

CLINICAL SCIENCE

Effect of physiological overload on pregnancy in women with mitral regurgitation

Vera T. M. Borges,^I Beatriz B. Matsubara,^{II} Claudia G. Magalhães,^I Jose C. Peraçoli,^I Marilza V. C. Rudge^I

^IDepartment of Obstetrics and Gynaecology, Botucatu Medical School, UNESP - São Paulo State University, Botucatu, São Paulo-Brazil. ^{II}Department of Internal Medicine, Botucatu Medical School, UNESP - São Paulo State University, Botucatu, São Paulo-Brazil.

OBJECTIVES: to evaluate the structural and functional heart abnormalities in women with mitral regurgitation during pregnancy.

INTRODUCTION: Women with mitral regurgitation progress well during pregnancy. However, the effects on the heart of the association between pregnancy and mitral regurgitation are not well established.

METHODS: This is a case-control, longitudinal prospective study. Echocardiograms were performed in 18 women with mitral regurgitation at the 12th and 36th week of pregnancy and on the 45th day of the puerperium. Twelve age-matched healthy and pregnant women were included as controls and underwent the same evaluation as the study group.

RESULTS: Compared with controls, women with mitral regurgitation presented increased left cardiac chambers in all evaluations. Increasing left atrium during pregnancy occurred only in the mitral regurgitation group. At the end of the puerperium, women with mitral regurgitation showed persistent enlargement of the left atrium compared with the beginning of pregnancy (5.0 ± 1.1 cm vs 4.6 ± 0.9 cm; $p < 0.05$). Reduced left ventricular relative wall thickness (0.13 ± 0.02 vs 0.16 ± 0.02 ; $p < 0.05$) and an increased peak of afterload (278 ± 55 g/cm² vs 207 ± 28 g/cm²; $p < 0.05$) was still observed on the 45th day after delivery in the mitral regurgitation group compared with controls.

CONCLUSIONS: Pregnancy causes unfavorable structural alterations in women with mitral regurgitation that are associated with an aggravation of the hemodynamic overload.

KEYWORDS: Mitral regurgitation; Pregnancy; Echocardiogram; Ventricular function; Cardiac remodeling.

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E-mail: vborges@fmb.unesp.br

Tel.: 55 14 3811-6227

INTRODUCTION

It is well known that the maternal cardiovascular system undergoes significant circulatory changes, including increases in cardiac output (CO) and blood volume and reductions in systemic vascular resistance and arterial pressure.^{1,2} Although these physiological adaptations are well tolerated by healthy woman, they might result in heart failure and even death in those with heart disease.³

Maternal heart disease occurs in approximately 0.5–4% of all pregnancies and it is the most important indirect cause of maternal mortality. The prevalence of cardiac disease depends on the studied population. In developing countries, the most common cardiac disease is rheumatic heart disease, mainly mitral stenosis and/or regurgitation.⁴

Little information is available about cardiac alterations and the association between pregnancy and mitral regurgitation (MR), which probably results from the concept that MR is usually well tolerated during pregnancy because of the physiological decrease in systemic vascular resistance and afterload.³

Chronic MR causes volume overload that can lead to eccentric hypertrophy. Most patients with MR remain asymptomatic for many years until decompensated hypertrophy occurs, leading to cardiac dysfunction and overt heart failure. In contrast, pregnancy-induced hypertrophy is known to be physiological, being reversible after pregnancy without harmful effects on cardiac function. Therefore, it is possible to hypothesize that women with MR present unfavorable structural and functional cardiac adaptation during pregnancy and the puerperal period.

The aim of this study was to evaluate the structural and functional heart abnormalities in women with MR during pregnancy and early puerperium.

MATERIAL AND METHODS

Patient selection

This is a case-control, prospective, longitudinal study performed in a university general hospital. The study protocol was approved by the Institutional Review Board of the School of Medicine of Botucatu – UNESP – Brazil and all participants gave informed consent.

Eighteen consecutive women with singleton pregnancy and isolated MR or with MR as the predominant lesion were included in the study. An assessment of functional class was made according to the criteria of the New York Heart Association (NYHA) at the time of examination. Women with moderate or severe mitral stenosis, atrial fibrillation or any other cardiovascular disease, or pregnancy-induced hypertension were excluded. All the results were compared with the control group of 12 healthy women. All participants received routine prenatal care and were followed at the antenatal and cardiologic clinics in the university teaching hospital.

Study protocol

Echocardiographic studies were performed in both groups at the 12th (T1) and 36th (T2) weeks of pregnancy and on the 45th day post partum (T3).

Height and weight were recorded before each echocardiogram. The clinical and echocardiographic examinations were performed by the same cardiologist. All measurements were obtained with the subjects in the left lateral recumbent position and allowed to rest for about 15 min. All studies were performed with a Hewlett Packard Sonos 2000 System, with a multifrequency phased-array transducer (2.5–3.5 MHz). All variables were the average of 3–5 consecutive measurements.

Blood pressure was measured from the brachial left artery with a manual cuff and with the subject in the left lateral decubitus position. Systolic blood pressure (SBP) was taken at the first Korotkoff sound and diastolic blood pressure (DBP) was taken at the fourth Korotkoff sound. Mean arterial pressure (MAP) was calculated from the equation $MAP (mmHg) = SBP + 2DBP/3$.

Stroke volume (SV) was the product of the cross-sectional area of the left ventricle (LV) outflow tract and the velocity time integral of the pulsed Doppler subaortic waveform measured in the five-chamber view. Cardiac output (CO) was calculated as the product of SV and heart rate (HR). Ejection time was obtained from the aortic-pulsed Doppler waveform, the sample volume being placed a few millimeters below the valve.

Left ventricular and atrial dimensions were calculated according to the recommendations of the American Society of Echocardiography⁵ from the parasternal long-axis view. The following indexes were calculated: 1) Ejection fraction (EF) = $[(LVDD^3 - LVSD^3) / LVDD^3]$; 2) Fractional shortening (FS) = $(LVDD - LVSD) / LVDD \times 100$; 3) Relative wall thickness (RWT) = $[(SWT + PWT) / 2] / LVDD$, where SWT is septal wall thickness, PWT is posterior wall thickness, LVDD is left ventricular diastolic diameter and LVSD is left ventricular systolic diameter.

Left ventricular mass (LVM) was calculated using the M-mode measurements by the formula of Devereux and Reichek⁶: $LVM = [(SWT + PWT + LVDD)^3 - LVDD^3] \times 1.04 \times 13.6$.

Total peripheral resistance (TPR) and peak systolic stress (PSS) were calculated from the formulas: $TPR (dyn/s/cm^5)$

Table 1 - Clinical characteristics.

Characteristics	Mitral regurgitation (n = 18)	Control (n = 12)	p-value
Maternal age (years)	24.1 ± 7.4	24.6 ± 4.9	ns
Weight (kg)	62.2 ± 15.2	59.1 ± 7.9	ns
Height (cm)	161 ± 0.06	157 ± 0.05	ns

Data are presented at the means ± SD; n = number of women; ns = not significant.

$= MAP \times 80/CO$; $PSS (g/cm^2) = [(SBP \times LVDD)/4DWT (1 + DWT/LVDD)] \times 1.36$. Where DWT is mean systolic wall thickness.

Statistical analyses

Data are presented as means and standard deviations. The results were statistically analyzed according to a split-plot design over time by considering the collection moments as plots and the groups as subplots. Multiple comparisons were performed using a test analogous to the Tukey test using the PDIF option of SAS PROC GLM, version 9.1. For all tests, a p value of <0.05 was considered statistically significant.

Using the mean of the left atrium diameter in the first and third trimester of normal pregnancies obtained from a previous study,² it was calculated that 11 subjects would be necessary, with a 5% level of significance ($p=0.05$) and power of 80% ($\beta = 0.20$).

RESULTS

At the time of the study 1 patient presented as NYHA class III, 6 were class II and the remaining patients were NYHA class I. The predominant etiology of mitral insufficiency was rheumatic fever; only 2 patients had congenital disease.

The clinical characteristics of the study groups are shown in Table 1. There were no statistically significant differences between the groups.

Table 2 and Figure 1 show the LV geometry data in the groups. The left atrium diameter (LAD), LVDD and LV mass were higher in the MR group in all evaluations. Pregnancy caused additional increases in the left atrium diameter only in the MR group. An increase in the relative wall thickness occurred in both groups during pregnancy. However, compared with controls, the MR group presented a decreased relative wall thickness during the puerperium, suggesting ventricular dilation (Figure 1).

Table 3 and Figure 2 show systemic hemodynamics in the groups. There were no changes in the heart rate (HR), MAP and total peripheral resistance (TPR) in the MR group during pregnancy. During the puerperium, HR decreased, and TPR and MAP increased. PSS was increased in the MR group at the end of pregnancy and puerperium.

Table 4 shows systolic function data. There was no difference between the groups where ventricular function was concerned.

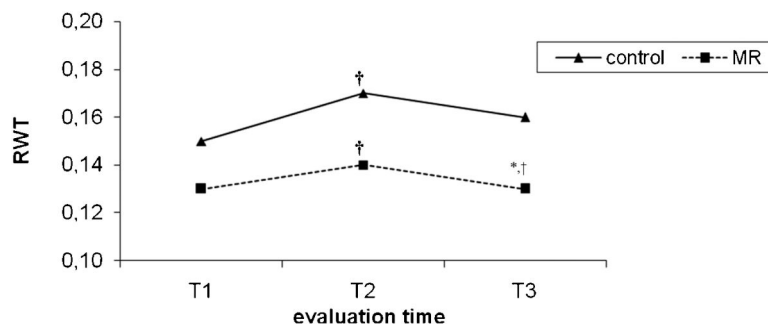
DISCUSSION

The results of this study have demonstrated that pregnancy represents an additional overload to the heart of women with MR, worsening cardiac remodeling.

Table 2 - Left ventricular geometry.

	Mitral regurgitation			Control		
	T1	T2	T3	T1	T2	T3
LAD (cm)	4.6 ± 0.9*	5.1 ± 1.0*, [†]	5.0 ± 1.1*	3.2 ± 0.4	3.5 ± 0.3	3.1 ± 0.4
LVDD (cm)	5.8 ± 0.6*	6.0 ± 0.6*	6.1 ± 0.6*	4.7 ± 0.3	4.7 ± 0.3	4.7 ± 0.4
PWT (cm)	0.76 ± 0.12	0.84 ± 0.10 [†]	0.81 ± 0.10	0.69 ± 0.09	0.81 ± 0.07 [†]	0.75 ± 0.08
LVM (g)	201 ± 68*	232 ± 77*	234 ± 66*	115 ± 30	145 ± 25	137 ± 26

Data are presented at the means ± SD. LAD = left atrial diameter; LVDD = left ventricular diastolic diameter; PWT = posterior wall thickness; LVM = left ventricular mass. *p<0.05 between mitral regurgitation and control (Student's t-test); [†]p<0.05 compared with previous examination (ANOVA for repeated measurements); [‡]p<0.05 compared with first trimester (ANOVA for repeated measurements).

**Figure 1 - Relative wall thickness obtained by echocardiograms during the protocol study.**

Various studies evaluated the LV response to a volume overload in normal pregnancies;^{7,8} however, no studies were found comparing healthy and MR women.

From the beginning of pregnancy, the heart size was increased in the MR group compared with control group,

suggesting significant heart disease at that time. None of patients presented with previous history of overt heart failure, indicating AHA/ACC stage B,⁹ although 2 patients presented criteria for diagnosis of decompensate heart failure at the time of inclusion in the study. During the

Table 3 - Systemic hemodynamics

	Mitral regurgitation			Control		
	T1	T2	T3	T1	T2	T3
HR (beats/min)	79 ± 13	84 ± 13	71 ± 19 [†]	75 ± 10	83 ± 15	76 ± 12
MAP (mmHg)	79 ± 8	84 ± 12	89 ± 7 [‡]	80 ± 7	83 ± 8	86 ± 8
TPR (dynes/s/cm ⁻⁵)	1558 ± 741	1403 ± 481	1946 ± 796 [†]	1433 ± 383	1258 ± 322	1802 ± 512

Data are presented at the means ± SD. HR = heart rate; MAP = mean arterial pressure; TPR = total peripheral resistance. [†]p<0.05 compared with previous examination (ANOVA for repeated measurements); [‡]p<0.05 compared with first trimester (ANOVA for repeated measurements).

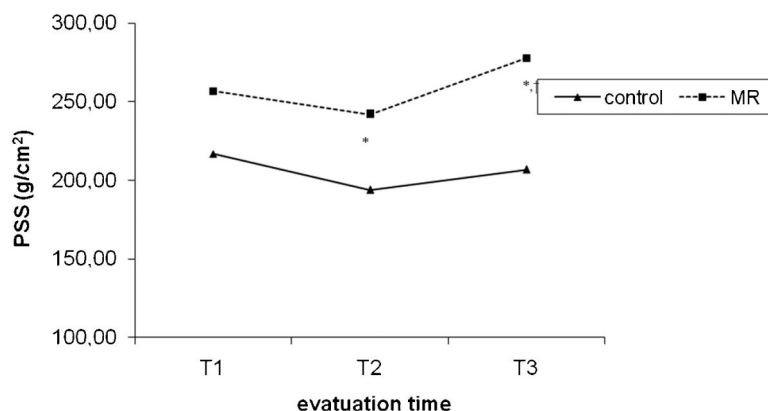
**Figure 2 - Peak of systolic stress obtained by echocardiograms and arterial blood pressure during the protocol study.**

Table 4 - Systolic function.

	Mitral regurgitation			Control		
	T1	T2	T3	T1	T2	T3
EF	0.74 ± 0.04	0.73 ± 0.05	0.74 ± 0.04	0.76 ± 0.05	0.75 ± 0.05	0.75 ± 0.05
FS(%)	36.1 ± 2.9	35.9 ± 4.6	36.4 ± 3.5	36.6 ± 4.6	36.6 ± 4.2	36.0 ± 4.5
SV (ml)	60.0 ± 19.5	65.1 ± 21.5	64.5 ± 22.6	62.4 ± 12.1	69.9 ± 12.3	56.1 ± 12.5
CO (l/min)	4.7 ± 1.6	5.4 ± 1.6	4.3 ± 1.5 [†]	4.6 ± 0.9	5.6 ± 0.8	4.2 ± 0.7 [†]

Data are presented at the means ± SD. EF = ejection fraction; FS = fractional shortening; SV = stroke volume; CO = cardiac output. [†]p<0.05 compared with previous examination (ANOVA for repeated measurements).

follow up protocol 6 patients presented with decompensated cardiac history of overt heart failure indicating AHA/ACC stage B.⁹

Physiologically, the LAD gradually increases during pregnancy, returning to normal in the puerperium.^{7,8} In the present study, the LAD was increased in the MR group, regardless of the time of evaluation. In addition, these patients presented with an additional enlargement that was irreversible during the study period. This is an important finding since the size of the left atrium is related to the severity of valve damage. As this chamber increases, the risk of atrial fibrillation also increases, worsening the prognosis of these patients.¹⁰

The absence of additional enlargement in the LV chamber in both groups was an interesting finding. Considering that both pregnancy and MR are conditions of volume overload, an increase in ventricular size would be expected. In accordance with other authors,^{7,11} no significant changes were observed in the diastolic dimensions of the left ventricle in healthy pregnant women. Robson et al¹² only observed enlargement of the left ventricle in pregnancy when comparisons were made with pre-pregnancy values. Therefore, it is reasonable to assume that MR women presented a physiological response to pregnancy as far as the LV chamber is concerned, although they presented increased LV size and mass during the study protocol period.

The most remarkable finding in the present study was the demonstration that at the puerperium, MR women showed a reduction in the relative thickness of the ventricular wall compared with controls, suggesting a persistent chamber dilation.

In chronic volume overload, cardiac dilation is associated with a worse prognosis, with a higher risk of overt cardiac failure. This is an important finding and might explain the increased afterload demonstrated in the MR group compared with the control group in the puerperium, resembling decompensated hypertrophy.

It was concluded that pregnancy causes unfavorable structural alterations in women with MR that are associated with an aggravation of the hemodynamic overload. The impact of such alterations in late clinical outcomes must be further evaluated in future studies.

Study limitations. Pre-pregnancy assessment of the left chamber was not possible because patients were already pregnant when included in the study. However, the control

group allowed comparisons between healthy and heart disease.

Echocardiography evaluation did not include current indexes, such as left atrial volume or Simpson's biplane, which are more accurate for detection of cardiac changes. However, we were able to show remarkable differences between the groups, indicating a need for more studies focusing on this issue.

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