RESEARCH PAPER

Asymmetric Septal Hypertrophy in Appropriate for Gestational Age Infants Born to Diabetic Mothers

Ma Martha Vela-Huerta[1], Norma Amador-Licona[2], Helena Victoria Orozco Villagomez[1], Antonio Heredia Ruiz[3] and Juan Manuel Guizar-Mendoza[2]

From Departments of [1]Neonatology and [3]Cardiology, Hospital General de Leon; and [2]Department of Research, University De La Salle Bajio; Leon: Mexico.

Correspondence to: Dr Norma Amador Licona, University De La Salle Bajio. Department of Research, Av Universidad 602, Col Lomas del Campestre, ZC 37150, Leon, Gto, Mexico.
licoamador@gmail.com
Received: July 20, 2017;
Initial review: November 15, 2017;
Accepted: January 24, 2019.

Objective: To compare the frequency of asymmetric septal hypertrophy in appropriate for gestational age infants born to diabetic mothers with those born to non-diabetic mothers. **Methods**: We compared 38 full term infants born to diabetic mothers with 85 full term infants of non-diabetic mothers. 2-D echocardiography was obtained in the first 24 hours after birth. **Results**: Asymmetric septal hypertrophy was only present in infants born to diabetic mothers (50% *vs*. 0%; *P*<0.001). Intraventricular septum thickness and intraventricular septum/posterior wall of the left ventricle ratio was also significantly higher in the first group (*P*<0.001). We found no correlation between mother´s glycated hemoglobin levels and intraventricular septum thickness in newborns. **Conclusions**: Asymmetric septal hypertrophy is a common finding in infants born to diabetic mothers, even if they are appropriate for gestational age.

Keywords: *Cardiac abnormality, Echocardiography, Glycated hemoglobin*.

In spite of advances in perinatal medicine, infants of diabetic mothers (IDM) continue to show increase morbidity and mortality [1]. Asymmetric septal hypertrophy (ASH) is a well-recognized cardiac functional abnormality in IDM. This term describes the special feature of the interventricular septum thickness >6 mm and septal/posterior wall thickness ratio >1.3 [2-4]. Its etiology is not clear, but endogenous catecholamines, insulin, and other growth factors have been involved [2], and its evolution is usually benign [2-4]. However, some cases of ASH and severe hypertrophic cardiomyopathy have been reported in spite of appropriate prenatal glucose control [5,6]. In Mexican macrosomic infants born to diabetic or non-diabetic mothers, ASH has been identified in 38.8% and 7.1%, respectively, though appropriate for gestational age (AGA) infants were not evaluated [4]. The aim of this study was to compare the frequency of ASH in AGA infants born to diabetic with non-diabetic mothers.

Methods

An analytical cross-sectional study was carried out in General Hospital in Leon, Mexico from July 2015 to March 2016. Thirty-eight AGA babies of diabetic mothers and 85 AGA babies of non-diabetic mothers were compared. The study included singleton fetuses without malformations and other diseases that could interfere with the fetal development. AGA infants were considered according to intrauterine growth curves as gestational age between 37-41.6 weeks and birthweight between 10-90 percentiles [7]. Neonates of diabetic mothers (IDM) were hospitalized and managed according to the recommendations of the STABLE program [8]. Neonates of mothers without diabetes mellitus (INDM) correspond to a historical group reported in a previous publication [4].

Cardiac structures and function parameters were evaluated by two-dimensional pulsed Doppler M echocardiogram using a Phillips HD11XE transducer S8-3, within the first 24 hours of extrauterine life by a single experienced pediatric cardiologist, who was blinded to the mother´s glycemic control. Intraventricular Septum (IVS), Intraventricular Septum/Posterior Wall of the Left Ventricle (IVS/PWLV) index, Ejection Fraction of the Left Ventricle (EFLV), Diastolic Diameter of the Left Ventricle (DDLV), Transmitral Doppler (TMD), Transtricuspid Doppler (TTD) and Transaortic Doppler (AoD) were measured.

Diabetes mellitus was classified according to the ADA criteria [9], and good metabolic control was considered in case of glycosylated hemoglobin (HbA1C) levels <6% [10]. Signed consent was obtained from mothers to allow

clinical chart review and ongoing echocardiographic evaluation. The study was approved by the local ethics committee.

Statistical analysis: The fitness to the normal distribution was determined using the Kolmogorov-Smirnov test. Differences between AGA IDMs or INDMs were tested using the unpaired Student's t-test or the Mann-Whitney U-test when data showed significant departure from normality. The correlation between HbA1C and echocardiographic parameters was evaluated by Pearson´s correlation test.

RESULTS

No difference in sex, birthweight, gestational age or mode of delivery was found between IDM and INDM groups (***Table* I**). ASH was found in 50% of the patients in the group of IDMs, and in none of the INDMs (P<0.0001).

Gestational diabetes mellitus was the most frequent type of diabetes 28 (73.7%), followed by type 2 DM, 9 (23.7%). ASH was found in 15 (54%) and 4 (44.4%) infants born to mothers with gestational diabetes and type 2 diabetes, respectively without difference (P=0.60) between groups.

IVS/PWLV, EFLV, DDLV and AoD were higher in IDMs than in INDMs, while TMD and TTD were lower (***Table* II**). IVS did not show any relationship with HbA1C (r=0.02; P=0.87). ASH was not different in newborns born to mothers with HbA1C >6% *vs.* ≤6% (60.5% *vs.* 39.5%; P=0.08), respectively.

Three infants (7.9%) in the IDM group were detected with patent ductus arteriosus without any hemodynamic repercussions and hypoglycemia was detected in two patients (5.2%).

DISCUSSION

This study showed high ASH frequency in AGA IDMs. The IVS/PWLV index, DDLV and AoD were higher in infants with than in infants without ASH, while the EFLV was not different between groups. On the other hand, the TMD and TTD values were lower in IDMs than in INDMs.

ASH frequency in this study could be related to the poor metabolic control or just the interval of the disease prevalence. However, a limitation of the study is the convenience sampling and the historical control group. Furthermore, insulin levels were not measured either in the newborn or amniotic fluid, and some grade of hyperinsulinemia could still maintain glucose and glycosylated hemoglobin in control limits without general fetal macrosomia induction. It has been reported that adequate metabolic control especially in the third trimester, decreases ASH [11,12]. We do not know if the mechanisms of ASH development are different from the development of large for gestational age infants, but recently Gordon, *et al*. [13], found that only transient hyperglycemic exposure is required to induce cardiac septal overgrowth in fetal rats, explaining why markers of chronic hyperglycemia often do not predict the degree of overgrowth. However**,** results require additional translational studies. This could explain the lack of correlation between IVS size and Hb1Ac levels, also the association may be non-linear with a threshold effect and our sample size may be inadequate to show this effect. The IVS/PWLV index and DDLV higher in infants with than infants without ASH has been previously described [2,3,5]. However, it seems that IVS thickness was not enough to affect the left ventricle systolic function, except for obstructed left ventricle outflow as it has been pointed out [2].

Diastolic dysfunction in both ventricles can be considered by lower TMD and TTD values in IDMs than

TABLE I BASELINE CHARATERSTICS OF APPROPRIATE FOR GESTATIONAL AGE INFANTS BORN TO DIABETIC AND NON-DIABETIC MOTHERS

	AGA IDM n=38	*AGA INDM n=85*
Male	24	55
Birthweight (g)	3227 (335)	3285 (351)
Gestational age (wk)	38.2 (1.0)	38.2 (0.8)
Delivery (vaginal/Caesarean)	12/26	25/60

IDM: Infants born to Diabetic Mothers; INDM: Infants born to Non-diabetic Mothers; All P>0.05.

TABLE II ECHOCARDIOGRAPHIC MEASUREMENTS IN AGA BABIES OF DIABETIC AND NON-DIABETIC MOTHERS

Variables	*AGA IDM n=38*	*AGA INDM n=85*
*IVS (mm)	6.2 (0.9)	3.9 (0.6)
*IVS/PWLV	1.3 (0.1)	0.9 (0.2)
$EFLV (%)	70.2 (3.1)	68.3 (11.3)
*DDLV (mm)	16.0 (1.2)	14.3 (3.1)
*TMD (m/s)	0.5 (0.1)	0.9 (0.2)
#TTD (m/s)	0.6 (0.1)	0.8 (0.2)
*AoD (m/s)	0.8 (0.1)	0.6 (0.1)

*IVS: Intraventricular Septum; [b]IVS/PWLV: Intraventricular Septum/ Posterior Wall of the Left Ventricle; [c]EFLV: Ejection Fraction of the Left Ventricle; DDLV: Diastolic Diameter of the Left Ventricle; TMD: Transmitral Doppler; TTD: Transtricuspid Doppler; AoD: Transaortic Doppler; Data are showed as mean (SD); *P<0.001; #P=0.001; $P>0.05.*

WHAT THIS STUDY ADDS?

- Asymmetric septal hypertrophy is frequent in infants of diabetic mothers even when they are appropriate for gestational age.

in INDMs, and the difference in AoD between the two groups could be related to the turbulent flow through the outflow tract of the left ventricle. However, no child required hemodynamic support or returned to the hospital because of heart alterations. So we consider there is not enough support to indicate an echocardiogram in all IDMs.

To conclude, ASH is a common finding in IDMs even if they are AGA infants, but it does not require hemodynamic support. There was not a linear correlation between IVS and the metabolic control.

Contributors: MVH, NA: designed the study; HOV, AHR: collected and analyzed the data; JGM, NA: wrote the manuscript. All authors read and approved the final manuscript.
Funding: None; *Competing interests*: None stated.

REFERENCES

1. Persson B, Hanson U. Neonatal morbidities in gestational diabetes mellitus. Diabetes Care. 1998;21:B79-84.
2. Breitweser JA, Meyer RA, Sperling MA, Tsang RC, Kaplan S. Cardiac septal hypertrophy in hyperinsulinemic infant. J Pediatr. 1980;96:535-9.
3. Cooper MJ, Enderlein MA, Tarnoff H, Rogé CL. Asymmetric septal hypertrophy in infants of diabetic mothers. Am J Dis Child. 1992;146:226-9.
4. Vela-Huerta MM, Vargas-Origel A, Olvera-López A. Asymmetrical septal hypertrophy in newborn infants of diabetic mothers. Am J Perinatol. 2000;2:89-94.
5. Weber H, Copel J, Reece MA, Green J, Kleinman CS. Cardiac growth in fetus of diabetic mothers with good metabolic control. J Pediatr. 1991;18:103-7.
6. Vincent M, Benbrik N, Romefort B, Colombel A, Bézieau S, Isidor B. Three patients presenting with severe macrosomia and congenital hypertrophic cardiomyopathy: a case series. J Med Case Rep. 2017;11:78.
7. Lubchenco LO. The estimation of gestational age in the high-risk infant. Philadelphia WB Saunders, 1976:9.
8. Taylor RM, Price-Douglas W. The STABLE program: postresuscitation/ pretransport stabilization care of sick infants. J Perinat Neonatal Nurs. 2008;22:159-65.
9. American Diabetes Association. Classification and diagnosis of diabetes. Diabetes Care. 2017;40:S11-S24.
10. Kitzmiller JL, Block JM, Brown FM, Catalano PM, Conway DL, Coustan DR, *et al*. Managing preexisting diabetes for pregnancy: summary of evidence and consensus recommendations for care. Diabetes Care. 2008;31:1060-79.
11. Zielinsky P, Piccoli AL Jr. Myocardial hypertrophy and dysfunction in maternal diabetes. Early Hum Dev. 2012;88:273-8.
12. Mert MK, Satar M, Özbarlas N, Yaman A, Özgünen FT, Asker HS, *et al*. Troponin T and NT ProBNP levels in gestational, type 1 and type 2 diabetic mothers and macrosomic infants. Pediatr Cardiol. 2016;37:76-83.
13. Gordon EE, Reinking BE, Hu S, Yao J, Kua KL, Younes AK, *et al*. Maternal hyperglycemia directly and rapidly induces cardiac septal overgrowth in fetal rats. J Diabetes Res. 2015; 479565:1-11.