

# Peripartum cardiomyopathy and acute heart failure associated with prolonged tocolytic therapy in pregnancy

## A case report

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### Abstract

**Rationale:** Peripartum cardiomyopathy (PPCM) is a rare and sometimes fatal systolic heart failure that affects women during late pregnancy or the early postpartum period. Heart failure symptoms can mimic the physiological changes of normal pregnancy, and the diagnosis is based on echocardiography.

**Patient concerns:** A 38-year-old multiparous woman with a history of cervical incompetence underwent cervical cerclage and received tocolysis for 100 days.

**Diagnoses:** She delivered vaginally at 37 weeks of gestation but developed postpartum decompensated acute heart failure with low left ventricular ejection fraction (LVEF: 34%) and was diagnosed with PPCM.

**Interventions:** She received standard therapy for acute heart failure.

**Outcomes:** The patient's pulmonary edema cleared, and she was fully ambulatory 6 days after admission. A follow-up echocardiogram 3 months later demonstrated recovery of LVEF to 66%.

**Lessons:** Prolonged tocolysis may contribute to cardiomyopathy and should be used with caution. PPCM management requires standard treatments for acute heart failure with modifications for fetal safety.

**Abbreviations:** ESC = European Society of Cardiology, LV = left ventricular, LVEF = left ventricular ejection fraction, PPCM = peripartum cardiomyopathy.

**Keywords:** acute heart failure, cervical insufficiency, peripartum cardiomyopathy, tocolysis

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The authors have no conflicts of interests to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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## 1. Introduction

Peripartum cardiomyopathy (PPCM) is a rare, life-threatening form of dilated cardiomyopathy defined as systolic cardiac heart failure in the last month of pregnancy or the first 5 months after delivery.<sup>[1]</sup> The incidence of PPCM has increased in the past decade and ranges from one in 1000 to 4000 live births in the United States.<sup>[2]</sup> Risk factors include pre-eclampsia, advanced maternal age, multiparity, multifetal gestation, long-term tocolysis with beta-agonists, and African American ethnicity.<sup>[3]</sup> Delayed diagnosis and treatment may result in irreversible cardiac dysfunction or mortality.<sup>[2]</sup>

Mid-trimester loss or premature birth can be caused by cervical insufficiency or a short and dilated cervix. Cerclage should be considered if the cervical length is  $\leq 25$  mm at less than 24 weeks.<sup>[4]</sup>

Tocolytics are frequent adjunctive therapy for patients who undergo cervical cerclage.<sup>[5]</sup> However, adverse side effects can be caused by beta-2 adrenergic agonists, which are widely used tocolytic agents, including maternal pulmonary edema<sup>[6]</sup> and vasodilatation, which leads to a compensatory increase in heart rate, stroke volume, cardiac output, and systolic blood pressure.<sup>[7]</sup> Cardiovascular decompensation may occur after prolonged use of beta-2 adrenergic agonists. The direct effects of



**Figure 1.** Chest x-ray showing cardiomegaly and pulmonary edema.

beta-2 adrenergic agonists on cardiovascular function have not been fully investigated.

We report the case of a woman who received tocolytic therapy for 3.5 months after cervical cerclage and presented with acute symptoms and signs of decompensated heart failure 3 days after delivery. The patient provided informed consent for the publication of the case.

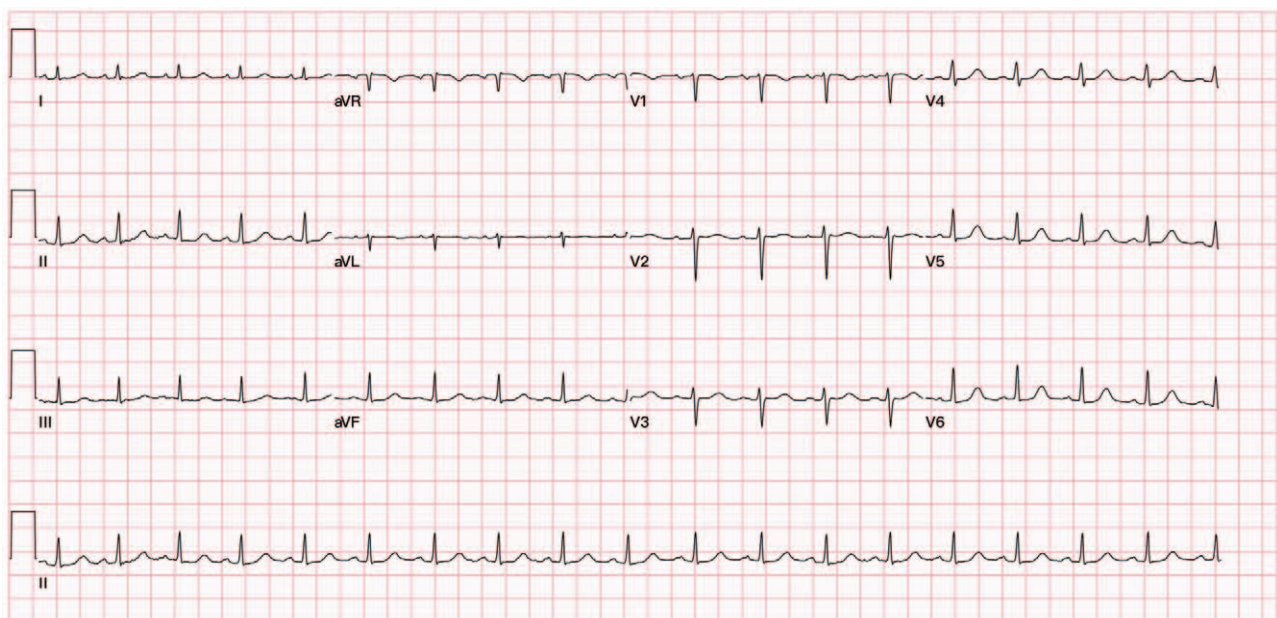
## 2. Case report

A 38-year-old postpartum woman, gravida 3, para 2, ab 1, with no history of diabetes, hypertension, or cardiovascular disease was admitted to the hospital for acute dyspnea and leg edema.

The patient had a preterm delivery at 36 weeks of gestation in her first pregnancy 12 years ago, which did not require cervical cerclage or tocolysis. Her father had hypertension. She presented to the obstetric department at 21 weeks of gestation and underwent cerclage after her cervical length was found to be <19 mm. She was given tocolytic therapy with ritodrine, nifedipine, and diclofenac, which continued for 100 days until her delivery. The patient remained healthy until the last day of pregnancy when she developed mild dyspnea and increased leg swelling. She had a vaginal birth at 37 weeks of gestation.

Three days after delivery, the patient presented to the emergency department with progressive dyspnea, orthopnea, and significant bilateral leg swelling. Her blood pressure was 161/110 mmHg, respiratory rate 30/min, and tachycardia 118/min. Laboratory data showed her troponin T level at 0.13 ug/l and N-terminal pro-brain natriuretic peptide level at 5,430 pg/ml. Chest imaging revealed pulmonary edema and bilateral pleural effusion (Fig. 1). A computed tomography pulmonary angiogram was negative for pulmonary emboli and electrocardiography revealed sinus tachycardia (Fig. 2). An echocardiogram showed generalized hypokinesia of left ventricular (LV) wall motion and a low ejection fraction of 34% (Fig. 3).

The patient was diagnosed with PPCM and given standard therapy for acute heart failure, including inotropes, vasodilators, ACE-inhibitors, beta-blockers, and diuretics; she improved clinically and the pulmonary edema cleared by the fifth day of hospitalization. The patient was fully ambulatory and was discharged 6 days after admission. A follow-up echocardiogram at 3 months and 12 months showed normalization of her ejection fraction to 64% and 80%, respectively. The patient showed complete recovery from PPCM and remained asymptomatic.



**Figure 2.** Twelve lead electrocardiograms showing sinus tachycardia at a rate of 111 beats per min with a QRS duration of 64 ms.

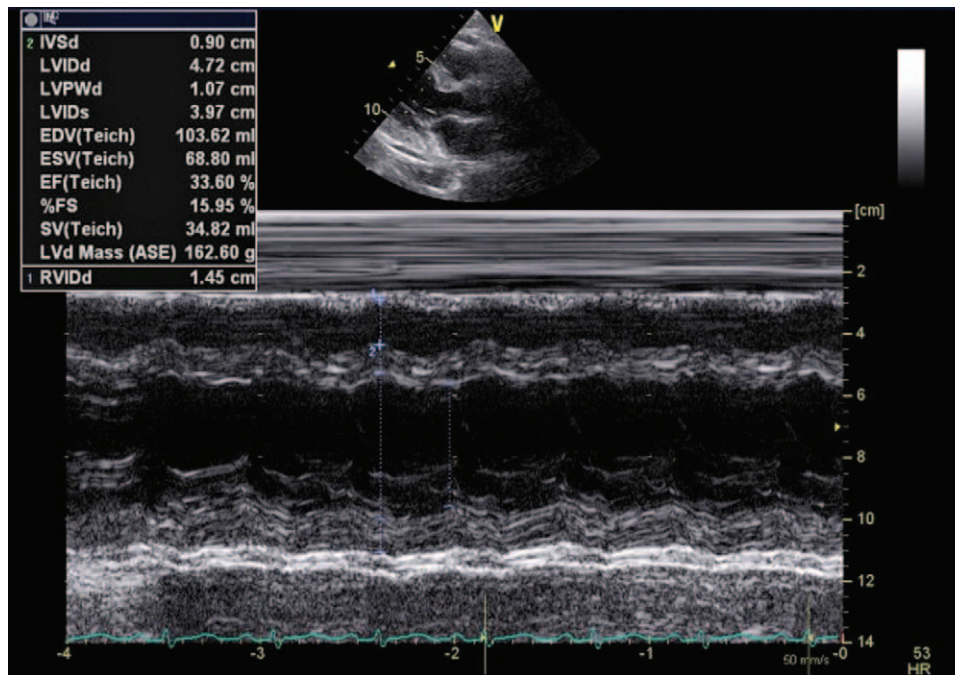


Figure 3. M-mode echocardiography demonstrating low left ventricular ejection fraction.

### 3. Discussion

We describe a multiparous female patient with cervical incompetence treated with a cervical cerclage and long-term tocolysis. Three days after delivery, she developed decompensated acute heart failure and was diagnosed with PPCM, which is a rare and sometimes fatal disease of unknown etiology. The 2010 Heart Failure Association of the European Society of Cardiology (ESC) Working Group defined PPCM as idiopathic cardiomyopathy with heart failure secondary to LV systolic dysfunction with a left ventricular ejection fraction (LVEF) of <45% during the last month of pregnancy or within 5 months following delivery. Their study finds no identifiable cause for heart failure but they speculate that it could be due to ventricular dilatation.<sup>[8]</sup>

The proposed pathogenesis of PPCM includes viral vasculitis,<sup>[9]</sup> endothelial dysfunction,<sup>[10]</sup> selenium deficiency,<sup>[11]</sup> increased levels of prolactin,<sup>[12]</sup> oxidative stresses from the vascular hormone soluble fms-like tyrosine kinase receptor 1,<sup>[13]</sup> autoimmune response,<sup>[14,15]</sup> or genetic predisposition.<sup>[16,17]</sup> Previous studies have shown advanced age, black race, pre-eclampsia, hypertension, multiple gestations, anemia, and prolonged tocolysis to be risk factors for PPCM.<sup>[18]</sup> Long-term use of tocolytic agents may contribute to cardiovascular dysfunction. A previous case series by Witlin et al reported PPCM in 2 patients out of 28 who had been administered tocolysis, including magnesium sulfate, ritodrine, terbutaline, and indomethacin.<sup>[19]</sup> Lampert et al retrospectively reviewed 15 patients who had PPCM and found that 4 had undergone prolonged tocolytic therapy for 4 to 11 weeks, with a mean duration of treatment of 6.7 weeks.<sup>[20]</sup>

Cardiovascular events have been associated with ritodrine use in pregnancy, including chest pain, pulmonary edema, cardiac arrhythmias, and peripheral vasodilatation.<sup>[21,22]</sup> Studies also found that ritodrine decreased cardiac baroreflex sensitivity,

resulting in dysregulation of the vagal heart rate and increased blood pressure variability.<sup>[7]</sup> Following a rise in heart rate, decompensated heart failure may occur because of reduced time for left atrial emptying, diastolic ventricular filling, and systolic ejection.<sup>[6]</sup> On the other hand,  $\beta$ -adrenergic regulation also affects the balance between cardio-protection and cardiotoxicity.<sup>[7,23]</sup> Cardiomyopathy may be triggered by beta-stimulation.

There is a high prevalence of pre-eclampsia in women with PPCM, and the 2 may share the same pathophysiology.<sup>[24]</sup> Recent data suggest that antiangiogenic factor sFlt-1 from the placenta antagonizes circulating vascular endothelial growth factor and placental growth factor, leading to hypertension and endothelial dysfunction in pre-eclampsia. Higher serum soluble fms-like tyrosine kinase receptor 1 levels have also been found in women with PPCM, which correlates with poor myocardial recovery.<sup>[13]</sup> However, our patient was treated with a calcium channel blocker to inhibit preterm labor, possibly concealing and delaying a pregnancy-induced hypertension diagnosis. Early detection of pre-eclampsia may help to enhance alertness and recognition of PPCM.

The management of PPCM requires a multidisciplinary team involving obstetricians, cardiologists, and anesthesiologists. The treatment goals are similar to non-pregnant acute heart failure with special consideration for fetal safety. Treatments for heart failure that are compatible with pregnancy status and breastfeeding include sodium restriction, loop diuretics,  $\beta$  blockers, hydralazine, nitrates, digoxin, and heparin. However, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are contraindicated during pregnancy due to fetotoxicity. According to ESC<sup>[25]</sup> and American Heart Association<sup>[26]</sup> guidelines, an urgent cesarean delivery should be considered in women presenting with acute heart failure and hemodynamic instability. In hemodynamically stable patients, vaginal delivery is preferable with epidural analgesia.



The reported mortality rate ranges from 2.0% to 12.6%<sup>[25]</sup>; however, recent evidence suggests that the LVEF recovers to a normal range within the first 3 to 6 months in 50% to 80% of women with PPCM.<sup>[27]</sup> However, an LVEF of <30% at the time of diagnosis indicates lower recovery rates and increased adverse events.<sup>[31]</sup> In addition, approximately 50% of recovered patients could experience recurrent PPCM and deterioration of LV function in subsequent pregnancies.<sup>[28,29]</sup> Therefore, both the ESC and American Heart Association guidelines recommend contraception to PPCM patients without normalized LVEF.<sup>[25,26]</sup>

PPCM is a significant cause of maternal morbidity and mortality worldwide. The rising incidence of PPCM may be related to the higher prevalence of predisposing disorders such as advanced maternal age, hypertension, diabetes, and multifetal pregnancies, and possibly to increased recognition of the disease. A major challenge is distinguishing the physiologic peripartum changes in healthy women from the pathological symptoms of PPCM. Diagnosis of PPCM is difficult and requires close attention to heart failure signs and symptoms, especially in late pregnancy and the puerperium.

The present case was that of a multiparous woman of advanced maternal age, who did not have a history of hypertensive disease. Long-term intravenous tocolytic therapy not only results in fluid overload but also dysregulation of heart rate and blood pressure. Hemodynamic stress results in decompensated heart failure. As a result, tocolytic agents, especially  $\beta$  agonists, should be used with considerable caution in pregnant women with underlying cardiovascular disorders. The best prognosis can be achieved with early attention to cardiac failure symptoms in women who receive tocolysis and medical treatment.

## Author contributions

**Writing – original draft:** Pei-Chen Li.

**Writing – review & editing:** Huai-Ren Chang, Sheng-Po Kao.

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