CLINICAL AND ECHOCARDIOGRAPHIC FINDINGS IN NEWBORNS OF DIABETIC MOTHERS

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SUMMARY – The aim of the study was to assess the use of echocardiographic measurements in newborns of diabetic mothers. Maternal diabetes is associated with an increased risk of morbidity and mortality in pregnancy and in perinatal period. Thirty-five newborns of diabetic mothers (pregestational or gestational diabetes; case group) and thirty-five controls (control group), born between January 2009 and December 2012 in Cluj-Napoca (north-west of Romania), were included in this study. A Logiq e ultrasound with an 8 MHz transducer was used to measure echocardiographic parameters. The interventricular septal thickness in case group was higher as compared with control group (at end systole = 6.61±1.64 mm *vs.* 5.75±0.95 mm, p=0.0371; at end diastole = 4.61±1.59 mm *vs.* 3.42±0.70 mm, p=0.0001). A risk ratio of 2.333 (0.656, 8.298) was obtained for septal hypertrophy. A higher proportion of septal hypertrophy was identified in the newborns of mothers with gestational diabetes compared to the newborns of pregestational diabetes mothers (p=0.0058). The mean birth weight was significantly higher in newborns of diabetic mothers (3695.57±738.63) as compared with controls (3276.14±496.51; p=0.0071). Infants born to mothers with diabetes proved to be at a high risk of septal hypertrophy.

Key words: *Infant, newborn; Pregnancy - complications; Diabetes mellitus; Echocardiography; Hypertrophy; Heart septum – pathology*

Introduction

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia that is the result of secretion deficiency and/or dearth of activity[1]. Diabetes is associated with an increased risk of morbidity and mortality both in pregnancy and in perinatal period[2]. Fetal and neonatal complications depend on the time of gestational diabetes onset[3]. In the first quarter, diabetes can cause early slowing of growth and an early increased risk of congenital anomalies. In the second quarter, macrosomia, selective organomegaly, and slowing of the central nervous system development occur. In the third quarter, chronic hypoxemia and death *in utero* are caused by diabetes. Perinatal mortality of infants born to mothers with diabetes has declined over the past 30 years but remains high when compared with the general population. Two multicenter trials have reported mortality of 4.4% *versus* 0.7% (France[4]), and 4.6% *versus* 1.25% (New Zealand[5]). The risk of fetal death is 4-5 times higher in pregnancies with pre-existing insulin-dependent diabetes mellitus and it becomes even higher when associated with acidosis, hypertension or preeclampsia[4]. Fetal hypoxia occurs in infants of diabetic mothers as a result of the increased demand of oxygen because of hyperinsulinism and decrease in the capacity of the placenta to compensate for this increased demand.

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The incidence is 25% of newborns of mothers with diabetes mellitus[6]. The risk of respiratory distress in this category of newborns is 3-5 times higher than in the general population (25%-38%) and it is due to qualitative surfactant deficiency[7]. Congenital malformations are 2 to 4 times more common in cases with pregestational diabetes than in normal pregnancy. The incidence is variable, i.e. 4.1% if only severe malformations are taken into account, or 7.9% as also reported in the respective literature[6,8]. There are multicenter studies which have identified an incidence of malformations of 8.3% for cases in which glycosylated hemoglobin was higher than 8% in the first trimester and 2.5% for cases in which glycosylated hemoglobin was lower than 8%[9,10]. Isolated septal hypertrophy is present in 35%-40% of the infants born to diabetic mothers, but only 10% show signs of heart failure[11]. The cause is maternal hyperinsulinemia and it occurs in late pregnancy, week 34-40, when the process of glycogen storage in the septum is present. Myocardial hypertrophy, however, may occur despite adequate control of the maternal blood glucose. It is mostly asymptomatic, but severe forms with obstruction in the left ventricular ejection may also appear, leading to heart failure. In most cases, complete regression can be noticed before the age of 6 months. In addition, the risk of developing pulmonary hypertension is higher in infants of mothers with diabetes mellitus[12].

The progress made in recent years in monitoring the newborns of diabetic mothers has reduced perinatal mortality, but significant morbidity is still recorded[6,12]. Considering this trend, the aim of our study was to evaluate the newborns of diabetic mothers by echocardiography to early identify any heart problems.

Subjects and Methods

This cross-sectional study included infants born at the 1st Clinical Hospital of Obstetrics and Gynecology, a teaching hospital in the north-west of Romania and a Tertiary-Care Perinatal Center in Romania. The study was conducted between January 2009 and December 2012 and included a total of 70 subjects. Two groups of newborns were investigated: a group of newborns of diabetic mothers (diabetes mellitus type 1 or 2 diagnosed before pregnancy or gestational diabetes as case group) and a group of newborns of non-diabetic mothers (control group). For each subject meeting the inclusion criteria in the case group, a matched subject in terms of gender and gestational age was identified and included in the control group. No macrosomic newborns of non-diabetic mothers were included in the study. An informed consent for including newborns in the study was obtained from all parents.

The following maternal variables were collected: type of diabetes (pregestational or gestational), when diabetes was diagnosed (maternal age for pregestational diabetes and gestational age expressed in weeks for gestational diabetes), the highest maternal blood glucose level (mg/dL) and glycosylated hemoglobin (%) during pregnancy.

The following data were collected for each newborn included in the study:

- Demographic characteristics: gender (female/male), weight (g), head circumference (cm), and type of delivery (vaginal/cesarean). Ponderal index (PI) was calculated for each subject using the following formula: PI = 100·weight (kg)/height (cm^3)[13]. Furthermore, the brain:body weight ratio (BBR) as an indicator of head-to-body proportionality was calculated by applying the following formula: BBR = 100· [0.037·cranial-perimeter)$^{2.57}$]/ birth-weight (g)[14]. The weight at discharge was also recorded.
- Clinical characteristics: Apgar score at 1 and 5 minutes after birth, obstetric trauma, hyperbilirubinemia, and jaundice were recorded. Moreover, the application of resuscitation procedures (dichotomous variable yes/no), as well as the length of hospital stay were also recorded.
- Para-clinical characteristics: glycemia and ASTRUP parameters were investigated for infants of diabetic mothers using the Critical Care Express, Nova Biomedical. Post-birth glycemia of newborns of diabetic mothers was evaluated by the blood sugar level (mg/dL) at 1 hour after birth (a value less than 40 mg/dL was considered as hypoglycemia). The glucose required for correcting the glycemia to normal values (40-120 mg/dL) was calculated for each newborn with hypoglycemia.
- Echocardiographic assessment by M-mode included right ventricular anterior wall thickness (RVAWT, expressed in mm), right ventricular end

diastolic dimension (RVEDD, expressed in mm), right ventricular end systolic dimension (RVESD, expressed in mm), thickness of interventricular septum at end systole (IVSs, mm), thickness of interventricular septum at end diastole (IVSd, mm), left ventricular end diastolic dimension (LVEDD, mm), left ventricular end systolic dimension (LVESD, mm), left ventricular posterior wall thickness (LVPWT, mm), and left ventricular fractional shortening (FS, %).

Echocardiographic measurements of the cardiac chamber section parasternal long axis were made in M-mode in all study subjects. Echocardiography dimensions were reported as weight at birth in the infants weighing between 2000 and 4000 grams because the corporeal surface changes are minimal[15]. Over the weight of 4000 grams, the cardiac chamber dimensions were assessed in relation to the calculated corporeal surface by the DuBois and DuBois formula[16].

Echocardiography was performed with a Logiq e General Electric ultrasound, 8 MHz transducer corresponding to the newborn examination and cardiac examination, while the measurements were performed in M-mode, parasternal long axis from the left ventricle as determined by standard echocardiography. The results were related and compared with the corresponding ones in normal infants in Central Europe[15]. The shortening fraction was assessed representing the left ventricular end diastolic diameter minus left ventricular systolic diameter × 100/left ventricular end diastolic diameter. The same physician in the same conditions performed echocardiography examination in all subjects included in the study.

The local Ethics Committees approved the study, and the study was conducted in accordance with the Helsinki Declaration.

Statistical analysis

Qualitative variables were summarized as absolute and relative frequencies; relative frequencies were accompanied by 95% confidence intervals calculated with an optimized formula similar to the one presented by Jäntschi and Bolboacă[17]. The lower and upper limits of the 95% confidence intervals are provided along the manuscript in square brackets. Comparison between two proportions was conducted with the Z test for proportions at a significance level of 5%.

Quantitative variables were summarized as mean ± standard deviation (SD) when data proved normally distributed; otherwise, median and interquartile range was provided (interquartile range was provided as IQ=(Q1-Q3), where Q1=1st quartile, Q3=3rd quartile). The means for normally distributed variables were compared using Student's t-test for independent samples. Quantitative variables not normally distributed were compared using Mann-Whitney test.

Statistical analysis was conducted using the Statistica (v.8, StatSoft Inc., USA) software at a significance level of 5%.

Results

Seventy subjects were investigated, with identical distribution of gender and gestational age according to the method used for identification of subjects. In each group, we included 20 females (57.14% [40.08, 74.20]) and 15 males (42.86% [25.80, 59.92]) with no significant gender difference (Z=-1.373, p=0.0943). The distribution of subjects according to gestational age (weeks) was identical for both groups and it was as follows: ≤36 weeks, 6 subjects (17.14% [5.80, 34.20]); 37-38 weeks, 13 subjects (37.14% [20.08, 54.20]); 39-40 weeks, 15 subjects (42.86% [25.80, 59.92]); and 41 weeks, 1 subject (2.86% [0.08, 14.20]).

The mean of glycemia was significantly higher in mothers with gestational diabetes (148.91±59.03, min = 100, max = 330; t-stat = 2.49, p=0.0183) compared to that in mothers with pregestational diabetes (109.73±31.34, min = 90, max = 200). In the case group, 9 of 35 mothers also presented hypertension (25.71%, [11.51, 42.78]). Glycosylated hemoglobin (normal values from 4% to 5.9%) was above the normal limits in 9 cases (25.71%, [11.51, 42.78]).

In the case group, 11 infants (31.43% [17.22, 48.49]) were born to mothers with pregestational diabetes (mean age at diabetes diagnosis 12.91±6.66 years) and 24 infants (68.57% [51.51, 82.78]) were born to mothers with gestational diabetes mellitus (28.59±7.42 gestational age; n=22; 4 cases treated with insulin) (Z statistics = 4.733, p<0.0001).

Demographic characteristics of the subjects included in the study are presented in Table 1 and clinical and para-clinical characteristics in Table 2.

Table 1. Demographic characteristics of study subjects according to groups

Variable	Case group	Control group	Statistics
Type of delivery			-0.2401^{ns}
Vaginal	15 (42.86 [25.80, 59.92])	16 (45.71 [28.65, 62.78])	
Cesarean section	20 (57.14 [40.08, 74.20])	19 (54.29 [37.22, 71.35])	
Birth weight (gr)			
≤1999	1 (2.86 [0.08, 14.20])	0 (0.00 [0.00, 8.49])	0.9987^{ns}
2000-2499	1 (2.86 [0.08, 14.20])	2 (5.71 [0.08, 19.92])	-0.6047^{ns}
2500-2999	2 (5.71 [0.08, 19.92])	8 (22.86 [11.51, 39.92])	-2.1148*
3000-3499	9 (25.71 [11.51, 42.78])	14 (40.00 [22.93, 57.06])	-1.2877^{ns}
3500-3999	8 (22.86 [11.51, 39.92])	9 (25.71 [11.51, 42.78])	-0.2782^{ns}
4000-4999	13 (37.14 [20.08, 54.20])	2 (5.71 [0.08, 19.92])	3.4690***
≥5000	1 (2.86 [0.08, 14.20])	0 (0.00 [0.00, 8.49])	0.9987^{ns}
Head circumference (cm)			
≤31	1 (2.86 [0.08, 14.20])	0 (0.00 [0.00, 8.49])	1.0098^{ns}
32-34	13 (37.14 [20.08, 54.20])	16 (45.71 [28.65, 62.78])	-0.7306^{ns}
35-37	19 (54.29 [37.22, 71.35])	19 (54.29 [37.22, 71.35])	0.0000^{ns}
38-39	2 (5.71 [0.08, 19.92])	0 (0.00 [0.00, 8.49])	1.4520^{ns}
Ponderal index			
≤1.9	2 (5.71 [0.08, 19.92])	7 (20.00 [8.65, 37.06])	-1.8282^{ns}
2.1	11 (31.43 [17.22, 48.49])	11 (31.43 [17.22, 48.49])	0.0000^{ns}
2.3	7 (20.00 [8.65, 37.06])	11 (31.43 [17.22, 48.49])	-1.1035^{ns}
2.5	7 (20.00 [8.65, 37.06])	6 (17.14 [5.80, 34.20])	0.3079^{ns}
2.7	6 (17.14 [5.80, 34.20])	0 0 (0.00 [0.00, 8.49])	2.6882**
≥2.9	2 (5.71 [0.08, 19.92])	0 0 (0.00 [0.00, 8.49])	1.4520^{ns}
Brain:body ratio			
≤8	3 (8.57 [2.94, 22.78])	0 (0.00 [0.00, 8.49])	1.8080^{ns}
8.9	9 (25.71 [11.51, 42.78])	3 (8.57 [2.94, 22.78])	1.9538^{ns}
9.9	12 (34.29 [20.08, 51.35])	12 (34.29 [20.08, 51.35])	0.0000^{ns}
10.9	9 (25.71 [11.51, 42.78])	10 (28.57 [14.37, 45.63])	-1.1630^{ns}
11.9	1 (2.86 [0.08, 14.20])	10 (28.57 [14.37, 45.63])	-4.1061****
≥12	1 (2.86 [0.08, 14.20])	0 (0.00 [0.00, 8.49])	1.0098^{ns}

Data are presented as n (%, [95%CI]); Z test for comparison of two proportions; ^{ns}=not statistically significant; *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001

The mean birth weight in newborns of diabetic mothers (3695.57±738.63) proved to be significantly higher compared to the mean birth weight in newborns of nondiabetic mothers (3276.14±496.51) (Student's t-test = 2.7881, p=0.0071). The same difference was observed when the weight at discharge (day when the baby left the hospital) was compared between the groups (case: 3490.57±623.88; control: 3064.00±448.58; t-test = 3.28, p=0.0017). Comparison of head circumference yielded no significant between-group difference (34.80±1.94 for case group, 34.43±1.20 for control group, t-test = 0.9653, p=0.3384). PI proved significantly higher in case subjects (2.29±0.32) compared to control subjects (2.08±0.22; t-test = 3.12, p=0.0027).

Ten subjects from the case group required resuscitation procedures (25.71% [14.37; 45.63]).

The following values (expressed as mean ± SD) were obtained for ASTRUP parameters (n=27): pH=7.31±0.08; pCO_2=39.50±9.20; pO_2=43.68±7.83; and BE (base excess)=-6.71±2.64. No significant differences were observed in ASTRUP parameters when infants of pregestational diabetic mothers were compared with infants of gestational diabetic mothers (p≥0.2267).

In the case group, global evaluation recorded two babies with hydronephrosis (5.71% [0.08, 19.92]), two

Table 2. Clinical and para-clinical characteristics of study subjects according to groups

Variable	Case group	Control group	Statistics
Apgar 1 min			
6	2 (5.71 [0.08, 19.92])	0 (0.00 [0.00, 8.49])	1.4520^{ns}
7	8 (22.86 [11.51, 39.92])	0 (0.00 [0.00, 8.49])	3.7659***
8	3 (8.57 [2.94, 22.78])	8.57 [2.94, 22.78])	0.0000^{ns}
9	12 (34.29 [20.08, 51.35])	21 (60.00 [42.94, 77.06])	-2.2298*
10	10 (38.57 [14.37, 45.63])	11 (31.43 [17.22, 48.49])	0.6280
Apgar 5 min			
7	1 (2.86 [0.08, 14.20])	0 (0.00 [0.00, 8.49])	1.0098^{ns}
8	7 (20.00 [8.65, 37.06])	0 (0.00 [0.00, 8.49])	2.9556**
9	14 (40.00 [22.93, 57.06])	4 (11.43 [2.94, 25.63])	2.8935**
10	13 (37.14 [20.08, 54.20])	31 (88.57 [74.37, 97.06])	-5.2593****
Presence of:			
Jaundice	21 (60.00 [42.94, 77.06])	20 (57.14 [40.08, 74.20])	0.2548^{ns}
Hyperbilirubinemia	9 (25.71 [11.51, 42.78])	5 (14.29 [5.80, 31.35])	1.2067^{ns}
Birth injuries	17 (48.57 [31.51, 65.63])	6 (17.14 [5.80, 34.20])	2.9705**
Hypoglycemia	16 (45.71 [28.65, 62.78])	0 (0.00 [0.00, 8.49])	5.4058****

Data are presented as n (%, [95%CI]); Z test for comparison of two proportions; ^{ns}not statistically significant; *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001

newborns with interatrial septal defect (5.71% [0.08, 19.92]), one with persistent ductus arteriosus (2.86% [0.08, 14.20]) and one with cardiac hemangioma (2.86% [0.08, 14.20]).

In ten infants of diabetic mothers (28.57% [14.37, 45.63], 3 infants of pregestational diabetic mothers and 7 infants of gestational diabetic mothers, Z=2.7603, p=0.0058) septal hypertrophy was present compared to one infant of nondiabetic mother (2.86% [0.08, 14.20]). Thus, this percentage was statistically higher in the case group compared with controls (Z=3.1588, p=0.0016). One of the newborns (10%

Table 3. Echocardiographic measurements

Variable	Infants of diabetic mothers		Infants of nondiabetic mothers		Statistics
	Mean ± SD	Median (IQ)	Mean ± SD	Median (IQ)	
RVAWT^{a} (mm)	4.72±1.10	4.80 (3.90-5.50)	4.54±1.11	4.70 (3.50-5.30)	0.6804 ^{ns}
RVESD^{b} (mm)	9.46±3.18	9.30 (8.00-12.30)	9.85±2.69	10.30 (7.60-12.20)	-0.1116 ^{ns}
RVEDD^{a} (mm)	6.25±2.03	6.10 (5.50-7.60)	5.44±1.48	5.50 (4.20-6.50)	1.9125 ^{ns}
IVSs^{b} (mm)	6.61±1.64	6.10 (5.50-7.70)	5.75±0.95	5.70 (5.30-6.40)	2.0791 *
IVSd^{b} (mm)	4.61±1.59	4.50 (3.50-5.40)	3.42±0.70	3.40 (3.00-3.90)	3.7000 ***
LVEDD^{b} (mm)	15.81±2.22	15.40 (14.10-18.00)	15.71±2.40	16.40 (14.50-17.50)	0.1757 ^{ns}
LVESD^{b} (mm)	11.43±2.64	11.90 (9.00-13.40)	10.97±2.56	11.30 (8.70-13.20)	0.5697 ^{ns}
LVPWT^{b} (mm)	4.47±0.94	4.10 (3.90-5.00)	4.16±1.19	3.90 (3.30-4.80)	1.6856 ^{ns}
FS^{b} (%)	28.21±13.06	24.14 (18.71-38.94)	30.37±11.31	25.81 (22.67-36.59)	-1.4976 ^{ns}

IQ = interquartile range (Q1-Q3) where Q1 = first quartile; Q3 = third quartile; ^{a}Student's t-test; ^{b}Mann-Whitney test;
RVAWT = right ventricular anterior wall thickness; RVEDD = right ventricular end diastolic dimension; RVESD = right ventricular end systolic dimension; IVSs = thickness of interventricular septum at end systole; IVSd = thickness of interventricular septum at end diastole; LVEDD = left ventricular end diastolic dimension; LVESD = left ventricular end systolic dimension; LVPWT = left ventricular posterior wall thickness; FS = left ventricular fractional shortening; ^{ns}not statistically significant; *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001

[1.00, 39.00]) with septal hypertrophy, born to mother with gestational diabetes, presented signs of heart failure (such as severe respiratory distress with pulmonary hypertension) and needed respiratory support such as synchrony ventilation (SIMV) for 4 days; low cardiac output manifested hypotension and required treatment with propranolol. Considering the presence of diabetes during pregnancy as a risk factor for septal hypertrophy, a risk ratio of 2.333 [0.656, 8.298] was obtained.

Echocardiography measurements regarding maternal diabetes status are presented in Table 3.

No significant echocardiographic measurement differences were identified in the newborns of diabetic mothers when comparing newborns of pregestational diabetes mothers and newborns of gestational diabetes mothers ($p \geq 0.3487$).

Hospital stay was significantly longer (Mann-Whitney test=-2.891; p=0.004) for the newborns of diabetic mothers (median (IQ)=7 days (4.5-8)) compared to newborns of nondiabetic mothers (median (IQ)=5 days (3-5)).

Discussion

The investigated newborns of diabetic and nondiabetic mothers were successfully evaluated by echocardiographic measurements. In our case group, 31.43% of mothers had pregestational diabetes and 68.57% of mothers had gestational diabetes, the difference being statistically significant ($p<0.01$). The mean gestational age of the mothers with gestational diabetes was 28.59±7.42 weeks of gestation; in one of 24 cases, insulin treatment was applied. Screening for gestational diabetes usually is performed around 24-28 weeks of pregnancy[18]. The usual treatment is putting pregnant women on a diet, but in 31% insulin is needed as well[19]. It is well-known that the consequences of diabetes are different depending on whether it is of pregestational or gestational type. Pregestational diabetes occurs in 0.1%-0.3% of all pregnancies in the US[20]. On the other hand, gestational diabetes is more frequent compared to pregestational diabetes and could be seen in almost 90% of pregnancies in the American population[21,22]. Thus, the higher frequency of gestational diabetes obtained in our study is in keeping with the results published in the literature. As other authors have shown[6], the blood sugar level of mothers with gestational diabetes was significantly higher compared to the values of pregestational diabetes. In almost 26% of cases, the mothers with diabetes also had associated hypertension, while almost 26% of the women presented higher values of glycosylated hemoglobin compared to the expected normal values. These results are comparable with the results reported from other studies[6,20,23,24]. Note that no changes in the left ventricular systolic function were identified in women with diabetes[25].

In our sample, glycosylated hemoglobin (normal values from 4% to 5.9%) was above the normal limits in 9 (25.71%) cases. Mothers with values of less than 7% have no greater risk of having an infant with congenital anomalies than mothers without diabetes. For mothers with values between 7% and 8.5%, the risk is 5%; the risk rises to 22% in mothers with hemoglobin A1c values of more than 10%[12,26]. In our study, there were no differences according to type of delivery or head circumference between cases and controls ($p>0.05$) (Table 1). The mean birth weight of the newborns of diabetic mothers (3695.57±738.63) proved significantly higher compared to the mean birth weight of the newborns of nondiabetic mothers (3276.14±496.51) (Student's t-test=2.7881, p=0.0071) and this difference could be attributed to the number of newborns with birth weight higher than or equal to 4000 g ($p<0.01$) (Table 1). The presence of macrosomia is one of the adverse outcomes of diabetes in pregnancy, besides congenital anomalies, preterm birth, neonatal hypoglycemia, and neonatal death[4,7,27,28]. Galić and Grgurić proved that newborns of employed parents had higher birth weight compared to those of unemployed parents[29]. Depending on the maternal metabolic and proinflammatory derangements, macrosomia is explained by excessive availability of nutrients and an increase in fetal insulin release, a phenotype related to the programming of glucose intolerance[30]. Because of the higher birth weight, PI was also significantly higher in the newborns of diabetic mothers compared to newborns of nondiabetic mothers ($p<0.01$). Furthermore, BBR equal to 11.9 was identified in a significantly lower number of newborns of diabetic mothers compared to the newborns of nondiabetic mothers. This result could be explained by the presence of macrosomia in the newborns of diabetic mothers.

Besides macrosomia, which was the most frequent morbidity in our sample, we also identified a significantly higher number of newborns with hypoglycemia and birth injuries ($p<0.01$ both) in the newborns of diabetic mothers compared to the newborns of nondiabetic mothers (Table 2). The prevalence of hypoglycemia in our case group was 45.71%. A study from India on 574 newborns of gestational diabetes mothers showed a 9.3% incidence of hypoglycemia and 2.5% incidence of birth injuries[31]. The percentage of newborns with Apgar score 8 or 9 at 5 minutes proved significantly higher compared to controls, while the percentage of newborns of diabetic mothers with Apgar score 10 at 5 minutes proved significantly lower compared to the newborns of nondiabetic mothers (see Table 2). These results could be explained by both obstetric trauma (see Table 2) and the need of resuscitation (28.57% of newborns of diabetic mothers compared to no newborn of nondiabetic mother), which were more frequent in the newborns of diabetic mothers compared to the newborns of nondiabetic mothers. Other comorbidities observed in our newborns of diabetic mothers were as follows: two newborns with hydronephrosis, two newborns with interatrial septal defect, one newborn with persistent ductus arteriosus, and one newborn with cardiac hemangioma. Several epidemiological studies have demonstrated strong association between maternal glycemic level control at the time of conception and during early gestation and the incidence of congenital anomalies[26,32]. More than 50% of these anomalies affect the central nervous system or cardiovascular system[12,31].

The most common renal anomalies are hydronephrosis, renal agenesis, and cystic kidneys[26]. In our study, there were just two newborns with hydronephrosis (5.7%).

Echocardiographic measurements performed on the case group showed similar results in both newborns of diabetic mothers and those of nondiabetic mothers (see Table 3), with significant differences just in case of interventricular septum thickness at end systole and interventricular septum thickness at end diastole ($p<0.05$), the differences being greater in systole. Besides differences in echocardiographic measurements, a significantly higher percentage of newborns of diabetic mothers had septal hypertrophy as compared with newborns of nondiabetic mothers ($p<0.01$).

Isolated septal hypertrophy is present in 35%-40% of infants born to mothers with diabetes, where echocardiographic screening is performed[11]. The incidence of symptomatic forms is 10%-12%[9,27]. In our study, the incidence of septal hypertrophy was 28.57%, which is less than the percentage mentioned in the literature[9,27]. This can be explained by the small number of subjects in the study group or by differences between the groups.

Seven of ten infants with septal hypertrophy identified in our study were born from pregnancies with gestational diabetes. This result may indicate the need of early diagnosis and correct treatment of diabetes, with appropriate monitoring. In our study, the mean age at the diagnosis was 28.59±7.42 weeks of gestation and the mean blood glucose during pregnancy was higher in patients with gestational diabetes. Only 10% of the newborns with hypertrophic cardiomyopathy showed signs of heart failure[8,26]. Only one of ten (10%) infants with septal hypertrophy in the case group showed signs of heart failure, while the others were asymptomatic. These results are similar to those reported in the literature[8,26].

Given the complications in infants born to mothers with diabetes, the length of hospital stay was longer (7 days) compared to that in controls (5 days).

The association of diabetes in pregnancy and neonatal septal hypertrophy was investigated and a value of 2 was obtained. This value showed that in our sample, a newborn of diabetic mother had a twofold higher risk to have septal hypertrophy than a newborn of nondiabetic mother. Since the value of 1 is included in the 95% confidence interval of risk ratio, the result obtained was true for our sample but could not be generalized.

Echocardiographic measurements in the newborns of diabetic mothers were not significantly different from those of the newborns of nondiabetic mothers, with the exception of the interventricular septum thickness. In our study, the incidence of septal hypertrophy was 28.57%. This comorbidity proved to be more frequent in the newborns of gestational diabetes mothers compared to the newborns of pregestational diabetes mothers. This result could be explained by the presence of better glucose control in the mothers with pregestational diabetes as compared to those with gestational diabetes. The association of maternal

diabetes and cardiomyopathy, specifically septal wall hypertrophy, is a well-known phenomenon, and it has been previously described[33,34].

Our study had some limitations, the most important being generalizability, which was limited by both the population sample and sample size. So, the results obtained are certainly true for the investigated sample, but are they also true for the Romanian population? Furthermore, the small sample size in this study did not ensure a reasonable power for our study (post-hoc power is ~50%). In this study, financial resources limited the sample size and thus this study could be seen as a pilot study able to generate further research hypothesis. Another limitation is related to study design; since our design was cross-sectional, the causal relationship could not be investigated.

Nevertheless, according to our knowledge, this is the first study conducted on Romanian infants of diabetic mothers that evaluated the presence of septal wall hypertrophy and echocardiographic changes at birth. As a result, this study suggests that even if symptoms appear only in 10% of cases, echocardiographic morphological changes are common in infants born to diabetic mothers.

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Sažetak

KLINIČKI I EHOKARDIOGRAFSKI NALAZI U NOVOROĐENČADI DIJABETIČNIH MAJKI

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Cilj je bio procijeniti primjenu ehokardiografskih mjerenja u novorođenčadi dijabetičnih majki. Majčin dijabetes udružen je s povećanim rizikom pobola i smrtnosti u trudnoći i tijekom perinatalnog razdoblja. U ispitivanje je bilo uključeno 35 novorođenčadi dijabetičnih majki (predgestacijski ili gestacijski dijabetes; ispitna skupina) i 35 kontrolne novorođenčadi (kontrolna skupina) rođene između siječnja 2009. i prosinca 2012. godine u području Cluj-Napoca (sjeverozapadna Rumunjska). Ehokardiografski parametri mjereni su pomoću ultrazvučnog uređaja Logiq e s pretvornikom od 8 MHz. Debljina interventrikulskog septuma bila je viša u ispitnoj skupini u usporedbi s kontrolnom skupinom (na kraju sistole = 6,61±1,64 mm prema 5,75±0,95 mm, p=0,0371; na kraju dijastole = 4,61±1,59 mm prema 3,42±0,70 mm, p=0,0001). Omjer rizika za septalnu hipertrofiju bio je 2,333 (0,656; 8,298). U novorođenčadi majki s gestacijskim dijabetesom zabilježen je veći udio hipertrofije septuma u usporedbi s novorođenčadi majki s predgestacijskim dijabetesom (p=0,0058). Srednja porođajna težina novorođenčadi dijabetičnih majki (3695,57±738,63) bila je značajno viša u usporedbi s kontrolnom skupinom (3276,14±496,51; p=0,0071). Kod novorođenčadi majki s dijabetesom utvrđen je visok rizik od hipertrofije septuma.

Ključne riječi: *Novorođenče; Trudnoća – komplikacije; Dijabetes melitus; Ehokardiografija; Hipertrofija; Srčana pregrada – patologija*