

Pregnancy-Associated Cardiomyopathy Clinical Characteristics and a Comparison Between Early and Late Presentation

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Background—Cardiomyopathy associated with pregnancy was first described more than half a century ago. However, because of its rare occurrence and geographical differences, the clinical profile of this condition has remained incompletely defined.

Methods and Results—Data obtained from 123 women with a history of cardiomyopathy diagnosed during pregnancy or the postpartum period were reviewed. One hundred women met traditional criteria of peripartum cardiomyopathy; 23 were diagnosed with pregnancy-associated cardiomyopathy earlier than the last gestational month. Peripartum cardiomyopathy patients had a mean age of 31 ± 6 years and were mostly white (67%). Common associated conditions were gestational hypertension (43%), tocolytic therapy (19%), and twin pregnancy (13%). Left ventricular ejection fraction at the time of diagnosis was $29 \pm 11\%$ and improved to $46 \pm 14\%$ ($P \leq 0.0001$) at follow-up. Normalization of left ventricular ejection fraction occurred in 54% and was more likely in patients with left ventricular ejection fraction $>30\%$ at diagnosis. Maternal mortality was 9%. A comparison between the peripartum cardiomyopathy and early pregnancy-associated cardiomyopathy groups revealed no differences in age, race, associated conditions, left ventricular ejection fraction at diagnosis, its rate and time of recovery, and maternal outcome.

Conclusions—This study helps to define the clinical profile of patients with pregnancy-associated cardiomyopathy diagnosed in the United States. Clinical presentation and outcome of patients with pregnancy-associated cardiomyopathy diagnosed early in pregnancy are similar to those of patients with traditional peripartum cardiomyopathy. These 2 conditions may represent a continuum of a spectrum of the same disease. (*Circulation*. 2005;111:2050-2055.)

Key Words: cardiomyopathy ■ heart failure ■ pregnancy

Recognized as early as the 18th century, heart failure associated with pregnancy was first described as a distinctive form of cardiomyopathy in 1937.¹ In 1971, Demakis et al² published data on 27 patients with pregnancy-associated cardiomyopathy (PACM) that presented in the peripartum period. These investigators defined the condition as peripartum cardiomyopathy (PPCM) and established its diagnostic criteria. Despite the early recognition and because of its relative rarity,³ geographical differences, and heterogeneous presentation,³⁻⁵ this condition continues to be incompletely characterized.^{3,6} Classic criteria for the diagnosis of PPCM as established by Demakis et al² limited the diagnosis to the last gestational month and first 5 months after delivery. Several reports published later, however, described women who presented with cardiomyopathy earlier during pregnancy.⁷⁻¹³ The purpose of the present study was therefore 2-fold: to further define the clinical profile of PPCM in a large number of patients diagnosed in the United States and to

compare the clinical characteristics of patients who meet the traditional criteria of PPCM with those diagnosed with cardiomyopathy earlier during pregnancy.

Methods

Clinical information was obtained by a survey among members of the American College of Cardiology. A questionnaire was mailed to $\approx 15\,000$ members in 1997 and 1998. The responding physicians who indicated that they cared for patients with PPCM were asked to obtain from their patients written informed consent to participate in the study and to release their medical records to the investigators. Two hundred thirty-three of these patients did not have a history of subsequent pregnancy. Of these patients, 76 had sufficient records and were included in our analysis. Clinical data also were obtained from patients cared for by or who consulted the Heart Failure Program of the University of Southern California. Cases analyzed in a previous report on patients with PPCM with a history of subsequent pregnancies were not included.¹⁴ Data were collected through review of medical records and by interviews of the referring physicians or the patients. The Institutional Review Board of the University of

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Comparison Between Patients With Traditional PPCM and Early PACM

Parameter	Traditional PPCM (n=100)	Early PACM (n=23)	P
Mean age, y	30.7±6.4 (16–43)	30±6.0 (20–44)	0.67
Age >30 y, %	58	49	0.36
White, %	67	65	0.8
Black, %	19	17	1.0
Hispanic, %	10	4	0.69
Gravidity	2.6±2.2 (1–11, n=87)	2.5±1.7 (1–6, n=23)	0.83
Parity	2.1±1.7 (0–10)	1.9±1.5 (0–5)	0.64
Hypertension, %	43	30	0.56
Twin pregnancy, %	13	26	0.009
Tocolytic therapy, %	19	26	0.5
Index pregnancy, %			
First	37	44	1.0
Second	15	13	0.76
Third	14	17	1.0
Fourth	10	9	1.0
Fifth	11	17	0.51
Caesarian delivery, %	40	43	1.0
Duration of pregnancy, wk	37.7±3.5 (24–42, n=56)	32.4±6.2 (20–42, n=22)	0.00001
LVEF at diagnosis, %	28.8±11.2 (10–45, n=100)	26.6±10.5 (10–45, n=23)	0.4
LVEF at last follow-up, %	46±14.4 (10–77, n=92)	43.8±15.6 (16–63, n=20)	0.54
Birth weight, g	3092±745 (1350–5000, n=51)	2238±949 (457–4500, n=19)	0.0002
Heart transplantation, %	4	4.3	1.0
Maternal morbidity, %	9	13	0.7

Data presented as mean±SD. Values in parentheses represent ranges.

Southern California approved the study protocol and consent form. The diagnosis of PPCM was established from 4 criteria adapted from the work of Demakis et al^{2,3} and recently recommended by a workshop convened by the National Heart Lung and Blood Institute and the Office of Rare Diseases of the National Institutes of Health in 1997⁸: (1) development of cardiac failure in the last month of pregnancy or within 5 months of delivery, (2) absence of an identifiable cause for the cardiac failure, (3) absence of recognizable heart disease before the last month of pregnancy, and (4) left ventricular systolic dysfunction with left ventricular ejection fraction (LVEF) <45% by echocardiography. Patients were included in the group of early PACM if they met the criteria for PPCM but presented earlier than the last gestational month.

Statistical analyses were performed with the use of the Fisher exact test and Student *t* tests. Paired *t* tests were used when records on the same women were compared. All data are presented as mean±SD.

Results

The 409 physicians who returned the study questionnaire identified 233 women with PACM. We were able to review clinical and echocardiographic information for 76 of these women, in addition to 33 women who consulted and 14 who were cared for by our Heart Failure Program. None of the patients in this cohort had subsequent pregnancies. The survey group was somewhat younger (29±6 versus 32±6 years; *P*=0.016) and had more white patients (82% versus 59%; *P*=0.01) and fewer black women (10% versus 25%; *P*=0.06). Other parameters were comparable, including incidence of twin pregnancies (14% versus 18%; *P*=0.61), history of gestational

hypertension (41% versus 40%; *P*=0.99), LVEF on diagnosis (29±11% versus 28±11%; *P*=0.77), and follow-up LVEF (45±15% versus 47±19%; *P*=0.46). A total of 100 patients met traditional diagnostic criteria for PPCM; 23 met the criteria of early PACM.

PPCM Group

The clinical characteristics of these patients are shown in the Table. Ages ranged between 16 and 43 years (mean, 30.7±6.4 years); 58% were >30 years of age. The ethnic background was as follows: white, 67%; black, 19%; Hispanic, 10%; Asians, 1%; and unknown, 3%. Parity ranged between 0 and 10 (mean, 2.1±1.7); gravidity ranged from 1 to 11 (mean, 2.6±2.2). Time of diagnosis (Figure 1) was established before delivery in 7% and after delivery in 93%. The vast majority of patients (75%) were diagnosed during the first month postpartum; 56 were diagnosed within the first week. Eighteen were diagnosed 2 to 5 months after delivery (9 in the second month, 6 in the third month, 2 in the fourth month, and 1 in the fifth month).

Associated Conditions

History of hypertension during pregnancy was obtained in 43% of the patients (chronic hypertension in 3, preeclampsia in 15, both in 15, pregnancy-induced hypertension in 7, and eclampsia in 3). Twin pregnancies were reported in 13% of the patients, and the use of tocolytic therapy was reported in 19%.

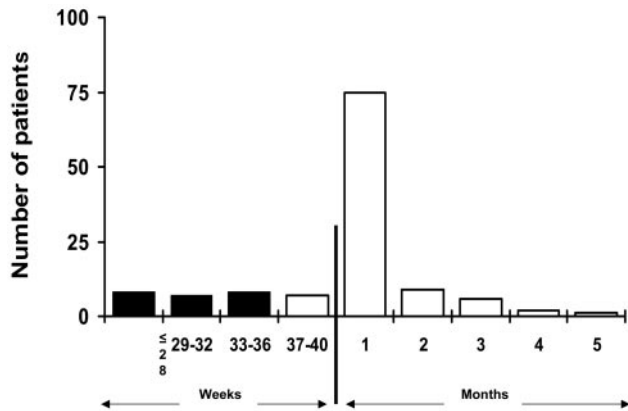


Figure 1. Time of diagnosis of cardiomyopathy in 123 patients. Black bars represent 23 patients with early PACM; white bars, 100 patients with traditional PPCM.

Index Pregnancy

Thirty-seven percent of all patients with PPCM developed cardiomyopathy in association with their first pregnancy, 15% with the second pregnancy, 14% with the third pregnancy, 10% with the fourth pregnancy, and 11% with the fifth or later pregnancy (Figure 2). Information on the index pregnancy was not available in 13% of the cases.

Left Ventricular Function

LVEF at the time of diagnosis ranged between 10% and 45% (mean, $29 \pm 11\%$) and increased to $46 \pm 14\%$ (range, 10% to 77%) at the last follow-up at a mean of 23 ± 28 months postpartum (92 patients, $P < 0.0004$ versus baseline). A complete set of echocardiographic measurements was obtained in 40 patients (Figure 3); mean values were $30 \pm 11\%$ at diagnosis, $45 \pm 13\%$ at 6 months postpartum ($P < 0.0001$ versus diagnosis), $48 \pm 13\%$ at 12 months ($P = 0.31$ versus 6 months and $P < 0.0001$ versus diagnosis), and $46 \pm 15\%$ at last follow-up at a mean of 30 ± 29 months ($P = 0.85$ versus 6 months, $P = 0.45$ versus 12 months, and $P < 0.0001$ versus diagnosis).

Recovery of LVEF ($>50\%$), observed in 54% of the patients, occurred within the first 6 months postpartum in most patients. Improvement in LVEF at the last follow-up

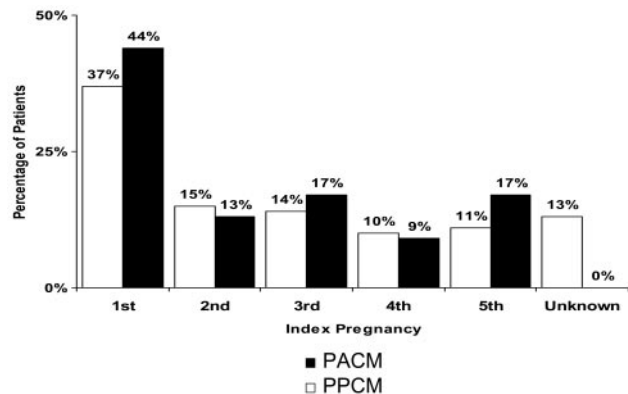


Figure 2. Index pregnancy associated with development of cardiomyopathy in patients with early PACM (black bars) and traditional PPCM (white bars).

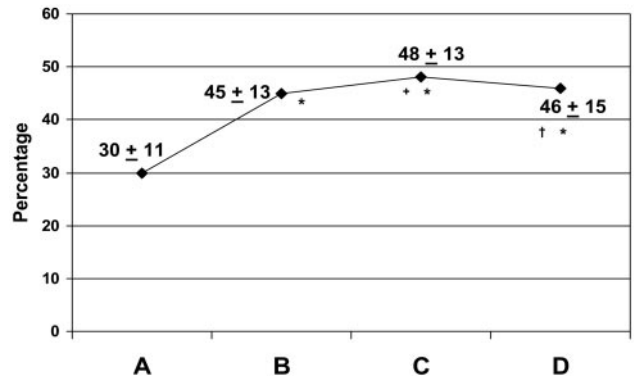


Figure 3. LVEF at time of diagnosis (A), 6 months (B), 12 months (C), and last follow-up at mean of 30 ± 29 months postpartum (PP) (D) in 40 patients with PPCM. * $P < 0.0001$ vs A; † $P = 0.31$ vs B; † $P = 0.45$ vs C and $P = 0.85$ vs B.

was significantly larger in women with LVEF $>30\%$ at time of diagnosis.

Obstetrical and Neonatal Outcome

Mode of delivery was a cesarean section in 40 patients, which was performed for obstetrical reasons in 70% of the patients, cardiac reasons in 10%, and unknown reasons in 20%. Duration of pregnancy (56 patients) ranged from 24 to 42 weeks, with an average of 37.7 ± 3.5 weeks. Premature delivery (<37 weeks) was reported in 25% of these patients. Birth weight (51 patients) ranged between 1350 and 5000 g, with a mean of 3092 ± 745 g, and the incidence of small-for-date infants was 5.9%. There were 2 stillbirths and 1 neonatal death. Congenital anomalies in the newborn were reported in 4 cases and included hypospadias, coarctation of the aorta, dysmorphogenesis, and macrosomia. Neonatal complications were reported in 6 cases and included 1 case each of hypothermia, poor suckling, apnea with seizure requiring intubation, hypoglycemia, and death and 2 cases of pulmonary edema.

Maternal Outcome

Heart transplantation was reported in 4% of the patients (2 and 4.5 months postpartum in 1 patient each and 6 months postpartum in 2 patients). Death was reported in 9% and was described as sudden in 4 patients (4 months, 1 year, and 9 years postpartum in 1 patient each, time not available in 1 patient) and as a result of complications from heart transplantation in 2 patients. Cause of death was not available in 3 patients (7 months, 2 years, and 3 years postpartum). Three percent of the patients required implantation of an automatic implantable cardioverter-defibrillator, and 2% required implantation of a permanent pacemaker during the follow-up period.

Comparison Between PPCM and Early PACM Groups

Twenty-three patients were diagnosed with PACM before the last gestational month, with the earliest diagnosis made during the 17th week. Eight patients were diagnosed before the 28th week, 7 during weeks 29 to 32, and 8 during weeks 33 to 36. The Table gives results of a comparison between the

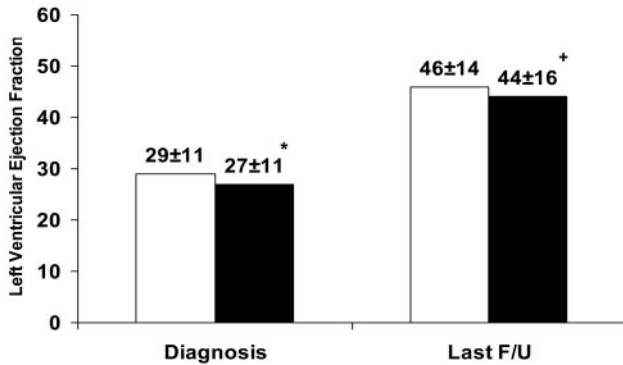


Figure 4. LVEF at time of diagnosis (all patients) and last follow-up (F/U) in 20 patients with early PACM (black bars) and 93 patients with traditional PPCM (white bars). * $P=0.4$ (early vs traditional); + $P=0.54$ (early vs traditional).

PPCM and early PACM groups. There was no statistically significant difference between the 2 groups in mean age; percent of patients >30 years of age; race; obstetrical history, including gravidity and parity; and incidence of pregnancy-associated hypertension. The development of cardiomyopathy occurred in >50% of the patients in both groups in association with the first or second pregnancy (Figure 2). There was also no statistically significant difference in mean LVEF at either time of diagnosis or last follow-up (between 1 to 168 months with a mean of 23 ± 28 months for the PPCM group, and 3 to 120 months with a mean of 29 ± 35 months for the PACM group; Figure 4), rate of heart transplantation, or maternal mortality. In contrast, the incidence of twin pregnancies was higher (26% versus 13%; $P=0.009$), duration of pregnancy was shorter (32.4 ± 6.2 versus 37.7 ± 3.5 weeks; $P=0.00001$), and birth weight was lower (2238 ± 949 versus 3092 ± 745 g; $P=0.0002$) in the early PACM group.

Discussion

Clinical Profile of PPCM

The present study provides the largest database on patients with PPCM and a comprehensive description of the clinical characteristics of this condition as presented in the United States in the recent era. Because of the potential detrimental effect of subsequent pregnancy on the outcome of these patients,¹⁴ only patients without a history of additional pregnancies were included. Our findings demonstrate that PPCM can occur at any age but confirm a higher incidence in women >30 years of age.² In contrast to the previously reported higher prevalence of PPCM in black women,^{2,3} most patients included in this study were white. Although this ethnic representation may be influenced by a referral bias, our findings clearly show that PPCM in the United States is not limited to black women. Although multiparity may be a risk factor for the development of cardiomyopathy in other populations,⁵ the present study does not support a strong association in the United States because almost 40% of the cases occurred in association with their first pregnancy and >50% with the first 2 pregnancies. The present study also shows a strong association between PPCM and gestational hypertension and twin pregnancies. The incidence of gesta-

tional hypertension in patients with PPCM was 43%, which is substantially higher than the reported rate of 8% to 10% in the overall pregnant population¹⁵ but similar to the incidence reported in women with PPCM by Demakis et al² and Lang et al,³ who reported preeclampsia in 22%, and Witlin et al,¹⁶ who described chronic hypertension or preeclampsia in 68% of their patients. A strong association with hypertension raises the question as to whether increased blood pressure may be a cause of heart failure seen in patients with PPCM. This suggestion is not supported by infrequent cardiovascular complications reported in a large number of patients with hypertension resulting from aortic coarctation during pregnancy.¹⁷ In addition, studies in women with preeclampsia have revealed no change in systolic left ventricular function.^{17,18}

The rate of twin pregnancy reported in our study, 13%, was markedly higher than the normal rate of 1% to 2% in healthy women.¹⁹ This interesting association between PPCM and twin pregnancies may support an autoimmune mechanism for PPCM. Such a mechanism has recently been proposed by Ansari et al,²⁰ who found high titers of autoantibodies against normal human cardiac tissue proteins in the sera of PPCM patients that were not present in patients with idiopathic cardiomyopathy. This finding may be due to hematopoietic lineage cell traffic (chimerism) from the fetus to the mother during gestation, which is increased in twin pregnancies.²¹

The present study also shows a high incidence of tocolytic therapy in our patients. Although long-term use of terbutaline tocolysis was suggested as a potential cause for the development of cardiomyopathy,²² the association between tocolysis and PPCM is probably a reflection of the increased incidence of premature labor in this patient population.

Obstetrical and Neonatal Outcome

The present study shows a high rate of cesarean delivery in patients with PPCM performed, for the most part, for obstetrical reasons. This rate of cesarean delivery is higher than the reported national rate of 22%²³ and the rates reported in women with congenital (29%) and valvular (29%) heart disease.^{24–26} Potential reasons for the high rate of cesarean section are a high incidence of gestational hypertension, twin pregnancy, and older maternal age.^{19,27,28} Preterm delivery in the studied patients (25%) was higher than the rate of 4% to 8% published recently for healthy women²⁹ and probably was due to the increased incidence of gestational hypertension and twin pregnancies.^{19,27}

Left Ventricular Function

More than half of the patients with PPCM showed normalization of the initially observed left ventricular dysfunction that occurred in most cases within 6 months after delivery. The likelihood for normalization of cardiac function was significantly higher in patients with LVEF >30% at the time of diagnosis.

Maternal Outcome

Of the 100 PPCM patients, 9 died during a mean follow-up of ≈ 2 years. A higher mortality rate was reported by 2 previous prospective groups, including Witlin et al,¹⁵ who described

18% mortality and 11% rate of heart transplantation in a group of 28 women diagnosed in the United States, and Sliwa et al,⁴ who reported a 32% mortality at 6 months in 28 patients studied in South Africa. The lower mortality rate observed in the present study is probably due to reporting and referral bias. At the same time, however, <10% mortality over 4.4 years has recently been reported in 51 women with PPCM and may reflect a favorable effect of improved medical therapy for heart failure.³⁰ Death was reported to be sudden in more than half of the patients. This finding, in addition to the use of implantable defibrillators in 3 additional patients, indicates a risk of life-threatening arrhythmias in women with PPCM.

Early Versus Late Presentation

Diagnostic criteria for PPCM established by Demakis et al² in 1971 limited the diagnosis to the last gestational month or the first 5 months after delivery. These criteria, however, were based on data obtained in a relatively small group of 27 women diagnosed in 1 medical center in an earlier diagnostic era. Numerous later publications have described early development of cardiomyopathy during pregnancy.^{7–13} Almost 20% of our patients developed symptoms of heart failure and were diagnosed with PACM earlier than the last gestational month. A comparison between patients with early presentation and those with traditional criteria of PPCM revealed no significant differences in age, ethnic background, obstetrical history, and rate of gestational hypertension. Furthermore, maternal outcome, LVEF at the time of diagnosis, and its recovery over time were extremely similar between the 2 groups. An increased rate of premature deliveries was observed in the early PACM group and was probably related to early development of cardiac dysfunction, a higher incidence of twin pregnancies, and the reluctance of physicians to continue the pregnancy after a diagnosis of a cardiomyopathy. Recent review has raised concern that patients with early diagnosis may represent previously undiagnosed cardiomyopathy uncovered by the hemodynamic burden of pregnancy.⁶ This assumption is not supported by our findings, which show a similar lack of evidence for previous heart disease in both groups, an almost identical clinical profile and maternal outcome, and a similar degree of left ventricular dysfunction at the time of diagnosis and its rate of recovery over time. These findings strongly suggest that these 2 groups represent different parts of a spectrum of the same condition. Clinicians should therefore be cognizant of the possibility of early presentation of PACM to prevent a delay in diagnosis, which occurred in a number of patients in this study, and allow a timely and appropriate management of this life-threatening condition.

Study Limitations

The results of our study may be somewhat limited by the mostly retrospective nature of the data. The collection of information could also have been dependent on the responses of physicians and patients and could have been influenced by ascertainment, selection, and recall biases. In addition, the comparisons between the PPCM and PACM groups have a limited power because there are only 23 subjects in the latter

group. Furthermore, our echocardiographic information was obtained in most cases from the patient records and was based on the interpretation of individual physicians. Despite these limitations, our study presents the largest database available to date and provides a comprehensive description of the clinical profile of PACM diagnosed in the United States in the current era.

In summary, PPCM in the United States can affect women of various ethnic backgrounds at any age; it is more common, however, in women >30 years of age. Strong association of PPCM with gestational hypertension and twin pregnancy should raise the level of suspicion for the development of cardiomyopathy in patients with these conditions who develop symptoms of heart failure. Left ventricular function is markedly depressed at the time of diagnosis and normalizes in more than half of the patients, especially in these with LVEF >30% at the time of diagnosis. Clinical presentation and outcome of patients with PACM diagnosed early in pregnancy are similar to those of patients with traditional PPCM and probably represent the same disease. Early recognition of PACM should allow a timely diagnosis and appropriate care of this life-threatening condition.

References

- Gouley BA, McMillan TM, Bellet S. Idiopathic myocardial degeneration associated with pregnancy and especially the peripartum. *Am J Med Sci*. 1937;19:185–199.
- Demakis JG, Rahimtoola SH, Sutton GC, Meadows WR, Szanto PB, Tobin JR, Gunnar RM. Natural course of peripartum cardiomyopathy. *Circulation*. 1971;44:1053–1061.
- Lang RM, Lampert MB, Poppas A, Hameed A, Elkayam U. Peripartum cardiomyopathy. In: Elkayam U, Gleicher N, eds. *Cardiac Problems in Pregnancy*. 3rd ed. New York, NY: Wiley-Liss; 1998:87–100.
- 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;35:701–705.
- 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;186:1005–1010.
- Pearson GD, Veille JC, Rahimtoola S, Hsia J, Oakley CM, Hosenpud JD, Ansari A, Baughman KL. Peripartum cardiomyopathy: National Heart, Lung and Blood Institute and Office of Rare Diseases (National Institutes of Health) workshop recommendations and review. *JAMA*. 2000;283:1183–1188.
- Brown G, O'Leary M, Douglas I, Herkes R. Perioperative management of a case of severe peripartum cardiomyopathy. *Anaesth Intensive Care*. 1992;20:80–83.
- Abou Awdi N, Joseph K. Hemopump left ventricular support in the peripartum cardiomyopathy patient. *J Cardiovasc Nurs*. 1994;8:36–44.
- Forssell G, Laska J, Olofsson C, Olsson M, Mogensen L. Peripartum cardiomyopathy: three cases. *J Intern Med*. 1994;235:493–496.
- Yahagi N, Kumon K, Nakatani T, Ishikawa T, Tanigami H, Eishi K, Takahashi S. Peripartum cardiomyopathy and tachycardia followed by multiple organ failure. *Anesth Analg*. 1994;79:581–582.
- Rizeq MN, Rickenbacher PR, Fowler MB, Billingham ME. Incidence of myocarditis in peripartum cardiomyopathy. *Am J Cardiol*. 1994;74:474–477.
- Mellor DJ, Bodenham A. Infiltration anesthesia in the management of caesarian section in a patient with peripartum cardiomyopathy. *Med Tropicale*. 1996;56:376–380.
- Alvarez Navasques R, Marin R, Testa A, Paneda F, Alvarez Grande J. Preeclampsia and peripartum cardiomyopathy: infrequent association. *Nefrologia*. 2001;21:84–87.
- Elkayam U, Tummala PP, Rao K, Akhter MW, Karaalp IS, Wani OR, Hameed A, Gviazda I, Shotan A. Maternal and fetal outcomes of subsequent pregnancies in women with peripartum cardiomyopathy. *N Engl J Med*. 2001;344:1567–1571.

15. Chari RS, Frangieh AY, Sibai BM. Hypertension during pregnancy: diagnosis, pathophysiology and management. In: Elkayam U, Gleicher N, eds. *Cardiac Problems in Pregnancy*. 3rd ed. New York, NY: Wiley-Liss; 1998:257–273.
16. Witlin AG, Mabie WC, Sibai BM. Peripartum cardiomyopathy: an ominous diagnosis. *Am J Obstet Gynecol*. 1997;176:182–188.
17. Beauchesne LM, Connelly HM, Ammash NM, Warnes CA. Coarctation of the aorta: outcome of pregnancy. *J Am Coll Cardiol*. 2001;38:1728–1733.
18. Borghi C, Esposti DD, Immordino V, Cassani A, Boschi S, Bovicelli L, Ambrosioni E. Relationship of systemic hemodynamics, left ventricular structure and function, and plasma natriuretic peptide concentrations during pregnancy complicated by preeclampsia. *Am J Obstet Gynecol*. 2000;183:140–147.
19. Hogle KL, Hutton EK, McBrien KA, Barrett JF, Hannah ME. Cesarean delivery for twins: a systematic review and meta-analysis. *Am J Obstet Gynecol*. 2003;188:220–227.
20. Ansari AA, Neckelmann N, Wang YC, Gravanis MB, Sell KW, Herskowitz A. Immunologic dialogue between cardiac myocytes, endothelial cells, and mononuclear cells. *Clin Immunol Immunopathol*. 1993;68:208–214.
21. Bianchi DW. Fetomaternal cell trafficking: a new cause of disease? *Am J Med Genet*. 2000;91:22–28.
22. 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;168:493–495.
23. Cesarean delivery and cesarean hysterectomy. In: Cunningham FG, MacDonald PC, Gant NF, Leveno KJ, Gilstrap LC, Hankins GDV, Clark SL, eds. *Williams Obstetrics*. 20th ed. Stamford, Conn: Appleton and Lange; 1997:509–531.
24. Siu SC, Colman JM, Sorensen S, Smallhorn JF, Farine D, Amankwah KS, Spears JC, Sermer M. Adverse neonatal and cardiac outcomes are more common in pregnant women with cardiac disease. *Circulation*. 2002;105:2179–2184.
25. Silversides CK, Colman JM, Sermer M, Siu SC. Cardiac risk in pregnant women with rheumatic mitral stenosis. *Am J Cardiol*. 2003;91:1382–1385.
26. Silversides CK, Colman JM, Sermer M, Farine D, Siu SC. Early and intermediate-term outcomes of pregnancy with congenital aortic stenosis. *Am J Cardiol*. 2003;91:1386–1389.
27. Gofton EN, Capewell V, Natale R, Gratton RJ. Obstetrical intervention rates and maternal and neonatal outcomes of women with gestational hypertension. *Am J Obstet Gynecol*. 2001;185:798–803.
28. Zhang J, Meikle S, Grainger DA, Tumble A. Multifetal pregnancy in older women and perinatal outcomes. *Fertil Steril*. 2002;78:562–568.
29. Perkins JT. Hemolytic disease of the newborn. In: Gleicher N, ed. *Principles and Practice of Medical Therapy in Pregnancy*. 2nd ed. Stamford, Conn: Appleton & Lange; 1992:1040–1045.
30. Felker GM, Thompson RE, Hare JM, Hruban RH, Clemetson DE, Howard DL, Baughman KL, Kasper EK. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. *N Engl J Med*. 2000;342:1077–1084.