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Cardiovascular Complications in Infants of Diabetic Mothers: An Observational Study in a Pediatric Cardiology Clinic in Tehran

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ABSTRACT

Background: Despite improvements in medical care provided during pregnancy to diabetic mothers, the cardiac complications in their infants are still more frequent than in the infants of general population.
Objectives: The primary objective of this study was to explore the spectrum of cardiovascular complications in infants of diabetic mothers (IDMs). The study was also aimed at investigating probable relations between infants' heart lesions, the type of maternal diabetes, and the neonatal somatic data.
Patients and Methods: Between July 2010 to June 2011, two-dimensional/M-mode and Doppler echocardiography evaluations were performed in IDMs at the out-patient clinic of the pediatric cardiology ward of a University hospital in Tehran.
Results: A total of 32 IDMs (18 male and14 female) were studied. Congenital heart disease (CHD) was found in 6 (18.7%) neonates and 3 of them suffered from conotruncal malformations. Hypertrophic cardiomyopathy (HCM) was observed in 15(46.9%) cases. There were 22 (68.8%) large for gestational age (LGA) infants. Gestational diabetes was found in 21(65.6%) mothers. We did not find a significant relation between the types of maternal diabetes and the frequency of CHD (P = 0.9), and the frequency of HCM in their infants (P = 0.9). Also a significant relation could not be found between LGA and the rate of CHD (P = 0.6) or the rate of HCM (P = 0.4).
Conclusions: Our data showed a high prevalence of CHD in IDMs in our pediatric cardiology clinic. Neither the types of maternal diabetes nor the somatic findings of newborns were related to the occurrence of cardiac complications.

Keywords: Cardiomyopathy; Heart Disease; Newborn

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Implication for health policy/practice/research/medical education:
This paper shows the relationship between maternal diabetes as a risk factor and neonatal congenital heart disease (CHD) as an outcome.

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1. Background

The incidence of cardiac anomalies is 3-6% in offsprings of diabetic mothers. It is five times higher than in normal pregnancies and commonly includes complex lesions (1, 2). Conotruncal abnormalities such as transposition of great arteries (TGA), tricuspid atresia, and truncus arteriosus are reported more frequently. The frequency of TGA in live born babies of mothers with pre-existing diabetes is 17 times more than that in normal population (3). The closure of ductus arteriosus and postnatal decrease in pulmonary artery pressure are delayed in IDMs when compared with control infants during the first days of life (4, 5). Better glycemic control of diabetic mothers is associated with lower occurrence of fetal heart disease but not necessarily with the lower development of fetal myocardial hypertrophy (6).

HCM occurs even in fetuses of well controlled diabetic mothers without relation to the type of maternal diabetes or to maternal glucose metabolism (7). Pildes gave an HCM incidence rate of 30% in offsprings of type 1 diabetic mothers, but prevalence in type 2 and gestational diabetes pregnancies is less recognized (8). Diabetic cardiomyopathy is often a self-limiting problem with no clinical consequence and is not recognized as a structural malformation of the heart. This transient phenomenon usually regresses within the first few months of life (3).

The association of maternal diabetes mellitus and congenital malformations is well established. Certain anomalies are reported with higher frequencies, such as cardiovascular, skeletal, and genitourinary defects. The risk of child's malformation in IDMs is three to four times greater than in infants of non-diabetic mothers (9). While there is no doubt about the teratogenecity of pregestational diabetes, the association of gestational diabetes and fetal malformations is still under discussion (9).

Infants of diabetic mothers are prone to be large for gestational age (LGA) because of their characteristic fetal metabolic abnormalities such as hyperglycemia and hyper insulinemia. The rate of preterm labor is higher in diabetic mothers.

2. Objectives

We have conducted this study to assess the frequency of heart defects and HCM in a group of Iranian IDMs. In addition we made a comparison between echocardiographic findings of LGA and non-LGA infants, as well as infants of pre-gestational diabetic mothers with infants of gestational diabetic mothers.

3. Patients and Methods

This is a cross sectional descriptive study. It evaluated the IDMs passing through the out-patient clinic of the pediatric cardiology ward at a university hospital in Tehran during a period of one year (2010-2011). Offspring of mothers with confirmed diagnosis of diabetes mellitus were included in the study. Thirty-two IDMs were examined during the mentioned period. All the babies were in the first 10 days of life. At first, a data sheet was completed for each infant and the following pieces of information were collected from the patients' medical records: birth weight, gestational age, neonatal blood glucose level in the first day of life, extra cardiac malformation, maternal name and age, type of maternal diabetes, type of delivery, and maternal blood glucose level. Then all the infants underwent a thorough physical examination with special attention to cardiovascular system. Physical examination was performed by one pediatric cardiologist. After physical examination, echocardiography was performed for all cases using a "system five Vingmed scanner" with a 5 MHz transducer. Left ventricular fractional shortening and ejection fraction were measured using a standard method for M-mode echocardiography taken from the parasternal long-axis view. HCM was diagnosed when the absolute values of inter ventricular septum and left ventricular posterior wall diameters were above normal ranges, and in addition, the ratio of left ventricular septum in diastole to the left ventricular posterior wall in diastole exceeded 1:3 (10, 11). Tricuspid regurgitation flow was determined by a continuous wave Doppler method from the apical four-chamber view. Pulmonary artery pressure was measured when tricuspid regurgitation was present. The high left parasternal short axis view of great arteries was used to evaluate the ductal shunting through the ductus arteriosus. The velocity of the shunt was recorded at the ductal pulmonary opening with pulsed or continuous wave Doppler echocardiography. When the above flow was absent, the ductus was considered closed. Cardiovascular malformations were carefully searched by all standard views of M-mode, 2-D, and color Doppler echocardiography. We defined cardiovascular malformation as a structural abnormality of the heart or intra thoracic great vessels that are actually or potentially of functional importance (3). Maternal diabetes had been divided into 3 types. Type 1 diabetes mellitus was defined as insulin dependent diabetes that is diabetes beginning from childhood. Type 2 diabetes mellitus was defined as insulin resistance or adult type diabetes. Type 3 or gestational diabetes for the first time appeared during pregnancy period (1). Both type1 and type 2 were considered pre-gestational diabetes. Facilities for measurement of HbA1c and HbF1c were not available. LGA was defined as a birth weight above the 90th percentile level for gestational age. Appropriate for gestational (AGA) was defined as a birth weight between the 10th and 90th percentile level for gestational age. Small for gestational age (SGA) was defined as a birth weight below the 10th percentile level for gestational age. Both AGA and SGA were considered non-LGA infants. Prematurity was defined as gestational age < 37 weeks at birth time. Hypoglycemia was defined when blood glucose level of newborn was $\leq$ 35 mg/dL at any time during the first day of life. The study

was approved by the local ethical committee of the hospital and an informed consent was obtained from mothers.

Data were recorded and processed using SPSS software version 16. Continuous variables were expressed as Mean ± SD. Categorical variables were expressed in percentage. The variables were compared using Fisher's exact test or Pearson Chi-Square test. A $P < 0.05$ was considered statistically significant.

4. Results

The population consisted of 32 IDMs (18 male, and 14 female). The mean age of patients was 6.3 ± 2.5 days with a range from 2 to 10 days. The mean birth weight of cases was 3613.7 ± 826.0 g with a range from 1100 to 5100 g. LGA occurred in 22 (68.8%) cases, 9(28.1%) cases were AGA, and 1 (3.1%) case was SGA. 22 newborns were full-term, while10 were premature with a mean gestational age of 34.4 weeks (range 31 to 36 weeks). The mean blood glucose level at the first postnatal day was 40.5 ± 12.2 mg/dL with a range from 20 to 65 mg/dL. Hypoglycemia became evident in 14 (43.8%) neonates. There was a significant difference between the rate of hypoglycemia in LGA [12/22 (54.5 %)] and hypoglycemia in non-LGA infants [2/10(20.0%)] P = 0.02. We did not find a significant relation between neonatal hypoglycemia and maternal diabetes types [hypoglycemia in GD (10/21) versus hypoglycemia in pre-GD (4/11), P = 0.7]. Extra cardiac malformation was detected in one patient, a 6-days old boy with hypospadias.

The mean age of mothers was 29.3 ± 5.4 years with a range from 19 to 39 years. Type 3 diabetes was diagnosed in 21 (65.6%) mothers, followed by type 2 in 9 (28.1%) mothers, and type 1 in 2 (6.3%) mothers. So 21 mothers suffered from gestational diabetes (GD), and 11 mothers had pregestational diabetes (Pre-GD). The frequency of LGA in GD was 17/21 (80.9%), versus the frequency of LGA in pre-GD 5/11 (45.4%), and the difference was not significant, P = 0.05. Cesarean section (C-section) was performed in 27 (84.4%) mothers, whereas 5 mothers gave birth to their babies by normal vaginal delivery. The mean value of maternal fasting blood glucose level was 160.3 ± 48.4 mg/dL with a range from 110 to 208 mg/dL. Detailed data about control of maternal diabetes were not available.

4.1. Echocardiographic Findings

Patients' fractional shortening ranged from 27 to 50 % with a mean of 37.6 ± 5.7%. Ejection fraction ranged from 60 to 88% with a mean of 75.3 ± 7.8%. HCM was found in 15 (46.9%) newborn. *Table 1* shows the results of M-mode echocardiography. *Figure 1* shows the thickening of inter ventricular septum in a 10-days old boy. None of our HCM cases suffered from either left ventricular outflow obstruction or congestive heart failure. Patent ductus arteriosus (PDA) was detected in 6 (18.7%) cases. In 4 patients PDA was a component of CHD, and in 2 cases it was an isolated closing duct. Tricuspid regurgitation flow was recorded in 15 patients and was absent in the remaining 17 cases. The range of regurgitation flow was 6 to 30 mm HG with a mean of 21.4 mm Hg. We did not find pulmonary hypertension in our patients.

Table 1. Findings of M-mode Echocardiography

Parameter	Minimum, cm	Maximum, cm	Mean ± SD, cm
IVS[a] Diastole	0.24	1.28	0.49 ± 0.18
LVD[a] Diastole	0.94	2.28	1.67 ± 0.34
PW[a] Diastole	0.18	0.53	0.38 ± 0.88
IVS Systole	0.24	1.23	0.50 ± 0.21
LVD[a] Systole	0.48	1.80	1.10 ± 0.30
PW[a] Systole	0.18	0.52	0.39 ± 0.88

[a] Abbreviations: IVS, Inter ventricular septum; LVD, Left ventricular dimension; PW, Posterior wall

Echocardiographic examination revealed CHD in 6 (18.7%) babies. Cyanotic and complex conotruncal abnormalities with various combination of TGA were noticed in 3 cases. In one case cyanotic lesion was associated with dextrocardia. *Table 2* Shows the complete configuration of different types of CHDs. *Table 3* summarizes the relations between maternal diabetes types and the frequency of CHD or HCM in their offspring. This table also shows the frequency of CHD and HCM in LGA and none-LGA infants and the comparison between them. We did not find a significant difference in the prevalence of CHD or HCM in offsprings of GD or pre-GD mothers. We did not find a significant difference in the prevalence of CHD or HCM in LGA and non-LGA infants. HCM was resolved in 10 of 15 infants during a follow-up period of 1 to 3 months.

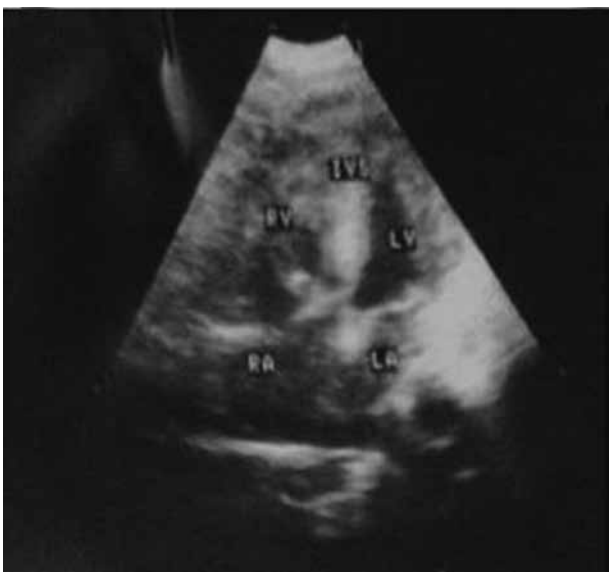

Figure 1. Thickening of Inter Ventricular Septum in a 10-days old boy

Table 2. Types of CHD, Maternal Diabetes, and Weight for Gestational age In IDMs

Type of CHD	Type of Maternal Diabetes	Weight for Gestational age
L –TGA[a]+ VSD[a]+PDA[a]+ Dextrocardia	GD	AGA
VSD[a]+ CoA[a]+ PDA[a]	GD	AGA
D-TGA[a]+ Pulmonary atresia + VSD[a]+ PDA[a]	Pre GD	SGA
D-TGA +DORV[a]+ VSD + PDA	GD	AGA
VSD[a]+ ASD[a]	Pre GD	LGA
PS[a]	GD	AGA

[a] Abbreviations: TGA, Transposition of great arteries; VSD, Ventricular septal defect; PDA, Patent ductus arteriosus; CoA, Coarctation of aorta; DORV, Double outlet right ventricle; ASD, Atrial septal defect; PS, Pulmonary stenosis

Table 3. RelationsBetween Cardiac Complications, Type of Maternal Diabetes, and Somatic Features of Newborns

Variable	No. (%)	*P*
CHD[a]in GD[a]	4/21 (19.0)	0.9
CHD[a]in pre- GD[a]	2/11 (18.1)	
HCM[a]in GD[a]	10/21 (47.6)	0.9
HCM[a]in pre-GD[a]	5/11 (45.4)	
CHD[a]in LGA[a]	2/22 (9.0)	0.6
CHD[a]in non-LGA[a]	4/10 (40.0)	
HCM[a]in LGA[a]	9/22 (40.9)	0.4
HCM[a]in non-LGA[a]	6/10 (60.0)	

[a] Abbreviations: CHD, Congenital heart disease; HCM, Hypertrophic cardiomyopathy; GD, Gestational diabetes; Pre-GD, Pre-gestational diabetes; LGA, Large for gestational age

5. Discussion

According to the results of our study, 6 of 32 (18.7%) IDMs suffered from CHD and conotruncal abnormalities were found in 50% of CHD cases. The incidence of CHD in IDMs has a wide range. In a series of 18 diabetic mothers with good glycemic control, no case of CHD was found among offsprings (12). In a report from Saudi Arabia the incidence of CHD in a group of 100 IDMs was 15% and the maternal diabetic control was poor (10). The incidence of CHD in our study was more than the higher range of previous reports, but like the other studies (1-3); conotruncal malformations were common in affected patients. The incidence of gestational diabetes in previous studies varied from 100% to 21.3% (4, 5). The incidence of maternal GD in our report (65.6%) is within the above range. We did not find a significant relation between maternal diabetes types and the rate of CHD in their offsprings. In a meta-analysis by Wren *et al.* the prevalence of CHD in 609 infants of pre-GD mothers was 3.6% (3). Another meta-analysis by Lisowski *et al.* showed that approximately half of the CHD in infants of type 1 diabetic mothers were conotruncal anomalies (2). In a previous meta-analysis by Loffredo *et al.* the defects of early-stage cardio genesis was strongly associated with pre-GD maternal diabetes (13). It is important to remember that diabetic embryopathy whether as a result of GD or pre-GD seems to have a multi factorial basis. Genetic influences on congenital anomalies in diabetic pregnancies of both types have to be considered (9). The high frequency of CHD in our IDMs group may be due to the influence of the genetic and environmental factors as well as to the high maternal blood glucose level. Another reason may be the location of sampling, because our patients had been referred to a pediatric cardiology clinic to be evaluated for the presence or absence of CHD. Embryogenesis in an environment with high glucose concentration has an adverse effect on cardiac morphogenesis (2). Sheffield *et al.* reported that in GD the presence of fasting hyperglycemia > 105 mg/dL seems to be a risk factor for fetal malformation, while mothers with normal fasting glucose did not have an increased rate of fetal malformation (14). In pre-GD, the fetuses are exposed to hyperglycemia during the whole period of pregnancy, whereas in GD this exposition occurs during the last trimester (12). Women with GD are prone to develop diabetes mellitus later in life and may possibly suffer from subclinical diabetes before or early in pregnancy (7). The mean fasting blood glucose level in our mothers was 160 .3 ± 48.4 mg/dL with a range from 110 to 208 mg/dL. The high blood glucose level in our diabetic mothers indicated their poor metabolic control. It is possible that some of our GD mothers were in fact, previously unknown type 2 diabetic patients. So their fetuses were exposed to hyperglycemia during the whole period of pregnancy.

The frequency of HCM is different in previous reports. Its range is from 13% to 59% (1, 4). The incidence of 46.9% HCM in our series is within the above range. Oberhoffer *et al.* studied 104 infants of 100 tightly controlled diabetic mothers. HCM was found in 25% of the 104 neonates, which predominantly involved inter ventricular septum. CHD was diagnosed in only 2 babies. There was no LVOT obstruction, and HCM resolved within 6 months (7). In a research by Zielinsky *et al.* there was spontaneous regression of ventricular septum thickness in IDMs during the first 6 months of life. The association between hyper insulinism and HCM was present up to the first month of life (15). The results of our study, like several previous reports (7, 16), showed that neither the type of maternal diabetes, neonatal metabolic data, nor neonatal somatic features serve as a predictor for HCM. It is suggested that fetal hyper insulinism contributed directly to the septal hypertrophy; however some studies could not find a relation between the degree of maternal metabolic control and

the incidence and severity of myocardial hypertrophy (7, 17). It might be possible that other intra uterine environmental factors in addition to glucose metabolism contributed to myocardial hypertrophy.

The incidence of LGA infants among the offspring of diabetic mothers is variable. Its range is from 11.1% to 41% in previous reports (12, 13). The frequency of 68.7% LGA in our series is higher than in literature because all 10 premature babies in our population were LGA. The rate of prematurity in our study was in the upper range when compared with the literature (7, 10). We, like other researchers (7, 16), did not find a significant difference in frequency of LGA between infants of GD and pre-GD mothers. The rate of neonatal hypoglycemia in our study (43.8%) was comparable to those described in the literature (7, 12, 16). We, as well as other researchers (7), observed that neonatal hypoglycemia may appear independently of the maternal diabetes type. The rate of extra cardiac malformations in our cases (3.1%) was in the lower range when compared with the previous researches with a frequency of zero (5, 12) to 25% (13).

In two previous studies it was shown that PDA closure was significantly delayed in IDMs, and there was a delayed fall in pulmonary artery pressure (4, 5). They suggested that transient disturbances in the immediate postnatal adaptation of pulmonary circulation may be related to delayed pulmonary maturation. We did not find pulmonary hypertension in our patients because the majority of them were evaluated after the first few days of life. PDA in 4 of our patients was associated with other CHD, and in 2 infants it was not of clinical significance.

The limitation of our study included the small sample size, lack of detailed profile of maternal blood glucose in each trimester, as well as lack of HbA1c and HbF1c measurement. A multicenter study with better facilities is needed to challenge our results.

In conclusion, our study showed a high frequency of CHD in the IDMs group. It also showed that cardiac complications could not be related to the neonatal parameters of carbohydrate metabolism or the type of maternal diabetes.

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Authors' Contribution

Shahla Roodpeyma proposed the study and wrote the first draft. Sima Rafieyian performed echocardiography and collected data. Nastaran Khosravi and Ashkan Hashemi contributed in review of literature and data analysis. All the authors contributed to the intellectual content of the study and approved the final version of manuscript. Shahla Roodpeyma is the guarantor.

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References

1. Ullmo S, Vial Y, Di Bernardo S, Roth-Kleiner M, Mivelaz Y, Sekarski N, et al. Pathologic ventricular hypertrophy in the offspring of diabetic mothers: a retrospective study. *Eur Heart J*. 2007;**28**(11):1319-25
2. Lisowski LA, Verheijen PM, Copel JA, Kleinman CS, Wassink S, Visser GH, et al. Congenital heart disease in pregnancies complicated by maternal diabetes mellitus. An international clinical collaboration, literature review, and meta-analysis. *Herz*. 2010;**35**(1):19-26
3. Wren C, Birrell G, Hawthorne G. Cardiovascular malformations in infants of diabetic mothers. *Heart*. 2003;**89**(10):1217-20
4. Vela-Huerta M, Aguilera-Lopez A, Alarcon-Santos S, Amador N, Aldana-Valenzuela C, Heredia A. Cardiopulmonary adaptation in large for gestational age infants of diabetic and nondiabetic mothers. *Acta Paediatr*. 2007;**96**(9):1303-7
5. Seppänen Marko P, Ojanperä Outi S, Kääpä Pekka O, Kero Pentti O. Delayed postnatal adaptation of pulmonary hemodynamics in infants of diabetic mothers. *J pediatrics*. 1997;**131**(4):545-548
6. Jensen DM, Damm P, Moelsted-Pedersen L, Ovesen P, Westergaard JG, Moeller M, et al. Outcomes in type 1 diabetic pregnancies: a nationwide, population-based study. *Diabetes Care*. 2004;**27**(12):2819-23
7. Oberhoffer R, Hogel J, Stoz F, Kohne E, Lang D. Cardiac and extracardiac complications in infants of diabetic mothers and their relation to parameters of carbohydrate metabolism. *Eur J Pediatr*. 1997;**156**(4):262-5
8. Pildes RS. Infants of diabetic mothers. *N Engl J Med*. 1973;**289**(17):902-4
9. Versiani BR, Gilbert-Barness E, Giuliani LR, Peres LC, Pina-Neto JM. Caudal dysplasia sequence: severe phenotype presenting in offspring of patients with gestational and pregestational diabetes. *Clin Dysmorphol*. 2004;**13**(1):1-5
10. Abu-Sulaiman RM, Subaih B. Congenital heart disease in infants of diabetic mothers: echocardiographic study. *Pediatr Cardiol*. 2004;**25**(2):137-40
11. Henry WL, Clark CE, Epstein SE. Asymmetric septal hypertrophy. Echocardiographic identification of the pathognomonic anatomic abnormality of IHSS. *Circulation*. 1973;**47**(2):225-33
12. Kozak-Barany A, Jokinen E, Kero P, Tuominen J, Ronnemaa T, Valimaki I. Impaired left ventricular diastolic function in newborn infants of mothers with pregestational or gestational diabetes with good glycemic control. *Early Hum Dev*. 2004;**77**(1-2):13-22
13. Loffredo CA, Wilson PD, Ferencz C. Maternal diabetes: an independent risk factor for major cardiovascular malformations with increased mortality of affected infants. *Teratology*. 2001;**64**(2):98-106
14. Sheffield JS, Butler-Koster EL, Casey BM, McIntire DD, Leveno KJ. Maternal diabetes mellitus and infant malformations. *Am J Obstet Gynecol*. 2002;**100**(5, Part 1):925-30
15. Zielinsky P, da Costa MH, Oliveira LT, Bonow FP, da Silva NI, Hagemann LL. [Natural history of myocardial hypertrophy and its association with hyperinsulinism in infants of diabetic mothers]. *Arq Bras Cardiol*. 1997;**69**(6):389-94
16. Demiroren K, Cam L, Oran B, Koc H, Baspinar O, Baysal T, et al. Echocardiographic measurements in infants of diabetic mothers and macrosomic infants of nondiabetic mothers. *J Perinat Med*. 2005;**33**(3):232-5
17. Vela-Huerta MM, Vargas-Origel A, Olvera-Lopez A. Asymmetrical septal hypertrophy in newborn infants of diabetic mothers. *Am J Perinatol*. 2000;**17**(2):89-94