Cardiovascular Malformations in Infants of Diabetic Mothers: A Retrospective Case-Control Study

Parvin Akbariasbagh[1], Mamak Shariat[2], Naseredin Akbariasbagh[3], and Bita Ebrahim[4]

[1] *Department of Cardiology, Maternal/Fetal and Neonatal Research Center, Family Health Institute, Tehran University of Medical Sciences, Tehran, Iran*

[2] *Maternal/Fetal and Neonatal Research Center, Family Health Institute, Tehran University of Medical Sciences, Tehran, Iran*

[3] *Department of Cardiology, Baharloo Hospital, Tehran University of Medical Sciences, Tehran, Iran*

[4] *Breastfeeding Research Center, Family Health Institute, Tehran University of Medical Sciences, Tehran, Iran*

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Abstract- Maternal diabetes has teratogenic effects on the evolution of the fetal cardiovascular system; as a consequence, cardiovascular malformations are the most common anomalies in infants of diabetic mothers. The present study focuses on the association of all types of diabetes in mothers with the incidence of congenital cardiovascular malformations in their infants. In this retrospective case-control study performed between the years 2008 and 2010, 35 infants of diabetic mothers were selected as a case group, and another 35 infants of mothers with normal blood glucose levels were selected as a control group. Data has been extracted from patients' files and registered. Finally, the association of data has been performed according to statistical analysis. According to the results, the prevalence of cardiovascular anomalies was significantly higher in infants of diabetic mothers (P=0.018). The most common malformations in the case group were PDA 10%, hypertrophic cardiomyopathy 9% and PFO 8%. Maternal diabetes type (overt or gestational diabetes), duration and control method did not correspond with any significant differences in the prevalence of cardiac anomalies. The results of this study indicate that diabetes in pregnant women plays an important role in the incidence of certain types of cardiac anomalies, such as PFO, HCMPT, and PDA. As a result, the performance of diagnostic procedures (like embryonic echo, before and after birth), provision of special prenatal care to diabetic mothers, and providing supportive and therapeutic care to symptomatic infants seems highly advisable in such cases.

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Introduction

Congenital cardiac anomalies are the most common type of birth defect, and the rate of these anomalies is estimated at 6 to 8 cases in 1000 live births (1). The cause of this anomaly is usually unknown, with 1% of all cases relating to diabetes of pregnant mothers (1). Prior studies indicate that maternal diabetes has teratogenic effects on the evolution of the fetal cardiovascular system, which increases the risk of the occurrence of anomalies (2).

Reports show that around 3 million Iranians (ca. 5%) are diabetics. This means that Iran is among the countries with the highest rates of diabetes (3). Moreover, according to the World Health Organization, this number may reach 7 million by 2030 if no effective measures are taken. Statistics show that 5.4% of Iranian women are diabetics, most of whom are at the age of fertility (3). Furthermore, gestational diabetes with a rate of 5% is the most common illness in pregnant women (4).

These facts and data indicate the utmost importance for investigation of this disease with adequate care. One of the significant aspects of this disease is the effects on the fetuses of such mothers. For this reason, we have performed this study with the purpose of determining the relationships between various types of maternal diabetes, glycemic control and the prevalence of various types of cardiovascular complications in neonates and comparing these findings to infants of non-diabetic mothers. We hope that this study will lead to more

Corresponding Author: B. Ebrahim
Breastfeeding Research Center, Family Health Institute, Tehran University of Medical Sciences, Tehran, Iran
Tel: +98 21 61192357, Fax: +98 21 66591315, E-mail address: BitaEbrahim@yahoo.ca

comprehensive research in the future.

Materials and Methods

A retrospective case-control study was performed between the years 2008-2010 on two groups of newborns at Vali-e-Asr Hospital which is affiliated with Tehran University of Medical Sciences in Iran.

The case group consisted of infants born to mothers with diabetes (including overt diabetes 51.4% and gestational diabetes 48.6%), and the control group was made up of infants born to non-diabetic mothers based on GDM and diagnosis of gestational diabetes. Diagnostic criteria for diabetes has been made according to WHO criteria and diagnosis of GDM were based on the recommendations of the Second International Conference (1,2).

Both groups were selected using an easy and simple sampling method. Inclusion criteria for the case group were: infants born to mothers with diabetes (including overt diabetes and gestational diabetes), term infants, and mothers who received prenatal care. Inclusion criteria for the control group included: non-diabetes and healthy mother, term infants, and mothers who received prenatal care. Exclusion criteria were: preterm and IUGR infants, low Apgar score, mothers who did not receive prenatal care and mothers who did not have GDM diagnostic tests.

After the selection of the two infant groups-infants with diabetic mothers and infants with non-diabetic mothers-general information was recorded, including: age, gender, birth weight and gestational age at birth, Apgar score at birth, echocardiography records of newborns, clinical manifestations, maternal age, history of maternal disease, the type and duration of diabetes diagnosis and treatment, records of previous pregnancies and the presence of or lack of prenatal care. Information for mothers and infants was collected from the data records. Physical examinations were performed by a gynecologist and a pediatrician. The echocardiography was done by a pediatric cardiologist. Echocardiography was also performed on healthy infants. Data were analyzed by SPSS Version 19 software. The qualitative data of the absolute and relative frequency and quantitative data were analyzed using mean and standard deviation. Statistical analyses were also extracted from the chi-square test to compare qualitative information between the two groups; quantitative data were collected from an Independent-*t*-test. A *P*.value<0.05 was considered to be significant. The power of the study was 80%, and β was 0.20. The present study was approved by the Ethics Committee of Tehran University of Medical Sciences.

Results

Data were extracted from medical records, and the descriptive and analytical statistics of this information was duly applied. Some of the relevant information is given in Table 1.

Table 1. Comparison of variable backgrounds in infants of diabetic and non-diabetic mothers between the years 2008 and 2010, Vali-e-Asr Hospital

Variable Group		Infants of diabetic mothers (percentage, number)	Infants of non-diabetic mothers (percentage, number)	Total newborns (percentage, number)	*P*.value
Gender	Female	(51.5) 18	(51.5) 36	0.594	-
	Male	(48.5) 17	(48.5) 34	0.594	-
Birth weight (gr.)		3247±570	2942±477	3095±524	0.018
Maternal age birth (week)		37.4±1.5	36.9±2	37.2±1.7	0.328
Average age of mother		29.9±6	28.6±4.5	--	0.359
Prenatal care		35-100%	35-100%	(100%) 70	--
Maternal hypertension		7-20%	8-22/8%	--	--
Gestational diabetes screening		35-100%	35-100%	(100%) 70	--
Apgar score		8.8±1	9.2±0.8	--	0.08

In the group of infants of diabetic patients, 15 cases (42.8%) with various cardiovascular anomalies were observed while in the group of infants of non-diabetic mothers only 6 cases (17%) of cardiovascular anomalies

were reported (*P*=0.018). Thus, in a total of 70 studied infants, 21 cases (30%) of cardiovascular anomalies have been diagnosed.

In the majority of cases (76.2%), multiple cardiac complications were detected, and only a single cardiac anomaly out of 5 infants (23.8%) was reported by echocardiography. Most of the single cardiac anomaly was hypertrophic cardiomyopathy. Eleven infants out of 15 from the case group were diagnosed with congenital anomalies such as patent ductus arteriosus, patent foramen ovale, pulmonary arterial hypertension, tricuspid insufficiency and hypertrophic cardiomyopathy which merely require supportive care and follow-ups. The four (11.4%) remaining cases of cardiovascular diseases that were observed included one case of ventricular septal defect, one case of pulmonary atresia and two cases of transposition of great vessels with ventricular septal defect.

In the control group, of the 6 infants that had malformations, 2 cases (5.7%) had cardiovascular complications, including atrial septal defect in one case and one case of atrial and ventricular septal defect with transposition of mediastinal great vessels. Prevalence of cardiovascular anomalies can be observed in Table 2.

Table 2. Frequency of all cardiovascular anomalies in infants of mothers diagnosed with diabetes (overt diabetes and diabetes mellitus) and non-diabetic mothers at Vali-e-Asr Hospital between the years 2008-2010

Cardiac anomalies	Infants of Diabetic mothers			Infants of non-diabetic mothers number (percentage)	All the infants number (percentage)	*P*.value	*OR*	$CI_{95\%}$
	Gestational diabetes number	Diabetes mellitus number	Total number (percentage)					
****PFO**	2	6	(22.8) 8	(5.7) 2	(14.3) 10	0.04	4.88	1.95-24.97
PDA	4	6	(28.5) 10	(17.1) 6	(22.9) 16	0.19	1.93	0.61-6.07
TR	3	1	(11.4) 4	(2.8) 1	(7.1) 5	0.18	4.38	0.46-41.40
HCMP	4	5	(25.7) 9	0	(12.9) 9	0.001	0.74	0.61-0.90
PHTN	2	2	(11.4) 4	(5.7) 2	(8.6) 6	0.33	2.12	0.36-12.45
VSD	1	1	(8.9) 3	(2.8) 1	(5.7) 4	0.30	3.18	0.31-32-44
ASD	0	0	0	(5.7) 2	(2.8) 2	0.24	1.06	0.97-1.15
TGA	1	1	(5.7) 2	(2.8) 1	(4.3) 3	0.50	2.06	0.17-23.82
PA	0	1	(2.8) 1	0	(1.4) 1	0.50	0.97	0.91-1.02
PI	0	0	0	(2.8) 1	(1.4) 1	0.50	1.02	0.97-1.09

All of the 70 infants (100%) that participated in the study underwent echocardiography after birth. The average time interval for the performance of echocardiography on these infants was overall 3.45±2 days after birth (3.36±1.9 days in the first group and 3.75±2.8 days in the second group). Three (4.2%) of the 70 Infants had undergone fetal echocardiography, confirming prenatal cardiac anomaly.

In the group of 35 diabetic mothers, 18 (51.4%) suffered from overt diabetes, and the other 17 (48.6%) had gestational diabetes. Nine out of 18 infants born to mothers with overt diabetes (50%) had cardiovascular anomalies. While among the 17 infants born to mothers with gestational diabetes, 6 patients (35.3%) had cardiovascular anomalies (*P*=0.29).

In mothers with hypertension during pregnancy (including gestational hypertension and chronic hypertension) one case (14.3%) of cardiac anomalies was reported in the case group and one (12.5%) in the non-diabetic mother's group.

The mean duration of overt diabetes in diabetic mothers was 5.28 years. The mean duration of overt diabetes of diabetic mothers having infants with cardiac anomalies was 6.42±1.2 years and for mothers with healthy infants was 4.13±1.9 years (*P*=0.336).

The mean duration of gestational diabetes in mothers diagnosed with GDM was 4.43 months, 4.83±2.5 months for those who had newborns with anomalies, and 4.2±2.2 months for mothers diagnosed with GDM who had infants without malformations (*P*=0.612).

The infants with cardiac anomalies had an average Apgar score of 8.33±1.15, and the newborns without malformations had an average of 9.24±0.69 (*P*=0.002).

Among infants with cardiovascular malformations, there were 6 cases (28.6%) of cyanosis, 5 cases (23.8%) of bradycardia, 3 cases (14.3%) of respiratory distress and 3 patients with jaundice at the initial examination. Four of these infants (19%) had normal initial screenings.

In addition, there was one infant born to a diabetic mother who suffered from cleft palate and spina bifida occulta and another infant that was diagnosed with galactosemia.

Table 3. Frequency of diabetes control methods in the first group of mothers before and during pregnancy and frequency of anomalies in their infants

Diabetes control method	Total users of this treatment number (percentage)	Cases associated with infants diagnosed with Cardiac anomalies** number (percentage)
Insulin therapy in pregnancy	(71.5)25	(48)12
Diet in pregnancy	(22.8)8	(25)2
Untreated diabetes in pregnancy	(5.7)2	(50)1
Pre-pregnancy insulin treatment *	(22.2)4	(50)2
Pre-pregnancy oral medication treatment	(55.5)10	(50)5
Pre-pregnancy diet	(5.6)1	0
Pre-pregnancy untreated diabetes	(16.7)3	(66.7)2

* Control methods of pre-pregnancy diabetes in diabetic mothers for those who have overt diabetes.
***P*.value of various control methods of diabetes during pregnancy considering the impact is 0.508 and before pregnancy is 0.721

Discussion

The results of echocardiography performed on infants in each group of this study are predominantly compatible with the results of previous studies. In this study, the incidence of cardiovascular anomalies in infants of diabetic mothers is significantly higher than the infants of non-diabetic mothers (*P*=0.018); accordingly, the frequency of anomalies is 2.5 times higher among these infants. The comparable results were also obtained in a similar study performed on 64 infants hospitalized at Vali-e-Asr Hospital in 2004 by Najafian study (5). These results were also seen in other similar studies conducted by Wren, Birrell and Hawthorne, 2003 (1) and Schaefer *et al.*, 2000 (2).

Regarding the current study, the most common cardiac anomalies in infants of diabetic mothers were PDA, PFO, and hypertrophic cardiomyopathy. The most common anomaly observed in the study by Najafian was PDA and, thereafter, ventricular hypertrophy, mitral valve prolapse and mitral regurgitation (5). In our study, none of these anomalies, including mitral valve prolapse or mitral regurgitation, was reported; however, four cases (11.4%) of infants born to diabetic mothers suffered from some degree of tricuspid insufficiency.

In the study by Abu-Sulaiman and Subaih conducted in Saudi Arabia the most common cardiac anomalies observed in infants of diabetic mothers were HCMP, PFO and PDA (6). These anomalies can be related to the natural evolution of an infant's circulatory system. Following up on the changing conditions of these anomalies was impossible by use of serial echoencephalography since the study was retrospective.

In the present study, a few cases of TGA, ASD, and VSD anomalies were observed in both groups with no significant difference between them. The total prevalence was estimated at 8.5%.

The prevalence of cardiovascular anomalies for all types of malformations in infants born to diabetic mothers is 42.8% and the incidence of other diseases, such as ventricular septal defect, atrial septal defect, displacement of mediastinal great vessels and valve atresia, is estimated at 11.4%. In the study by Najafian, the prevalence of cardiovascular malformations in infants of diabetic mothers was estimated at 46.9%, and the incidence of VSD was about 3% (5). Also, in a study performed by Dimitriu *et al*., the prevalence of cardiac anomalies was reported at 23% regardless of pulmonary hypertension and hypertrophic cardiomyopathy (7).

In the present survey conducted on the associated anomalies in infants of diabetic mothers, except for a single case of cleft palate and spina bifida and another case of galactosemia, no other case was observed. This could be due to a higher prevalence of cardiovascular anomalies in infants of diabetic mothers compared to the anomalies in other organ systems which is also mentioned in other studies such as Schafer *et al*., (2). In that study, 37.6% of the total anomalies consisted of cardiovascular anomalies and, thereafter, skeletal anomalies with an estimation of 14.7%.

According to the present results, the type of maternal diabetes (diabetes mellitus, overt or gestational diabetes) did not bring about any significant difference in the incidence of cardiac malformations in infants (*P*=0.29). However, in a study conducted by Ferencz *et al*., (8), a greater connection was noted between the prevalence of cardiac anomalies of infants and overt diabetes of the mother.

In addition, according to our study, the duration of diabetes mellitus both in terms of years of overt diabetes and in months of gestational diabetes during pregnancy did not cause any significant difference in the incidence

of cardiovascular anomalies in infants. However, the mean duration of diabetes mellitus in mothers who had infants with cardiac anomalies was 6.4 years and only 4.1 years for mothers of infants without cardiac anomaly. In a study conducted by Weber, Botti, and Baylen (1994), it was concluded that appropriate glycemic control of the expectant mother could reduce cardiovascular anomalies in her infant (9). In Wong *et al.*, (2003) it was determined that the effect of glycemic control preventing cardiac anomalies in infants during pregnancy had been underestimated (10).

Regarding the results of the present study, control methods for diabetes in pregnant mothers (i.e. insulin treatment and proper diabetic diet) and control methods for overt diabetes in pregnant mothers (i.e. insulin treatment, oral medication treatment and proper diet) did not bring about any significant differences in the prevalence of cardiovascular anomalies in infants. Considering the absence of glycated hemoglobin measurement of blood level in this study, there was no possibility to check the diabetes control status of diabetic mothers. It should be added as well that the association between maternal serum Hb1c and infant anomalies was not the objective of this research.

In this study, the frequencies of the prenatal visit were obtained 100% in both diabetic and non-diabetic mothers. All pregnant women performed screening tests for gestational diabetes after 24 weeks of pregnancy. According to this study, pregnancy complications, such as intrauterine fetal death (IUFD) and macrosomia in infants of diabetic mothers were more common than in non-diabetic mothers.

The frequencies of IUFD, as well as macrosomia, were estimated at 11.4% in mothers diagnosed with gestational diabetes while no record was found for these diseases in non-diabetic mothers. In the present study, 4 infants of diabetic mothers (11.4%) had respiratory distress, 5 cases (14.3%) developed bradycardia and 3 cases (8.3%) were diagnosed with sepsis. Respiratory distress has been also reported as an important cause of hospitalization of infants born to diabetic mothers in other studies (7).

In the study conducted by Najafian, the frequency of respiratory distress and sepsis was reported 6% and 12.5%, respectively (5). Thus, these clinical symptoms can be considered the most important clinical signs in infants of diabetic mothers.

In this study, 4 cases of infants diagnosed with cardiac anomaly (19%), didn't show any initial clinical symptom. These findings indicate the importance of clinical examination and follow-up for infants born to diabetic mothers. While the Apgar score at birth in infants of diabetic mothers and non-diabetics do not differ that much, the average Apgar scores of infants with cardiac anomalies are significantly lower than in infants without cardiac anomalies (P=0.002).

In accordance with the present research in comparison with the results of similar studies, the importance of medical care for maternal diabetes and its effect on the prevalence of cardiac disease in infants is clearly apparent. Among 70 patients participating in this survey, only 3 performed fetal echocardiography. Thus, despite 42% prevalence of cardiac anomalies in newborns of diabetic mothers, only 8.5% of these complications were found during prenatal diagnosis. Postnatal diagnostic procedures for diabetic mothers were performed 3.3 days after birth (delivery). However, in the Najafian study, the average time for diagnostic procedures was estimated at 8.6 days (5).

Early diagnostic procedures can lead to better supportive care for infants of diabetic mothers. However, special care to infants of diabetic mothers is essential to prevent complications such as respiratory distress, sepsis, and hypoglycemia. Further prospective studies should be proposed for diabetic pregnant women with diabetes control and serum glucose level monitoring in order to reveal the impact of therapeutic interventions on reducing infant morbidity among diabetic mothers.

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