Fetal Cardiac Function in Maternal Diabetes: A Conventional and Speckle-Tracking Echocardiographic Study

Joana O. Miranda, MD, Rui J. Cerqueira, MD, Carla Ramalho, MD, PhD, José Carlos Areias, MD, PhD, and Tiago Henriques-Coelho, MD, PhD, *Porto, Portugal*

Background: Intrauterine exposure to a diabetic environment is associated with adverse fetal myocardial remodeling. The aim of this study was to assess the biventricular systolic and diastolic function of fetuses exposed to maternal diabetes (MD) compared with control subjects, using a comprehensive cardiac functional assessment and exploring the role of speckle-tracking to assess myocardial deformation. The authors hypothesized that fetuses exposed to MD present signs of biventricular dysfunction, which can be detected by deformation analysis.

Methods: A cross-sectional study was conducted in 129 fetuses with structurally normal hearts, including 76 fetuses of mothers with diabetes and 53 of mothers without diabetes. Maternal baseline characteristics, standard fetoplacental Doppler indices, and conventional echocardiographic and myocardial deformation parameters were prospectively collected at 30 to 33 weeks of gestation.

Results: Fetuses of mothers with diabetes had a significantly thicker interventricular septum compared with control subjects (median, 4.25 mm [interquartile range (IQR), 3.87–4.50 mm] vs 3.67 mm [IQR, 3.40–3.93 mm), $P < .001$), but no effect modification was demonstrated on myocardial deformation analysis. No significant differences were found in conventional systolic and diastolic functional parameters for the left ventricle and right ventricle, except for lower left ventricular cardiac output in the MD group (median, 320 mL/min [IQR, 269–377 mL/min] vs 365 mL/min [IQR, 311–422 mL/min], $P < .05$]. Deformation analysis demonstrated a significantly lower early diastolic strain rate (SRe) and late diastolic strain rate (SRa) for both ventricles in the MD group (left ventricle: SRe 1.85 ± 0.72 vs 2.26 ± 0.68 sec^{-1}, SRa 1.50 ± 0.52 vs 1.78 ± 0.57 sec^{-1}; right ventricle: SRe 1.57 ± 0.73 vs 1.97 ± 0.73 sec^{-1}, SRa 2 ± 0.77 vs 1.68 ± 0.79 sec^{-1}; $P < .05$), suggesting biventricular diastolic impairment. Additionally, the right ventricle presented a lower global longitudinal strain in the study group (−13.67 ± 4.18% vs −15.52 ± 3.86%, $P < .05$). Multivariate analysis revealed that maternal age is an independent predictor of left and right ventricular global longitudinal strain ($P < .05$), with a significant effect only in MD after group stratification.

Conclusions: Fetuses of mothers with diabetes present signs of biventricular diastolic dysfunction and right ventricular systolic dysfunction by deformation analysis in the third trimester of pregnancy. They may represent a special indication group for functional cardiac assessment, independently of septal hypertrophy. Two-dimensional speckle-tracking could offer an additional benefit over conventional echocardiography to detect subclinical unfavorable changes in myocardial function in this population. (J Am Soc Echocardiogr 2017;■:■-■.)

Keywords: Gestational diabetes, Cardiac function, Fetal echocardiography, Fetus, Speckle-tracking

Exposure to a diabetic intrauterine environment has long been recognized as a risk to the fetus, with a double impact on the fetal heart. During embryogenesis it has a teratogenic effect, increasing the incidence of structural cardiac anomalies.[1] More commonly, infants of mothers with diabetes are at higher risk for developing fetal hypertrophic cardiomyopathy,[2,3] characterized by asymmetric

From the Department of Pediatric Cardiology (J.O.M., J.C.A.), the Department of Cardiothoracic Surgery (R.J.C.), and the Center of Prenatal Diagnosis, Department of Gynecology and Obstetrics (C.R.), São João Hospital Centre, Porto, Portugal; and the Department of Surgery and Physiology (J.O.M., R.J.C.), Department of Pediatrics (J.C.A., T.H.-C.), and Cardiovascular R&D Centre (UnIC) (T.H.-C.), Faculty of Medicine, and Instituto de Investigação e Inovação em Saúde (C.R.), University of Porto, Porto, Portugal.

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Reprint requests: Joana O. Miranda, MD, Department of Pediatric Cardiology, Hospital São João, Alameda Professor Hernâni Monteiro, Porto 4200-319, Portugal (E-mail: *joanam@gmail.com*).

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Abbreviations
2D = Two-dimensional
ICC = Intraclass correlation coefficient
MD = Maternal diabetes

myocardial hypertrophy, more evident in the third trimester of pregnancy and affecting mainly the interventricular septum.

Advances in high-resolution echocardiography and Doppler interrogation of the fetal heart have improved our understanding of fetal cardiac function and response to adverse intrauterine conditions. It has been suggested that diastolic dysfunction may represent the earliest change on fetal hypertrophic cardiomyopathy in fetuses of mothers with diabetes, preceding systolic dysfunction, and in some cases progression to symptomatic heart failure.[4-7] However, the commonly applied evaluation methods provide only indirect information about systolic and diastolic function and do not measure deformation of the myocardium itself. Speckle-tracking echocardiography is a recent development based on the tracking of unique speckle patterns or "kernels" in the myocardium throughout the cardiac cycle. It has the potential to provide new insights into fetal origins of disease and into the understanding of fetal heart function in specific disease states.

The aim of this study was to assess biventricular systolic and diastolic function in fetuses of mothers with diabetes compared with control subjects, using conventional fetal echocardiography and exploring the potential role of deformation analysis by speckle-tracking on cardiac functional assessment. We hypothesized that fetuses exposed to maternal diabetes (MD) present signs of biventricular dysfunction and that deformation analysis could be a sensitive and reproducible technique to assess global and segmental cardiac function of fetuses in this condition.

METHODS

Study Population

We conducted an observational cross-sectional study at a tertiary referral center for fetal cardiology. Patients were selected at the time of the examination appointment, following a convenience sampling strategy, between July 2016 and June 2017. Echocardiographic data were acquired in a prospective manner specifically for the purpose of the study. The study protocol was approved by the local ethics committee, and written informed consent was obtained from all study participants.

A total of 129 subjects were recruited. The MD group comprised 76 pregnant women with gestational diabetes diagnosed by current international recommendations (fasting plasma glucose at first trimester or glucose tolerance test using 75 g glucose between 24 and 28 weeks of gestation) or with pregestational diabetes. The control group comprised 53 pregnant women without diabetes with normal results on fetal echocardiographic evaluation. Referral reasons for control group were family history of congenital heart disease ($n = 13$), unconfirmed suspicion of heart disease on obstetric anomaly scan ($n = 8$), polyhydramnios ($n = 8$), increased nuchal translucency thickness in the first trimester ($n = 8$), intracardiac echogenic focus ($n = 7$), exposure to teratogens in the first trimester ($n = 4$), advanced maternal age ($n = 3$), and mild tricuspid regurgitation on obstetric scan ($n = 2$). Exclusion criteria applied to both groups were structural or chromosomal fetal anomalies, fetal arrhythmias, fetal growth restriction, evidence of fetal infection, multiple pregnancies, pregnancies conceived by assisted reproductive technology, and maternal chronic disease other than diabetes mellitus. All control group subjects had normal findings on postnatal clinical examinations, which included medical history and physical examination.

For a subgroup analysis, the MD group was divided into subjects receiving no pharmacologic treatment ($n = 42$) and those receiving pharmacologic treatment (insulin and/or metformin; $n = 34$).

Fetal examinations were performed between 30 and 33 weeks of gestation in both groups, with gestational age calculated on the basis of crown-rump length measurement on first-trimester ultrasound.

Maternal baseline characteristics including age, height, and weight (for body mass index calculation), smoking habit, multiparity, and diabetes treatment were collected at the time of the ultrasound examination. Detailed fetal echocardiography was performed by an experienced cardiologist to exclude congenital heart disease. A standard fetoplacental Doppler evaluation and comprehensive fetal echocardiography were added to routine fetal echocardiography.

Imaging Protocol

All ultrasound studies were performed using a single high-resolution ultrasound platform (Vivid E95; GE Healthcare, Little Chalfont, United Kingdom) equipped with a C1-6 curved-array fetal transducer. Two-dimensional (2D) echocardiographic data were acquired at a high frame rate (60–150 frames/sec). Pulsed-wave Doppler parameters were recorded from three or more waveforms, with insonation angle $< 20°$. For offline postprocessing, EchoPAC version 201.71 (GE Healthcare) was used for both conventional and deformation analysis.

Fetoplacental Doppler Evaluation

Estimated fetal weight was calculated using the formula of Hadlock *et al.*[8] Standard obstetric Doppler evaluation comprised measurement of the pulsatility index for the umbilical artery, middle cerebral artery, ductus venosus, and aortic isthmus.[9] The cerebroplacental ratio was calculated by dividing middle cerebral artery and umbilical artery pulsatility indices.

Fetal Echocardiography

Cardiovascular evaluation comprised morphometric measurements and functional assessment of the heart, the latter by both conventional echocardiography and deformation analysis. The following parameters, measured as described previously,[10] were included.

Cardiac morphometry: cardiothoracic ratio (by the ellipse method in a cross-sectional view of the fetal thorax at end-diastole), ventricular sphericity index (base-to-apex length/basal diameter in a four-chamber view of the heart at end-diastole), interventricular septal wall thickness (by M-mode echocardiography in a transverse four-chamber view at end-diastole), and left and right atrial areas (on 2D images of a four-chamber view at end-ventricular systole, the maximum point of atrial distension)

Conventional systolic function: left and right cardiac output (cross-sectional aortic or pulmonary annular area × aortic or pulmonary flow velocity integral × heart rate), left ventricular shortening fraction (by M-mode echocardiography from the transverse four-chamber view using the Teichholz formula), and mitral and tricuspid annular plane systolic excursion (by M-mode echocardiography in an apical or basal four-chamber view)

Conventional diastolic function: mitral and tricuspid early (E) and late (A) diastolic filling ratio (E/A ratio) and isovolumic relaxation time