

## Cardiac Malformations in Fetuses of Gestational and Pre Gestational Diabetic Mothers

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### Abstract

**Objective:** In this study we aimed to determine the prevalence of cardiac malformations in fetuses of Iranian diabetic mothers with pre-gestational and gestational diabetes mellitus (GDM) and to find the patterns of different cardiac malformations.

**Methods:** One-hundred and seventy diabetic pregnant women (68 preGDM and 102 GDM) (mean age: 32.17±4.8 years) and 85 healthy controls (mean age: 31.35±4.55 years) were recruited from September 2008 to July 2012. Fetal echocardiography was performed to assess cardiac malformation. In order to study major factors that may affect the results, a complete history was obtained.

**Findings:** Fetal echocardiography was performed at mean gestational age of 24.7±5.4 and 20.27±3.9 weeks in diabetic patients and control group, respectively. Fifteen (8.8%) fetuses of diabetic mothers were detected to have cardiac malformations compared with 1 (1.17%) fetus in control group (OR: 8.13, 95%CI: 1.1-62.61, P-value=0.02). Hypertrophic cardiomyopathy noted as the most common cardiac malformation occurred in 6 out of 15 (40%) fetuses, and was found significantly more common in pre-GDM compared to GDM group (7.4% vs 1%, P-value =0.04). Despite the higher incidence of cardiac malformation in pre-GDM compared to GDM group, the difference was not significant. Further, no significant association was observed between the variables including; parity, diabetic regimen, parents' consanguinity, maternal history of hypertension or hypothyroidism and occurring cardiac malformations (P-value >0.05).

**Conclusion:** In this study we detected cardiac malformations in 8.8% of our diabetic referrals. The result of the present study shows that screening diabetic mothers for fetal cardiac malformations could be beneficial.

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**Key Words:** Congenital Heart Disease; Diabetes Mellitus; Gestational Diabetes Mellitus

### Introduction

Pre-gestational diabetes mellitus (Pre GDM) is not an uncommon condition in pregnancy and occurs in nearly 0.5% of the pregnant population<sup>[1]</sup>. Prevalence of gestational diabetes mellitus (GDM) in Iranian pregnant women

according to national diabetes data group (NDDG) criteria is 4.5 %<sup>[2]</sup>.

Due to the teratogenic effect of maternal diabetes<sup>[4,5]</sup>, the reported incidence of congenital malformations among the newborns of diabetic mothers is five times greater than that of the general population<sup>[3,4,18]</sup>. Cardiac malformations

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are one of the most common types of these malformations which occur in about 8.5% of cases that is about 10 times more than its incidence in normal population (0.8%)<sup>[4,6,7]</sup>.

The most common heart malformations in fetuses of diabetic mothers include: ventricular septal defect, transposition of great arteries, aortic stenosis, pulmonary atresia, dextrocardia, and conotruncal defects (tetralogy of Fallot, truncus arteriosus and double outlet right ventricle)<sup>[1,4,8-10]</sup>.

Despite good glycemic control, hyperinsulinism and fetal hyperglycemia can cause hypertrophic cardiomyopathy, which is the most common congenital abnormality of the heart in the infants of diabetic mothers and is found in 30% of cases, 13% of which are asymptomatic<sup>[10]</sup>. Despite the aforementioned asymptomatic complications and the availability of diagnostic methods and palliative surgery postnatally, there was no study in Iran to assess the prevalence and incidence of congenital heart disease in fetuses of diabetic mothers. Delivery of newborns with cardiovascular abnormalities is associated with a high level of risk for the newborn. With identification of such a case, the physician and the parents have the opportunity to lower the risk by providing the necessary facilities in a timely manner. Regarding the relative expensiveness of screening methods in our country (performing fetal echocardiography as a part of routine prenatal care in diabetic mothers), evaluation of the cost-effectiveness of the methods is contingent upon the prevalence and incidence of the abnormalities in comparison with the normal population. As there is no statistical picture of the problem in Iran, in this study we aimed to determine the prevalence of cardiac malformations in fetuses of Iranian diabetic mothers with pre-existing and gestational diabetes and to find the pattern of cardiac malformations.

## Subjects and Methods

After approval of the study protocol by the institutional review board and ethics committee of Tehran University of Medical Sciences (TUMS),

this case-control study was performed on 170 patients with maternal diabetes (case group) (mean age: 32.17±4.8 years, range 20 to 42 years) who referred to Rajaie Cardiovascular Medical & Research Center in order to perform fetal echocardiography from September 2008 to September 2012. Eighty-five age-matched healthy pregnant women (mean age: 31.35±4.55, range 21 to 41 years) with no risk factor were recruited as control group.

Patients with family history of congenital heart disease, eclampsia, phenylketonuria and history of exposure to cardiac teratogens (radiation, intrauterine infection, CMV, rubella, drugs, alcohol, warfarin) were excluded from the study. The diagnosis of GDM and pre GDM was based on the patient's medical history. The gestational age of the pregnant women ranged from 16 weeks to term.

In order to study major factors that may affect the results, a complete history including maternal age, number of pregnancies, method of diabetes control, history of teratogen exposure, chronic diseases, acute febrile diseases in pregnancy were obtained.

A cardiac anatomy survey was assessed using fetal echocardiography utilizing VIVID-3 echocardiography device with convex probe and the frequency of 5.7 MHz by an experienced pediatric cardiologist. In the case of inappropriate quality of obtained images, the echocardiography was performed for the second time.

Continuous variables are expressed as mean±SD and categorical data as number (%). Comparison of categorical variables in case and control group were assessed by using chi square( $\chi^2$ ) or Fisher's exact tests; and continuous variables by Mann-Whitney U test. A value of  $P<0.05$  was considered statistically significant. Data were analyzed by SPSS version 16 software.

## Findings

Diabetic pregnant women were classified into two subgroups: 68 (40%) which had diabetes before their pregnancy (pre-GDM group) and 102 (60%) patients with gestational diabetes mellitus (GDM group). Fetal echocardiography was performed at

mean gestational age of 24.7±5.4 (range 17 to 38) weeks and 20.27± 3.9 (range 16 to 33) weeks in patients and control group, respectively.

The cardiac malformations were detected in 1 (1.17%) fetus of non-diabetic mothers compared with 15 (8.8%) fetuses of diabetic mothers (OR: 8.13, 95%CI: 1.1-62.61,  $P$ -value=0.02); of which 7 (46.6%) were born to pre-GDM mothers and 8 (53.4%) to GDM mothers with no significant difference ( $P$ =0.3).

The frequency and patterns of different cardiac malformations in fetuses of diabetic mothers were as follows: 6 cases of hypertrophic cardiomyopathy (HCMP); 2 cases of ventricular septal defect (VSD). Tetralogy of Fallot (TOF); truncus arteriosus (TA); dextrocardia; severe mitral and aortic stenosis (MS, AS); pulmonary atresia with myxomatous tricuspid valve with severe tricuspid regurgitation (PA-TR); transposition of the great arteries (TGA); double inlet left ventricle (DILV), each found in 1 fetus. Hypoplastic left heart syndrome (HLHS) was detected in a fetus of non diabetic mother in control group.

The most common cardiac malformation was HCMP noted in 6 (3.5%) of fetuses, which was found significantly more common in pre-GDM compared to GDM group (7.4% vs. 1%,  $P$ =0.04). None of the mothers of 15 fetuses with congenital heart disease had history of acute febrile disease in the first trimester. There was also no significant association in maternal age and parity in detecting cardiac malformation. However, no significant association was observed between diabetic regimen, parents' consanguinity, maternal history of hypertension or hypothyroidism and congenital heart disease (Table 1) ( $P$ >0.05).

## Discussion

The results of present study on increased risk of cardiac malformations in fetuses of diabetic mothers is concordance with other studies<sup>[3,4,10,11]</sup>. Loffredo et al, demonstrated epidemiological evidences that maternal diabetes may affect the early development of the heart including major cardiovascular and atrioventricular anomalies, defects of the cardiac outflow and atrioventricular valves<sup>[11]</sup>. A review reported by Lisowksi et al, indicated an increased incidence of complete transposition of the great arteries (TGA), persistent truncus arteriosus (PTA), visceral heterotaxia, and single ventricle (SV) variants compared to nondiabetic population, suggesting that cardiac malformations may occur at early stages in heart development<sup>[3]</sup>.

Among the factors that may affect the prevalence and severity of cardiac malformation in fetuses of diabetic mothers, poorly controlled diabetic pregnancy has been associated with poorer cardiac function<sup>[3,4,6,7,12]</sup>. As pre-conceptual maternal glycated hemoglobin is increased cardiac function is reduced<sup>[13]</sup>.

Studies have reported impaired ventricular function even while the mothers had been appropriately controlled for diabetes<sup>[3,11]</sup>. Lisowks et al reported increased congenital heart disease (CHD) even with slightly elevated HbA1c in their study, therefore they concluded that near-normoglycemia is not good enough<sup>[15]</sup>. In addition a significant increased incidence of congenital malformations reported among neonates of women with type 1 diabetes despite a good glycemic control and folic acid supplementation

**Table 1:** Association between the maternal variables and congenital heart malformation in study participants

Variable		Total n (%)	Malformation		P. value
			Yes	No	
Diabetes Mellitus	PreGDM	68 (40)	7 (10.3)	95 (89.7)	0.3
	GDM	102 (60)	8 (7.8)	61 (92.2)	
Regimen	Dietary	53 (31.2)	4 (7.5)	49 (92.5)	0.9
	Insulin	117 (68.8)	11 (9.4)	107 (90.6)	
Parents Consanguinity	Yes	38 (26.5)	3 (7.9)	35 (92.1)	0.7
	No	128 (77.1)	10 (7.8)	118 (92.2)	
Hypertension	Yes	14 (8.3)	2 (14.3)	12 (85.7)	0.3
	No	155 (91.7)	12 (7.7)	143 (92.3)	
Hypothyroidism	Yes	29 (17.1)	3 (10.3)	26 (89.7)	0.2
	No	141 (82.9)	12 (8.5)	129 (91.5)	

GDM: gestational diabetes mellitus

intake before and during pregnancy (70% of women had an HbA1c <7%)<sup>[3]</sup>.

On the other hand, particular abnormalities seem to be related to the mothers glycemic control before and during pregnancy<sup>[7,11,14]</sup>. Fetal myocardial hypertrophy, reported in about 25-30% of cases as a complication of gestational or previous maternal diabetes, was associated with an increased level of insulin growth factor-1<sup>[13]</sup>.

In our study 170 diabetic pregnant mothers and 86 healthy controls underwent fetal echocardiography, a complete history of related factors was taken and analyzed, so we were able to eliminate additional factors that may increase risk of malformations other than maternal diabetes. Cardiac malformations were detected in 15 of the 170 (8.8%) fetuses. Previous report by Meyer-Wittkopft et al, has reported an incidence of CHD in 3.2 to 6.9% of infants of diabetic mothers<sup>[15]</sup>. Other studies showed an incidence of 8.5 % of cardiac malformations in fetuses of diabetic pregnancies<sup>[3]</sup>.

In this study, HCMP noted as the most common cardiac malformation occurred in 40% of cases, found more common in fetuses of pre GDM group compared GDM. Wren et al concluded that cardiac malformations such as transposition of the great arteries, truncus arteriosus, and tricuspid atresia, are at least 15 times more prevalent than in offspring of non-diabetic pregnancies<sup>[4]</sup>.

Some studies suggest that gestational diabetes may be a risk factor for heart defects, but there are still controversies about the extent of such association and whether it was driven by pregestational diabetes uncovered by or diagnosed during pregnancy or not<sup>[16]</sup>.

In the present study, despite the higher prevalence of cardiac malformation in both pre-GDM and GDM group than in controls, no significant differences was observed between these diabetes groups. Moreover the incidence of HCMP was significantly higher in pre-GDM compared to GDM. The data base of descriptive variables on cases in our study was used to assess whether maternal diabetes accounted as basic risk of cardiac malformation or other risk factors were associated with the disease. Analyses of maternal factors such as maternal age, history of hypertension, hypothyroidism, and acute febrile disease in pregnancy, revealed no effect modification of the diabetes association.

The ascertainment of diabetes by self-report, the historical classification of pre-conceptual and gestational diabetes and the lack of some data in patients' files were the limitations in our study. However, most patients had a documented history from their family physicians or gynecologists.

Fetal echocardiography has a sensitivity of 90% and a specificity of 99.7% and has a positive predictive value (PPV) of 90%<sup>[4,5,15]</sup>. It is also an adequate and non invasive method in order to detect cardiac malformations in fetuses<sup>[5]</sup>. Necessary equipments in order to detect most cases of major CHD and some cases of minor CHD prenatally, are available. Early detection of these cases during pregnancy gives us options and saves time.

Diabetic mothers and their newborns specially the ones with major cardiac malformations may encounter difficulties while giving birth, and would probably need to be referred to a specialized care center<sup>[17]</sup>. Based on high prevalence of complicated cases, selective screening of high risk fetuses seems to be useful.

## Conclusion

Fetal cardiac malformations were detected in 8.8% of mothers with diabetes mellitus in our study. The result of present study shows that screening diabetic mothers for fetal cardiac malformations in our country could be beneficial.

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**Conflict of Interest:** None

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