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Prevalence of Hypertrophic Cardiomyopathy in Neonates of Diabetic Mothers: A Six-month Follow-up Study

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ABSTRACT

Background: Hypertrophic cardiomyopathy (HCM) is known to be the most common cardiac disorder in fetuses of diabetic mothers, especially when diabetes is not controlled in pregnancy. This study aimed as to estimate the prevalence of HCM in neonates born to diabetic mothers and to evaluate therapeutic interventions with follow-up after six months. We also focused on the possible association of neonatal HCM with the maternal type of diabetes.

Methods: A cross-sectional study was conducted between October 2016, and September 2017, in the Cardiac Clinic of Yazd, a city in the center of Iran. The subjects were 150 neonates of mothers with diabetes. We determined HCM through fetal echocardiography before treatment and assessed the maternal and fetal factors. Finally, after a 6-month follow-up period, the data were analyzed statistically.

Results: According to the results, the prevalence of HCM in neonates of diabetic mothers was 14% ($P < 0.0001$). The results showed that there is a relationship between maternal uncontrolled diabetes and the incidence of HCM in the infant ($P < 0.0001$), but there is no relationship between the type of diabetes and the incidence of HCM. Our results also showed that propranolol was effective in improving HCM, and spontaneous recovery of HCM was low in infants.

Conclusion: We concluded that controlling maternal diabetes has the greatest effect on the prevention of HCM in neonates. Also, neonates of diabetic mothers need more heart tests and follow-ups. Therefore, more studies on the effects of maternal diabetes-induced HCM in neonates are needed.

Introduction

Hypertrophic cardiomyopathy (HCM) is the most typical heritable cardiovascular disease described by left ventricular hypertrophy that is characterized by abnormal loading states, with cardiomyocyte hypertrophy and confusion, and raised cardiomyocyte fibrosis as key histopathological hallmarks.[1,2] These changes can cause heart failure and death. Cardiac difficulties owing to congenital heart deformity and ventricular hypertrophy are the main reasons for morbidity and mortality in fetuses and neonates of mothers with diabetes. The incidence of HCM varies widely, ranging from 10% and 71%.[3] Generally HCM has an incidence of 0.47/100,000 children and accounts for 42% of childhood cardiomyopathy. It represents a heterogeneous group of disorders with a diversity that is more apparent in childhood than at any other age.[4]

The connection between maternal diabetes and congenital abnormality is well documented.[5] The prevalence of diabetes in gestation has been rising in concordance with the worldwide epidemic of obesity. Not only is the prevalence of type I diabetes and type II diabetes rising in women of reproductive years, but even there is a surprising increase in the declared rates of gestational diabetes mellitus (GDM).[6,7] Also, maternal hyperglycemia is a critical risk factor for congenital heart disease (CHD).[8,9] The reason for this anomaly is usually unidentified, with 1% of all subjects associated with diabetes of pregnant mothers.[10,11] Some writers assert that fetal echocardiography should be advised to all pregnant women with diabetes.[12]

Fetal hyperinsulinemia in response to maternal hyperglycemia has been seen as the reason for HCM in neonates of diabetic mothers.[11] An expansion in the ventricular wall thickness may also be affected in the cardiovascular transformations seen in fetuses of mothers with diabetes, but septal hypertrophy is extensively investigated given the higher number of insulin receptors (IR) in the septum of the heart.[12] More suitable glycemic control of diabetic mothers is related to a lower occurrence of fetal heart disorder but not necessarily with lower fetal myocardial hypertrophy.[5] Diabetic HCM is usually a self-limiting issue with no significant clinical outcome and is not identified as a structural malformation of the heart. This temporary event usually regresses within the first few months of life.

Statistics display that 5.4% of Iranian women are diabetics, most of who are at the years of productivity.[13] Due to the increase of diabetes in pregnant mothers, the exact prevalence of hypertrophy in the babies of these mothers has not yet been determined. Therefore, we aimed to investigate the prevalence of HCM in fetuses of diabetic pregnant women before drug use with fetal echocardiography and evaluate therapeutic interventions with follow-up after six months.

Materials and Methods

This cross-sectional study was performed between October 2016, and September 2017, and 150 neonates of diabetic mothers were enrolled. After the approval of the Research Ethics Committee of Shahid Sadoughi University and obtaining written consent from all the parents of the infants, they were included in the study. Statistical analysis was performed on the data obtained from patients' files. The research included singleton fetuses of pregnant women identified with diabetes, without malformations and other disorders that could interfere with fetal growth. The identification of diabetes was established on the standards provided by the American Diabetes Association (ADA), that is, blood glucose (sugar) level. To assess hereditary heart problems in neonates, myocardial thickness, left ventricular myocardial performance index (LVMPI), ejection fraction (EF), shortening fraction and right ventricular myocardial performance index (RVMPI), and tricuspid flow and mitral E/A ratio were assessed in echocardiographic tests with Doppler.

Table 1. Prevalence of Hypertrophic Cardiomyopathy in Neonates of Mothers with Type I and II Diabetic

Variable		Number	Number (%) of HCM	P
Type of diabetes	Type I	43	7 (16.3)	0.392
	Type II	107	14 (13.0)	

Statistical analysis: All variables were descriptively investigated, with quantitative variables represented as means and standard deviations. Data were statistically analyzed utilizing the Statistical software (SPSP version 20). The analysis and frequency were calculated using the Fisher's exact testwith the 95% confidence interval (95%CI).

Results

In this cross-sectional study, 150 neonates born to a diabetic mother who had been referred to the Yazd Heart Clinic by a neonatologist were studied and followed up. All the neonates were full term and singleton. The following results were obtained. We categorized diabetic mothers by type of diabetes: 47 mothers had type I diabetes and 103 mothers had type II diabetes (Table 1). We only considered the type of diabetes in mothers and have insufficient information on mothers with GDM and pre-GDM.

Examination of maternal blood sugar and HBA1C in the first trimester of pregnancy showed that diabetes was controlled in 126 mothers (84%) and not controlled in 24 mothers (16%) (Table 2). Examination of neonatal echocardiography results at the first visit showed that 21 neonates (14%) had HCM. For clinical follow-up of the therapeutic effect on heart problems, propranolol was randomly administered (one in half) to neonates.

Relationship between maternal type of diabetes and the incidence of HCM in neonates: we examined the relationship between the type of diabetes and the incidence of HCM in neonates and the results showed that out of 43 neonates born to mothers with type I diabetes, 7 neonates (16.3%) had HCM, in other words, 33.3% of HCM patients were born to a mother with type I diabetes. Also from 107 neonates born to mothers with type II diabetes, 14 neonates (13.1%) had HCM, in other words, 66.7% of HCM patients were born to a mother with type II diabetes. These results were tested by Fisher's exact test and are not statistically significant by calculating P = 0.392, which means that in this study there is no relationship between the type of maternal diabetes and the incidence of HCM (Table 1).

Incidence of HCM in neonates of diabetic mothers based on controlled or uncontrolled diabetes: In our research, diabetes was controlled in 126 mothers (84%) and not controlled in 24 mothers (16%) (Table 2). All of the 21 neonates with HCM were born from mothers whose diabetes was uncontrolled (87.5%). Also, none of the 126 neonates from the diabetic mothers whose diabetes was controlled had HCM. In other words, 100% of HCM patients were born to mothers whose diabetes was not controlled. This result was tested by Fisher's exact test and is statistically significant by calculating P < 0.0001, which means that in this study there is a direct relationship between maternal uncontrolled diabetes and the incidence of HCM in the infant (Table 2).

Results of six-month follow-up: Among 21 neonates with HCM, 10 (47.6%) neonates were randomly selected and given propranolol for 6 months (Table 3).

Table2. Prevalence of Hypertrophic Cardiomyopathy in Neonates of Mothers with Controlled and Uncontrolled Diabetic

Controlled Diabetes	Number	Number (%) of HCM	P
No	24	21 (87.5)	< 0.0001
Yes	126	0 (0.0)	

Table 3. Six-month Follow-up After Birth for Neonates with Hypertrophic Cardiomyopathy with Prescription Propranolol

Prescription of propranolol in HCM (n = 21)	Number	Follow up after 6 months	Number (%)	P
Yes	10	Improving	10 (100)	< 0.0001
		Persistent	0 (0)	
No	11	Improving	3 (27.3)	< 0.0001
		Persistent	8 (72.7)	

Since the treatment of hereditary congenital malformations is more effective in infants, we performed drug intervention to increase the speed of hypertrophy treatment in 10 infants. In some symptomatic neonates, we had chosen propanol to decrease the course of spontaneous treatment of cardiomyopathy. According to previous studies, propanol does not have any specific side effects in low and standard doses. At the end of 6 months, after control echocardiography, it was found that all (100%) neonates with HCM who took propranolol had a full recovery. This result was tested by Fisher's exact test and was statistically significant by calculating $P < 0.0001$, which meant that in this study, propranolol consumption was effective in improving HCM. Our results also showed, out of 11 neonates (52.4%) with HCM who were not prescribed propranolol at the end of 6 months, 8 neonates (72.7%) still had HCM after echocardiography. This result was tested by Fisher's exact test and was significant by calculating $P < 0.0001$, which meant that in this study the rate of spontaneous improvement of HCM was low among neonates (Table 3).

Discussion

Prior investigations have demonstrated that maternal hyperglycemia may lead to HCM and heart diastolic action disability,[14] and described HCM related to diabetes during pregnancy. Distinct from sarcomeric HCM, neonatal HCM related to diabetes during gestation is self-limiting and in fact, tend to settle in weeks to months.[15] Previous reports demonstrate that maternal diabetes has teratogenic impacts on the development of the fetal cardiovascular system, with a reported risk of malformation in published investigations of 1.7-4.0%.[10]

Gestational diabetes is related to difficulties during pregnancy and raised the risk of type II diabetes subsequently in mothers.[16] Type II diabetes is an advanced disorder that positions important stress on patients and their families and creates a vicious cycle of metabolic disorders for future generations.[17] Despite advances in medical care supplied during gestation to diabetic mothers, the cardiovascular difficulties in their neonates are yet more recurring than in the neonates of the global population.[5] HCM is a well-recognized comorbidity in neonates of diabetic mothers and is ascribed to a compensating addition in fetal insulin secretion. Neonates with congenital hyperinsulinism have extreme antenatal and postnatal insulin secretion because of defects in pathways of insulin secretion (most typically the KATP channel). When at more developed gestational ages, fetal hyperinsulinemia following insufficient maternal glycemic control raises the expression of insulin receptors (IR) in cardiomyocytes, Insulin, an anabolic hormone, induces hypertrophy and hyperplasia of cardiomyocytes, followed by myocardial hypertrophy.[18-20]

HCM has been documented in some neonates with hyperinsulinism, but its expanse and risk factors for its expansion have not been assessed.[11] One Cohort study assessed the overall prevalence of hypertrophy in children. In a 10‐Year Medicaid Cohort in pediatrics, Nandi et al. achieved a prevalence rate for pediatric HCM of 1.2/1,000,000 and an annual incidence rate

of 1.3/100,000. In their cohort study, cardiac-related mortality was 2.9% and 70.0% of those who died were ≤ 13 months of age.[21] This suggests that in the general population, the prevalence of hypertrophy is very low. But in neonates of diabetic mothers, the incidence of hypertrophy is very high.

The results of this research demonstrate that diabetes in pregnant women plays a critical role in the prevalence of HCM. According to our results, the prevalence of HCM was 14% in neonates of diabetic mothers (P = 0.0001). The most similar result to this study was done by Akbariasbagh et al. in 2016. They assessed cardiovascular malformations in infants of diabetic mothers. According to their results, the prevalence of cardiovascular anomalies was significantly higher in infants of diabetic mothers and the prevalence of HCM was 9%.[13]

Other studies evaluating the prevalence of HCM in neonates of diabetic mothers reported a higher prevalence than our results. Muhammad et al. in Egypt estimated the frequency of cardiac complications in infants of diabetic mothers in NICU. They achieved the frequency of HCM was 30% in infants of diabetic mothers.[22] Palmieri et al. evaluated the prevalence of HCM in fetuses of mothers with gestational diabetes before beginning treatment. They showed the prevalence of HCM in fetuses of pregnant women with GDM before treatment was 54% (95%CI: 41.3-65.1%).[12] Roodpeyma et al., in 2013 evaluated cardiovascular disease in neonates of diabetic mothers. They also investigated possible associations between neonates' heart lesions and the type of maternal diabetes. They demonstrated a high prevalence of CHD in IDDM (type II) in their pediatric cardiology clinic and the prevalence of HCM was observed in 46.9% of cases. In their study neither the types of maternal diabetes nor the somatic results of newborns were associated with the happening of cardiovascular disease.[5]

While HCM in infants of diabetic mothers is reversible and often mild or asymptomatic, it can be harmful and lead to infant or fetal death. Most symptomatic neonates require only supportive care with supplemental oxygen, but β-adrenergic blockers such as propranolol may be essential to improve ventricular output.[11] In one study, Ostman-Smith showed in patients with heart failure due to HCM, side effects of beta-blockers are surprisingly rare, even at very high doses.[23] We used propanol therapy to increase the recovery rate of HCM. The recovery rate was 100%, but in the control group, the spontaneous recovery rate was 27%.

As a consequence, the efficiency of diagnostic methods (such as fetal echocardiography, before and after birth), providing particular attention to diabetic mothers, and requiring therapeutic and supportive care to symptomatic neonates appears very recommendable in such subjects.[13] We conclude that knowing the prevalence of HCM among newborns in diabetic mothers provides a good basis for accurately managing diabetes during pregnancy and early diagnosis and treatment of postpartum abnormalities, which may reduce the severity of HCM.

Conclusion

The prevalence of HCM in our study was 14%, which percentage is very high compared to the total prevalence of HCM. This suggests that the assessment of infants of diabetic mothers is very important. Regardless of the type of maternal diabetes, control of diabetes in pregnant women seems to be essential in preventing HCM in neonates. Early echocardiography in neonates is effective in diagnosing HCM. Therefore in all diabetic mothers, the echocardiography of their neonates should be done. In some symptomatic neonates, we had prescribed propanol to decrease the course of spontaneous treatment of cardiomyopathy due to the low rate of spontaneous recovery in neonates. This suggests that propranolol may be effective for the treatment of affected infants with HCM.

Conflict of Interest

The authors have no conflict of interest.

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