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ORIGINAL ARTICLE

Assessment of Cardiac Dysfunction in the Intrauterine Growth-restricted Fetuses from Pre-eclamptic Mothers

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ABSTRACT

Background: Although it is known that cardiac parameters have abnormal values in severely affected fetuses with intrauterine growth restriction (IUGR), recent research suggested that subclinical cardiac dysfunction may be present from the early stages of fetal deterioration. The identification and monitoring of cardiac dysfunction may be relevant for the management of these cases.

Materials and methods: In this prospective observational study, we evaluated 17 IUGR fetuses from nulliparous pregnant women diagnosed with pre-eclampsia. Cardiac structural assessment was performed using segmental sequential analysis. Cardiac function was assessed by conventional echocardiography and Tissue Doppler Imaging (TDI).

Results: Gestational age at admittance ranged between 24 and 30 weeks. A severe form of pre-eclampsia was diagnosed in 2 of 17 cases. Conventional cardiac examination showed low left and right ventricular diastolic filling with low E and A velocities, and increased myocardial performance indexes for both ventricles. Using TDI we observed decreased myocardial velocities and impaired contractility (demonstrated by low left and right diastolic velocities, as well as increased E'/A' ratios).

Conclusion: Our study confirms the presence of early cardiac dysfunction in IUGR fetuses. Further studies are warranted to confirm the utility of TDI in obstetric ultrasound routine examination for monitoring fetal cardiac function in high-risk pregnancies.

Keywords: IUGR, Cardiac, Myocardial, Echocardiography.

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INTRODUCTION

Placental insufficiency, defined as impaired placental flow with increased peripheral vascular resistance, is a leading cause of intrauterine growth restriction (IUGR). It is diagnosed in 3 to 10% of all pregnancies and represents both an economic and a public health burden due to its significantly increased rate of perinatal mortality and morbidity.[1,2]

Fetal hypoxia, resulting from increased placental impedance, leads to alteration of the cardiac function, with recent research suggesting that subclinical cardiac dysfunction is present from the early stages of fetal deterioration.[2] A possible mechanism of the diastolic malfunction associated with placental insufficiency is the right ventricular afterload with consequent pulmonary and systemic vasoconstriction and shift of the cardiac output on the left ventricle. The fetuses face a gradual worsening in the cardiovascular function and velocity indices change as the fetal condition progressively deteriorates.[1]

Fetal cardiovascular status can be assessed by both conventional Doppler ultrasonography and myocardial Tissue Doppler Imaging (TDI).[3] This former echocardiographic technique allows a quantitative measurement of motion and timing of myocardial events.[3]

Considering the importance of assessing the fetal cardiac function pattern, especially in the case of fragile IUGR fetuses, from the obstetrical management and neonatal prognosis perspective, diastolic dysfunction may be an early marker of fetal hypoxia.[4]

In this context, the aim of the present study was to assess the cardiac dysfunction pattern by conventional ultrasonography and TDI in IUGR fetuses.

MATERIALS AND METHODS

This prospective, observational study enrolled pregnant women admitted between February and May 2013 in the Maternal-Fetal Medicine Department of the Gynecology I Clinic in Cluj-Napoca, Romania. The inclusion criterion was the diagnosis of a mild or severe form of pre-eclampsia as the main cause of IUGR. Exclusion criteria were represented by IUGR due to structural/chromosomal anomalies, evidence of fetal infection and fetuses whose mothers used tobacco and drugs. The study protocol was approved by the local Ethics Committee and patients signed written informed consent.

Gestational age was determined by first-trimester ultrasound in all fetuses. For the diagnosis of pre-eclampsia, the following criteria were used: gestational age between 20

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and 33 weeks + 6 days; blood pressure in pregnant women ≥ 140/90 mmHg or increases of systolic blood pressure ≥ 30 mmHg and/or of diastolic blood pressure ≥ 15 mmHg, compared to values noted before 20 gestational weeks; proteinuria ≥ 300 mg/l/24 h; generalized edema. Severe pre-eclampsia was diagnosed when blood pressure was >160/110 mm Hg, proteinuria >500 mg/24 hours and one of the following occurred: symptoms of central nervous system dysfunction, symptoms of liver capsule distension, hepatocellular injury, or thrombocytopenia.[5] IUGR due to placental insufficiency was defined by fetal weight below the 10th percentile for the gestational age, in combination with abnormal Doppler indices (umbilical artery resistivity index RI >95th percentile).

Ultrasonographic assessments were performed using a Voluson 730 Expert machine (GE Healthcare) with a 4-6 MHz curved array probe.

At admittance, an ultrasound examination was performed in all cases for fetal well-being assessment. This examination included fetal biometry, placental biometry, evaluation of amniotic fluid index, measurement of umbilical artery pulsatility index (PI), fetal middle cerebral artery PI, cerebro-placental ratio, ductus venosus A-wave flow pattern and determination of the presence of notching of both uterine arteries (mean velocity was not measured at the time of the study). The umbilical artery was sampled in a free loop, during fetal apnea, after a sequence of more than 10 cycles; arterial waveforms were recorded with the venous signal in the opposite direction. Additionally, the middle cerebral artery of the fetus was sampled during fetal apnea, after a constant sequence of more than 10 beats. Mothers' left and right uterine arteries were sampled using conventional views to determine the presence of the protodiastolic notch.

Cardiac structural assessment used segmental sequential analysis. In all pregnancies cardiac function was assessed by conventional echocardiography and TDI.

Conventional atrioventricular flow velocity waveforms were obtained from the apical four chamber view. The Doppler sample volume was placed slightly distal to the tricuspid and mitral annuli between the tips of the leaflets. We calculated diastolic parameters (left and right E, A waves and the E/A ratio), systolic parameters (left and right peak aortic and pulmonary valve velocity) and the myocardial performance index or Tei index. The E-wave was defined as the early, passive diastolic filling, which is dependent on ventricular wall relaxation. The A-wave was defined as the active diastolic filling known as the 'atrial kick'. The E/A ratio was calculated as the ratio between the two peaks in flow velocity observed over the atrioventricular valve during diastole. Peak annular aortic and pulmonary velocities were measured using the in-built autotracing system. The ejection time (ET) was measured as the duration of flow through the outflow tract, aortic and pulmonary valves. The isovolumetric contraction time (ICT) was measured between cessation of AV valve flow and the onset of outflow tract flow. The interval between cessation of outflow tract flow and the onset of AV valve flow defined the isovolumetric relaxation time (IRT). For the myocardial performance index determination, the Doppler sample volume was positioned, as described by Hernandez-Andrade et al, in a cross-sectional image of the fetal thorax and an apical four-chamber view, placing the Doppler sample volume on the medial wall of the ascending aorta and including the aortic and mitral valves.[6] For the right ventricle, inflow and outflow measurements were obtained in series from separate cardiac cycles. The movements (clicks) of the valves in the Doppler tracing were used as landmarks to calculate the ICT, IRT, and the ET. Myocardial performance index (MPI) was calculated as (ICT + IRT)/ET.[7]

TDI was performed by spectral Doppler from the apical four chamber view. The Doppler settings were automatically adjusted for the size of the sample volume (width 2 mm), low filter, low gain (below 30 decibels) and Nyquist limit of 0 to 30 cm/s. The sample volume was placed on the left and right ventricular lateral walls, just below the level of the atrioventricular valves. The angle of insonation to the long axis of the heart was kept as small as possible.

Statistical Analysis

Our data were analyzed using SPSS for Windows 15.0 (SPSS Inc, Chicago, IL). Results were expressed as mean ± standard deviation.

RESULTS

The current study was conducted on a population of 17 IUGR fetuses from nulliparous pregnant women diagnosed with pre-eclampsia. Gestational age at admittance was between 24 and 30 weeks. A severe form of pre-eclampsia was diagnosed in two of these cases. Patients had an average 31 years of age and the mean body mass index (BMI) was 26. In 2 of the 17 cases umbilical artery flow was severely affected and showed the reverse flow pattern. All patients had bilateral uterine artery protodiastolic notch. The characteristics of the study group are described in Table 1.

Table 2 includes the values of conventional echocardiographic parameters in our series of IUGR fetuses. E and A velocities and the E/A ratio were in the normal ranges after adjusting for the gestational age and fetal weight. For the two cases with umbilical artery reverse flow, we measured

Table 1: Baseline characteristics of the mothers and fetuses included in the study

Characteristics		*Cases*
Clinical characteristics		
Pre-eclampsia	Mild	15
	Severe	2
Gestational age	24-28 weeks	10
	29-30 weeks	7
BMI	<25	6
	≥25	11
Smoker status	—	3
Basic Doppler data		
Gestational age by ultrasound, weeks*		24-30
Umbilical artery reverse flow		2
Cerebroplacental ratio >1		4
Ductus venosus reverse flow		1

*Range; Body mass index calculated as weight in kilograms divided by the square of the height in meters. The cerebro-placental ratio (Arbeille index) is defined as the ratio between the cerebral resistive index (measured at the level at the middle cerebral artery) and the umbilical artery resistive index

Table 2: Cardiac function of IUGR fetuses evaluated by conventional echocardiography

Parameters	*Mean value (standard deviation)*
Diastolic parameters	
Right E velocity (cm/s)	32.1 (6.2)
Right A velocity (cm/s)	40 (7.3)
Right E/A	0.82 (0.2)
Left E velocity (cm/s)	33.9 (6.8)
Left E velocity (cm/s)	38.2 (7.01)
Left E/A	0.89 (0.16)
Systolic parameters	
Aortic peak velocity (cm/s)	82.2 (11.1)
Pulmonary peak velocity (cm/s)	83.7 (17.1)
MPI	
Right (ms)	82 (0.17)
Left (ms)	86 (0.11)

A: Atrial contraction; E: Early diastole; IUGR: Intrauterine growth restriction; MPI: Myocardial performance index

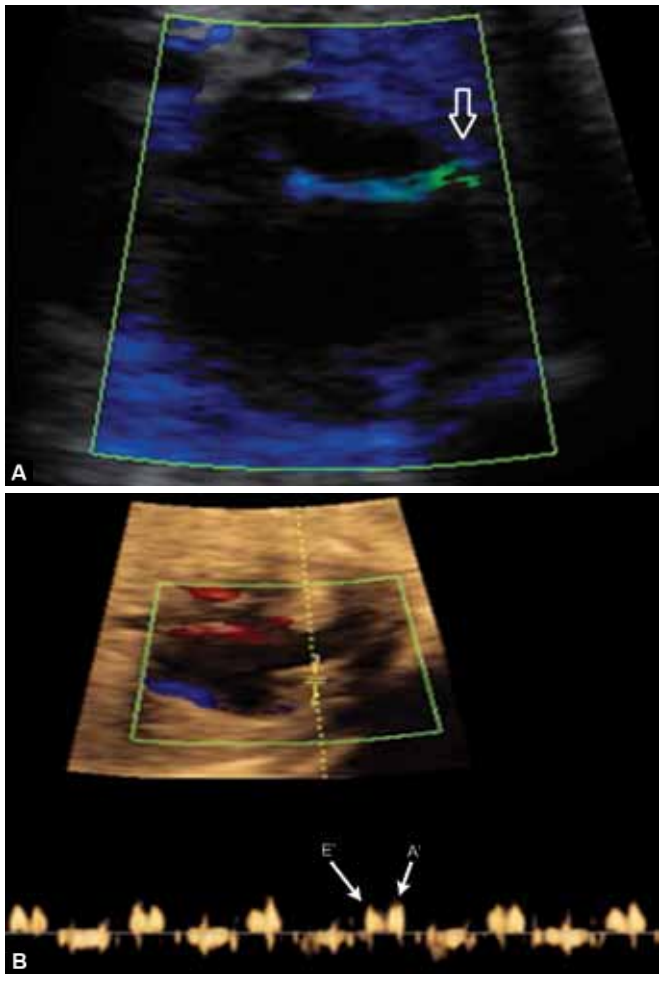
extreme values of peak aortic and pulmonary velocities, and MPI, compared to the mean value of the study group. Values were 58.04 cm/s and 70.92 cm/s for the aortic peak flow and 38.85 cm/s and 46.25 cm/s for the pulmonary artery peak flow. Values of MPI were 178 ms and 104 ms for the left ventricle and 169 ms and 110 ms for right ventricle.

Regarding cardiac function evaluation by TDI, satisfactory myocardial diastolic velocities measurements were performed in all fetuses (Table 3). We observed low left and right diastolic velocities and increased E'/A' ratios (Figs 1A and B).

Table 3: Cardiac function evaluation by TDI in IUGR fetuses

Parameters	*Mean value (standard deviation)*
Diastolic parameters	
Right E' velocity (cm/s)	6.4 (0.75)
Right A' velocity (cm/s)	6.02 (0.53)
Right E'/A'	1.06 (0.12)
Left E' velocity (cm/s)	6.9 (1.18)
Left A' velocity (cm/s)	8.77 (1.04)
Left E'/A'	0.79 (0.14)

IUGR: Intrauterine growth restriction



Figs 1A and B: Tissue Doppler imaging (TDI): (A) dyskinetic area in the basal right lateral ventricular wall (arrow) with (B)—an abnormal E'/A' ratio of 0.9

DISCUSSION

Lately, the focus of ultrasound fetal heart scanning is shifting from the purely descriptive approach toward a functional, quantitative modality. All the techniques used bear the shortcoming that, even though they may strongly imply the presence of cardiac dysfunction, they do not necessarily pinpoint the etiology or the causal mechanism.[8,9] As such, these techniques seem more appropriate for surveillance of

cases with a formerly known pathology, which is the case in our study series.

Our study aimed to assess the cardiac function in a series of IUGR fetuses from pre-eclamptic mothers by both conventional ultrasound and TDI. Using conventional echocardiography, we found significantly lower velocities—despite ventricular filling—with E/A ratios similar to those encountered in normal pregnancies. These findings are in line with those reported in other studies.[3,4,7] However, reduced or increased E/A ratios have also been reported.[10,11] The lack of significant differences in our study may be explained by the inclusion of only two cases with an umbilical artery reverse flow pattern as an indirect marker of an advanced fetal heart distress.

Outflow tract parameters are sampled to evaluate cardiac output. In our study, the aortic and pulmonary artery peak velocities values were similar to those recorded for normal pregnancies, which is consistent with data reported by other authors.[4,12,13]

The MPI index comprises both systolic and diastolic components, and can be used to analyze each ventricle independently. As it utilizes only time intervals, it is independent of heart rate and ventricular structure.[7,14,15] In our study, the left MPI, an early marker of systolic and diastolic dysfunction, was considerably elevated in IUGR fetuses due to placental insufficiency. Additionally, we observed increased values for left and right MPI compared to values cited for normal pregnancies.[14,15] Recent study showed that MPI correlates with the clinical hemodynamic deterioration of IUGR fetuses and reported increased values of the myocardial performance index in these fetuses.[4]

A possible explanation for our results could be the influence of the extreme values of the MPI in the 2 cases with umbilical artery reverse flow pattern. Another explanation is that the required measurements were performed in different cardiac cycles and could be affected by fluctuations of the cardiac output.

Data regarding the functional assessment of human fetal myocardium are limited. The possibility to analyze myocardial velocities (e.g. examination of ventricular wall motion by TDI) provides new insights into this issue and allows for a direct evaluation of myocardial motion. TDI evaluation is less dependent on load conditions than conventional Doppler studies and less affected by fetal heart rate, thus allowing a more accurate assessment of diastolic function.[16,17] Furthermore, given the longitudinal orientation of left ventricle muscle fibers in the subendocardial and subepicardial layers, with subendocardial fibers having the highest susceptibility to reduced flow in the coronary arteries, it was assumed that TDI is a more sensitive technique to identify minor abnormalities of myocardial function.[12,18]

In contrast with conventional ultrasound measurements, we observed differences in the TDI diastolic velocities parameters in the series of fetuses with IUGR included in this analysis as compared to values recorded in literature for fetuses from normal pregnancies. Our findings are similar to those reported by Naujorks et al,[3] which observed higher values of the E/A ratios at the interventricular septum in a group of IUGR fetuses with placental insufficiency as compared with appropriate for gestational-age fetuses from normal mothers. In contrast, other studies did not shown significant differences in TDI measurements in IUGR fetuses defined only by reduced weight or found similar TDI measurements in fetuses coming from healthy pregnancies and IUGR affected fetuses.[4,19]

CONCLUSION

Our study confirmed the presence of early cardiac dysfunction in IUGR and supports the inclusion of TDI together with conventional echocardiography in pathophysiologic and clinical research on fetal cardiac dysfunction.

Larger sample size studies, with properly constructed control groups, are warranted to confirm the utility of TDI in obstetric ultrasound routine examination for monitoring fetal cardiac function in high-risk pregnancies.

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