Peripartum Cardiomyopathy Reached Progressive Recovery Despites Poor Initial Ejection Fraction

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Peripartum cardiomyopathy (PPCM) is a pregnancy-associated, idiopathic cardiomyopathy secondary to marked left ventricular dysfunction, which manifests between the last month of pregnancy and the first five months postpartum. While it is relatively rare, PPCM is associated with significant morbidity and can be fatal. Its diagnosis is often delayed because its symptoms closely resemble those within the normal spectrum of pregnancy and the postpartum period. When PPCM is misdiagnosed or is not diagnosed in time, the consequences for patients could be deadly. We present a rare case which was first misdiagnosed but had a continuous progressive recovery of LV systolic function (LVSF) within five years after it was finally diagnosed and treated.

A 23 year-old female, P1A0, 8-weeks postpartum, was admitted to the emergency unit of our hospital because of dyspnea and fatigue, which developed three days after the delivery of her child. A week prior to delivery she was admitted to the hospital due to coughing, proteinuria and edema of her lower extremities. She was then diagnosed with severe preeclampsia. The patient, however, refused the administration of Magnesium-sulfate as a therapy because of personal reasons. 48 hours later, the patient was induced with oxytocin and she delivered a living female infant via vaginal delivery with no labor complications and was later discharged. Three days after delivery, the patient complained about having shortness of breath and fatigue. She went to a general practitioner who thought her symptoms were normal after a delivery. Two months later she went to an obstetric clinic for a check-up and was referred to the cardiology unit at our hospital. She stated that for the past two months, she had been experiencing symptoms such as exhaustion, palpitations, an inability to lay flat, decreased exercise tolerance and severe dyspnea.

PPCM is a rare but potentially lethal disease that remains a challenge to diagnose, prognosticate, and treat. It is increasingly recognized that the condition is often diagnosed late which may indicate a poor prognosis. However, there are cases in which the initial severity of left ventricular dysfunction or dilatation is not necessarily predictive for long-term functional outcome.

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Keywords: peripartum cardiomyopathy, PPCM, heart failure, pregnancy

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Kardiomiopati peripartum (PPCM) merupakan suatu keadaan kardiomiopati idiopatik yang berhubungan dengan kehamilan. Penyakit ini bermanifestasi sebagai gagal jantung akibat disfungsi ventrikel kiri dan dapat terjadi pada satu bulan terakhir kehamilan sampai dengan lima bulan setelah melahirkan. Meskipun prevalensinya tergolong rendah, PPCM dikaitkan dengan angka morbiditas yang signifikan dan dapat berakibat fatal. Diagnosis sering tertunda karena gejala yang muncul pada kehamilan normal dan periode setelah melahirkan. Ketika PPCM salah atau terlambat terdiagnosis, konsekuensinya dapat berakibat fatal. Kami menajikan sebuah kasus yang jarang terjadi ketika PPCM terlambat terdiagnosis namun mengalami pemulihan progresif dan terus menunjukkan perbaikan fungsi sistolik ventrikel kiri dalam waktu lima tahun.

Seorang wanita berusia 23 tahun, P1A0, 8 minggu pospartum, diterima di Unit Gawat Darurat karena dispnea dan rasa lelah yang dirasakannya tiga hari setelah melahirkan. Seminggu sebelum melahirkan, pasien dirawat di rumah sakit karena batuk, proteinuria, dan edema pada anggota gerak tubuh bagian bawah. Pasien kemudian didiagnosis preeklampsia berat. Empat puluh delapan jam kemudian pasien melahirkan bayi perempuan dengan persalinan normal tanpa komplikasi setelah diinduksi dengan oksitosin dan diperbolehkan kembali ke rumah. Tiga hari setelah melahirkan, pasien mengeluhkan sesak napas dan rasa lelah. Pasien kemudian diinduksi dengan persalinan normal tanpa komplikasi setelah diinduksi dengan oksitosin dan diperbolehkannya melahirkan. Tiga hari setelah melahirkan, pasien mengeluhkan sesak napas dan rasa lelah. Pasien kemudian memeriksa diri di dokter umum yang menganggap bahwa gejala tersebut normal dialami setelah melahirkan. Dua bulan kemudian pasien melakukan pemeriksaan di klinik bersalin dan dirujuk kepada unit kardiologi dengan keluhan kelelahan, palpitasi, tidak bisa berbaring, telesentang, batas toleransi rendah terhadap kegiatan fisik, dan dispnea berat.

Kardiomiopati peripartum adalah penyakit yang jarang ditemukan namun berpotensi fatal. Penyakit ini sulit terdiagnosis, terprognosis, dan diobati. Sering kali penyakit ini terlambat didiagnosis yang bisa mengindikasikan prognosis buruk. Meskipun demikian, ada kasus-kasus ketika tingkat kematian awal disfungsi atau dilatasi ventrikel kiri belum tentu bisa memprediksi hasil jangka panjang.

Kata Kunci: kardiomiopati peripartum, PPCM, gagal jantung, kehamilan

**Introduction**

Peripartum cardiomyopathy (PPCM) is a pregnancy-associated, idiopathic cardiomyopathy secondary to marked left ventricular dysfunction, which manifests between the last month of pregnancy and the first five months postpartum. While it is relatively rare, PPCM is associated with...
significant morbidity and can be fatal. Its diagnosis is often delayed because its symptoms closely resemble those within the normal spectrum of pregnancy and the postpartum period. When PPCM is misdiagnosed or is not diagnosed in time, the consequences for patients could be deadly. We present a rare case which was first misdiagnosed but had a continuous progressive recovery of LV systolic function (LVSF) within five years after it was finally diagnosed and treated.

**Case Illustration**

A 23 year-old female, P1A0, 8-weeks postpartum, was admitted to the emergency unit of our hospital because of dyspnea and fatigue, which developed three days after the delivery of her child. A week prior to delivery she was admitted to the hospital due to coughing, proteinuria and edema of her lower extremities. She was then diagnosed with severe preeclampsia. The patient, however, refused the administration of Magnesium-sulfate as a therapy because of personal reasons. Forty eight hours later, the patient was induced with oxytocin and she delivered a living female infant via vaginal delivery with no labor complications and was later discharged. Three days after delivery, the patient complained about having shortness of breath and fatigue. She went to a general practitioner who thought her symptoms were normal after a delivery. Two months later she went to an obstetric clinic for a check-up and was referred to the cardiology unit at our hospital. She stated that for the past two months, she had been experiencing symptoms such as exhaustion, palpitations, an inability to lay flat, decreased exercise tolerance and severe dyspnea. The patient also complained of lower extremity edema. The patient denied ever having any heart problems before and was never diagnosed with any heart abnormalities nor had any family history of heart disease. The patient had regular antenatal care (ANC) with an OB-GYN, with data as follows: body weight=43 kg, height=152 cm, Body Mass Index (BMI)=18.6 kg/m$^2$, blood pressure (BP)=110/70, heart rate (HR)=82 beats/minute. The patient's body weight during 38th week of the pregnancy was 58 kg, with a BMI of 25.1 kg/m$^2$.

Initial vital signs were a BP of 118/78 mmHg, HR of 120 beats/minute, respiratory rate (RR) 28 rates/minute, temperature of 36.6°C, and an oxygen saturation of 97%. Upon physical examination she had an apparent jugular venous distension. Cardiac auscultation showed normal first and second heart sounds. No significant cardiac murmurs were detected. Vesicular breathing in both lungs with significant bilateral crackles was detected. Other physical findings include ascites and edema of the lower extremities.

Initial laboratory results were as follows: white blood cells=7.7x10$^3$/mm$^3$; hemoglobin=10.0 g/dL; hematocrit=30.5%; platelets=153x10$^3$/mm$^3$; albumin=2.9 g/dL; aspartate aminotransferase=29 U/L; alanine aminotransferase=47 U/L; serum urea nitrogen=17 mg/dL; creatinine=0.81 mg/dL. The electrocardiogram showed Sinus Tachycardia of 123 beats/minute. Chest X-ray showed a cardiomegaly with increased vascular congestion, bilaterally. Initial 2D Transthoracic Echocardiography (TTE) showed General hypokinetic heart, Right and Left ventricle failure with poor left ventricular ejection fraction (LVEF 14.2%). The patient was hospitalized for further treatment in the Intensive Care Unit.

Treatment of PPCM includes O2 therapy 3 l/min through nasal cannula, albumin correction with extra IV furosemide and oral potassium slow release, with maintenance furosemide dose of 20 mg/day, warfarin 2 mg/OD, Angiotensin Converting Enzyme Inhibitors (Captopril) 6.25 mg TDS, Digoxin 0.125 mg/BID, and Coenzyme Q 25 mg/BID.

She was treated in the Intensive Care Unit for three days. During the treatment, the pulmonary edema regressed and the patient was discharged after one week from the hospital for out-patient treatment of heart failure. The patient was also advised against subsequent pregnancies. During the follow-up there was a continuous improvement of left ventricle dimensions and function.

Six months later, repeated 2D TTE showed normokinetic, normal-sized cardiac cavities, normalized diastolic and improved systolic function with LVEF of 53.1%. She was treated with Mineralocorticoid receptor Antagonists (Spironolactone) 12.5 mg OD, Angiotensin Converting Enzyme Inhibitors (Captopril) 6.25 mg TDS, B-blocker (Bisoprolol) 1.25 mg OD and Coenzyme Q 25mg/BID. Digoxin, warfarin and furosemide were all discontinued. The patient was then scheduled for monthly follow-ups to reassess the cardiac function. After five years of routine follow-ups, repeated echocardiography showed normal-sized cardiac cavities, fully recovered with LVEF of 71% with normal cardiac valves function as shown by Table 1 and Figure 1-4, the patient was then taken off any treatment regimes.
Peripartum Cardiomyopathy (PPCM) is an uncommon disorder associated with pregnancy in which the heart dilates and weakens, leading to symptoms of heart failure. The incidence has been fully agreed upon but it estimated to be 0.025% to 0.03%, i.e. (1/4000) to (1/3000) births respectively. PPCM may be difficult to diagnose because symptoms of heart failure can mimic those of pregnancy. Affected women may recover normal heart function, stabilize on medicines, or progress to severe heart failure requiring mechanical support or heart transplantation. Even when the heart recovers, another pregnancy may be associated with a risk of recurrent heart failure. This disorder carries a high mortality rate, since a misdiagnosis or a delayed diagnosis could consequently lead to death. Therefore, reaching a proper diagnosis is the initial challenge in caring for patients with PPCM.

Risk factors that are associated with PPCM include advanced maternal age, multiparity, obesity, multi-fetal pregnancy, hypertension (chronic, pregnancy induced, or preeclampsia), low socioeconomic status and African American race. However, none has emerged as a convincing single etiology. This may be because PPCM represents a heterogeneous group of disease process with a multifactorial etiology.

The underlying cause of PPCM remains unknown. A number of proposed mechanisms include: genetic, viral myocarditis, abnormal immune response, hemodynamic response to pregnancy, hormonal abnormalities, and malnutrition. However, none has emerged as a convincing single etiology. This may be because PPCM represents a heterogeneous group of disease process with a multifactorial etiology.

Classic heart failure symptoms include dyspnea, dyspnea on exertion, lower extremity edema, and fatigue, and these are often presenting symptoms. Unfortunately, these symptoms can be indistinguishable from symptoms common in late pregnancy and the postpartum period, making the diagnosis challenging and often missed, as shown by our case report.

Physical exam findings in PPCM may reveal signs of volume overload such as pulmonary rales, increased
respiratory rate, tachycardia, pathologic S3 or S4 heart sounds, distended neck veins, and lower extremity edema. While there are no specific electrocardiography (ECG) findings that are particularly helpful in diagnosing PPCM. As can be seen in this case, symptoms such as these can make diagnosis of PPCM difficult because some patients with preeclampsia may experience dyspnea, fatigue, and lower extremity edema.

The National Heart, Lung and Blood Institute (NHLBI) and the National Institutes of Health (NIH) in the U.S., published a diagnostic criteria for PPCM to direct more accurate research on epidemiology, pathophysiology, and outcomes. Current diagnosis of PPCM is based on the presence of four clinical criteria: (1) Development of heart failure (HF) in the last month of pregnancy or within five months after delivery; (2) Absence of an identifiable cause for HF; (3) Absence of recognizable heart disease prior to the last month of pregnancy; (4) Echocardiography (TTE) criteria of left ventricular systolic dysfunction (left ventricular ejection fraction, LVEF<45%), fractional shortening of<30%, or both. In this case, peripartum cardiomyopathy was diagnosed upon exclusion of other reasons for the heart failure, according to the diagnostic criteria of peripartum cardiomyopathy.

Treatment of PPCM is based on guidelines for standard HF treatment, including angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, spironolactone, digoxin, diuretics, vasodilators and inotropes if needed. The mainstays of treatment for acute decompensated PPCM include diuretics and renin angiotensin inhibiting agents for patients that are hemodynamically stable. Once stabilized, beta-blockers, aldosterone-antagonists and additional therapies should be initiated and up-titrated in the out-patient setting, particularly in the setting of persistent LV dysfunction. Although early improvement in EF (i.e. within the first 3-6 months) predicts a good outcome, some women will have slow, gradual improvement in EF over years.

An important additional therapy that we considered for this patient is anticoagulation therapy. Considering that the patient is in a hypercoagulable state and the depressed systolic function caused by PPCM, she is at a higher risk for thrombus formation and thromboembolic events. Warfarin anticoagulation should be considered for prevention of morbidity or mortality from thromboembolism.

Figure 2-4. Transthoracic echocardiography results from 12 July 2010 – 25 February 2016
Images showing the echocardiography results taken during three separate routine follow-ups: 12 July 2010 (Figure 2), 17 January 2011 (Figure 3) and 25 February 2016 (Figure 4). Short axis view shows an improvement in LVEF of 14.2%, 53.8% and 71%, respectively.
Since the patient had a poor initial LV ejection fraction (<25%), she was also given counseling against subsequent pregnancies in order to avoid risk of recurrence of heart failure.\textsuperscript{13}

Recently, a growing body of evidence has pointed to abnormal prolactin metabolism as crucial in the etiology of PPCM, and prolactin inhibition is being explored as a novel treatment for PPCM.\textsuperscript{12,14,16} The basis for the use of Prolactin inhibition (e.g. Bromocriptine) in PPCM is based on the hypothesis that PPCM is originated by increased oxidative stress in the postpartum heart through the enhancement of the cathepsin D-mediated cleavage of prolactin into its 16-kDa subform. 16-kDa prolactin has angiostatic and proapoptotic properties, which in turn, promotes vasoconstriction, inhibits endothelial cell proliferation and migration, and favors myocardial micro-vascular injury.\textsuperscript{17} However, a larger scale study is still needed to confirm the efficacy of prolactin inhibitors as a component of a treatment regime for PPCM. Other alternatives, such as pentoxifylline and intravenous immunoglobulin, are also being studied as other possible treatments for PPCM.\textsuperscript{18,19}

The decision of when to discontinue medications depends not only on left-ventricular function and structure, but also on lingering symptoms, as proposed by the European Society of Cardiology (ESC) guideline.\textsuperscript{10} Digoxin had been given since patient was discharged but then switched to beta-blocker after 6-months of out-patient care and the patient is clinically stable and no longer shows any symptoms of congestion. Warfarin was also discontinued after the risk of thrombus formation is no longer prominent due to the gradual and consistent improvement of left ventricular function. B-blocker and ACE-inhibitor were continued as essential treatment of PPCM, along with mineralocorticoid receptor antagonist (MRA), with expectation of fully restoring the LV structure, as the patient still had LV structural problem (Table 1).

Prognosis of PPCM is positively related to the recovery of ventricular function.\textsuperscript{5,20} Effective treatment helps women recover cardiac function and reduces morbidity and mortality.\textsuperscript{21} Thus, it is important that general practitioners to be familiar with PPCM and therefore consider it when diagnosing dyspneic patients to ensure prompt medical treatment for a potentially lethal condition.

A fractional shortening less than 20% and a left ventricular diastolic dimension of 6 cm or greater at the time of diagnosis are associated with a more than three-fold higher risk for persistent cardiac dysfunction.\textsuperscript{22} The correlation between a depressed ejection fraction (EF) at the time of diagnosis and worse outcomes has been supported by several studies.\textsuperscript{5,21,23,24} However, other researchers have found no correlation between initial left-ventricular ejection fraction (LVEF) and survival, or recovery of LV function.\textsuperscript{9,20,25,26} In our case report, with an initial LVEF 14.2%, our patient managed to reach a better prognosis than expected. Thus, the initial severity of left ventricular dysfunction or dilatation is not necessarily predictive for long-term functional outcome.\textsuperscript{20,27}

\textbf{Conclusion}

PPCM is a rare but potentially lethal disease that remains a challenge to diagnose, prognosticate, and treat. It is increasingly recognized that the condition is often diagnosed late which may indicate a poor prognosis. However, there are cases in which the initial severity of left ventricular dysfunction or dilatation is not necessarily predictive for long-term functional outcome.

\textbf{Abbreviations}

\begin{itemize}
\item ACE: angiotensin converting enzyme
\item AML: anterior mitral leaflet
\item ANC: antenatal care
\item AR: aortic regurgitation
\item ARBs: angiotensin receptor blockers
\item BMI: Body Mass Index
\item BP: blood pressure
\item EJ: ejection fraction
\item ECG: electrocardiography
\item ESC: European Society of Cardiology
\item FS: fractional shortening
\item HF: heart failure
\item HR: heart rate
\item LV: left-ventricular
\item LVE: left-ventricular enlargement
\item LVEDD: left-ventricular end-diastolic diameter
\item LVESD: left-ventricular end-systolic diameter
\item LVEF: left-ventricular ejection fraction
\item LVSF: left-ventricular systolic function
\item MR: mitral regurgitation
\item MRA: mineralocorticoid receptor antagonist
\item MVP: mitral valve prolapse
\item NIH: National Institutes of Health
\end{itemize}
References
