Relationship between PPCM and Preeclampsia: Pathophysiology, Cardiovascular Alterations, and Echocardiographic Characteristics

Bayu Priangga[a,b] Erry Gumilar Dachlan[a,b], Akhsananta Lian Ferdiansyah[a,b]

[a]Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Airlangga, Indonesia
[b]Dr. Soetomo General Academic Hospital, Surabaya, Indonesia

Corresponding author: Bayu Priangga, Obstetrics and Gynecology Department, Faculty of Medicine Universitas Airlangga - Dr. Soetomo General Academic Hospital,
Address: Major General Prof. Dr. Moestopo Street, No.6-8, Surabaya 60286, East Java, Indonesia.
Email: bayupriangga@gmail.com

Abstract

The three primary causes of maternal mortality are beginning to alter, including hemorrhage, pregnancy-related hypertension, and novel reasons, such as cardiac illness during pregnancy, one of which is peripartum cardiomyopathy. The pathophysiology of preeclampsia and cardiomyopathy may be observed. sFlt-1 generated in excess by the placenta may result in preeclampsia and/or PPCM. This may be recognized in preeclampsia and PPCM by cardiovascular alterations and echocardiographic characteristics.

Keywords: Peripartum Cardiomyopathy, Preeclampsia, Pathophysiology, Cardiovascular Alterations, Echocardiography

1. Introduction

The three primary causes of maternal mortality are beginning to alter, including hemorrhage, pregnancy-related hypertension, and newcomers such as heart disease in pregnancy, one of which is peripartum cardiomyopathy. Preeclampsia was the most prevalent concomitant condition associated with PPCM in a case study from our institution (Dr. Soetomo General Academic Hospital Surabaya). Both illnesses affect the maternal cardiovascular system. PPCM is also connected with preeclampsia due to its pathophysiology. Thus, the purpose of this research was to investigate the relationship between PPCM and preeclampsia using pathophysiology, maternal cardiovascular alterations, and echocardiographic characteristics in order to improve diagnosis and therapy.

2. Peripartum Cardiomyopathy (PPCM)

According to the European Society of Cardiology's (ESC) Working Group on Peripartum Cardiology (2010), Peripartum Cardiomyopathy is idiopathic cardiomyopathy defined as heart failure caused by left ventricular systolic dysfunction occurring during late pregnancy or several weeks after delivery in the absence of other causes of heart failure. In other circumstances, the left ventricle may not be dilated, but the left ventricular ejection fraction may fall below 45% (1). Three classic diagnostic criteria were verified and supplemented by echocardiographic criteria at a workshop sponsored by the National Heart, Lung, and Blood Institute (NHLBI) and the National Institutes of Health (NIH).

- Classic Criteria:
    1. Symptoms of heart failure manifest in the last months of pregnancy or five months

after delivery.
2. No other cause was found for heart failure.
3. There was no history of previous heart disease until the last month of pregnancy (2)

- Additional Criteria:
  4. Left ventricular dysfunction was found on echocardiography, namely depressed shortening fraction (> 2.7 cm/m2) or ejection fraction (LVEF < 45%) (3)

3. Preeclampsia

Preeclampsia is defined as hypertension during pregnancy (systolic blood pressure 140 mmHg and diastolic blood pressure 90 mmHg in two examinations four hours apart) with proteinuria or hypertension associated with organ dysfunction with or without proteinuria after 20 weeks of gestation in women who had normal blood pressure prior to pregnancy. Preeclampsia may be diagnosed without proteinuria in pregnant women who have new-onset hypertension with signs or symptoms of substantial end-organ failure. Preeclampsia with severe symptoms may be diagnosed if the following conditions exist:

a. Systolic blood pressure ≥ 160 or diastolic blood pressure ≥ 110 with proteinuria
b. Systolic blood pressure ≥ 140 or diastolic blood pressure ≥ 90 (with or without proteinuria) and one or more signs and symptoms of end-organ dysfunction, including:
   - New onset of cerebral or visual disturbances: Photopsia or scotomata
   - Great headache
   - Right upper quadrant pain that does not respond to medication
   - Transaminated serum concentration is two times higher than normal
   - Platelets < 100,000/microL
   - Pulmonary edema
   - Progressive renal insufficiency (Creatinine serum > 1.1 mg/dL)

4. Pathophysiology

Preeclampsia

Preeclampsia's pathogenesis is yet unknown. Preeclampsia may be caused by faulty placental development, an inflammatory response, immunological causes, genetic factors, or environmental factors. However, two ideas are interconnected: defective placentation and maternal inflammatory response. Placentation is the process through which the fetoplacental unit is balanced. In normal pregnancy, uterine blood flow increases, ensuring enough blood supply to the intervillous area, which aids in future fetal growth. As a result, the uterus experiences trophoblast invasion. The decidua is first invaded, followed by intra-arterial migration of trophoblast cells, which results in the intramural vascular invasion, in which the central layer of these blood vessels is replaced by connective tissue. Reendothelialization of blood arteries and maternal adaption are the last stages. Preeclampsia significantly reduces this vascular remodeling, particularly in the placental bed. Atherosclerosis of the arterial blood arteries will ensue, resulting in tissue ischemia.

This causes tissue apoptosis and the formation of pro-inflammatory chemicals that enter the maternal blood. These chemicals create a widespread inflammatory response inside the blood vessels, which contributes to the development of preeclampsia. The oxidative stress produced by cell death disrupts the equilibrium of proangiogenic and antiangiogenic molecules. Preeclampsia results in an increase in the anti-angiogenic factors VEGFR-1 and sFlt-1 and a reduction in the anti-angiogenic factor PlGF(4).

Peripartum Cardiomyopathy

The specific cause of PPCM is unclear at this time. PPCM is thought to be caused by various factors, including angiogenic imbalance and oxidative stress, prolactin, and VEGF signaling, and preeclampsia.

a. Angiogenic imbalance and oxidative stress
   Oxidative stress results from a mismatch between the production of reactive oxygen species (ROS) and the ability of biological systems to detoxify or repair the damage. Oxidative stress levels rise throughout, and late pregnancy and are connected with the development of oxidation-prone particles (high LDL levels) and increased oxidative damage.
b. Prolactin
   Increased reactive oxygen species (ROS) will result in the release of cathepsin D or matrix metalloproteinases. This extracellular peptide cleaves prolactin into 16-kDa fragments that induce endothelial cell death. Additional investigation revealed that 16 kDa-PRL induces vasorelaxation and angiogenesis via blocking Ca2+ ion channels on endothelial nitric oxide synthase (eNOS) and is also related to higher asymmetric dimethylarginine levels (ADMA) (5). Prolactin 16 kDa increases the production of miR-146a in endothelial cells through activation of nuclear factor kappa-light enhancer of activated B cells (NF-kB). MiR-146a is required for endothelial cell injury, pro-apoptosis, and antiangiogenic activity. Prolactin 16 kDa stimulates endothelial cells and subsequently transports miR-146a into exosomes, tiny fat-encapsulated particles that are released and enter cardiomyocytes. MiR146a inhibits the neuregulin/ErbB pathway in cardiomyocytes, resulting in cardiomyocyte death. The mechanism is that miR-146a inhibits metabolism and decreases Erb-B2 tyrosine kinase 4 (ErbB4) receptors in cardiomyocytes, while the ErbB4/Neureglin system acts as a cardioprotective and ventricular remodeling factor during pregnancy (6).
c. sFlt-1 / VEGFR-1
   In mouse research, a decrease in PGC-1 (a proangiogenic regulating factor similar to VEGF) was seen in the heart of patients with PPCM. VEGFR-1 (sFlt-1) release from the placenta may also cause damage to blood vessels in cases of multiple pregnancies or preeclampsia. This antiangiogenic factor (sFlt-1) is produced in abundance throughout the middle to late stages of pregnancy (7).
d. Inflammatory factors
   Inflammation is a possible pathogenic component in PPCM, as shown by higher levels of circulating cytokines such as interleukin-6 (IL-6), tumor necrosis factor (TNF), and C reactive protein in cohort studies and animal studies (CRP). Additionally, interferon-gamma (IFN). Inflammation may play a role in PPCM. Early clinical research demonstrates that pentoxifylline, a xanthine-derived drug known to decrease TNF production and often used to treat heart failure, increases the cure rate of PPCM patients (6). Heart failure is characterized by activating proinflammatory cytokines such as CRP, TNF, and IL-6. CRP is a protein produced during acute inflammation that recognizes pathogens, including apoptotic cell membranes. Cardiac biomarkers, such as B-type natriuretic peptides, will also be raised in individuals with PPCM, but these markers are not specific to PPCM. MicroRNA, especially miR146a, was recently shown to be a biomarker in PPCM patients compared to postpartum women or women with idiopathic DCM. Myocarditis is also a recognized etiology of PPCM; in PPCM patients, a biopsy revealed an inflammatory infiltrate on the right side of the endomyocardial. MiR146a may be used as a biomarker in individuals with

PPCM compared to postpartum women or women with idiopathic DCM. MiR146a may serve as a biomarker in individuals with PPCM compared to postpartum women or women with idiopathic DCM. Myocarditis is also a recognized etiology of PPCM; in PPCM patients, a biopsy revealed an inflammatory infiltrate on the right side of the endomyocardial. Myocarditis is also a recognized etiology of PPCM; in PPCM patients, a biopsy revealed an inflammatory infiltrate on the right side of the endomyocardial. However, similar penetration was also seen in some control patients and myocarditis caused by parvovirus B19, suggesting that myocarditis may play a role in PPCM (5).

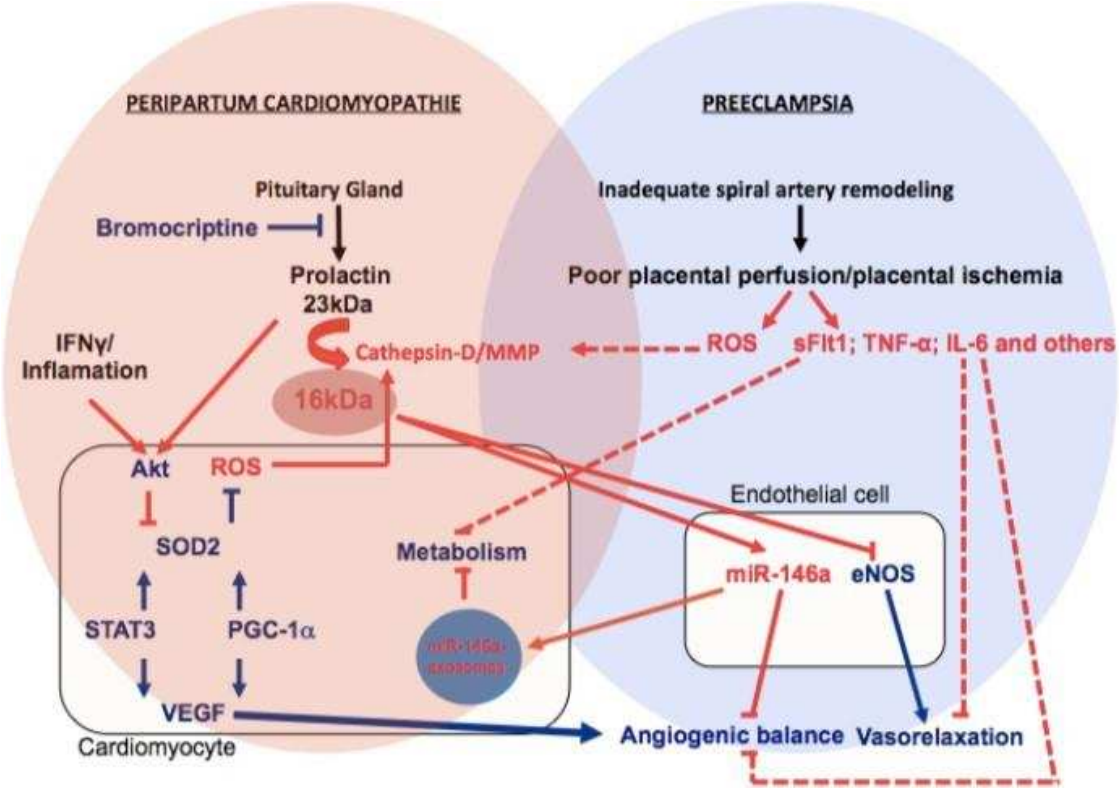

Figure 1. Schematic Overlapping Mechanism of PPCM and Preeclampsia(8)

From figure 1, the pituitary gland will create prolactin with a molecular weight of 23 kDa, which has a proangiogenic impact. However, Cathepsin-D and MMP will convert this kind of prolactin to 16 kDa prolactin. Prolactin is an anti-angiogenic hormone. This form of prolactin increases miR-146a and inhibits Nitric Oxide, disrupting the angiogenic balance and preventing vasodilation. Preeclampsia may also result in aberrant spiral artery remodeling, resulting in decreased uteroplacental perfusion and tissue ischemia. This tissue ischemia results in the formation of Reactive Oxidative Stress (ROS), sFlt-1, IL-6, and TNF-a, which disrupt the angiogenic equilibrium. SFlt-1 will also affect cardiomyocyte metabolism. Preeclampsia will result in the placenta failing to mature normally. Endothelial dysfunction as a result of systemic circulation will raise systemic resistance. The heart will then develop cardiomyopathy, resulting in cardiomyopathy. As a result of this association, peripartum cardiomyopathy and preeclampsia have the same pathophysiology (9).

5. Cardiovascular Alterations

Preeclampsia is caused by an inadequate invasion of trophoblasts into the spiral arteries. This increases vascular resistance, which increases cardiac output. The left ventricle's hyperdynamic state places a constant strain on the need for higher afterload. Eventually, left ventricle hypertrophy will arise, which might progress to ventricular dysfunction. This condition will increase the risk of developing heart failure. On the other hand, in PPCM, the left ventricular cardiomyocytes are damaged, lowering the left ventricular ejection fraction. Pregnancy-induced increased heart strain, compounded by preeclampsia, resulting in a poorer prognosis.

Table 1. Cardiovascular alterations in normal pregnancy, preeclampsia, and PPCM in late pregnancy

	Normal Pregnancy*(10)	**Preeclampsia****(11)	**PPCM*****(5)
Blood Volume	**increased**	**Decreased**	**Same with normal pregnancy**
Red Blood Cell	**increased**	**Same with normal pregnancy**	**Same with normal pregnancy**
Cardiac Output	**increased**	**increased**	**Decreased**
Blood Pressure	**Decreased in mid pregnancy**	**increased**	**Same with normal pregnancy**
Vascular Resistance	**Decreased**	**Increased in Mid Gestation**	**Same with normal pregnancy**
Myocardial Contractility	**Unchanged**	**Unchanged in Mild Impaired in Severe or Preterm Preeclampsia**	**Decreased**

6. Echocardiographic Characteristics

Normal pregnancy results in maternal cardiovascular adaptations, including increased cardiac output, lowered blood pressure, and decreased systemic vascular resistance. Cardiac output grew more rapidly in the third trimester than in the first or second trimesters. This increase lasts until term. A Doppler Echocardiography research corroborated this result, revealing that maximal cardiac output occurs at 32 weeks gestation. Pregnancy in the normal state is related to a reduction in blood pressure and systemic vascular resistance. This is due to the fact that the afterload and uterine vascular resistance are lowered. A reduction in afterload and an increase in preload will increase left ventricular systolic function physiologically. The middle and late third trimesters of gestation significantly rise left ventricular mass. In preeclamptic women, echocardiography may be used to measure systolic and diastolic function, structural changes in the heart, and changes in end-diastolic volume. In comparison to healthy pregnant women, preeclamptic women have an increased left ventricular mass, pericardial effusion, diastolic dysfunction secondary to cardiac decompensation, and greater left ventricular fraction shortening (12).

Research conducted in India compared 200 women with preeclampsia to controls and found substantial alterations in the left ventricle. Elevated afterload is related to reduced left ventricular emptying and increased end-systolic pressure in women with preeclampsia (13).

There is an increase in cardiac output in preeclampsia. Another research concluded that blood pressure alone was insufficient to predict the risk of cardiovascular problems in preeclampsia patients (14). In preeclamptic individuals, a reduced ejection fraction is caused by heart failure and results in pulmonary edema. This may develop as a result of hypertensive heart disease or a

decreased ejection fraction caused by heart failure. Alterations in preload, afterload, and myocardial contractility can occur as a result of these changes (15).

Table 2. Echocardiographic characteristics in normal pregnancy, preeclampsia, and PPCM

	Normal Pregnancy*(16)	Mild Preeclampsia (17)(18)	Severe Preeclampsia (17)(18)	PPCM (19)(20)
Left ventricular wall and thickness	**Increased**	**Increased**	**Increased**	**Increased**
Left Ventricular Ejection Fraction	**Unchanged**	**Unchanged**	**Impending Reduced (Preserved)**	**Reduced**
Left Ventricular Fractional Shortening	**Unchanged**	**Unchanged**	**Impending Reduced (Preserved)**	**Reduced**
Right Ventricular Ejection Fraction	**Unchanged**	**Unchanged**	**Impending Reduced (Preserved)**	**Reduced in Severe**
Left Atrial Size and Volume	**Increased**	**Increased**	**Increased**	**(No data)**
Stroke Volume	**Increased**	**Reduced**	**Reduced**	**Reduced**
Remodeling	**Unchanged**	**Unchanged or Coccentric**	**Unchanged or Coccentric**	**Eccentric**

7. Conclusion

Pregnancy is intimately linked to alterations in the maternal cardiovascular system, altered further by concomitant diseases like preeclampsia and heart failure or cardiomyopathy. There is a correlation between the incidence of PPCM and preeclampsia based on the pathophysiology. Cardiovascular alterations and echocardiographic results were also shown to be linked in both patients.

Conflicts of Interest

No declaration

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