Peripartum Cardiomyopathy: Balancing Heart Failure and Motherhood

Mark H. Drazner, M.D., M.Sc.

Internal Medicine Grand Rounds
University of Texas Southwestern Medical Center
Dallas, Texas

November 13, 2003

Disclosure Statement: This is to acknowledge that Mark Drazner, MD, MSc has disclosed a financial interest or other relationships with commercial concerns related directly or indirectly to this program. Dr. Drazner will be discussing "off-label" uses in his presentation.

Biographical Information

Mark Drazner, M.D., M.Sc.
Associate Professor
Department of Internal Medicine
Division of Cardiology

Interests:

Left ventricular hypertrophy
Heart failure
Cardiac transplantation
Genetics of cardiac hypertrophy and failure

Heart failure is a syndrome that is associated with substantial morbidity and mortality. Although it can be devastating to any patient, perhaps no greater tragedy is when it affects a young woman as a result of pregnancy, an entity entitled peripartum cardiomyopathy. Caring for a new baby can be demanding under the best of circumstances. Consider for a moment the strain imposed on the family by the development of symptomatic heart failure in this setting – both in the sense of the physical limitations that impair the mother's ability to help care for her child, as well as the psychological impact of learning that she has a potentially fatal illness.

This review will highlight our present understanding of the diagnosis, epidemiology, natural history, etiology, and treatment of peripartum cardiomyopathy.

I. Diagnosis

Although pregnancy-associated heart failure was described in the1800s (1), investigators reporting two case-series in 1937 are credited with recognizing peripartum cardiomyopathy as a distinct clinical entity (2,3). Formal diagnostic criteria for this disorder were proposed in 1971 (4) (see Table 1, criteria 1 – 3). More recently, a fourth criterion based on demonstration of depressed left ventricular systolic function (Table 1, point 4) has been proposed (5,6). Some believe left ventricular chamber dilation (increased left ventricular end-diastolic dimension of > 2.7 cm/m^2) (6) should be demonstrated as well.

Table 1. Diagnostic Criteria for Peripartum Cardiomyopathy

1. Heart failure develops in the last month of pregnancy or first 5 months after delivery.
2. No other identifiable cause of heart failure.
3. No demonstrable heart disease prior to last month of pregnancy.
4. Depressed left ventricular ejection fraction (<45%) or fractional shortening (<30%)

The importance of restricting this diagnosis to women who develop heart failure in the last month of pregnancy or 5 months after delivery was emphasized by a recent National Heart and Lung Blood Institute Workshop panel. This time-frame restriction is an attempt to avoid misdiagnosing women with an antecedent cardiomyopathy, who may have clinical deterioration secondary to the hemodynamic alterations of the gravid state, as having peripartum cardiomyopathy (5). The majority of the hemodynamic alterations of pregnancy, including an increase in plasma volume, cardiac output, and heart rate, occur before the last month of pregnancy (7). Thus, it is believed that women with previously undiagnosed or asymptomatic left ventricular dysfunction would develop symptoms prior to the last month of pregnancy.

As with all patients, other potential etiologies of heart failure and/or depressed left ventricular systolic function should be considered including anemia, hypo- or hyperthyroidism, and unrecognized valvular abnormalities. Similarly, peripartum myocardial infarction, either due to coronary dissection, vasospasm, or epicardial

atherosclerotic disease (8) and anomalous origin of the left main coronary artery (9) may mimic peripartum cardiomyopathy. Cardiomyopathies such as arrhythmogenic right ventricular dysplasia (10) or sarcoid (11) can masquerade as peripartum cardiomyopathy and should remain in the differential diagnosis. Other pregnancy-related clinical entities such as preeclampsia, sepsis, pulmonary or amniotic fluid embolism (6), noncardiogenic pulmonary edema (12), and iatrogenic volume overload in the setting of obstetrical hemorrhage (12) need to be considered as well.

A more difficult component to making this diagnosis, however, is recognizing the syndrome of heart failure in a woman near-term. In the last month of pregnancy, many women are dyspneic, fatigued, orthopneic, and may have edema. The presence of a third heart sound may occur in the absence of heart failure (13).To my knowledge, the utility of B-type natriuretic peptide (BNP), a neurohormone approved by the FDA for the diagnosis of heart failure in the acutely dyspneic patient (14), as a diagnostic biomarker in this specific setting has not yet been reported. Its utility may be hampered by the normal rise of BNP levels (a doubling) in normal pregnancy (15) and by the low prevalence of peripartum cardiomyopathy.

Given all of these above difficulties, it is not surprising then that the diagnosis of peripartum cardiomyopathy is often made in the postpartum period (1,12,16,17), when the expected improvements in functional status of the mother are not realized or when there is further clinical deterioration.

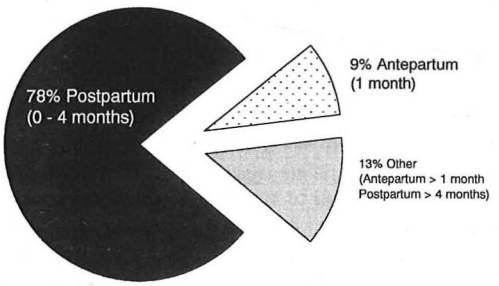

Figure 1. Timing of presentation of peripartum cardiomyopathy. Data gathered from 13 studies of 419 patients with peripartum cardiomyopathy. From reference (17)

Clinical presentation

The presentation of peripartum cardiomyopathy is similar to patients with idiopathic dilated cardiomyopathy and thus will be well recognized, saving for the complicating feature of overlapping symptoms (dyspnea, fatigue, and edema) of pregnancy in otherwise healthy women. Most patients with peripartum cardiomyopathy will have symptoms related to elevated filling pressures and/or low cardiac index including dyspnea, cough, orthopnea, paroxysmal nocturnal dyspnea, peripheral edema,

fatigue, and gastrointestinal symptoms. Many patients will have chest pain. **A particularly high incidence of thromboembolism has been noted** (e.g., 25% (18)) and hemoptysis should raise the specter of pulmonary embolism. Physical examination, electrocardiography, chest radiography, and echocardiography will have comparable findings to a patient with an idiopathic dilated cardiomyopathy, except perhaps for a higher rate of ventricular mural thrombi in this disorder (13,17,19).

II. Epidemiology

A. *Incidence*

Peripartum cardiomyopathy is a rare disease. Its incidence is estimated to be between 1 per 1,300 to 1 per 15,000 live births, with a consensus of between 1 per 3000-4000 live births (5). Reassuringly, two recent reports found a similar incidence of echocardiographically-confirmed peripartum cardiomyopathy in disparate clinical settings. The first was from the E. H. Crump Women's Hospital of the University of Tennessee, Memphis which serves predominantly African-American obstetrical patients. Between 1986 and 1994, 28 of 68,369 deliveries were associated with peripartum cardiomyopathy (1 per 2,406) (16). The second report was from the Central Baptist Hospital in Lexington, Kentucky which serves predominantly white patients (20). In their experience, 11 of 22,579 deliveries (1 per 2,053) between 1992 and 1998 were associated with peripartum cardiomyopathy. Extrapolating these data to the United States, it would be expected that 1000 – 2000 women annually develop peripartum cardiomyopathy.

The lowest estimate of the incidence of peripartum cardiomyopathy (1 per 15,000) is from Dr. Cunningham's frequently cited report summarizing the experience at Parkland Memorial Hospital between 1973 and 1984 (12). Although 28 cases of peripartum heart failure were identified from more than 106,000 deliveries (1 per 3,800 deliveries), 21 of these cases had clinical states such as hypertension, morbid obesity, and mitral stenosis that were felt to contribute to the heart failure. Excluding those cases led to the aforementioned incidence of 1 per 15,000. These data emphasize the need for close evaluation of women with potential peripartum cardiomyopathy before assigning this diagnosis. They also highlight some lack of clarity in the literature about whether to consider hypertension as an identifiable cause of cardiac failure, and thereby reserve the diagnosis of peripartum cardiomyopathy to non-hypertensive patients.

Despite the relatively low incidence of peripartum cardiomyopathy, cardiomyopathy remains an important cause of maternal mortality. Of all maternal deaths (pregnancy related mortality ratio: 13.2 per 100,000 live births in 1999), 9% are now attributed to cardiomyopathy. This is in contrast to the estimate of <4% in 1979-1986 (21,22), suggesting that the proportion of maternal deaths attributed to cardiomyopathy is increasing.

B. *Special populations*

Two populations that have an unusually high prevalence of peripartum heart failure warrant specific mention. In the late 1970s, it was reported from the Ahmadu Bellow University Hospital, located in Zaria in northern Nigeria, that approximately 1%

of deliveries among Hausa-Fulani women were followed by heart failure, an incidence at least 10-fold higher than any previously reported (23). Interestingly, despite a relatively constant delivery frequency throughout the year, there was an association of peripartum heart failure with the months of June through October which comprise the hot, humid, rainy season in this locale. Furthermore, it became apparent that this syndrome was associated with a particular cultural practice:

"For 40 days or more after delivery, the traditional Hausa mother does not leave her compound and lies twice daily for hours on a baked mud bed over a fire, which makes her hut very hot, splashes herself with scalding hot water, and eats highly spiced food and a pap laced with *kanwa*, a dried lake-salt" (from reference (24)).

A subsequent echocardiographic study from this hospital showed that the majority of such patients had relatively preserved ejection fraction and in those who underwent right-sided heart catheterization, a normal to high cardiac output (25). Thus, it was felt that this syndrome represented primary volume overload, in some way related to the exposure to heat and excessive sodium intake from *kanwa* ingestion, rather than a true cardiomyopathy.

More recently, it has been reported that the incidence of peripartum cardiomyopathy in the Hospital Albert Schweitzer, located in west central Haiti, is 1 per 400 live births (26), a rate 5-10 fold higher than seen in the United States. An ongoing epidemiological investigation (the HAS PPCM Project) is attempting to elucidate the basis for this observation (27).

C. *Risk factors for peripartum cardiomyopathy*

Risk factors for the development of peripartum cardiomyopathy have been identified by comparing baseline characteristics of women with this entity to those who do not develop cardiomyopathy following pregnancy.

Table 2. Risk Factors for Developing Peripartum Cardiomyopathy.

1. Older age (1,4,18,28)
2. Greater parity (1,4,18,28,29)
3. Multifetal pregnancy (1,4,30)
4. African-American ethnicity (1,18)
5. Chronic hypertension (12) or gestational hypertension/preeclampsia
6. Cocaine (31)
7. Prolonged tocolytic therapy (32)
8. Family history of peripartum cardiomyopathy (29,33-35)

D. *Is peripartum cardiomyopathy different than (occult) idiopathic dilated cardiomyopathy?*

An important question is whether peripartum cardiomyopathy is a different clinical entity than dilated cardiomyopathy. There is general agreement that this is the case (5) based on several observations. First, the frequency of peripartum

cardiomyopathy is said to be higher than the expected frequency of idiopathic cardiomyopathy in women of this age group, though accurate population-estimates of heart failure in age-matched nonpregnant women are not truly available (5). Second, patients with antecedent cardiomyopathy may be expected to have a different course *during pregnancy* than those with peripartum cardiomyopathy. As discussed above, it would be anticipated that if patients with idiopathic dilated cardiomyopathy develop symptoms of decompensated heart failure they would do so earlier in pregnancy in concert with the hemodynamic alterations that occur before the last month of pregnancy. One case report from China would support this contention (36). An interesting comparison of the course of pregnancy in patients with antecedent dilated cardiomyopathy (n=8) versus peripartum cardiomyopathy (n=23) has recently been published (37). Patients with antecedent dilated cardiomyopathy tolerated their pregnancy significantly better than women who developed peripartum cardiomyopathy. 7 of 8 patients with dilated cardiomyopathy remained NYHA class 1 – 2 throughout the pregnancy and postpartum period, and the left ventricular ejection fraction (in the four who were studied) remained stable. In contrast, 12/23 women with peripartum cardiomyopathy had adverse outcomes (death, transplant, or deterioration to NYHA class 3 or 4) with subsequent pregnancy, suggesting that peripartum and idiopathic dilated cardiomyopathy are distinct clinical entities. Third, the natural history of patients with idiopathic dilated cardiomyopathy is different from that of patients with peripartum cardiomyopathy. Peripartum cardiomyopathy was associated either with a more rapid decline and death OR a fairly high rate of spontaneous recovery, which contrasted with the slow decline among those with dilated cardiomyopathy (38) in the pre-beta blocker era. Fourth, some (39,40) (but not all (41)) studies have shown that myocarditis is more common in patients with peripartum cardiomyopathy than in dilated cardiomyopathy, perhaps explaining the association of peripartum cardiomyopathy with either rapid demise or recovery, and again suggesting that it is a distinct entity versus dilated cardiomyopathy. Finally, the recurrence of heart failure with subsequent pregnancy despite recovery of left ventricular function strongly suggests that peripartum cardiomyopathy is not simply unmasking of occult (asymptomatic or previously undiagnosed) cardiomyopathy. The table below summarizes these points.

Table 3. Peripartum and Idiopathic Dilated Cardiomyopathy are Distinct Entities.

1. Higher frequency in young women than would be expected (caveat: limited population-estimates of dilated cardiomyopathy).
2. Onset of peripartum cardiomyopathy does not follow the time course of hemodynamic stress of pregnancy.
3. Patients with dilated cardiomyopathy may tolerate pregnancy better.
4. Different natural history – peripartum cardiomyopathy associated with fulminant decline or rapid recovery.
5. Higher incidence of myocarditis in peripartum cardiomyopathy (possible).
6. Recurrent heart failure with subsequent pregnancy in peripartum cardiomyopathy.

III. Natural history

Peripartum cardiomyopathy can be associated with premature death OR rapid, complete recovery. This pattern was evident even in the earliest case series, where 4 patients died from complications of heart failure but another 3 completely recovered (2). Other studies have confirmed these widely divergent outcomes.

About 35-60% of women with peripartum cardiomyopathy will have significant recovery of left ventricular function (4,16,18,20,28,42-44).

Baseline characteristics that are risk factors for an adverse outcome are shown.

Table 4. Risk Factors at Presentation for Adverse Outcome.

1. Older age (16,18,45)
2. African-American ethnicity (18)
3. Multiparity (16,18,45)
4. Later symptom onset (18,45)
5. Larger LV volume or lower EF (18,38,39,43,45)
6. Greater hemodynamic disturbance – PA, PCWP, CI (39,45,46)
7. Conduction disease on EKG (45)

Whether a patient develops reverse remodeling and recovery of left ventricular ejection fraction by 6 -12 months is a critical predictor of long term outcome.

Table 5. Cardiac Size at 6 Months Predicts Outcome. From reference (4).

Cardiomegaly at 6 months	*Follow-up (years)*	*Death*
No	10.7	2/14 (14%) noncardiac
Yes	5.4	11/13 (85%)

The variability in the estimate of mortality associated with peripartum cardiomyopathy is large for unclear reasons, but possibly secondary to case selection, baseline characteristics of the treated patient population, or treatment strategies. A composite of selected series is shown.

Table 6. Outcome in Peripartum Cardiomyopathy.

Location	Investigator	Year	N	Race*	F/U (years)	**Death or Transplant N (%)**
Parkland	Cunningham (12)	1973-84	7	71% AA 43% W	~2	**4 (57%)**
Brazil	Carvalho (18)	1982-88	19		1.8	**4 (21%)**
Australia	Aroney (47)	1978-85	5	80% W	1.4	**5 (100%)**
Loyola (Chicago)	O'Connell (39)	< 1986	14	?	1	**6 (43%)**
Johns Hopkins	Felker (48)	1982-97	51	53% W 47% AA	5	**3 (6%)**
India	Ravikishore (45)	?	20		0.8	**1 (5%)**
Memphis	Witlin (16)	1986-94	28	75% AA 21% W	?	**8 (29%)**
Lexington	Ford (20)	1992-8	11	91% W	?	**1 (9%)**
South Africa	Sliwa (43)	1996-7	29	100% Black	0.5	**14 (48%)**
	TOTAL		**184**		**~2.5 (Crudely)**	**46 (25%)**

*W=White, AA=African-American.

Thus, most studies suggest that peripartum cardiomyopathy is associated with substantial mortality though it remains unclear why there is a nearly 10-fold range in mortality estimates. The large series from Johns Hopkins merits further analysis. This group has compared the outcome of patients with peripartum cardiomyopathy to patients with other types of cardiomyopathy (48).

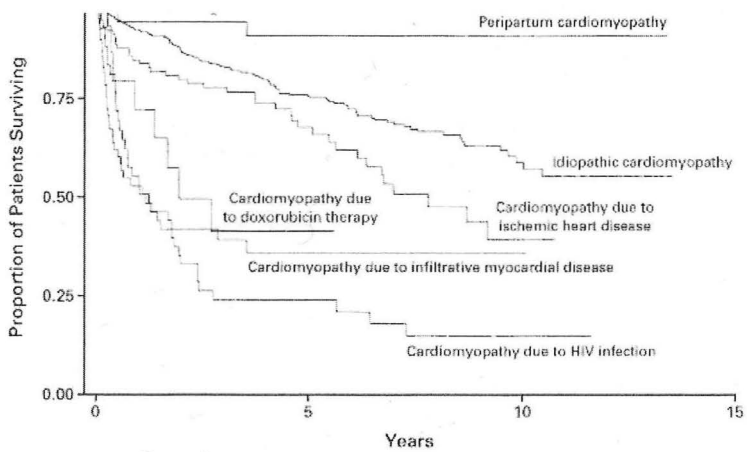

Figure 2. Peripartum Cardiomyopathy has Better Outcome than Other Cardiomyopathies: Johns Hopkins experience. From reference (48).

The lower risk associated with peripartum cardiomyopathy persisted in multivariable analysis (relative risk 0.31, 95% confidence intervals 0.09-0.98, p=0.05) (48).

To summarize, the following important points regarding the natural history of peripartum cardiomyopathy can be made:

1. Patients may have rapid recovery with restoration of normal left ventricular function OR have deterioration to fulminant cardiac failure and death (in the absence of transplantation). Recovery can be expected in 35-60% of patients.
2. Baseline characteristics may offer prognostic value.
3. Recovery of left ventricular function at 6 -12 months has important prognostic value.
4. A wide range in the estimate of the mortality associated with peripartum cardiomyopathy has been reported for unclear reasons.

IV. Etiology

The etiology of peripartum cardiomyopathy is not known. There has been surprisingly slow progress in this regards, especially when contrasted to other cardiomyopathies such as familial dilated or hypertrophic cardiomyopathy. Three potential etiologies (autoimmunity, infectious (myocarditis), and genetic predisposition) are most likely based on available data.

A. *Autoimmunity* – The suggestion that peripartum cardiomyopathy is an autoimmune disease, perhaps similar to other postpartum autoimmune diseases such as thyroiditis, has been spearheaded by investigators from Emory University School of Medicine (50). In women with peripartum cardiomyopathy, they have identified autoantibodies to 27, 33, and 37 kDa proteins expressed by the heart (51). In the NHBLI Peripartum Workshop (5), data were presented showing that the presence of such autoantibodies was higher in patients with peripartum than idiopathic dilated cardiomyopathy.

Table 7. Serum Levels of Antibodies to Cardiac Muscle Proteins in Peripartum and Idiopathic Dilated Cardiomyopathy. From (5) .

	Antibody Titer Levels†		
Patient Group	**<1:20**	**1:20-1:160**	**>1:160**
	ANT		
Idiopathic CM	16/56 (28)	29/56 (52)	11/56 (20)
Peripartum CM	1/10 (10)	1/10 (10)	8/10 (80)
	BCKD		
Idiopathic CM	30/56 (53)	21/56 (38)	5/56 (9)
Peripartum CM	0/10 (0)	2/10 (20)	8/10 (80)
	Myosin		
Idiopathic CM	18/56 (32)	27/56 (48)	11/56 (20)
Peripartum CM	1/10 (10)	1/10 (10)	8/10 (80)

*A. Ansari, MD, unpublished data, 1997.
†Reciprocal of the highest dilution of serum samples showing reactivity arbitrarily divided into those with low (<1:20), medium (1:20-1:160), and high (>1:160) titers. ANT indicates adenine nucleotide translocator. BCKD, branched chain α-keto acid dehydrogenase. Data presented as No./Total (%) of patients in each group.

At least one other group has reported the presence of anti-cardiac antibodies in patients with peripartum cardiomyopathy (52).

The inciting trigger for the development of autoimmunity is not known. However, fetal cells and DNA (53) are found in the maternal circulation during pregnancy, and male fetal progenitor cells are able to persist there for over 2 decades (54). By exposing a woman to paternal antigens, it is postulated that microchimerism (persistent low level presence of a cell population or DNA from a different individual) may contribute to the development of peripartum cardiomyopathy (50), as has been previously postulated in other autoimmune diseases such as scleroderma (55). Though interesting, much work remains in this field. Perhaps most important is to determine whether these auto-antibodies are central to the pathophysiology of this disorder or merely epiphenomenon.

B. *Infectious (Myocarditis)* – The possibility that myocarditis may be an important cause of peripartum cardiomyopathy was suggested in 1982 by a case series of 3 patients who had myocarditis diagnosed by transvenous endomyocardial biopsy (56). Subsequent groups (39,40,48) have found high rates of myocarditis among women with peripartum cardiomyopathy (29-51%), though one reported a much lower (9%) prevalence (41). *The inciting etiology of the myocarditis, e.g., autoimmunity (as above) or infectious, remains unknown.* Animal data do suggest an enhanced sensitivity to viral myocarditis (57,58) during pregnancy. In one model using a Coxsackie B-3 virus to inoculate Balb/c mice, non-pregnant female mice were relatively resistant to myocarditis in contrast to their male counterparts (58). However, once pregnant, female mice became equally susceptible. The enhanced sensitivity to myocarditis during pregnancy was ascribed to elevated progesterone levels, since administration of exogenous progesterone was similarly associated with increased susceptibility to myocarditis.

C. *Genetic* – Familial peripartum cardiomyopathy was first reported in 1963 (35). This entity was confirmed by others (29,34). However, there are no reported linkage analyses or candidate gene association studies reported to date. The advances in the genetics of familial dilated and hypertrophic cardiomyopathy (49) suggest that this area is fertile for future investigation.

Other potential etiologies of peripartum cardiomyopathy such as nutritional deficiency (selenium (59-61)), prolonged administration of tocolytic therapy (32), and an exaggeration of pregnancy-related remodeling (5) have less supporting data.

D. *Role of Gqα*: Insights from transgenic mice

The angiotension II, α1 adrenergic, or endothelin receptors initiate a signal for cardiac hypertrophy in cell culture mediated via Gqα (62-64). Thus, it was not surprising that transgenic mice overexpressing Gqα developed cardiac hypertrophy (65). Subsequently, it was shown that these mice develop cardiomyopathy in response to pregnancy, in contrast to 2 other transgenic models of cardiac hypertrophy which do not (66). The cardiomyopathy was associated with high rates of apoptosis. Interestingly, there were

similarities between this murine model of peripartum cardiomyopathy and its human equivalent. Specifically, the pregnant mice developed heart failure with a dilated cardiomyopathy at a peak incidence of 1 week post-partum and had markedly diminished survival that was related to the number of pregnancies. In contrast, however, no myocardial inflammation was seen on histological analysis of the mice that developed peripartum cardiomyopathy.

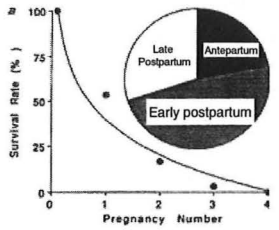

Figure 3. Survival and timing of symptom onset in transgenic Gqα murine model of peripartum cardiomyopathy. From reference (66).

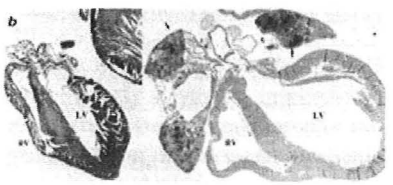

Figure 4. Gross morphology of wild-type (left side) and Gqα transgenic mice (right side) after pregnancy. The transgenic mice develop a dilated cardiomyopathy. From reference (66).

A more recent investigation from this group has shown that a protein, Nix/BnipEL, is induced by cardiac hypertrophy, localizes to the mitochondria, and is involved in cardiac apoptosis. Experiments in which either Nix or a dominant negative inhibitor of Nix were overexpressed demonstrated that Nix was both necessary and sufficient for the development of peripartum cardiomyopathy in the transgenic Gqα mice (67). How these insights relate to human peripartum cardiomyopathy are not yet clear but open an exciting new line of investigation with considerable promise.

V. Treatment

The treatment of peripartum cardiomyopathy in the postpartum setting will be considered first, followed by a discussion of special therapeutic considerations for the patient diagnosed while still pregnant.

A. *Treatment in the postpartum period.*

There are no large randomized clinical trials available to guide clinical decision making, perhaps not surprising given the low incidence of this disorder. Thus, therapy for patients with heart failure from peripartum cardiomyopathy in the postpartum setting is based on results of evidence gathered from studies of patients with other types of heart failure due to systolic dysfunction, with a few notable exceptions that will be discussed. Standard measures including dietary sodium restriction, diuretics, digoxin, angiotensin-converting-enzyme inhibitors, and beta-adrenergic blockers are recommended (5,43,68). Though there are no data in this setting, if the patient is ACE-inhibitor intolerant, an angiotensin receptor blocker should be used (69). Similarly, aldosterone blockade in this setting has not been studied but given its benefit in other types of heart failure (70,71) this too seems appropriate.

i. Particular therapeutic considerations for peripartum cardiomyopathy

Due to the high rates of embolic disease (2,18,72), anticoagulation with warfarin is recommended, especially for those with more severe cardiac dilation or dysfunction (e.g., ejection fraction < 35%) (5). The addition of pentoxifylline to conventional medical therapy in a consecutive series of 30 patients improved their outcomes as compared to the 29 patients treated immediately prior to the study (73). The authors postulated that the benefits of pentoxifylline were mediated through its inhibitory effect on tumor necrosis factor α (73), a cytokine implicated in the pathogenesis of heart failure (74). In another small study, the administration of intravenous immune globulin (2 g/kg) was associated with a greater improvement in ejection fraction in 6 patients as compared to 11 recent historical controls (increase of 26 ± 8 vs.13 ±13 ejection fraction units, respectively, p=0.04), suggesting further study of this approach is warranted. A larger (n = 62) randomized trial of intravenous immunoglobulin (Intervention in Myocarditis and Acute Cardiomyopathy trial) in the setting of new-onset (< 6 months) cardiomyopathy in adults, however, did not show benefit (75) though this was a different patient population.

Perhaps the most challenging question in the treatment of patients with peripartum cardiomyopathy is whether immunosuppressive therapy should be administered in the presence of documented myocarditis and clinical deterioration. As described above, myocarditis is documented in 9% to 51% (39-41,48) of patients. The presence of myocarditis does not appear to be related to prognosis (46). Some believe that immunosuppressive therapy is associated with improved survival in the setting of myocarditis (39) but others are more cautionary (76). The Myocarditis Treatment Trial did not find any benefit to the addition of immunosuppressive therapy in the management of patients with myocarditis (77) but patients with peripartum cardiomyopathy were not included and thus this issue remains open. The NHLBI Workshop panel concluded that "Immunosuppressive therapy can be considered if an endomyocardial biopsy indicates myocarditis, and if there is no improvement after 2 weeks of standard heart failure therapy" (5). This strategy implies that endomyocardial biopsy should be performed in the patient who does not improve after 2 weeks of conventional medical therapy, and perhaps sooner if there is a more fulminant course.

ii. Treatment for patients failing medical therapy

Because of the potential for subsequent complete recovery, aggressive attempts should me made to support patients long enough for improvement to occur. However, in those who cannot be supported despite parenteral inodilator therapy, implantation of a left ventricular assist device as a "bridge" to cardiac transplantation is indicated (78).

Cardiac transplantation: A modest experience assessing the safety of cardiac transplantation for patients with peripartum cardiomyopathy has accumulated (79-81). One study compared 10 women who underwent heart transplantation for peripartum cardiomyopathy to 39 who underwent transplant for dilated cardiomyopathy (80). In comparing these 2 groups, women with peripartum cardiomyopathy had slightly higher rates of rejection and infection but comparable 2-year survival rates. In contrast, another study that compared 8 women with peripartum cardiomyopathy to 9 age-matched women heart transplant recipients showed similar rates of rejection, infection, and survival between these 2 groups (79). The largest experience to date comes from the Cardiac Transplant Research Database, a multi-institutional consortium of predominantly US Medicare-approved heart transplant centers (including UT Southwestern) (81). In their analysis comparing 40 women with peripartum cardiomyopathy to 200 women of childbearing ages who were transplanted for other reasons, they found no difference in rates of rejection or survival between the 2 groups, providing considerable reassurance to proceed with cardiac transplantation when necessary in women with peripartum cardiomyopathy.

Given the increasing numbers of women undergoing cardiac transplantation for peripartum cardiomyopathy, it is not surprising to see reports of subsequent pregnancies in such patients (82-84). In the small number reported to date, recurrent cardiac failure did not occur. Nevertheless, pregnancy in heart transplant recipients is associated with a high rate of pregnancy complications including hypertension, preeclampsia, preterm labor, and neonatal complications (85) and should be managed in a high risk center.

Table 8. Treatment of Peripartum Cardiomyopathy (postpartum period only).

1. Standard medical therapy for dilated cardiomyopathy including sodium restriction, digoxin, diuretics, ACE-inhibitors, β-blockers, and possibly aldosterone blockade. If patient is ACE-inhibitor intolerant, use angiotensin receptor blocker. Do not use ACE-inhibitor or ARB if patient still pregnant.
2. Anticoagulation, especially if ventricle is large or LVEF < 35%. Avoid coumadin if the patient is pregnant.
3. Consider endomyocardial biopsy if no improvement after 2 weeks, and immunosuppressive therapy if myocarditis is found.
4. For patients failing medical therapy, cardiac transplantation in appropriate candidates is an effective option. Left ventricular assist devices may be needed to "bridge" such patients to transplant.
5. Single studies support use of pentoxifylline and IVIG but further data are needed before these approaches are used.

B. *Treatment when patient is still pregnant.*

In the less common situation when the diagnosis of peripartum cardiomyopathy is made while the patient is still pregnant (1,12,16,17), additional considerations regarding medical therapy and planning for the expected delivery are needed.

i. Medical therapy: The recommendations for medical therapy are slightly altered due to concerns regarding teratogenicity and fetal safety. Specifically, **ACE-inhibitors and angiotensin receptor blockers should not be used in pregnancy**. In their place, hydralazine and possibly nitrates could be substituted. Second, **warfarin should be avoided** (last month of pregnancy) since this will be associated with increased risk of fetal and maternal hemorrhage. Unfractionated heparin should be used in its place when anticoagulation is felt necessary. The role of low molecular weight heparin in pregnancy is emerging (86,87). Beta-blockers are felt to be safe during pregnancy (88), though there is some concern that they are related to small-for-gestational age infants and possibly neonatal bradycardia (89). Other therapies such as sodium restriction, diuretics, and digoxin are felt safe in this setting.

ii. Management of labor and delivery: There are few data available to guide decisions regarding the timing and mode of delivery. The NHLBI workshop states "The need for early delivery and the mode of delivery should be assessed through collaboration with cardiologists and anesthesiologists" and provided no references on this topic (5). Other recommendations in the literature include 1. use of an arterial and pulmonary artery catheter (90,91) 2. have the patient labor in the left-lateral decubitus position (90), 3. proceed with vaginal delivery and reserve cesarean section for obstetrical indications (90,92), and 4. use forceps to shorten the second stage of labor (90,92). Regional (epidural) anesthesia is preferred by some over general anesthesia (91).

VI. Another pregnancy?

Perhaps the most pivotal question for physicians involved in the care of a woman with peripartum cardiomyopathy is to decide whether it is safe for her to become pregnant again. The available evidence suggests the following 2 important points.

Point 1: *Women with peripartum cardiomyopathy are at risk for clinical deterioration with a subsequent pregnancy.*

For example, among 10 women who became pregnant again, 6 had clinical deterioration with recurrent heart failure (42). Interestingly, in 2 of these cases, the pregnancy complicated by heart failure alternated with or followed a pregnancy that had been uneventful. Numerous series have confirmed that women with peripartum cardiomyopathy are at increased risk of heart failure with subsequent pregnancy (4,16,28,93,94).

Point 2: *The ability to safely undertake a pregnancy is related to whether there was complete recovery following the initial episode of peripartum cardiomyopathy.*

In the above described 6 of 10 cases who developed recurrent heart failure, the 2 patients whose heart size remained enlarged after the initial episode died in heart failure following the subsequent pregnancy (42). The importance of improved left ventricular function before embarking upon another pregnancy was reinforced by a series from Cook County Hospital in Chicago that was gathered from 1947 – 1967 (4). Of 27 women with peripartum cardiomyopathy, 14 had a decrease in their cardiac silhouette to normal 6 months postpartum while 13 had persistent cardiomegaly. Among those with a normal cardiac silhouette, 2 of 8 subsequent pregnancies were complicated by heart failure, but both episodes were easily treated and resolved prior to hospital discharge. In contrast, among 6 women who had persistent cardiomegaly following their index pregnancy, 3 (50%) developed intractable heart failure and died. A subsequent series of 4 patients who had documented improved left ventricular ejection fraction following their index pregnancy with heart failure (95) reported that all 4 subsequent pregnancies were uneventful and serial echocardiography showed no deterioration in left ventricular function. However, one case was reported of a woman who had improved left ventricular function in the postpartum period but developed recurrent heart failure 4 years later during her subsequent pregnancy (93) (though echocardiography was not performed immediately prior to the subsequent pregnancy).

The largest study addressing this issue has recently been published (94). A survey was sent to all ~15,000 members of the American College of Cardiology inquiring about women with peripartum cardiomyopathy who had a subsequent pregnancy. 409 surveys were returned to the investigators and led to information about 44 women with peripartum cardiomyopathy who had a subsequent pregnancy. The definition for peripartum cardiomyopathy used in this study was laxer than the standardized definition, including women who had heart failure in the last six months of pregnancy (rather than last month) or the first 6 months (rather than 5) following delivery, but did require evidence of a left ventricular ejection fraction < 40% and the absence of another identifiable cause of heart failure. 5 women had developed heart failure prior to the last month of their index pregnancy. The study cohort was divided into women who had recovery of left ventricular function (LVEF ≥ 50%) prior to their subsequent pregnancy (group 1) and those who did not (group 2). The outcomes of these 2 groups are shown below.

Table 9. Outcome with subsequent pregnancy stratified by LV function. From (94)

LV function before subsequent pregnancy	Δ LVEF during pregnancy	>20% fall in LVEF	CHF	Death	Premature delivery*	Therapeutic abortion
LVEF ≥ 50 (n = 28)	56 to 49	21%	21%	0	11%	4%
LVEF < 50 (n = 16)	36 to 32	25%	44%	19%	37%	25%

* Premature delivery was defined as < 37 weeks gestation.

The methodology of this study design is undoubtedly associated with important biases. Nevertheless, these data emphasize that recurrent pregnancy in women with antecedent peripartum cardiomyopathy is associated with adverse fetal and maternal outcomes. **Women with persistently depressed left ventricular ejection should be counseled not to become pregnant again due to an unacceptable risk including death. The more difficult question is what to recommend for women who have recovery of left ventricular ejection fraction.** Many such women will not have heart failure or a fetal complication and are unlikely to die with a subsequent pregnancy, but some are at risk for adverse outcomes. This observation raises 2 further questions.

Question 1: Why are women who have recovery of left ventricular function at risk from a subsequent pregnancy?

Question 2: Is there any way to identify those women with a normal resting left ventricular ejection fraction who can or cannot safely undergo a pregnancy?

These are two difficult, and as of yet unanswered, questions, which perhaps is not surprising given the poor understanding of the underlying etiology of peripartum cardiomyopathy. However, there is some progress in this area. Some women who have recovery of cardiac function following peripartum cardiomyopathy, have impaired contractile reserve following infusion of dobutamine 5 μg/kg/min (96) despite normal resting baseline left ventricular function. Perhaps it is this impaired contractile reserve that predisposes to recurrent heart failure under the hemodynamic stress of pregnancy. Importantly, though, it is not known whether the women who have impaired contractile reserve on dobutamine echocardiography are the same individuals who will not tolerate a subsequent pregnancy. Nevertheless, given the risks of this decision, it does seem reasonable to me to have women who have recovered left ventricular ejection fraction undergo a dobutamine stress echocardiogram prior to subsequent pregnancy to provide additional (albeit not yet known if useful) information. If pregnancy is undertaken, serial echocardiography should be performed. As recommended in an editorial by Drs. J. Rutherford and S. Reimold, a discussion should be undertaken with the woman prior to the pregnancy and "...an understanding should be reached that the pregnancy should be terminated if ventricular function deteriorates and increases the woman's risk to an unacceptable degree" (68).

A diagram depicting an approach to a woman with peripartum cardiomyopathy considering a subsequent pregnancy is shown.

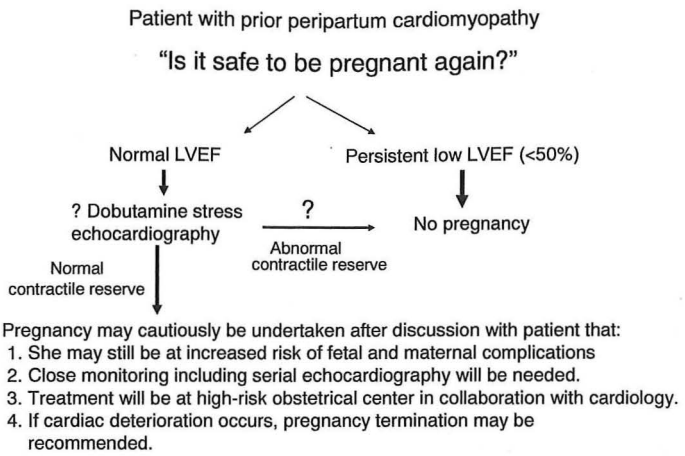

Figure 5. Potential Approach for Women with Previous Peripartum Cardiomyopathy Considering Another Pregnancy. Whether an abnormal response to dobutamine echocardiography should preclude a subsequent pregnancy, or a normal response dobutamine echocardiography implies a safe outcome, is not yet known.

References

1. Veille JC. Peripartum cardiomyopathies: a review. Am J Obstet Gynecol 1984;148:805-18.
2. Gouley B, McMillan, TM, Bellet, S. Idiopathic myocardial degeneration associated with pregnancy and especially the puerperium. Am J Med Sci 1937;194:185-199.
3. Hull E HE. "Toxic" postpartal heart disease. New Orleans Med Surg J 1937;89:550-557.
4. Demakis JG, Rahimtoola SH, Sutton GC, et al. Natural course of peripartum cardiomyopathy. Circulation 1971;44:1053-61.
5. Pearson GD, Veille JC, Rahimtoola S, et al. Peripartum cardiomyopathy: National Heart, Lung, and Blood Institute and Office of Rare Diseases Workshop recommendations and review. JAMA 2000;283:1183-8.
6. Hibbard JU, Lindheimer M, Lang RM. A modified definition for peripartum cardiomyopathy and prognosis based on echocardiography. Obstet Gynecol 1999;94:311-6.
7. Elkayam U. Pregnancy and Cardiovascular Disease. In: Braunwald E, Zipes, DP, Libby, P., ed. Heart Disease: A textbook of cardiovascular medicine. 6th ed. Philadelphia: W.B. Saunders Company, 2001:2172-2191.
8. Mansur LI, Minns GO, Steckley RA. Postpartum myocardial infarction: association with primary coronary artery dissection. Cleve Clin J Med 1995;62:261-8.
9. Daniels C, Bacon J, Fontana ME, Eaton G, Cohen D, Leier CV. Anomalous origin of the left main coronary artery from the pulmonary trunk masquerading as peripartum cardiomyopathy. Am J Cardiol 1997;79:1307-8.
10. Lui CY, Marcus FI, Sobonya RE. Arrhythmogenic right ventricular dysplasia masquerading as peripartum cardiomyopathy with atrial flutter, advanced atrioventricular block and embolic stroke. Cardiology 2002;97:49-50.
11. Seballos RJ, Mendel SG, Mirmiran-Yazdy A, Khoury W, Marshall JB. Sarcoid cardiomyopathy precipitated by pregnancy with cocaine complications. Chest 1994;105:303-5.
12. Cunningham FG, Pritchard JA, Hankins GD, Anderson PL, Lucas MJ, Armstrong KF. Peripartum heart failure: idiopathic cardiomyopathy or compounding cardiovascular events? Obstet Gynecol 1986;67:157-68.
13. Homans DC. Peripartum cardiomyopathy. N Engl J Med 1985;312:1432-7.
14. de Lemos JA, McGuire DK, Drazner MH. B-type natriuretic peptide in cardiovascular disease. Lancet 2003;362:316-22.
15. Yoshimura T, Yoshimura M, Yasue H, et al. Plasma concentration of atrial natriuretic peptide and brain natriuretic peptide during normal human pregnancy and the postpartum period. J Endocrinol 1994;140:393-7.
16. Witlin AG, Mabie WC, Sibai BM. Peripartum cardiomyopathy: an ominous diagnosis. Am J Obstet Gynecol 1997;176:182-8.
17. Lampert MB, Lang RM. Peripartum cardiomyopathy. Am Heart J 1995;130:860-70.

18. Carvalho A, Brandao A, Martinez EE, et al. Prognosis in peripartum cardiomyopathy. Am J Cardiol 1989;64:540-2.
19. Brown CS, Bertolet BD. Peripartum cardiomyopathy: a comprehensive review. Am J Obstet Gynecol 1998;178:409-14.
20. Ford RF, Barton JR, O'Brien J M, Hollingsworth PW. Demographics, management, and outcome of peripartum cardiomyopathy in a community hospital. Am J Obstet Gynecol 2000;182:1036-8.
21. Chang J, Elam-Evans LD, Berg CJ, et al. Pregnancy-related mortality surveillance--United States, 1991--1999. MMWR Surveill Summ 2003;52:1-8.
22. Berg CJ, Chang J, Callaghan WM, Whitehead SJ. Pregnancy-related mortality in the United States, 1991-1997. Obstet Gynecol 2003;101:289-96.
23. Fillmore SJ, Parry EH. The evolution of peripartal heart failure in Zaria, Nigeria. Some etiologic factors. Circulation 1977;56:1058-61.
24. Davidson NM, Parry EH. Peri-partum cardiac failure. Q J Med 1978;47:431-61.
25. Sanderson JE, Adesanya CO, Anjorin FI, Parry EH. Postpartum cardiac failure--heart failure due to volume overload? Am Heart J 1979;97:613-21.
26. Fett JD, Carraway RD, Dowell DL, King ME, Pierre R. Peripartum cardiomyopathy in the Hospital Albert Schweitzer District of Haiti. Am J Obstet Gynecol 2002;186:1005-10.
27. Fett JD, Carraway RD, Perry H, Dowell DL. Emerging insights into peripartum cardiomyopathy. J Health Popul Nutr 2003;21:1-7.
28. Seftel H, Susser M. Maternity and myocardial failure in African women. Br Heart J 1961;23:43-52.
29. Fett JD, Sundstrom BJ, Etta King M, Ansari AA. Mother-daughter peripartum cardiomyopathy. Int J Cardiol 2002;86:331-2.
30. Rolfe M, Tang CM, Walker RW, Bassey E, George M. Peripartum cardiac failure in The Gambia. J Trop Med Hyg 1992;95:192-6.
31. Mendelson MA, Chandler J. Postpartum cardiomyopathy associated with maternal cocaine abuse. Am J Cardiol 1992;70:1092-4.
32. Lampert MB, Hibbard J, Weinert L, Briller J, Lindheimer M, Lang RM. Peripartum heart failure associated with prolonged tocolytic therapy. Am J Obstet Gynecol 1993;168:493-5.
33. Voss EG, Reddy CV, Detrano R, Virmani R, Zabriskie JB, Fotino M. Familial dilated cardiomyopathy. Am J Cardiol 1984;54:456-7.
34. Pearl W. Familial occurrence of peripartum cardiomyopathy. Am Heart J 1995;129:421-2.
35. Pierce JA, Price BO, Joyce JW. Familial occurrence of postpartal heart failure. Arch Intern Med 1963;111:651-5.
36. Chan F, Ngan Kee WD. Idiopathic dilated cardiomyopathy presenting in pregnancy. Can J Anaesth 1999;46:1146-9.
37. Bernstein PS, Magriples U. Cardiomyopathy in pregnancy: a retrospective study. Am J Perinatol 2001;18:163-8.
38. van Hoeven KH, Kitsis RN, Katz SD, Factor SM. Peripartum versus idiopathic dilated cardiomyopathy in young women--a comparison of clinical, pathologic and prognostic features. Int J Cardiol 1993;40:57-65.

39. O'Connell JB, Costanzo-Nordin MR, Subramanian R, et al. Peripartum cardiomyopathy: clinical, hemodynamic, histologic and prognostic characteristics. J Am Coll Cardiol 1986;8:52-6.
40. Sanderson JE, Olsen EG, Gatei D. Peripartum heart disease: an endomyocardial biopsy study. Br Heart J 1986;56:285-91.
41. Rizeq MN, Rickenbacher PR, Fowler MB, Billingham ME. Incidence of myocarditis in peripartum cardiomyopathy. Am J Cardiol 1994;74:474-7.
42. Meadows WR. Idiopathic myocardial failure in the last trimester of pregnancy and the puerperium. Circulation 1957;15:903-14.
43. Sliwa K, Skudicky D, Bergemann A, Candy G, Puren A, Sareli P. Peripartum cardiomyopathy: analysis of clinical outcome, left ventricular function, plasma levels of cytokines and Fas/APO-1. J Am Coll Cardiol 2000;35:701-5.
44. Cole P, Cook F, Plappert T, Saltzman D, St John Sutton M. Longitudinal changes in left ventricular architecture and function in peripartum cardiomyopathy. Am J Cardiol 1987;60:871-6.
45. Ravikishore AG, Kaul UA, Sethi KK, Khalilullah M. Peripartum cardiomyopathy: prognostic variables at initial evaluation. Int J Cardiol 1991;32:377-80.
46. Felker GM, Jaeger CJ, Klodas E, et al. Myocarditis and long-term survival in peripartum cardiomyopathy. Am Heart J 2000;140:785-91.
47. Aroney C, Khafagi F, Boyle C, Bett N. Peripartum cardiomyopathy: echocardiographic features in five cases. Am J Obstet Gynecol 1986;155:103-6.
48. Felker GM, Thompson RE, Hare JM, et al. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. N Engl J Med 2000;342:1077-84.
49. Towbin JA, Bowles NE. The failing heart. Nature 2002;415:227-33.
50. Sundstrom JB, Fett JD, Carraway RD, Ansari AA. Is peripartum cardiomyopathy an organ-specific autoimmune disease? Autoimmun Rev 2002;1:73-7.
51. Fett JD. Peripartum cardiomyopathy. Insights from Haiti regarding a disease of unknown etiology. Minn Med 2002;85:46-8.
52. Yagoro A, Tada H, Hidaka Y, et al. Postpartum onset of acute heart failure possibly due to postpartum autoimmune myocarditis. A report of three cases. J Intern Med 1999;245:199-203.
53. Lo YM, Tein MS, Lau TK, et al. Quantitative analysis of fetal DNA in maternal plasma and serum: implications for noninvasive prenatal diagnosis. Am J Hum Genet 1998;62:768-75.
54. Bianchi DW, Zickwolf GK, Weil GJ, Sylvester S, DeMaria MA. Male fetal progenitor cells persist in maternal blood for as long as 27 years postpartum. Proc Natl Acad Sci U S A 1996;93:705-8.
55. Artlett CM, Smith JB, Jimenez SA. Identification of fetal DNA and cells in skin lesions from women with systemic sclerosis. N Engl J Med 1998;338:1186-91.
56. Melvin KR, Richardson PJ, Olsen EG, Daly K, Jackson G. Peripartum cardiomyopathy due to myocarditis. N Engl J Med 1982;307:731-4.
57. Farber PA, Glasgow LA. Viral myocarditis during pregnancy: encephalomyocarditis virus infection in mice. Am Heart J 1970;80:96-102.

58. Lyden DC, Huber SA. Aggravation of coxsackievirus, group B, type 3-induced myocarditis and increase in cellular immunity to myocyte antigens in pregnant Balb/c mice and animals treated with progesterone. Cell Immunol 1984;87:462-72.
59. Fett JD, Ansari AA, Sundstrom JB, Combs GF. Peripartum cardiomyopathy: a selenium disconnection and an autoimmune connection. Int J Cardiol 2002;86:311-6.
60. Kothari SS. Aetiopathogenesis of peripartum cardiomyopathy: prolactin-selenium interaction? Int J Cardiol 1997;60:111-4.
61. Cenac A, Simonoff M, Moretto P, Djibo A. A low plasma selenium is a risk factor for peripartum cardiomyopathy. A comparative study in Sahelian Africa. Int J Cardiol 1992;36:57-9.
62. Shubeita HE, McDonough PM, Harris AN, et al. Endothelin induction of inositol phospholipid hydrolysis, sarcomere assembly, and cardiac gene expression in ventricular myocytes. A paracrine mechanism for myocardial cell hypertrophy. J Biol Chem 1990;265:20555-62.
63. Sadoshima J, Izumo S. Molecular characterization of angiotensin II--induced hypertrophy of cardiac myocytes and hyperplasia of cardiac fibroblasts. Critical role of the AT1 receptor subtype. Circ Res 1993;73:413-23.
64. Knowlton KU, Michel MC, Itani M, et al. The alpha 1A-adrenergic receptor subtype mediates biochemical, molecular, and morphologic features of cultured myocardial cell hypertrophy. J Biol Chem 1993;268:15374-80.
65. D'Angelo DD, Sakata Y, Lorenz JN, et al. Transgenic Galphaq overexpression induces cardiac contractile failure in mice. Proc Natl Acad Sci U S A 1997;94:8121-6.
66. Adams JW, Sakata Y, Davis MG, et al. Enhanced Galphaq signaling: a common pathway mediates cardiac hypertrophy and apoptotic heart failure. Proc Natl Acad Sci U S A 1998;95:10140-5.
67. Yussman MG, Toyokawa T, Odley A, et al. Mitochondrial death protein Nix is induced in cardiac hypertrophy and triggers apoptotic cardiomyopathy. Nat Med 2002;8:725-30.
68. Reimold SC, Rutherford JD. Peripartum cardiomyopathy. N Engl J Med 2001;344:1629-30.
69. Granger CB, McMurray JJ, Yusuf S, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. Lancet 2003;362:772-6.
70. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999;341:709-17.
71. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 2003;348:1309-21.
72. Stuart KL. Cardiomyopathy of pregnancy and the puerperium. Q J Med 1968;37:463-78.

73. Sliwa K, Skudicky D, Candy G, Bergemann A, Hopley M, Sareli P. The addition of pentoxifylline to conventional therapy improves outcome in patients with peripartum cardiomyopathy. Eur J Heart Fail 2002;4:305-9.
74. Levine B, Kalman J, Mayer L, Fillit HM, Packer M. Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. N Engl J Med 1990;323:236-41.
75. McNamara DM, Holubkov R, Starling RC, et al. Controlled trial of intravenous immune globulin in recent-onset dilated cardiomyopathy. Circulation 2001;103:2254-9.
76. Mason JW, O'Connell JB. A model of myocarditis in humans. Circulation 1990;81:1154-6.
77. Mason JW, O'Connell JB, Herskowitz A, et al. A clinical trial of immunosuppressive therapy for myocarditis. The Myocarditis Treatment Trial Investigators. N Engl J Med 1995;333:269-75.
78. Hovsepian PG, Ganzel B, Sohi GS, Kupersmith J, Gray L, Jr. Peripartum cardiomyopathy treated with a left ventricular assist device as a bridge to cardiac transplantation. South Med J 1989;82:527-8.
79. Joseph SG. Peripartum cardiomyopathy--successful treatment with cardiac transplantation. West J Med 1987;146:230-2.
80. Keogh A, Macdonald P, Spratt P, Marshman D, Larbalestier R, Kaan A. Outcome in peripartum cardiomyopathy after heart transplantation. J Heart Lung Transplant 1994;13:202-7.
81. Johnson MR, Naftel DC, Hobbs RE, et al. The incremental risk of female sex in heart transplantation: a multiinstitutional study of peripartum cardiomyopathy and pregnancy. Cardiac Transplant Research Database Group. J Heart Lung Transplant 1997;16:801-12.
82. Camann WR, Goldman GA, Johnson MD, Moore J, Greene M. Cesarean delivery in a patient with a transplanted heart. Anesthesiology 1989;71:618-20.
83. Carvalho AC, Almeida D, Cohen M, et al. Successful pregnancy, delivery and puerperium in a heart transplant patient with previous peripartum cardiomyopathy. Eur Heart J 1992;13:1589-91.
84. Kreitmann B, D'Ercole C, Yao JG, Ambrosi P, Metras D. Successful pregnancy 5 years after cardiac transplantation for peripartum cardiomyopathy. Transplant Proc 1997;29:2457.
85. Scott JR, Wagoner LE, Olsen SL, Taylor DO, Renlund DG. Pregnancy in heart transplant recipients: management and outcome. Obstet Gynecol 1993;82:324-7.
86. Schulman S. Unresolved issues in anticoagulant therapy. J Thromb Haemost 2003;1:1464-70.
87. Ginsberg JS, Chan WS, Bates SM, Kaatz S. Anticoagulation of pregnant women with mechanical heart valves. Arch Intern Med 2003;163:694-8.
88. Koren G, Pastuszak A, Ito S. Drugs in pregnancy. N Engl J Med 1998;338:1128-37.
89. Magee LA, Duley L. Oral beta-blockers for mild to moderate hypertension during pregnancy. Cochrane Database Syst Rev 2003:CD002863.
90. Lee W. Clinical management of gravid women with peripartum cardiomyopathy. Obstet Gynecol Clin North Am 1991;18:257-71.

91. George LM, Gatt SP, Lowe S. Peripartum cardiomyopathy: four case histories and a commentary on anaesthetic management. Anaesth Intensive Care 1997;25:292-6.
92. Rutherford JD, Hands, M. E. Therapeutics and management during pregnancy. In: Douglas PS, ed. Heart Disease in Women. Philadelphia: Davis, 1989:113-125.
93. Ceci O, Berardesca C, Caradonna F, Corsano P, Guglielmi R, Nappi L. Recurrent peripartum cardiomyopathy. Eur J Obstet Gynecol Reprod Biol 1998;76:29-30.
94. Elkayam U, Tummala PP, Rao K, et al. Maternal and fetal outcomes of subsequent pregnancies in women with peripartum cardiomyopathy. N Engl J Med 2001;344:1567-71.
95. Sutton MS, Cole P, Plappert M, Saltzman D, Goldhaber S. Effects of subsequent pregnancy on left ventricular function in peripartum cardiomyopathy. Am Heart J 1991;121:1776-8.
96. Lampert MB, Weinert L, Hibbard J, Korcarz C, Lindheimer M, Lang RM. Contractile reserve in patients with peripartum cardiomyopathy and recovered left ventricular function. Am J Obstet Gynecol 1997;176:189-95.