Peripartum cardiomyopathy (PPCM) is a pregnancy-associated myocardial disease, reported to occur in different parts of the world (1). The disease is heterogeneous and seems to have important phenotypic variations in different geographical regions; for this reason as well as differences in the availability and delivery of care, it is difficult to formulate uniform recommendations throughout different parts of the world. The purposes of this review are therefore to describe the clinical characteristics of PPCM in the United States and to provide recommendations for the diagnosis and treatment of this condition.

**Historical Perspective and Definition**

Heart failure (HF) associated with pregnancy was first described as a definitive form of cardiomyopathy in 1937 (2). In 1971, Demakis et al. (3) published data on 27 patients with pregnancy-associated cardiomyopathy who presented in the peripartum period. These investigators coined the term “peripartum cardiomyopathy” and defined diagnostic criteria on the basis of their patients’ characteristics and available diagnostic tools at the time. These criteria included: 1) the development of HF in the last month of pregnancy or within 5 months of delivery; 2) the absence of a determinable etiology for HF; and 3) the absence of demonstrable heart disease before the last month of pregnancy. A workshop organized by the National Heart, Lung, and Blood Institute and the Office of Rare Diseases Research in 1997 (4) added an additional criterion proposed by Hibbard et al. (5) of left ventricular (LV) systolic dysfunction demonstrated by echocardiography with left ventricular ejection fraction (LVEF) <45%, fractional shortening <30%, or both. Additional information has indicated that although the majority of patients with PPCM are diagnosed in the peripartum period (Fig. 1), early presentation during pregnancy is not uncommon (6,7). A recent study of 23 cases with pregnancy-associated cardiomyopathy diagnosed between the 17th and 36th weeks of gestation found them to be indistinguishable from 100 women meeting classic criteria for PPCM (8). These findings, supported by numerous other reports (6,9–15), clearly indicate that PPCM and pregnancy-associated cardiomyopathy represent a continuum of the same disease (7,8). A recent position statement from a European Society of Cardiology working group on PPCM has therefore expanded the definition of PPCM to “an idiopathic cardiomyopathy presenting with HF secondary to LV systolic dysfunction towards the end of pregnancy or in the months following delivery, where no other cause of heart failure is found” (16). The majority of patients who are diagnosed during pregnancy present in the third trimester, with a few in the second trimester (8).

PPCM is a diagnosis of exclusion, and other causes of cardiac dysfunction should be ruled out. At the same time, however, transient and unexpected depression of LV function typical to PPCM has been described in women with other forms of heart disease (6). These findings therefore
suggest that the diagnosis of PPCM should not be excluded in patients with heart disease, which is otherwise not likely to cause LV dysfunction during or after pregnancy.

Incidence

A number of recent studies have provided information regarding the incidence of PPCM in the United States, ranging from 1 in 1,149 to 1 in 4,350 live births (11,17–19), with a mean of 1 in 3,186 live births (Table 1). Differences in incidence among published reports are probably due to variations in patient populations but also study design, sample size, and degree of underreporting (20). Mielniczuk et al. (18) reported a trend toward an increase in incidence over time from 1 in 4,350 in 1990 to 1993 to 1 in 2,229 in 2000 to 2002 (Fig. 2). This suggested increase in the incidence of PPCM in the U.S. might be related to a rise in maternal age, a substantial increase in the rate of multifetal pregnancies due to contemporary reproductive techniques, and possibly to increased recognition of the disease. A population study in Southern California (19) found the greatest incidence of PPCM in African Americans (1 in 1,421) and the lowest in Hispanics (1 in 9,861). The incidence in Caucasians was 1 in 4,075 and in Asians was 1 in 2,675. Higher incidence in African American women has recently been confirmed by Gentry et al. (21), who conducted a case-control study in Augusta, Georgia, and Memphis Tennessee, and found almost a 16-fold higher incidence of PPCM in African American compared with non–African American women.

In summary, the incidence of PPCM in the U.S. seems to be increasing and is estimated to be approximately 1 in 3,200 deliveries, with a significantly higher incidence in African American women and possibly lower incidence in Hispanics compared with non–Hispanic whites. Because the number of live births in the United States is >4,300,000 per year (22), the estimated annual number of new patients with PPCM in the U.S. is approximately 1,350.

Etiology

The etiology of PPCM is still unknown, and many potential causes have been proposed but not proven (1,16,23). These include viral myocarditis, abnormal immune response to pregnancy, abnormal response to increased hemodynamic burden of pregnancy, hormonal abnormalities, malnutrition, inflammation, and apoptosis. Most recently, experimental work has suggested a novel and specific pathogenic mechanism by demonstrating the development of PPCM in female mice with a cardiomyocyte-specific deletion of the transcription factor signal transducer and activator of tran-
scription 3 (STAT3) protein (24). Absence of cardiomyocyte STAT3 in the postpartum heart resulted in increased oxidative stress secondary to blunted induction of the antioxidant enzyme manganese superoxide dismutase, leading to increased expression and proteolytic activity of cardiac cathepsin D and resulting in cleavage of the nursing hormone prolactin into an antiangiogenic and proapoptotic 16-kDa form with a detrimental effect on the myocardial microvasculature resulting in myocardial hypoxemia and apoptosis and the development of PPCM. Preliminary data in human demonstrating a favorable effect of bromocriptine, a pharmacological inhibitor of prolactin in a limited number of patients with PPCM (25).

**Associated Conditions**

Strong associations have been shown between PPCM and older maternal age, history of hypertension, multiple pregnancies, and African American background.  

**Age.** Although the disease has been reported in women between the ages of 16 and 44 years, the mean age of women with PPCM in the United States has ranged from 27 to 33 years (8,11,17–19) (Table 1), with >60% of patients reported in 1 study to be >30 years of age (8).

**Race.** PPCM in the United States has been reported to affect women of different ethnic groups, including non-Hispanic whites, African Americans, Hispanics, and Asians. However, the incidence of the disease seems to be considerably higher among African American patients (19,21).

**Hypertension.** Hypertension—chronic, pregnancy induced, or preeclampsia—has been described in 15% to 68% (mean 23%) of patients with PPCM in the United States (3,8,11,17,18,26,27), with a similar incidence reported in women diagnosed antepartum and postpartum (8). This incidence is considerably higher than the 8% reported in all pregnant patients (28,29). Symptoms of HF in patients with PPCM are often attributed to preeclampsia and hypertension in patients with both conditions, resulting in a delay of PPCM diagnosis and treatment. Although one can argue that LV dysfunction is not truly “idiopathic” in the setting of severe hypertension, chronic hypertension is not likely to cause marked LV systolic dysfunction in young women, and hypertensive pulmonary edema is due mostly to exacerbation of diastolic dysfunction by hypertension, not to transient systolic dysfunction (31). In fact, assessment of systolic LV function in pregnant women with hypertension by a number of investigators has shown it to be preserved (32–34). Preeclampsia can also present with signs and symptoms of HF, but systolic function is usually preserved or even improved (33,35–37). For all these reasons, as well as similar rates of LV recovery in patients with PPCM with and without histories of gestational hypertension (38), the latter does not seem to be a cause of LV systolic dysfunction but a strong associated condition to PPCM. Because brain natriuretic peptide (BNP) levels are only mildly elevated (36,39,40) in patients with preeclampsia, echocardiographic evaluation and measurement of BNP levels are advisable for the early diagnosis of PPCM in patients with preeclampsia who are suspected of having HF.

**Multifetal pregnancies.** Multiple births have been reported in 7% to 14.5% of patients with PPCM in the United States (3,17,26,27,38), compared with only 3% in...
the overall population (41), confirming a strong association between multifetal pregnancies and the development of PPCM.

**Parity.** Multiparity has been traditionally considered to be a risk factor for PPCM (1). However, most studies in the United States have reported the development of PPCM in conjunction with the first or second pregnancy in >50% of patients (8,17,26,27). Therefore, these data do not support a strong association between multiparity and PPCM in the United States.

**Genetics of Peripartum Cardiomyopathy**

PPCM has been classified as a nongenetic form of dilated cardiomyopathy (DCM) (10). However, a number of studies have reported familial clustering (42–45). Morales et al. (9) recently performed a systematic search of 110 women from 520 families of patients with nonischemic DCM and identified 45 patients with PPCM. Nineteen of the patients had been sequenced for genes known to be associated with DCM. This observation was further supported by a European study that found PPCM in 6% of 90 families with DCM (10). Screening of first-degree relatives of 3 patients with PPCM with persistent LV dysfunction revealed undiagnosed DCM in all 3 families. Furthermore, genetic analyses showed a mutation in the gene encoding cardiac troponin C (TNNC1) in 1 DCM family with members with PPCM. These findings may suggest that in a proportion of patients, PPCM is due to genetic causes (7) or represents cases of familial DCM that was unmasked or first recognized in pregnancy.

**Clinical Presentation**

Many of the signs and symptoms of normal pregnancy are similar to those of HF; for this reason, and because of the low incidence of this condition, the diagnosis of PPCM is often missed or delayed, allowing the development of preventable complications (15,30). Most patients present with typical signs and symptoms of HF, including dyspnea and orthopnea (6,17); in addition, cough, chest pain, and abdominal pain are frequently encountered and tend to confuse the initial clinical evaluation (6). Physical examination often reveals tachycardia and tachypnea, blood pressure may be elevated or reduced, and patients are often not able to lie down flat because of shortness of breath. There is usually increased jugular venous pressure, displaced apical impulse, right ventricular heave, murmurs of mitral and tricuspid regurgitation, third heart sound, pulmonary rales, and peripheral edema. Electrocardiography usually shows sinus tachycardia with nonspecific ST-T wave changes. LV hypertrophy can be found as well as left atrial enlargement and, occasionally, conduction abnormalities including left bundle branch block (11). Chest radiography usually shows cardiomegaly and pulmonary venous congestion or pulmonary edema, with or without pleural effusion (11,46). Echocardiography shows variable degrees of LV dilatation, with moderate to severe depression of systolic function. Right ventricular and biastral dilatation as well as moderate to severe mitral and tricuspid regurgitation are commonly seen, with increased pulmonary pressures and mild pulmonary regurgitation (5,8,11,17,46). Cardiac magnetic resonance imaging (MRI) has been used in a limited number of patients for the assessment of cardiac function and the detection of mural thrombi or myocardial fibrosis (25,48–51). Although MRI is probably safe during pregnancy (52,53), intravenous gadolinium crosses the placenta, and the 2007 American College of Radiology document on safe MRI practices recommends that it be avoided during pregnancy and used only if absolutely essential (53). Although only 0.04% of the maternal dose of gadolinium passes into the breast milk, it has been recommended to discontinue breast-feeding for 24 h after intravenous administration (53). In a group of 8 women with PPCM who were studied with MRI, none exhibited abnormal myocardial late enhancement, and no difference was found in the MRI patterns in 4 patients who recovered normal LV function compared with those who did not (47).

**Brain natriuretic peptide.** Levels of BNP do not change significantly during normal pregnancy or in the postpartum period (36,40,54,55). An early measurement of BNP could help in diagnosing PPCM, in which levels of BNP have been shown to be markedly elevated (56).

**Prognosis**

**Recovery of LV function.** Recent publications combining close to 300 U.S. patients have reported recovery of LV function (LVEF to ≥50%) at 6 months in 45% to 78% of patients, with a mean of 54% (26,27,30). Data from my group (8) in 40 patients with longitudinal follow-up of 30 ± 29 months showed that improvement usually occurred within the first 6 months after the diagnosis (Fig. 3).

![Figure 3 Pattern of Recovery of Left Ventricular Function in 40 Patients With PPCM](image)

There was a significant increase in left ventricular ejection fraction (LVEF) between time of diagnosis and 6 months (*p < 0.0001), with only a small and statistically insignificant further increase after 6 months. F/U = follow-up. Adapted from Elkayam et al. (8).
et al. (26) demonstrated LV recovery in 45% of 55 women, mostly occurring within the first 2 months, with continued improvement over 1 year (Fig. 4). Most recently, a preliminary report from a Utah PPCM registry described LV recovery in 62% of 58 patients, with an average time of 9 months (57). In contrast, Modi et al. (58) reported recovery of LV function in only 35% of 40 indigent patients, with a median time to recovery of 54 months. Because 87.5% of the patients in this group were African Americans, the investigators suggested that race and ethnicity might be responsible for poorer outcomes. This assumption is supported by a recent analysis by my group demonstrating a significantly lower rate of LV recovery in 52 African American patients compared with 104 Caucasians (40% vs. 61%, p = 0.02; Elkayam et al., unpublished data, 2011). In summary, the majority of available information in the U.S. demonstrates normalization of LV function in >50% of women with PPCM, mostly occurring within 2 to 6 months after diagnosis; later recovery, however, is possible and occurs in some patients. The rate of LV recovery seems to be significantly lower in African American patients compared with whites. More information will be needed to determine potential genetic and environmental causes for this difference.

**Predictors of LV recovery.** A number of factors have been shown to be associated with a higher likelihood of recovery, including LV diastolic dimension (<5.5 to 6.0 cm) and systolic function (LVEF >30% to 35% and fractional shortening ≥20%) at the time of diagnosis (5,11,17,27), lack of troponin elevation (59), a lower level of plasma BNP (56), absence of LV thrombus (26), breast-feeding (27), diagnosis after the delivery (27), and non-African American ethnicity (30). Recent multivariate analysis by Goland et al. in 187 patients with PPCM (38) found LVEF >30% and LV end-diastolic dimension <55 mm to be significantly related to LV recovery, suggesting a relationship between the degree of initial myocardial insult and recovery. These parameters, however, have limited sensitivity in predicting recovery in individual patients, as evidenced by full recovery found in 37% of patients with baseline LVEFs <20% and in 51% of those with LVEFs <30%. Baseline parameters of LV function should therefore not be used as an indication for the premature use of devices or heart transplantation.

Is LV recovery related to medical therapy? The relationship between standard HF therapy and recovery is not completely clear. The rates of recovery in early studies, before the era of contemporary HF therapy (3,60), were similar to rates reported in recent studies, and early recovery often occurred before up-titration of drugs to optimal therapeutic doses (26). In addition, similar to nonischemic DCM (61), preliminary reports have shown no significant difference in the use of beta-blockers in recovered compared with nonrecovered patients with PPCM (62,63).

**Complications**

PPCM can be associated with important and lasting complications, including severe HF, cardiogenic shock, cardiopulmonary arrest secondary to HF or arrhythmias, thromboembolic complications, and death. Goland et al. (30) recently described major adverse events in 25% of 182 patients with PPCM, with 80% of these occurring during the first 6 months after the diagnosis and one-third of the survivors having residual brain damage secondary to cardiopulmonary arrest or cerebral vascular events. Predictors of complications were LVEF <25%, non-Caucasian ethnic background, and delay of diagnosis.

**Thromboembolism.** PPCM is associated with increased incidence of thromboembolism compared with DCM of other etiologies, and LV thrombus has been found on initial echocardiography in 10% to 17% of patients (26,64). Several reports have described severe thromboembolic events, including embolization to the coronary, pulmonary, peripheral, and cerebral arteries (11,26,30,64–70). Increased incidence of thromboembolism is probably due to multiple reasons, including the hypercoagulable state of pregnancy (71), cardiac dilatation and dysfunction, endothelial injury, venous stasis, and prolonged bed rest after commonly performed instrumental deliveries and cesarean section in patients diagnosed during pregnancy.

**Mortality and heart transplantation.** Reported mortality rates associated with PPCM in the United States have varied widely between 0% and 19%, while rates of cardiac transplantation have ranged from 6% to 11% (11,17–19,26,30,58,72) (Table 2). Substantial differences in the reported
incidence of these complications are probably due to variations in patient populations, diagnostic criteria, and treatments, as well as reporting bias. Felker et al. (72), in a retrospective review of cardiomyopathies of various etiologies, reported markedly lower mortality in PPCM compared with other forms of myocardial disease. At the same time, however, PPCM has become an increasingly recognized cause of pregnancy-related maternal mortality (73,74).

Timing and mode of death. Goland et al. (30) provided detailed information regarding mortality in 13 patients, most of whom died either suddenly (38%) or of progressive HF (45%) between the day of delivery and 8 years postpartum. Whitehead et al. (74) reported on 17 cases of death due to PPCM between 1991 and 1997. Mortality increased with maternal age, in women with live birth order of ≥4, and in black women, who were 6.4 times more likely to die compared with whites. Eighteen percent of deaths occurred within 1 week and 87% within 6 months of diagnosis (Fig. 5), and mortality was due either to progressive HF or to sudden cardiac death. Mortality was found by Goland et al. (30) to be higher in women with baseline LVEFs <25% as well as in women in whom the diagnosis of PPCM was delayed.

### Outcome of Subsequent Pregnancy

Habli et al. (75) reported on 21 patients with a mean LVEF >40% who had subsequent pregnancy, with worsening of HF in 29% and in none of 8 other patients who terminated their subsequent pregnancies. Two patients with initial LVEFs <25% (follow-up LVEFs not provided) who had subsequent pregnancy and 5 of 8 women who terminated their pregnancies demonstrated clinical deterioration requiring referral for cardiac transplantation.

Modi et al. (58) described 44 indigent patients with PPCM and reported clinical worsening in 28% of those who had subsequent pregnancies (number of patients not provided) but no maternal death. Elkayam et al. (76) reported on the outcomes of 60 subsequent pregnancies in 44 women, 28 after recovery of LV function (group 1) and 16 with LV dysfunction (group 2). Subsequent pregnancies were associated with reductions in mean LVEF in the total

![Figure 5 Timing of Mortality After Diagnosis in Patients With PPCM](image-url)
creases in LV function have been reported in approximately 20% of patients, with persisting dysfunction after pregnancy in about one-half (76,79). Patients should be advised on the risk of subsequent pregnancy and on the safest and most effective contraceptive method by both their cardiologists and obstetricians (80). Patients who decide to become pregnant again should undergo baseline echocardiography before or early in pregnancy, as well as determination of serum BNP level. In patients on HF medications, baseline LVEF prior to subsequent pregnancy should be determined 3 months after the discontinuation of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), which cannot be used during pregnancy. In patients with LV dysfunction, ACE inhibitors or ARBs should be substituted with isosorbide dinitrate-hydralazine combination. Because no information is available regarding the safety of carvedilol during pregnancy, the use of metoprolol may be considered instead. Patients should be followed with repeat echocardiography during the early second and third trimesters, during the last gestational month, and early after delivery and at any time if new symptoms of HF develop. Repeat determination of BNP levels should be helpful in differentiating between HF-like symptoms associated with normal pregnancy and hemodynamic deterioration (55,56). Early termination of an unintentional pregnancy should be considered to prevent worsening of LV function and potential maternal mortality, especially in patients with persistent LV dysfunction.

Breast-Feeding

Breast milk is associated with health, nutritional, immunologic, physical, cognitive, and emotional developmental benefits to the infant (81). The American Academy of Pediatrics recommends human milk for all infants in whom breast-feeding is not specifically contraindicated. As shown in the following paragraphs, most drugs used for the management of HF are compatible with breast-feeding; in addition, a recent study reported breast-feeding in 67% of 55 patients with PPCM without adverse effects to the mothers (27). Moreover, the rate of recovery of LV function was significantly higher in lactating women. For all these reasons, clinically stable women with PPCM should not be discouraged from breast-feeding their infants.

Treatment

Drugs. Standard drug therapy for acute and chronic HF includes the potential use of diuretic agents, intravenous and oral vasodilators, intravenous inotropes, ACE inhibitors or ARBs, beta-blockers, spironolactone, and digoxin (82). In general, the treatment of HF in patients with PPCM should follow recent guideline recommendations, except during pregnancy and lactation, when drug therapy may need to be altered because of potential detrimental effects on the fetus or the lactating infant.

Diuretic agents. Loop diuretic agents are indicated for the correction of volume overload and excessive and rapid reductions in intravascular volume, but they should be used...
with caution during pregnancy to prevent hypotension and decreased uterine perfusion. Furosemide (risk category C) is excreted into breast milk, but no reports of adverse effects in nursing infants have been found, and it is listed as probably compatible with breast-feeding (83).

**Intravenous vasoactive medications.** Vasodilators are recommended in patients with decompensated HF for hemodynamic and symptomatic improvement (82). Among the available intravenous vasodilators, nitroglycerin (risk category B) is preferred during pregnancy because nitroprusside (risk category C) may be associated with thiocyanate toxicity, and no information is available regarding the safety of nesiritide. There are only limited data regarding the use of inotropic agents, including dopamine (risk category C), dobutamine (risk category B), and milrinone (risk category C), and these drugs should therefore be used as recommended (82) only in patients with advanced HF, low blood pressure, high filling pressure, and diminished peripheral perfusion due to low-output syndrome and in patients who are unresponsive or intolerant to intravenous vasodilators.

**ACE inhibitors and ARBs.** The use of these drugs (both risk category C) is contraindicated during pregnancy because of toxic effects, mostly on the developing fetal kidneys. Other potential side effects include oligohydramnios, intrauterine growth retardation, prematurity, bony malformation, limb contractures, patent ductus arteriosus, pulmonary hypoplasia, respiratory distress syndrome, hypotension, anuria, and neonatal death (84). During pregnancy, the combination of organic nitrates and hydralazine (both risk category C) should be used as a substitute for ACE inhibitors or ARBs.

**Beta-blockers.** There is lack of human pregnancy experience with the use of all 3 beta-blockers approved in the U.S. for the treatment of HF (carvedilol, bisoprolol, and metoprolol succinate, all risk category C), and their effects on the fetus are therefore unknown. Metoprolol tartrate has been more commonly used in pregnancy for the management of hypertension, arrhythmias, mitral stenosis, and myocardial ischemia (85). In addition, the use of beta-1-selective beta-blockers is preferred during pregnancy, because nonselective beta-blockade could facilitate uterine activity (85). Carvedilol and bisoprolol are excreted into the breast milk of lactating rats; no information is available on their use in lactating women (83). Metoprolol is secreted into breast milk, with a milk/plasma concentration ratio of 2 to 4, but the amount of drug estimated to be ingested by the infant is negligible, and the drug has been classified as compatible with breast-feeding (86).

**Spironolactone (risk category C).** There is no report of a teratogenic effect in humans, but there is concern regarding the antiandrogenic effect of the drug in humans and feminization reported in male rat fetuses (83). The rate of excretion of spironolactone in breast milk is unknown. Its principal metabolite, canrenone, is excreted into breast milk in a small amount (approximately 0.2% of the mother’s daily dose), which seems to be insignificant (83). The American Academy of Pediatrics (86) classifies spironolactone as compatible with breast-feeding.

**Digoxin (risk category C).** This drug has been used in pregnancy for both maternal and fetal indications without causing fetal harm. It is excreted into breast milk, but no adverse effects have been reported, and the drug is compatible with breast-feeding (86).

**Anticoagulation.** Because of the high incidence of thromboembolism associated with PPCM (26,64–70), anticoagulation from the time of the diagnosis until LV function recovers (LVEF >35%) is advisable. Anticoagulation seems particularly important during pregnancy and the first 6 to 8 weeks postpartum because of persistent hypercoagulable state (71). In contrast to warfarin (risk factor D), both unfractionated heparin and low-molecular-weight heparin (risk factor C) do not cross the placenta and are safe during pregnancy (83). Because of a high prevalence of premature labor and a possible need for urgent delivery because of maternal or fetal instability, the use of unfractionated heparin is preferred during pregnancy because of its shorter half-life and reversible effect. Neither warfarin nor heparin is secreted into breast milk, and both drugs are therefore compatible with breast-feeding (83).

**Experimental drug therapy.** **IMMUNE GLOBULIN.** Bozkurt et al. (87) added intravenous immune globulin to conventional HF therapy in 6 women with PPCM and reported a significantly greater improvement in LVEFs compared with 11 historical control patients who received conventional therapy alone. Although the results seemed encouraging, a very small number of patients and the lack of a blindly randomized, well-matched control group limited the study.

**PENTOXIFYLLINE.** Sliwa et al. (88) investigated the effect of pentoxifylline, a xanthine agent known to inhibit the production of tumor necrosis factor and prevent apoptosis, in 30 South African patients with PPCM. These patients received the drug at a dose of 400 mg 3 times daily for 6 months in addition to standard HF therapy and were compared with 29 patients with PPCM who received standard therapy alone. The results of the study demonstrated a significant improvement in a combined endpoint including death, failure to improve LVEF by 10 absolute points, or persistence of New York Heart Association functional class III to IV at the last follow-up (52% vs. 27%, p = 0.03). Despite these positive results, no further studies have been conducted, and this therapy has not been widely used. In addition, the safety of pentoxifylline during pregnancy and lactation has not been established; it is excreted into human milk and has been defined as probably compatible with breast-feeding (83).

**BROMOCRIPTINE.** On the basis of the concept of enhanced oxidative stress–mediated cleavage of the nursing hormone prolactin into an antiangiogenic and proapoptotic 16-kDa form that may be responsible for the development of PPCM (24), Sliwa et al. (25) attempted the use of bromocriptine, a prolactin blocker, in the treatment of 10 African patients.
with PPCM. The drug was given after diagnosis at a dose of 2.5 mg twice daily for 2 weeks, followed by 2.5 mg/day for 6 weeks, in addition to standard HF therapy and resulted in a significantly larger rate of LV recovery at 6 months compared with a control group of 10 women with PPCM treated with standard therapy alone (31% vs. 9%, p = 0.012). In addition, there was a lower rate of mortality in the treatment group (1 vs. 4 patients) and a lower rate of a combined endpoint of death, New York Heart Association functional class III or IV, or LVEF <35% at 6 months. Although the results are intriguing, the study suffered from important limitations, including a very small number of patients, excessive mortality and a lower recovery rate in the control group compared with rates reported in the United States and even previously by the same investigators in South Africa (89). In addition, the use of bromocriptine is associated with suppression of breast milk production and potential complications to the mother (90), and its approval for the prevention of lactation was withdrawn by the U.S. Food and Drug Administration for safety concerns (91). For all these reasons, further studies aimed at clearly establishing the efficacy and safety of bromocriptine are needed before it can be recommended for the treatment of PPCM.

Should drug therapy be stopped in women with PPCM after recovery? This is a commonly asked question by patients with PPCM who are eager to stop taking medications after recovery. Because only limited long-term, prospective data are available, no recommendations can be made. Amos et al. (26) reported a lack of deterioration of LV function during an average follow-up period of 29 months in 15 patients with full recovery who stopped taking ACE inhibitors, beta-blockers (n = 11), or both (n = 5). When discontinuation of drug therapy is desired, it should be done gradually, with repeated echocardiographic evaluations of cardiac function. Because the spontaneous deterioration of LV function was reported by my group in 3 patients after either complete recovery (n = 2) or partial (LVEF 45%) recovery (n = 1) 3 to 60 months after diagnosis (30), annual echocardiographic examinations are advisable in all patients with histories of PPCM.

Implantable cardioverter-defibrillators. Because early sudden death is likely in high-risk patients (8,30,74) and arrhythmias are common in the postpartum period (92), it is often tempting to consider the early implantation of implantable cardioverter-defibrillators (ICDs) in such cases. Recent guidelines, however, recommend consideration of ICDs only in patients with persistent LV dysfunction despite optimal drug therapy. These recommendations are especially applicable to patients with PPCM, in whom the improvement of LV function is likely, and failure to improve cannot be predicted in individual patients on the basis of initial LV function (38). For these reasons, and because recovery of LV function occurs in most patients within 2 to 6 months after the diagnosis (8,26), it may be advisable to consider the temporary use of wearable external defibrillators (93) or entirely subcutaneous ICDs (94) in high-risk patients as a bridge to recovery or to ICD implantation in patients with persistent LV dysfunction despite adequate trials of optimal medical therapy.

Cardiac assist devices. In patients demonstrating rapid deterioration not responding to medical therapy including vasoactive medications, intra-aortic balloon pumps, extracorporeal membrane oxygenation, and LV assist devices have been used successfully and should be considered (95–101). Because the rate of recovery in patients with PPCM is higher than in those with other forms of DCM, an attempt should be made to use such devices as a bridge to recovery before referral for cardiac transplantation (98,100,101).

Cardiac transplantation. This procedure has been performed successfully in patients with PPCM (102–104). A recent multi-institutional study by Rasmusson et al. (105) using data from a cardiac transplantation research database described 69 women who underwent heart transplantation for PPCM in 29 institutions in the United States. The risk for rejection was somewhat higher in patients with PPCM compared with men or women of similar age who did not have history of pregnancies and similar to that of women with histories of pregnancy. The cumulative risk for infections was lowest in patients with PPCM, while freedom from allograft vasculopathy and mortality was similar or higher compared with the other groups. These data indicate, therefore, that the overall outcome of heart transplantation in women with PPCM is comparable with that of transplantation for other reasons.

**Labor and Delivery**

The timing and mode of delivery in a patient diagnosed during pregnancy should be determined by the clinical status of the mother and the fetus. Termination of pregnancy or early delivery may result in improvement of both symptoms and cardiac function and should be considered in patients with deteriorating symptoms or cardiac function. Continuation of pregnancy can be allowed, with frequent monitoring, to allow fetal maturity in patients who can be stabilized on medical therapy. The mode of delivery in a stable patient with PPCM should be determined jointly by the obstetrician and the cardiologist. Vaginal delivery prevents potential risks associated with anesthesia and surgical delivery that include hemodynamic fluctuations, larger blood loss, pain, infections, respiratory and thromboembolic complications, damage to pelvic organs, and potential unfavorable effects on future reproductive health (106). At the same time, an elective cesarean section is more rapid and allows better planning of the time of delivery as well as the presence of the most experienced medical team during the delivery. Hemodynamic monitoring for labor and delivery is desirable in a patient with PPCM who is diagnosed during pregnancy and allows optimization of hemodynamic status before delivery as well as monitoring of changes related to fluid intake and blood loss during delivery and early hemo-
dynamic changes as a result of increased venous return and peripheral vascular resistance after delivery. In case of vaginal delivery, assisted second stage is recommended to reduce maternal efforts and shorten labor. Maternal vital signs as well as oxygen saturation, electrocardiogram, and fetal heart rate should be continuously monitored.

Ongoing Research

The IPAC (Investigation in Pregnancy Associated Cardiomyopathy) study is currently under way in the United States (107). This is a National Institutes of Health–sponsored multicenter study and the first prospective trial in the United States aiming to enroll 100 patients with newly diagnosed PPCM and evaluate systemic immune activation as the etiology of this disease and the relationship between autoimmune and LV dysfunction and recovery and in addition investigate the frequency of myocardial injury or inflammation on cardiac MRI and the ability of tissue characteristics to predict subsequent recovery of LVEF.

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