HEALTHY HEART

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Dear Friends,

Hope you all are keeping fine with a positive mind and fit physique. Solid health is the foundation to serve the society in difficult times.

Though peripartum cardiomyopathy has been a quite old and well known disease situation, it is often missed and physicians do have lack of clarity regarding its treatment and prognosis. I am sure, this short but comprehensive review will help all clinicians to deal better with unfortunate women suffering from this condition.

Peripartum Cardiomyopathy

Definition: Peripartum cardiomyopathy (PPCM) is an idiopathic cardiomyopathy wherein a woman presents with heart failure (HF) secondary to left ventricular (LV) systolic dysfunction near the end of pregnancy or within few months following delivery, where no other cause of heart failure is found. The diagnostic criteria include an LVEF of < 45% with or without LV dilatation. It is a condition with variable outcomes. Patients might have complete recovery, persistent myocardial dysfunction with or without symptoms of HF, or rapid deterioration, leading to urgent need for mechanical circulatory support and cardiac transplantation.

Incidence: It is difficult to know the true incidence, as many cases in India and across the globe go undetected. On the whole, incidence ranges from 1 in 1,000 to 1 in 4,000 pregnancies and may be increasing, due to the rise in maternal age, increased rates of multifetal pregnancies due to contemporary fertility techniques, and possibly to increased recognition of the disease.

Risk factors: Increased incidences or association with following conditions are noted.

- Pre-eclampsia or hypertension
- Multigestational pregnancies
- Higher maternal age
- African ancestry
- Genetic base -Family history of PPCM

Pathophysiology: The etiology of PPCM is not fully understood and is likely multifactorial. Suggested but unproven mechanisms for the development of PPCM have included nutritional deficiencies, viral myocarditis, and autoimmune processes. Hemodynamic stress of pregnancy has also been postulated as a potential etiology. Laboratory experimental models and epidemiological data support the notion that PPCM is a vascular disease to a good extent, triggered by the hormonal milieu of the peripartum.

Diagnosis:

Timing: The majority of women with PPCM are diagnosed after delivery, typically in the first month postpartum. Frequent delays in diagnosis occur due to under-recognition of this disease and the overlap in signs and symptoms of normal pregnancy with those of HF.

Clinical presentation: Most women present with signs and symptoms of HF including shortness of breath on exertion, paroxysmal nocturnal dyspnea, orthopnea, fatigue, edema, and chest heaviness. Physical examination often reveals tachycardia, tachypnea, elevated jugular venous pressure, pulmonary rales, and peripheral edema. A small number of patients may present with various serious arrhythmias, cardiogenic shock, or thromboembolic compli-cations.

Diagnostic tests: Echocardiography should be performed in all suspected cases as the LVEF is typically < 45% in PPCM. Additionally, echocardiogram might help to show left and right ventricular dilatation and/or dysfunction, functional mitral and/or tricuspid regurgitation, pulmonary hypertension, and left atrial or biatrial enlargement and LV thrombus.

ECG May show nonspecific abnormalities, but a normal ECG does not rule out PPCM.

Chest X-ray shows pulmonary venous congestion.

Cardiac MRI provides accurate LV ejection fraction and chamber measu-rements which supplements the echocardiogram findings.

Brain natriuretic peptide (BNP) and N-terminal pro-BNP levels are usually markedly elevated in PPCM. It is noteworthy that they do not change significantly during normal pregnancy and may be mildly elevated in the setting of pre-eclampsia.

Endomyocardial Biopsy is indicated uncommonly, when there is a suspicion for an alternative diagnosis that would require a different management plan.

Differential Diagnosis: PPCM is a diagnosis of exclusion, all common causes of HF to be considered and excluded. To avoid overdiagnosis, it is important to rule out any possible pre-existing heart disease like cardio-myopathies, valvular diseases etc. Severe pre-eclampsia can cause HF symptoms related to diastolic dysfunction.

Adverse Prognostic Factors:

- Lower LVEF at the time of diagnosis is the most reliable predictor of adverse events or long-term recovery.
- LV dilatation
- LV thrombus
- Right ventricular systolic dysfunction
- Concomitant pre-eclampsia is associated with lower 1-year survival
- Obesity
- African-American ethnicity is associated with lower rates of recovery, longer recovery time, more adverse outcomes, and higher mortality.
- Elevated troponin, NT-proBNP
- Late gadolinium enhancement in cardiac MRI indicates fibrosis associated with less myocardial recovery

Adverse Outcomes: Various adverse outcomes include pulmonary edema, thromboembolic complications, cardiopulmonary arrest, brain injury, need of mechanical circulatory support / cardiac transplantation, and death. Almost one-half of the patients with PPCM present with one of the major adverse events. Cardiopulmonary arrest and cerebro-vascular events are commonly associated with residual brain damage. LV thrombus has been identified in 10% to 17% of initial echocardiograms and thromboembolic complications have been reported in 5% to 9% of women. The increased incidence of thromboembolic events in PPCM is likely related to the hyper-coagulable state of pregnancy, cardiac dilatation and dysfunction, venous stasis, bed rest, and the post-operative status after cesarean section.

Mortality: It depends on many factors like racial groups, geographical region, time taken for diagnosis, availability and institution of proper treatment and duration of follow-up. One- and 2-year mortality up to 11% and 16% respectively, have been reported.

Recovery: PPCM has been associated with a higher rate of recovery than other forms of HF with reduced LVEF. Recovery frequently occurs within the first 3 to 6 months. Delayed recovery, even up to 2 years can also occur. On the whole, 1-year recovery (attainment of LVEF > 50%) rate of 45 – 75% has been reported.

Medical Management: Treatment of HF during pregnancy requires special modifications to ensure maternal and fetal safety. Following delivery, most HF medications are compatible with breastfeeding.

Guideline Based Optimum Medical Therapy for HF: As per the chart.

Anticoagulation: It should be considered for patients with severely decreased LVEF during late pregnancy and 6 to 8 weeks postpartum when the LVEF is < 30-35%. No published data are available to guide the

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Heart Failure and Anticoagulant Medications: Indications and Safety in Pregnancy and During Lactation

MEDICATION	DURING PREGNANCY	POTENTIAL ADVERSE EFFECTS	INDICATIONS	DURING LACTATION
HEART FAILURE MEDICATIONS				
Loop diuretics	Yes	Caution for hypovolemia or hypotension that may lead to decreased placental perfusion	For signs and symptoms of congestion and fluid overload.	Yes, but over-diuresis can lead to decreased milk production.
Beta blockers (metoprolol tartrate used most commonly)	Yes	IUGR; fetal bradycardia and hypoglycemia	For standard treatment of HF; consider treatment of women with subsequent pregnancy.	Yes
Hydralazine/nitrates	Yes	Caution with hypotension	Use for afterload reduction during pregnancy (instead of ACE-I/ARB) when needed.	Yes, but ACE-I/ARB typically chosen post-partum
Digoxin	Yes	No associated congenital defects	Can be used with symptomatic heart failure and/or systolic dysfunction during pregnancy, or afterwards per guidelines.	Yes
ACE-I/ARB	No	Anuria, oligohydramnios, fetal limb contractures, craniofacial deformation, pulmonary atresia, fetal hypocalvaria, intra uterine growth restriction, prematurity, patent ductus arteriosus, stillbirth, neonatal hypotension and death	Cannot use during pregnancy. After delivery, should be used as part of guideline-directed medical therapy for afterload reduction and LV remodeling.	Enalapril and captopril can be used
Aldosterone receptor antagonists	No	Spironolactone has been associated with antiadrenergic activity, feminization of male rat fetuses and permanent changes in reproductive tract in both sexes	As per guideline-directed medical therapy for heart failure.	Spironolactone can be used
Sacubitril-valsartan	No	Same as ACE-I/ARB	As per guideline-directed medical therapy for heart failure.	No information in human, present in rat milk
Ivabradine	Scant data in humans; would avoid due to concerns in animal studies	Scant data in humans, animal data suggest risk	As per guideline-directed medical therapy for heart failure.	No information in human, present in rat milk
ANTICOAGULANTS				
Low molecular weight heparin	Yes	Caution at time of delivery and with neuraxial anesthesia; does not cross placenta; consider the need for monitoring anti-Xa levels	For prevention and treatment of thromboembolic complications during pregnancy and as bridge to warfarin postpartum.	Yes
Warfarin	Avoid	Warfarin embryopathy and fetopathy	For prevention and treatment of thromboembolic complications postpartum.	Yes

Legend:

	Data or experience to support use
	Caution with using this medication
	Data is limited or inconclusive

Safety of medications need to be considered during pregnancy and lactation. ACE-I angiotensin-converting enzyme inhibitors; ARB angiotensin receptor blocker; HF heart failure; IUGR intra-uterine growth restriction; LV left ventricular; SSP subsequent pregnancy.

decision of therapeutic versus prophylactic anticoagulation. Warfarin crosses the placenta and is avoided during pregnancy for all indications other than that of mechanical heart valves. Low-molecular-weight heparin (LMWH) does not cross the placenta and can be used during pregnancy. Both, warfarin and LMWH are considered safe with lactation. The novel anticoagulants have not been studied during pregnancy or lactation and are generally avoided.

Bromocriptine: In one study patients treated with this experimental medicine (2.5 mg twice daily for 2 weeks, followed by 2.5 mg daily for 6 weeks) had greater improvement in LVEF at 6 months than the control group, and fewer experienced the composite endpoint (defined as death, New York Heart Association functional class III/IV, or LVEF < 35% at 6 months) compared with the control group. An observational registry of 115 German patients with PPCM reported that bromocriptine in addition to standard therapy was associated with a higher rate of improvement in LVEF, but there was no significant difference in overall rates of recovery. Recently, a randomized trial of 2 different regimens of bromocriptine (1 week in 27 patients vs. 8 weeks in 31 patients) in Germany found similar outcomes in both groups. Bromocriptine was added to standard HF therapy including ACE inhibitors /angiotensin receptor blockers, beta-blockers, mineralocorticoid antagonists, and diuretic agents. The 2018 European Society of Cardiology guidelines include a weak recommendation (Class IIb, Level of Evidence: B) for the use of bromocriptine. Due to the association with thrombotic complications, therapeutic anti-coagulation is recom mended in conjunction with bromo criptine.

Treatment of severe PPCM: Intravenous vasodilators, such as nitroglycerin, may be needed in the setting of acute decompensated HF during pregnancy. Nitroprusside is less desirable due to the theoretical risk of cyanide toxicity.

Inovenodilators like dobutamine, levosimendan and milrinone also have been tested in different studies. Temporary mechanical circulatory support with **intra-aortic balloon pump (IABP), percutaneous ventricular assist device therapy (VAD), and extracorporeal membrane oxygenation (ECMO)** have been used successfully in PPCM and should be considered early in patients with hemodynamic instability despite inotropic support. Temporary or durable LVADs may also be needed. In a trial of 99 women with PPCM who received LVAD, 6% recovered and 48% went on to cardiac trans-plantation. A study of 485 women with PPCM who received cardiac transplant between 1987 and 2010 reported higher rates of graft failure and lower age-adjusted survival, which may be explained by increased rejection, higher allosen-sitization, and higher pre-transplant acuity.

Labor and Delivery: Timing and mode of delivery in patients with PPCM during pregnancy should be discussed with the patient and coordinated by a team of experts from obstetrics, cardiology, fetal medicine, anesthesiology, neonatologist and nursing. An attempt to stabilize the mother to avoid potential fetal complications of prematurity is reasonable. Hemodynamic instability despite medical therapy should prompt early delivery (or termination if prior to fetal viability).

Stable patients are delivered vaginally unless there are obstetric reasons for cesarean section. Cesarean delivery is associated with a higher incidence of hemorrhage, infection, and throm-boembolic complications.

Unstable patients may benefit from hemodynamic optimization prior to delivery and monitoring during delivery and the early postpartum period. The post-partum risk of fluid overload and pulmonary edema must be anticipated as following delivery venous return increases significantly.

Lactation: Breastfeeding confers multiple benefits for infant and mother and is recommended by the WHO. Recent data demonstrated that breast-feeding was not associated with adverse outcomes, inflammatory markers, or persistent myocardial dysfunction. The observation that breastfeeding seems to be safe in PPCM suggests that continued stimulation of prolactin secretion may not be harmful. Most HF medications can be given safely with breastfeeding and should not be a reason to advise women against lactation.

Contraception: In a woman with persistent LV dysfunction, the risk of a subsequent pregnancy outweighs any risk associated with contraception. Therefore, women should be encouraged to select the method they will use most consistently. The importance of contraception should be emphasized by the cardiologist and obstetrician/ gynecologist. Use of estrogen-containing contraceptives is better avoided. Progesterone-releasing subcutaneous implants or the Mirena intrauterine device are safe and effective choices. Injectable depot medroxy-progesterone acetate is less effective and is considered a second-line option. Nonhormonal barrier methods are less effective. Tubal ligation and vasectomy are other options.

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Prevention of Sudden Death:

Unfortunately, women with PPCM may experience cardiac arrest in the early months following diagnosis and need to be protected. Premature placement of automatic implantable cardiac defibrillator (AICD) should be avoided because a large proportion of women will recover to LVEF >35% within the first 6 months postpartum and will not meet criteria for AICD placement. Despite conflicting data in small studies, and until more information becomes available, it may be reasonable to consider wearable cardioverter/defibrillators for women with new onset PPCM and severe LV dysfunction as a bridge to recovery or until an implantable AICD is indicated. Certain patients, who remain sick in spite of best proven optimum medical therapy, may benefit from cardiac resynchronization therapy (CRT).

Duration of Treatment: In the presence of persistent cardiac dysfunction, cardiac medications should be continued indefinitely. After LV recovery, optimal duration of treatment is unknown. A rationale for continuation of medical therapy is supported by evidence of subclinical LV systolic dysfunction and anecdotal reports of late deterioration of LV function. If the patient is free from congestive symptoms, diuretic medications can be stopped. Additional HF medications, if stopped, should be weaned in a stepwise fashion with frequent clinical assessment and echocardiographic monitoring of LVEF. Reassessment of LV function is advised after drug discontinuation followed by annual clinical and echocardiographic assessment.

Subsequent Pregnancy: The safety of a subsequent pregnancy is a frequent concern for patients and their families. Appropriate and accurate counseling is essential. The risks associated with a subsequent pregnancy depend primarily upon the extent of recovery of myocardial function and the pre-pregnancy LVEF, which is the strongest predictor of outcomes. If there is evidence of persistent myocardial dysfunction (i.e., LVEF < 50%), women should be advised on the reported high risk of recurrent HF, long term deterioration of cardiac function, and mortality. Fetal outcomes tend to be worse among women with persistent LV dysfunction, with higher rates of stillbirth, abortion, and pre-term delivery. Based on these data, the 2018 European Society of Cardiology guidelines for the management of cardiovascular diseases during pregnancy discourage subsequent pregnancy if the LVEF is not >50% to 55%. Women who recover LVEF >50% have lower risk of complications during a subsequent pregnancy, but there is still increased risk of recurrent HF.

Before deciding on subsequent pregnancy, ACE inhibitors/angiotensin receptor blockers and aldosterone receptor antagonists should be discontinued prior to conception. It may be prudent to ensure stability of LV function after at least 3 months off of these medications prior to considering the LV recovered. The prophylactic use of beta-blockers during subsequent pregnancies in women with recovered LVEF may be considered.

Conclusion: The diagnosis of PPCM should be considered in any pregnant or postpartum woman with symptoms suggestive of HF. Always an echocardiogram to assess LV systolic dysfunction be done. Prompt treatment with medications tailored for pregnancy and lactation may prevent adverse outcomes. Limited studies suggest breastfeeding is safe. Acutely ill women should be managed by specialized multidisciplinary teams, and may require advanced HF therapies. Women considering a subsequent pregnancy should be counseled and monitored by physicians familiar with PPCM. Long-term follow-up is important, but the optimal duration of medications following recovery is unknown. In spite of advancement, Important gaps in our knowledge still persist.

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