

## Case Report

# Methamphetamine Associated Cardiomyopathy in Pregnancy: The Distinctions and the Implications

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## Abstract

### Introduction

Methamphetamine associated cardiomyopathy (MAC) and peripartum cardiomyopathy (PPCM) are both rare obstetric conditions. Literature regarding methamphetamine associated cardiomyopathy in the obstetric population is limited, and it can be difficult to make the distinction between the two given the similarities in clinical presentation. However similar, there are significant distinctions in the pathophysiology of these two that can help clinicians with the management process.

### Clinical Findings and Outcomes

This case involves a 35-year-old Hispanic G6P5005 at 37 weeks gestation presenting with acute respiratory failure secondary to acute decompensated heart failure with reduced ejection fraction and superimposed preeclampsia leading to urgent cesarean section. The patient's course was also complicated by chronic methamphetamine use with a possible withdrawal component, which resulted in rapid sequence intubation and mechanical ventilation. Ultimately the patient's respiratory and cardiac symptoms resolved with appropriate treatment. Resolution of reduced ejection fraction was also demonstrated by repeat echocardiogram.

### Conclusions

In this article, we will compare the pathophysiology, diagnostic criteria, treatment and prognosis of MAC, specifically in pregnancy, versus PPCM. We also discuss how we ultimately conclude that a diagnosis of MAC can be made rather than PPCM or stress cardiomyopathy. We also find that studies involving methamphetamine use in pregnancy are limited, and ultimately more longitudinal data is needed to achieve a better understanding of patient outcomes, especially given the increasing prevalence of methamphetamine use in the United States.

### Keywords

methamphetamine/adverse effects; cardiomyopathies; methamphetamine cardiomyopathy; peripartum cardiomyopathy; methamphetamine abuse; substance-related disorders; amphetamine-related disorders; pregnancy complications; critical care; obstetrics; reversible cardiomyopathy; stress induced cardiomyopathy; Takotsubo cardiomyopathy

## Introduction

The field of critical care is all-encompassing and applies to all specialties of medicine including obstetrics. The number of obstetric conditions requiring intensive care admission is relatively small (compared to the general non child-bearing adult population) and is typically related to hypertensive or hemorrhagic causes.<sup>1</sup> However, the rates of mortality with these conditions can be as high as 60%.<sup>2</sup> Thus, maintaining knowledge of critical care obstetrics remains

pertinent in any setting.

Methamphetamine use is on the rise, and the widespread pattern of abuse and household production is reminiscent of the crack cocaine epidemic of the 1980s. Data recently published by the Centers for Disease Control and Prevention showed that between 2015 and 2018, 1.6 million Americans used methamphetamine within the past year.<sup>3</sup> A study from 2006 estimated that approximately 5% of women

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used methamphetamine during pregnancy, and with current trends it is likely this number has increased over time.<sup>4</sup> With evidence of this extensive use, it is clear that physicians of all specialties will encounter patients suffering from this addiction in a variety of different scenarios.

The case involves a patient presenting with acute respiratory failure secondary to acute decompensated heart failure with reduced ejection fraction (EF) with superimposed preeclampsia leading to urgent cesarean section. The patient's course was also complicated by chronic methamphetamine use (as confirmed by a positive urine drug screen and the patient's own admission) with a possible withdrawal component, which resulted in mechanical ventilation.

We will compare the pathophysiology, diagnostic criteria, clinical presentation and treatment of methamphetamine associated cardiomyopathy (MAC) specifically in pregnancy, versus peripartum cardiomyopathy (PPCM), both of which are rare conditions.<sup>2,5,6</sup> We also discuss how we ultimately concluded that a diagnosis of MAC could be made rather than PPCM or stress-induced cardiomyopathy.

## Case Presentation

A 35-year-old Hispanic G6P5005 at 37 weeks gestation presented to the emergency department with a complaint of worsening shortness of breath and lower extremity edema for the past two days. Medical history included iron deficiency anemia and methamphetamine use. She reported having a history of new onset hypertension during her first pregnancy prior

to 20 weeks gestation, which resolved with no progression to gestational hypertension or preeclampsia. She was normotensive during the prenatal course for her current pregnancy and was not prescribed any anti-hypertensive medication. At presentation, she was in severe preeclampsia (blood pressure above 160 mm Hg with proteinuria) and desaturation (pulse oximetry was 91% on room air) with crackles in lung bases and pitting edema of the lower extremities. Urine drug screen (UDS) was positive for methamphetamine. Additional urine and serum laboratory testing are listed in **Table 1** and **Table 2**. A chest x-ray (CXR) demonstrated bilateral edema with cardiomegaly. Bedside point of care echocardiography showed an estimated EF of 30–40%. The patient was placed on non-invasive ventilation (NIPPV) and admitted to the labor and delivery service for an urgent cesarean section that was done with epidural anesthesia. She received intravenous (IV) furosemide and fentanyl, and two units of packed red blood cells (PRBC) intraoperatively. The fetus was delivered without complication.

Upon returning to the post-anesthesia care unit (PACU), the patient's blood pressure readings from the brachial artery cuff were in the hypotensive range, and there was significant lochia. At this point, we had concerns for possible hemorrhagic shock secondary to uterine atony. A left radial arterial line was placed yielding systolic BP readings in the 180s disproving this theory, and we suspected the hypotensive value was due to an inaccurate telemetry from the cuff or user error; however, due to the volume of blood loss, she was transfused an additional

**Table 1.** Serum Labs.

N-terminal Brain Natriuretic Peptide	580 pg/mL (5–125)
Serial Troponin I Level (3 sets measured 6 hours apart)	0, 0, 0.028 ng/mL (0–0.045)
Creatine Kinase	361 U/L (26–192)
Serum Creatinine	0.61 mg/dL (0.52–1.23)
Complete Blood Count	Hemoglobin: 6 gm/dL (12–16) Hematocrit: 23.4% (37–47%) Platelets: 309,000 (150,000–450,000) White Blood Cells: 13,000 (4800–10800)
Liver Function Tests	Aspartate aminotransferase: 23 (15–37) Alanine aminotransferase: 9 (12–78) Alkaline phosphatase: 112 (45–117)

**Table 2.** Urine Labs.

Urine Drug Screen	Amphetamine: positive Cocaine: negative THC: negative Barbiturate: negative Benzodiazepines: negative Opiates: negative PCP: negative
Urinalysis	Color: amber Appearance: clear Glucose: negative Bilirubin: negative Ketones: negative Protein: 100 mg/dL (positive) Nitrite: negative Leukocyte esterase: negative RBC: 0–2 (negative) WBC: 0–2 (negative) Epithelial cells: 2–5 (2–5)
Random Urine Protein	85.5 mg/dL (< 11.9)
Random Urine Creatinine	61.8 mg/dL

unit of PRBC. An IV nitroglycerin drip was then started. A stat echocardiogram showed an EF of 30–35% with moderate diffuse hypokinesis, mildly increased wall thickness, grade 1 diastolic dysfunction and a normal left ventricle size. Left ventricular end diastolic volume (LVEDV) on 2 chamber and 4 chamber views were 61 ml and 86 ml, respectively.

Upon transfer to the intensive care unit, she continued to remain hypertensive despite nitroglycerin and was now tachypneic and tachycardic as well. The onset of tachycardia was concerning for possible methamphetamine withdrawal, and she was given lorazepam with no resolve. Due to concern for imminent respiratory compromise, she was intubated and placed on mechanical ventilation. A dexmedetomidine drip was started for sedation. Post-intubation CXR revealed persistent interstitial edema with a new left-sided effusion, and arterial blood gas (ABG) revealed a non-anion gap metabolic acidosis. Diuresis with IV high dose furosemide was initiated.

The following day, CXR was notable for improving edema and left-sided effusion. The patient was extubated, and her blood pressure stabilized with carvedilol and hydralazine. The next day, she was noted to have a new systolic murmur; therefore, a repeat echocardiogram was

ordered (day 4 of admission), which showed mild to moderate mitral regurgitation and improvement in ejection fraction to 55% to 60% with mild left ventricular dilation and grade 1 diastolic dysfunction. She was discharged home with follow up plans, and child protective services were contacted regarding custody of the newborn.

### Discussion

The case presents a difficult diagnosis, as the symptoms were multifactorial in nature. We believe the symptoms stem from a combination of preeclampsia and methamphetamine use rather than a case of PPCM, given methamphetamine use was an identifiable cause of heart failure (this will be elaborated on further). The diagnosis of preeclampsia with severe features was made given two systolic blood pressure measurements above 160 mmHg with proteinuria (100 mg/dl on urinalysis and 85.5 mg/dL on random urine protein sample) and the presence of pulmonary edema.<sup>7</sup>

We do not believe the symptoms were due to peripartum cardiomyopathy. Peripartum cardiomyopathy requires the following criteria for diagnosis: presentation late in pregnancy or several months postpartum, an EF less than 45% and the absence of prior cardiac disease or

other identifiable causes of heart failure.<sup>2,5</sup> Our patient presented late in pregnancy (37 weeks gestation). Echocardiogram on the day of presentation was read by two different cardiologists with one reporting EF as 30–35% and the other reporting it as 35–40%. The patient only met 2 of the 3 criteria and could not be diagnosed with peripartum cardiomyopathy as chronic methamphetamine use can also cause heart failure.

The exact underlying cause of PPCM is not well understood, however there are several proposed hypotheses in the current literature. These include the combination of oxidative stress and gestational hormone secretion leading to vascular endothelial damage and inflammation of cardiac myocytes. The main hormone involved in this process is prolactin.<sup>8,9</sup> Prolactin undergoes enzymatic cleavage to a form known as 16-kDa prolactin which induces apoptosis in cardiac myocytes. Another hormone, soluble Fms-like tyrosine kinase 1 (sFlt1), is also thought to play a role in this process by inhibiting the activity of vascular endothelial growth factor (VEGF). There is also a possible genetic component to PPCM. Patients with a mutation in the TTN gene, which encodes the sarcomere protein titin, were found to have a genetic predisposition to dilated cardiomyopathy in a recent study.<sup>8,9,10</sup>

The primary mechanism through which methamphetamine causes cardiomyopathy is catecholamine excess and a hyperadrenergic state.<sup>11</sup> Methamphetamine is a Central Nervous System (CNS) stimulant that acts by indirectly increasing levels of dopamine, serotonin, norepinephrine and epinephrine. Schurer et al. note that methamphetamine can have multiple effects on the myocardium including “direct toxic effects, vasospasm, ischemia, reactive oxygen species and mitochondrial and metabolic alterations.”<sup>12</sup> In their study, histopathological analysis of the myocardium in a non-pregnant patient with a minimum of 2 years of methamphetamine use was notable for fibrosis, myocyte damage and inflammation (characterized by positive staining for CD3 T cells and CD68 macrophages).<sup>12</sup>

Data regarding methamphetamine associated cardiomyopathy in pregnancy is limited, as most studies only involve non-pregnant women

or a majority male population. A recently published case series detailed MAC in five pregnant patients, with four out of the five presenting in the second trimester and one presenting in the third trimester.<sup>6</sup> In our case, the patient admitted to using methamphetamine 2 weeks prior to presentation and denied recent use; however, her UDS on admission was positive. Methamphetamine is detected up to 48 hours after use in most standard drug tests and has a half-life of 9 to 12 hours.<sup>13</sup> Therefore, it is highly likely the patient had recently used methamphetamine within that time frame.

The treatment for PPCM and MAC in pregnancy in the acute setting are consistent with management of an acute heart failure exacerbation, i.e., optimization of respiratory status, diuresis, beta blockade and if needed, hemodynamic support. Management of hypertension is also an important component in the overall scheme.

In cases of preeclampsia, labetalol is an effective anti-hypertensive. Although the current literature on the use of labetalol in meth users is limited and somewhat controversial. There is a concern that giving labetalol in patients with active methamphetamine use can worsen hypertension due to vasoconstriction from unopposed alpha receptor activity. Technically labetalol has both alpha and beta receptor blocking activity, therefore the risk of unopposed alpha activity is not thought to be high. Other options include hydralazine and nitroprusside. ACE inhibitors or ARBs are contraindicated in mothers who have not delivered due to their teratogenicity. Although prolactin is believed to play a role in PPCM, the use of bromocriptine (a dopamine receptor agonist that inhibits prolactin secretion) is not an approved treatment.

In addition to medical management, patients with MAC will need appropriate treatment of their addiction as this will ultimately determine their long-term prognosis. A University of Hawaii study found that implementation of a “harm-reduction model” consisting of services such as addiction medicine, social services and perinatal care yielded improvement in birth outcomes and a reduction in subsequent positive urine drug tests.<sup>14</sup>

The prognosis in PPCM is generally favorable as a recovery of ejection fraction (LVEF >50%) is typically seen within 6 months.<sup>8</sup> Several factors have been associated with a higher likelihood of recovery, such as LVEF above 30% at the time of diagnosis, Caucasian race and diagnosis in the postpartum period.<sup>15,16</sup> This phenomenon of reversibility is also documented in patients with MAC. The primary factor contributing to recovery is cessation of methamphetamine use.<sup>11,17</sup> It's important to note that a majority of this data is from methamphetamine use in non-pregnant adults, and more data assessing outcomes of methamphetamine use specifically in the obstetric population is needed.

Another etiology of reversible cardiomyopathy that warrants discussion given the rapid recovery of EF, is stressed cardiomyopathy (also known as Takotsubo cardiomyopathy and apical ballooning syndrome). It is typically precipitated by profound emotional or physical stress, and it usually occurs in post-menopausal women, but cases have been documented in pregnancy. Given the patient was using methamphetamine, the combination of a hyperadrenergic state and pregnancy makes stress-induced cardiomyopathy a plausible diagnosis.

There are, however, several factors in this case which we believe make stress cardiomyopathy less likely: normal troponin levels, patterns on electrocardiography (EKG) and echocardiographic findings that overall do not fit the stigmata of stress-induced cardiomyopathy. The patient had three serial troponin levels measured, which were negative. A study using data from the International Takotsubo Registry found that 80% of patients with stress-induced cardiomyopathy had troponin elevation.<sup>18</sup> QT prolongation and ST segment changes (typically elevation) are also a common finding. The patient in our case had an average corrected QT interval of 458 (considered within borderline range for females based on the *Journal of American College of Cardiology* classification) with no ST segment elevation or depression on three serial EKGs.<sup>18-20</sup> The stat echocardiogram mentioned previously, demonstrated moderate diffuse hypokinesis of the left ventricle and a normal size, rather than the classic pattern of apical akinesis and basal hyperkinesis seen in the majority of patients with stress-induced cardiomyopathy.<sup>20,21</sup> Right ventricular apical in-

volvement is also seen in up to 25% of patients, although the patient's right ventricle size and systolic function were reported to be normal.<sup>21</sup> Based on this data we henceforth conclude that a diagnosis of MAC is more likely than stress-induced cardiomyopathy.

## Conclusion

The treatment for methamphetamine associated cardiomyopathy and peripartum cardiomyopathy are essentially the same as the treatment of an acute heart failure exacerbation and both etiologies are potentially reversible causes of cardiomyopathy. Nevertheless, current evidence clearly shows a distinction in the pathophysiology between MAC, which is due to a hyperadrenergic state, versus PPCM, which is due to an adverse hormonal effect on the maternal vasculature and cardiac myocytes. Stress-induced cardiomyopathy shares a common pathophysiology with MAC; however, it has distinct echocardiographic features which weren't seen in this case. We can effectively conclude that the patient's symptoms were secondary to MAC rather than PPCM or stress-induced cardiomyopathy. Studies involving methamphetamine use in pregnancy are limited and ultimately more longitudinal data is needed to achieve a better understanding of patient outcomes.

## Conflicts of Interest

The authors declare they have no conflicts of interest.

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