SYSTEMATIC REVIEW

Updated study of peripartum cardiomyopathy and preeclampsia

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ABSTRACT

Objectives: This paper aims to review the literature related to peripartum cardiomyopathy (PPCM) and preeclampsia (PE) in order to know their frequency and relationship and the current knowledge on their pathophysiology and management.

Materials and Methods: The articles reviewed in this study were primary clinical studies published around 2016 and 2021, retrieved using Google Scholar and PUBMED databases. After several evaluations, 14 full-text studies written in English were examined.

Results: Overall prevalence of PE in PPCM cases varied, about 9.9% - 44% in the individual studies. The lactation hormone prolactin and placental-derived anti-angiogenic factor soluble Flt-1, which had been known to be able to cause cardiac dysfunction, were elevated in both PE and PPCM. This partly explained the pathophysiology that the incidence of concurrent PE in women diagnosed with PPCM was four times more than that in the general population.

Conclusion: Epidemiologic studies showed significant overlap between PE and PPCM, whether PE as the independent risk factor of PPCM or an early predictor of PPCM development.

Keywords: cardiomyopathy; peripartum; preeclampsia; pregnancy; cardiovascular disease

ABSTRAK

Tujuan: Tujuan dari tulisan ini adalah untuk meninjau literatur peripartum kardiomiopati (PPCM) dan preeklamsia (PE), untuk menentukan frekuensi dan hubungan antara PPCM dan PE, serta pengetahuan terkini tentang patofisiologi dan manajemennya.

Bahan dan Metode: Artikel yang diulas dalam penelitian ini adalah studi klinis primer yang diterbitkan sekitar tahun 2016 dan 2021, diambil dari database Google Scholar dan PUBMED. Setelah beberapa evaluasi, 14 studi teks lengkap yang ditulis dalam bahasa Inggris diperiksa.

Hasil: prevalensi PE secara keseluruhan pada kasus PPCM bervariasi, sekitar 9.9% - 44% pada setiap studi. Hormon laktasi prolaktin dan faktor anti-angiogenik yang diturunkan dari plasenta larut Fms-like tyrosine kinase 1 (sFlt-1), yang telah terbukti dapat menyebabkan disfungsi jantung, meningkat pada PE dan PPCM, hal ini menjelaskan sebagian patofisiologi kejadian PE pada wanita yang didiagnosis dengan PPCM empat kali lebih banyak dari populasi umum.

Simpulan: Studi epidemiologis menunjukkan tumpang tindih yang signifikan antara pasien PE dan PPCM. Namun, tidak cukup data berkualitas baik untuk sepenuhnya menarik kesimpulan tentang hubungan PE dan PPCM, apakah PE sebagai faktor risiko independen PPCM atau sebagai prediktor awal perkembangan PPCM.

Kata kunci: kardiomiopati; peripartum; preeklamsia; kehamilan; penyakit jantung

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INTRODUCTION

Cardiovascular disease (CVD) is one of the causes of maternal and fetal death causes in pregnancy. The smaller part of pregnancy-specific CVD is peripartum cardiomyopathy (PPCM), a rare but serious heart disease. 1 PPCM can be defined as new-onset heart failure that occurred during pregnancy and through several months following delivery, with no previous history of heart disease and abnormality.2,3

PPCM is a global disease with epidemiology that varies geographically. The incidence of PPCM in the United States was around 1:1000 to 1:4000 live births, in Japan about 1:20,000 live births, in South Africa at a ratio of 1:1000, meanwhile in Haiti and Nigeria, as the "hot spots", it occurred up to 1% of all pregnancies.4-6 PPCM related to death, the need for a left ventricular assist device, the need for a transplant, and the continued decrease in ejection fraction. The five-year mortality rate among PPCM women in developing countries is approximately 25%, with the infant mortality rate around 50-75%. PPCM accounts for 5% of U.S. women's heart transplants, but in most parts of the world, this is not the available treatment option.5-2

The exact etiology of PPCM is still unknown. Hypothetically, the etiology that has been proposed are autoimmunity, viral myocarditis, selenium deficiency, fetal microchimerism that leads to autoimmune response, and genetic factors.4-2 Recent studies have shown that PPCM is a kind of vascular disease triggered by potent anti-angiogenic agents secreted from the placenta and pituitary gland in the late phase of pregnancy. In this case, the frequent association between PPCM and preeclampsia (PE) is a particular concern because PE can also be caused by the excessive placenta secretion of those anti-vascular factors.2 Meanwhile, not all women with PE will continue to develop superimposed PPCM. It is not clear whether PE is an early marker for women with high-risk characteristics of future cardiovascular disease or the independent risk factor for future PPCM. Factors that predispose women to PE, such as obesity, metabolic abnormalities, insulin resistance, and endothelial dysfunction, are also found in the risk profile for CVD.1-2

The aims of this paper were to review the literature on PE and PPCM, and to determine their frequency of association. This study also aimed to review the current knowledge of its pathophysiology and management.

MATERIALS AND METHODS

The literature included was searched from Google Scholar and PUBMED databases using keyword combinations (MeSH term and free text), including ("PPCM" OR "peripartum cardiomyopathy") AND ("preeclampsia" OR "preeclampsia"). This review included clinical studies that evaluated both peripartum cardiomyopathy and preeclampsia, such as observational studies (cohort, case-control) and case report studies. The articles reviewed were novel studies that were published around 2016-2021. Non-English publications and secondary studies (literature review, systematic review) were excluded. A total of 4,699 publications were obtained from two databases. After several evaluations, 14 studies were examined in this review, showed in Figure 1.

RESULTS AND DISCUSSION

The included studies' information are listed in Table 1. Overall, almost 3 million subjects were included.1-13 Sample size of the cohort study varied from 21 to 1,088,063 women, with 1 - 35 years study period, and the majority of women were nulliparous. The women's mean age of PPCM patients was around the third decade of life. The overall prevalence of PE in PPCM case varied in the individual studies, which was around 9.9 - 44%.1-11 The case reports study presents PPCM with PE comorbid case from 22-41 year-old women with the most common symptoms of dyspnea and edema. PPCM was diagnosed in the antepartum, intrapartum, and postpartum periods. Most cases showed rapid changes in the patient's hemodynamic and dramatic improvement from the need for intensive care to sudden cardiac arrest, the return of spontaneous circulation, progressively improved general condition, and gradually increased LVEF after diuretic, anti-prolactin, and other cardiac medicine administration.12-15
Figure 1. Flowchart of included studies
It has been known that PE and PPCM share in risk factors and characteristics. The prevalence of both diseases is increased in women with a history of diabetes, obesity, multiple pregnancies, and extreme childbearing age. The overlap of risk factors between those two diseases indicates that there may be a pathophysiological relationship. Compared with age-matched PPCM in pregnant women without PE, patients with PE have a greater degree of diastolic dysfunction and decreased overall LV tone. There are two main theories about cardiac function alteration or change in PE. The first theory is about the increase of cardiac output (CO) that happens with slightly increased systemic vascular resistance (SVR). The other hypothesis is the theory that the low CO content is accompanied by increased SVR. Literature found that the elevation of the lactation hormone prolactin and placental-derived anti-angiogenic factor soluble Fms-like tyrosine kinase 1 (sFlt-1) were found in both PPCM and PE. It was shown that sFlt-1 could cause cardiac dysfunction. Gammill et al. (2018) reported that women with PE are more likely to carry protein-altering mutations in genes related to cardiomyopathy as seen in PPCM. About 55% of the mutations happened in the TTN gene to encode cardiac troponin C and troponin. These may at least partly explain the pathophysiology that the incidence of concurrent PE in a patient diagnosed with PPCM is more than four times higher than that of the general population. It also indicates that genetic variations likely cause geographical differences of the incidence around the world. MicroRNAs (miRNAs) are a class of small noncoding RNAs of ~22 nt in length, which are involved in the regulation of gene expression at the posttranscriptional level by degrading their target mRNAs and/or inhibiting their translation. Numerous biological processes, including cell division, proliferation, apoptosis, and the preservation of normal cellular physiology, are regulated by miRNAs. The heart in embryonic, postnatal, and adult stages all expresses many miRNAs. Heart development disruption, aberrant cardiac cell differentiation, or genetic loss of miRNAs are all linked to cardiac dysfunction.

Careful assessment of the risk factors in pregnant women could help prevent PPCM. Reducing the risk for relapse of heart failure in a subject with PPCM with or without a subsequent pregnancy is promoted if there is a more rapid return to LVEF 55% after initial diagnosis, especially if that occurs by 1-year postpartum. Delayed time to diagnosis is associated with lower rates of LV recovery. The diagnosis of PPCM in some studies months following delivery showed that the pre-existing heart disease had been ruled out; no other known etiology for heart failure; and the echocardiography examination showed more fractional shortening of < 30% or LVEF < 45% or both, and an end-diastolic dimension of > 2.7 cm/m². In clinical practice, there are no specific biomarkers that have been used for PPCM. Its presentations are generally similar to common sign and symptoms that appear in heart failure patients, which indicates volume overload and systemic hypoperfusion.

The management of the new onset of acute heart failure in PPCM is the same as any other cause of acute heart failure. Oxygen treatment is administered carefully in hypoxic patients (SpO₂ < 90%), as overtreatment in non-hypoxic women will lead to vasoconstriction, which can reduce cardiac output. Diuretics are used in the case of fluid retention and pulmonary congestion. Treatment with an inotropic regimen is considered in severe cases of low cardiac output and hypoperfusion. The administration of low molecular weight heparin as the prophylactic anticoagulation is indicated in cases of LVEF < 35% as PPCM may increase risk for thromboembolism. Nitroglycerine as a vasodilator agent is recommended to reduce preload-afterload and increase SV in cases of systolic blood pressure > 110 mmHg. In managing cardiogenic shock, the extracorporeal membrane oxygenation or left ventricular assist device are indicated as a bridge to recovery. The use of bromocriptine in the treatment of cardiomyopathy was reported effective. It works by inhibiting pituitary prolactin secretion. Excessive prolactin secretion is hypothesized to increase levels of the 16 kDa anti-angiogenic prolactin fragment, which has a key role in the pathological mediator of PPCM through impaired myocardial microvascularization. PE as comorbid PPCM is treated as common PE management, including the management in BP control and MgSO₄ therapy. Almost all studies reported that the majority of the patients experienced gradual recovery of LV systolic function. Lindley et al. reported a higher mortality risk among women with concomitant PE and PPCM than those with PPCM without PE.
Early diagnosis and close monitoring of the patients would improve the patient’s outcome. Most cases showed gradually improved general condition after diuretic, anti-prolactin, and other cardiac medicine administration after PPCM was diagnosed. A fresh perspective into the role of genetics, molecular pathogenesis, and clinical studies has yielded potential disease-specific therapies for PPCM and PE, but many questions remain unanswered.
DISCLOSURES

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Conflict of Interest

The authors declare there is no conflict of interest.

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Author Contribution

All authors have contributed to all processes in this research, including preparation, data gathering and analysis, drafting, and approval for publication of this manuscript.

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