Peripartum cardiomyopathy (PPCM), also known as pregnancy-associated cardiomyopathy (1), is an uncommon condition in which an idiopathic form of left ventricular (LV) systolic dysfunction develops during pregnancy or the postpartum (PP) period in women without previous heart disease (2). The incidence of this condition in the United States is approximately 1 in 3,000 deliveries, with a significantly higher incidence in African Americans, women older than 30 years of age, those with a history of pregnancy-associated hypertension, and in those with multifetal pregnancies (3). Higher incidences have also been reported in countries outside of the United States, particularly in Africa and in Haiti (4). Although PPCM can be associated with important complications, including severe symptomatic heart failure (HF), malignant arrhythmias, thromboembolic events, and death (5), the majority of women demonstrate a partial or complete recovery within 2 to 6 months after the diagnosis (1,6). An analysis of >100 women with PPCM in the United States demonstrated the development of PPCM in conjunction with their first or second pregnancy in more than half of the cases (1). It is, therefore, not surprising that many women with a history of PPCM desire to become pregnant again. The question of the risks of subsequent pregnancies (SSPs) has been the most common reason for consultation provided by us and by others to women with a history of PPCM and physicians taking care of such women (7). A recurring concern about PPCM is the potential risk of SSP, even if LV function returns to normal. Despite the critical importance of this issue, it is only briefly discussed in the most recent guidelines for the management of pregnancy-related heart disease (8).

REVIEW OF PUBLISHED CASES OF SUBSEQUENT PREGNANCIES

Ostrzega and Elkayam (9) conducted an early survey that relied solely on a questionnaire filled out by physicians. This questionnaire provided data on 67 SSPs in 63 women who had PPCM, 40 of whom had recovery of LV function and 23 of whom had persistent LV dysfunction (Table 1). Twenty-three percent of 43 pregnancies in women with normal LV function...
were associated with worsening cardiac function, and 1 (2%) resulted in death. The women with persistent LV dysfunction had 24 SSPs, of which 13 (54%) were associated with cardiac dysfunction; 2 women (9%) died. To confirm the results of this survey (published only as an abstract in 1995), the same investigators conducted a second survey in 1997 and 1998 of approximately 15,000 American College of Cardiology members and identified 60 well-documented SSPs in 44 women (23 white, 16 black, and 5 Hispanic) with a history of PPCM (10). The patients were divided into 28 women who recovered LV function (LV ejection fraction $\geq$50%) before their SSP (group 1) and 16 women who had persistent LV dysfunction (group 2). The mean LV ejection fraction (EF) decreased in both groups (Figure 1) in conjunction with pregnancy: from 56 ± 7% to 49 ± 10% in group 1 (p = 0.002) and from 36 ± 9% to 32 ± 11% in group 2 (p = 0.08). During the first SSP, 21% of group 1 patients and 44% of group 2 had symptoms of HF (Figure 2). Twenty-one percent of group 1 women and 25% of group 2 women had a substantial (>20%) decrease in LVEF during pregnancy or during the PP period, with a persistent decrease at the last follow-up (90 ± 87 months) in 14% of group 1 women and 31% of group 2 women (Figure 2). Although no mortality occurred in group 1, it was reported in 3 women in group 2 (19%). Two of these women died suddenly (one 2 months and the other 2 years after the SSP), and the third died of progressive HF 2 months PP.

Withlin et al. reported on 7 SSPs in 6 women with PPCM (11). One patient with normal LV function had 2 SSPs without relapse. Another patient with persistent LV dysfunction remained stable throughout her SSP on HF therapy. The remaining 4 patients, who were asymptomatic and clinically stable, had relapses with deterioration of LV function and symptoms between the 20th and 31st week of gestation.

Avila et al. reported no maternal complications in 6 SSPs with normal LV function and the development of congestive HF in 30% of 11 patients with LV dysfunction that was associated with pulmonary embolism in 1 patient and death in another (12). Two of the surviving patients had a >20% reduction in their EF post-partum.

Sliwa et al. reported on 6 SSPs, 4 in women with a LVEF <40% who were asymptomatic with unchanged EF during pregnancy, but who developed HF symptoms and a >10% decrease in EF after the delivery (13). In addition, 1 patient with normal LVEF before pregnancy, who was stable at 1 month PP, had a later deterioration. At 3 months post-delivery, 2 patients with impaired EF at the onset of SSP died due to HF, and the remaining 4 patients demonstrated persistent LV dysfunction, with LVEF reduced to an average of 25%.

Chapa et al. reported 8 SSPs, 4 of them after recovery of LVEF. All 4 women with recovered LV function became symptomatic and developed recurrent LV dysfunction in the third trimester that persisted after pregnancy in 3 of them. Surprisingly, the 2 patients with persistent LV dysfunction had no further change in EF or symptomatic deterioration during the SSP (14).

Fett et al. reported on the outcome of 16 SSPs in 15 Haitian women with PPCM (15). All but 1 became pregnant before complete recovery of LVEF. Eight patients (53%) exhibited worsening HF, and 1 patient (7%) died of severe HF 10 months PP. Only 1 of the relapsed patients was reported to regain normal LV function after pregnancy, whereas all patients without relapse regained a normal EF over time.
Habli et al. reported on 21 patients with PPCM with at least partial recovery of LV function (average EF 47 ± 9%). No mortality was reported, but 29% of patients exhibited worsening of HF related to their SSP, and 2 patients required cardiac transplantation (16).

Modi et al. provided information on 13 SSPs, with worsening of HF in all of them. No information was provided on LV function before the SSP (17).

Hilfiker-Kleiner et al. (18) reported on SSPs in 12 black African women with PPCM and persistent LV dysfunction (LVEF 40% to 45%). Six women demonstrated clinical deterioration, and 3 women died within 4 months PP.

Fett et al. (19) published data on 12 prospectively identified SSPs from a PPCM registry in Haiti (12 pregnancies in 11 women) and 49 SSPs from an Internet support group website in the United States. Relapse of LV dysfunction or worsening HF symptoms were reported in 17% of women with LVEF ≥55%, 33% of women with LVEF between 50% and 54%, 37% of women with LVEFs between 45% and 49%, and 67% of women with LVEF <45% (Figure 3). Recovery of LVEF to pre-pregnancy levels was observed in the majority (87.5%) of women with LVEF ≥50% before the SSP, but in only 20% of those with LVEF <50%. One death was reported 1 month PP in a woman who started her SSP with a markedly depressed LVEF of 25%.

In a small study in India, Mandal et al. (20) reported on 6 SSPs, 5 of them after improvement of LVEF to >45%. Two patients developed HF, and one of them subsequently developed persistent cardiomyopathy. The sixth patient had LV dysfunction before the SSP and died while delivering a stillborn baby at 27 weeks’ gestation. Two PPCM patients with SSP were described in a report from Malaysia by Chee (21); 1 woman had an early termination, and the second woman delivered vaginally with a normal LVEF.

In the last several years, I have consulted on several women with recovered LV function who presented with a substantial reduction in EF related to SSP. Table 2 provides a short history of 3 of these patients who presented with life-threatening complications. These complications included cardiac arrest, cardiogenic shock, ventricular arrhythmias, and the need for aggressive therapies (e.g., electrical cardioversion, temporary LV assist devices, and implantable cardioverter defibrillator).

In summary, the 2 largest studies with a total of 105 SSPs, with PPCMs mostly diagnosed in the United States (10,19), demonstrated relapse with worsening of symptoms and deterioration of LV function in almost one-third of the cases. These data are supported by several other reports on a smaller number of patients (11–18,20,21). The risk of relapse in patients with persistent LV dysfunction is...
substantially higher than in patients who have normalized LV function before SSP, and the risk approaches 50%, with a low likelihood of recovery after pregnancy (Table 3). In addition to the risk of relapse, which usually occurs in the last part of pregnancy or the early PP period (11,13), symptomatic deterioration during pregnancy in patients with persistent LV dysfunction could also be due to the increased hemodynamic burden of pregnancy.

Normalization of LV function after PPCM does not guarantee an uncomplicated SSP; approximately 20% of such patients are also at risk of moderate to severe deterioration of LV function, which persists after delivery in 20% to 50% of patients (10,13,14,19,21,22) (Table 4). Although the likelihood of maternal death seems to be low in women with recovered LV function, relapse of PPCM may be associated with a substantial, and at times, persistent reduction in EF, potentially leading to life-threatening complications that include cardiogenic shock and arrhythmias. These conditions require aggressive therapy, including electrical cardioversion, temporary LV assist devices, implantable cardioverter defibrillation implantation, and prolonged hospitalization (Table 4) (10,11,14,19,20,22).

The mortality rate, even in women with persistent LV dysfunction before SSP, was reported to be low (0% to 0.5%) in 3 studies in the United States (14,16,17), but was as high as 25% in another U.S. study (10) and even higher in South African women (13,18). Although it is reasonable to assume that some of the previously reported incidences of mortality could be preventable with early detection and aggressive contemporary management of LV dysfunction (as was provided to the cases presented in Table 4), the risk of SSP-related death remains a major concern, especially in women with persistent LV dysfunction.

### Outcome in Patients With More Than 1 Subsequent Pregnancy

Chapa et al. (14) reported on 1 woman with persistent LV dysfunction (EF not provided) who had 3 SSPs...
without deterioration of LV function. Fett et al. (15) reported on 1 patient who had 2 SSPs with worsening HF that occurred after the second SSP, but not after the first SSP. The same investigators later reported on 3 women who had 2 SSPs, 1 of whom developed HF during the second pregnancy but not during the first pregnancy, and a second woman who had 3 SSPs with relapse only during the third pregnancy (19). Elkayam et al. reported on 11 women with 16 additional SSPs (10). Five women with normal LV function had 1 additional SSP each, and 4 had 2 additional SSPs. Of those with persistent LV dysfunction, 1 patient had 1 additional pregnancy, and 1 woman had 2 additional pregnancies. None of these women were reported to have symptoms of HF during the later pregnancies. One woman with normal LV function who showed no change in cardiac function during the first SSP had a substantial decrease in EF from 55% to 40% during the second pregnancy, and did not recover after a follow-up of 3 months. In summary, this limited information suggests that 1 uneventful SSP cannot predict the risk of later pregnancies in women with a history of PPCM.

**TERMINATION OF PREGNANCY**

In the study reported by Elkayam et al. (10), the mean LVEF decreased by 14% (49 ± 12% to 42 ± 14%; p < 0.001) in 35 women who did not have abortions compared with a decrease of only 7% in 9 women who had abortions (from 46 ± 13% to 43 ± 11%; p = 0.20). Another study (16) that analyzed the outcome of SSPs on the basis of the initial EF at the time of PPCM diagnosis, and had limited information on cardiac function before the SSP, reported worsening of cardiac symptoms related to pregnancy without abortion in 21% of 19 women with an initial EF >25% compared with what was described as, “No end stage cardiac disease,” in all 8 women who underwent early abortion. In cases with an initial EF of <25%, 2 patients who did not have an abortion were placed on the heart transplantation list, whereas only 5 of 8 women were listed for heart transplantation among those who underwent early abortion. Although these available data are limited by the small number of patients and lack of information regarding reasons for termination, and are not sufficient to establish firm conclusions, it seems that in patients with severe LV dysfunction, early termination of SSP may prevent further deterioration.

**FETAL OUTCOME**

Limited information is available regarding the fetal outcome of SSP in women with a history of PPCM. A survey by Ostrzega and Elkayam (9) reported 93% live births and 5% abortion rates in women with recovered LV function compared with 83% and 17%, respectively, in women with abnormal LV function. In the second survey by the Elkayam et al. (10), 21 of 35 women who did not have an abortion had normal vaginal delivery, and 14 women delivered by cesarean section. Premature delivery occurred in 13% of women with normal LV function before SSP and in 50% of patients with persistent LV dysfunction (Figure 4).

**CAN RELAPSE OF PERIPARTUM CARDIOMYOPATHY IN SUBSEQUENT PREGNANCY BE PREDICTED?**

Available information suggests that the best predictor for SSP-associated relapse is pre-pregnancy LVEF. A normal contractile reserve measured by exercise

<table>
<thead>
<tr>
<th>First Author (Ref. #)</th>
<th>Year</th>
<th>No. of Pregnancies</th>
<th>Deterioration of LV Function</th>
<th>Symptoms of Heart Failure</th>
<th>Persistently Decreased LVEF at Follow-Up</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elkayam (10)</td>
<td>2001</td>
<td>23</td>
<td>4 (17)</td>
<td>6 (20)</td>
<td>2 (50)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Avila (12)</td>
<td>2002</td>
<td>6</td>
<td>NA</td>
<td>0 (0)</td>
<td>NA</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Sliwa (13)</td>
<td>2004</td>
<td>2</td>
<td>2 (10)</td>
<td>2 (100)</td>
<td>2 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Chappa (14)</td>
<td>2005</td>
<td>4</td>
<td>4 (100)</td>
<td>4 (100)</td>
<td>3 (75)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Habli (16)</td>
<td>2008</td>
<td>21</td>
<td>NA</td>
<td>6 (28)</td>
<td>NA</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Chee (21)</td>
<td>2009</td>
<td>2</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Fett (19)*</td>
<td>2010</td>
<td>35</td>
<td>8 (17)</td>
<td>NA</td>
<td>1 (12)</td>
<td>-</td>
</tr>
<tr>
<td>Mandal (20)</td>
<td>2010</td>
<td>5</td>
<td>NA</td>
<td>2 (40)</td>
<td>1 (50)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>98</td>
<td>18/66 (27)</td>
<td>20/63 (32)</td>
<td>9/71 (13)</td>
<td>0/63 (0)</td>
</tr>
</tbody>
</table>

Values are n (%). *Most patients in this study were identified by an Internet support group of living patients with history of peripartum cardiomyopathy; mortality rate was therefore not available. Abbreviations as in Table 2.
Echocardiography was suggested as a potential predictor of a low likelihood of relapse in women with normal LV function. This suggestion was made on the basis of 8 women with recovered LVEF and normal cardiac response to exercise who did not relapse during SSP (19). However, this hypothesis was not tested because no patients with an abnormal response to exercise were included. Thus, this idea remains unproven and cannot be used to predict the outcome of SSP.

**MONITORING SUBSEQUENT PREGNANCY.** Because of lack of prospective data, there are no established protocols for monitoring women with SSP. My protocol includes a baseline echocardiogram and measurement of B-type natriuretic peptide levels before or in the early stages of SSP. This is followed by close monitoring of symptoms throughout pregnancy, with repeat echocardiograms at the end of the first and second trimester, as well as 1 month before delivery, before discharge, 1 month after delivery, and at any instance of symptom development. Echocardiographic assessment of cardiac function and pulmonary pressures, as well as measurement of B-type natriuretic peptide levels, are helpful in differentiating the signs and symptoms of HF from normal pregnancy symptoms, which may be confusing.

Because of the limited information on long-term outcomes in women with PPCM, no recommendations can be made regarding continuation of HF therapy in women with complete recovery of LV systolic function and the use of such therapy during SSP. Women who are taking HF medications should ideally discontinue teratogenic drugs, such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers at least 3 months before conception, and the LVEF without these medications should be re-evaluated before SSP. These drugs should be substituted for a combination of hydralazine and isosorbide dinitrate in women with LV systolic dysfunction (3). Aldosterone antagonists like spironolactone (category C) have no reported teratogenic effects in humans, but there is a concern regarding reported antiandrogenic effects leading to feminization in male rat fetuses and endocrine dysfunctions that persist into adulthood in both sexes (23,24). There is a lack of human pregnancy experience with beta-blockers used to treat HF (carvedilol, bisoprolol, and metoprolol succinate), which are all risk category C; their effects on the fetus is unknown. Metoprolol tartrate, which is also risk category C, may be preferred because it has been more commonly used in pregnancy for the management of hypertension, arrhythmias, mitral stenosis, and myocardial ischemia (25). In addition, because nonselective beta-blockade could facilitate uterine activity, the use of beta-1-selective beta-blockers is generally preferred during pregnancy (23).

Preliminary information suggests a potential beneficial effect of bromocriptine in women with SSP. Hilfiker-Kleiner et al. (18) reported on 6 women with SSP who received bromocriptine in addition to standard therapy up to 3 months post-delivery (time of initiation not provided), who were compared with 6 other women who received standard treatment alone. Although the peripartum LVEF was similar in both groups, all 6 women treated with bromocriptine survived and had preserved or increased LV function and decreased LV dimensions at the 4-month observation. In contrast, LVEF in the non-bromocriptine-treated group deteriorated, and 3 women died within 4 months. In addition, prolactin serum levels, which were elevated >5-fold, returned to nonpregnant levels within 14 days of treatment in women who received bromocriptine. Although this report is exciting, and is supported by animal studies and small-scale human studies (26), it is limited by the small number of patients evaluated and by the unusually high rate of cardiac deterioration and mortality found in women on standard HF therapy. More data will therefore be needed to further establish a potential role for bromocriptine in preventing the relapse that is associated with SSP.

**BREASTFEEDING.** No information is available regarding breastfeeding after SSP in women with a history of PPCM. However, 1 recent study reported...
breastfeeding in 67% of women who were diagnosed with PPCM without adverse effects (27). The American Academy of Pediatrics recommends human milk for all infants for whom breastfeeding is not contraindicated (28). For these reasons, clinically stable women with a history of PPCM are considered to be compatible with breastfeeding (28). For beta-blockers, however, no reports are available on the use of carvedilol or metoprolol succinate during human lactation; the use of metoprolol tartrate may be preferred (29). Although metoprolol is concentrated in breast milk, the amount of the drug is very small (225 mg in 1,000 ml for an oral dose of 200 mg/day). To further minimize exposure, it has been suggested to refrain from breastfeeding for 3 to 4 h after taking the last dose. Information is available on the use of both captopril and enalapril during human lactation; the amount of these drugs that could be ingested by the infant is negligible and most likely insignificant (29). The excretion rate of spironolactone in breast milk is unknown, and its active metabolite, candrenone, is found in a minute, clinically insignificant dose (0.2% of the mother’s daily dose) (29).

### SUMMARY AND CONCLUSIONS

Although information is somewhat limited, the available data strongly suggest that SSP in women with a history of PPCM is associated with a risk of relapse. This risk is high in women with persistent LV dysfunction before their SSP, who are also at risk of deterioration due to the increased hemodynamic burden of pregnancy. Almost 50% of such women were reported to have deterioration of LV function during or following pregnancy, potentially leading to major morbidity and even mortality. The available information also suggests an increased risk of premature delivery and abortions in women with persistent LV dysfunction. Complete recovery of LV function before the SSP is associated with better prognosis, and most women are likely to have a normal pregnancy. However, uneventful pregnancy is not guaranteed, and approximately 20% will have a relapse of PPCM associated with a substantial decrease in LV systolic function. Although the rate of recovery is relatively high and the incidence of mortality is low, relapse of PPCM, even in this group, may be associated with deterioration of LV function, congestive HF, arrhythmias, and the need for aggressive therapy, including the use of temporary and permanent devices (Table 2) (10,11,13,16,19). In addition, in some cases, the persistence of LV systolic dysfunction (10,13,14,19,21) may have detrimental long-term consequences. Although limited data suggest that PPCM relapse occurs in late pregnancy or in the PP period, earlier deterioration can also occur (11). Careful and close monitoring is therefore recommended throughout pregnancy and the PP period for the early detection and treatment of recurrent PPCM and prevention of complications (Central Illustration).

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