.09 ± 7.45	0.99	0.01
Pulse Wave Doppler				
M-E/A	0.70 ± 0.08	0.67 ± 0.08	1.229	0.04
T-E/A	0.69 ± 0.07	0.66 ± 0.09	1.119	0.06
Tissue Wave Doppler				
LV-Ea(m/s)	0.040 ± 0.009	0.039 ± 0.010	0.289	0.02
RV-Ea(m/s)	0.044 ± 0.010	0.038 ± 0.010	0.188	0.03
LV-E/Ea	9.58 ± 2.77	9.93 ± 3.22	1.719	0.06
RV-E/Ea	9.01 ± 3.01	10.09 ± 3.52	1.176	0.002

6. Discussion

Fetuses of diabetic mothers are at increased risk of structural and functional cardiac dysfunction leading to significant perinatal morbidity and mortality. Fetal hyperglycemia and hyperinsulinism lead to myocardial hypertrophy which is a frequent finding in the fetuses of diabetic mothers. It may lead to increased ventricular stiffness thereby affecting diastolic ventricular filling as well as systolic cardiac function[18, 19].The advancement in techniques of high-resolution echocardiography, Doppler (Pulse wave Doppler (PW Doppler) and Tissue Doppler imaging (TDI)) investigation of heart of fetus have made the understanding of function of fetal heart better.[7]

This study demonstrated that fetal cardiac interventricular septal thickness is greater in patients with hyperglycemia (either GDM or OvertDM) as compared to normal pregnant females without hyperglycemia. This increase was independent of glycemic control of the patient. Similarly,**Raafat M et al. [13]** and **Darwish A et al.[15]** in their study confirm these findings. Fetal cardiac ejection fraction was found to be increased in hyperglycemicas compared to controls in our study. In accordance with our study, **Ren Y et al. [20]** found that fetal cardiac systolic function as revealed by EF, did not show any change during normal pregnancy, but was increased significantly ($P < 0.001$) in the GDM presence independently of glycemic control in mothers. In contrary to our study, **Al Wakeel M et al[21]** conducted a cross-sectional study in which he assessed the function and structure of heart in fetuses of gestational and pre-gestational mothers suffering with diabetes as compared to healthy mothers using fetal echocardiography. He found out that LV systolic function did not differ between 2 groups. **Atiq M et al.[8]** in his study found out that fetal cardiac systolic function was significantly less in the diabetic group (p = 0.01) which was independent of glycemic control.

We have also demonstrated decreased fetal ventricular diastolic function parameters using pulse wave doppler and tissue wave doppler indices i.e., E/A ratio and Ea in diabetic pregnant females. This may be due to decreased left ventricular compliance, contractility, or ventricular wall thickness. Another parameter of diastolic dysfunction i.e. E/Ea ratio was also found to be increased in diabetics suggesting increased left ventricular end diastolic pressure. Fetal cardiac diastolic dysfunction was dependent on glycemic control of the patient. TDI is a potential tool for fetal cardiac diastolic functional evaluation which is relatively independent of heart rate and heart load. Similarly, **Darwish A et al. [15]** in his study found that there was a significant decrease in mitral E/A ratio, mitral E, peak aortic velocity (PAV), ventricular filling time (VFT) and ventricular ejection time (VET) in the Diabetic group as compared to the patients of normal control group (p value < 0.05). These results were in accordance with previous studies by **Atiq M et al.[8] and Sanhal CY et al.[16]**There is lack of studies comparing E/Ea ratio. **Qingsha**

Hou et al.[17] in 2021 in his study found out that there was decreased in mitral E/A ratio andin contrary to our study, he found out that E/Ea ratio which correspond to ventricular filling pressure was significantly lower in GDM patients as compared to controls independent of glycemic control. He also found out Ea wave increases progressively faster than E-wave, thus E/Ea ratio decreases with an increasing GA and levels out in the early third trimester.

7. Conclusion

We concluded that fetuses of diabetic mothers are at increased risk of structural and functional heart diseases which is related to glycemic status of the patient. So, we emphasized that in order to fully comprehend the effect of maternal hyperglycemia on fetal cardiac development and function, current routine evaluation of fetal structural heart abnormalities may not be sufficient. Functional impairment is detected by fetal echocardiographic pulsed wave doppler, tissue wave doppler and dual gate doppler imaging. It should be further evaluated in relation to direct perinatal outcome and long-term offspring cardiovascular health. Although diabetes in mothers is clearly linked with a raised cardiovascular disease risk in neonates, but studies assessing the fetal cardiac health in relation to the long-term outcomes are deficient. Our study findings support the need for further longitudinal studies strongly that aimed at explaining the reasonable link between fetal cardiac function in utero and maternal diabetes in relation to clinical outcomes and development of offspring.

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