A MODIFIED DEFINITION FOR PERIPARTUM CARDIOMYOPATHY AND PROGNOSIS BASED ON ECHOCARDIOGRAPHY

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The diagnosis of peripartum cardiomyopathy is one of exclusion, made after careful search for an underlying cause. Research in this area is compromised by the reliance of some on clinical criteria alone without strict echocardiographic criteria. This article argues for uniform criteria that define peripartum cardiomyopathy, similar to the criteria for idiopathic dilated cardiomyopathy set forth by a National Heart, Lung, and Blood Institute–sponsored workshop and proposes that the new definition include heart failure within the last month of pregnancy or 5 months postpartum; absence of preexisting heart disease; no determinable etiology, the traditional definition; and strict echocardiographic criteria of left ventricular dysfunction: ejection fraction less than 45%, or M-mode fractional shortening less than 30%, or both, and end-diastolic dimension more than 2.7 cm/m^2. Mortality from peripartum cardiomyopathy remains high, 25–50%, and a recent review related long-term prognosis to echocardiographic measures of left ventricular chamber dimension and function at diagnosis and recovery. We describe a modified pharmacologic echocardiographic stress test that might be useful in determining left ventricular contractile reserve in women believed to be recovered by routine echocardiographic studies. The test reproduces hemodynamic stress akin to pregnancy, and the data might be useful when counseling women on future childbearing. Women who respond with reduced cardiac reserve might be advised to avoid pregnancy. (Obstet Gynecol 1999;94:311–6. © 1999 by The American College of Obstetricians and Gynecologists.)

Peripartum cardiomyopathy is a rare cause of heart failure late in pregnancy or during the postpartum period, with guarded prognosis. Traditionally it has been associated with older maternal age, greater parity, black race, and multiple gestation, but it also has been linked recently to β-mimetic tocolytic therapy and cocaine abuse.[1,2] The underlying cause remains elusive, and hypotheses include viral myocarditis, and autoimmune factors.[1,3,4] Diagnosis is essentially by exclusion, clinicians assuming that other problems such as volume overload, hypertension with systolic dysfunction, and sepsis, all of which occur at or after term, are absent. Review of the literature shows that diagnoses have varied, often made solely upon clinical evidence, whereas prognosis and course have been based purely on qualitative assessments. Attempts to use invasive endomyocardial biopsy for more specific diagnosis and prognosis have been disappointing, showing nonspecific evidence of myofiber hypertrophy, degeneration, and fibrosis.[5] Newer and easily available noninvasive technologies permit a modified definition, based not only on clinical findings but also on a set of strict echocardiographic criteria and more definitive diagnosis of peripartum cardiomyopathy.[5] These new criteria will be elaborated. Evaluation by echocardiographic measurements of left ventricular chamber dimension and function at diagnosis and recovery and by echocardiographic stress tests using pharmacologic stimulation with dobutamine to determine contractile reserve will be considered and recommended.

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Defining the Disease

Cardiac failure in the puerperium was first mentioned in the middle 19th century, but many years passed before toxic postpartal heart disease was characterized as a unique disorder related to pregnancy that occurred within 6 months after delivery. However, not all investigators agreed the disorder was dependent upon pregnancy.[1] Walsh and Burch[6] recommended that for inclusion as postpartal heart disease, the cause must be undetermined and unequivocally related to gestation, appearing de novo in the first to 20th week postpartum. Only then could diagnosis of this unique condition be assured, but still peripartum cardiomyopathy did not receive universal acceptance. Demakis et al[7] expanded the definition to include heart failure during the last month of pregnancy through the fifth month postpartum, without heart disease before the last gestational month, and no determinable cause.

Because peripartum cardiomyopathy can masquerade as other serious illnesses, it is crucial that any pregnant woman presenting with evidence of heart failure be carefully evaluated. Initial complaints might be confusing because the normal physiologic changes of pregnancy—increased blood volume, heart rate, and cardiac output—often result in symptoms and signs similar to those of congestive heart failure. This is especially true during the third trimester, when most gravidas have dyspnea, pedal edema, fatigue, and inability to lie supine.

When diagnosis of heart failure is suspected, every effort must be made to exclude preexisting cardiac

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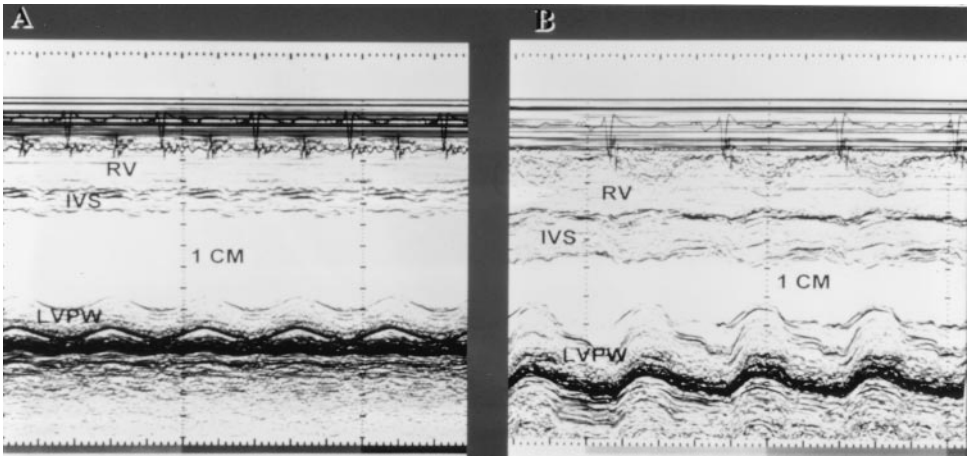

Figure 1. Two-dimensionally targeted M-mode echocardiogram in woman with peripartum cardiomyopathy (A) at diagnosis, showing left ventricular dilatation and severe reduction in ventricular performance, and (B) after clinical recovery of left ventricular function, confirmed by improvement in chamber dimension, and normalization of function. RV = right ventricle; IVS = interventricular septum; LVPW = left ventricular posterior wall. The left ventricular cavity lies between the IVS and LVPW.

disease or other underlying disorders. Establishing a specific cause for left ventricle failure excludes the diagnosis of peripartum cardiomyopathy. Left ventricular dysfunction and dilatation is essential for the diagnosis; gravidas who present with pulmonary edema and normal left ventricular function and dilatation should not be labeled with peripartum cardiomyopathy. Dysfunction of a hypertrophic ventricle, seen in long-standing chronic hypertension, does not qualify for this disease state. In that respect, pulmonary edema in pregnancy can be caused by congenital heart disease, rheumatic heart disease, pulmonary disease, thromboembolic phenomena, or sepsis, and in most of those clinical scenarios an echocardiogram will help identify the underlying disorder.

Other entities or situations that can present with signs and symptoms of heart failure include preeclampsia, overvigorous administration of tocolytic agents, fluid overload during steroid use or multiple gestation, and rarely amniotic fluid (AF) embolism. In most of those cases echocardiography will reveal a normal-sized left ventricle with preserved systolic function. Although physical examination, chest film, and electrocardiogram might support diagnosis of peripartum cardiomyopathy, echocardiography will measure ventricular size and function. In normal pregnancy, despite increased left ventricular volume and dimension, most echocardiographic characteristics of left ventricular function, such as ejection fraction, fractional shortening, and contractility, are the same as when not pregnant.[5]

An instructive case in point is that of the Zorian tribe in Nigeria, where peripartum cardiomyopathy was reported in 1% of pregnancies. Further investigation with echocardiography found that most of those women suffered volume overload, related to tribal customs but had normal left ventricular function.[8] Burch et al[9] noted that many women initially diagnosed with peripartum cardiomyopathy were, on later review, found to have sepsis, profound anemia, or toxemia, shedding doubts on the validity of the original diagnosis of peripartum cardiomyopathy. Cunningham et al[10] documented that 21 of 28 cases of presumed peripartum cardiomyopathy actually had underlying conditions that could account for its presentation. Heart failure in those women could be attributed instead to chronic hypertension, valvular disease, and medical complications such as thyrotoxicosis. However, even in their seven well-defined peripartum cardiomyopathy subjects, one lacked echocardiographic documentation of left ventricular dimensions and function, and upon death, no autopsy was done. It is likely that reports on peripartum cardiomyopathy that preceded the widespread use of echocardiography, or more recent articles in which echocardiography was not consistently used, included women who did not have the disease.[5]

It is surprising that no modifications have been added to the classic definition of peripartum cardiomyopathy since 1971. Veille in 1984[1] recommended inclusion of echocardiographic criteria in making this rare diagnosis but included no specific criteria.

Echocardiographic Characteristics

Echocardiography has the advantage over pulmonary artery catheterization of being noninvasive and allowing serial evaluations in pregnant women (Figure 1). It is superior to gated radionuclide scanning because it does not require radiation, it provides information on cardiac dimensions, wall thicknesses and function, it defines valvular abnormalities and congenital defects, and it diagnoses intracardiac masses.

O'Connell et al[3] and van Hoeven et al[11] compared the

cardiovascular characteristics of peripartum cardiomyopathy patients and those of women with idiopathic dilated cardiomyopathy and found that they are similar. Thus, applying echocardiographic criteria used to diagnose idiopathic dilated cardiomyopathy to peripartum heart failure would be sensible. Dec and Fuster[12] described echocardiographic criteria for diagnosing idiopathic dilated cardiomyopathy, of which they considered peripartum cardiomyopathy to be a subset. The authors included an ejection fraction of less than 45% with left ventricular dilatation in their criteria, but they did not provide specific criteria for left ventricular chamber dimension. More recently, the echocardiographic criteria for diagnosis of idiopathic dilated cardiomyopathy, recommended at a National Heart, Lung, and Blood Institute–sponsored workshop, were left ventricular ejection fraction of less than 45% or M-mode fractional shortening less than 30%, or both, with left ventricular end-diastolic dimension greater than 2.7 cm/m^2.[13]

Reports on peripartum cardiomyopathy vary in their inclusion of echocardiographic data. Table 1 details the available reports that provide echocardiographic documentation of left ventricular dysfunction in peripartum cardiomyopathy subjects. Most of the studies report left ventricular ejection fraction and percent fractional shortening well below the criteria for idiopathic dilated cardiomyopathy, and Figure 1A is an example of an M-mode echocardiogram with left ventricular dilatation in such a peripartum cardiomyopathy subject. We propose a modification of the classic clinical definition for diagnosing peripartum cardiomyopathy, incorporating strict echocardiographic criteria. This more stringent definition will make future reports in the obstetric literature more uniform and easier to compare, and will improve the overall quality of research reports on this disease.

Table 1. Echocardiographic Findings in Peripartum Cardiomyopathy

	n	Left ventricular end-diastolic dimension (cm + SD)	Ejection fraction (%)	Fractional shortening (%)
Aroney[14]	5	6.7 ± 0.7		13 ± 5
O'Connell[3]	14	6.2 ± 1.1	18.1 ± 10.9	
Cole[15]	10		29 ± 5	
Carvalho[16]				
Mild	8	5.8 ± 0.7		
Severe	11	6.9 ± 0.6		
Midei[4]	18	7.0 ± 0.2	17 ± 2	
Ravikishore[17]	20	6.2 ± 0.3	26 ± 8	16 ± 2
Hsieh[18]	6	6.6 ± 0.62	19.8 ± 4.2	
Lampert[2]	15	6.12 ± 0.6		15.7 ± 6.2
van Hoeven[11]				
Myocarditis	6	5.6 ± 0.5	20.2 ± 2.1	10 ± 2.0
No myocarditis	7	6.7 ± 0.3	25.9 ± 4.0	15 ± 3
Cloatre[19]	30	6.04 ± 0.7	24.6 ± 10.9	15.5 ± 6.5
Witlin[20]	28	6.5 ± 0.7		17.9 ± 6.8

Data are expressed as the mean ± standard deviation.

Table 2. Diagnostic Criteria for Peripartum Cardiomyopathy

All four of the following:
1. Heart failure within:
   Last month of pregnancy
   5 months postpartum
2. Absence of prior heart disease
3. No determinable cause
4. Strict echocardiographic indication of left ventricular dysfunction:
   - Ejection fraction <45%
     AND/OR
   - Fractional shortening <30%
   - End-diastolic dimension >2.7 cm/m^2

Our new criteria for defining peripartum cardiomyopathy are listed in Table 2. To the traditional clinical criteria, we have added echocardiographically defined left ventricular dysfunction criteria: left ventricular ejection fraction less than 45% or M-mode fractional shortening less than 30% (Figure 1A), or both, and increased end-diastolic diameter greater than 2.7 cm/m^2 (for a 70–80 kg woman, this is 4.3–4.8 cm). We are suggesting these criteria parallel those set forth for idiopathic dilated cardiomyopathy, described above because there are no widely used or accepted characteristics in obstetrics or cardiology for peripartum cardiomyopathy. The American Society of Echocardiography–recommended method for calculating left ventricular volumes, on which ejection fraction is based, is the biplane method of disks.[21] The formula, shown below, is relatively independent of geometric assumptions regarding ventricular shape. It requires tracing the endocardial border at end-diastole and end-systole for both apical four-chamber and apical two-chamber views, which should be 90° apart, and the apical long-axis dimension should be similar for both views.

$$V = \frac{\pi}{4}\sum_{i=1}^{20} a_i b_i \left(\frac{L}{20}\right)$$

where "a" is a two-chambered diameter, "b" is a four-chambered diameter, and "L" is the left ventricular long-axis length.

Long-term Prognosis

Prognosis in peripartum cardiomyopathy continues to be guarded, with mortality still 25–50% and most deaths within the first 3 months of diagnosis.[1,6,7,9,10]

Women who remit usually do so early and are recovered completely within 6 months. In the past, long-term prognosis was linked to cardiomegaly seen on chest film 6 months after initial diagnosis.[7] More recent reports correlated long-term prognosis with degree of left ventricular dysfunction at diagnosis. O'Connell et al[3] found that when women with idiopathic dilated cardiomyopathy and peripartum cardiomyopathy were compared, women with peripartum heart failure were younger and had shorter illnesses. Women who survived peripartum cardiomyopathy have higher ejection fractions and fractional shortening and smaller left ventricular end-diastolic diameters,[3,14] similar to the natural histories of women with idiopathic dilated cardiomyopathy. van Hoeven et al[11] also compared women with peripartum cardiomyopathy to a group with idiopathic dilated cardiomyopathy and agreed that long-term prognosis was related to ejection fraction but were unable to show that left ventricular end-diastolic dimension was a good predictor of outcome. Ravikishore et al[17] and Carvalho et al[16] showed that poor prognosis was related to greater left ventricular chamber dimensions in peripartum cardiomyopathy, whereas Witlin et al[20] noted no association between fractional shortening and long-term survival and documented a trend toward increased left ventricular diameters in women with progressive disease. Witlin et al[22] recently reported that women with left ventricular end-diastolic dimension at least 60 mm and fractional shortening at most 21% were unlikely to regain normal cardiac function on follow-up echocardiograms. Cole et al[15] compared peripartum cardiomyopathy subjects to normal postpartum subjects and were the only investigators unable to show that left ventricular size and function predicted outcome in peripartum heart failure. Therefore, we suggest that echocardiography be used serially, every 3 months, to evaluate long-term prognoses. Those with documented poor recovery might be considered for cardiac transplants, a successful treatment for those typically young women.

Prognosis in Future Pregnancy

Counseling women about future childbearing is often difficult. Women whose ventricular function has not returned to normal usually are advised against pregnancy. However, it is not clear how to advise the 50–75% of women who seem to have fully recovered, as indicated by normal left ventricular size and function, on prognosis with future childbearing. Recurrence rates for peripartum cardiomyopathy with additional pregnancies are 50–100% in older reports.[1,9] Demakis et al[7] in their classic article noted a 25–50% risk of recurrence. With more modern diagnostic and treatment methods, one might expect improved outcomes, and at least one author suggested it in a case report,[23] but Witlin et al[20] show a recurrence rate of 67% with subsequent pregnancies, which contradicts that belief.

It appears that only three investigators have tried to base future conception advice on quantitative evidence. Demakis et al[7] used chest radiographic findings done 6 months after initial diagnosis, in which cardiac size was predictive of outcome. Of women with normal-sized hearts who had subsequent pregnancies, 25% had recurrence of symptoms in those pregnancies. Among those in whom the cardiac size remained large, 50% with subsequent pregnancies experienced recurrence of the condition, and all of those died. Sutton et al[23] used echocardiography to quantitate left ventricular size and function in four women who wanted future pregnancies 3 years after their initial diagnoses of peripartum cardiomyopathy. All were considered normal and did well in their subsequent pregnancies. None had any change in left ventricular diameters or fractional shortening during or after the pregnancies.

Modified Dobutamine Stress Test to Quantitate Left Ventricular Contractile Reserve

We postulated that mimicking the cardiovascular stress of gestation in nonpregnant women recovered from postpartum cardiomyopathy would provide more objective data to counsel them on future pregnancies. A study was designed to quantitatively assess left ventricular contractile reserve in women with histories of peripartum cardiomyopathy.[24] Women recruited were similar to those of Sutton et al[23] in that their echocardiographic end-diastolic dimensions and fractional shortening had returned to the normal range of values (Figure 1B). The test was a modification of routine dobutamine stress echocardiography, a technique that assesses left ventricular contractile reserve. Dobutamine is a synthetic sympathomimetic amine that directly stimulates β-1 receptors in the myocardium to increase myocardial contractility, with only a mild increase in heart rate and a small decrease in peripheral arterial resistance. Dobutamine stress echocardiography, developed in this decade, has become a safe and accurate method of evaluating changes in the left ventricular contractile state, detecting coronary artery disease and localized wall motion abnormalities, and evaluating myocardial viability in women with acute and chronic left ventricular dysfunction.[25] In our study, the standard protocol for nonpregnant populations was modi-

fied to administer a small dose of dobutamine, but enough to challenge the left ventricle, mimicking many cardiovascular changes of normal pregnancy, especially increased cardiac output (on average 25%) and heart rate, and decreased total peripheral vascular resistance.[24] Contractile reserve, or left ventricular systolic reserve capacity, was quantitated using the change in rate-corrected velocity of fiber shortening.[25] The results showed that contractile reserve, or change in left ventricular contractility over baseline values, was significantly less in the women with recovered peripartum cardiomyopathy and normal routine echocardiography than in a group of normal matched control subjects challenged in an identical manner.[24]

Subclinical systolic dysfunction in seemingly recovered peripartum cardiomyopathy subjects raises concerns. We suspect that subjecting those women to the hemodynamic stress of pregnancy might cause the reappearance of clinical disease. Subclinical systolic dysfunction might explain the reported high incidence of recurrent peripartum cardiomyopathy with new pregnancies in those women, and might indicate decreased ventricular contractile reserve with continued hemodynamic stress induced by pregnancy, and not a true exacerbation of the disorder. The number of women in our study is small, and further studies are needed to evaluate outcomes of future pregnancies after stress testing. Still we consider women with histories of peripartum cardiomyopathy at increased risk, even when routine echocardiography is normal. We advise against conceiving again, urging the the most dependable contraceptive methods. If a woman has a strong desire to conceive again, and many do, we believe that a state-of-the-art cardiovascular evaluation should be done, including a dobutamine stress echocardiogram before a decision is made.

Conclusion

This disease's existence was once debated, but now it can be clearly and consistently defined, allowing more uniform investigation of underlying causes, new management schemes, and more accurate prognoses.

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