Neonatal Outcomes in Different Maternal Diabetes Types: Experience from a Tertiary Care Unit

Farklı Maternal Diyabet Tiplerinde Yenidoğan Sonuçları: Üçüncü Basamak Yoğun Bakım Ünitesi Deneyimi

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ABSTRACT

Objective: Infants of mothers with diabetes (IMD) may require hospitalization in neonatal intensive care units (NICU) for various reasons. In our study, our objective was to compare clinical and laboratory findings, as well as malformations and morbidities among IMD based on the types of maternal diabetes.

Material and Methods: The diabetic status of mothers of 4713 infants admitted to tertiary neonatal intensive care unit (NICU) at Ankara Bilkent City Hospital between January 1, 2020, and January 1, 2022, was examined. We retrospectively analyzed demographic data, clinical and laboratory characteristics, and morbidities for 616 infants born to mothers with impaired glucose tolerance (IGT), gestational diabetes mellitus (GDM), or pre-existing gestational diabetes mellitus (Pre-GDM).

Results: Of the 616 cases, 167 (27.1%) were infants of mothers with IGT, 394 (64%) with GDM and 55 (8.9%) with Pre-GDM. The prevalence of macrosomia was significantly higher in Pre-GDM (30.9%) than in the IGT (15%) and GDM (19.3%) groups (p=0.033). The most common malformations in the cases were related to the cardiovascular system (CVS) (77.4%). The frequency of septal hypertrophy was significantly higher in the Pre-GDM group compared to the IGT and GDM groups, and in the GDM group compared to the IGT group (p<0.001). The rates of septal hypertrophy, CVS malformation, LGA/macrosomia, and hypocalcemia were found to be significantly higher in infants of mothers with insulin requirement and high HbA1c levels, particularly in Pre-GDM group (p<0.001). According to the ROC analysis for the optimum maternal HbA1c value predicting septal hypertrophy, the threshold value was found to be 6% (AUC=0.693) with 62% sensitivity and 66% specificity. In logistic regression analysis, macrosomia and maternal HbA1c ≥6% were determined as independent risk factors for the presence of septal hypertrophy.

Conclusion: Despite variations in the type of maternal diabetes, IMD experience significant clinical challenges when hospitalized and monitored in the NICU. Infants born to mothers with IGT may also be subjected to maternal hyperglycemia. The likelihood of certain complications rises in infants born to pregnant women with inadequate glycemic control, particularly those with elevated HbA1c levels. By ensuring maternal glycemic control and closely monitoring these infants, it is possible to reduce both mortality and morbidity.

Key Words: Congenital abnormalities, Gestational diabetes, Septal hypertrophy, Type 1 Diabetes Mellitus, Type 2 Diabetes Mellitus

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ÖZ

Amaç: Diyabetik anne bebekleri (DAB) farklı nedenlerle yenidoğan yoğun bakım ünitelerine (YYBÜ) yatırılarak izlenebilir. Çalışmamızda DAB'lerinde perinatal ve postnatal dönemde ortaya çıkan malformasyonların, izlemde eşlik eden morbiditelerin, klinik ve laboratuvar bulguların maternal diyabet tiplerine göre karşılaştırılması amaçlandı.

Gereç ve Yöntemler: Ankara Bilkent Şehir Hastanesi'nde 3. Düzey YYBÜ'de 01.01.2020 ile 01.01.2022 tarihleri arasında yatırılarak izlenen 4713 yenidoğanın annelerinin diyabet durumu incelendi. Annelerinde bozulmuş glukoz toleransı (BGT), gestasyonel diyabetes mellitus (GDM) veya Pre-GDM olan 616 yenidoğan retrospektif olarak incelendi.

Bulgular: Altıyüzonaltı vakanın 167'si (%27.1) BGT'li, 394'ü (%64) GDM'li, 55'i (%8.9) Pre-GDM'li anne bebeğiydi. Makrozomi sıklığı Pre-GDM'de (%30.9), BGT (%15) ve GDM (%19.3) gruplarına göre anlamlı derecede yüksekti (p=0.033). Vakalarda en sık görülen malformasyonlar kardiyovasküler sistem (KVS) (%77.4) ile ilgiliydi. Septal hipertrofi sıklığı Pre-GDM'de BGT, GDM gruplarından, GDM grubunda da BGT grubundan anlamlı (p<0.001) olarak daha yüksekti. İnsülin ihtiyacı olan ve HbA1c düzeyi yüksek olan özellikle Pre-GDM'li anne bebeklerinde septal hipertrofi, KVS malformasyonu, LGA/makrozomi, hipokalsemi görülme oranları anlamlı olarak yüksek saptandı (p<0.001). Septal hipertrofiyi öngören optimum maternal HbA1c değeri için yapılan ROC analizi sonucuna göre %62 duyarlık ve %66 özgüllük ile eşik değer %6 (AUC: 0.693) olarak bulundu. Lojistik regresyon analizinde yenidoğanda makrozomi ve HbA1c ≥ %6 olması septal hipertrofi varlığı için bağımsız risk faktörü olarak belirlendi.

Sonuç: Maternal diyabet tipindeki farklılığa rağmen YYBÜ'ye yatırılarak izlenen diyabetik anne bebeklerinde ciddi klinik sorunlar yaşanmaktadır. BGT'li annelerin bebekleri de maternal hiperglisemiye maruz kalabilir. Glisemik kontrolü bozuk olan özellikle de HbA1c değeri yüksek gebelerden doğan bebeklerde potansiyel olarak bazı sorunların görülme sıklığı artmaktadır. Maternal glisemik kontrol sağlanarak ve bu bebekler yakın takip edilerek mortalite ve morbidite azaltılabilir.

Anahtar Sözcükler: Konjenital anomali, Gestasyonel Diyabet, Septal hipertrofi, Tip 1 Diyabetes Mellitus, Tip 2 Diyabetes Mellitus

INTRODUCTION

Diabetes Mellitus (DM) refers to a group of metabolic diseases that progress with increased blood sugar (1). If the diagnosis of DM is detected for the first time during pregnancy, it is called gestational diabetes mellitus (GDM), and if it is present before pregnancy, it is called pre-existing gestational diabetes mellitus (Pre-GDM) (2). It is one of the common complications of pregnancy and its frequency is increasing. Women diagnosed with pre-GDM or GDM are at increased risk for pregnancy complications compared to other pregnant women (3). Maternal hyperglycemia is thought to be the most important teratogen. Controlling diabetes before pregnancy and monitoring it throughout pregnancy is important to reduce the effects of diabetes on the fetus and newborn (4). Potential complications should be aware of the management of infants of diabetic mothers (IMD), and common problems that cause these infants to be admitted to the neonatal intensive care unit should be anticipated. In our study, we aimed to evaluate the IMD who were followed up in 3rd level neonatal intensive care unit (NICU) and to compare their accompanying morbidities and clinical and laboratory findings according to the types of maternal diabetes.

MATERIALS and METHODS

The diabetic status of mothers whose infants were admitted and monitored in the tertiary NICU at Ankara Bilkent City Hospital from January 1, 2020, to January 1, 2022, was examined. Our NICU is located at a hospital where approximately 16,000 births take place annually. It is a specialized tertiary-level NICU affiliated with a perinatal center. It is designed to handle the most complex and critical neonatal cases. It has the capability to perform neonatal surgeries and provides post-operative care for newborns with congenital anomalies. It is a center with approximately 2000 admissions annually. Demographic data, follow-up morbidities, and clinical and laboratory characteristics of IMD and their mothers were retrospectively evaluated. The exclusion criteria comprised infants with incomplete data, those born to mothers without diabetes, and those who did not undergo GDM screening during prenatal care follow-up.

Throughout the study period, a total of 4713 patients were hospitalized in the NICU. However, 226 patients who were referred to our hospital were excluded from the study due to the unavailability of their data. In our analysis, the oral glucose tolerance test (OGTT) and hemoglobin A1c (HbA1c) results of the mothers from 4487 cases with accessible data were evaluated. The results of both two-stage and one-stage screening for gestational diabetes mellitus (GDM) were analyzed retrospectively.

Mothers exhibiting impaired plasma glucose levels identified through a 50 g oral glucose solution test, yet registering a sole elevated value in the 100 g oral glucose tolerance test (OGTT), were assigned to the 'impaired glucose tolerance group' (IGT). In the two-stage approach, mothers were classified into the gestational diabetes mellitus (GDM) group if their 1st hour plasma glucose (PG) exceeded 180 mg/dl with 50 g glucose or if PG ranged between 140-179 mg/dl with 50 g, along with two elevated values in the 100g OGTT. Additionally, in the one-stage approach, mothers with a single elevated value in the 75 g OGTT were also considered part of the GDM group. Mothers with a documented diagnosis of Type 1 or Type 2 diabetes mellitus before pregnancy were categorized into the Pre-GDM group. Those who displayed impaired plasma glucose levels detected by the 50 g oral glucose solution but declined to undergo the 100g OGTT, as well as those who exhibited elevated HbA1c levels but refused any form of OGTT, were also included in the IGT group.

A total of 616 newborns, born to mothers with IGT, GDM, or Pre-GDM, were enrolled in the study. Detailed examination of the infants' demographic characteristics, clinical issues, and laboratory data was conducted utilizing the electronic patient information system, and the findings were documented in the study form. The study also recorded maternal diabetes types, diabetes control status, and demographic characteristics. Comprehensive data analyses were performed both collectively and by making comparisons between different groups.

The study was approved by the Ankara Bilkent City Hospital clinical research ethics committee no. 2 (23.08.2023/E2-23-4767).

Statistical analysis

Mean, standard deviation, median, minimum, maximum, frequency and percentages were used in descriptive statistics of the data. Distribution of variables was measured with the Kolmogorov-Simirnov test. Kruskal-Wallis and Mann-Whitney u test were used in the analysis of quantitative independent data. Chi-square test was used in the analysis of qualitative independent data, and Fischer test was employed when chi-square test conditions were not met. IBM Statistical Package for the Social Sciences, version 27.0 (SPSS Inc., Armonk, NY, IBM Corp., USA) software was used in the analyses. The results were considered statistically significant for p <0.050 in the analyses conducted in this study.

RESULTS

Out of 4713 infants hospitalized during the study period, maternal data of 4487 infants were obtained; 167 (3.7%) had IGT, 394 (8.7%) had GDM, 38 (0.84%) had Type 2 DM, 17 (0.37%) had Type 1 DM and 3871 were healthy. Demographic characteristics of mothers and infants were analyzed according to maternal diabetes type (Table I). Maternal preeclampsia rate was significantly higher in the Pre-GDM (18.2%) group compared to the IGT (4.8%) and GDM (6.1%) groups (p=0.002).

Clinical problems and laboratory findings that may be observed in cases according to the type of maternal diabetes were analyzed (Table II). The frequency of macrosomia was found to be significantly higher in the Pre-GDM group (30.9%) compared to the IGT (15%) and GDM (19.3%) groups (p=0.033).

When the infants were grouped according to the diabetes control status of their mothers, the incidence of macrosomia, hypomagnesemia and hypocalcemia was found to be significantly higher in the insulin-requiring group compared to those who were regulated with diet alone (p<0.001). In infants with macrosomia and hypomagnesemia, the HbA1c values of their mothers were significantly higher (p<0.001).

There was no difference in terms of gastrointestinal system (GIS), central nervous system (CNS) and cardiovascular system (CVS) malformations in the study groups. There were a total of 83 (13%) cases with genitourinary system (GUS) malformations. In the GDM group, GUS anomalies were significantly higher than in the IGT group (p=0.048). Hydronephrosis (10%) was the most common type of GUS anomaly.

The incidence of CVS malformations was similar between the study groups (90.7% in Pre-GDM, 79% in GDM, 75.3% in IGT) (Table III).

TableI: Demographic characteristics of mothers and infants according to maternal diabetes type

	IGT (n=167)	GDM (n=394)	Pre-GDM (n=55)	p
Maternal age*	30 (26- 35)	32 (26-36)	33 (28-39)	0.026
Gravida*	2 (1-3)	2 (1-4)	3 (2-4)	0.126
Preeclampsia†	8 (4.8)	24 (6.1)	10 (18.2)	0.002
Hypertension†	8 (4.8)	36 (9.1)	8 (14.5)	0.056
Hypothyroidism†	15 (9)	46 (11.7)	11 (20)	0.088
Maternal HbA1c‡	5.9 (4.5-7)	5.7 (4.3-9.5)	7.15 (5.3-11.5)	<0.001
Maternal Diabetes Control				
Diet†	167 (100)	277 (70.3)	7 (12.7)	<0.001
Diet and Insulin†	0 (0)	117 (29.7)	48 (87.3)	<0.001
C/S†	135 (80.8)	330 (83.8)	49 (89.1)	0.347
Gestational age*	35 (33-38)	35 (33-37)	35 (32-36)	0.219
Male Gender†	91 (54.5)	247 (62.7)	31 (56.4)	0.165
Multiple Pregnancy†	26 (15.6)	59 (15)	2 (3.6)	0.064
Birth weight*	2590 (1860-3260)	2660 (1818-3190)	2690 (1920-3390)	0.761
LGA†	25 (15)	76 (19.3)	17 (30.9)	0.033
SGA†	19 (11.4)	55 (14)	5 (9.1)	0.484

***:** *median (IQR),* **†:** *n(%),* **‡:** *median (min-max),* ***IGT:** Impaired Glucose Tolerance, **GDM:** Gestational Diabetes Mellitus, **Pre-GDM:** Pregestational Diabetes Mellitus, **IQR:** Interquartile range, **HbA1c:** Glycosylated hemoglobin A1c, **C/S:** Caesarean section, **LGA:** Large for gestational age, **SGA:** Small for gestational age*

Table II: Clinical and laboratory findings in infants according to maternal diabetes type

	IGT* (n=167)	GDM* (n=394)	Pre-GDM* (n=55)	p
Macrosomia	25 (15)	76 (19.3)	17 (30.9)	0.033
Fetal Growth Restriction	20 (12)	56 (14.2)	5 (9.1)	0.500
Preterm birth	104 (62.3)	263 (66.8)	42 (76.4)	0.154
Respiratory Distress	128 (76.6)	316 (80.4)	50 (90.9)	0.070
TTN	56 (33.5)	157 (40.2)	21 (38.2)	0.337
RDS	30 (18.1)	96 (24.6)	10 (18.2)	0.177
Pneumonia	16 (9.8)	34 (8.8)	6 (11.1)	0.839
PHT	11 (6.7)	20 (5.2)	3 (5.7)	0.790
Pneumothorax	4 (2.4)	13 (3.4)	4 (7.4)	0.557
EOS	82 (50)	189 (48.8)	34 (61.8)	0.196
LOS	34 (20.7)	85 (22.1)	14 (25.9)	0.727
Birth injury	0 (0)	3 (0.8)	0 (0)	0.558
Asphyxia	11 (6.7)	15 (3.9)	5 (9.3)	0.147
Portal Vein Thrombosis	2 (1.2)	5 (1.3)	2 (3.7)	0.936
Syndromic Infant	3 (1.8)	11 (2.8)	0 (0)	0.743
Feeding Intolerance	10 (6.1)	41 (10.6)	2 (3.7)	0.086
NEC	3 (1.8)	9 (2.3)	1 (1.9)	0.706
Hydrops fetalis	3 (1.8)	1 (0.3)	0 (0)	0.892
Hypoglycemia	27 (16.4)	53 (13.7)	12 (21.8)	0.251
Polycythemia	27 (16.3)	71 (18.3)	10 (18.2)	0.850
Thrombocytopenia	16 (9.6)	45 (11.6)	7 (12.7)	0.745
Anemia	7 (4.2)	23 (5.9)	3 (5.5)	0.721
Hyperbilirubinemia	123 (75.5)	290 (75.3)	47 (87)	0.156
Hypocalcemia	87 (53)	199 (51.7)	39 (72.2)	0.017
Hypomagnesemia	10 (6.1)	33 (8.6)	9 (16.7)	0.058

***:** *n(%),* ***IGT:** *Impaired Glucose Tolerance,* ***GDM:** *Gestational Diabetes Mellitus,* ***Pre-GDM:** *Pregestational Diabetes Mellitus,* ***TTN:** *Transient Tachypnea of the Newborn,* ***RDS:** *Respiratory Distress Syndrome,* ***EOS:** *Early Onset Sepsis,* ***LOS:** *Late Onset Sepsis,* ***PHT:** *Pulmonary Hypertension,* ***NEC:** *Necrotizing enterocolitis*

Table III: CVS malformations according to maternal diabetes type

	IGT* (n=167)	GDM* (n=394)	Pre-GDM* (n=55)	p
Septal Hypertrophy	5 (3)	53 (13.8)	14 (25.9)	<0.001
PDA	58 (35.2)	127 (33)	23 (42.6)	0.370
PFO	85 (51.5)	225 (58.4)	36 (66.7)	0.111
ASD	55 (33.3)	102 (26.5)	17 (31.7)	0.242
VSD	11 (6.7)	26 (6.8)	2 (3.7)	0.689
TGA	0 (0)	1 (0.3)	0 (0)	0.892
AoC	1 (0.6)	2 (0.3)	0 (0)	0.988
LVH	1 (0.6)	4 (1)	0 (0)	0.979
TOF	1(0.6)	3 (0.8)	0 (0)	0.986
Aortic Stenosis	0 (0)	1 (0.3)	0 (0)	0.899

***:** *n(%),* ***IGT:** *Impaired Glucose Tolerance,* ***GDM:** *Gestational Diabetes Mellitus,* ***Pre-GDM:** *Pregestational Diabetes Mellitus,* ***PDA:** *Patent Ductus Arteriosus,* ***PFO:** *Patent Foramen Ovale,* ***ASD:** *Atrial Septal Defect,* ***VSD:** *Ventricular Septal Defect,* ***TGA:** *Transposition of great arteries,* ***AoC:** *Aortic coarctation,* ***LVH:** *Left ventricular hypoplasia,* ***TOF:** *Tetralogy of Fallot*

Table IV: Independent risk factors for the development of septal hypertrophy

	OR	95% CI	p
LGA	4.5	2.3-8.7	<0.001
HbA1c≥ 6	2.26	1.15-4.46	0.018

CI: *confidence interval*

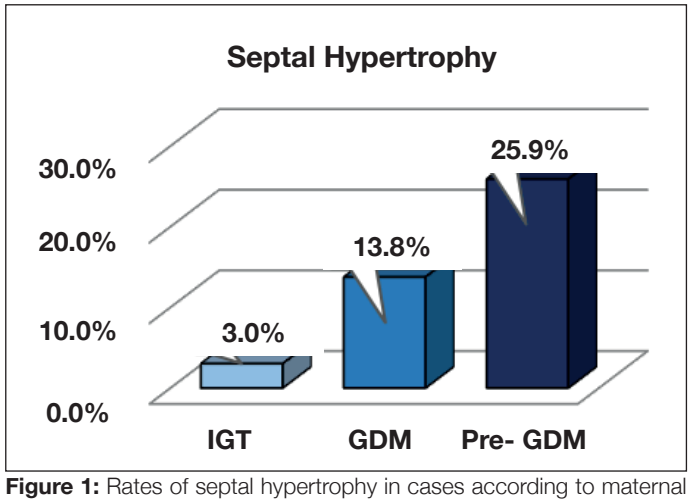

Figure 1: Rates of septal hypertrophy in cases according to maternal diabetes type.

IGT: Impaired Glucose Tolerance, **GDM:** Gestational Diabetes Mellitus, **Pre-GDM:** Pregestational Diabetes Mellitus

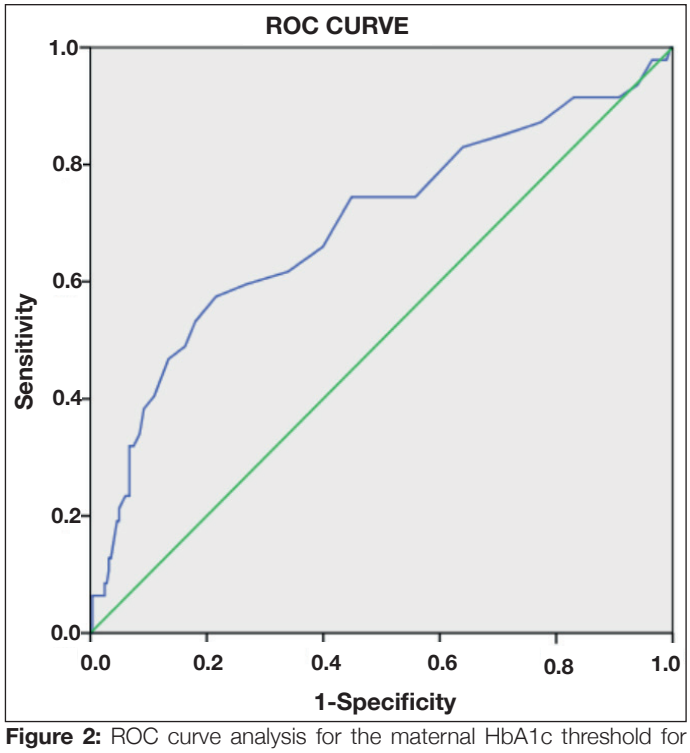

Figure 2: ROC curve analysis for the maternal HbA1c threshold for predicting septal hypertrophy.

In our study, the rate of septal hypertrophy in the Pre-GDM group was found to be significantly higher than the other groups (Figure 1). When all cases were compared based on the diabetes management approach in mothers, the incidence of CVS malformation, septal hypertrophy and PFO was significantly higher in the insulin-regulated group compared to the diet-regulated group (p<0.001). At the same time, HbA1c values of mothers were significantly higher in infants with septal hypertrophy and CVS malformations (p<0.001 and 0.007, respectively).

According to the ROC analysis for the optimum maternal HbA1c value predicting septal hypertrophy, the threshold value was found to be 6% (AUC=0.693) with a sensitivity of 62% and specificity of 66% (Figure 2).

In multivariate logistic regression analysis, macrosomia and maternal HbA1c ≥ 6% were determined as independent risk factors for the presence of septal hypertrophy (Table IV).

DISCUSSION

In our study, we observed that IMD who were hospitalized in the NICU frequently encountered similar clinical issues, regardless of the specific type of maternal diabetes. Higher rates of septal hypertrophy, CVS malformation, large for gestational age (LGA)/ macrosomia, and hypocalcemia were noted in infants born to mothers with elevated HbA1c levels and insulin requirements, particularly within the pre-GDM group.

A significant association was found between a HbA1c value of 6% and the occurrence of septal hypertrophy. Furthermore, it was demonstrated that having an HbA1c level of 6% or higher approximately doubled the risk of septal hypertrophy.

Congenital anomalies observed in infants of mothers with gestational DM and Type 2 DM have been reported to affect the same organ systems as those previously identified in pregnancies with Type 1 diabetes. High levels of hyperglycemia in mothers have been shown to lead to an increased risk of abnormalities in general (5,6). When the congenital malformations seen in IMD were examined in our study, it was determined that the same organ systems were affected in the IGT, GDM and Pre-GDM groups. This also suggests that the IGT group may be undiagnosed GDM patients.

In a study conducted in Canada between 2002 and 2010, involving approximately 2.3 million infants, a strong association was demonstrated between Type 1 or Type 2 DM and the risk of congenital heart disease (7). In our study, the rate of CVS malformation, septal hypertrophy, and PFO was found to be significantly higher in the group that needed insulin for diabetes control compared to the group that was regulated only by diet. When the literature is examined, it has been shown that the risk of septal hypertrophy is higher in infants of mothers with Pre-GDM than in infants of mothers with GDM (8). Septal hypertrophy is associated with fetal hyperinsulinism. High blood sugar levels in the mother cause fetal hyperglycemia, which in turn leads to fetal hyperinsulinemia. The anabolic effects of insulin can cause fetal macrosomia by increasing the amount of total body protein, glycogen and fat, as well as cellular

hypertrophy and hyperplasia in internal organs such as the heart and interventricular septum (9,10). In a retrospective study in which newborns diagnosed with congenital heart disease during hospitalization and follow-up between 2013 and 2017 were evaluated, septal hypertrophy was reported in 20.6% of IMD (11). In our study, the frequency of septal hypertrophy was 11.7% in all groups, but it was found to be 25.9% in Pre-GDM, 13.8% in GDM, and 3% in IGT. Septal hypertrophy rate was found to be significantly higher in the Pre-GDM group than in the IGT and GDM groups, and in the GDM group than in the IGT group. It is usually a benign and transient pathology in IMD. This condition usually has no clinical manifestations and is often detected incidentally during routine echocardiographic examination.

Due to standardization challenges and uncertainty regarding diagnostic thresholds, HbA1c has not been recommended as a diagnostic tool for diabetes for many years. Individuals with IGT or HbA1c levels ranging from 5.7% to 6.4% are noted to have prediabetes. The HbA1c cut-off point determined for the diagnosis of diabetes in the guidelines is accepted as 6.5% (12). In the presence of hemoglobinopathy or in situations that accelerate the erythrocyte life cycle (recent bleeding or blood transfusion, pregnancy, hemodialysis, erythropoietin treatment, etc.), HbA1c test is not preferred as a reliable diagnostic tool for the diagnosis of diabetes. We also found it to be high in infants of mothers with Pre-GDM in our study. In our study, we determined the optimal maternal HbA1c value predicting the presence of septal hypertrophy in infants born to mothers with Pre-GDM as 6%. We also identified that HbA1c ≥ 6% was an independent risk factor for the presence of septal hypertrophy.

When GDM mothers and their infants were retrospectively examined by Bai et al. (13), it was demonstrated that as the severity of OGTT abnormalities increased, the risk of fetal macrosomia also increased. In a study conducted by Persson et al.(14), it was shown that being an infant of a mother with Type 1 diabetes mellitus increased the risk of macrosomia. In a multicenter study conducted between 2000 and 2006, involving 23.316 pregnant women to examine the outcomes of maternal hyperglycemia, a strong relationship between hyperglycemia and increased birth weight was demonstrated. In infants of mothers with DM, the incidence of fetal macrosomia or LGA varies between 15-45% compared to 5-15% observed in the general population (15, 16). In a study investigating the effect of maternal hyperglycemia on macrosomia, a positive relationship was reported between increased maternal HbA1c and risk of macrosomia (17). In our study, consistent with the literature, the incidence of LGA was 19.2% in all groups, but the rate of macrosomia or LGA in the Pre-GDM group was found to be significantly higher than in the IGT and GDM groups. In our study, the significantly higher maternal HbA1c value in the Pre-GDM group suggests that infants are exposed to hyperglycemia for a longer period of time, which increases the incidence of macrosomia.

Our study's retrospective design and the single-center nature were identified as limitations. Infants of non-diabetic mothers could not be included in our study. Our data should also be evaluated considering the large number of mothers who did not undergo GDM screening during pregnancy follow-up processes.

In conclusion, the presence of comparable clinical issues and congenital malformations across both groups suggests that infants born to mothers with IGT are similarly exposed to maternal hyperglycemia. Vigilant monitoring during the postnatal period is essential for infants of mothers with IGT. Given that close perinatal and postnatal follow-up is believed to potentially reduce mortality and morbidity, it becomes crucial to educate mothers about potential conditions. The incidence of certain complications rises in pregnant women with inadequate glycemic control, particularly with elevated HbA1c levels, and affects infants born from such pregnancies. Further research supporting the significance of oral glucose tolerance tests should be undertaken.

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