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Research paper

Fetal cardiac remodelling in pregnancies complicated by gestational diabetes mellitus: a prospective cohort study

Giuseppe Rizzo[1,2], Maria Elena Pietrolucci[1], Ilenia Mappa[1], Victoria Bitsadze[1,2], Jamilya Khizroeva[1,2], Alexander Makatsariya[2]

[1]Division of Maternal Fetal Medicine Ospedale Cristo Re Roma, Università di Roma Tor Vergata, Roma, Italy
[2]Department of Obstetrics and Gynaecology, The First I.M. Sechenov Moscow State Medical University, Moscow, Russia

Abstract

Introduction: Pregnancies complicated by gestational diabetes mellitus (GDM) have a higher risk of fetal and neonatal cardiac remodelling. Our aim was to evaluate the sphericity index (SI), a variable reflecting the severity of cardiac shape changes, in fetuses of GDM mothers and correlate the quality of glycaemic control expressed by glycated haemoglobin (HbA_{1c}) levels.

Material and methods: This was a prospective cross-sectional study including 276 pregnancies complicated by GDM (185 with good control [$HbA_{1c} \leq 5.5$] and 91with poor control [HbA1c > 5.5]) and 140 uncomplicated gestations. All women underwent ultrasound biometric evaluation, Doppler and echocardiographic assessment, including evaluation of the SI at a median gestational age of 30 weeks. Comparisons among groups were performed.

Results: Compared to the control group, fetuses from GDM mothers showed a higher body mass index ($p = 0.003$), estimated fetal weight ($p = 0.037$), gestational age at delivery ($p = 0.042$), birthweight ($p = 0.006$), and birthweight centile ($p = 0.012$). There was no difference in maternal age, parity, gestational age at ultrasound, and maternal or fetal Dopplers. In pregnancies with GDM right ventricle SI (1.42 for good control and 1.33 for poor c control) the SIs were higher compared to control pregnancies (1.55; $p = 0.001$). No difference was found in left ventricle SI (1.51 for good and 1.59 for poor control) when compared to the control group (1.76; $p = 0.08$). When stratifying the analysis according to glycaemic control, right SI was lower in pregnancies with poor compared to good control ($p = 0.002$).

Conclusions: The risk of fetal cardiac remodelling is higher in pregnancies complicated by GDM, and it is independent of maternal and fetal Doppler. These changes occur at the level of the right ventricle and are influenced by glycaemic control.

Key words: gestational diabetes mellitus, fetal echocardiography, cardiac remodelling, sphericity index, glycaemic control.

Corresponding author:
Giuseppe Rizzo, MD
Università di Roma Tor Vergata
Division of Maternal Fetal Medicine
Ospedale Cristo Re
00167 Roma, Italy
tel. +39 06 612451
e-mail: giuseppe.rizzo@uniroma2.it

Introduction

The incidence of gestational diabetes mellitus (GDM) ranges from 5 to 20% of all pregnancies in relation to population characteristics [1, 2]. Despite significant advances in screening, diagnostic criteria, and management protocols, GDM persists as a prominent contributing factor to fetal abnormal development [2]. Women with GDM have increased insulin resistance, which can lead to maternal hyperglycaemia and increased glu-

cose transport across the placenta, with resultant fetal hyperinsulinaemia [3]. The fetal heart is one of the major organs affected by hyperinsulinaemia, and myocardial hypertrophy has been reported extensively in neonates of diabetic mothers [4, 5]. Infants of diabetic mothers are also at increased risk of cardiovascular morbidity and mortality in later life, presumably through a mechanism of cardiac remodelling that affects the myocardial fibre architecture influencing cardiac geometry, myocardial deformation, and ventricular function [6]. These changes are often subtle during fetal life and detectable by conventional Doppler studies or tissue Doppler imaging (TDI) and speckle-tracking imaging (STI), which are difficult to apply in a clinical setting [7, 8]. The sphericity index (SI), calculated as the ratio between the end-diastolic mid-basal-apical and transverse lengths, can be easily obtained by standard four chamber view of the fetal heart [9]. The sphericity index is among the most reproducible parameters used to quantify cardiac remodelling and has been shown to be reduced in pregnancies complicated by late FGR and in fetuses of pregnancy from in vitro fertilisation [10–12].

We speculated that SI may vary in fetuses of mothers of GDM and may be related to the quality of glycaemic control. We therefore designed a prospective cross-sectional cohort study on fetal cardiac function in fetuses from pregnancies with GDM.

Material and methods

Study population

This was a prospective study on consecutive singleton pregnancies complicated by GDM and attending the antenatal clinic of the Department of Obstetrics and Gynaecology of the Università Roma Tor Vergata for third trimester ultrasonographic evaluation between January 2016 and September 2019. Criteria of inclusion were: 1) absence of any maternal chronic disease (pre-gestational diabetes, hypertension, renal or autoimmune diseases), 2) absence of maternal smoking or medication, 3) absence of fetal structural or chromosomal anomalies, and 4) delivery scheduled in our unit. As a control group, we selected from pregnancies undergoing ultrasonography during the same study period 140 uncomplicated singleton spontaneously conceived pregnancies accurately dated by first trimester crown rump length and with a normal 75 g oral glucose tolerance test (OGTT).

Screening for gestational diabetes was done by OGTT at 24 weeks of gestation. The diagnosis of gestational diabetes was made if one or more of the following criteria were met: fasting plasma glucose level ≥ 92 mg/dl, a one-hour level of 180 mg/dl and two-hour level ≥ 153 mg/dl. GDM was initially treated with diet and lifestyle recommendations. If this resulted in insufficient glycaemic control, insulin was prescribed. Insufficient control was considered when fasting blood glucose concentration was ≥ 95 mg/dl or two-hour glucose was > 120 mg/dl on one-third or more occasions within a one-week interval despite dietary therapy.

Measurements of glycated haemoglobin (HbA_{1c}) levels were done every four weeks. The HbA_{1c} levels close to ultrasonographic control were used for the purpose of this study and categorised in ≤ 5.5% as good control and in > 5.5% as poor control.

The local institutional Ethical Committee approved the study protocol (IRB 2015/Ob6), and each woman gave written, informed consent to take part in the study.

Ultrasound assessment

Recordings were performed using a Samsung W80 or Hera W10 ultrasound device equipped with a 1–8 MHz volumetric probe. Fetal ultrasonographic evaluation included estimation of fetal biometric measurements, fetal weight, maternal and fetal Doppler, and fetal echocardiography.

The considered fetal biometric measurements included the biparietal diameter, head circumference, abdominal circumference femur length, obtained following ISUOG recommendations [13], and fetal weight computed with the Hadlock 4 formula [14]. Doppler assessment included pulsatility index (PI) measurements of the uterine artery umbilical artery and middle cerebral artery and the calculation of cerebroplacental ratio (middle cerebral artery PI/umbilical artery PI) according to a previously published methodology [15].

Fetal echocardiography included a comprehensive anatomic and functional evaluation. Cardiac measurements were obtained from two-dimensional images of the four-chamber view with the interventricular septum at an angle between 45° and 90° to the ultrasound beam using a previously reported technique [12]. Images were optimised to enhance the borders of cardiac walls, and cine clips were stored. Ventricular base-to-apex lengths and basal diameters at end diastole. Left and right ventricular sphericity indexes were calculated as base-to-apex length divided by basal diameter (Figure 1).

The left and right SI were calculated at end diastole as base-to-apex length/transverse diameter of the left and right ventricles, respectively.

Statistical analysis

Categorical variables are presented as number (n) and percentage (%) and continuous variables as median and interquartile range (IQR). Maternal and fetal characteristics were compared using the χ^2 test for categorical variables, whereas continuous variables were compared using Kruskal-Wallis (K). When the Kruskal-Wallis test resulted in a significant value, Dunn's post-hoc test was applied for multiple comparisons. A two-sided p value of < 0.05 was considered statistically significant. Statistical analysis was performed with SPSS software (version 23 IBM Corp., Armonk, NY).

Results

Of 322 eligible pregnancies complicated by GDM, 276 were included in the study. Causes of exclusion were inadequate cardiac imaging or incomplete acquisition of all the ultrasonographic variables (n = 34) and lost at follow-up

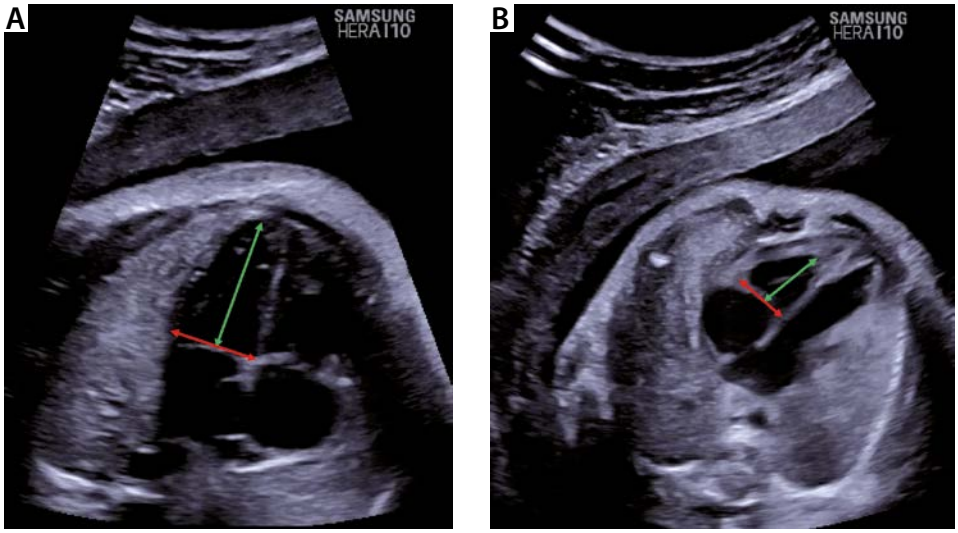

Figure 1. Echocardiographic images of two fetuses at 30 weeks of gestation from an uncomplicated pregnancy (**A**) and poorly controlled GDM (**B**). Right ventricle sphericity index (SI) was 1.46 and 1.19, respectively. For the computation of SI, the end-diastolic mid-basal-apical length (green arrows) is divided by the basal transverse length (red arrows)

(n = 12). Good glycaemic control was present in 185 pregnancies, while poor control was found in the remaining 91 women. The general characteristics of the study population are reported in Table 1. Pregnancies complicated by GDM showed a higher body mass index and an earlier gestational at delivery when compared to control pregnancies. Similarly, estimated fetal weight, birthweight, and birthweight centile were higher in GDM pregnancies than in controls. Gesta-

Table 1. General characteristics of the study population

Variables	Control group (n = 140)	GDM good glycaemic control (n = 185)	GDM poor glycaemic control (n = 91)	p
Maternal age (years)	29 (24-34)	28 (15-35)	30 (23-33)	0.7231
BMI (kg/m^2)	24.4 (20.3-28.5)	27.7 (22.3-29.1)	28.5 (21.8-28.7)	0.003
Nulliparous, n (%)	102 (72.8)	123 (66.5)	58 (63.7)	0.290
Caucasian, n (%)	122 (87.1)	156 (84.3)	79 (86.1)	0.735
Gestational age at delivery (weeks)	40.2 (38.4-40.6)	39.0 (38.1-39.3)	39.1 (38.0-39.6)	0.042
Birthweight (g)	3310 (2990-3720)	3520 (3140-3560)	3750 (3020-3820)	0.006
Birthweight centile	51 (33-72)	67 (44-75)	76 (44-82)	0.012
Male newborn, n (%)	69 (49.3)	92 (49.7)	48 (52.7)	0.861

GDM – gestational diabetes mellitus, BMI – body mass index

Table 2. Ultrasonographic characteristics of the study population

Variables	Control group (n = 140)	GDM good glycaemic control (n = 185)	GDM poor glycaemic control (n = 91)	p
Gestational age at ultrasonographic examination (weeks)	30.2 (29.3-31.4)	30.1 (29.9-31.7)	30.4 (29.7-32.1)	0.423
Estimated fetal weight (g)	1710 (1660-1822)	1790 (1731-1824)	1810 (1714-1835)	0.037
Mean uterine artery PI	0.75 (0.68-0.81)	0.73 (0.66-0.80)	0.76 (0.65-0.84)	0.324
Umbilical artery PI	0.99 (0.88 -1.12)	0.95 (0.85-1.09)	0.96 (0.84-1.12)	0.121
Middle cerebral artery	1.92 (1.86-2.01)	1.89 (1.79-1.99)	1.90 (1.84-2.02)	0.212
PCR	1.93 (1.21-1.45)	1.98 (1.18-1.47)	1.94 (1.22-1.46)	0.346
Left SI	1.76 (1.61-1.88)	1.51 (1.41-1.61)	1.59 (1.47-1.68)	0.080
Right SI	1.55 (1.33-1.66)	1.42 (1.29-1.58)	1.33 (1.23-1.59)	0.001

GDM – gestational diabetes mellitus, PI – pulsatility index

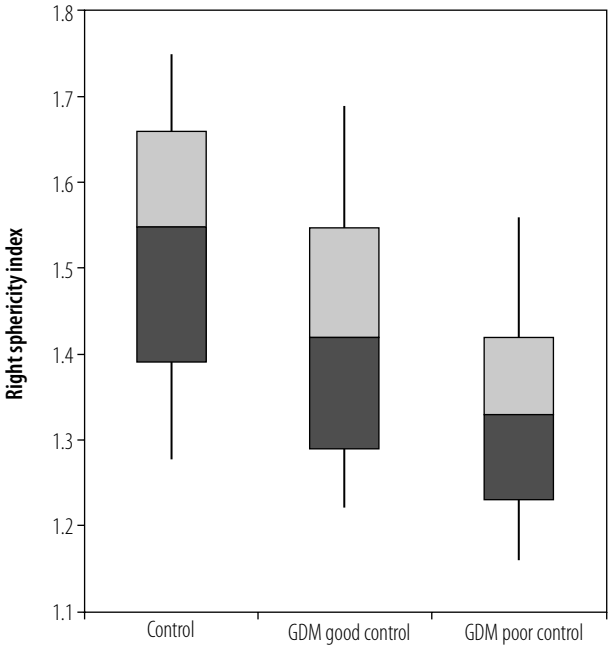

Figure 2. Box-whisker plots showing right sphericity index (SI) in the three groups of pregnancies investigated

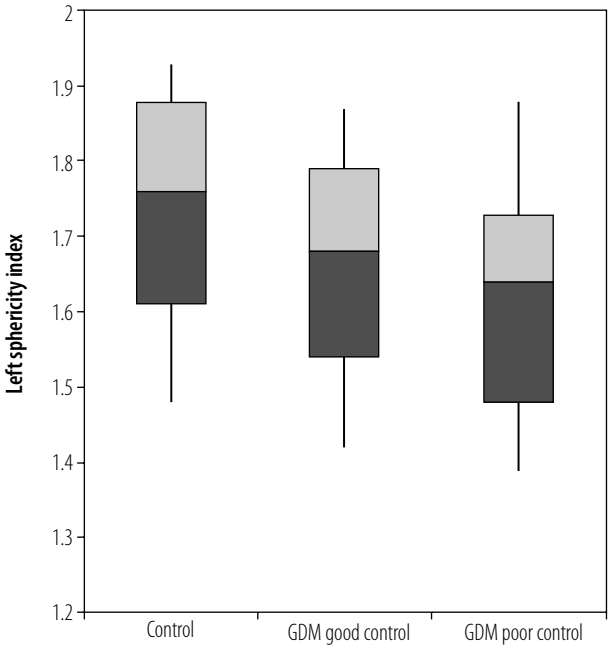

Figure 3. Box-whisker plots showing left sphericity index (SI) in the three groups of pregnancies investigated

tional age at examination, estimated fetal weight, and maternal and fetal Doppler PI values were similar between groups (Table 2). Subgroup analysis did not demonstrate differences between GDM pregnancies with good and poor control.

Fetuses of mothers with GDM showed lower right SI (Kruskal-Wallis test H 47.9, $p = 0.001$) (Figure 2), and no difference was found for left SI (Kruskal-Wallis test H 2.4, $p = 0.08$) (Table 2, Figure 3). Comparison according to the quality of glycaemic control evidenced lower values of right SI ($p = 0.002$) in poorly controlled diabetes (Figure 2).

Discussion

Main findings

In this prospective, cross-sectional study, we showed that in fetuses of pregnancies complicated by GDM the right ventricle is more globular, as expressed by the reduction of the right SI. When fetuses were compared according to the quality of glucose control, those with a poorer showed more marked cardiac modification. Despite this remodelling in fetal heart, no difference was found among groups in fetal and maternal Doppler indices, suggesting no impairment of peripheral haemodynamic condition in this population of GDM.

Comparison with other studies

The findings of this study are in line with those of previous reports showing cardiac dysfunction in fetuses of pregnancies of diabetic mothers, both pregestational and GDM [16–19]. These prenatal cardiac changes persist after birth and are associated with thicker ventricular walls, which is indicative of a more globular heart and impaired LV systolic and diastolic function [20, 21]. These studies were mainly performed using new technology, including STI and TDI echocardiography [21, 22]. Although there is evidence that these new techniques have a superior prognostic value over conventional measures for predicting major adverse cardiac events [23], the difficulties in acquisition and their reproducibility limits their application during the perinatal period, suggesting the use of simpler indices of cardiac function. Patey et al. [24] studied in 21 diabetic pregnancies, 14 with GDM and seven with pre-gestational diabetes – fetal cardiac function near term and in the first day of life using both conventional TDI and STI echocardiography. In agreement with our observations, they found that the SI of the right ventricle but not of the left SI was impaired in both fetal and neonatal hearts. They showed that the increased wall thickness resulted in a reduction of the diameters of the right ventricle. On the other hand, in the left ventricle the increase in both end diastolic basal diameter and length in diabetic pregnancies resulted in an unchanged LV SI compared with the control pregnancies.

Strengths and limitations

Prospective design, inclusion of consecutive pregnancies, and large sample size represent the major strengths of the present study. Another major strength of the study is the control of potential confounder variables such glycaemic control and maternal and fetal Doppler characteristics.

The limitations include the cross-sectional design, which does not take into account any serial changes during pregnancy and after birth. Furthermore, only a limited number of echocardiographic variables were evaluated and more complex indices evaluable by TDI or STI were not considered [21, 22, 24]. However, the relative ease in measuring SI from standard four-chamber view of the fetal heart should be pointed out, suggesting a potential role of these indices in identifying fetuses with cardiac dysfunction among GDM pregnancies.

Implications for clinical practice

Prenatal detection of fetuses at higher risk of cardiac remodelling in pregnancies complicated by GDM is of paramount importance because it may allow different strategies aimed at improving the long-term cardiovascular outcome of these children. Indeed, there is evidence that early intervention in these fetuses promoting breastfeeding and consumption of a diet with a high polyunsaturated-to- saturated fat ratio in early childhood, lifestyle modifications, reduction of exposure to other risk factors, and blood pressure monitoring may help in reducing cardiovascular risk [25–27]. Furthermore, in fetuses identified by abnormal SI it may useful to extend the echocardiographic evaluation during the perinatal period using the advantages of imaging techniques.

Conclusions

Cardiac remodelling, as expressed by a reduction of right ventricle SI, occurs in fetuses of GDM pregnancies. These changes are dependent on the quality of glycaemic control and are unaffected by maternal and fetal peripheral arterial Doppler haemodynamics. These findings may be considered in the identification of such fetuses and may prompt postnatal monitoring and intervention aimed at reducing their cardiovascular risk.

Conflict of interest

The authors declare no conflict of interest.

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Division of work:
Giuseppe Rizzo (ORCID: 0000-0002-5525-4353): research concept and design, data analysis and interpretation, writing the article, critical revision of the article, final approval of the article
Maria Elena Pietrolucci (ORCID 0000-0002-9444-6374): collection and/or assembly of data, data analysis and interpretation, critical revision of the article, final approval of the article
Ilenia Mappa (ORCID: 0000-0002-9866-3050): collection and/or assembly of data, data analysis and interpretation, critical revision of the article, final approval of the article
Victoria Bitsadze (ORCID: 0000-0001-8404-1042): collection and/or assembly of data, data analysis and interpretation, writing the article, final approval of the article
Jamilya Khizroeva (ORCID: 0000-0002-0725-9686): collection and/or assembly of data, data analysis and interpretation, critical revision of the article, final approval of the article
Alexander Makatsariya (ORCID: 0000-0001-7415-4633): research concept and design, writing the article, critical revision of the article, final approval of the article