

Peripartum cardiomyopathy

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Abstract

Peripartum cardiomyopathy (PPCM) is a rare form of cardiomyopathy of unknown aetiology that develops at the end of pregnancy or within five months after delivery; immune and viral causes have been postulated. It has an incidence of 1:1,500 to 1:4,000 live births.

Many cases of PPCM improve or resolve completely but others progress to heart failure; an early diagnosis and medical treatment may affect the patient's long-term prognosis.

The symptoms and signs are similar to those of the other kinds of heart failure: paroxysmal nocturnal dyspnoea, chest pain, pulmonary crackles, increased jugular venous pressure, hepatomegaly, change in blood pressure, tachycardia and third heart sound.

The first steps of the therapy include lifestyle measures and diuretics. ACE-inhibitors are the mainstay of treatment after delivery, while hydralazine, nitroglycerin, amlodipine are the choice during pregnancy. Digoxin is only used for the atrial fibrillation, while β -blocking agents only in patients with excessive sympathetic nervous system activation. Anticoagulants are indicated in pregnant women with poor cardiac function (Fraction Ejection, FE <35%) who are at increased risk of thromboembolism. Immunosuppressive therapy can be considered for myocarditis confirmed by cardiac biopsy.

Keywords

Peripartum cardiomyopathy, pregnancy, heart failure

Disease name and synonyms

Peripartum cardiomyopathy

Cardiomyopathy in pregnancy

Definition

The peripartum cardiomyopathy (PPCM) is classified as a specific cardiomyopathy that develops in the last period of pregnancy or in the first period of puerperium (1,2). It was described as early as 1849 (3) but it was not well characterized until 1971 when Demakies *et al.* (4) established the current diagnostic criteria.

PPCM is defined on the basis of the following criteria, adapted from Demakies *et al.* (4,5):

- development of cardiac failure in the last month of pregnancy or within 5 months of delivery;
- absence of recognizable heart disease prior to the last month of pregnancy;
- absence of identifiable causes for the cardiac failure;
- left ventricular systolic dysfunction demonstrated by classic echocardiographic criteria, such as depressed shortening fraction or ejection fraction.

Epidemiology

Peripartum cardiomyopathy has an incidence of 1:1,500 to 1:4,000 live births (4). In the United States, the prevalence is estimated to be 1 case per 1,300-15,000 live births. The prevalence is reported to be 1 case per 6,000 live births in Japan, 1 case per 1,000 live births in South Africa, and 1 case per 350-400 live births in Haiti.

PPCM is associated with several risk factors such as older maternal age, greater parity, black race and multiple gestations (4,5). It is unclear whether race is an independent risk factor: the African-American women have an increased risk but probably a greater incidence of hypertension in this group may influence this observation (4).

Etiology

The pathogenesis of PPCM is controversial and many possible causes have been proposed: myocarditis, abnormal immune response to pregnancy, maladaptive response to hemodynamic stresses of pregnancy, cytokine production, and prolonged tocolysis (5). Some familial cases of PPCM have been reported (6,7), raising the possibility that sometimes PPCM is actually a familial dilated cardiomyopathy unmasked by the pregnancy.

In the light of the presence of dense lymphocytic infiltrate, myocyte edema, necrosis, and fibrosis in ventricular biopsies of patients with PPCM, Melvin *et al.* (8) proposed myocarditis as the cause of PPCM. This hypothesis is consistent with the clinical improvement that is typically associated with immunosuppressive treatment (prednisone and azathioprine).

It has also been suggested that PPCM may have a viral cause (9-11).

Another important factor, which may cause PPCM, is the abnormal immune response to pregnancy associated with high titres of autoantibodies against particular cardiac tissue proteins (12). Rand *et al.* (13) postulated an immunological cause on the basis of the presence of heart muscle antibodies in cord blood and serum of neonates born from cardiomyopathic mother. The authors show that, after delivery, the fast degeneration of the uterus results in fragmentation of tropocollagen by collagenolytic enzymes releasing actin, myosin, and their metabolites; these antibodies are formed against actin and cross-react with the myocardium (14).

The hemodynamic stresses of pregnancy are considered a possible cause of PPCM: during pregnancy there are some alterations in the hemodynamic set-up (15) with subsequent transient hypertrophy (16). In the second and third trimesters of pregnancy a reversible decrease in the left ventricular systolic function

occurs, it persists up to the early postpartum period, but returns to baseline thereafter. It is possible that PPCM is due to exaggeration of this decrease in the systolic function (17).

Other possible etiologic factors include: prolonged tocolysis (18,19), proinflammatory cytokines (TNF, IL1, IL6) (20,21), excessive ingestion of salt (4,22,23). Abnormalities of relaxin, an ovarian hormone produced during pregnancy, can have positive inotropic and chronotropic properties and cause excessive relaxation of the cardiac skeleton (24). Deficiency of selenium may increase the heart-susceptibility to viral infection, hypertension or hypocalcemia (25).

It is unclear whether nutritional deficiencies may play a role in the pathogenesis of PPCM (22).

Clinical description

The women affected by PPCM have generally no case history except that in the last month of pregnancy, they show dyspnoea, fatigue and peripheral oedema. Coughing, orthopnoea and haemoptysis are frequently encountered and haemoptysis may be the presenting feature of a pulmonary embolus, to which these patients are particularly predisposed (4).

Signs and symptoms suggest a common heart failure and they are non-specific: paroxysmal nocturnal dyspnoea, chest pain, nocturnal cough, pulmonary crackles, increased jugular venous pressure, hepatomegaly. The use of NYHA (New York Heart Association) classification is not relevant because it lists the occurring signs and symptoms of normal pregnancy that may be similar to those of PPCM women; this classification may not accurately reflect the severity of the underlying cardiac dysfunction (26).

Physical examination frequently reveals an increase in blood pressure, although it may be normal or even decreased (1); tachycardia and third heart sound are noted in 85% of patients with PPCM and are typical signs of congestive failure (27).

Differential diagnosis

The distinction of PPCM from other forms of cardiomyopathy depends on the history and clinical features; the diagnosis is based on the exclusion of other known causes of cardiomyopathy.

Many of the symptoms and signs of pregnancy (dyspnoea, fatigue and pedal oedema) are similar to those of the early congestive heart failure, therefore an early heart failure can be easily missed in a pregnant patient. The diagnosis of PPCM should be seriously considered in all patients with persistent or worsening heart failure in the last month of

pregnancy or in the early puerperium. When the diagnosis of PPCM is considered, nearly every other cause of left ventricular dysfunction must be excluded such as myocardial infarction, sepsis, severe pre-eclampsia, pulmonary embolism, idiopathic dilated cardiomyopathy, valve disease (mitral and aortic stenosis) and pulmonary vasculitides (systemic lupus erythematosus, scleroderma, rheumatoid disease) (28).

Idiopathic dilated cardiomyopathy has clinical characteristics similar to PPCM, but the onset is not restricted to the peripartum period and can occur in the second trimester (29); for the other conditions, the differential diagnosis is not so difficult because the clinical aspects are evocative on the basis of radiological and blood evaluation.

Diagnostic methods

Electrocardiogram (ECG), chest radiogram, M-mode and two-dimensional Doppler echocardiographic studies should be routinely performed.

The ECG may be normal, but it usually demonstrates sinus tachycardia or atrial fibrillation. It is also possible to discover normal or low voltage and some criteria of left ventricular hypertrophy. Non-specific ST and T waves changes may be present; Q waves may be seen in the anteroseptal precordium; PR and QRS intervals may be prolonged showing intraventricular conduction defects; bundle branch blocks are occasionally present (4,30).

Chest-X-ray should be performed with abdominal shielding to evaluate the aetiology of hypoxia and exclude pneumonia. The chest-X-ray is not specific: it shows cardiomegaly with small bilateral pleural effusions; pulmonary venous congestion and bibasilar infiltrates are commonly seen (4,31,32).

Echocardiography is very important to exclude other causes of heart failure such as mitral valve disease, left atrial myxoma and pericardial disease (33). The echocardiogram usually shows a dilated left ventricle with marked impairment of overall systolic performance (4,34). The following echocardiographic criteria have been recommended: left ventricular fraction ejection of less than 45%, fractional shortening of less than 30% on an M-mode echocardiographic scan, or both, and a left ventricular end-diastolic dimension of more than 2.7 cm per square meter of body-surface area (35).

Hemodynamic examinations are not usually performed but may show an elevated right-heart and left-heart filling pressure, with diminished cardiac output; the left ventriculography usually demonstrates a global reduction in the left

ventricular systolic performance; coronary arteriograms are generally normal (35).

The endomyocardial biopsy should be considered to confirm the diagnosis if the nature of PPCM remains unclear (36).

Finally, to rule out infection as the cause of the cardiomyopathy, serum samples should be tested by bacterial and viral culture and for Coxsackie's B virus titres.

Treatment

Non-medication regimen is very important, particularly in women with symptoms and signs of heart failure; it includes salt (sodium < 4 mg/day) and water restriction (< 2 L/day). Once heart failure symptoms have been controlled, modest exercise such as walking and cycling has been proven to improve survival. Bed rest is not recommended because it predisposes pregnant women to develop deep venous thrombosis with subsequent pulmonary embolism.

Diuretics are indicated when sodium restriction alone is therapeutically unsuccessful (4,37). Maternal complications of diuretic therapy include pancreatitis, volume contraction, alkalosis, decreased carbohydrate tolerance, hypokalaemia, hyponatraemia and hyperuricaemia (37). Bleeding diathesis and hyponatraemia have been reported in neonates of patients who have taken diuretics during pregnancy.

Since in PPCM patients it is necessary to reduce both the heart preload and afterload and to increase the inotropy force of the heart; the therapy is similar to that for the other forms of heart failure.

Angiotensin-converting enzyme (ACE) inhibitors (captopril, enalapril, lisinopril, and others, more recently introduced) or angiotensin II receptors blockers are effective in reducing the afterload and should be considered a mainstay of treatment for PPCM after delivery (38,39). They are contraindicated during pregnancy for severe adverse neonatal renal effects (40,41); neonatal deaths (40) have been reported after ACE-inhibitors therapy during pregnancy. ACE-inhibitors are excreted into breast milk (42,43) and the breastfeeding should be discouraged in patients who require ACE inhibitor therapy.

Hydralazine in combination with nitroglycerin or amlodipine (44,45) is the first choice treatment of the prepartum PPCM. Hydralazine has been used parenterally and orally for decades in the treatment of severe hypertension in pregnancy and appears to be safe for the mother and the fetus (44).

Amlodipine is the only calcium-blocker used for the treatment of PPCM; other calcium blockers

may be associated with a negative inotropic effect and should be avoided (46).

Oral inotropic therapy is provided by digoxin (47,48), that is also useful in cases of atrial fibrillation. Digoxin is believed to be safe in pregnancy even if crosses the placental barrier. Digoxin is also secreted in breast milk (42), the infant typically ingests a very small percentage of the dose, but no side effects have been reported in newborns (43).

β -blocking agents may have beneficial effects in selected patients with dilated cardiomyopathy. The deleterious effects of excessive sympathetic nervous system activation may be blocked with low-dose β -blockers (49,50). During pregnancy, β -blockers may improve hemodynamic function by reducing heart rate, reducing catecholamine toxicity, up-regulating myocardial β -adrenergic receptors, and improving ventricular diastolic function and rate of the survival (51,52). It is necessary to remember that the long-term use of β -blockers during pregnancy may be associated with low-birth-weight babies (42).

In highly symptomatic patients or in those treated for acute illness, intravenous preload and afterload reducing agents (such as nitroprusside, nitroglycerin) or inotropic agents (such as dobutamine, dopamine, milrinone) should be considered. In particular, the risks of nitroprusside therapy should be evaluated, because the thiocyanate and cyanide may accumulate in the foetus (42).

Immunosuppressive therapy (prednisone or azathioprine) can be considered for pregnant women with myocarditis demonstrated by cardiac biopsy and those who did improve after antifailure treatment (53).

A recent retrospective study suggested that women with PPCM treated with intravenous immune globulin had greater improvement in ejection fraction during follow-up than patients treated conventionally (54).

For patients with poor cardiac function, as evidenced by fraction ejection <35% and risk of thromboembolism anticoagulation should be considered (55) and continued until at least 6 weeks postpartum.

Oral anticoagulants such as warfarin are absolutely contraindicated in pregnancy because they cross the placenta carrying a risk of teratogenic effects (56) and spontaneous fetal cerebral hemorrhage but they are safe in the post partum period. Before delivery, unfractionated or low molecular weight heparins are the drugs of choice (57). Heparin does not cross the placental barrier; it has short half-life and can be discontinued before delivery to prevent maternal haemorrhage. Heparin has several side effects (depletion of antithrombin III,

thrombocytopenia, premature maternal osteoporosis) infrequently seen in patients with PPCM. Low-molecular weight heparins have been used widely in pregnancy for treatment of venous thrombosis and have the advantage to be measured out easily; it reduced the risks of thrombocytopenia and osteopenia (57). Neither heparin nor warfarin are secreted into the breast milk and therefore do not have anticoagulant effect in the breast-fed infant (43).

References

1. Homans DC. Peripartum cardiomyopathy. *N Engl J Med* 1985;312:1432-7
2. Lampert MB, Lang RM. Peripartum cardiomyopathy. *Am Heart J* 1995;130:860-70.
3. Richie C. Clinical contribution to the pathology, diagnosis and treatment of certain chronic diseases of the heart. *Edinb Med Surg J* 1849;2:333-42.
4. Demakis JG, Rahimtoola SH, Sutton GC, Meadows WR, Szanto PB, Tobin JR, et al. Natural course of peripartum cardiomyopathy. *Circulation* 1971;44:1053-61.
5. Demakis JG, Rahimtoola SH. Peripartum cardiomyopathy. *Circulation* 1971;44:964-8.
6. Pierce JA, Price BO, Joyce JW. Familial occurrence of postpartal heart failure. *Arch Inter Med* 1963;111:651-5.
7. Pearl W. Familial occurrence of peripartum cardiomyopathy. *Am Heart J* 1995;129:421-422.
8. Melvin KR, Richardson PJ, Olsen EG, Daly K, Jackson G. Peripartum cardiomyopathy due to myocarditis. *N Engl J Med* 1982;307:731-4.
9. Woolford RM. Postpartum myocarditis. *Ohio State Med* 1952;48:924-30.
10. Midei MG, DeMent SH, Feldman AM, Hutchins GM, Baughman KL. Peripartum myocarditis and cardiomyopathy. *Circulation* 1990;81:922-8.
11. Cenac A, Gaultier Y, Devillechabrolle A, Moulias R. Enterovirus Infection in peripartum cardiomyopathy. *Lancet* 1988;2:968-9.
12. Witlin AG, Mable WC, Sibai BM. Peripartum cardiomyopathy: an ominous diagnosis. *Am J Obstet Gynecol* 1997;176:182-8.
13. Rand RJ, Jenkins DM, Scott DG. Maternal cardiomyopathy of pregnancy causing stillbirth. *BJOG* 1975;82:172-5.
14. Hauck AJ, Kearney DL, Edwards WD. Evaluation of postmortem endomyocardial biopsy specimens from 38 patients with lymphocytic myocarditis: implications for role of sampling error. *Mayo Clin Proc* 1989;64:235-45.
15. Geva T, Mauer MB, Striker L, Kirshon B, Pivarnik JM. Effects of physiologic load of pregnancy on left ventricular contractility and remodeling. *Am Heart J* 1997;133:53-59.

16. Mone SM, Sanders SP, Colan SD. Control mechanism for physiological hypertrophy of pregnancy. *Circulation* 1996;94:667-672.
17. Julian DG, Szekeley P. Peripartum cardiomyopathy. *Prog Cardiovasc Dis* 1985;27:233-246.
18. Witlin AG, Mable WC, Sibai BM. Peripartum cardiomyopathy: an ominous diagnosis. *Am J Obstet Gynecol* 1997;176:182-188.
19. Ludwig P, Fischer E. Peripartum cardiomyopathy. *Aust N Z J Obstet Gynaecol* 1997;37:156-160.
20. Mann DL. Stress activated cytokines and the heart. *Cytokine Growth factor Rev* 1996;7:341-354.
21. 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.
22. O'Connell JB, Costanzo-Nordin MR, Subramanian R, Robinson JA, Wallis DE, Scanlon PJ, et al. Peripartum cardiomyopathy: clinical, hemodynamic, histologic and prognostic characteristics. *J Am Coll Cardiol* 1986;8:52-6.
23. Carvalho A, Brandao A, Martinez EE, Alexopoulos D, Lima VC, Andrade JL, et al. Prognosis in peripartum cardiomyopathy. *Am J Cardiol* 1989;64:540-2.
24. Coulson CC, Thorp JM Jr, Mayer DC, Cefalo RC. Central hemodynamic effects of recombinant human relaxin in the isolated, perfused rat heart model. *Obstet Gynecol* 1996;87:610-12.
25. Kothari SS. Aetiopathogenesis of peripartum cardiomyopathy: prolactin-selenium interaction? *Int Cardiol* 1997;60:111-114.
26. Lee W. Clinical management of gravid women with peripartum cardiomyopathy. *Obstet Gynecol Clin North Am* 1991;18:257-71.
27. Veille JC. Peripartum cardiomyopathies: a review. *Am J Obstet Gynecol* 1984;148:805-18.
28. Report of the WHO/ISFC task force on the definition and classification of cardiomyopathies. *Br Heart J* 1980;44:672-3.
29. Yacoub A, Martel MJ. Pregnancy with primary dilated cardiomyopathy. *Obstet Gynecol* 2002;99:928-30.
30. Rosen SM. Puerperal cardiomyopathy. *BMJ* 1959;2:5-9.
31. Meadows WR. Idiopathic myocardial failure in the last trimester of pregnancy and the puerperium. *Circulation* 1957;15:903-14.
32. Walsh JJ, Burch GE, Black WC, Ferrans VJ, Hibbs RG. Idiopathic myocardopathy of puerperium. *Circulation* 1965;32:19-31.
33. Mann MS, Cossham PS, Baker JL, Hurley PA. Left atrial myxoma in the second trimester of pregnancy. Case report. *BJOG* 1987;94:592-3.
34. Sanderson JE, Adesanya CO, Anjorin FI, Parry EO. Postpartum cardiac failure: heart failure due to volume overload. *Am Heart J* 1979;97:613-21.
35. Hibbard JU, Linheimer M, Lang RM. A modified definition for peripartum cardiomyopathy and prognosis based on echocardiography. *Obstet Gynecol* 1999;94:311-6.
36. Hauck AJ, Kearney DL, Edwards WD. Evaluation of postmortem endomyocardial biopsy specimens from 38 patients with lymphocytic myocarditis: implications for role of sampling error. *Mayo Clin Proc* 1989;64:235-45.
37. Lindheimer MD, Katz AI. Sodium and diuretics in pregnancy. *N Engl J Med* 1973;288:891-4.
38. Schubiger G, Flury G, Nussberger J. Enalapril for pregnancy-induced hypertension: acute renal failure in a neonate. *Ann Inter Med* 1998;108:215-6
39. SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;325:293-305.
40. Rosa FW, Bosco LA, Fosum-Graham C. Neonatal anuria with maternal angiotensin-converting enzyme inhibition. *Obstet Gynecol* 1989;4:371-4.
41. Schubiger G, Flury G, Nussberger J. Enalapril for pregnancy-induced hypertension: acute renal failure in a neonate. *Ann Inter Med* 1998;108:215-6.
42. Briggs GG, Freeman RH, Yaffe SJ. *Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk*. 2nd. Baltimore: Williams & Wilkins, 1986.
43. White WB. Management of hypertension during lactation. *Hypertension* 1984;6:297-300.
44. Cohn JN, Johnson G, Ziesche S, Cobb F, Francis G, Tristani F, et al. A comparison of enalapril with hydralazine and isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med* 1991;325:303-10.
45. Packer M, O'Connor CM, Ghali JK, Pressler ML, Carson PE, Belkin RN, et al. for the PRAISE Study Group. Effect of amlodipine on morbidity and mortality in severe chronic heart failure. *N Engl J Med* 1996;335:1107-14.
46. O'Connor CM, Belkin RN, Carson PE, et al. Effect of amlodipine on mode of death in severe chronic heart failure: the PRAISE Trial. *Circulation* 1995;92:1-143.
47. Uretsky BF, Young JB, Shahidi FE, Yellen LG, Harrison MC, Jolly MK. Randomised study assessing the effect of digoxin with-drawl in

patients with mild to moderate chronic congestive heart failure: result of the PROVED trial. *J Am Coll Cardiol* 1993;22:955-62.

48. Packer M, Gheorghide M, Young JB, Costantini PJ, Adams KF, Cody RJ et al. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting enzyme inhibitors. *N Engl J Med* 1993;329:1-7.

49. Waagstein F, Bristow MR, Swedberg K, Camerini F, Fowler MB, Silver MA. Beneficial effect of metoprolol in idiopathic dilated cardiomyopathy. *Lancet* 1993;342:1441-6.

50. CIBIS Investigators and Committees. A randomized trial of beta-blockade in heart failure: the Cardiac Insufficiency Bisoprolol Study (CIBIS). *Circulation* 1994;90:1765-73.

51. Anderson JL, Gilbert EM, O'Connell JB, Renlund D, Yanowitz F, Murray M, et al. Long-term (2 year) beneficial effects of beta-adrenergic blockade with bucindolol in patients with idiopathic dilated cardiomyopathy. *J Am Coll Cardiol* 1991;17:1373-81.

52. Anderson B, Blomstrom-Lundqvist C, Hedner T, Waagstein F. Exercise hemodynamics and

myocardial metabolism during long-term beta-adrenergic blockade in severe heart failure. *J Am Coll Cardiol* 1991;18:1059-66.

53. National Heart, Lung, and Blood Institute and Office of Rare Diseases (National Institutes of Health) Workshop Recommendations and Review. Peripartum cardiomyopathy. *JAMA* 2000;9:1183-88.

54. Bazkurt B, Villaneuva FS, Holubkov R, et al. Intravenous immune globuline in the therapy of peripartum cardiomyopathy. *J Am Coll Cardiol*. 1993;34:177-180.

55. Ginsberg JS, Hirsch J. Anticoagulants during pregnancy. *Annu Rev Med* 1989;40:79-86.

56. Leitman PS. Congenital malformations associated with the administration of oral anticoagulants during pregnancy. *J Pediatr* 1975;86:459-62

57. Sanson BJ, Leansing AW, Prins MH, Ginsberg JS, Barkagan ZS, Lavenne-Pardonge E et al. Safety of low-molecular-weight heparin in pregnancy: a systematic review. *Thromb Haemost* 1999;81:668-72.