# Pregnancy-Associated Cardiomyopathy (PACM) in a Preeclamptic Woman with Twin Pregnancy: A Case Report

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SOUHRN

Peripartální kardiomyopatie (peripartum cardiomyopathy, PPCM) není časté onemocnění; jedná se o typ dilatační kardiomyopatie postihující ženy v posledním měsíci těhotenství a v prvních pěti měsících po porodu. Tomuto onemocnění předchází podobné, označované jako těhotenská kardiomyopatie (pregnancy-associated cardiomyopathy, PACM). Morbidita i mortalita v souvislosti s oběma onemocněními jsou vysoké. U žen s preeklampsií a vícečetným těhotenstvím existuje výrazně vyšší riziko rozvoje PACM/PPCM. Na oddělení urgentního příjmu se dostavila 40letá multipara ve 20. týdnu vícečetného těhotenství s kašlem, dyspnoe, výraznými bilaterálními chrůpky, otoky končetin, kardiomegalií, hypertenzí, proteinurií a s hodnotou ejekční frakce levé komory 26 %. Byla u ní stanovena diagnóza akutního otoku plic, PACM a preeklampsie. Těhotenství bylo ukončeno a byla zahájena farmakologická léčba srdečního selhání. Při PACM může být odklad diagnostického vyšetření spojen se závažnou morbiditou matek a mortalitou novorozenců. Případ poukázal na nutnost věnovat pozornost preeklampsii a vícečetnému těhotenství jako rizikovým faktorům; tyto ženy mohou být i kandidátkami monitorování funkce levé komory. Časné a vhodné řešení může zabránit rozvoji ireverzibilní PACM.



*Keywords:*
Peripartum cardiomyopathy
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Pregnancy-associated cardiomyopathy
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ABSTRACT

Peripartum cardiomyopathy (PPCM) is an uncommon disease, a dilated cardiomyopathy type occurs in the final gestation month and within 5 months after giving birth. A related term, pregnancy-associated cardiomyopathy (PACM) occurs before it. The morbidity and mortality rates are high. Women with preeclampsia with twin pregnancies are at a markedly elevated risk of developing PACM/PPCM. A 40-year-old multiparous woman with twin pregnancy came to the emergency room at gestational week 20, exhibited cough, dyspnea, full bilateral rales, extremities edema, cardiomegaly, hypertension, proteinuria, and the left ventricular ejection fraction was 26%. She was diagnosed with acute lung edema, PACM, and preeclampsia. The pregnancy was terminated and treated with drug therapy of heart failure. Delay of diagnostic procedures may lead to severe maternal morbidity and infant mortality in this PACM case. It emphasized the need for attention of the risk factors, preeclamptic and twin pregnancy, and may be candidates for monitoring of left ventricular function. Early and appropriate management may prevent irreversible PACM.

## Introduction

Peripartum cardiomyopathy (PPCM) is a pregnancy-related dilated cardiomyopathy that is not common and it is correlated with the occurrence of new onset left ventricular dysfunction.[1] The classic criterion for the diagnosis of PPCM which was made in 1971 by Demakis et al.[2] limits diagnosis in the final month of pregnancy and the first 5 months after giving birth. But several published reports state that cardiomyopathy in women occurs earlier during pregnancy.[1,3] Pregnancy-associated cardiomyopathy (PACM) is a similar condition with symptoms such as PPCM but earlier before the last month of pregnancy. Although PACM has not been studied further, it has been recommended that PACM is identical to PPCM in a phenotypic manner and without differences in clinical presentation, management, or prognosis.[3] Thus both will be considered the same in this report.

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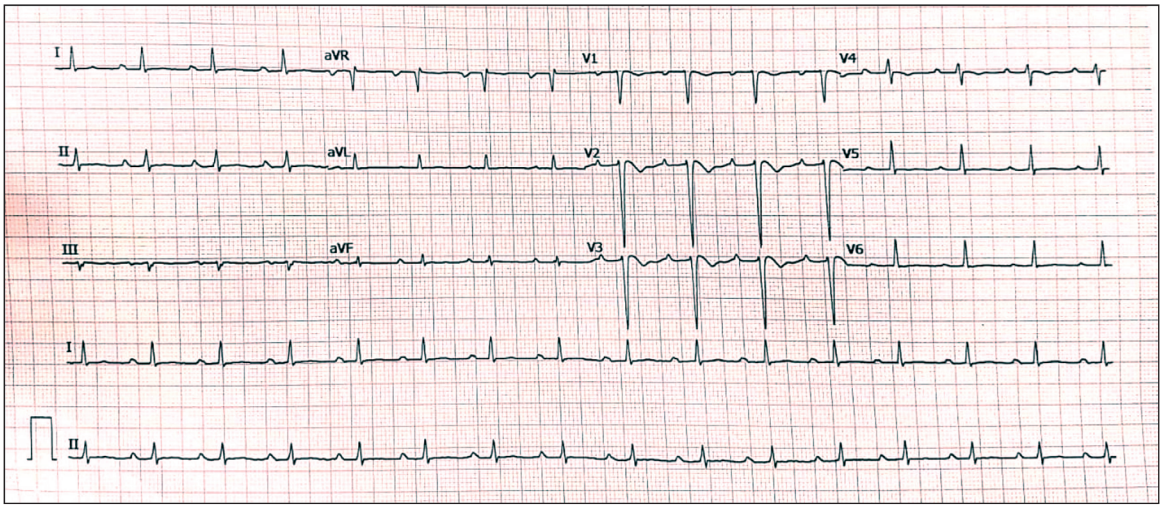


**Fig. 1 – Initial electrocardiogram.**

This disease is uncommon, with different rates in each geographical location. Events described in the literature range from 1 : 300 to 1 : 15,000 (<0.1% in pregnancy).[4] Ranging from 5% to 32%, the morbidity and mortality rates are high. Prognosis depends on recovery from heart failure during the first 6 months postpartum with 28% of deaths.[5] False diagnosis of PACM/PPCM, which often causes clinical worsening and in some cases death, is a target for prevention and early treatment.[4]

In epidemiological studies, multiple pregnancies and hypertensive disorders in pregnancy are consistent and important risk factors in the occurrence of PACM/PPCM, 7–15% and 15–68%, respectively.[6,7] This case states that the risk of PACM/PPCM is indeed higher in preeclamptic women with multiple pregnancies. In this report, we present the details of PACM case which emphasizes the need for attention to these two risk factors.

## Case description

A multiparous woman aged 40 years with twin pregnancies aged 20 weeks came in the Emergency Room of Dr. General Hospital Soetomo with a major complaint of shortness of breathing when walking and can only sleep with a burdensome half-sitting position for 1 month. The patient also complained of coughing and swelling of both legs. The patient already has one child born healthy and has never had health problems during pregnancy and childbirth. The patient has no history of heart disease and previous metabolic abnormalities. The family also did not have a history of similar diseases. Initial vital signs were notable for heart rate 140/min, blood pressure 143/117 mmHg, respiratory rate 35, and oxygen saturation 89% in room air. On physical examination, the head and neck appear with dyspnea and there is an increase in the jugular vein, there is a bilateral widening of the heart, vesicular and fine rhonchi on lung examination, and there is edema in bilateral inferior extremities. Laboratory values at the admission were notable for transaminitis (AST [aspartate aminotransferase] 171 IU/L, ALT [alanine aminotransferase] 202 IU/L), hypoalbuminemia (albumin 1.96 g/dL), increased renal function test values (BUN [blood urea nitrogen] 77 mg/dL, creatinine 3.08 mg/dL), and proteinuria (+4). The electrocardiogram showed sinus tachycardia with normoaxis and unspecific T inversion in $V_1$–$V_4$ (Fig. 1). The chest X-ray showed cardiomegaly and pulmonary congestion (Fig. 2). Transthoracic echocardiogram was relevant for left ventricular ejection fraction (LVEF) of 26% with severe global hypokinesis, eccentric left ventricular hypertrophy, left atrial and ventricular dilatation, moderate mitral and pulmonary regurgitation, and mild tricuspid regurgitation. She was diagnosed with acute lung edema, PACM, and preeclampsia. Then she was admitted to the Resuscitation Room and intubated.

Medical treatment that was given is aggressive diuresis, isosorbide dinitrate (ISDN), and dobutamine pump considering the inadequate urine production to improve

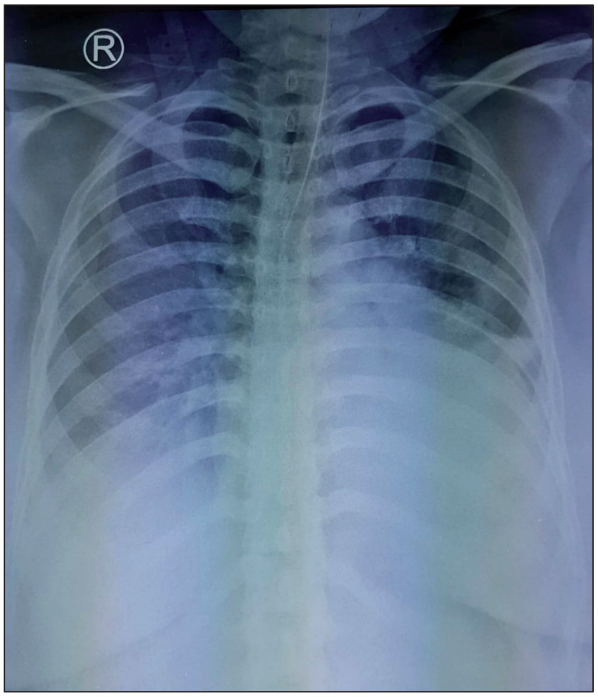


**Fig. 2 – Chest X-ray.**

organ perfusion. The obstetric division has been informed about termination of pregnancy and the termination of pregnancy was approved by the family. After pregnancy termination, her condition gradually stabilized, and then she was admitted to the Low Care Unit and initiated on loop diuretic, mineralocorticoid receptor antagonist (MRA), angiotensin converting enzyme (ACE) inhibitor, digoxin, and selective beta blocker. After several days having undergone treatment in Low Care Unit, she unfortunately reported continued fatigue and lethargy, and electrocardiogram showed premature ventricular contraction (PVC) occasional which was worsening, become more frequent. Then ventricular fibrillation and cardiac arrest occurred. She was successfully resuscitated so that she achieved return of spontaneous circulation (ROSC) state and then was referred to the Cardiac Intensive Care Unit.

One week after having cardiac arrest, she had no complaint and stable hemodynamics. Although her HF emerged compensated clinically, repeat echocardiography carried out before discharge was without improvement. Transthoracic echocardiogram still showed the same results, LVEF of 26% with severe global hypokinesis.

## Discussion

### *PACM and PPCM*

PPCM was diagnosed with 4 criteria, conformed to a study by Demakis et al.[2] and recommended by the European Society of Cardiology (ESC) recently:[8] (1) the occurrence of heart failure in the last gestational month or during 5 months after labor, (2) there is no identifiable cause of heart failure, (3) there is no heart disease that can be identified before the last gestational month, and (4) left ventricular systolic dysfunction with LVEF <45% from echocardiography. Patients were diagnosed with PACM if they had the criteria for PPCM but they occurred earlier than the last month in pregnancy.[3] Mostly, clinical symptoms and signs typically represent heart failure, which most often show dyspnea, fatigue, dizziness, chest pain, cough, neck venous distention, and extremities edema.[9] Patients also commonly present with acute heart failure, arrhythmias, and sudden cardiac arrest[8] that was also reported in this case.

Elkayam et al. reported no significant differences between PACM and PPCM in age, race, obstetric history, and the occurrence of pregnancy-related hypertension. There were also no significant differences in LVEF on average at the latest diagnosis or follow-up, the incidence of heart transplantation, or maternal death. In contrast, in the PACM group, the incidence of multiple pregnancies was higher, the duration of pregnancy was shorter, and fetal birth weight was lower. Comparisons between the two groups showed no statistically significant differences in age, race, obstetric history, and rates of gestational hypertension. Besides the impact on the maternal LVEF at the time of diagnosis, improvement occurred over almost the same time. The increase in the incidence of preterm births was reported in the PACM group and may be associated with the cardiac dysfunction that develops early, the higher incidence of twin pregnancies, and the aversion of doctors to continue pregnancy after the diagnosis of cardiomyopathy.[3]

### *Pathophysiology*

Initially, it was important to know the pathophysiology of PACM/PPCM, so we know how preeclampsia and twin pregnancies trigger the disease in this case. The exact mechanism leading to PACM/PPCM is still not well defined. Many pathogenetic processes have been proposed: viral myocarditis, abnormal immune responses to fetal microchimerism, malnutrition, maladaptive responses to pregnancy hemodynamic pressures, systemic angiogenic imbalances, hormone abnormalities, cytokines activated by stress, apoptosis, and prolonged tocolysis.[1,4,6,10,11]

A 'two-hit' model of angiogenic imbalance in the cardiac has recently been proposed, where systemic antiangiogenic signals act on host susceptibility conditions with insufficient local proangiogenic defenses at the heart.[5,12,13] Damp et al. found higher levels of relaxin-2 in women with less remodeling and more recovery; on the contrary, symptoms and poorer prognosis are associated with higher soluble fms-like tyrosin kinase (sFlt1) concentrations. Because vascular endothelial growth factor (VEGF), which is inhibited by sFlt1, partially mediates the vasodilatory and proangiogenic effects of relaxin-2.[14]

### *Preeclampsia and twin pregnancy as risk factors*

Preeclampsia is defined as an increase in blood pressure after pregnancy at 20 weeks with proteinuria or other end-organ dysfunction.[15] The patient with twin pregnancy was diagnosed with preeclampsia. She had had no history of hypertension until hypertension was discovered when she was admitted to the emergency room at 20 weeks of gestation. On laboratory examination, proteinuria (+4) and end-organ dysfunction were detected which was characterized by an increase in the value of liver and kidney function tests.

The incidence of gestational hypertension in patients with PPCM is 43%, which is higher than the rate of 8% to 10% reported in the population of woman with pregnancy.[3] Chronic hypertension, superimposed gestational, or preeclampsia have been described in 15% to 68% of patients with PPCM. This incidence is higher than the rate of 8% reported in all pregnant patients.[6] Scardovi et al. reported that higher rates of hypertension and preeclampsia disorders (22% vs 3–5%) found in PPCM patients than those observed during pregnancy supported the general vascular pathobiology hypothesis.[4] Twin pregnancy rates are reported to be 13%, much higher than the rate of 1% to 2% reported in healthy women.[3] Multifetal pregnancy has been reported in 7% to 14.5% of PPCM patients, compared with 3% in the general population, which confirms a strong correlation between multifetal pregnancy and the incidence of PPCM.[6]

A strong association with hypertension induces the question whether heart failure in patients with PACM/PPCM can be caused by an increase in blood pressure. This theory is not proven by studies in a large number of hypertension patients due to coarctation of the aorta as cardiovascular complications rarely occur during pregnancy.[3] Chronic hypertension does not cause LV systolic dysfunction and hypertensive pulmonary edema is

largely caused by exacerbations of diastolic dysfunction by hypertension, not because of transient systolic dysfunction.[16] Actually, according to several researchers, LV systolic function is preserved in pregnant women. Also, preeclampsia can appear with clinical signs and symptoms of heart failure, but systolic function commonly remains or even improves. For all these reasons, LV recovery rates were similar in patients with PACM/PPCM with and without a history of gestational hypertension, hypertension did not appear to be the mechanism of LV systolic dysfunction but the correlated conditions were strong with PACM/PPCM. Echocardiographic examination and measurement of BNP levels are recommended for early diagnosis of PACM/PPCM in patients with preeclampsia who are suspected of having heart failure.[6]

During pregnancy, the placenta secretes a soluble version of VEGF receptor 1 and soluble Fms-like tyrosine kinase 1 (sFlt1).[17] The excess sFlt1 damages the heart blood vessels that may cause cardiomyopathy as showed by an experimental study.[10] Extensive endothelial dysfunction is also associated with an increase in sFlt1 which can increase vascular permeability that allows excess water retention.[9] The placental secretion of sFlt1 is obviously elevated in patients with preeclampsia that may be observed from 2nd trimester onwards.[18] Consistent with this and assuming that sFlt1 is cardiac toxic, preeclampsia in pregnant women has been shown to have deterioration of cardiac function, as observed on echocardiography.[13] Bdolah et al.[19] proposed two hypotheses that might explain the relationship between multigestational pregnancies and higher sFlt1 levels. The first hypothesis is that the placenta is programmed to produce more sFlt1 per placental unit in multigestational pregnancies, perhaps because it is more hypoxic. The second hypothesis is that sFlt1 does not increase per placental unit but that there are more trophoblastic placental tissues, so the total production and concentration of sFlt1 in serum increases.[9] An interesting relationship between PACM/PPCM and twin pregnancy can also support autoimmune mechanisms for PACM/PPCM that was suggested by Ansari et al. who observed a high autoantibody titer against normal human heart tissue proteins in the serum of PACM/PPCM patients that were not present in patients with idiopathic cardiomyopathy.[20] This finding may be caused by an increase in hematopoietic cell circulation (chimerism) from the fetus to the normal state during pregnancy in twin pregnancies.[21] A strong association with PACM/PPCM with preeclampsia and multiple pregnancies should increase the suspicion of cardiomyopathy in patients with symptoms of heart failure.

### *Management*

Management of PACM/PPCM therapy is a standard treatment of other heart failure types.[4,8,12] Caution must be directed at the safety of fetus and excretion of drugs or drug metabolites during lactation after giving birth.[12,14] Heart failure therapy focuses on preload and afterload reduction and cardiac inotropy improvement in order to improve the hemodynamics, minimize signs and symptoms, and optimize outcomes.[8,12] Therapies such as renin inhibitors, angiotensin-receptor blockers, angiotensin-converting enzyme (ACE) inhibitors, hydralazine, nitrates, beta-blockers, mineralocorticoid receptor antagonists (MRA), ivabradine, diuretics should be administered.[8] Optimization the oxygenation is one of the main targets and intravenous positive inotropic drug is needed to restore hemodynamics in cases of cardiogenic shock.[12] Bromocriptine may prevent deterioration in LV size and systolic function.[16] Anticoagulation should also be initiated in all patients with acute PACM/PPCM and severe decrease in LV systolic function (LVEF ≤35%).[4] Arrhythmias must be treated aggressively to optimize heart function and to minimize thrombus formation.[22] Intra-aortic balloon pumps (IABP) or ventricular assist devices as mechanical cardiovascular support may be needed as a "bridge to recovery" or transplant.[12,22]

In subsequent pregnancies, there is a risk of recurrence of 30–50% PACM/PPCM. When EF is not normal, the next pregnancy must be stopped. Even if EF is normalized, counseling is still needed because of the risk of recurrence in subsequent pregnancies. In each case, intensive monitoring during pregnancy and after delivery is important to detect early recurrence so immediate treatment of heart failure is given. Predictors that can be examined are clinical characteristics, echocardiographic features, biohumoral factors, vascular homeostasis, and genetic profiles. Serum natriuretic peptides, miR-146a levels, and C-reactive protein can help establish early diagnosis and risk stratification.[8]

## Conclusions

PACM is diagnosed if the patient meets the criteria for PPCM but occurs earlier than the last gestational month. It is a potentially fatal condition that requires timely identification and therapy, considering the long-term sequelae and its prognostic implications. Recognizing risk factors such as preeclampsia and multiple pregnancies is very important. If we recognize the risk factors that can cause PACM, we can increase awareness earlier than the time used as a traditional PPCM diagnosis criterion. In pregnant women with risk factors such as preeclampsia and multiple pregnancies, we must make strict observations regularly. When clinical symptoms of clinical heart failure are found in pregnant women, an echocardiographic examination, BNP level, and other tests to make the diagnosis and appropriate therapy must be carried out immediately. So that mother and child safety can be maintained.

**Conflict of interest**
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**Ethical statement**
This case report does not require ethical approval as it is not a human or animal research.

**Informed consent**

Written informed consent was obtained from a legally authorized representative for anonymized patient information to be published in this article.

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