

Outcome of Subsequent Pregnancy in Patients With Documented Peripartum Cardiomyopathy

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Subsequent pregnancy in 6 patients with previous peripartum cardiomyopathy resulted in reduction of ejection fraction by >10% in 5 patients at 1 month postpartum. Two patients with impaired ejection fraction at onset of subsequent pregnancy died 3 months postpartum due to heart failure despite optimal medical therapy. Deterioration of left ventricular function occurred uniformly postpartum and was accompanied by elevation of tumor necrosis factor- α plasma levels from 2.4 ± 1.1 pg/ml at onset of subsequent pregnancy to 6.2 ± 2.4 pg/ml at 1 month postpartum.

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Peripartum cardiomyopathy (PC) is a disorder of unknown origin in which symptoms of heart failure occur between the last month of pregnancy and 5 months postpartum. A high mortality rate and overall poor clinical outcome has been reported in a high percentage of these patients.¹⁻⁵ Similar to other causes of heart failure,⁶⁻⁸ we found elevated plasma levels of tumor necrosis factor (TNF)- α , interleukin-6, and Fas/Apo-1 (a marker of apoptosis) in this population. Although the definition of PC specifies the development of clinical heart failure within a defined time period, the occurrence and timing of objective left ventricular dysfunction in relation to symptoms and gestation period are unknown. Between November 1996 and March 2001 we prospectively followed 6 patients who became pregnant for a second time from a previously published cohort of 59 consecutive black patients with documented PC¹ attending the Cardiac Clinic at Chris Hani Baragwanath Hospital. Serial echocardiography and TNF- α measurements were performed.

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Inclusion criteria were: (1) age ≥ 16 and ≤ 40 years, (2) New York Heart Association functional class II to IV, (3) symptoms of congestive heart failure that developed in the last month of pregnancy or in the first 5 months postpartum, (4) no other identifiable cause for heart failure, (5) left ventricular ejection fraction $\leq 40\%$ by transthoracic echocardiography, and (6) sinus rhythm.

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Exclusion criteria were: (1) significant organic valvular heart disease, (2) systolic blood pressure >170 mm Hg and/or diastolic blood pressure >105 mm Hg, and (3) clinical conditions other than cardiomyopathy that could increase the cytokine levels, (i.e., rheumatoid arthritis, sepsis, acquired immunodeficiency syndrome).

Clinical assessment, echocardiography, and cytokine measurements were performed at baseline and after 6 and 12 months of therapy. All patients received treatment with digoxin, diuretics, enalapril, and carvedilol. Patients attended the cardiac clinic monthly. They were advised to avoid new pregnancies and were followed up prospectively. In the group of patients with subsequent pregnancy, echocardiography was performed at 8 weeks and 8 months of pregnancy and 1 and 3 months postpartum. At the same time intervals, blood was taken for cytokine measurements. The protocol was approved by the Committee for Research on Human Subjects of the University of the Witwatersrand.

Fifteen milliliters of blood was drawn from an antecubital vein and collected into prechilled evacuated tubes containing ethylenediaminetetraacetic acid. Plasma was separated by centrifugation at 2,500 rpm for 12 minutes within 15 minutes of collection; the aliquots were frozen at -70°C . TNF- α measurements were performed using a commercially available enzyme-linked immunoassay (Amersham, Maidstone, United Kingdom). In addition, plasma was obtained from 20 age-matched healthy black volunteers.

Two-dimensional targeted M-mode echocardiography with Doppler color flow mapping was performed using a Hewlett Packard Sonos 5500 echocardiograph (Philips, Bothell, Washington) attached to a 2.5- or 3.5-MHz transducer. All studies were recorded on videotape and were done by the same operator. Left ventricular dimensions were measured according to the American Society of Echocardiography guidelines.⁹ For left ventricular measurements, an average of ≥ 3 beats were obtained. Left ventricular ejection fraction was determined as previously described.¹⁰

Data are presented as mean \pm SD. Wilcoxon matched pairs test was used for comparison of baseline data and the results 1 and 3 months after subsequent pregnancy. Data were analyzed on a personal computer using a commercially available statistical program (Statistica, Tulsa, Oklahoma). Significance was assumed at a 2-tailed value of $p < 0.05$.

All 6 patients were indigenous black women (age range 26 to 39 years). Four patients were para 2, gravida 2, and 2 were para 3, gravida 3. The subsequent pregnancy occurred 1 to 2 years after the initial pregnancy in all patients. None were twin or multiple

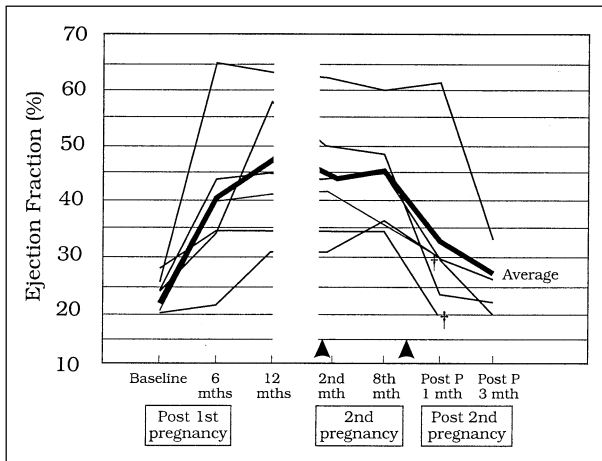


FIGURE 1. Time course pattern of left ventricular function in patients with PC and subsequent pregnancy. † $p \leq 0.05$ comparing 8 months of pregnancy versus 3 months postpartum.

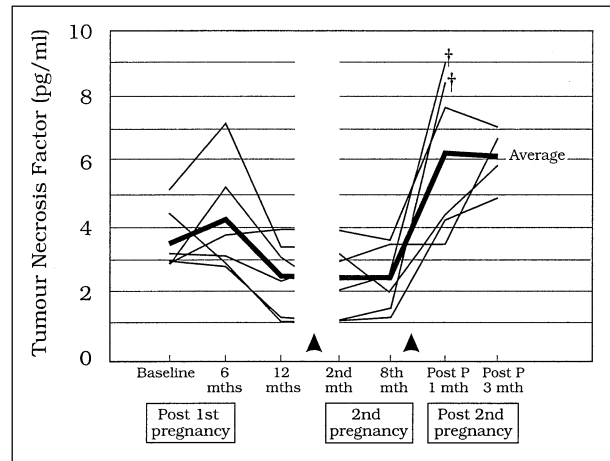


FIGURE 2. Time course pattern of TNF- α in patients with PC and subsequent pregnancy. † $p \leq 0.05$ comparing 8 months of pregnancy versus 3 months postpartum.

pregnancies and none of the patients had pregnancy-related hypertension or eclampsia. All patients had a normal vaginal delivery at term. All patients were in New York Heart Association functional class I at onset of subsequent pregnancy and remained asymptomatic until delivery. Heart failure symptoms occurred uniformly in all patients in the postpartum period. Furosemide (mean dose 105 ± 15 mg/day), digitalis 0.25 mg/day, enalapril 20 mg twice daily, and carvedilol (mean dose 25 ± 6 mg/day) were started as soon as clinical heart failure or worsening left ventricular function was noted. Two patients died within 8 weeks after delivery from severe refractory heart failure, despite admission to intensive care unit and optimal medical treatment. The remaining 4 patients continued to remain symptomatic.

Changes in ejection fraction during follow-up are shown in Figure 1. Four of the 6 patients had persistent cardiomegaly and impaired ejection fraction ($<40\%$) at onset of the subsequent pregnancy. At 8 months of pregnancy, ejection fraction remained unchanged. At 1 month postpartum a significant deterioration ($>10\%$ decrease in ejection fraction) was observed in all but 1 patient. The single patient whose ejection fraction remained unchanged had a normal ejection fraction to start with. At 3 months postpartum, 2 of the 6 patients died due to heart failure, with no improvement in ejection fraction in the remaining patients. Both deaths occurred in patients who had persistent cardiomegaly and impaired ejection fraction at onset of subsequent pregnancy.

Figure 2 demonstrates the time course pattern of TNF- α plasma levels. TNF- α levels were 2.4 ± 1.1 pg/ml at onset of subsequent pregnancy ($n = 6$) and 2.3 ± 0.9 pg/ml at 8 months ($n = 6$). There was a significant increase in the TNF- α levels to 6.2 ± 2.4 pg/ml at 1 month postpartum ($n = 6$) and 6.1 ± 0.9 pg/ml at 3 months postpartum ($n = 4$). TNF- α levels 3 months after the subsequent pregnancy were signif-

icantly higher in the study population compared with 20 age-matched healthy volunteers ($p = 0.0001$).

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A recent study by Elkayam and colleagues¹¹ found that subsequent pregnancy in women with PC was associated with a significant decrease in left ventricular function that resulted in clinical deterioration and even death. However, theirs was a retrospective survey; serial echocardiography was not performed in a systematic fashion, and echocardiographic data were based on the interpretation of patient physicians as contained in the patients' records. We followed 6 patients with PC who subsequently became pregnant again, and we believe this to be the first prospective evaluation of left ventricular function and cytokine measurement in this group of patients.

Our study confirms that the mortality during subsequent pregnancy is high, especially in patients with persistent left ventricular dysfunction after the first pregnancy.

The mechanism of recurrent left ventricular dysfunction associated with subsequent delivery is not clear. Reimold and Rutherford¹² suggest that the hemodynamic stress of pregnancy is responsible for deterioration in left ventricular function. Our data do not support this hypothesis, as all patients maintained their ejection fraction throughout the pregnancy, and deterioration of left ventricular dysfunction and an increase in the inflammatory cytokine TNF- α occurred uniformly postpartum.

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Safety of Stress Testing in Patients With Hypertrophic Cardiomyopathy

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Two hundred sixty-three consecutive patients with hypertrophic cardiomyopathy underwent stress testing. Major complications occurred in 0.04% of patients and minor events occurred in 23%. ©2004 by Excerpta Medica, Inc.

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Hypertrophic cardiomyopathy (HC) often presents with exercise-induced symptoms, arrhythmias, or the occurrence of sudden cardiac death.^{1,2} Concomitantly, exercise testing could theoretically play a role in diagnosis, risk assessment, determination of response to medical therapy, and selection of patients for percutaneous or surgical intervention. However, because of the potential risks in patients with HC, American College of Cardiology/American Heart Association guidelines have considered exercise testing to be relatively contraindicated.³ Thus, many clinicians remain reluctant to perform exercise testing, although few studies have directly addressed its safety. The purpose of our study was to determine the incidence of complications during stress testing in patients with HC.

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We prospectively evaluated collected data on 263 consecutive stress metabolic exercise echocardiograms performed on patients with HC between October 1997 and September 2002 at our institution. All patients had HC diagnosed by a transthoracic echocardiogram before stress testing; all patients able to exercise are routinely referred for exercise testing. Patients are routinely given amyl nitrite to induce left ventricular obstruction, although stress testing is considered a more physiologic measure of gradients that does not always correlate with amyl nitrite.⁴ The database was approved by the institutional review board

at the Cleveland Clinic for ongoing data collection on patients with HC undergoing stress testing. HC was defined by the presence of a hypertrophied (≥ 1.5 cm), nondilated left ventricular cavity, associated with the presence of systolic anterior motion of the mitral valve and left ventricular outflow tract (LVOT) obstruction. Mid-cavitary nonobstructers and apical forms of HC were included. Patients who were in New York Heart Association functional class III to IV were generally excluded from stress testing.

Echocardiographic studies were performed primarily with an ATL 5000 ultrasound machine (Philips Instruments; Andover, Massachusetts). A complete baseline echocardiogram included determination of resting and peak stress LVOT gradients using continuous-wave Doppler. Exercise and metabolic stress testing (measurement of oxygen consumption) was performed with a MedGraphics Cardiorespiratory Diagnostic System (St. Paul, Minnesota). Stress testing was symptom limited or terminated if severe complications occurred. The Cornell 5 stress protocol was used with few exceptions and all patients performed treadmill exercise. Regional wall motion abnormalities were assessed with stress, although most patients had nondiagnostic tests for ischemia. Patients were instructed to take their medications the day of the test, including atrioventricular nodal blocking and antiarrhythmic agents. Data were collected regarding symptoms, exercise capacity, blood pressure response, and arrhythmias. Complications recorded included major (death, cardiac arrest, sustained ventricular or atrial arrhythmias associated with severe symptoms, hemodynamic compromise, or the need for cardioversion) and minor events (decrease in blood pressure, transient symptoms, or nonsustained arrhythmias).

The mean age of patients was 51 ± 16 years (range 15 to 85) and 164 (62%) were men. The initial rhythm was sinus in 84%, paced in 12%, and other (including atrial arrhythmias or junctional rhythm) in the remaining 4%. The mean LVOT gradient at rest was 38 ± 34 mm Hg and the peak LVOT gradient was 74 ± 50 mm Hg. Patients achieved a calculated exercise capacity of

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