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Pregnancy and Cardiovascular Disease (N Scott, Section Editor)

Management of Heart Failure and Cardiogenic Shock in Pregnancy

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Abstract

Purpose of review While the prognosis of peripartum cardiomyopathy (PPCM) is generally more favorable than other cardiomyopathies, PPCM can be associated with cardiogenic shock and significant maternal morbidity in young women. The management of a pregnant woman in cardiogenic shock necessitates consideration of harm to the fetus. This review focuses on the management of these women.
Recent findings A number of advances have increased the repertoire of therapies available to manage PPCM. Increased understanding of PPCM pathophysiology has led to a number of new and experimental medications. In the current era, mechanical circulatory support has been gaining a stronger presence in critical care and can be used in cardiogenic shock of the pregnant patient refractory to medical therapy.
Summary We discuss medical therapies, mechanical circulatory support, arrhythmia management, and a delivery plan in the setting of cardiogenic shock secondary to PPCM.

Introduction

Pregnancy-related mortality and morbidity in the USA is strikingly high. Every year, over 700 women die and more than 50,000 women face a life-threatening complication during pregnancy and childbirth [1]. Women in the USA are more likely to die from pregnancy- or childbirth-related causes than women in any other high-income countries [2]. Cardiovascular disease is the leading cause of pregnancy-related death in the USA, accounting for 25–30% of all maternal deaths, and cardiomyopathies account for one-half to two-thirds of these cases [3•, 4].

Peripartum cardiomyopathy (PPCM), an idiopathic dilated cardiomyopathy that occurs late in pregnancy or in the postpartum period, is a leading offender, particularly in cases of cardiogenic shock [5]. However, it is important to recognize that not all cases of heart failure and cardiogenic shock in pregnancy are due to PPCM. In this article, we will briefly review etiologies of heart failure and cardiogenic shock in pregnancy and then focus on the management of heart failure and cardiogenic shock in PPCM.

Identifying a pregnant woman in heart failure can be challenging. During pregnancy, women can commonly experience symptoms that mimic cardiovascular disease including dizziness, palpitations, dyspnea, orthopnea, and peripheral edema [6]. While mild variants of the aforementioned signs and symptoms are benign, severe or progressive variants should prompt a heart failure workup. The etiologies of heart failure in a pregnant woman to consider can be grouped into 4 categories: (1) the unmasking of preexisting cardiovascular disease by pregnancy; (2) an identifiable acute cardiac insult; (3) preeclampsia/eclampsia; and (4) PPCM. In pregnancy, blood volume increases up to 50% to meet uterine blood flow and fetal perfusion needs. Cardiac output also increases by about 50%, initially through an increase in stroke volume and then with increases in heart rate in later stages of pregnancy [7]. These changes can unmask preexisting cardiomyopathies, valvular heart disease, and congenital heart disease that are intolerant of the volume load. In contrast to PPCM, these conditions typically present by the second trimester. Acute insults for which pregnant women may be at risk include pregnancy-associated myocardial infarction, including spontaneous coronary artery dissection, pulmonary thromboembolism, and amniotic fluid embolism. Each of these conditions can result in a heart failure syndrome, including cardiogenic shock. Finally, severe preeclampsia and eclampsia can manifest with volume overload [3•, 8].

If a workup for the aforementioned etiologies is negative, then, PPCM should be considered as it is principally a clinical diagnosis of exclusion. The commonly used European Society of Cardiology definition of PPCM is heart failure secondary to idiopathic left ventricular systolic dysfunction (ejection fraction < 45%) that occurs towards the end of pregnancy or in the months following delivery [9]. As alluded to, the clinical presentation of PPCM consists of heart failure symptoms late in pregnancy or postpartum. Risk factors for PPCM include maternal age > 30 years, African-American race, hypertension, preeclampsia/eclampsia, and a multigestational status [10]. Diagnostic workup most importantly includes a transthoracic echocardiogram that confirms the state of ventricular dysfunction. PPCM prognosis is generally more favorable than other cardiomyopathies. However, in some cases, PPCM can be associated with cardiogenic shock and significant maternal morbidity [11]. In this article, we will focus on this population in particular, discussing the management of heart failure and cardiogenic shock in critically ill PPCM patients.

Medications

The general principles of medication therapy for heart failure and cardiogenic shock in pregnant patients are the same as for non-pregnant patients—restoring perfusion in cardiogenic shock and, when hemodynamics and renal status permit, initiating neurohormonal inhibition. However, the risk of fetal toxicity limits the repertoire of medications available. Additionally, the unique pathophysiology of PPCM has led to the development of targeted therapeutic medical therapies. Arrigo et al. recently proposed a label to group together essential therapies in PPCM, "Welcome on BOARD"—*B*romocriptine, *O*ral heart failure therapies, *A*nticoagulants, vaso*R*elaxing agents, and *D*iuretics [12•]. This mnemonic succinctly categorizes PPCM treatments and is easily accessible to clinicians. Therefore, we will use this label to frame our discussion of medical therapy in PPCM.

Targeted therapies ("*B*romocriptine")

Prolactin production is increased in pregnancy and the postpartum period to induce lactation and promote reverse remodeling of the uterus. In its full-length 23-kDa form, prolactin is proangiogenic and cardioprotective. Excess oxidative stress, however, mediated in part by STAT3 deficiency, can result in the cleavage of prolactin to a 16-kDa form. This subform is anti-angiogenic and destroys the cardiac microvasculature, promoting ventricular dilatation and potentially PPCM [13].

Given this mechanism, bromocriptine, a dopamine receptor agonist that blocks the release of prolactin, has shown promising results in experimental animal models and small human trials [14, 15]. Most recently, in a German study of 63 PPCM patients with LVEF < 35%, only 7% of women treated with bromocriptine for 8 weeks had persistent LVEF < 35% at 6-month follow-up. No patients required transplantation or left ventricular assist device (LVAD) therapy. Remarkably, even patients treated with 1 week of bromocriptine showed significant recovery [16]. Notably, however, there was no control arm in this study.

Bromocriptine therapy, however, is not without risk. Bromocriptine has been associated with thrombotic complications and suppresses lactation, preventing mothers from breastfeeding their newborns [17]. Given the risks and benefits, current guidelines are mixed. The 2018 European Society of Cardiology (ESC) guidelines for the management of cardiovascular diseases during pregnancy make a class IIB recommendation for "bromocriptine (2.5 mg once daily) for at least 1 week in uncomplicated cases of PPCM" and "prolonged treatment (2.5 mg twice daily for 2 weeks, then 2.5 mg once daily for 6 weeks) in patients with an ejection fraction of less than 25% and/or are in cardiogenic shock. As per these recommendations, bromocriptine therapy should always be accompanied by prophylactic anticoagulation [18•]. In contrast, the American Heart Association (AHA) guidelines categorize bromocriptine as an experimental therapy. These guidelines, published in 2016, precede the aforementioned German trial, and it remains to be seen whether this will prompt a revision in the next set of AHA guidelines [3•, 19•].

Several other emerging therapies are under investigation. MicroRNA-146a is thought to play a role in prolactin 16 kDa-mediated damage. As such, antisense therapy against microRNA-146a is currently under therapeutic investigation, especially as this strategy would not disrupt full-length prolactin signaling and thereby potentially permitting women to breastfeed [20]. Furthermore, proangiogenic therapies such as vascular endothelial growth factor (VEGF) agonists are being studied in mouse models and may be beneficial not only in PPCM but also in preeclampsia [21].

Neurohormonal modulators ("*O*ral heart failure therapies")

Neurohormonal inhibition is a well-established and guideline-directed strategy to promote reverse cardiac remodeling in heart failure syndromes. The safety of these drugs needs to be considered separately in pregnancy versus during lactation. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are contraindicated throughout pregnancy [22]. A systematic review of 186 fetuses exposed to ACEi or ARBs revealed complications in 48% and 87%, respectively, including renal failure, oligohydramnios,

and death [23]. Hydralazine and nitrates can be used as alternatives, both of which have safety data in patients with preeclampsia [11]. Beta-blockers can be used throughout pregnancy. β1 selective agents are preferred to prevent inhibition of β2-mediated myometrial relaxation [24]. Notably, beta-blockers have been linked to impaired fetal growth and neonatal hypoglycemia, bradycardia, and hypotension [25, 26]. However, the overall magnitude of these neonatal complications is not thought to outweigh the maternal benefits of beta-blockers in conditions such as PPCM [22]. Aldosterone antagonists are generally not recommended during pregnancy. Based on rodent studies showing feminization of males exposed to spironolactone in utero, spironolactone is not recommended in pregnancy [27]. Eplerenone has not shown similar effects in animal models but is not recommended in pregnant women unless other diuretics are ineffective [22].

After delivery, women can be started on ACE inhibitors. Captopril and enalapril, in particular, are preferred based on data showing clinically insignificant milk concentrations during lactation and lack of adverse effects on neonates. In terms of beta-blockers, metoprolol is excreted into breast milk at negligible concentrations and the preferred agent. There is limited/scarce data on bisoprolol and carvedilol. Finally, spironolactone can also be started after delivery with human data showing minimal excretion of the drug in breast milk [19•, 28, 29].

Anticoagulation

The incidence of thromboembolism in PPCM is high with an estimation at approximately 6% [30]. Hypercoagulability during the peripartum period is hypothesized to be an evolutionary adaptation to decrease uterine hemorrhage. The stasis of blood as a result of a low ejection fraction and body immobility further compounds thrombotic risk [17]. In patients that receive bromocriptine therapy, the thrombotic risk increases even further. The AHA and ESC recommend anticoagulation in patients with PPCM with an ejection fraction less than 30% and 35%, respectively [18•, 19•]. Other experts recommend anticoagulation in all cases of PPCM and to continue anticoagulation for 2-month postpartum [17]. Unfractionated and low molecular weight heparin do not cross the placenta and are the agents of choice in PPCM for women who are pregnant. After delivery, warfarin can be used [3•]. Data on direct oral anticoagulants during pregnancy and breastfeeding is too scarce at this time to make recommendations [31].

Perfusion ("vaso*R*elaxing agents")

In the setting of cardiogenic shock in the pregnant patient, decision-making regarding the use of vasodilators versus inodilators to improve perfusion should follow the same considerations as the non-pregnant patient. If vasodilators are chosen, nitroglycerin is preferred to nitroprusside based on animal model data showing lethal levels of cyanide in fetuses in utero with maternal intravenous infusion of nitroprusside [32]. Although this finding has not been confirmed in human fetuses exposed to nitroprusside, this drug is generally avoided in pregnancy [33, 34]. If a continuous infusion is not necessary, methyldopa and hydralazine may be used for afterload reduction in pregnancy and can be used in this clinical setting [35].

If inotropic support is necessary, use of beta agonists should be minimized given data suggesting harm in PPCM patients. In a retrospective analysis of 27 patients with severe PPCM, all 7 patients receiving dobutamine required heart transplantation or left ventricular assist device. In contrast, only 1 out of 20 patients not receiving dobutamine required such advanced heart replacement therapies. This study group further went on to show that in mice with cardiac STAT3 deletion, a protein reduced in PPCM patients, isoproterenol administration induced heart failure. Heart failure was not induced with isoproterenol in wild-type mice [3•, 36]. Although data against beta agonists is limited, it may be prudent to choose alternative inotropes such as milrinone or levosimendan, with the caveat that levosimendan is not available in the USA [34]. Both agents act via PDE3 inhibition. Levosimendan additionally increases myofilament Ca^{2+} sensitization [37].

Diuretics

Guidelines regarding diuretic therapy for PPCM are vague with both the AHA and ESC recommending cautious use of diuretic agents to treat volume overload given concerns for decreased placental blood flow [19•, 29]. However, a meta-analysis of patients receiving diuretics during pregnancy did not show any significant adverse effects on the fetus [38]. On the contrary, in decompensated heart failure, diuretics can improve cardiac hemodynamics and hence systemic perfusion including the placenta [8]. Neither loop nor thiazide diuretics have been shown to have teratogenicity. Conventionally, furosemide is used in pregnancy [39]. Aldosterone antagonists should be avoided as mentioned in the neurohormonal inhibition section above.

Mechanical circulatory support

Acute mechanical circulatory support (MCS) should be considered an early intervention in pregnant patients in cardiogenic shock. An analysis by Banayan et al., of over 53 million peripartum hospitalizations in the USA between 2002 and 2013, demonstrated that women who received early MCS, defined as 6 days or less from the onset of cardiogenic shock, had a lower mortality rate than women who received delayed MCS therapy (18% versus 38%, respectively) [5]. Although this was a retrospective analysis and these findings may be confounded by patient and clinical characteristics, they do urge consideration of early MCS implementation for hemodynamic support when coupled with the aforementioned data suggesting that beta agonists can be particularly detrimental in patients with PPCM [36].

Given the higher rates of improved systolic function in patients with PPCM compared with other cardiomyopathies, temporary MCS is often employed as a "bridge to recovery" or "bridge to durable MCS" if recovery is delayed or, if necessary, cardiac transplantation [9]. Pregnancy aside, clinicians have a range of options for acute MCS in cardiogenic shock but are faced with a lack of high-quality evidence to guide optimal device selection. The selection of a device is often based on hemodynamic acuity, such as cardiac arrest, the severity of cardiogenic shock by end-organ dysfunction and vasoactive therapy requirements, the predominance of either uni- versus biventricular failure, anatomical considerations, and

institutional factors including specific device availability and associated expertise [41].

Utilizing a cardiopulmonary requirement approach to acute circulatory support device selection is critical in the PPCM patient in cardiogenic shock. The intra-aortic balloon pump provides the least amount of hemodynamic support (0.5 to 1.0 L/min) among acute MCS devices and does not support oxygenation. However, it can be quickly and easily placed at the bedside and may not mandate anticoagulation. In comparison, the Impella (Abiomed, Danvers, MA) is a minimally invasive micro-axial left ventricular catheter that comes in Impella CP and Impella 5.0 models that can provide up to 3.5 to 5.0 L/min, respectively. If additional hemodynamic support, including biventricular support, is required or the patient is vulnerable to arrhythmia or hypoxia, extracorporeal membrane oxygenation (ECMO) provides oxygenation and maximum circulatory support by providing a cardiopulmonary bypass circuit.

However, these devices are typically limited in their duration of use owing to concerns for bleeding, emboli, and infection. The risk of device thrombosis is not trivial as pregnancy, heart failure, and, if utilized for peripartum cardiomyopathy, bromocriptine are all procoagulants [8, 42]. Therefore, using the Impella and ECMO mandate strict anticoagulation monitoring and adherence, which comes with its own challenges during delivery. Special consideration is needed regarding the use of anticoagulation peri-delivery given the importance of epidural anesthesia during labor and for uterine hemostasis after delivery [43]. Another challenge with ECMO in the pregnant patient is that prolactin levels have been shown to increase in ECMO versus control patients and elevated prolactin levels are associated with poor outcomes [44]. Although this has only been reported in one study, the ESC recommends suppression of prolactin while on ECMO with doses of bromocriptine up to 10 mg twice daily [9].

For those PPCM patients with persistent ventricular systolic dysfunction, the use of durable MCS has been reported in the literature through analyses of large MCS registries as well as case reports. An analysis of the 1258 women registered in the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) between June 2006 and March 2012 identified 99 women with PPCM who underwent surgically implanted left, right, or biventricular assist devices. PPCM women had improved survival compared with non-PPCM women likely as a result of fewer comorbidities and younger age [40].

Cardiac transplantation

In cases of persistently severe PPCM despite optimal medical and device therapy, cardiac transplantation should be considered. Reassuringly, however, many women have ventricular recovery. In the multicenter North America IPAC (Investigations of Pregnancy Associated Cardiomyopathy) study, 72% of women achieved an ejection fraction of at least 50% by 1 year postpartum, whereas 13% had a persistent ejection fraction of less than 30%, required LVAD, or underwent cardiac transplantation at 1 year [45]. Besides the likelihood of ventricular recovery, another reason to exercise caution in pursuing cardiac transplantation too early is that PPCM patients may have poorer survival outcomes compared with all transplant recipients. A review of data from 485 PPCM patients transplanted between 1987 and 2010 demonstrated both a

higher incidence of allograft rejection within the index hospitalization first year post-transplant, and higher rate of mortality. Rasmusson et al. hypothesized that the poor outcomes in the PPCM population were partly a reflection of their baseline demographics—younger age, female sex, history of pregnancy, and increased pre-transplant panel reactive antibody (PRA) that may predispose to higher cardiac allograft rejection rates. However, it should be emphasized that PPCM patients should not be excluded from transplant consideration but rather that we may need to treat rejection and protect allograft function more aggressively in PPCM patients post-transplant [46].

Delivery considerations

PPCM patients are at high risk for hemodynamic decompensation at the time of labor and delivery. As such, the care of the PPCM patient warrants an awareness of the hemodynamic shifts that can occur during labor and the labor and delivery techniques that may minimize these shifts. Data supporting the optimal timing and mode of delivery are scarce, and therefore, these decisions are patient and situation-specific. If labor is induced, particular care needs to be taken with the use of prostaglandin E analogues given the possibility of systemic vasodilation and reflex tachycardia. During labor, a woman should be placed in the left lateral decubitus position to avoid inferior vena cava compression by the gravid uterus [47]. Maternal effort with labor should be minimized, prompting early consideration of forceps- or vacuum-assisted delivery, to decrease the hemodynamic effects of the Valsalva maneuver [48].

In terms of anesthetic considerations, spinal-epidural analgesia is recommended. Both a natural delivery without analgesia and systemic anesthetics are avoided if possible. The goal of this anesthetic approach is to minimize the sympathetic stimulation of labor while also avoiding the myocardial depression and systemic vasodilation of general anesthesia [47]. One challenge that often arises in pregnant patients with cardiovascular disease is balancing the benefit of epidural analgesia, the need for anticoagulation, and the risk of spinal epidural hematoma. Recognizing this challenge, a consensus statement was created to guide clinicians and patients in decision-making regarding neuraxial procedures in obstetric patients receiving thromboprophylaxis or higher dose anticoagulants [49]. In PPCM patients, the decision about spinal analgesia will need to take into account, among other factors, the necessity of anticoagulation depending on the ejection fraction, the use of bromocriptine, and the use of mechanical circulatory support.

Arrhythmia risk management

Arrhythmias are common in patients with heart failure and cardiomyopathy. Specifically, in the PPCM population, the risk of ventricular tachyarrhythmias is estimated to approximate 12% in the first 3–6 months [50]. Electrical cardioversion can be used in hemodynamically unstable patients. In late pregnancy, there is a theoretical risk of initiating labor with electrical cardioversion, and although only a small amount of electricity reaches the fetus, there is a small risk of fetal arrhythmia necessitating emergency cesarean delivery [51]. The use of antiarrhythmic drugs needs to take into consideration the risk to the fetus in

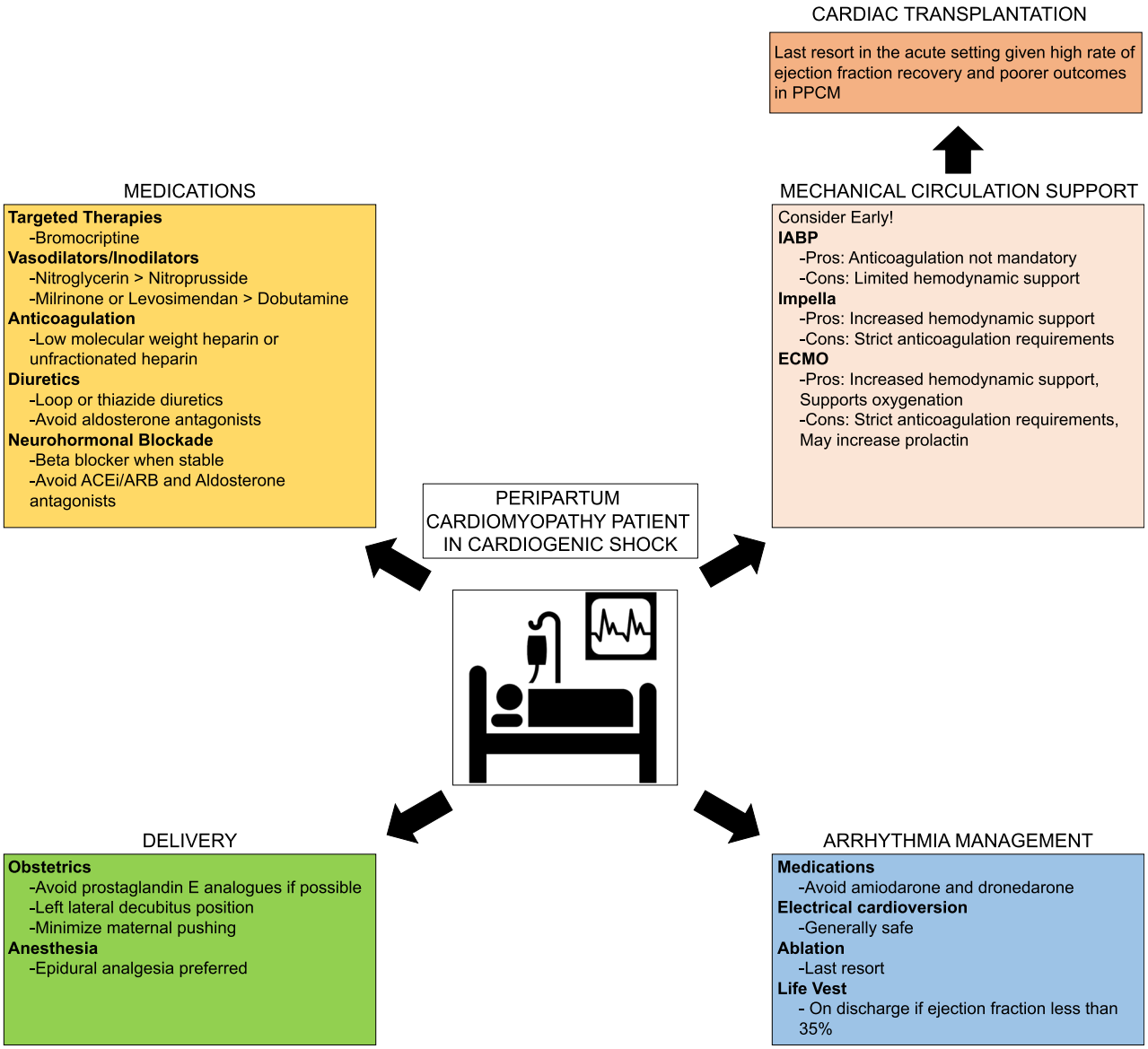

Fig. 1. Management of cardiogenic shock in pregnancy.

pregnancy. Notably amiodarone and dronedarone should not be used in pregnancy or while breastfeeding [52]. There have been case reports of successful catheter ablation in pregnant patients. However, ablation should be reserved for patients with unstable arrhythmias refractory to medical management and electrical cardioversion given the radiation exposure to the fetus during the procedure and the risk for maternal hemodynamic compromise [52].

Both the ESC and AHA state that it is reasonable to consider a wearable defibrillator life vest for primary prevention in patients with an ejection fraction less than 35% for 3–6 months [9, 19•]. Although the sample size is small, early data shows that PPCM patients receive more appropriate shocks from life vests than the general non-ischemic cardiomyopathy population [53]. In patients

without myocardial recovery after optimal medical therapy, the ESC and AHA recommend following conventional guidelines for the use of implantable cardioverter defibrillator or cardiac resynchronization therapy devices in PPCM patients [9, 19•].

Conclusion

Medical therapies, mechanical circulatory support, arrhythmia management, and a delivery plan are the cornerstones of management of the PPCM patient, Fig. 1. Management of heart failure and cardiogenic shock in PPCM necessitates, first and foremost, consideration of the impact of such therapies on fetal health. The discovery of unique pathophysiologic mechanisms underlying PPCM and the potential for targeted therapies promise innovation and optimism for an improved prognosis in a condition that affects not only one but also both mother and fetus.

Compliance with Ethical Standards

Conflict of Interest
Shilpa Sharma declares no conflict of interest.
Sunu S. Thomas declares no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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