

Cardiac Hypertrophy in Neonates Born to Diabetic Mothers at Farhat Hached of Sousse University Hospital

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Abstract: *Introduction:* The association between cardiac hypertrophy and hyperinsulinism is mainly observed in the newborn, although the onset in older infants has also been described. The aim of our study is to research a cardiac hypertrophy in newborns of diabetic mothers. *Methodology:* This was a cross-sectional study, involving one hundred and twenty (120) newborns of diabetic mothers from August 1st to November 30, 2020. These newborns of diabetic mothers had received an echocardiographic examination at the laboratory of the FARHAT HACHED University Hospital in Sousse (Tunisia) regardless of the associated cardiac or extracardiac pathology, during the study period, to detect cardiac hypertrophy. *Results:* The sex ratio was in favor of the female gender at 0.90. The average weight was 3554.04 g, with extremes ranging from 1,600 g to 5,200 g. Twelve (12) newborns had a weight greater than or equal to 4,000 g (10.00% of macrosomes). Among mothers, there were 03 types of diabetes: type 1 diabetes (2.65%), type 2 diabetes (0.88%) and gestational diabetes (96.46%). Echocardiography was normal in 91 neonates (75.83%) and abnormal in 29 neonates (24.17%). The prevalence of cardiac hypertrophy was 09.17% and that of other associated cardiac abnormalities was 21.66%. There were 11 cases of patent foramen ovale, 11 cases of patent ductus arteriosus, 02 cases of ostium secundum atrial septal defect, 01 case of interrupted aortic arch, 01 case of pulmonary stenosis. These abnormalities were associated on the one hand with the septal hypertrophy and on the other hand, associated with each other in the same newborn. Left ventricular ejection function was normal in all neonates with an average of 66% and extremes between 59% and 76%. *Conclusion:* Cardiac hypertrophy described in the newborn of diabetic mother is characterized by hypertrophy of the ventricular walls more often predominating over the septum. Transthoracic echocardiography is the reference (non-invasive) technique for diagnosing and monitoring these hypertrophies.

Keywords: Cardiac Hypertrophy, Newborns, Diabetic Mothers, Echocardiography

1. Introduction

Hypertrophic cardiomyopathy is defined as a disease in

which the heart muscle becomes abnormally thick in the absence of abnormal load conditions (hypertension, valvular disease), with histological disturbance of myocardial structure/composition and in the absence of systemic disease

[1]. Cardiac hypertrophy indicates the presence of left or septal ventricular hypertrophy as defined by measured echocardiography of diastolic septal thickness or diastolic left ventricular wall thickness 2 standard deviations above average (Z-score 1.96; adjusted for age, sex and body size) [2 - 3].

The association between cardiac hypertrophy and hyperinsulinism is mainly observed in the newborn, although the onset in older infants has also been described. The etiology of neonatal hyperinsulinism can be divided into three categories: maternal diabetes, congenital (transient and persistent) hyperinsulinism and insulin resistance syndrome. Hyperglycemia associated with maternal diabetes can lead to fetal hyperinsulinism that persists transiently during the neonatal period [1]. Myocardial hypertrophy described in the newborn of a diabetic mother is characterized by hypertrophy of the ventricular walls, most often predominant on the septum. This abnormality is traditionally considered secondary to hyperinsulinism [4].

The objectives of our study were to evaluate the ultrasound profile of newborns of diabetic mothers in order to determine the prevalence of septal hypertrophies among newborns of diabetic mothers in a Tunisian population.

2. Patients and Method

2.1. Framework and Type of Study

Our study took place in the Cardiology department of the FARHAT HACHED University Hospital in Sousse (Tunisia) located 143 kilometers south of the capital Tunis.

Our study was cross-sectional, descriptive from August 1st, 2020 to November 30th, 2020 and had focused on newborns of diabetic mothers examined at the Echocardiography laboratory of the Department of Cardiology of the University Hospital FARHAT HACHED of Sousse, regardless of the associated cardiac or extracardiac pathology.

2.2. Inclusion Criteria

We performed transthoracic echocardiography (TTE) for septal hypertrophy screening for all newborns of diabetic mothers referred by the Neonatology department (hospitalized or not) to the Echocardiography Laboratory of the Department of Cardiology of the FARHAT HACHED University Hospital in Sousse.

2.3. Criteria for Non-Inclusion and Exclusion

Newborns of non-diabetic mothers, addressed by the Neonatal Department at the Echocardiography Laboratory for the detection of possible congenital heart disease.

2.4. Definition of the Parameters Studied

Socio-demographic data and clinical history of the parturients were collected and glycemic tests were conducted.

Fasting blood glucose is defined for any value between 0.7 g/l and 1.10 g/l (3.8 to 6.1 mmol/l). Above the upper limit,

we have hyperglycemia. Diabetes, on the other hand, is characterized by a blood glucose above 1.26 g/l fasting [5].

In neonates, the normal value of the left ventricular septal diameter on ultrasound varies from 2.28 to 4.28 millimeters. These values are related to the Z-score [6].

Left ventricular septal hypertrophy is defined by a measured diastolic septal thickness or diastolic left ventricular parietal thickness 2 standard deviations above the mean (Z score 1.96; adjusted for age, sex and body size) [2 - 3].

2.5. Conduct of the Study

Glycemic tests had been proposed and performed on pregnant women who were overweight before pregnancy (BMI greater than 25 kg/m²), aged over 35 years, with a family history of first-degree diabetes (parents and siblings), history of fetal macrosomia and/or gestational diabetes in previous pregnancies. Screening for oral hyperglycemia was done through completion in the second trimester, between 24 and 28 weeks of amenorrhea. A blood test is done on an empty stomach, then another two hours after the absorption of 75 grams of sugar. In the normal individual, the intestinal absorption of glucose is rapid and the blood concentration increases to a maximum value of 1.50 g/l. The tissue collection of glucose is sufficient to cause a hypoglycemic wave (approximately 02 hours after test start). Blood glucose levels are normal if:

- 1) Fasting glucose is less than or equal to 0.92 g/l;
- 2) Blood glucose at one hour is less than or equal to 1.80 g/l;
- 3) Blood glucose at two hours is less than or equal to 1.53 g/l.

If one of the values is abnormal, that is, above the threshold value, there is gestational diabetes [7].

In newborns, we used a Model Vivid E9 cardiac Doppler ultrasound device and 12 MHz (high frequency) probes. The measurement was performed using M-Mode and bidimensionnal-mode using the 04-chamber apical view by two cardiopediatricians. Control echocardiography was performed three months later in newborns with septal hypertrophy.

2.6. Data Analysis

For this work, the calculations concerned simple frequencies and relative frequencies (in percentage) for qualitative variables, as well as means and standard deviations for quantitative variables. The data collected was captured and analyzed using Excel 2020. They were analyzed using SPSS 23.0 software. We used Chi2 tests (Pearson and Yates) to study the different correlations. We have set a "threshold" value of 1 % for significant associations. This corresponds to a 99% confidence interval.

3. Results

3.1. General Characteristics of the Study Population

At the end of the study, 120 newborns of diabetic mothers realized an echocardiography. The average age was 3.48 days with extremes of two (02) days to seven (07) days. The

predominance was female with 63 cases (52.50%) versus 57 cases (47.50%) for the male gender, and a sex ratio of 0.90.

The average weight was 3554.04 g with extremes between 1600 g and 5200 g. Twelve (12) had a weight greater than or equal to 4000 g (or 10.00% of cases of macrosomia).

One hundred and thirteen (113) cases of pregnancies of women with diabetes, of which 106 mono-foetal (93.80%) and 07 twin (6.20%) were well followed. There were 112 full-term deliveries (99.12%) and one premature delivery (0.88%).

Three (03) types of diabetes were identified, including:

- 1) 03 insulin-dependent cases (2.65%) balanced on insulin therapy;
- 2) 01 cases of non-insulin-dependent diabetes (0.88%), balanced under Metformin 850 mg;
- 3) 109 cases of gestational diabetes, or 96.46% balanced on diet.

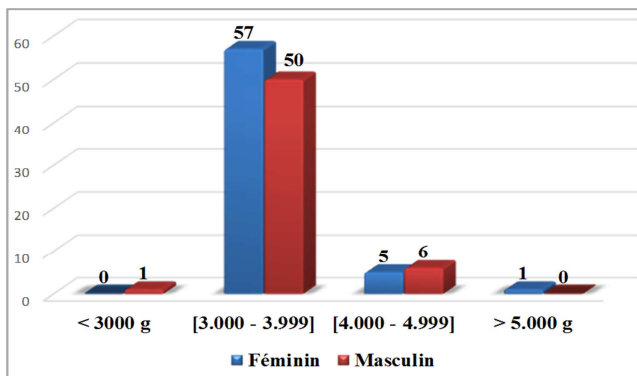


Figure 1. Distribution by weight and sex.

3.2. Prevalence of Ventricular Hypertrophy

Echocardiography data were normal in 91 neonates or 75.83% of cases compared to 29 abnormal ultrasound scans or 24.17% of cases.

Septal hypertrophy was noted in 11 cases (09.17% of cases) versus 109 cases of normal end-diastolic left ventricular septum diameter (90.83%).

The left ventricular ejection fraction (LVEF) was normal in all neonates with an average of 66% and extremes between 59% and 76%.

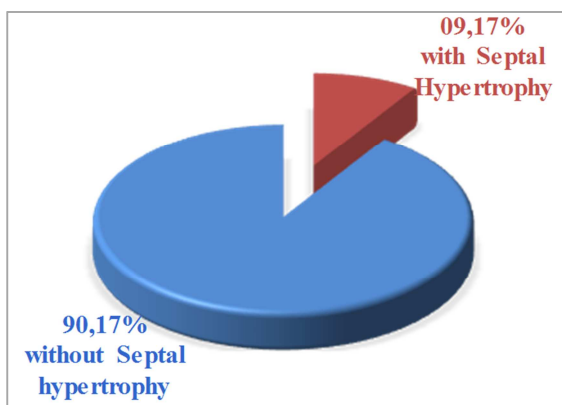


Figure 2. Distribution by presence or lack of septal hypertrophy.

Of the 11 cases of septal hypertrophy, there was male predominance, with 07 male cases (63.64%) and 04 female cases (36.36%); a sex ratio of 1.75. There is a statistically significant relationship between septal hypertrophy and sex (P 0.002).

Table 1 shows the correlation between SIV hypertrophy and sex (Appendix 1).

We have 05 cases (45.45%) that were macrosomes with a weight greater than or equal to 4000 grams with a statistically significant relationship between septal hypertrophy and fetal macrosomia (P 0.009).

Table 2 shows the correlation between septal hypertrophy and weight (Appendix 2).

Only one (01) case had clinically presented, a neonatal pathology that associated respiratory distress and hemodynamic distress.

Table 3 shows the relationship between septal hypertrophy and neonatal conditions (Appendix 3).

A case of Down's syndrome genetic disease was observed in a female newborn.

In mothers of newborns with septal hypertrophy, there were 10 cases (90.90%) of gestational diabetes compared to one (01) case (09.10%) of type I diabetes. There is a significant correlation between gestational diabetes and the presence of septal hypertrophy (P 0.003).

Table 4 shows the relationship between septal hypertrophy and the type of diabetes (Appendix 4).

3.3. Associated Echocardiographic Abnormalities

Echocardiography identified 26 other abnormalities (Table 5) in the following proportions:

- 1) Eleven (11) cases of patent foramen ovale (PFO) (42.30%);
- 2) Eleven (11) patent ductus arteriosus (PDA) (42.30%);
- 3) Two (02) ostium secundum atrial septal defect (ASD) (07.69%);
- 4) One (01) case of interrupted aortic arch (03.85%);
- 5) One (01) case of pulmonary stenosis (03.85%);

It should be noted that these abnormalities are often associated on the one hand with septal hypertrophy and on the other hand, associated with each other in the same newborn.

Thus, the associations of ultrasound abnormalities are as follows:

- 1) Four (04) cases of PFO associated with PDA;
- 2) One (01) case of PFO associated with ostium secundum ASD;
- 3) One (01) case of association of PFO, PDA and pulmonary stenosis.

Table 5 shows the other abnormalities (Appendix 5).

Only 02 cases of male septal hypertrophy showed an association of which 01 cases with a PFO and 01 other macrosome in addition, with a PDA. The evolution was favorable in all babies. Indeed, we found the regression of septal hypertrophy during echocardiographic control.

4. Discussion

The limitations of this work are as follows: This is a single center study and some of the diaries were incomplete, particularly those of the non-hospitalized newborns.

In our study, we noted a female predominance with 52.50% of cases for a sex ratio at 0.90 unlike Boiro *et al.* who found as many boys as girls, 50% - 50% [8]. Similarly Amelie Beyler and *al.* in Strasbourg in their series, had noted a male predominance [9]. Nacer Faiza and *al.* in Tlemcen (Algeria) also noted a male predominance, with a sex ratio of 1.32 [10]. All these series are different from ours.

The average weight in our study was 3554.04 (extremes between 1,600 g and 5,200 g) with 12 cases of macrosomia (10.00%), with both male and female sex. D. Boiro and *al.*, found an average weight of 3250 g with extremes between 1,200 g and 5050 g, and the prevalence of macrosomes was 19.19% [8]. While the average weight of the D. Boiro and *al.* series is almost similar to ours, the number of macrosomes born was higher (19.19% versus 10.00%). Amelie Beyler and *al.* in Strasbourg (France) reported 25.89% of macrosomes cases [9]. Nacer Faiza and *al.* noted a higher number of macrosomes with 41% of cases [10]. These results are superior to our series.

In our series, mothers of newborns suffered from the three (03) types of diabetes, 2.65% of which were type 1; type 2 in 0.89% of cases and gestational in 96.46% of cases.

It should be noted that diabetes was balanced in all these mothers regardless of the type of diabetes.

Amelie Beyler and *al.* found that all mothers of newborns had gestational diabetes [9]. Our results are almost similar. In 2013, Wery *et al.* in a study on the impact of screening criteria on the prevalence of gestational diabetes found an increase in its prevalence [11]. In France, at the university hospital of Nimes, the prevalence of gestational diabetes increased from 6% in 2009 to 19.6% in 2013 [12].

This could be explained by the incidence of diabetes during pregnancy, which is constantly increasing in the current context of a pandemic of obesity and type 2 diabetes. Approximately 3-10% of pregnancies are marked by a disorder of glycemic regulation [13].

The left ventricular septum diameter in our study ranged from 03 mm to 06 mm with an average of 4 mm (04 mm). LVEF using the biplane Simpson and Teicholz methods was normal in all newborns with an average of 66% and extremes ranging from 59% to 76%.

We reported 11 cases of septal hypertrophy (09.17%). In contrast to our study, D. Boiro and *al.* reported one (01) single case of septal hypertrophy which represented 1.01% of cases [8]. This septal hypertrophy is part of hypertrophic cardiomyopathy. Tan *et al.* [14] and Ullmo and *al.* [15] in their series reported 13% of cases of cardiac hypertrophy in newborns of diabetic mothers. These two results are almost similar to our series. However, several studies including Esmaeili and *al.* [16], El-Ganzouriy and *al.* [17], Deorari and *al.* [18], Huang and *al.* [19] reported high rates of cardiac hypertrophy in newborns of diabetic mothers in 38%,

respectively, 44%, 26% and 40% of cases of cardiac hypertrophy. All these results are different from those of our study and that of D. Boiro and *al.* [8]. El-Ganzouriy and *al.* found that higher values of glycated hemoglobin were associated with septal hypertrophy in these neonates [17 - 12]. Several studies have shown a tendency for hypertrophic cardiomyopathy in high birth weight infants [17-20]. Nacer Faiza and *al.* [10], in their series, reported 1.9% of cases of septal hypertrophy in hypertrophic cardiomyopathy. This is different from our series and those of literature, but this result is almost similar to that of the series of D. Boiro and *al.* [8]. P. Amedro and *al.* [21] reported 3.88% of cases of significant septal et hypertrophy (6 mm to 13 mm). Although this result is different from our study, it is similar to the results of the series of D. Boiro and *al.* [8] and Nacer Faiza and *al.* [10].

In some studies, the incidence of cardiac hypertrophy can be reduced by rigorous blood glucose monitoring [15-22]. However, other studies show that fetal cardiac hypertrophy can occur even with good glycemic control [19 - 23]. According to Oberhoffer and *al.* [23], cardiac hypertrophy in newborns of diabetic mothers is reversible because the stimulus for insulin production disappears, and in most situations, it is no longer detected on ultrasound after 6 post-natal months. This abnormality is traditionally considered secondary to hyperinsulinism, as a study had shown a link with the concentration of HbA1c in the mother [4]. This has not been confirmed by other authors [22] and the pathophysiological mechanisms behind cardiomyopathy are currently unknown. The evolution of cardiac hypertrophy in general is parallel to serum insulin levels [24]. In newborns of diabetic mothers, cardiac hypertrophy is mainly reversible and rarely fatal [19].

We also identified 26 other associated abnormalities (21.66%). These abnormalities were represented by 11 PFO cases, 11 PDA cases, 02 ostium secundum ASD cases, one (01) interrupted aortic arch case, one (01) pulmonary stenosis case. Nacer Faiza *et al.* [10], in their series, reported 3.87% of cases of associated congenital heart disease, including 1.37% of cases of ostium secundum ASD and 2.5% PFO which is different from our study. D. Boiro and *al.* [8] reported one (01) case of congenital heart disease at 1.01%. This is cyanogenic heart disease without specifying the type. This rate is very low compared to our series. According to Mitanchez D. [25], in his series, the prevalence of congenital malformations varies between 2 and 7%. Cordero and *al.* [26], report 5% congenital heart malformations. Anjum and *al.* [27], found 34% of cardiac defect in infants born to diabetic mothers in India. These rates differ from our series. The risk is higher in patients with pregestational diabetes, but the heart defects described in gestational diabetes are similar to those reported in pregestational diabetes [25-28].

5. Conclusion

Septal hypertrophy is rare in newborns of diabetic mothers, although there is a growing incidence of diabetes during pregnancy that is steadily increasing in the context of a

pandemic of obesity and type 2 diabetes. Left ventricular septal hypertrophy is most often reversible within six (06) months.

Echocardiography is the reference technique, which makes it possible to make the diagnosis in the first ten days of life and to make regular follow-up of these septal hypertrophy in newborns of diabetic mothers.

Appendix

Table 1. Correlation between septal hypertrophy and gender.

Septal hypertrophy	Number	Percentage (%)	P-value
Male	07	63,64 %	P=0,002
Female	04	36,36 %	
Total	11	100,00 %	

P < 0,01

Table 2. Correlation between septal hypertrophy and weight.

Septal hypertrophy	Number	Percentage (%)	P-value
Newborn Normal Weight	06	54,55	P=0,009
Macrosomic Newborns	05	45,45	
Total	11	100,00	

P < 0.01

Table 3. Relationship between septal hypertrophy and neonatal pathologies.

Number	Percentage (%)
Septal hypertrophy and signs	01 09,10 %
Total	10 90,90 %
Total	11 100,00 %

Table 4. Relationship between septal hypertrophy and type of diabetes.

Number	Percentage (%)
Septal hypertrophy and Type 1 Diabetes	01 09,10 %
Septal hypertrophy and Type 2 Diabetes	00 00,00 %
Septal hypertrophy and Gestational Diabetes	10 90,902 %
Total	11 100,00 %

P < 0.01

Table 5. Other Cardiac Abnormalities.

Other cardiac abnormalities	Number	Percentage (%)
PFO	11	42,30
PDA	11	42,30
Ostium-secondum ASD	02	07,69
Interrupted aortic arch	01	03,85
Pulmonary stenosis	01	03,85
Total	26	100,00

PFO: patent foramen ovale; PDA: patent ductus arteriosus; ASD: atrial septal defect

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