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Peripartum cardiomyopathy-diagnosis, management, and long term implications☆,☆☆

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ABSTRACT

Peripartum cardiomyopathy (PPCM) is a potentially life-threatening pregnancy-associated disease that typically arises in the peripartum period. While the disease is relatively uncommon, its incidence is rising. It is a form of idiopathic dilated cardiomyopathy, defined as pregnancy-related left ventricular dysfunction, diagnosed either towards the end of pregnancy or in the months following delivery, in women without any other identifiable cause. The clinical presentation, diagnostic assessment and treatment usually mirror that of other forms of cardiomyopathy. Timing of delivery and management require a multidisciplinary approach and individualization. Subsequent pregnancies generally carry risk, but individualization is required depending on the pre-pregnancy left ventricular function. Recovery occurs in most women on standard medical therapy for heart failure with reduced ejection fraction, more frequently than in other forms of nonischemic cardiomyopathy. The purpose of this review is to summarize the current state of knowledge with regard to diagnosis, treatment and management, with a focus on long term implications.

Background

Heart failure during or after pregnancy has been recognized since the late 19th century [1]. However, it was not termed "peripartum cardiomyopathy" until the seminal work of Demakis and Rahimtoola was published in 1971 [2]. Their work proposed to include the diagnostic criterion of the onset between the last month of pregnancy and 5 months following delivery. Since that time, the diagnostic criteria have evolved to include left ventricular systolic dysfunction (i.e., left ventricular ejection fraction of $< 45\%$) and the absence and exclusion of any other identifiable cause of cardiomyopathy [3] as proposed by the National Institutes of Health in 2000. The European Society of Cardiology (ESC) published their own definition in 2010, with the modification of a less strict diagnostic time frame and level of left ventricular dysfunction [4]. The current working definition from the ESC states that peripartum cardiomyopathy (PPCM) is a form of idiopathic form of cardiomyopathy, defined as pregnancy-related left ventricular dysfunction, diagnosed either at the end of pregnancy or in the months following delivery, in women without any other identifiable cause [4]. PPCM occurs in previously healthy women and is considered a diagnosis of exclusion, and the left ventricular function is nearly always reduced below 45%.

Prevalence

The incidence of PPCM varies according with geographic region. Estimates of the incidence of PPCM are approximately 1 in 2000 to 1 in 4000 live births in the United States [5]. The incidence of PPCM may be increasing in the US [6,7] and may be closer to 1:1000 [8]; however, the incidence is reportedly much higher in other parts of the world, such as South Africa (1:1000), Haiti (1:300) and Nigeria (1:100) [4]. While PPCM is not restricted to any particular age group, it appears to be most common in women over the age of 30 [9,10].

Outcomes and risk factors

PPCM ranks as one of the leading causes of pregnancy-related morbidity and mortality worldwide [11], with a high rate of relapse with subsequent pregnancies [12,13]. Contemporary reports demonstrate the 1 year mortality is at least as high as 4% in the US [14], while reports from other parts of the world may be higher [15]. PPCM patients are at high risk for cardiovascular events at the

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time of delivery compared to those other forms of cardiomyopathy [9]. Outcomes with PPCM are highly variable. Although clinical presentations and outcomes vary substantially, as many as 70% of women recover their left ventricular systolic function (LVEF > 50%) on standard medical therapy for heart failure with reduced ejection fraction in the US [14]. Little is known about the outcomes of the offspring of PPCM mothers. One study reported that neonates born to women with PPCM were likely to be premature, have low or very low birth weight, be small for gestational age and have lower 5-minApgar score compared to neonates of healthy women [16]. Neonatal death was 3% in a recent international registry [10].

Risk factors for the development of PPCM that have been proposed are pre-eclampsia or eclampsia, gestational hypertension, multiparity and multiple gestation, older age and non-African ethnicity [17,18]. The cause of PPCM remains unknown with multiple possible etiologies including viral myocarditis, nutritional deficiencies, autoimmunity, hemodynamic stresses, vascular dysfunction, hormonal insults and underlying genetics [19]. A shared genetic predisposition has been determined in peripartum and dilated cardiomyopathies [20], underscoring the genetic piece of the etiology. More recently, a vasculohormonal mechanism has been postulated, related to the concept that the etiology may be vascular in etiology triggering endothelial damage by hormonal changes of late pregnancy. This mechanism includes a role for prolactin, soluble Fms-like tyrosine kinase 1 (SFlt1), vascular endothelial growth factor (VEGF), among others [19,21–24]. A novel finding is the discovery that oxidative stress-mediated cleavage of the nursing hormone prolactin into a smaller biologically active subfragment, 16-kDa prolactin, may be a major factor initiating and driving PPCM [24]. Additionally, among patients with PPCM, identification of autoantibodies against cardiac sarcomeric myosin or troponin I have been associated with significantly lower baseline LV dysfunction and longer rate of full cardiac recovery [25].

Clinical presentation and diagnosis

Due to the overlap of clinical symptoms with a normal pregnancy, the diagnosis of PPCM can be missed or present late when the presentation of acute heart failure is more obvious. The recognition of heart failure in a pregnant or postpartum woman is often difficult since the normal physical exam in pregnancy can often mimic disease. Increased plasma volume may result in a systolic flow murmur, which can be heard in most normal pregnant patients. This murmur is usually systolic and soft (usually ≤ grade II/VI). Moreover, distended or mildly increased neck veins, mild lower extremity edema and tachycardia are normal, commonly observed findings. In addition, common complaints of a normal pregnancy such as palpitations, fatigue, decreased exercise tolerance and orthopnea can often be identical to those with occult or overt heart failure. However, when the symptoms persist, or are out of proportion to what is expected for pregnancy, such as marked lower extremity edema, evaluation should be pursued. PPCM should be suspected and definitive evaluation undertaken so that appropriate monitoring and treatment can be initiated. There are no specific signs or symptoms to PPCM. Rather, a patient may present with congestive symptoms (shortness of breath, dyspnea on exertion, cough, excessive weight gain) or low-flow symptoms (fatigue, exercise intolerance) that can occur with any form of heart failure. A spectrum of disease severity can be present, from signs and symptoms that are subtle and mild in a stable outpatient to severe in another woman presenting in cardiogenic shock. Signs and symptoms as well as abnormalities of diagnostic tests are summarized in Table 1.

When the diagnosis of PPCM is suspected, the following steps aid in confirming the diagnosis (see algorithm on Fig. 1): (1) A careful history and physical examination determining the onset of symptoms related to pregnancy and to exclude a prior cardiomyopathy if possible or other causes of cardiomyopathy; (2) Diagnostic testing that includes an assessment of left ventricular function usually with echocardiography, chest X-ray, electrocardiogram, and laboratory testing including B-type natriuretic peptide (BNP) or N-terminal pro-NBP (NT-pro-BNP). Most healthy pregnant women have low and stable concentrations of serum B-type natriuretic peptide (BNP) or N-terminal pro-NBP (NT-pro-BNP) levels in pregnancy. BNP or NT-pro-BNP levels can be elevated in PPCM, although not specific to the diagnosis of PPCM, and requires further investigation [27]. Measurement of troponin T may predict persistent left ventricular dysfunction in PPCM [28]. Transthoracic echocardiography is the most important tool for diagnostic confirmation or exclusion of PPCM and should be performed in any suspected case (online Videos 1–4).

A differential diagnosis of PPCM should be considered prior to definitive diagnosis. Other potential etiologies in a woman of childbearing years include other forms of chronic or pre-existing cardiomyopathy (genetic, noncompaction, idiopathic, dilated), HIV cardiomyopathy, myocarditis, primary valvular heart disease, anemia, thyroid disorders, myocardial infarction, sepsis, severe preeclampsia/eclampsia and Takotsubo cardiomyopathy, among others [29]. Hypertensive disorders, whether new onset or superimposed on chronic hypertension in pregnancy, preeclampsia, and eclampsia affect up to 8% of pregnant women worldwide [30]. Preeclampsia is a leading cause of premature delivery, and there is high risk for maternal, fetal and neonatal morbidity and mortality. The cardiac involvement in preeclampsia is mainly related to diastolic dysfunction with elevated intracardiac filling pressures, with normal cardiac function and cardiac output [31]. However, there may be some mechanistic commonalities that have not been entirely elucidated [17,32], as large cohorts of PPCM display a high prevalence of hypertensive disorders and preeclampsia during pregnancy [9,33]. An undiagnosed pre-existing cardiomyopathy may present by the first or second trimester, when cardiac output and plasma volume have peaked, and can be unmasked by pregnancy [4,34]. If investigation of PPCM is negative, then consideration of noncardiac causes of symptoms should be considered. The diagnosis of PPCM ultimately is one of exclusion.

Assessment of ventricular function is most easily assessed with echocardiography. Cardiac magnetic resonance imaging (MRI) as an adjunctive imaging modality may be considered to assess and quantify the degree of LV dysfunction, presence of intracardiac thrombus and detect possible inflammatory changes in the acute phase of the disease, although controversy exists as to whether it is truly diagnostic of PPCM, and can exclude other forms of cardiomyopathy [35]. Cardiac MRI is generally not recommended for routine use. Notably, cardiac MRI is not recommended during pregnancy due to concerns of fetal toxicity of gadolinium. Moreover, routine use of endomyocardial biopsy is also not recommended [36].

Acute management of PPCM

Treatment of PPCM requires addressing issues unique to the pregnant woman, possibility of teratogenicity to the fetus, timing of delivery, mode of delivery, and the safety of medications during pregnancy and lactation. Management decisions will vary depending on the clinical stability of the mother and fetus (Table 2). If hemodynamic instability is present, rapid decision making is required and should include a multidisciplinary team of specialists including cardiologists with expertise in pregnancy, high risk obstetricians, neonatologists, and intensivists [4].

The initial management of acute heart failure in women with suspected PPCM is no different than those applied to those arising from other causes with adjustments made for pregnancy status

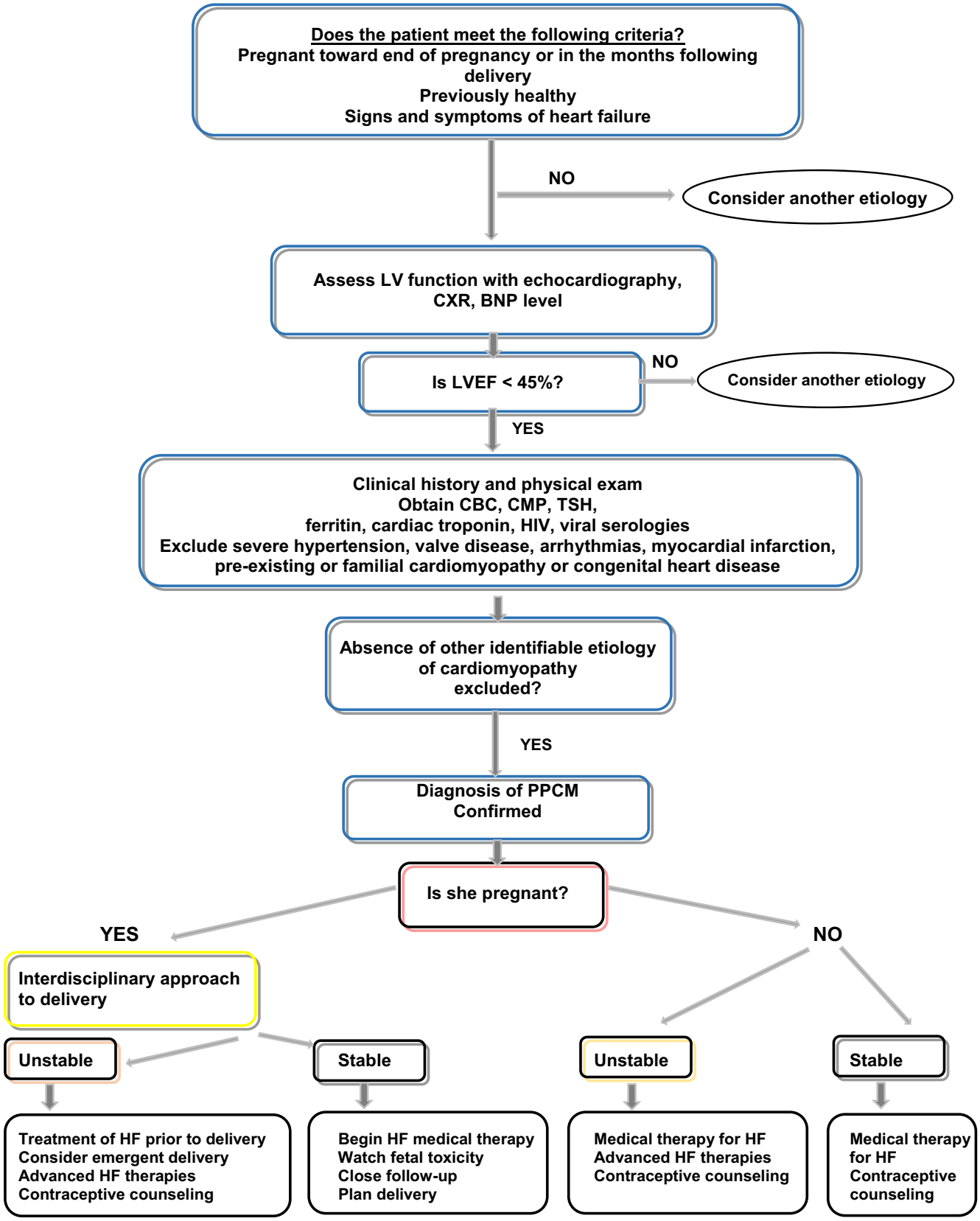

Fig. 1. Proposed algorithm for diagnosis and initial management of peripartum cardiomyopathy. LVEF, left ventricular ejection fraction; CXR, chest X-ray; BNP, B-type natriuretic peptide; CBC, complete blood count; CMP, comprehensive metabolic panel; TSH, thyroid stimulating hormone; HIV, human immunodeficiency virus; PPCM, peripartum cardiomyopathy; HF, heart failure.
Adapted with permission, Kfoury et al. [26].

Table 1
Peripartum cardiomyopathy: signs, symptoms, and possible abnormalities on diagnostic testing.

Symptoms	Signs	Possible abnormalities on diagnostic tests
• Dyspnea • Orthopnea • Paroxysmal nocturnal dyspnea • Cough • Edema • Chest pain/pressure • Palpitations • Abdominal pain/discomfort • Fatigue • Activity intolerance	• Hypotensive, normotensive or hypertensive • Tachypnea • Hypoxia • Tachycardia • Jugular venous distention • Rales • Third heart sound/S3[a] • Right ventricular heave[a] • Laterally displaced PMI • Murmur of mitral or tricuspid valve regurgitation • Marked edema	• **BNP or NT-pro BNP:** elevation above upper limit of normal • **ECG:** ST-T wave abnormalities, sinus tachycardia, left bundle branch block, left ventricular hypertrophy, new onset atrial or ventricular arrhythmias, conduction abnormalities • **CXR:** cardiomegaly, pulmonary congestion, interstitial infiltrates, pleural effusion(s) • **Echocardiogram:** left ventricular systolic dysfunction (LVEF < 45%)-with or without dilation, right ventricular enlargement with reduced function, restrictive or pseudonormal diastolic filling pattern, mitral and tricuspid valve regurgitation, pulmonary hypertension • **Cardiac MRI:** fibrosis (later finding), thrombus (early finding)

BNP, brain natriuretic peptide; NT-pro BNP, N-terminal pro-brain natriuretic peptide; ECG, electrocardiogram; CXR, chest X-ray; MRI, magnetic resonance imaging (generally not used in pregnancy).
Adapted with permission, Kfoury et al. [26].
[a] May be normal in pregnancy but should raise concern.

Table 2
Acute management of PPCM patients.

Hemodynamically stable and pregnant
- Consult specialist in pregnancy and heart disease
- High risk obstetric (Maternal-Fetal Medicine) specialist and neonatologist consultation
- Multidisciplinary approach to delivery
- Delivery planning: mode and timing
- Planned fetal monitoring
- Heart failure treatment prior to delivery (diuretics, nitrates, digoxin, hydralazine)
- Avoid ACEI, ARB, AA; medically optimize volume status
- Close monitoring in hospital

Hemodynamically unstable and *pregnant*
- Consult specialist in pregnancy and heart disease and/or heart failure specialist if available, critical care consultation
- High risk obstetric and perinatology consult
- Fetal monitoring
- May use dobutamine, milrinone and nitroglycerine; medically optimize prior to delivery
- Delivery planning: mode and timing (Cesarean delivery most common in unstable patients)
- Advanced heart failure therapies: mechanical circulatory support and/or cardiac transplantation consideration if failure to medical therapy and delivery

Hemodynamically stable and *post-partum*
- Consult specialist in pregnancy and heart disease
- Initiate heart failure treatment with proven benefit (ACEI, ARB, BB, AA, diuretics)
- Consider anticoagulation with warfarin until left ventricular function recovers
- Address lactation preferences and medication safety profile
- Discuss family planning and contraception
- Follow up closely with repeat echocardiogram to assess response to therapy, uptitration of medication

Hemodynamically unstable and *post-partum*
- Consult specialist in pregnancy and heart disease and/or heart failure specialist if available, critical care consultation
- Consider advanced heart failure therapies including mechanical circulatory support and/or cardiac transplantation consideration
- Initiate medical therapy including dobutamine, milrinone, and nitroglycerine
- Consider anticoagulation with warfarin until left ventricular function recovers
- Discuss family planning and contraception

ACEI, angiotensin receptor inhibitor; ARB, angiotensin receptor blocker; AA, aldosterone antagonist; BB: beta-blocker (appropriate for heart failure therapy).
Adapted with permission, Kfoury et al. [26].

(Table 3) [37]. Rapid treatment of pulmonary edema and hypoxia are essential with oxygen and/or noninvasive positive pressure ventilation, intravenous diuretics for congestion and volume overload, and intravenous nitroglycerine for preload reduction. Inotropic support should be considered in patients with a low output state, indicated by hypoperfusion (cold, clammy skin, vasoconstriction, acidosis, renal impairment, liver dysfunction, and impaired mentation). Inotropic agents include dobutamine and dopamine should be administered without delay and withdrawn once organ perfusion has been restored and is stable.

During pregnancy, the following medications are contraindicated due to their teratogenic effects: (1) angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are contraindicated in women who are pregnant or may become pregnant due to the teratogenic effects on the fetal kidneys [38,39]; (2) aldosterone antagonists (spironolactone and epleronone) are generally not used in pregnant women given the paucity of data on their safety and potential fetal risk. While epleronone is considered FDA Class B and spironolactone is Class C, the benefit would need to outweigh the risk in pregnancy. Beta-blockers for the treatment of chronic heart failure can be given during pregnancy. Vasodilator therapy, when necessary, can be achieved with hydralazine or amlodipine, as there is literature supporting safety of these medications in pregnancy particularly in the setting of hypertension [40], especially in combination with long acting nitrates can be safely used in pregnancy. Sodium restriction is recommended for all patients, while loop diuretics are indicated for the symptomatic relief of significant peripheral edema or pulmonary congestion, and should be used cautiously due to fetal hypoperfusion and decreased placental blood flow [18]. Moreover, digoxin can be added or continued during pregnancy for the symptomatic relief of heart failure symptoms, after beta-blockers and vasodilators have been maximized.

After delivery, medical therapy for PPCM should be performed in accordance with current society recommendations for guideline-directed medical therapy [37]. Whenever possible, the continuation of chronic therapies that improve long-term outcomes in women with heart failure remains an important consideration (Table 3).

Management of labor and delivery in PPCM patients

PPCM patients are at high risk for adverse events at the time of labor and delivery [9]. Compared with other forms of cardiomyopathy, including dilated and hypertrophic cardiomyopathies, 46% of PPCM experienced major adverse cardiac events, and the presence of PPCM was associated with major adverse cardiac events during the hospitalization for labor and delivery. Valvular heart disease (mitral valve disease) was associated with a higher risk of adverse

Table 3
Medical management of PPCM in pregnancy and post-partum.

Drug/class	Purpose	Comment
Diuretics Furosemide	• Generally reserved for treatment of pulmonary edema • Use of lowest possible dose	• Can result in uteroplacental hypoperfusion • Contra-indicated in settings in which uteroplacental hypoperfusion is already reduced (IUGR, pre-eclampsia) • FDA Class C[a]
Digoxin	• Not considered first line therapy for heart failure in nonpregnant patients • No improvement in mortality • Considered useful in pregnancy given limitations of medical armamentarium	• Generally considered safe • Useful in treatment of persistent symptoms despite standard therapy • FDA Class C
Vasodilators Hydralazine	• Commonly used oral antihypertensive agent in pregnancy • Can be substituted for ACE inhibitor during pregnancy • Would not be agent of choice postpartum • Hydralazine/nitrates may add additional benefit to standard therapy for persistently symptomatic women	• Demonstrated efficacy in hypertension • Risk of hypotension • Pregnancy already reduces SVR • Avoid large or precipitous decreases in blood pressure • FDA Class C
ACE Inhibitors/ARB	• Proven benefit in treatment of chronic heart failure in nonpregnant patients; used postpartum as first line agent	• Contraindicated throughout pregnancy due to teratogenic effects. Associated with oligohydramnios, neonatal death secondary to renal failure, renal agenesis. • FDA Class C for first trimester; D for second and third trimesters
Amlodipine	• Alternative to ACE inhibitor in pregnancy • Not first choice postpartum	• Can be used with hydralazine if needed • FDA Class C
Nitrates	• May be used to treat decompensated heart failure; particularly helpful intravenously	• FDA Class C (isosorbide) • FDA Class B (IV nitroglycerine)
Beta-blockers Metoprolol tartrate or succinate Bisoprolol Carvedilol	• Essential component to chronic heart failure therapy • Beta-blockers can be continued throughout pregnancy • Can initiate in pregnancy or postpartum • Most available data on metoprolol	• Generally safe and effective in pregnancy • Can cause IUGR • Infants born to mothers on beta-blockers should be observed for at least 72 hours after birth FDA Class C for bradycardia and hypoglycemia • Atenolol is contraindicated in pregnancy
Aldosterone antagonists Spironolactone, Epleronone	• Prolong survival in selected heart failure patients • Not routinely used in pregnancy • Can use postpartum	• No data to support safety in pregnancy • FDA Class C (spironolactone), Class B (epleronone)
Warfarin	• Risk/benefit ratio needs to be discussed with the patient for treatment and prophylactic anticoagulation in moderate and severe left ventricular dysfunction in the postpartum period (LVEF < 40%)	• First trimester teratogenesis • Dosing is complicated in pregnancy • FDA Class X
Dobutamine	• May be needed in an unstable patient	• FDA Class B
Dopamine	• Preferred agent in hypotensive patient • May be needed in an unstable patient	• FDA Class C
Milrinone	• Vasodilator • May be needed in an unstable patient	• FDA Class C

ACE inhibitor, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; IUGR, intrauterine growth restriction; SVR, systemic vascular resistance.
Adapted with permission from Ref. [29].
[a] FDA class: A (controlled studies show no risk), B (no evidence of human risk in controlled studies), C (risk cannot be ruled out), D (positive evidence of risk), X (contraindicated in humans).

cardiac events, likely related to severity of left ventricular function, as was severe pre-eclampsia. Delivery at a teaching hospital was associated with a reduction in MACE in this cohort. A multidisciplinary team is crucial to adequate management of patients at the time of labor and delivery (Table 4). Although most women will present with symptoms and adverse events within 1 month after delivery, some will present prior to delivery [5]. Therefore, consultation among the patient's obstetrician, obstetrical anesthesiologist and the cardiologist is recommended prior to initiation of labor and delivery. Prior to delivery, women with PPCM should be transferred, if possible, to a tertiary care center or academic/teaching hospital for better access to specialist care and intensive monitoring for mother and newborn. In addition, patients with heart failure or underlying cardiomyopathy should be monitored carefully throughout labor and delivery, as well as in the early postpartum period, when hemodynamic decompensation is most likely to occur. This includes continuous maternal electrocardiographic monitoring and noninvasive blood pressure monitoring. Invasive central monitoring such as right heart catheterization and arterial line monitoring can be employed on an individual basis, but are rarely needed. While no official recommendations exist, right heart catheterization is occasionally used in pregnant women with severe clinical heart failure and/or severely reduced left ventricular systolic function at the time of delivery. Arterial line monitoring

Table 4
Management during labor and delivery and post-partum concerns.

- Short vaginal delivery with excellent anesthesia, with consideration of assisted second stage of labor
- Left lateral decubitus position
- Cesarean section per obstetric indications
- Invasive monitoring if needed (right heart catheterization, invasive arterial blood pressure monitoring)
- Medical therapy optimization of loading conditions
- Monitoring and treatment of pulmonary edema

Anesthetic choices for labor and delivery in the setting of heart failure

General anesthesia

- Volatile agents include sevoflurane, isoflurance, desflurane which can decrease SVR
- Reserved for emergency situations
- Rapid sequence induction can lead to cardiovascular instability
- Mortality is highest at the time of induction and intubation

Regional anesthesia

- Includes spinal, epidural or combined spinal-epidural
- Technique of choice in patients with heart failure and pregnancy for delivery
- Offers afterload reduction and blunts hemodynamic response of labor and delivery
- Low concentration of bupivicaine and lipophillic opiates allow for hemodynamic stability

Sedation

- Can accompany regional techniques if needed
- Agents such as propofol, midazolam, and fentanyl have been used without fetal issues
- Aspiration risk exists

Post-partum concerns and follow up

- Medical therapy to treat failure, prolong life and prevent rehospitalization
- Maintain euvolemic volume status
- Hemodynamic and telemetry monitoring
- Consider contraception (intra-uterine device) or sterilization long term
- Consider use of wearable cardioverter defibrillator as a bridge-to-decision for 3–6 months with serial echocardiographic assessments of LV function
- Echocardiographic follow up every 6 months
- Future consideration of ICD or CRT[a]
- Standard heart failure medications in women with recovery of LVEF, longer in those with reduced LVEF

SVR, systemic vascular resistance; LV, left ventricular; LVEF, left ventricular ejection fraction; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy.
Adapted with permission from Ref. [29].
[a] Indications for implantation of an ICD would follow accepted society guidelines; however, recovery of left ventricular function may be delayed 6–12 months in PPCM.

is considered helpful and low risk. Right heart catheterization, although not required, may be needed to optimize hemodynamics when large shifts in volume are anticipated such as during a Cesarean section or when there is evidence of clinical instability [41].

While there are few studies evaluating the ideal mode of delivery in women with heart disease, the decision regarding the timing and mode of delivery is individualized, and is made based on the hemodynamic status of the patient (Table 4). Early delivery is not required for all patients with PPCM. The decision is made based on failure of the patient to respond to medical therapy and the overall hemodynamic status of the patient. The issue of the timing of delivery for critically ill pregnant women with heart failure requires a coordinated decision between the cardiologist, obstetrician, and anesthesiologist that balances the risks of continuing a pregnancy to the mother and fetus versus the risk of delivery and how that delivery should take place. If the patients' heart failure is refractory to medical therapy, delivery needs to be strongly considered. While some recommendations exist [42], an individualized approach is sought. In general, a vaginal delivery poses less cardiac risk, as cesarean delivery is accompanied by approximately twice as much blood loss. Patients who are considered stable from a cardiac perspective can be allowed to spontaneously progress through the various stages of labor. However, if there are concerns about the functional adequacy of the heart and circulation, labor can be induced under controlled conditions. The timing of induction can be individualized, taking into account the patient's cardiac status, inducibility of the cervix, and fetal lung maturity. In general, a long induction in a woman with an unfavorable cervix should be avoided. Induction of labor in a patient with a favorable cervix usually requires only oxytocin administration and artificial rupture of membranes. An unfavorable cervix, however, should be treated with a prostaglandin E analogue. Even this should be done cautiously in women with underlying cardiomyopathies, as prostaglandin analogues may be absorbed systemically, causing unwanted hemodynamic consequences including a decreased systemic vascular resistance and reflex tachycardia. Once in labor, women with cardiac disease should be placed in a left lateral decubitus position in order to avoid inferior vena cava compression by the gravid uterus. The obstetrician should allow the fetal head to descend to the perineum without maternal assistance, an attempt to avoid the undesirable circulatory effects of the Valsalva maneuver. The second stage of labor can be shortened via assistance with low forceps or by vacuum extraction as needed. Throughout this process, the clinical scenario should dictate the need to abandon further attempts at vaginal delivery, and to proceed with Cesarean delivery. In a recent study in the US, over 60% of women with PPCM delivered by Cesarean approach [7]; in a worldwide registry, 43% delivered by Cesarean approach [10]. In general, if the patient cannot be stabilized hemodynamically, or requires emergent delivery, or there are obstetric indications, Cesarean delivery may be required. Similarly, the timing and mode of delivery should be individualized.

Anesthetic considerations in pregnant women with new onset heart failure requires a specialized approach [29]. Women with cardiomyopathy and/or evidence of clinical heart failure should not expect a trial of natural childbirth without the use of some form of anesthesia when a vaginal delivery is decided upon. The goal of the anesthetic agents is to blunt the physiologic increased metabolic demands and hemodynamic stress that normally accompanies labor and delivery. The goals of management are mainly to avoid excessive anesthetic-induced myocardial depression, maintenance of normovolemia, and minimize the inherent sympathetic stimulation associated with labor. A combination of intravenous opiates and lumbar epidural anesthesia are highly effective to relieve pain during labor and delivery and is considered the technique of choice. Epidural anesthesia, if introduced slowly and carefully, produces changes in preload and afterload that can be advantageous in the setting of reduced ventricular function. It provides excellent operative analgesia, thus limiting pain-induced elevations of sympathetic activity, but also reduces the maternal urge to push (Valsalva maneuver). Additionally, the accompanying venodilatation reduces venous return, which may also be favorable for those patients with evidence of volume overload. Decreases in systolic blood pressure may require treatment with vasoactive agents rather than intravenous fluids. Alternatively, the use of general anesthesia incurs the risks of hemodynamic instability associated with systemic anesthetic administration, as well as adequate sedatives to tolerate endotracheal intubation.

Breastfeeding

Breastfeeding after delivery in PPCM patients remains controversial and the discussion should be individualized given the lack of data on the subject. Notably, in the IPAC study, there was no association between breastfeeding and left ventricular function recovery [14] However, some investigators, on the basis of possible

negative effects of prolactin sub-fragments [43], do not recommend breastfeeding in patients with PPCM, even if this practice is not fully evidence-based [4]. In some centers, when there is hemodynamic stability, breastfeeding is not discouraged, and the discussion is individualized. Another consideration in developing countries is the availability and safety of clean water and formula, rather than breastfeeding. While several medical therapies for the management of chronic heart failure are considered safe during breastfeeding (captopril, enalapril, and quinapril), others such as long acting carvedilol and many other routine medications have no considerable data available. Notably, metoprolol is considered safe in breastfeeding and is commonly utilized postpartum. Moreover, transmission to the fetus is possible, and may result in adverse effects and prolonged neonatal intensive care monitoring for hypoglycemia and bradycardia. Practice variation likely exists on this matter, and patient preference must be considered. However, the priority should be to treat the cardiomyopathy and heart failure as best as possible in order to result in the fastest possible recovery, with full return to normal or near normal left ventricular function. Therefore, in women who are highly symptomatic and hemodynamically unstable, bottle-feeding should be encouraged [34,37].

Contraceptive options

In women with a history of PPCM, maternal complication rates of pregnancy are high, and in many cases, repeat pregnancy may not be desired. Even if a patient experienced a relatively event free first pregnancy, repeat pregnancies in this patient population can carry significant adverse events, even after the return of left ventricular function to normal or near normal. Therefore, adequate and reliable contraception is required and is a part of the discussion in the early post-partum days to months thereafter [44]. Due to the potential for thromboembolic complications, combined hormonal contraceptives (COCs; estrogen/progestin formulations) in the form of pills, transdermal patches or vaginal rings are not recommended. While both estrogen and progestins have adverse cardiac effects, the most clinically important are those of estrogens which cause thromboembolic events and hypertension. In women with reduced left ventricular function, progesterone-only forms of contraception and intrauterine devices are appropriate options, as well as barrier methods in combination. Intrauterine devices (copper and progesterone-releasing IUDs) are very effective and long lasting, and do not increase the risk of thromboembolism. Sterilization (tubal ligation) is another option once medical and cardiac stabilization are apparent; vasectomy can be considered at any point. While progestin-only forms of contraception are often suitable for women with severe cardiomyopathies, the oral form or the "mini-pill" has a high failure rate (5%–10%). Therefore, injectable or implantable versions of progestin-only formulations may be a better choice. Preconception counseling in women with heart disease regarding contraception is being poorly done or not at all [45,46], and remains the responsibility of both the cardiologist and obstetrician/gynecologist to work together to find an appropriate solution. In particular, in women with a prior history of PPCM, it is the responsibility of cardiologists to counsel women on their risks.

Long term implications

Outcome and complications

Until recently, there were no large-sized outcomes data for patients with PPCM. Lima et al. [9] describe 1039 patients with peripartum CDM from a large US administrative dataset, analyzing patients at the time of delivery. In total, 478 (46.1%) experienced major adverse cardiac events (MACE; Table 5). Maternal mortality was low (< 1%) for this inpatient cohort, but 36% experienced heart failure, and over 12% experienced arrhythmias. Independent predictors of MACE during the hospitalization for delivery include the presence of valvular heart disease (OR 2.16, 95% CI: 1.49–3.14), severe pre-eclampsia (OR 1.54, 95% CI: 1.08–2.21), and Cesarean delivery (OR 1.36, 95% CI: 1.04–1.78).

Table 5
Outcomes in peripartum cardiomyopathy.

Clinical sequelae and complications
- Heart failure
- Arrhythmias (atrial and ventricular)
- Thromboembolism
- Sudden death/cardiac arrest/ventricular arrhythmias
- Left ventricular or right ventricular thrombus
- Pulmonary embolism
- Mitral regurgitation
- Right ventricular dysfunction

Risk factors for in-hospital major adverse cardiac events
- Severe preeclampsia, eclampsia
- Valvular (mitral and tricuspid) disease
- Cesarean delivery

Predictors of poor functional recovery at 6–12 months
- LVEDD ≥ 60 mm
- LVEF ≤ 30%
- African American race
- Late presentation (> 6 weeks postpartum)

In the IPAC (Investigations of Pregnancy-Associated Cardiomyopathy) study, clinical outcomes in North America were defined in 100 prospectively enrolled women who were followed for 1 year [14]. While the initial LVEF was 35% on average, 72% of women experienced recovery (LVEF ≥ 50%) with standard medical therapy for heart failure. However, 13% had major events or persistent severe cardiomyopathy. Black women had more severe LV dysfunction at presentation and at 6–12 months postpartum. During the first year postpartum, 4 women died, 4 had left ventricular assist device (LVAD) implantations, and 1 had a heart transplant.

Recent data from the EURObservational Research Programme [10] describe the results of a large, worldwide, prospective registry of PPCM patients. PPCM occurs in women from different ethnic backgrounds in all continents. Despite marked differences in socioeconomic backgrounds and ethnicity, the timing and mode of presentation were remarkably similar. The short-term (1 month post-diagnosis) was lower than expected (2.4%) while morbidity, including persistent heart failure symptoms, need for LVAD and embolic events were common.

Prognosis and recovery of left ventricular function

The prognosis of PPCM is more favorable than other forms of nonischemic cardiomyopathy. However, PPCM may be associated with mortality or severe morbidities and complications. Those include ventricular and atrial arrhythmias, stroke or transient ischemic attack, heart failure, sudden cardiac death, intractable heart failure and cardiogenic shock (Table 5) [11]. The prognosis of PPCM may vary depending on the geographic region [4] and follow up time measured, although registry data collected worldwide suggests that these differences are not as wide as originally thought [10]. Mortality at 6–12 months can range from 6% in the US [14] to as high as approximately 30% [47], with 10%–15% in South Africa and Haiti [18,48,49]. Common predictors of recovery and stability of left ventricular function include LVEF ≥ 30%, without significant remodeling (LVEDD < 6.0 cm) at initial presentation [14,50]. Black race was associated with poorer recovery in a US cohort. More than 70% of patients had recovery of LV function at 1 year in the US [14], but lower in estimates from other parts of the world and in indigent US populations [5,50,51]. Additionally,

recent data demonstrates that African American women compared to non-African American women are often presenting later in their pregnancy, at a younger age, with LVEF < 30%, and take over two-fold longer to recover despite similar treatments [14,52]. Right ventricular function at presentation, as assessed echocardiographically by fractional area change, has been independently associated with subsequent left ventricular recovery [53]. The most challenging group are those that have multiple predictors of poor recovery, including LV remodeling, LVEF < 30%, late presentation and potentially black race. The response to therapy should be closely monitored with echocardiography and clinically to assess for recovery, or the need for escalation of medical therapy or further heart failure therapies such an internal cardioverter defibrillator (ICD) or cardiac resynchronization therapy (CRT). However, since LV recovery may be delayed up to 12 months, early interventions with an ICD or transplant should be delayed or avoided to allow for full recovery of the myocardium. PPCM patients do have an increased risk of sudden death and seem to benefit from ICD and CRT [54,55]. Anticoagulation with warfarin needs to be considered in the postpartum patient with an LVEF < −30%, or if another indication such as atrial fibrillation, deep vein thrombosis or pulmonary embolism, left ventricular or right ventricular thrombus, particularly in the first several months after delivery (approximately 8 weeks), due to the increased thromboembolic state of the postpartum woman, with left ventricular dysfunction (online Videos 1–4) [56]. Some authors propose use of LVEF 40% or less as a cutoff for consideration of systemic anticoagulation [56,57].

Some studies have reported beneficial effects of the prolactin-blocker bromocriptine when added to heart failure medications in patients with acute onset PPCM [58]. Likewise, the majority of patients in the German PPCM registry (96%) who had obtained this therapy concept improved their condition [33]. Notably, in this registry the proportion of patients with persistent advanced LV dysfunction was significantly higher across those patients not receiving bromocriptine. Recently, a randomized multicenter trial in Germany investigated the efficacy of bromocriptine in addition to standard heart failure therapy among 63 patients with PPCM [59]. The analysis from this trial showed that both 1 week and 8 week treatment periods with bromocriptine were associated with faster recovery rates of left ventricular ejection fraction and very low adverse event rates. The study recorded no mortalities, heart transplants, or left ventricular assist device use. The small size of the study, regional centers, lack of a control arm of the study, and short follow up limit generalizability of the treatment. In addition, use of bromocriptine has been controversial given concerns regarding its risk for stroke, intracranial bleeding, cerebral edema, seizure, and myocardial infarction [60,61]. All patients in this study were fully anticoagulated.

Long term medical management

Discontinuation of heart failure therapy in patients with recovery of left ventricular function remains controversial. Since most women recover left ventricular function to above 50%, the question often arises as to the need for continuation of medical therapy long term. For women without improvement in LVEF, medical therapy is continued indefinitely. For patients with sustained recovery of left ventricular structure and function (with echocardiographic follow up every 6 months), consideration can be given to weaning off β-blockers and then ACE-inhibitor/ARB slowly and carefully, and not simultaneously, with re-evaluation of LV function [34]. Until more data are available, it is reasonable to continue medical therapy and these decisions need to be individualized.

Subsequent pregnancy

There is little definitive evidence on this subject and recommendations are usually made on an individualized basis. This topic has been extensively reviewed [62]. There is concern that PPCM may recur in a subsequent pregnancy, and that any subsequent pregnancy would be high risk. However, the level of risk appears to be determined by several factors. In women with persistent left ventricular dysfunction, there is a higher risk of relapse with subsequent pregnancy with approximately 50% showing further deterioration in left ventricular function, and increased morbidity and mortality (mortality may be as high as 20%). In women with complete recovery of left ventricular, there appears to be a better prognosis with subsequent pregnancy; approximately 20% may have relapse, the rate of recovery is higher with lower morbidity and mortality. The long term implications of these women who recover their left ventricular function is largely unknown, whether they have a higher risk of late heart failure, progressive ventricular dysfunction or need for advanced heart failure therapy or transplant. A recent investigation in South Africa, Germany, and Scotland among PPCM patients, showed that even with fully recovered cardiac function after initial pregnancy there remains a significant risk for relapse during subsequent pregnancies [63]. If the LVEF < 25% at initial diagnosis or when the LVEF has not normalized after adequate medical therapy and ample time, the patient should be counseled that pregnancy can have a negative effect on her cardiac function, and there is a risk of recurrent heart failure, permanent decline in LVEF and death. In these situations, pregnancy is considered World Health Organization Class IV, and pregnancy is contraindicated [42]. In a case of a subsequent pregnancy after PPCM, the patient should be treated during pregnancy, with beta-blockers, followed closely by an interdisciplinary team throughout the pregnancy with echocardiography and BNP levels [34]. The highest risk periods are the third trimester and postpartum, at which time medical therapy for heart failure should begin promptly. Importantly, mothers need to be counseled regarding the risks of subsequent pregnancy prior to contemplating another pregnancy and that there is considerable uncertainty regarding the level of evidence of the data.

The available data suggest that the best predictor of relapse in subsequent pregnancy is pre-pregnancy LVEF. A normal contractile reserve as predicted by exercise echocardiography was suggested as a potential predictor of a low likelihood of relapse in women with normal left ventricular function in small studies, and requires further investigation [64,65].

Cardiac transplantation after PPCM

The number of patients who may require a cardiac transplant long term in the modern era is not known. In a large report from the United Network for Organ Sharing database between 1987 and 2010, women who had PPCM as the initial diagnosis had higher rates of post-transplant rejection during the index hospitalization and during the first year, higher sensitization, and graft survival was inferior compared to women who received a cardiac transplant for another reason, or all other patients receiving cardiac transplant [66].

Quality of life

Little data exist with regard to the effect of PPCM on quality of life. Few diseases in medicine are as dramatic as PPCM in their clinical presentation. This rare illness unexpectedly afflicts a woman right at the moment when she brings forth new life. The unexpected nature of the presentation, acuity of illness, and/or the disease itself affects women profoundly, and might irreversibly

stain them emotionally. These are young women, in the prime of their lives, responsible for the care of a newborn, often other children and households, now caring for themselves with heart failure. In a study using a survey distributed to members of an online support group on a social networking site, 116 women completed the quality of life survey with 4.9 ± 0.5 years since the initial diagnosis [67]. Many women (41%) never returned to their baseline level of activity, and 28% discontinued their job because of the diagnosis. Most respondents (56%) never returned to their baseline emotionally after the diagnosis of PPCM, and most patients (73%) were dissatisfied with their current level of heart failure symptoms. Most patients (67%) felt discouraged frequently (more than several times per month) due to heart failure. Only 26% of women were satisfied with the counseling they received from their providers. The emotional and physical burden of PPCM on young mothers with PPCM years after the diagnosis is striking. Identifying strategies that promote better emotional health and potential treatment strategies may be required.

Conclusions

Peripartum cardiomyopathy is an important cause of systolic heart failure. There may be a lack of awareness among physicians, nurses/midwives, which can lead to late diagnosis and treatment. PPCM remains a difficult condition to both diagnose and treat. Management has important caveats that pertain to young women who are pregnant, postpartum or breastfeeding. Timing and management of delivery and postpartum care requires a multidisciplinary team including cardiologists, obstetricians, and anesthesiologists with expertise in the management of pregnant women with PPCM.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tcm.2018.07.012.

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