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Peripartum Cardiomyopathy: Current Management and Outcome

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ABSTRACT

Peripartum Cardiomyopathy (PPCM) is a clinical condition of heart failure that occurs in the last trimester of pregnancy or after childbirth in the early postpartum period. The aetiology of this condition is still uncertain, but it is connected with high mortality and morbidity. PPCM can be difficult to find because the symptoms of heart failure can resemble those of late pregnancy, such as swelling of the feet and legs, orthopnea and paroxysmal nocturnal dyspnea. PPCM is diagnosed with Hibbard diagnostic criteria which are heart failure in the last month of pregnancy and 5 months after birth, lack of previous heart disease, there is no definitive cause and strict echocardiography of left ventricular dysfunction: Left Ventricular Ejection Fraction (LVEF) <45% and/or M-model fraction <30% and Left Ventricular End Diastolic dimension (LVEDd) greater than 2.7 cm/m^2. A multidisciplinary strategy involving cardiologist, obstetrician, intensivist and paediatrician is vital for the management of PPCM patients.

Keywords: Peripartum Cardiomyopathy (PPCM), Orthopnea, Paroxysmal nocturnal dyspnea, Ventricular dysfunction, Postpartum period

INTRODUCTION

Heart failure associated with pregnancy is a global problem with common causes such as pre-existing structural heart disease, peripartum cardiomyopathy and hypertension [1]. Heart failure in pregnancy and peripartum period was recognized in the early 1800's and well defined in 1971 by Demakis and Rahimtoola. This syndrome is introduced as peripartum cardiomyopathy [2]. The term Peripartum Cardiomyopathy (PPCM) define as idiopathic cardiomyopathy with LV dysfunction (LVEF<45%) that happens at the end of pregnancy or in the postpartum period [3]. Patients with clinical conditions of PPCM with LVEF function around 45%-50% can also be considered peripartum cardiomyopathy [4]. The aetiology of this condition is still uncertain, but it is connected with high mortality and morbidity. This disease mimics dilated cardiomyopathy but consider as a different subtype of cardiomyopathy [5].

LITERATURE REVIEW

Epidemiology

The incidence of PPCM varies determined by the background of the women. African, Americans are more common than the Caucasian population to be diagnosed with this condition. The estimated incidence in Nigeria is around 1:100 pregnancies and 1:299 pregnancies in Haiti. While in other countries, it is reported 1:2229 in Southern California to 1:4000 pregnancies in the US [6]. In Indonesia, based on a study done in Soetomo general hospital Surabaya, the estimated incidence 1:149 live births [7]. Other risk factors are presumed to be associated with this condition, including hypertension, pre-eclampsia, multiple childbirth and older maternal age [8].

Aetiology and pathophysiology

During pregnancy, the body undergoes many changes to cope with the baby's development and the accompanying demands on the mother's body. Significant hemodynamic changes occur during pregnancy. This includes changes that happen in the heart in response to pregnancy. These changes are expected, such as a lower blood pressure (slightly increased towards the end in the early stages of pregnancy), water retention and increased preload due to increased red blood cell and blood volume (about 40%). Heart rate and stroke volume also increase by 15%-25%, which increases to 40%-50% in the first six weeks of pregnancy. All of these changes occur during the first and second trimesters and at that moment, a patient with structural heart disease begins to develop symptoms. Compared to PPCM, these symptoms develop during the perinatal period. For this reason, it is not clear whether hemodynamic stress is the leading cause of PPCM [9,10].

The aetiology of PPCM is unclear, however it is probably multifactorial. A combined 'two-hit' version, which are systemic angiogenic imbalance and host susceptibility (predisposition) have a crucial role in the pathophysiology of PPCM. Possible factors that cause PPC are genetic predisposition, low selenium levels, viral infections, stress activated cytokines, inflammation, autoimmune reaction, pathological reaction to hemodynamic stress, unbalanced oxidative stress and induction of antiangiogenic elements. Nevertheless, none of those mechanisms has been thoroughly proven yet. In the last few years, a shift in the angiogenic balance to an anti-angiogenic environment has a capability in initiating PPCM. The up regulated anti-angiogenic that's considered pivotal is the cleaved N-terminal 16-kDa prolactin fragment and sFlt-1 [11].

Prolactin

Prolactin levels are associated with increased blood volume, decreased blood pressure, decreased angiotensin response, decreased water, sodium and potassium levels. Prolactin also increases circulating erythropoietin and thus haematocrit. Due to increased oxidative stress, the overall length of 23 kDa prolactin is divided into anti-angiogenic, pro-inflammatory, pro-apoptotic 16 kDa prolactin fragments by proteolytic enzymes such as cathepsin D and matrix metalloproteinase. 16kDa-prolactin induces endothelial cells to package miR146 into exosomes (small particles encapsulated in lipids). These particles are secreted and taken up by cardiomyocytes. Second, miR146a endogenous to cardiomyocytes suppress the neuregulin/ErbB signaling pathway, promoting cardiomyocyte apoptosis. It is noteworthy that the circulation level of miR146a is dramatically increased in women with PPCM.

sFLT1

Another anti-angiogenic factor released by the placenta and endothelial cells during mid to late pregnancy is soluble FMS like tyrosine kinase 1 (sFlt1 or vascular endothelial growth factor receptor 1). A mouse model of PPCM suggests loss of Vascular Endothelial Growth Factor (VEGF) in the pathogenesis of PPCM. The research was done by Patten. They induced PPCM with severe impairment of cardiac function in a mouse model in which vascular dysfunction caused by sFlt1 up regulation lacks the cardiac peroxisome growth factor activated receptor Gamma Co-activator 1 alpha (PGC1α). sFlt1 peaks at birth inhibit VEGF activity, cause endothelial dysfunction and are associated with an imbalance in systemic angiogenesis. Elevated sFlt1 levels may play an essential role in developing PPCM in some women [12].

Diagnostic peripartum cardiomyopathy

Within the first week of postpartum, most patients with symptoms of PPCM immediately go to the hospital. PPCM can be difficult to find because the symptoms of heart failure can resemble those of late pregnancy, such as swelling of the feet and legs, orthopnea and paroxysmal nocturnal dyspnea. In more extreme cases, there is severe shortness of breath and prolonged swelling after birth. Most affected patients have class III or IV roles in the New York Heart Association (NYHA). Other symptoms are non-specific malaise, palpitation, chest and abdominal discomfort, orthostatic hypotension. Common signs of perinatal cardiomyopathy include changes in apical impulses, the presence of S3 and signs of mitral regurgitation or tricuspid regurgitation. Swelling of the veins in the neck, crackles in the lungs, hepatomegaly and edema of the feet may also be present [13-15].

As with the new HF presentation, standard tests for women with suspected PPCM include a detailed medical history, physical examination and other tests such as complete blood count, urine analysis, serum electrolytes (including calcium and magnesium), blood urea nitrogen, serum creatinine, blood glucose, liver function tests, lipid profile and thyroid stimulating hormone [16].

The results of some of these studies are as follows:

- Type B natriuretic peptide and N-terminal proBNP are usually elevated in PPCM.
- ECG may show non-specific changes such as sinus tachycardia with non-specific ST segment and T wave changes, inter-ventricular delay and in some cases LBBB pattern.
- The TTE test should show a decrease in the diagnosed LVEF. Other TTE findings include LV and/or other ventricular dilation, heart valve insufficiency including moderate to the severe mitral valve and tricuspid regurgitation, mild to moderate pulmonary valve regurgitation, and pulmonary hypertension. May include illness.
- Chest X-rays usually show pulmonary edema and may show an enlarged heart silhouette and/or pleural effusion.
- Echocardiographic findings include overall reduced contractility and LV enlargement without hypertrophy, left ventricular contractile dysfunction, right ventricular and biventricular enlargement, mitral and tricuspid regurgitation, pulmonary hypertension, and includes intracardiac thrombosis.
- Cardiac MRI can also be used for diagnosis when the accurate estimation of Ejection Fraction (EF) is required.
- Cardiac biopsy is usually not indicated unless another cause of heart failure (cardiac sarcoidosis, giant cell myocarditis, etc.) is suspected.

PPCM is diagnosed when the following four criteria (Hibbard diagnostic criteria) are met: (1) Heart failure in the last month of pregnancy and 5 months after birth, (2) Lack of previous heart disease, (3) There is no definitive cause, (4) Strict echocardiography of left ventricular dysfunction: Left Ventricular Ejection Fraction (LVEF) <45% and/or M-model fraction <30%, and Left Ventricular End Diastolic dimension (LVEDd) greater than 2.7 cm/m^2.

Differential diagnosis

PPCM is an exclusion diagnosis. A thorough examination is necessary to avoid over diagnosis of other possibilities such as cardiomyopathies and valvular heart disease. Several pre-eclampsia can also cause diastolic dysfunction, but PPCM is only diagnosed when systolic dysfunction is present. The differential diagnosis that is cardiac caused are Takotsubo cardiomyopathy or myocardial infarction and pulmonary caused are acute pulmonary edema as a result of preeclampsia or tocolysis, pneumonia due to immune intolerance during pregnancy and pulmonary embolism due to hypercoagulable peripartum period. According to JACC, there are certain particularities in each differential diagnosis, which are:

- **Takotsubo cardiomyopathy:** Echocardiogram may show classic apical ballooning.
- **Familial cardiomyopathy**: Family history, genetic testing.
- **Pre-existing cardiomyopathy:** History of HF prior to pregnancy, prior echo studies with low LVEF before pregnancy.
- **Recurrent peripartum cardiomyopathy:** Ask about symptoms in a prior pregnancy.
- **Pre-eclampsia:** Preserved systolic function on echocardiogram.
- **Hypertrophic cardiomyopathy:** Left ventricular hypertrophy, LVOT obstruction, preserved systolic function, genetic testing.
- **Myocarditis:** Consider if viral prodrome, histological diagnosis, fulminant presentation.

- **Arrhythmogenic right ventricular cardiomyopathy:** Consider with family history, genetic testing, echocardiographic findings.
- **Left ventricular non-compaction:** Echocardiographic and CMR findings.
- **Chemotherapy related cardiomyopathy:** History of chemotherapy, particularly doxorubicin.
- **Valvular heart disease:** Echocardiographic findings; congenital aortic stenosis; mitral stenosis from rheumatic heart disease in an endemic country. Patients with PPCM may also have valve disease, *i.e.* mitral regurgitation.
- **Congenital heart disease:** May be diagnosed for the first time during pregnancy by echocardiography.
- **Tachycardia arrhythmia mediated cardiomyopathy:** Consider if specific underlying rhythm abnormality. Note that sinus tachycardia may be secondary to heart failure during pregnancy.
- **Hypertensive heart disease:** Left ventricular hypertrophy; less common in young people unless very longstanding history of hypertension.
- **Ischemic heart disease:** Cardiovascular risk factors, angina, prior CAD, consider SCAD and MINOCA diagnoses.
- **Cardiomyopathy related to other systemic medical diseases:** Consider in the appropriate context, *i.e.* systemic lupus erythematosus, antiphospholipid syndrome, hemochromatosis.
- **Cardiomyopathy related to other acute conditions:** Consider if a patient has other conditions such as sepsis, treatment in the intensive care unit, post-respiratory arrest
- **Pulmonary embolism:** Dyspnea, tachycardia with preserved LVEF.

Treatment

A multidisciplinary strategy involving cardiologist, obstetrician, intensivist and pediatrician is vital for the management of PPCM patients. The treatment for PPCM is similar to heart failure in general, which is usually supportive and aimed to manage the symptoms of heart failure. Optimizing preload and volume status is the goal of treatment for patients with PPCM, which is achieved through diuresis and keeping a steady intravascular and extravascular volume. There is a consideration on how this condition and the drugs used to manage it affect pregnancy. For example, the use of diuretics during pregnancy ought to be done carefully and in very low doses as they might impair perfusion of the placenta and instigate harm to the foetus.

Diuretics such as hydrochlorothiazide and furosemide are safe to use during pregnancy and lactation but should be under close monitoring and used at a low dose.

The use of Angiotensin Converting Enzyme (ACE) inhibitors and Angiotensin II Receptor Blockers (ARBs) are contraindicated during pregnancy and breastfeeding. It's contraindicated during pregnancy due to the teratogenic effects and contraindicated during breastfeeding because it can cause neonatal hypotension.

Beta blockers can be used during pregnancy but with caution (beta-1 selective agents are preferred); however, they are contraindicated during breastfeeding because they are excreted in the breast milk. Carvedilol is effective for PPCM management; it is a combination of beta blocker and alpha blocker that decreases afterload. Other preferred beta blockers are metoprolol and bisoprolol; however, metoprolol is more commonly prescribed due to its shorter half-life.

Vasodilators such as hydralazine, amlodipine and nitro-glycerine are considered safe during pregnancy, but nitroprusside is contraindicated due to concerns of cyanide toxicity.

Anticoagulant use in PPCM patients is controversial, since both heart failure and pregnancy are hypercoagulable states. Anticoagulation has been proposed in patients with PPCM if LVEF is less than 35%, but it's still is not recommended in general. The use of anticoagulation is recommended if bromocriptine is used or if there is a documented left ventricular thrombus is present. Warfarin is the preferred agent if the dose is less than 5 mg and is used in the second and third trimesters. Warfarin should be discontinued prior to vaginal delivery and transitioned to dose adjusted continuous infusion of unfractionated heparin to avoid risks of fetal intracranial hemorrhage. Direct oral anticoagulants are considered not safe during pregnancy.

DISCUSSION

Recent studies suggest that an increase in oxidative stress during the peripartum increases the formation of abnormal 16 kDa prolactin, which stimulates toxic effects on cardiac myocytes. A dopamine receptor agonist with prolactin blocking properties such as bromocriptine minimizes the effect of 16 kDa prolactin on cardiac myocytes and is associated with better outcomes for PPCM patients in small. The 2018 European society of cardiology guidelines gave an IIb recommendation for the use of bromocriptine.

Cardiac resynchronization therapy has shown to progress ejection fraction and outcomes when the use of medical therapy alone is unsuccessful.

Prognosis

With standard medical treatment, around 50% of PPCM patients improve; however, 25% develop chronic heart failure and the rest die during the disease's progression. Recovery is estimated to be around 48 months after delivery. There are several factors associated with the prognosis. Good prognosis is associated with small LV diastolic dimension (less than 5.5 cm), LVEF greater than 30% to 35% and fractioning of shortening greater than 20% at the time of diagnosis, absence of troponin elevation and absence of LV thrombus and Non-African American ethnicity. Furthermore, a bad prognosis is associated with QRS greater than 120 milliseconds, delayed diagnosis, high NYHA class, multiparity and African descent. If patient's EF remains low, they are advised against pregnancy, as mortality is high in such circumstances. However, pregnancy is allowed at least five years after patient's EF has normalized.

CONCLUSION

In conclusion, increased prolactin production and placental secretion of sflt1 in late pregnancy can be toxic to both the vascular system and cardiomyocytes. The role of sFlt1 provides an increased incidence of PPCM in patients with pre-eclampsia or twin pregnancies.

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