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Abnormal maternal cardiac function and morphology in pregnancies complicated by intrauterine fetal growth restriction

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ABSTRACT

Objective *To explore maternal cardiac function through an echocardiographic evaluation, in a group of nulliparous patients with intrauterine fetal growth restriction during the third trimester of pregnancy.*

Methods *Twenty-one consecutive nulliparous pregnant women who had fetuses with intrauterine growth restriction (IUGR) and abnormal umbilical artery Doppler pulsatility index (PI) underwent maternal echocardiographic examination during the third trimester of gestation. The data were then compared with those obtained from 21 normal nulliparous women who had fetuses with an estimated fetal weight > 10th percentile and a normal umbilical artery Doppler PI who were considered as the control group.*

Results *Heart rate was slightly lower in the IUGR group, whereas blood pressure and total vascular resistance were higher compared with the control subjects. End-diastolic volume, stroke volume and cardiac output were lower in the IUGR patients compared with normal patients. The IUGR group had smaller left atrial maximal dimensions and greater left atrial minimal areas compared with the control subjects. Left atrial function was depressed in the IUGR group. A smaller left ventricular mass was present in the IUGR patients compared with the control subjects. Isovolumetric relaxation time (IVRT) was prolonged in the IUGR patients compared with the controls.*

Conclusions *The absence of a 'correct' maternal cardiovascular compensatory response to abnormal trophoblastic invasion, might be one of the factors that slowly determine the conditions of reduced placental perfusion and eventually of the development of fetal growth restriction.*

INTRODUCTION

The clinical expression of intrauterine growth restriction (IUGR) during pregnancy appears to be triggered by a defective interaction between trophoblast and uterine tissues (suboptimal placentation)[1]. It is unknown whether the defective trophoblast invasion and maternal maladaptation are triggered by a common factor or an abnormal trophoblast development results in poor placentation and subsequently decompensation of maternal adaptation to pregnancy[2–4]. Recently, interesting data on the maternal cardiovascular system in pregnancies complicated by IUGR have been reported[5,6]. In particular, Duvekot *et al.* observed, in very early pregnancies subsequently complicated by IUGR[5], a small left atrial diameter accompanied in the second half of pregnancy by a smaller left ventricular end-diastolic dimension and left ventricular mass. Moreover, in the past, during the late 1950s and early 1960s, investigators in Finland and Sweden had observed that women with a 'small heart volume' had an increased risk for delivering small-for-gestational-age infants[7,8]. Veille *et al.* found no difference in the left ventricular size and function in women whose fetuses were affected by 'idiopathic' asymmetrical fetal growth restriction[9]. Nisell *et al.* observed that stroke volume and cardiac output were significantly lower in hypertensive mothers with small-for-gestational-age infants compared with hypertensive mothers with appropriate-for-gestational-age fetuses[10].

With these controversial results in mind, the aim of this study was to explore maternal cardiac function by echocardiographic evaluation, in a group of nulliparous patients with intrauterine fetal growth restriction associated with abnormal umbilical artery (UA) Doppler pulsatility index (PI) during the third trimester of pregnancy. These data were

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then compared with those collected from normal subjects with uneventful pregnancies.

METHODS

Patient selection

A case control study was performed. Twenty-one consecutive nulliparous pregnant women recruited between 25 and 36 weeks of gestation with the following criteria entered into the study: (a) normal fetal anatomy; (b) fetal abdominal circumference < 5th centile for gestational age by local reference values; (c) UA PI more than two standard deviations (SDs) above the gestational mean by local reference values; (d) birth weight below the 10th centile for gestational age.

Exclusion criteria included the following: multiple pregnancies and cases with chromosomal abnormalities or preterm rupture of the membranes, intrauterine infection, undetermined gestational age, history of heart disease, tobacco use, pre-existing chronic medical problems, the association with pregnancy-induced hypertension. Women with blood pressure (BP) values of at least 140/90 mmHg at the time of echocardiographic examination were checked again 4–6 h later and all showed BP values < 140/90 mmHg. No patient had an increase of systolic blood pressure (SBP) > 20–30 mmHg and diastolic blood pressure (DBP) > 15–20 mmHg compared with the first trimester.

Gestational age was determined by last menstrual period and sonographic examination prior to 20 weeks of gestation.

For each patient with IUGR, a normal nulliparous woman with an estimated fetal weight > 10th centile and a normal UA PI, was matched for age and gestational age as a control. The course of these pregnancies was uneventful and all subjects in this group delivered healthy appropriately grown infants with birth weights ranging from the 10th to the 90th centiles of the reference population[11].

None of these women received medication other than iron supplements and vitamins before and after their enrolment in the study.

Approval of the university ethics committee was obtained, and written informed consent was collected from all patients.

Ultrasound examination

For all ultrasound examinations, a 3.5-MHz sector ultrasound transducer (Esaote AU5, Genova, Italy) was used with the high-pass filter at 100 Hz. Doppler measurements were obtained from the UA, middle cerebral artery (MCA) and ductus venosus (DV) by previously described methods[12–14]. During examinations, each Doppler result was verified by at least three measurements and the best result was included for the final analysis. Since the normal distribution of Doppler indices changes with gestational age, individual measurements were normalized for statistical analysis by converting measurements into Z-scores (SD from the gestational age mean).

For the UA the elevation of the index > 2 SD above the mean and pulsatile flow in the free umbilical vein were considered abnormal. An MCA PI more than 2 SD below the gestational age mean was considered as evidence of 'brain sparing'. The assessment of non-reassuring fetal status and the indications for delivery were based on a combination of principal Doppler indicators of deterioration (worsening UA PI, advent of 'brain sparing', absent or reversed UA end-diastolic velocity, 'normalization of the PI' of the MCA, abnormal DV), the occurrence of late decelerations at the cardiotocographic recording and an acute flattening of the fetal growth curve. All patients with IUGR were hospitalized and underwent Doppler ultrasound examination at least three times a week. Fetal biometry was assessed every 10–14 days, the evaluation of the amniotic fluid index (AFI) once a week, and cardiotocographic recordings were obtained at least once a day.

Echocardiographic evaluation

The echocardiographic study was performed with a commercially available echo machine (Acuson Sequoia 256, Mountain View, CA, USA) using second harmonic imaging.

M-mode and two-dimensional echocardiography

Left atrial and aortic root diameters, left ventricular end-diastolic and end-systolic diameters (LVDd and LVDs, respectively), interventricular septum and posterior wall diastolic thickness (IVSd and PWd, respectively) were detected in the parasternal long-axis view during M-mode tracing, according to the recommendation of the American Society of Echocardiography[15]. The diameter of the left ventricular outflow tract (LVOT) during systole, was measured at the base of the aortic leaflets[16] from the two-dimensional parasternal long-axis view.

Left ventricular mass (LVM) in grams was calculated by the Devereux[17] formula as follows:

$$LVM = 0.832 \times [(LVDd + IVSd + PWd)^3 - LVDd^3] + 0.6$$

LVM index (LVMi) was then calculated as follows:

$$LVMi = LVM/m^{2.7}$$

where m was the height of the patient in meters[18].

Diastolic function

Assessment of diastolic function was obtained by pulsed-wave Doppler interrogation of transmitral flow pattern, recorded in the apical four-chamber view.

Mitral flow velocities were detected by placing the sample volume between the tips of the mitral leaflets[19]. The following variables were measured: peak flow velocity in early diastole (E-wave) and during atrial contraction (A-wave); peak E/A ratio; E- and A-wave time–velocity integrals; deceleration time of the E-wave (DtE) and duration of the A-wave (dA). When atrial contraction occurred before the mitral deceleration had decreased to zero, DtE was calculated as the time between peak E-wave and the deceleration slope, extrapolated to a zero baseline[19]. Left ventricular isovolumetric relaxation time (IVRT) was also measured, as the interval between the aortic valve closure click and the start of mitral flow.

Systolic function

Left ventricular end-diastolic and end-systolic volumes (EDV and ESV, respectively) were calculated according to the Teichholz formula[20] as follows:

$EDV = 7D^3/(2.4 + D)$

where D represents the end-diastolic diameter.

$ESV = 7S^3/(2.4 + S)$

where S represents the end-systolic diameter.

Stroke volume (Str. Vol.) was calculated as the difference between EDV and ESV. Cardiac output (CO) was calculated as the product of stroke volume multiplied by heart rate (HR) derived from electrocardiographic monitoring. Ejection fraction (EF%) was also calculated.

Total vascular resistance

Prior to maternal echocardiographic and uterine artery color Doppler examination blood pressure was measured from the brachial artery with a manual cuff. Mean arterial pressure (MAP) was calculated using the following formula:

$MAP = DBP + (SBP - DBP)/3$

where SBP is the systolic blood pressure and DBP is the diastolic blood pressure.

Total vascular resistance (TVR) was calculated in dyne/s/cm^5 according to the following formula:

$TVR = (MAP[mmHg]/CO[L/min]) \times 80$

Planimetric study of left atrial maximal and minimal areas

In a two-dimensional standard apical four-chamber view, planimetry of both maximal and minimal left atrial areas (LAmax and LAmin, respectively) was obtained through the integrated software of the machine. Assessment of left atrial function was obtained through left atrial fractional area change (LAFAC%)[21–23].

Outcome

Neonatal evaluation included Apgar scores assigned by the attending pediatric team, birth weight and birth weight percentile according to local reference values for gestational age and gender.

Statistical analysis

Data are expressed as mean ± SD. Comparison between normal and IUGR patients was performed with a Student's *t*-test for paired data according to gestational age.

Intraobserver and interobserver variability were tested in previous reports[21–23].

RESULTS

Gestational age at the time of examination was 30.4 ± 4.2 (range 25–36) weeks.

The subjects' characteristics are listed in Table 1. There were three perinatal deaths in the IUGR group: one intrauterine sudden fetal death, two neonatal deaths (one for neonatal respiratory distress and one for neurological complications due to neonatal cerebral hemorrhage). Age and prepregnancy and delivery body mass indices were similar in the two groups. The length of gestation was shorter in the IUGR group compared with the normal group.

Table 2 reports the main hemodynamic characteristics found in the two groups and the statistical difference between them. Heart rate was slightly but significantly lower in the IUGR group, whereas blood pressure and TVR were higher in comparison with the control subjects. End-systolic volume was slightly greater in the IUGR group compared with the normal group. End-diastolic volume, stroke volume, cardiac output, as well as ejection fraction, were smaller in the IUGR patients compared with normal patients.

Left atrial and ventricular morphology, as well as left atrial function are shown in Table 3. Left ventricular end-systolic dimensions were slightly larger in the IUGR patients compared with the normal women. IUGR patients had smaller left atrial maximal dimensions and greater left atrial minimal areas compared with the normal women. Left atrial function was depressed in the IUGR group. A smaller left ventricular mass was present in the IUGR patients compared with the control subjects.

Transmitral flow pattern is shown in Table 4. A lower E-wave velocity and time–velocity integral, as well as a lower E/A ratio, were present in the IUGR group. The isovolumetric

Table 1 Baseline data and characteristics of the two study groups

	Normal (n = *21*)	*IUGR* (n = *21*)	P-*value*
Maternal age (years)	30 ± 4	31 ± 2	0.78
Prepregnancy body mass index	22.2 ± 2.1	23.1 ± 2.2	0.81
Body mass index at delivery	24.4 ± 1.6	24.8 ± 1.7	0.62
Gestational age at delivery (weeks)	39.0 ± 1.0	32.2 ± 4.3	< 0.0001
Newborn weight (g)	3080 ± 432	1408 ± 591	< 0.0001
Weight centile at delivery (%)	52 ± 17	8.5 ± 0.6	< 0.0001
Cesarean section (*n* (%))	3 (14.3%)	15 (71.4%)	< 0.0001
Intrauterine death (*n* (%))	—	1 (4.8%)	< 0.0001
Neonatal death (*n* (%))	—	2 (9.5%)	< 0.0001

IUGR, intrauterine growth restriction.

Table 2 Hemodynamic features of the two groups

Parameter	*Normal* (n = *21*)	*IUGR* (n = *21*)	P-*value*
Maternal heart rate (bpm)	86 ± 4	82 ± 10	0.03
Systolic blood pressure (mmHg) (range)	118 ± 5 (110–125)	130 ± 9 (120–140)	0.0003
Diastolic blood pressure (mmHg) (range)	62 ± 6 (50–75)	79 ± 10 (70–90)	< 0.0001
Mean blood pressure (mmHg)	81 ± 4	96 ± 10	< 0.0001
Total vascular resistance (dyne/s/cm^5)	973 ± 97	1705 ± 190	< 0.0001
End-diastolic volume (mL)	104 ± 7	89 ± 11	< 0.0001
End-systolic volume (mL)	26 ± 5	33 ± 9	0.05
Stroke volume (mL)	78 ± 7	56 ± 9	< 0.0001
Cardiac output (L)	6.7 ± 0.5	4.6 ± 0.8	< 0.0001
Ejection fraction (%)	75.0 ± 4.7	63.4 ± 8.4	0.001

IUGR, intrauterine growth restriction.

Table 3 Morphologic and atrial function parameters

Parameter	*Normal* (n = *21*)	*IUGR* (n = *21*)	P-*value*
Left atrial dimensions and function			
Left atrial diameter (cm)	3.9 ± 0.1	3.6 ± 0.2	< 0.0001
Left atrial maximal area (cm^2)	14.5 ± 1.3	13.9 ± 1.3	0.03
Left atrial minimal area (cm^2)	6.6 ± 0.9	8.6 ± 0.8	0.009
Left atrial fractional area change (%)	54.2 ± 2.6	37.6 ± 6.3	< 0.0001
Left ventricular morphology			
Left ventricular outflow tract (cm)	2.01 ± 0.10	1.89 ± 0.11	0.005
Left ventricular mass (g)	166 ± 13	147 ± 24	0.04
Left ventricular mass index (g/m$^{2.7}$)	43.5 ± 3.8	37.0 ± 4.3	0.0002
Left ventricular dimensions in diastole (cm)	4.7 ± 0.1	4.4 ± 0.2	< 0.0001
Left ventricular dimensions in systole (cm)	2.6 ± 0.2	2.9 ± 0.3	0.055
Interventricular septal thickness in diastole (cm)	1.00 ± 0.04	0.97 ± 0.13	0.80
Posterior wall thickness in diastole (cm)	0.99 ± 0.05	1.00 ± 0.12	0.57
Relative wall thickness	0.42 ± 0.01	0.44 ± 0.07	0.055

IUGR, intrauterine growth restriction.

Table 4 Transmitral flow pattern

Parameter	*Normal* (n = *21*)	*IUGR* (n = *21*)	P-*value*
E-wave (cm/s)	90 ± 11	78 ± 11	0.002
E-wave velocity–time integral (s)	15 ± 2	12 ± 2	< 0.0001
Deceleration time of the E-wave (ms)	207 ± 12	206 ± 30	0.81
Isovolumetric relaxation time (ms)	75 ± 9	90 ± 11	0.0001
A-wave (cm/s)	64 ± 12	66 ± 13	0.68
A-wave velocity-time integral (s)	7 ± 1	6 ± 2	0.13
Duration of A-wave (ms)	142 ± 9	129 ± 18	0.004
Peak E/peak A ratio	1.4 ± 0.2	1.2 ± 0.1	0.002

IUGR, intrauterine growth restriction.

relaxation time was prolonged in the IUGR patients compared with the controls; the value remained significantly longer also after normalization for maternal heart rate. Duration of the A-wave was longer in the IUGR group as compared with women with a normal evolution of pregnancy.

DISCUSSION

During normal pregnancy, an increase in maternal vascular bed capacity, blood volume and cardiac output occur[6,21,22,24]. Plasma volume expansion is a physiological event that appears to be linked to an enhancement in physiological cardiac function[21,24]. Maternal cardiovascular maladaptation appears to be correlated to an abnormal outcome of pregnancy: it has been reported that pregnancies complicated by IUGR are associated with a reduced expansion of the maternal intravascular space and a lack of increase in cardiac output in the very early phase of pregnancy[5]. Nisell *et al.*[10] report that in hypertensive pregnancies complicated by IUGR, the uteroplacental blood flow impairment might be linked to a lower perfusion pressure, as a result of a diminished cardiac output.

In our study the maternal cardiac parameters, evaluated in the IUGR group, were significantly different when compared with the cardiac parameters of women with normal fetal growth paired for gestational age.

The IUGR patients had a lower heart rate, stroke volume and cardiac output compared with control subjects. The lower stroke volume is due to the smaller end-diastolic volume and the larger end-systolic volume found in the IUGR group compared with the control group. The concomitant presence of a small left atrial diameter and maximal area together with a small left ventricular end-diastolic volume testifies to the existence in these patients of an inadequate preload increase, probably due to a lack of a hemodilution process and a lack of plasma volume expansion, typically present in physiological pregnancies[21,25]. IUGR patients had an end-systolic volume greater than that in normal women. This might be partially explained by the elevated left ventricular end-systolic pressure generated by the increased afterload present in IUGR. The higher afterload, and therefore the greater end-systolic volume, might contribute to the lower stroke volume and ejection fraction of the IUGR group compared with the control group. Both the lower stroke volume and the lower heart rate cause a lower cardiac output in the IUGR group compared with normal outcome pregnancies.

Our data on left atrial dimensions are in accordance with those reported by Duvekot *et al.* who observed that the left atrial diameter, during the early weeks of gestation, appeared to be consistently smaller in the women destined to deliver growth-restricted infants[5]. This finding supports the etiopathogenetic hypothesis of a hypovolemic state that accompanies fetal growth restriction. By contrast the same authors[5] described no differences in heart rate, stroke volume and cardiac output, in IUGR pregnancies during the second and third trimesters of gestation. These different findings might be explained by the particular selection of the patients used in that study. The occurrence of growth restriction may have been triggered by factors linked to the previous infertility.

We observed in the IUGR group higher systolic, diastolic and mean blood pressure values than those in women with a normal outcome of pregnancy. This finding is in accordance with Tranquilli *et al.*[26] who reported that IUGR patients had evidence of higher blood pressure values in 24 h of ambulatory blood pressure monitoring, compared with women with normal pregnancy outcome.

In our results the high mean blood pressure and the low cardiac output explain the high TVR found in the IUGR group. The linkage between high TVR and fetal growth restriction has been described previously by Nisell *et al.*[10]. They observed that hypertensive pregnancies complicated by IUGR had higher TVR, lower stroke volume and lower cardiac output compared with hypertensive patients with appropriate-for-gestational-age infants. Veille *et al.*[9] on the contrary, did not find any difference in cardiac function and TVR between uneventful pregnancies and those with IUGR; however, in that study the clinical reports of patients with IUGR (delivery at a mean gestational age of 37 weeks, no fetal Doppler assessment reported, no perinatal complications described) suggest the existence of a less severe pathological condition.

Normal pregnancy represents an excellent model of acute 'physiological' myocardial hypertrophy and it has been described in several studies[21,25,27–29]. A normal pregnancy resembles a sustained hemodynamic state similar to that of the trained long-distance runner[27,30]. The term 'physiological' is linked to a reversible increase in left ventricular mass as a compensatory mechanism to pregnancy. Our results provide evidence of a significantly lower left ventricular mass in IUGR patients compared with the normal women as if these patients lacked a stimulus for the physiological myocardial hypertrophy although in the presence of elevated peripheral resistance. This finding is in agreement with other reports[5] indicating a smaller left ventricular mass and end-diastolic dimension in pregnancies complicated by fetal growth restriction. This interesting result differentiates IUGR from hypertensive pregnancies: the latter show a higher left ventricular mass compared with the normotensive patients[22]. Our results confirm an old observation of three decades ago in which Scandinavian investigators suggested that women with a smaller heart volume on chest X-rays had an increased risk of delivering small-for-gestational-age infants[7,8].

An interesting finding of our study regards the reduced left atrial function and the altered left ventricular compliance of IUGR pregnancies. Left atrial function appears to be significantly lower in IUGR pregnancies due to both small left atrial maximal area and large left atrial minimal area. This results in a lower left atrial fractional area change (LAFAC%) in the IUGR group compared with the control group with a reduced left ventricular filling. The finding of a low E-wave and E-wave velocity–time integral supports this hypothesis and suggests that the reduced filling of the left ventricle occurs in the early phase of the diastole. The low E-wave velocity and the longer isovolumetric relaxation time suggest an impairment of the left ventricular compliance in the IUGR group compared with the control group even in the presence of normal pressure values. We hypothesize that the high TVR might favor the altered left ventricular compliance.

Fetal growth restriction is not a specific disease entity per se, but rather a manifestation of many possible fetal and maternal disorders and presents a complex management problem for the clinician. Several intrinsic and extrinsic factors have been found to be associated with fetal growth restriction. We believe that an important role may be played by the response of the maternal cardiovascular system to the defective placentation process. The trophoblastic invasion and vasoactive agents might induce an adaptation of the maternal 'cardiac pump'. The absence of a 'correct' maternal cardiovascular compensatory response to abnormal trophoblastic invasion, might be one of the factors that would slowly determine the conditions of reduced placental perfusion and eventually of the development of fetal growth restriction. The findings in our study of several functional and morphologic cardiac differences in pregnancies complicated by isolated IUGR compared with normal pregnancies, would testify to the lack of a 'compensatory response' to the peripheral vascular state. In this view, the maternal 'cardiac pump' would be the main determinant of the evolution of pregnancy and echocardiographic evaluation could help in understanding the actual maternal cardiovascular response

(or the lack of a response) to an inadequate placentation process, improving the prognostic capability of the clinician.

Although the number of IUGR fetuses in this study was relatively small, we are satisfied that we have accurately identified those patients with isolated IUGR.

The hypothesis of a primary lack of a maternal cardiovascular adaptation in IUGR patients could be susceptible to criticism in view of the fact that fetal growth restriction had already been established in all the study patients.

The finding of reduced preload and stroke volume in our study group could be the result of a maternal cardiovascular maladaptation from the early stages of pregnancies. Alternatively, an insult in later pregnancy might negatively influence maternal hemodynamic state. It is difficult to determine whether the differences found between normal and IUGR groups during the third trimester of pregnancy are already present in the early stages of gestation, although data from different studies suggest maternal cardiovascular maladaptation from the first trimester of pregnancy[5]. Only subsequent longitudinal studies may confirm these data.

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