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Predictors of postnatal complications and congenital cardiac diseases in infants of mothers with pregestational and gestational diabetes

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Abstract

Aim: In this study, we aimed to evaluate the postnatal problems of infants of mothers with pregestational and gestational diabetes and the clinical properties of infants who were found to have congenital cardiac disease.

Material and Methods: We retrospectively examined the records of 337 newborns who were followed up with a diagnosis of infant of diabetic mother between January 2010 and January 2012 in our Neonatology Unit. The demographic data of the diabetic mothers and their babies, the postnatal problems of the babies of diabetic mothers and congenital heart diseases found on transthoracic echocardiography were examined.

Results: The patients were classified as group A, B and C in accordance with the recommendations of The American Congress of Obstetricians and Gynecologists (ACOG) according to the type of diabetes. The most common postnatal problems included hyperbilirubinemia, respiratory distress, hypoglycemia and hypocalcemia. The rate of congenital heart disease was found be 17.3% in group A, 50% in group B and 9% in group C. No correlation was found between congenital heart disease and gender, multiple pregnancy, diabetes type, diet treatment, use of oral antidiabetic drugs and drug usage. A positive significant correlation was found between congenital heart disease and genetic disease, murmur, cyanosis and presence of gestational hypertension. It was shown that use of insulin, genetic disease and presence of gestational diabetes increased the risk of congenital heart disease.

Conclusions: In our study, the overall incidence of congenital heart disease was found to be 24% in infants of diabetic mothers. It should be kept in mind that it is important to investigate the infants of mothers with pregestational and gestational diabetes in terms of the risk of congenital heart disease. (Türk Ped Arş 2014; 49: 299-306)

Key words: Postnatal complications of diabetes, congential heart disease, transthoracic echocardiography, infant of mother with pregestational and gestational diabetes

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Introduction

Diabetes mellitus accompanies 1-2% of all pregnancies. Despite this low level, it has a high level of prenatal morbidity and mortality risk (1). In the etiological classification made by the American Diabetes Association (ADA) in January 2013 (2), there are mainly four groups. These include type 1 diabetes, type 2 diabetes, diabetes which occurs as a result of specific mechanisms and diseases, gestational diabetes. The key manifestation of diabetes is development of diabetic fetopathy. Significant congenital problems are observed in 5-8% of the babies of diabetic mothers (3). In some studies, no relation could be found between minor anomalies observed in babies of diabetic mothers and maternal variables (4).

Hyperglycemia speficially affects the development of the cardiovascular system. Congenital cardiac problems observed in babies of diabetic mothers suggest that the defects in these infants arise from exposure to teratogenic effects in the very early stages of cardiac formation (5). Fetal cardiac anomalies may include transposition of great arteries, mitral atresia, pulmonary atresia, double outlet right ventricle, fallot tetratolgy and fetal cardiomyopathy (6).

In this study, we aimed to evaluate the problems in relation with diabetes in the neonatal period in the babies of diabetic mothers who had been followed up in our hospital and to determine the properties and predictors of the babies of diabetic mothers who were found to have congenital cardiac disease.

Material and Methods

Our study was conducted by retrospectively examining the recordings of 337 babies who were being followed up in İzmir Dr. Behçet Uz Pediatric Diseases and Surgery Education and Research Hospital, Premature Neonatology Unit and Neonatology Wards between January the 1st, 2010 and January the 1st 2012 and who were diagnosed with infant of diabetic mother after obtaining approval from the ethics committee of İzmir Dr. Behçet Uz Pediatric Diseases and Surgery Education and Research Hospital.

The properties belonging to the diabetic mothers including maternal age, type of diabetes (type 1, type 2 and gestational diabetes) and period of diabetes were recorded according to the information obtained from mothers.

The classification of the diabetic mothers was made according to [ACOG (The American Congress of Obstetricians and Gynecologists)]. Accordingly, glucose tolerance disorder which occured during pregnancy for the first time or diagnosed during pregnancy were classified as class A [the subjects with a fasting blood glucose level <105 mg/dL and postprandial blood sugar at the second hour <120 mg/dL were classifed as class A1 and the subjects with postprandial blood sugar at the second hour ≥120 mg/dL were classified as class A2], the subjects with an age of onset >20 years and diabetes for shorter than 10 years were classified as class B (group B) and the subjects with an age of onset of 10-20 years and diabetes for 10-20 years were classifed as class C (group C) (7).

The diagnosis of gestational diabetes was made according to the results of the glucose tolerance test applied to pregnant women between the 24-28th weeks with no previous history of diabetes in accordance with ADA recommendations by assessing fasting and postprandial blood glucose levels. Following 8 hours fasting overnight, oral glucose tolerance test was performed by giving 75 mg glucose. The subjects with a fasting plasma glucose ≥92 mg/dL (5.1 mmol/L), postprandial plasma glucose at the first hour ≥180 mg/dL (10 mmol/L) and postprandial plasma glucose at the second hour ≥153 mg/dL (8.5 mmol/L) were considered gestational diabetes (2).

Properties belonging to the infant of diabetic mother; gestational age, birth weight, height, head circumference, other problems belonging to the infant of diabetic mother, birth trauma, presence of cyanosis on physical examination, accompanying congenital anomalies were recorded in detail.

Transthoracic echocardiography was performed by-Vivid S6 (GE, Milwaukee, USA) device using variable frequency transducers without sedation in the supine position and when the babies were quiet status. Echocardiography reports of the subjects who were diagnosed with congenital heart disease by transthoracic echocardiography were taken out of the archive and the diagnoses were recorded in detail. The subject who were assessed in the first three days and who had very mild paternt ductus arteriosus (PDA) flow, less than 3 mm opening in the interatrial septum and very mild regurgitation flow in the atrioventricular valves were not evaluated as congenital heart disease (8).

Statistical analysis

Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) 17,0 was used for statistical analyses in the study. Chi-square test was used for comparison of categorical variables. Quantitative variables were given as mean±SD and independent t-test was used in inter-group comparison of these variables. The correlation degree between two categorical variables was determined using Spearman correlation analysis. The results were evaluated in a 95% confidence interval and at a p value of <0,05. Binary logistic regression analysis was performed to determine the variables which might affect presence of congenital heart disease and Exp (B) coefficients and confidence intervals were obtained.

Results

When 337 subjects who were followed up in our hospital between January the 1st, 2010 and January the 1st, 2012 and diagnosed with infant of diabetic mother and their mothers were evaluated, the mean age of the diabetic mothers was lower in group B in babies who were found to have congenital heart disease. The median value for diabetes time was found to be 11.7 for the mothers in group B and 26,6 for the mothers in group C and the difference was statistically significant (p=0.000). The demographic properties of the diabetic mothers is given in Table 1.

The most common accompanying systemic disease other than diabetes was hypothyroidism (7.3%) in the group who were born at term and hypertension (10.6%) in the group who were born preterm. Only two mothers had a history of macrosomic birth. In all groups, 26 mothers (7.7%) used different drugs during pregnancy. Congenital heart disease was not found in the babies of the mothers who used oral antidiabetic drugs. While the mothers (n=11) in group C were using insulin regularly, 77% of the mothers in group B (n=26) were using insulin and blood glucose was regulated by diet in 23%. Twenty-three mothers in group A (7.6%) did not compile with diet therapy and did not let their blood glucose level to be monitored regularly.

One hundred and thirty-two (39%) of the infants of diabetic mother were preterm and 205 (61%) were born at term. 113 (85.6%) of the preterm subjects were classified as group A according to ACOG, 13 (9.8%) were classified as group B and 6 (4.6%) were classified as group C. 187 (91.2%) of the term subjects were classified as group A, 13 (6.3%) were classifed as group B and 5 (2.5%) were classified as group C. There was no significant difference between the groups in terms of cyanosis (p=0.081). The demographic properties of the infants of diabetic mothers are shown in Table 2.

Congenital anomaly was found in 6 babies in group A and B and in only 1 baby in group C (2%, 23% and 9%, respectively). Brachial plexus paralysis was present in 3 babies, clavicula fracture was present in 1 baby, pneumothorax was present in 2 babies and pneumomediastinum was present in 1 baby in group A. Other problems which are observed frequently in infants of diabetic mothers are summarized in Table 3. Polysthemia or hypomagnesemia was not found in any of the babies in these three groups.

Transthoracic echocardiography findings: Echocardiography reports belonging to 267 (80%) of 337 patients in the three groups could be reached. Congenital heart disease was present in 52 subjects (17.3%) in group A, in 13 subjects (50%) in group B and in 1 subject (9%) in group C (Table 4). The subject who had hypoplastic left heart syndrome in group A was lost before being operated in the follow-up. One subject in group A and one subject in group B were operated because of transposition of great arteries. Blalock-Taussing shunt was performed in a subject who was found to have single ventricle physiology in group B. In group A, one subject who was found to have aorto-pulmonary window was sent for operation. No significant narrowing was found in the ventricular outlet in a total of 11 subjects who were found to ahve hypertro-

Table 1. Demographic properties of diabetic mothers

Groups		Group A (n=300)	Group B (n=26)	Group C (n=11)	
Maternal age[µ]	CHD (+)	32.91±5.88	25.40±7.02	36.6±5.22	
	CHD (-)	30.77±5.45	28.08±4.96	34.23±3.32	
Diabetes period (years)[$]			11.64	26.67	0.000[$]

[$]Mann-Whitney U test p value (only group B and C were compared), CHD: congenital heart disease; [µ]Mean±SD

phic cardiomyopathy. While there was a significant relation between presence of Down syndrome, murmur and presence of cyanosis (p=0.000, p=0.001, p=0.000, respectively), no significant relation could be found between gender and multiple pregnancy and congenital heart disease (p=0.237, p=0.554, respectively) (Table 5). No significant relation could be found between diabetes type, diet therapy, drug usage and oral antidiabetic usage and occurence of congenital heart disease (p=0.219, p=0.148, p=0.311, p=0.851, respectively), but a positive significant relation was found between insulin usage and presence of gestational hypertension and congenital heart disease (p=0.010, p=0.034; respectively) (Table 6). When the independent variables which might affect presence of

Table 2. Demographic properties of the babies of diabetic mothers

		Group A (n=300)	Group B (n=26)	Group C (n=11)	
Gestational week		37±3	36±2	36±3	
Birth weight (g)		3112±824	3082±1074	2991±939	
Birth height (cm)		49±4	49±4	48±5	
Head circumference (cm)		34±2	33±3	33±3	
Term (n=205)		187 (91.2)	13 (6.3)	5 (2.5)	
Preterm baby (n=132)		113 (85.6)	13 (9.8)	6 (4.6)	
Cyanosis	Present	43	8	3	0.081[#]
	Absent	257	18	8	

[#]χ^2:chi-square test p value, [µ]Mean±SD; SD: standard deviation

Table 3. Other problems observed in infants of diabetic mothers

	Groups					
	Group A		Group B		Group C	
	(n=187)	(n=113)	(n=13)	(n=13)	(n=5)	(n=6)
Problems	Term baby (%)	Preterm baby (%)	Term baby (%)	Preterm baby (%)	Term baby (%)	Preterm baby (%)
Hyperbiluribinemia	70 (37)	49 (43)	6 (46)	3 (23)	2 (40)	2 (33)
Respiratory distress	41 (21)	50 (44)	3 (23)	8 (61)	-	3 (50)
Hypocalcemia	12 (6)	8 (7)	2 (15)	2 (15)	1 (20)	-
Hypoglycemia	18 (9)	16 (14)	3 (23)	2 (15)	2 (40)	1 (16)
Thrombocytopenia	10 (5)	6 (5)	-	1 (7.6)	1 (20)	1 (16)
Hypernatremia	14 (7)	1 (0.8)	1 (7)	-	-	-
Hyponatremia	2 (1)	-	-	-	-	-
Urinary tract infection	10 (5)	2 (1.7)	1 (7)	-	-	-
Meconium stained delivery	10 (5)	3 (2.6)	-	-	-	-
Convulsion	11 (6)	4 (3.5)	-	-	-	-
Dehydratation	16 (8)	5 (4.4)	1 (7)	-	-	-
Hypothroidism	3 (2)	2 (1.7)	-	-	-	-
Sepsis	1 (0.5)	7 (6.1)	-	1 (7.6)	-	-
Cyanosis	11 (6)	5 (4.4)	2 (15)	-	1 (20)	2 (33)
Birth trauma	6 (3)	1 (0.8)	-	-	-	-
Mortality rate	1 (0.5)	-	-	-	-	-

Table 4. Congenital heart diseases found by transthoracic echocardiography

	Groups					
	Group A		Group B		Group C	
	(n=187)	(n=113)	(n=13)	(n=13)	(n=5)	(n=6)
Congenital heart disease*	Term baby (%)	Preterm baby (%)	Term baby (%)	Preterm baby (%)	Term baby (%)	Preterm baby (%)
HLHS	1 (0.5)	-	-	-	-	-
VSD						
Perimembranous	3 (1.6)	4 (3.5)	1 (7.6)	3 (23)	-	1 (16)
Muscular	4 (2.1)		1 (7.6)			
Asymmetrical septal hypertrophy	4 (2.1)	2 (1.7)	2 (15)	-	-	-
HCMP						
LVH	4 (2.1)	4 (3.5)	1 (7.6)	-	-	-
RVH	1 (0.5)		1 (7.6)			
TGA	1 (0.5)	-	1 (7.6)	-	-	-
Single ventricle physiology	-	-	1 (7.6)	-	-	-
APW	-	1 (0.9)	-	-	-	-
FT	-	1 (0.9)	-	-	-	-
MVP	-	1 (0.9)	-	-	-	-
ASD	3 (1.6)	1 (0.9)	1 (7.6)	-	-	-
PDA	9 (4.8)	6 (5.3)	1 (7.6)	-	-	-
Bicuspid AV	1 (0.5)	1 (0.9)	-	-	-	-
Total of subgroups	**31 (16)**	**21 (18)**	**10 (76)**	**3 (23)**	**-**	**1 (16)**
Total of groups	**52 (17.3)**		**13 (50)**		**1 (9)**	

APW: aorto-pulmonary window; ASD: atrial septal defect; AV: aortic valve; TGA: transposition of great arteries; FT: fallot tetralogy; HCMP: hypertrophic cardiomyopathy; HLHS: hypoplastic left heart syndrome; LVH: left ventricular hypertrophy; MVP: mitral valve prolapsus; PDA: patent ductus arteriosus; RVH: right ventricular hypertrophy; VSD: ventricular septal defect

*More than one pathology are present in some babies.

Table 5. Relation between congenital heart disease and presence of genetic disease, gender, multiple pregnancy, murmur and cyanosis

	Phi coefficient	p$
Presence of genetic disease	0.207	0.000
Gender	0.064	0.237
Single/multiple pregnancy	0.032	0.554
Presence of murmur	0.183	0.001
Presence of cyanosis	0.213	0.000

p$: p values of Phi test

congenital heart disease were determined by number of subjects and significance degree and evaluated by logistic regression analysis, it was found that use of insulin increased the possibility of congenital heart disease by 1.4-5.5-fold, gestational hypertension increased this possibility by 1-4.9-fold and presence of genetic disease (Down syndrome) increased this possibility by 27.8-fold (Table 7).

Disccusion

Postnatal short-term complications in infants of diabetic mothers include hypoglycemia, hypocalcemia, hypomagnesemia, hyperbilirubinemia and polystemia and these are mainly related with fetal hyperinsulinemia, hypoxemia and preterm delivery (9, 10). In our study, the most commpn problem in the babies in group A and C was hyperbilirubinemia and the other common metabolic problems included hypoglycemia and hypocalcemia. Hypomagnesemia and polystemia were not found in any of the three groups.

Table 6. Relation between congenital heart disease and the properties belonging to the mother

	Phi coefficient	p[$]
Diabetes type	0.095	0.219
Use of insulin	0.141	0.010
Diet treatment	-0.079	0.148
Oral antidiabetic usage	-0.010	0.851
Presence of hypertension during pregnancy	0.115	0.034
Use of medicine	-0.055	0.311

p[$]: p values of Phi test

Table 7. Results of the logistic regression analysis belonging to independent variables which might affect presence of congenital heart disease

			95% CI* Exp (B)[$]	
	p value	Exp (B)	Lower	Upper
Insulin usage	0.003	2.805	1.423	5.528
Presence of genetic disease	0.004	27.874	2.977	260.995
Presence of gestational hypertension	0.037	2.273	1.050	4.923

*CI: confidence interval; [$]Exp (B): risk ratio

Strict glycemic control especially in the prenatal period decreases the frequency of fetal macrosomia, birth trauma and neonatal respiratory distress syndrome (9). In our study, presentation with respiratory distress occured with a rate of 30% in group A, 42% in group B and 27% in group C. Another system which is a cause of morbidity in the neaonatal period is the neurological system; Erb paralysis, Klumpke paralysis, diaphragma paralysis, laryngeal nerve damage and brachial plexus paralysis may be observed (9). In our study, all babies with birth trauma were group A infants of diabetic mothers. Diaphragma paralysis, Klumpke paralysis and laryngeal nerve paralysis were not observed. The main risk factors for hypoglycemia include babies who are large for gestational age and infants of mothers with insulin dependent diabetes mellitus (11). In our study, hypoglycemia was observed with a rate of 11% in group A infants of diabetic mothers, with a rate of 19% in group B infants of diabetic mothers and with a rate of 27% in group C infants of diabetic mothers. The rates of hypoglycemia observed in the groups were found to be compatible with the literature.

When the problems of 186 patients who had diabetes before pregnancy were examined, the rates of premature delivery and prenatal death were found to be higher in the pregnant women who had poor glycemic control (12). The rate of premature delivery was found to be 39% in our study. The rate of premature delivery was higher in infants in group B and C where glycemic control was poor, but statistical significance could not be found. Hypoplastic left heart syndrome was found in an infant in group A and this infant was lost in the follow-up. While mortality was not observed in the other babies in the groups, the general mortality rate was found to be 0.3% (n=1/337).

In our study, the rate of history of drug usage was 7.7% in all groups. The most commonly used drugs included propylthiouracil and thyroxin directed to goitre. In the literature, no difference has been reported between the groups who receive oral antidiabetics and insulin treatment in terms of the frequency of congenital anomalies (13, 14). There were three mothers in group A and four mothers in group B who received oral antidiabetic drugs. No congenital anomaly was found in the babies of these mothers.

When the pregnancy results of 365 pregnant women who had diabetes before pregnancy and gestational diabetes, the rate of congenital malformation was found to be 7.6% (15). In our study, the rate of congenital anomaly was found to be 2% in group A, 23% in group B and 9% in group C and these rates showed compatibility with the literature. Hypertension and preeclampsia are observed with a 2-fold higher rate in diabetic mothers compared to the mothers who are not diabetic (16). In our study, preeclampsia was found with a rate of 14% in group A, 7% in group B and 9% in group C and no significant relation was found between presence of hypertension and preeclampsia during pregnancy and congenital heart disease (p=0.053, r=0.108). When hypertension accompanies gestational diabetes, it can be predicted that these babies carry a higher risk in terms of developing congenital heart disease.

In the study of Martinez-Frias (17), 19 039 babies with anomaly were evaluated and it was found that the most common congenital anomaly was cardiac anomaly in babies of diabetic mothers. No significant difference was found between the mothers of the babies with congenital heart disease and the mothers of the babies with normal echocardiographic findings in terms of HbA1c levels (8.1%±3.4-7.6%±1.9) (18). The sensitivity of HbA1c in predicting congenital heart disease is 50% and the specificity is 54% (19). In our study, we had no

data related with HbA1c levels just before pregnancy and during the first three months of pregnancy, since the mothers of the infants of diabetic mothers were being followed up in different centers. Thus, we could not make an assessment related with this issue. However, only one baby who had renal agenesis was the infant of a mother with type 1 diabetes mellitus. The other 6 patients with congenital anomaly were the infants of mothers with gestational diabetes and the other 6 patients were the infants of mothers with type 2 diabetes mellitus.

It is known that fetal hyperinsulinemia leads to global cardiac enlargement and septal hypertrophies. Hypertrophic cardiomyopathy may affect the left or right ventricle. Disproportional septal hypertrophy may also be observed (20). In our study, hypertrophic cardiomyopathy was found with a rate of 6%. In a study which investigated the frequency and types of congenital heart disease in infants of diabetic mothers, the most common echocardiographic findings included PDA (70%), patent foramen ovale (68%), atrial septal defect (5%), small muscular ventricular septal defect (4%). Hypertrophic cardiomyopathy was found in 38% of the patients. When hypertrophic cardiomyopathy and PDA were excluded, the general prevalence of congenital heart disease was found to be 15% in babies of diabetic mothers (9). In our study, the most common three defects included hypertrophic cardiomyopathy (n=19), ventricular septal defect (n=17) and PDA (n=16). The general prevalence of congenital heart disease was found to be 24%. The rate of congenital heart disease was found to be 17.3% in group A, 50% in group B and 9% in group C.

Conclusively, we support transthoracic echocardiography which is a non-invasive technique performed in infants of diabetic mothers directed to investigate congenital heart disease independent of presence of any pathology in prenatal history, physical examination and familial history because of the general prevalence of 24% we found in our study. In cases of infant of diabetic mother, decreasing the fetal-maternal morbidity and mortality rates to a minimum level using appropriate diagnostic and therapeutical approaches in the prenatal period and during pregnancy and a management system including feasibility of fetal echocardiography and consultancy service before other pregnancies should be targeted.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Dr. Behçet Uz Pediatrics and Surgery Training and Research Hospital (26.05.2011/13-2011).

Informed Consent: Informed consent forms were not obtained because the study was retrospective.

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