

Influence of Pregnancy on Clinical Course and Fetal Outcome of Women with Hypertrophic Cardiomyopathy

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Summary

Objectives: To study clinical evolution of women with HCM during pregnancy; the influencing factors of gestation on natural course of HCM and the frequency of HCM in their children in early childhood.

Methods: A prospective study was conducted in 35 women with HCM; there were 23 pregnant women (PG group) and 12 nonpregnant control patients (NP group), matched for age and functional class (FC). Clinical monthly evaluations were carried out and electrocardiogram and transthoracic echocardiography tests were performed. The offspring endpoints included stillbirth and prematurity rates and investigation of HCM during childhood.

Results: No deaths occurred in either group. Cardiac arrhythmias were significantly ($p < 0.05$) more frequent in the NP group (33.3% vs 13.4%), and no differences were observed between the groups ($p > 0.05$) in heart failure (30.3% vs 16.6%) or ischemic stroke (4.3% vs 8.3%) rates. In the PG group, required hospitalization for treatment of cardiac complication was more frequent ($p = 0.05$) in patients with family history of HCM (71.4% vs 25.0%). Cesarean section was performed in 12 (52%) patients, for obstetrical reasons; there were 7 (30.4%) premature babies and 1 (4.3%) neonatal death. One child was clinically diagnosed as having HCM, and his genetic study identified a mutation in the beta myosin heavy chain gene, located on chromosome 14.

Conclusion: Heart failure is a frequent cardiac complication in women with HCM during pregnancy, particularly in patients with family history of the disease, but this did not influence the natural course of HCM. In one child, clinical examination allowed HCM identification during early childhood.

Key words: Hypertrophic cardiomyopathy; pregnancy; clinical evolution, maternal-fetal evolution.

Introduction

Pregnancy constitutes a potential risk for women with hypertrophic cardiomyopathy (HCM); however, its prognosis is not yet clear. The interaction of physiologic hemodynamic changes in pregnancy, such as high cardiac output¹ and HCM pathophysiological changes, including left ventricular outflow obstruction, diastolic dysfunction and myocardial ischemia², may cause substantial maternal morbidity rates during gestation, delivery, and puerperium³.

Thus far published reports are limited to small series⁴⁻⁶ or are based on review³ and retrospective studies⁷, making it difficult to obtain appropriate data for assessment of women with HCM during pregnancy. The wide variations of cardiovascular complications rates during pregnancy, reportedly from 5% to 40%⁷⁻⁹, has been attributed to patient selection and especially to the heterogeneity of the phenotype of this cardiac disease¹⁰.

Another important issue to be considered in pregnancy of woman with HCM is the high potential risk of genetic

transmission of this disease to her child. HCM is inherited as the Mendelian autosomal dominant trait and may be also caused by mutations in any one of 10 genes, each encoding protein components of the cardiac sarcomere¹¹.

Although molecular genetic studies over the past decade have provided important insight into the clinical and genetic heterogeneity of HCM¹², its complexity, at present, has not permitted the determination of the real incidence of HCM in apparently healthy newborn without abnormalities in two-dimensional echocardiogram tests.

Therefore, the aims of this study were to analyze prospectively, the evolution of patients with HCM during gestation; to analyze factors influencing pregnancy in maternal prognosis and to assess the occurrence of HCM in their children in early childhood.

Methods

Study population - From 1985 to 2002, a prospective study was conducted on 35 women with HCM. The study group included 23 pregnant women (PG group) and 12 nonpregnant control patients (NP group), matched for age and functional class according NYHA (FC). All patients were followed-up at the Heart Institute (InCor) of São Paulo, during an observation period ranging from 12 to 18 (mean = 16 ± 3.5) months. At

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start, all patients were in FC I/II with sinus rhythm, except for 3 patients in the NP group, who were in atrial fibrillation. The diagnosis of HCM was based on demonstration by two-dimensional echocardiography of a hypertrophied, nondilated left ventricle (wall thickness of at least 15mm in adults) in the absence of another cardiac or systemic disease capable of producing a similar degree of hypertrophy¹³. Obstruction of the left ventricular outflow tract was considered to be present when the peak instantaneous outflow gradient was estimated to be at least 30mmHg with the use of continuous-wave Doppler echocardiography under basal (resting) conditions¹⁴. Baseline characteristics of the PG and NP groups are depicted in (Tab.1).

Study protocol - According to our prenatal care routine, monthly clinical evaluations recorded FC changes and cardiac complications, such as heart failure, cardiac arrhythmias, ischemic stroke (embolic episode) and infective endocarditis. Patients who had complications were admitted to the hospital for clinical control and therapy adjustment. The protocol study included electrocardiogram and transthoracic echocardiogram tests performed twice: at the beginning of the study and six months later in both groups (third trimester of gestation in the PG group). The electrocardiogram study considered cardiac rhythm variations, and the echocardiogram test measured the thickness of the ventricular septum and the free wall of the left ventricle dimension, and the degree of mitral valve regurgitation and left ventricular outflow tract obstruction. The electrocardiogram and echocardiogram registers were compared with baseline data before the study.

Management of cardiac complications during the study was based on conventional treatment strategies; in accordance with clinical presentation¹⁵, beta-blockers (propranolol) and calcium antagonists (verapamil) were the first options for the pharmacological therapy.

Obstetrical follow-up registered the occurrence of stillbirth and premature infants (delivery before 37 weeks of gestation). All newborns were examined by the pediatric team to rule out congenital malformations, and during their childhood (from one up to 10 years) they underwent physical heart examinations and transthoracic echocardiograms. In addition, a genetic study using DNA extraction analysis, polymerase chain reaction (PCR) and electrophoresis techniques was made

on the children with clinical diagnosis of HCM.

Statistical analysis - Variables are presented as means and standard deviations (SD). Categorical data were evaluated by the chi-square or Fisher test. Parametric data were compared with the Student paired and unpaired *t* tests. The *p* value <.05 was considered to be statistically significant. This protocol was approved by the Ethics and Scientific Committee of the Heart Institute (InCor) of the University of São Paulo Medical School, and all patients and their guardians gave written informed consent.

Results

Clinical outcome - In the PG group there were no maternal deaths and 12 (52.2%) patients had an uneventful outcome. Eleven (47.8%) patients had cardiac complications, including 7 (30.4%) cases of heart failure (one during the second trimester and six during the third trimester of pregnancy), 3 (13.4%) cases of cardiac arrhythmia, such as paroxysmal atrial fibrillation in two and supraventricular tachycardia in one, and, finally, one (4.3%) case of ischemic stroke. Out of the 11 patients who experienced complications, 6 (85.7%) needed hospitalization due to severe heart failure; all of them were medicated with propranolol, verapamil, or both, in doses up to 160 mg/day and 240 mg/day, respectively, plus furosemide at 40 mg/day. Three patients (27.2%) were required to remain at rest in the hospital until delivery to control symptoms.

In the NP group, no deaths occurred and five (41.7%) patients had an uneventful outcome. Seven (58.3%) patients had clinical complications, including 4 (33.3%) new cases of cardiac arrhythmia, 3 with atrial fibrillation and one with non sustained ventricular tachycardia, 2 (16.6%) cases of heart failure, and one (8.3%) of ischemic stroke.

A comparative analysis between the PG and NP groups showed that cardiac arrhythmias were more frequent in the NP group (13.4% vs 33.3% - *p*<0.05). There was no significant difference between the groups in heart failure (30.3% vs 16.6%) and stroke (4.3% vs 8.3%) percentages.

In the PG group, the comparison between 7 patients who had severe complications requiring hospitalization and 16 patients who were not admitted showed no differences

Table 1 - PG and NP group baseline characteristics

	PG	NP	value p
Mean age (years)	27.6 ± 5.1	28.2 ± 6.1	ns
Non white ethnic patients	13 (56%)	8 (75%)	ns
Family history of HCM	9(39.1%)	7(66.7%)	ns
Therapy*	12(52%)	5 (41.6%)	ns
Doppler echocardiogram data			
LV septum mm	20.1±5.1	19±5.4	ns
LV posterior wall mm	11.1±2.5	11±2.6	ns
LV gradient mmHg	13.4± 26.7	24.7±14.7	ns

HCM – hypertrophic cardiomyopathy ; LV – left ventricular; NP – nonpregnant; PG – pregnant; Continuous use of Beta-blocker plus Calcium antagonists

regarding age, ethnicity, and echocardiography variables. The hospitalization rate was higher ($p = 0.05$) in patients with family history of HCM (Tab. 2).

Echocardiography data - PG group echocardiograms before gestation showed that 17 (73.9%) patients had left ventricular outflow tract obstruction and 12 (56.5%) had mitral valve regurgitation. Comparative analyses of echocardiography data showed that left ventricular gradient increased significantly during gestation (Fig. 1). The echocardiogram analyses of the NP group showed left ventricular outflow tract obstruction in 5 (41.6%) patients and mitral valve regurgitation in 4 (33.3%) patients; these data remained unchanged during the study.

Obstetrical and neonatal outcomes - Mean gestational age upon delivery was 37.06 ± 2.78 weeks. Based on obstetric reasons, cesarean section was indicated in 12 (52%) patients, and 7 (26%) babies were premature. Mean birth weight was 2.550 ± 578 grams; in 3 (13%) cases intrauterine growth retardation occurred, and there was one neonatal death (on the 20th day after birth) caused by pulmonary bleeding attributed to extreme prematurity. Gestational age at delivery and newborn birth weight were lower ($p < 0.05$) in patients who required hospitalization for clinical event control. Mode of delivery, obstetric complications, and Apgar scores (newborn's vitality) in the first, second, and fifth minute after birth were similar in both subgroups (Table 1). Clinical examination of the children during childhood (mean age 3.5 years) showed heart murmur in one at his seventh months.

Echocardiogram study of 13 children showed HCM in one at the seventh month of life. In this case, an echocardiographic study repeated at age four showed a progression of ventricular septum thickness (13 vs 25 mm), posterior wall of the left ventricle (11 vs 12 mm), and ventricular pressure gradient (25

vs 76 mm Hg). The mother of this child had an obstructive form of disease and family history of sudden cardiac death. A genetic study was carried out on the child, and a mutation was found in the beta myosin heavy chain gene, located on chromosome 14q1.

Discussion

The present study, encompassing a large series of woman with HCM under prospective and controlled follow-up, showed that pregnancy indeed represents high risk for patients with HCM. Although there were no maternal deaths, almost half of the pregnant women experienced cardiac events and a great number of them required hospitalization for heart failure control during gestation.

Overall prevalence of HCM has been estimated to occur in 0.02 to 0.2 per cent of the population¹⁶ and was found in 0.015% in a cohort-study of pregnant women with cardiac disease¹⁷. This low incidence and the diversity of previous reports on the clinical evolution of women with HCM during pregnancy have not permitted its prognosis to be determined and, consequently adequate counseling before gestation.

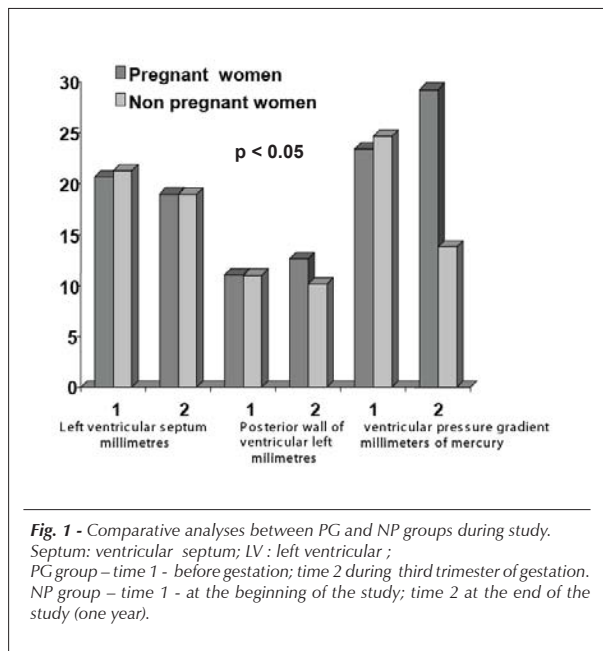
Oakley et al¹⁸ observed good pregnancy outcome of 54 gestations in 23 women with HCM, without record of maternal death, leading to the conclusion that pregnancy can be well tolerated in patients with HCM. Another study¹⁹ including 41 women with HCM did not report any deaths either, nor a worsening of FC during gestation. However, both studies lack data on the morphological type of the disease and its correlation with the clinical evolution during pregnancy.

On the other hand, the review by Elkayam et al³ showed worsening of FC in 58% of patients, a 20% of heart failure rate,

Table 2 - Comparison of variables among patients who required hospitalization to treatment of complication during pregnancy

	Hospitalization		p value
	No 16 cases	Yes 7 cases	
Age/years	27.6 ± 1.3	27.5 ± 1.7	ns
Nonwhite n/%	9 (56.5%)	4 (57.4%)	ns
Family history	4 (25.0%)	5 (71.4%)	<0.05
Doppler echocardiogram data			
Outflow obstruction	11 (68.7%)	6 (85.7%)	ns
Mitral regurgitation	11 (68.7%)	5 (71.4%)	ns
Ventricular septum (mm)	20.7 ± 1.4	22.3 ± 2.3	ns
LV posterior wall (mm)	11.7 ± 0.80	14.6 ± 2.1	ns
Mean LV gradient (mmHg)	21 ± 6.5	47 ± 15	ns
Obstetrical data			
Gestational week at delivery	37.9 ± 0.40	35.1 ± 1.49	ns
Baby's weight at birth (g)	2709 ± 104.6	2186 ± 284.4	<0.05
Cesarean section	7 (43.7%)	5 (71.4%)	ns
Obstetrical complications	4 (25.0%)	4 (57.1%)	ns

LV - Left ventricular.



and one sudden death in the 39th week of gestation and thus, concluded that pregnancy represents high risk to women with HCM. In addition, Autore et al⁷ reported a higher maternal mortality rate in pregnant woman with HCM than the general Italian population and a progression of FC to III and IV in 42% of patients during gestation.

The considerable heart failure rate in the PG group of 30.3% illustrated the poor tolerance of HCM patients to pregnancy-related circulatory overload¹. Really, the progressive increase in blood volume and cardiac output, from the 6th to the 33rd week, at levels 50% higher than before pregnancy, are aggravating factors of the diastolic dysfunction of HCM. These hemodynamic changes could explain the progression to FC III/IV in 35.9% of patients, the higher incidence of heart failure in PG group and the difficulty to control it, including the necessity of hospitalization in 6 of 7 patients, who experienced this complication.

In this aspect, our higher occurrence of heart failure, higher than that previously related in retrospective studies, could be related to the known heterogeneity of HCM. In this study, all patients, pregnant or non pregnant women, were enrolled after they had been referred to a tertiary hospital, establishing a selection bias to a more severe form of disease.

The cardiac arrhythmia found in the NP group is compatible to previous reports of HCM natural history, usually expressed as supraventricular tachycardia and atrial fibrillation²⁰, particularly in cases with major mitral regurgitation or ventricular obstruction. In a single case of paroxysmal atrial fibrillation in the PG group, in the third trimester of gestation did not impair fetal development, possibly because of a successful electrical cardioversion.

A similar incidence of cardiac events found in PG and NP groups, demonstrated that despite the transitory hemodynamic burden, pregnancy had no influence on the natural course of women with HCM. The investigation of the

relationship between clinical deterioration and the clinical and echocardiographic data profile of PG group patients showed that family history of HCM was more frequent in patients who needed hospitalization (Table 1), allowing assumptions about the possible correlation between familial form and worst maternal outcome during pregnancy.

With respect to echocardiogram data, the 73.9% incidence of obstructive form in the PG group, higher than that reported in general HCM patients²¹, may be justified by the sample selected from tertiary hospitals. A ventricular gradient increase in the PG group during gestation confirms the functional aggravation of left ventricular outflow tract obstruction due to pregnancy-related increase in blood volume and myocardial contractility. Despite left ventricular outflow tract obstruction at rest being considered an independent predictor of progression to severe symptoms of heart failure²¹, in the present study we did not observe correlation between clinical evolution and the degree of outflow tract obstruction.

The management of clinical complications with propranolol and/or verapamil, both considered as having no teratogenic effects^{22,23}, and eventual hospitalization when required, allowed clinical control in all the cases, resulting in no maternal and fetal deaths. The use of propranolol in doses up to 160 mg/day was not associated with potential obstetrical complications, such as premature labor, nor with neonatal complications, such as bradycardia, hypoglycemia, hyperbilirubinemia and polycythemia. However, propranolol, as much as output restriction due to HCM, may have contributed to growth restriction and low birth weight rates.

Occurrence of obstetrical complications in 57% of PG patients who needed hospitalization confirms the poor fetal prognosis in HCM women, particularly in cases of heart failure. These results agree with the Elkayam³ review of 82 HCM patients in gestation that showed 20% of spontaneous abortion and 10% of low birth weight babies. In this series, most indications for cesarean section were determined by impaired fetal evolution in nearly half of the cases related to intrauterine growth-retardation fetus and/or fetal distress.

Considering that two thirds of HCM patients have a family history of disease^{24,25}, clinical screening of first-degree relatives should be recommended, employing history and physical examination, 12-lead ECG, and two-dimensional echocardiography at evaluations of offspring and during their adolescence. Nevertheless, myocardial hypertrophy is rarely documented in childhood, even in those who have a genetic defect.

Maron & Spirito²⁶ observed that the progression of hypertrophy in children is rarely associated with symptoms, which become apparent after adolescence. On the other hand, Suda et al²⁷, in a retrospective study of 9 children with HCM aged less than one year, found a strong correlation between progressive hypertrophy of the posterior wall of the left ventricle with poor outcome of the disease.

In this series, HCM was identified in a single case among 13 children who were clinically and echocardiographically examined, and a fact worth pointing out is that this child's mother had the obstructive form of the disease and a family history of HCM with sudden cardiac death.

A genetic study²⁸ of asymptomatic children and adolescents with family history of HCM could allow the identification of "healthy" mutation carriers. However, there are important obstacles to the clinical applications of genetic research, such as genetic heterogeneity, the low frequency with which each causal mutation occurs in the general HCM population and, finally, methodological difficulties, such as identification of a single disease-causing mutation among 10 different genes, and time consuming and expensive laboratory techniques.

Due to these factors, a genetic study in this series was performed in the child with family history, and clinical features of HCM showed a mutation at the beta myosin heavy chain gene.

It seems likely that clinical application of genetic screening will remain complex; nevertheless, efforts made for this identification can help to trace subjects with this disease, thus laying the ground for a stratification of risks, establishment of prognosis, and also the design a treatment for HCM.

Limitations of the study - This series may be considered one of the largest experiments in pregnancy of women with HCM, which includes control-case study, followed up by the same clinical and obstetrical team; this, however, resulted in a small number of patients, which might have narrowed the analysis of prognosis factors of the disease during pregnancy.

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