

## Cardiomyopathy and Pregnancy

# Risk Associated With Pregnancy in Hypertrophic Cardiomyopathy

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<b>OBJECTIVES</b>	We sought to assess mortality and morbidity in pregnant women with hypertrophic cardiomyopathy (HCM).
<b>BACKGROUND</b>	The risk associated with pregnancy in women with HCM is an important and increasingly frequent clinical issue for which systematic data are not available and a large measure of uncertainty persists.
<b>METHODS</b>	Maternal mortality in 91 consecutively evaluated families with HCM was compared with that reported in the general population. The study cohort included 100 women with HCM with one or more live births, for a total of 199 live births. Morbidity related to HCM during pregnancy was investigated in 40 women evaluated within five years of their pregnancy.
<b>RESULTS</b>	Two pregnancy-related deaths occurred, both in patients at a particularly high risk. The maternal mortality rate was 10 per 1,000 live births (95% confidence interval [CI] 1.1 to 36.2/1,000) and was in excess of the expected mortality in the general Italian population (relative risk 17.1, 95% CI 2.0 to 61.8). In the 40 patients evaluated within close proximity of their pregnancy, 1 (4%) of the 28 who were previously asymptomatic and 5 (42%) of the 12 with symptoms progressed to functional class III or IV during pregnancy ( $p < 0.01$ ). One patient had atrial fibrillation and one had syncope, both of whom had already experienced similar and recurrent events before their pregnancy.
<b>CONCLUSIONS</b>	Maternal mortality is increased in patients with HCM compared with the general population. However, absolute maternal mortality is low and appears to be principally confined to women at a particularly high risk. In the presence of a favorable clinical profile, the progression of symptoms, atrial fibrillation, and syncope are also uncommon during pregnancy. (J Am Coll Cardiol 2002;40:1864-9) © 2002 by the American College of Cardiology Foundation

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In recent years, clinical and genetic screening of families with hypertrophic cardiomyopathy (HCM), as well as a more widespread use of echocardiography, has led to the identification of a growing number of young women with this disease who were previously unaware of their condition (1-4). Many such patients may contemplate the possibility of pregnancy. Therefore, more so than in the past, cardiologists are confronted with the difficult issue of the risk associated with gestation and delivery in this disease. However, the few studies on the course of pregnancy in women with HCM were performed >20 years ago in relatively small, selected patient populations, and they reported no deaths (5,6). In contrast, several case reports have described severe cardiac complications and death during pregnancy (7-13). Therefore, a large measure of uncertainty persists regarding the risk associated with gestation and delivery in women with HCM.

In the present study, maternal mortality was assessed in

>90 families with HCM and was compared with that reported in the general population. In addition, morbidity related to HCM during pregnancy was investigated in a group of patients evaluated within close proximity of their pregnancy. Our findings offer an estimate of the risk of death during pregnancy in HCM and characterize the clinical profile of those patients more likely to experience disease-related complications.

## METHODS

**Study population.** The populations of patients with HCM consecutively evaluated at three centers between 1984 and 2000 were combined. The patients known to have the familial form of the disease were selected, and their pedigrees were reconstructed. The affected family members and their first-degree relatives were included in the pedigrees. The occurrence of death during pregnancy was assessed in women with HCM. Maternal mortality in the general Italian population was used for comparison. As modern statistics on maternal mortality in Italy were available from 1955 (14), only women with a first pregnancy after 1954 were examined.

Because HCM is an autosomal-dominant disease, it could be expected that a proportion of the family members who were not evaluated were affected. Therefore, to prevent

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Manuscript received April 16, 2002; revised manuscript received June 20, 2002, accepted July 24, 2002.

#### Abbreviations and Acronyms

CI	= confidence interval
HCM	= hypertrophic cardiomyopathy
LV	= left ventricle or ventricular

an underestimation of maternal mortality due to undiagnosed disease, the occurrence of pregnancy-related death was also assessed in an extended cohort that included the affected women, as well as the first-degree relatives with a pregnancy after 1954 who had not been clinically and echocardiographically evaluated. Maternal mortality was defined as death either during gestation or at or shortly after delivery.

The potential relationship between clinical features of HCM and disease-related morbidity during pregnancy was investigated in patients evaluated at the participating centers either shortly before or within five years of their pregnancy. This five-year interval was arbitrarily selected as one brief enough to allow the patients to recall with sufficient accuracy the severity of their clinical limitation before pregnancy, as well as to justify the assumption that their functional profile (i.e., presence or absence of left ventricular [LV] outflow obstruction) had remained unchanged from the time of pregnancy. Cardiac deterioration with development of heart failure during pregnancy was defined as a marked increase in shortness of breath and fatigue to New York Heart Association functional class III or IV. Syncope was defined as a sudden and brief loss of consciousness associated with a loss of postural tone and a spontaneous recovery (15). The potential relationship between morphologic features assessed by echocardiography and the course of pregnancy was evaluated only in those patients in whom an echocardiogram had been obtained before pregnancy.

**Echocardiographic diagnosis and evaluation.** The diagnosis of HCM was based on the two-dimensional echocardiographic demonstration of a hypertrophied, nondilated LV (wall thickness  $\geq 15$  mm) in the absence of another cardiac or systemic disease capable of producing a similar magnitude of wall thickening (1,4). In relatives of patients with HCM, a wall thickness  $\geq 13$  mm was used as a criterion for diagnosis (16). The extent and distribution of LV hypertrophy was evaluated, and the magnitude of hypertrophy was expressed in terms of maximal wall thickness (17-19). The LV end-diastolic cavity dimension and left atrial size were assessed by M-mode echocardiography in a standard fashion. Left ventricular outflow obstruction was diagnosed on the basis of the presence of prolonged systolic contact between the mitral leaflets and interventricular septum or a Doppler-estimated pressure gradient  $\geq 30$  mm Hg under basal conditions (4,17-19).

**Statistical analysis.** Results are presented as the mean value  $\pm$  SD or proportions, as appropriate. Maternal mortality was computed as the ratio between the number of deaths during pregnancy and the total number of pregnan-

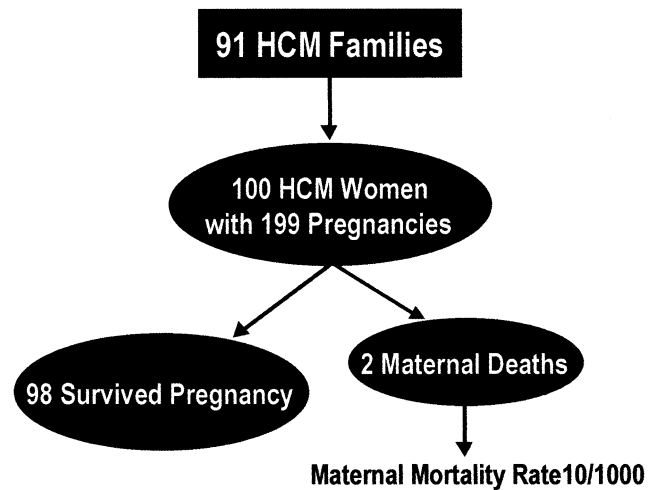
cies in each group. The maternal mortality observed in the present study cohort was compared with that of the general Italian population. Statistics on maternal mortality in Italy were available only between 1955 and 1984. During the 1955 to 1984 period, maternal mortality decreased substantially from 1.33 per 1,000 live births in 1955 to 0.11 per 1,000 live births in 1984 (14). Therefore, age- and year-specific mortality rates were used to compare the mortality in the study cohort with that reported in the Italian population. Expected maternal deaths were computed by indirect standardization (i.e., by summing age- and year-specific expected deaths, which were calculated by multiplying age- and year-specific rates for the number of pregnancies in each age and year group). Relative risks were estimated as the ratio between the number of observed and the number of expected deaths. Ninety-five percent confidence intervals (CIs) for maternal mortality and relative risks were calculated with the assumption of an underlying Poisson distribution for rare events. Proportions between subgroups of patients were compared by means of the chi-square or Fisher exact test, as appropriate. A *p* value  $< 0.05$  was considered as statistically significant.

## RESULTS

In the three patient cohorts, a total of 91 HCM-affected families were identified that included women with a first pregnancy after 1954. Of these families, 32 were evaluated at the University La Sapienza, Rome; 20 at the Ospedale Rivoli, Turin; and 39 at the Ente Ospedaliero Ospedali Galliera, Genoa. In these families, 100 women known to have HCM had pregnancies after 1954; their age at first pregnancy ranged from 15 to 37 years (mean 25). The total number of live births was 199 (range 1 to 5, mean 2). A family history of sudden death in a first-degree relative  $< 50$  years of age was present in 48 (48%) of the 100 women; these 48 patients belonged to 27 (30%) of the 91 HCM-affected families.

Of these 100 family members with HCM and pregnancies after 1954, 78 were evaluated at the participating centers. Of the remaining 22, 11 could not be directly assessed because they had died of either HCM-related causes (*n* = 9) or noncardiac causes (*n* = 2) before our first evaluation of the proband, and 11 could not be directly assessed because they lived in distant areas. Documentation of diagnosis (either as an echocardiographic report or hospital chart) was verified at our centers in 17 of the 22 patients who were not directly evaluated. The remaining five women had died suddenly before the age of 50 years.

Of the 78 women with HCM and previous pregnancies who were evaluated at our centers, 75 (96%) were in functional class I or II, and 3 (4%) were in functional class III or IV at the time of our initial evaluation. Left ventricular outflow obstruction under basal conditions was present in 18 (23%). On the echocardiogram, the LV



**Figure 1.** Maternal mortality (i.e., the number of maternal deaths divided by the total number of pregnancies) in 100 women with hypertrophic cardiomyopathy (HCM).

end-diastolic dimension was  $43 \pm 6$  mm; maximal LV wall thickness was  $19 \pm 4$  mm; and left atrial size was  $43 \pm 8$  mm. **Maternal mortality.** Two deaths occurred during pregnancy in the 100 women with HCM, both were sudden. The maternal mortality rate was 10 per 1,000 live births (95% CI 1.1 to 36.2/1,000) (Fig. 1). In Italy, during the period 1955 to 1984, maternal mortality decreased substantially, from 1.33 per 1,000 live births in 1955 to 0.11 per 1,000 live births in 1984 (14). Maternal mortality in the women with HCM was in excess of the age- and year-specific mortality rates in the general Italian population (relative risk 17.1, 95% CI 2.0 to 61.8).

To prevent an underestimation of maternal mortality due to undiagnosed disease, the occurrence of pregnancy-related death was also assessed in an extended cohort that included the affected women, as well as 96 first-degree relatives with a pregnancy after 1954 who had not been clinically and echocardiographically evaluated. In these 96 first-degree relatives, age at first pregnancy ranged from 16 to 43 years (mean 24). The total number of live births was 202 (range 1 to 7, mean 2). There were no maternal deaths in these first-degree relatives. Maternal mortality in the overall cohort, including the 100 women with HCM and the 96 first-degree relatives not assessed for HCM, was 5 per 1,000 live births (95% CI 0.6 to 18.0/1,000) and was in excess of the age- and year-specific mortality rates in the general Italian population (relative risk 8.3, 95% CI 1.01 to 32.2) (Table 1).

**Clinical profile of women who died during their pregnancy.** Both of the patients who died during pregnancy were known to be affected; both had been judged to be at a particularly high risk and had been strongly advised against becoming pregnant. One of these two women had massive LV hypertrophy with a maximal wall thickness of 30 mm and LV outflow obstruction under basal conditions (outflow gradient 115 mm Hg at cardiac catheterization). During two previous pregnancies, this patient had experienced clinical deterioration with progression to functional class III. In 1987, during her last pregnancy, at age 39 years, the patient deteriorated to class IV. At the time, Doppler echocardiography confirmed the presence of LV outflow obstruction under basal conditions, and treatment included beta-blocking agents and diuretics. Four days after delivery, while at home, the patient complained of palpitations, collapsed, and died suddenly a few minutes after the onset of symptoms. Relatives witnessed the event.

The second patient had a particularly malignant family history of death due to HCM, with a total of eight deaths in young relatives: five were sudden and three were due to congestive heart failure. The morphologic and functional presentation of the disease in five members of her family evaluated at our centers had shown mild LV hypertrophy (14 to 18 mm), with evolution to end-stage disease and systolic dysfunction in three members. In 1990, at age 26 years, the patient became pregnant. At the time, she was in functional class II. The patient was considered at high risk because of her family history of multiple cardiac deaths and was carefully clinically monitored throughout pregnancy. At labor, epidural analgesia was performed during continuous cardiovascular monitoring. Six hours after the beginning of labor, the patient developed prolonged and recurrent runs of ventricular tachycardia associated with a marked decrease in systemic arterial blood pressure. Flecainide was administered intravenously. During infusion of the drug, the patient developed marked bradycardia with broad electrocardiographic ventricular complexes. Cardiopulmonary resuscitation was immediately started and, in consideration of the critical clinical condition of the patient, a classic cesarean section was performed. The child was born alive and well, although the mother died despite prolonged resuscitation attempts.

**Morbidity related to HCM during pregnancy.** Morbidity related to HCM during pregnancy was assessed in 40 patients who were evaluated at the participating centers either shortly before or within five years of their pregnancy.

**Table 1.** Observed and Expected Maternal Mortality in the Study Women With a First Pregnancy After 1954, and Relative Risk According to Age- and Year-Specific Maternal Mortality Rates in the General Italian Population Between 1955 and 1984

	n	Live Births (n)	Observed Deaths (n)	Expected Deaths (n)	Relative Risk (95% CI)
Women with HCM	100	199	2	0.12	17.1 (2.0-61.8)
Women with HCM and first-degree relatives without assessment for HCM	196	401	2	0.24	8.3 (1.01-32.2)

CI = confidence interval; HCM = hypertrophic cardiomyopathy.

**Table 2.** Clinical Features and Echocardiographic Findings in 40 Women With Hypertrophic Cardiomyopathy and a Pregnancy Within Five Years of Evaluation

Patients (no.)	40
Age at diagnosis (years)	24 ± 6
Age at pregnancy (years)	25 ± 5
NYHA functional class	
I	28 (70%)
II	11 (27%)
III	1 (3%)
LVOT obstruction	12 (30%)
History of syncope	6 (15%)
During exercise	3 (7%)
At rest	2 (5%)
Postural	1 (3%)
Chronic atrial fibrillation	0
Paroxysmal atrial fibrillation	1 (3%)
Myotomy-myectomy operation	1 (3%)
Medications during pregnancy	
None	27 (67%)
Beta-blockers	10 (25%)
Calcium antagonists	2 (5%)
Amiodarone	1 (3%)
Echocardiographic findings before pregnancy (n = 19)	
LVIDD (mm)	43 ± 4
Maximal LV wall thickness (mm)	21 ± 6
Left atrial size (mm)	41 ± 6

Data are expressed as the mean value ± SD or number (%) of patients.  
LV = left ventricular; LVIDD = left ventricular internal diastolic diameter; LVOT = left ventricular outflow tract; NYHA = New York Heart Association.

The patient cohort included 28 of the 100 women with familial HCM and 12 additional women with sporadic HCM. Their clinical features are reported in Table 2. Hypertrophic cardiomyopathy was diagnosed before pregnancy, at age 22 ± 6 years, in 19 of the 40 patients, and after pregnancy, at age 31 ± 7 years, in the remaining 21 patients. A cesarean section was performed in 13 (68%) of the 19 patients diagnosed before pregnancy and in 2 (10%) of the 21 diagnosed after pregnancy ( $p < 0.05$ ). Of these 15 cesarean sections, 11 were managed with general anesthesia and 4 with epidural anesthesia.

During pregnancy, 6 (15%) of these 40 patients experienced worsening of cardiac symptoms, with a substantial increase in shortness of breath and fatigue. Of these six patients, two progressed to class IV with pulmonary rales and orthopnea, and four developed shortness of breath on minimal effort, without signs of pulmonary congestion. In proximity of their delivery, each of these six patients was hospitalized in centers with a department of cardiology, and four were managed with a cesarean section. Worsening of their clinical condition was significantly associated with their functional class before pregnancy, occurring in only 1 (4%) of the 28 previously asymptomatic patients and in 5 (42%) of the 12 patients with symptoms ( $p < 0.01$ ). With regard to the impact of LV outflow obstruction, clinical deterioration occurred in 3 (25%) of the 12 patients with obstruction and in 3 (11%) of the 28 patients without obstruction ( $p > 0.05$ ). None of the 40 patients experienced sustained ventricular arrhythmias during pregnancy. The

only patient who had episodes of paroxysmal atrial fibrillation during pregnancy also had a history of paroxysmal atrial fibrillation before pregnancy. One patient experienced a syncopal episode during labor. This patient was one of the six with a history of syncope before pregnancy and was the only one with recurrent episodes of postural syncope before pregnancy.

The potential relationship between echocardiographic variables and the occurrence of complications during pregnancy was assessed in 19 (48%) of the 40 patients in whom an echocardiogram had been obtained before pregnancy. The LV end-diastolic cavity dimension ranged from 35 to 51 mm (mean 43 ± 4); the maximal LV wall thickness ranged from 14 to 38 mm (mean 21 ± 6); and the left atrial size ranged from 28 to 52 mm (mean 41 ± 6). No significant relationship was identified between these echocardiographic variables and the occurrence of complications during pregnancy.

## DISCUSSION

The published data on pregnancy in HCM are scarce and contain some inconsistencies. The available studies were published >20 years ago and did not document maternal deaths (5,6). These investigations, however, were based on a small number of patients followed at tertiary-care referral centers and were likely to include highly selected women who were allowed to become pregnant because of their favorable clinical profile. In contrast, several case reports have described major cardiac complications and death during pregnancy, generating a certain alarm regarding the potential risk associated with gestation and delivery (7-13). Such reports, however, did not take into account the much higher proportion of women with HCM who survive pregnancy.

**Complexity of the study design.** The difficulties of the design of a study on maternal mortality in HCM may explain why such a major issue has not been addressed for >20 years. A retrospective investigation of the clinical course of pregnancy in HCM-affected women would have the important selection bias of excluding patients who died during pregnancy either before they came under observation or before their diagnosis (mean age at diagnosis in HCM is ~40 years) (4,20,21). A prospective investigation would avoid these limitations but is unrealistic and virtually impossible because of the low rate of cardiac events and the need for a particularly large population of young and pregnant patients with a disease as uncommon as HCM. In addition, a prospective study would include the major bias of selectively enrolling those patients judged (on the basis of arbitrary criteria) to have a clinical profile favorable enough to experience a pregnancy.

To overcome all of these limitations, our investigation was conceived as a reconstruction of the frequency of maternal mortality in consecutively evaluated families with HCM. Despite the retrospective design, the devastating

experience of a maternal death in a first-degree relative guaranteed the accuracy of the information on the number of such events. Although the selection of families could have been a source of bias, each of the three centers participating in the study predominantly followed a community-based and regional HCM cohort (1,18,20). Consequently, the great majority of the HCM families consisted primarily of relatives of probands from the metropolitan areas and adjacent regions of the three centers. Therefore, our study families reflect a relatively unselected cohort, free of important tertiary-care referral bias, which offered us the opportunity to establish a credible estimate of maternal mortality in HCM.

**Maternal mortality.** Two women died during pregnancy. Both women died suddenly and were known to be affected before pregnancy. The total mortality rate in the women with HCM was 10 per 1,000 live births. To prevent the risk of underestimating HCM-related maternal mortality because of undiagnosed disease at the time of pregnancy, our analysis was extended to a larger cohort that also included first-degree relatives who had not been evaluated for the presence of HCM. No additional maternal deaths were identified in this group. The mortality rates in the women with HCM and in the extended cohort were higher than those in the general Italian population. However, the absolute mortality rate was low. In addition, both of the patients who died had a particularly high-risk profile; their high risk had been identified; and both had been strongly advised against a pregnancy. Finally, one of the two deaths, which occurred in the hospital >10 years ago, was triggered by recurrent episodes of ventricular tachycardia in a patient with a particularly malignant family history of sudden death (five sudden deaths in close relatives) and might have been prevented by the current management of complex arrhythmias. This detailed analysis of our findings leads to the conclusion that pregnancy is safe for most patients with HCM. Therefore, in the overall HCM population, many young women who have a low-risk clinical profile should be reassured about pregnancy.

**Prognostic role of a family history of sudden death.** Although a family history of sudden death is generally considered an indicator of increased risk in HCM, previous investigations could not document a statistically significant relationship between this variable and the risk of sudden death, possibly because of the relatively small number of events in the study populations (4,19,21). Because only two of our patients died during pregnancy (one without a family history of sudden death and one with a particularly malignant pedigree), we cannot exclude that a sudden death in a first-degree relative is associated with an increased cardiac risk during pregnancy. However, the high number of our study patients with a family history of sudden death who survived gestation and delivery suggests that such a history is not associated with a major increase in risk.

**Morbidity related to HCM during pregnancy.** We also investigated the clinical course of pregnancy, as well as the

relationship between the clinical profile and the risk of cardiac morbidity during gestation, in 40 women with HCM who were evaluated within (either before or after) five years of their pregnancy. Delivery was accomplished by a cesarean section in ~40% of these patients. Of note, this procedure was performed in ~70% of the women diagnosed before pregnancy, but in only 10% of those in whom the diagnosis of HCM was unknown at the time of pregnancy, suggesting that the frequency of cesarean section in our patient population may partly reflect an excess of caution by the physician.

Clinical deterioration with the development of important symptoms of heart failure was relatively uncommon, occurring in <5% of the patients without symptoms before pregnancy and in ~15% of the overall cohort, and it was significantly related to their functional class before pregnancy. This observation indicates that the HCM-affected heart, despite marked hypertrophy, a small LV cavity, and reduced compliance, usually tolerates well the hemodynamic burden imposed by the volume overload associated with pregnancy (22-24). These findings, however, also suggest caution in the management of symptomatic patients with HCM who are contemplating pregnancy.

Clinical deterioration was twice as common in patients with outflow obstruction than in those without obstruction. This difference did not reach statistical significance, possibly because of the relatively low number of patients in the two groups. Arrhythmias and symptoms other than heart failure were particularly uncommon during pregnancy: sustained ventricular arrhythmias did not occur in any of the patients; paroxysmal atrial fibrillation occurred in one; and syncope occurred in one. Patients in these last two categories had also experienced similar and recurrent events before pregnancy.

In the subgroup of patients with an echocardiogram obtained within five years before pregnancy, none of the cardiac morphologic features showed a significant correlation with clinical deterioration during gestation. This negative finding may be partly due to the small number of patients in this subgroup. However, the fact that one of the two maternal deaths in the HCM families occurred in a patient with massive hypertrophy (30 mm), a phenotype associated with a high long-term risk of sudden death (19,25), suggests that such a LV morphology might have an impact on risk during pregnancy.

**Conclusions.** Our results indicate that the risk of death during pregnancy is increased in patients with HCM compared with the general population. However, our findings show that absolute maternal mortality is low and appears to be principally confined to women who are at a particularly high risk. Major progression of symptoms, atrial fibrillation, and syncope are uncommon and significantly related to the patient's clinical condition before pregnancy. Therefore, most young women with HCM can be reassured about their potential risks of pregnancy.

## Acknowledgment

We are indebted to Enrica Bagnato for her secretarial assistance.

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