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## MATERNAL AND FETAL OUTCOMES OF SUBSEQUENT PREGNANCIES IN WOMEN WITH PERIPARTUM CARDIOMYOPATHY

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### ABSTRACT

**Background** Peripartum cardiomyopathy is a rare but sometimes fatal form of heart failure. Little is known about the outcomes of subsequent pregnancies in women who have had the disorder.

**Methods** Through a survey of members of the American College of Cardiology, we identified 44 women who had had peripartum cardiomyopathy and had a total of 60 subsequent pregnancies. We then reviewed the medical records of these women and interviewed the women or their physicians.

**Results** Among the first subsequent pregnancies in the 44 women, 28 occurred in women in whom left ventricular function had returned to normal (group 1) and 16 occurred in women with persistent left ventricular dysfunction (group 2). The pregnancies were associated with a reduction in the mean ( $\pm$ SD) left ventricular ejection fraction both in the total cohort (from  $49\pm 12$  percent to  $42\pm 13$  percent,  $P<0.001$ ) and in each group separately (from  $56\pm 7$  percent to  $49\pm 10$  percent in group 1,  $P=0.002$ ; and from  $36\pm 9$  percent to  $32\pm 11$  percent in group 2,  $P=0.08$ ). During these pregnancies, symptoms of heart failure occurred in 21 percent of the women in group 1 and 44 percent of those in group 2. The mortality rate was 0 percent in group 1 and 19 percent in group 2 ( $P=0.06$ ). In addition, the frequency of premature delivery was higher in group 2 (37 percent vs. 11 percent), as was that of therapeutic abortions (25 percent vs. 4 percent).

**Conclusions** Subsequent pregnancy in women with a history of peripartum cardiomyopathy is associated with a significant decrease in left ventricular function and can result in clinical deterioration and even death. (N Engl J Med 2001;344:1567-71.)

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PERIPARTUM cardiomyopathy is a rare form of heart failure of unknown cause that occurs during pregnancy or during the postpartum period.<sup>1-3</sup> Although approximately 20 percent of women with the disorder either die or survive only because they receive cardiac transplants, the majority recover partially or completely. Although the women who recover may desire to become pregnant again, there is a concern that such pregnancies may be associated with an increased risk of recurrence of cardiomyopathy.<sup>1-4</sup> Information about the outcome of additional pregnancies, however, is limited.<sup>4-8</sup> There is therefore no consensus regarding recommendations for future pregnancies in women who have had peripartum cardiomyopathy.<sup>3</sup> We undertook a study to determine maternal and fetal outcomes of subsequent pregnancy among women with a history of peripartum cardiomyopathy.

### METHODS

We obtained information about subsequent pregnancies in women who had had peripartum cardiomyopathy by sending a questionnaire in 1997 and 1998 to all members of the American College of Cardiology in the United States (approximately 15,000 persons) and to 2 members of one cardiology group in South Africa, seeking information about women with peripartum cardiomyopathy who had subsequent pregnancies. The physicians who responded were asked to obtain from their patients written informed consent to participate in the study and to release their medical records to the investigators. Data were then collected by the investigators through the review of medical records and supplemented, if necessary, by information elicited in telephone interviews of the referring physicians or the patients. The study protocol and the consent form were approved by the institutional review board of the University of Southern California.

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The criteria for the diagnosis of peripartum cardiomyopathy included the development of congestive heart failure during the last six months of pregnancy or the first six months after delivery, the absence of another identifiable cause of heart failure, and evidence of depressed left ventricular function, defined as a left ventricular ejection fraction of less than 40 percent, as measured by echocardiography.

Comparisons between groups were made with the use of Fisher's exact test. Comparisons of left ventricular ejection fractions were made with the use of Student's paired t-test. All statistical tests were two-sided.

## RESULTS

Of the approximately 15,000 physicians who were contacted, 409 returned the questionnaire. On the basis of these responses, we identified 92 women with a history of peripartum cardiomyopathy who had had a subsequent pregnancy. We were able to review the clinical and echocardiographic information for 44 of these women, of whom 23 were white, 16 were black, and 5 were Hispanic. Their ages at the time of diagnosis of peripartum cardiomyopathy ranged from 19 to 39 years (mean [ $\pm$ SD],  $29\pm 6$ ); parity ranged from 1 to 9 (mean,  $1.9\pm 1.5$ ), and gravidity ranged from 1 to 10 (mean,  $2.8\pm 2.5$ ). The diagnosis of cardiomyopathy was made before delivery in 7 women (1 woman each in the fifth, sixth, and seventh months of pregnancy, 2 women in the eighth month of pregnancy, and 2 women in the last month of pregnancy), during the first month after delivery in 28 women, and between two and six months after delivery in 9 women (2 women in the second month after delivery, 1 in the third month, 1 in the fifth month, and 5 in the sixth month after delivery). Ten women had preeclampsia, and four had a history of chronic hypertension. None of the women had severe anemia or a history of hyperthyroidism. Seven were reported to have undergone endomyocardial biopsy, and in three of these the biopsy results were reported to be positive for myocarditis.

The mean interval between the pregnancy complicated by peripartum cardiomyopathy (index pregnancy) and the first subsequent pregnancy was  $27\pm 18$  months, and the duration of follow-up after the index pregnancy was  $90\pm 87$  months. A total of 33 of the women had one subsequent pregnancy, 6 had two subsequent pregnancies each, and 5 had three subsequent pregnancies each. At diagnosis, the mean left ventricular end-diastolic dimension, as measured by echocardiography, in the 44 women was  $56\pm 7$  mm (normal range, 36 to 52),<sup>9</sup> the end-systolic dimension was  $44\pm 8$  mm (normal range, 23 to 39), and the ejection fraction was  $32\pm 11$  percent (normal range,  $59\pm 6$ ) (Fig. 1).

### First Subsequent Pregnancies

The mean left ventricular ejection fraction in the total cohort of 44 women was  $32\pm 11$  percent at diagnosis and increased significantly to  $49\pm 12$  percent before the first subsequent pregnancy ( $P<0.001$ ).

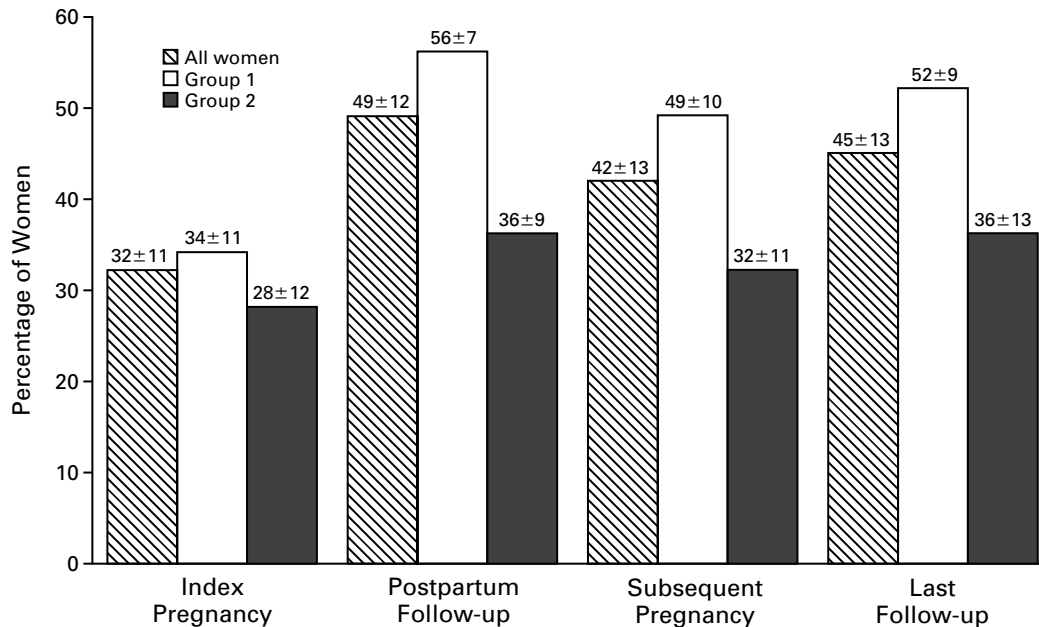
During the subsequent pregnancy, the mean left ventricular ejection fraction decreased to  $42\pm 13$  percent ( $P<0.001$ ), and the mean value was  $45\pm 13$  percent a mean of 72 months after the subsequent pregnancy (Fig. 1). The normalization of ventricular function, defined as an increase in the left ventricular ejection fraction to at least 50 percent, was documented in 28 women (group 1) before their first subsequent pregnancy, whereas 16 women (group 2) had persistent left ventricular dysfunction (an ejection fraction of less than 50 percent) (Fig. 1). The mean left ventricular ejection fraction decreased in both groups during the subsequent pregnancy, from  $56\pm 7$  percent to  $49\pm 10$  percent in group 1 ( $P=0.002$ ) and from  $36\pm 9$  percent to  $32\pm 11$  percent in group 2 ( $P=0.08$ ).

### Maternal Outcome

During the first subsequent pregnancy, 6 of the 28 women in group 1 (21 percent) and 7 of the 16 women in group 2 (44 percent) had symptoms of heart failure (Table 1). Twenty-one percent of the women in group 1 and 25 percent of those in group 2 had a decrease of more than 20 percent in the left ventricular ejection fraction during the first subsequent pregnancy, and 14 percent of the women in group 1 and 31 percent of those in group 2 had a decreased ejection fraction at the last follow-up. None of the women in group 1 died during or after the first subsequent pregnancy; three of the women in group 2 (19 percent) died after the first subsequent pregnancy. Two of the women died suddenly (one died two months after the subsequent pregnancy and the other two years after the subsequent pregnancy), and one woman died of progressive heart failure two months after the subsequent pregnancy.

### Outcome of Pregnancies That Were Not Terminated

Because the early interruption of pregnancy may prevent complications in the pregnant woman, we separately evaluated the outcome of the 35 first subsequent pregnancies that were not terminated. In the 35 women who did not have abortions, the mean ejection fraction decreased by 14 percent (from  $49\pm 12$  percent to  $42\pm 14$  percent,  $P<0.001$ ), as compared with a decrease of only 7 percent in the 9 women who had abortions (from  $46\pm 13$  percent to  $43\pm 11$  percent,  $P=0.20$ ). The mean decrease in the left ventricular ejection fraction was 8 percent in the 23 women in group 1 who did not have abortions ( $P<0.01$ ) and 5 percent in the 12 women in group 2 who did not have abortions ( $P<0.05$ ). Among the women who did not have abortions, a greater proportion of those in group 2 than of those in group 1 had symptoms of heart failure, a decrease in the ejection fraction of more than 20 percent during the subsequent pregnancy, or a decreased ejection fraction at last follow-up (Table 1). There were no deaths in group 1, but three women in this subgroup of group 2 died.



**Figure 1.** Mean ( $\pm$ SD) Left Ventricular Ejection Fraction in 44 Women at the Time of the Diagnosis of Peripartum Cardiomyopathy (Index Pregnancy), at Postpartum Follow-up, during the First Subsequent Pregnancy, and at the Last Follow-up a Mean of 72 Months after the First Subsequent Pregnancy.

Group 1 included all the women with a left ventricular ejection fraction of 50 percent or higher before subsequent pregnancies, and group 2 included all those with a left ventricular ejection fraction of less than 50 percent before subsequent pregnancies. For the total cohort (all women),  $P < 0.001$  for the comparison between postpartum follow-up and the index pregnancy,  $P < 0.001$  for the comparison between subsequent pregnancy and postpartum follow up, and  $P = 0.06$  for the comparison between last follow-up and subsequent pregnancy. For group 1,  $P < 0.001$  for the comparison between postpartum follow-up and the index pregnancy,  $P = 0.002$  for the comparison between subsequent pregnancy and postpartum follow-up, and  $P = 0.06$  for the comparison between last follow-up and subsequent pregnancy. For group 2,  $P = 0.05$  for the comparison between postpartum follow-up and the index pregnancy and  $P = 0.08$  for the comparison between subsequent pregnancy and postpartum follow-up.

**Fetal Outcome**

Among the 35 women who had a subsequent pregnancy and did not have an abortion, 21 had a normal vaginal delivery, and 14 delivered by cesarean section. Premature delivery (defined as delivery at less than 37 weeks' gestation) occurred in three women (13 percent of the subgroup) in group 1 (at 30, 32, and 36 weeks) and in six women (50 percent of the subgroup) in group 2 (two women at 30 weeks, one at 34 weeks, one at 35 weeks, and two at 36 weeks). There was no perinatal mortality. Of the nine abortions, five were therapeutic; one of these occurred in group 1 (4 percent of the first subsequent pregnancies) and the other four in group 2 (25 percent of the first subsequent pregnancies).

**Additional Pregnancies**

Eleven of the women had 16 additional pregnancies. Of the women in group 1, five women had one additional pregnancy each and four women had two additional pregnancies each; of those in group 2, one

**TABLE 1.** INCIDENCE OF MATERNAL COMPLICATIONS DURING THE FIRST SUBSEQUENT PREGNANCY IN WOMEN WHO HAD HAD PERIPARTUM CARDIOMYOPATHY.\*

GROUP	NO. OF WOMEN	SYMPTOMS OF HEART FAILURE	>20% DECREASE IN LVEF	DECREASED LVEF AT FOLLOW-UP	DEATH
All women	44				
Group 1	28	6 (21)	6 (21)	4 (14)	0
Group 2	16	7 (44)	4 (25)	5 (31)	3 (19)†
Women who did not have abortions	35				
Group 1	23	6 (26)	4 (17)	2 (9)	0
Group 2	12	6 (50)	4 (33)	5 (42)	3 (25)‡

\*Group 1 consisted of women with recovered left ventricular function, defined as a left ventricular ejection fraction (LVEF) of 50 percent or higher, before the subsequent pregnancy; group 2 consisted of women with persistent left ventricular dysfunction (an LVEF of less than 50 percent).

† $P = 0.06$  for the comparison with group 1.

‡ $P = 0.05$  for the comparison with group 1.

woman had one additional pregnancy, and one woman had two additional pregnancies. None of these women were reported to have symptoms of heart failure during these later pregnancies. One woman who had no change in the left ventricular ejection fraction during her first subsequent pregnancy had a substantial decrease in the ejection fraction — from 55 percent to 40 percent — during her second subsequent pregnancy, and the decreased ejection fraction persisted at three months of follow-up.

## DISCUSSION

Determination of the risk associated with subsequent pregnancies in women with a history of peripartum cardiomyopathy has obvious clinical implications. This study demonstrates that in women who have had peripartum cardiomyopathy, subsequent pregnancies may be associated with deleterious fetal and maternal outcomes such as premature delivery and maternal cardiac dysfunction, including symptomatic heart failure and even death. We found the outcomes of subsequent pregnancies to be poor, not only in women with persistent left ventricular dysfunction after the initial diagnosis of peripartum cardiomyopathy, but also, in contrast to the results of a small study conducted by Sutton et al.,<sup>6</sup> in women whose left ventricular function returned to normal after the initial pregnancy complicated by peripartum cardiomyopathy. When pregnancies that were ended by abortion were excluded, the risk of unfavorable maternal and fetal outcome was even higher, especially in the women who had had persistent left ventricular dysfunction (group 2).

Of the 44 women we studied, 3 (7 percent) died during a mean follow-up period of more than seven years; all of those who died had had persistent left ventricular dysfunction after their first episode of peripartum cardiomyopathy. Two of the deaths occurred soon after delivery, but the third death occurred suddenly four years after the initial diagnosis and two years after the subsequent pregnancy. The lower mortality rate in the present study than in previous reports<sup>5,9</sup> may be due to differences in the study subjects, criteria for diagnosis, or treatments; to the high rate of abortions (20 percent), which could have prevented the deterioration of cardiac function as well as other complications and death; or simply to reporting bias. The possibility that the diagnosis and treatment of heart failure have improved in recent years is supported by a recent finding of less than 10 percent mortality over 4.4 years among 51 women with peripartum cardiomyopathy diagnosed between 1982 and 1997.<sup>10</sup>

The exact mechanism of recurrent depression of cardiac function associated with subsequent pregnancy in women who have had peripartum cardiomyopathy is not clear. The persistence of such dysfunction in some of the women suggests a reactivation of the underlying idiopathic process responsible for the ini-

tial cardiomyopathy. Unmasked subclinical myocardial dysfunction may also be related to clinical worsening with subsequent pregnancies. Lampert et al.<sup>11</sup> reported reduced contractile reserve in women with peripartum cardiomyopathy even after the apparent recovery of left ventricular function. In addition, a transient decrease in myocardial contractility during the second and third trimesters of pregnancy and the early postpartum period has been described.<sup>12</sup> Such a change in myocardial performance is normally compensated for by a change in loading conditions during normal pregnancy, but it may unmask decreased contractile reserve in women with peripartum cardiomyopathy.

The data for this study were collected by a retrospective survey that was completely dependent on the responses of physicians and patients. Data collected in this way can be strongly influenced by ascertainment bias, selection bias, and recall bias, and they are likely to be incomplete. In addition, our echocardiographic data were based on the interpretations of individual physicians as contained in the patients' records. Although we studied more women than did previous investigators, the numbers of women in the two groups, and especially in the subgroups, were small. In spite of these limitations, the findings are strongly supported by a previous survey that we conducted.<sup>13</sup> That survey, which relied solely on a questionnaire filled out by physicians, provided data on 67 subsequent pregnancies in 63 women who had had peripartum cardiomyopathy and who were not included in the present study. In the survey, there were 40 women with normal left ventricular function after peripartum cardiomyopathy and 23 women with persistent left ventricular dysfunction. The women with normal left ventricular function had 43 subsequent pregnancies, of which 10 (23 percent) were associated with cardiac dysfunction; one of the women in this group (2 percent) died. The women with persistent left ventricular dysfunction had 24 subsequent pregnancies, of which 13 (54 percent) were associated with cardiac dysfunction; two of the women in this group (9 percent) died.

The present study demonstrates an important effect of subsequent pregnancy — in terms of both maternal and fetal outcome — among women with a history of peripartum cardiomyopathy, especially those with persistent depression of left ventricular function. This information should be useful for decision making in cases in which women with a history of peripartum cardiomyopathy desire to become pregnant again.

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**CORRECTION**

**Maternal and Fetal Outcomes of Subsequent Pregnancies in Women with Peripartum Cardiomyopathy**

Maternal and Fetal Outcomes of Subsequent Pregnancies in Women with Peripartum Cardiomyopathy . On page 1569, the y axis of Figure 1 should have read, "Left Ventricular Ejection Fraction (%)," not "Percentage of Women," as printed.