SYSTEMATIC REVIEW

Updated study of peripartum cardiomyopathy and preeclampsia

I Gusti Ngurah Agung Trisnu Kamajaya*, Made Bagus Dwi Aryana
Mangusada Regional General Hospital, Badung, Bali, Indonesia

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 Fms-like tyrosine kinase 1 (sFlt-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 patients. However, there were not enough good quality data to fully draw conclusions about the relationship 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 kinase1 (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 epidemiologi 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

***Correspondence:** I Gusti Ngurah Agung Trisnu Kamajaya, Made Aryana, Mangusada Regional General Hospital, Badung, Bali, Indonesia. E-mail: trisnukamajaya@gmail.com

● pISSN:0854-0381 ● eISSN: 2598-1013 ● doi: http://dx.doi.org/10.20473/mog.V30I22022.101-107
● Maj Obs Gin. 2022;30:101-107 ● Received 17 Mar 2022 ● Revised 10 May 2022 ● Accepted 10 Jun 2022 ● Published 1 Aug 2022

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.[1,2,4] 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.[5-7]

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.[1,7] 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.[7] 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.[1,7]

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.[1-15] 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]

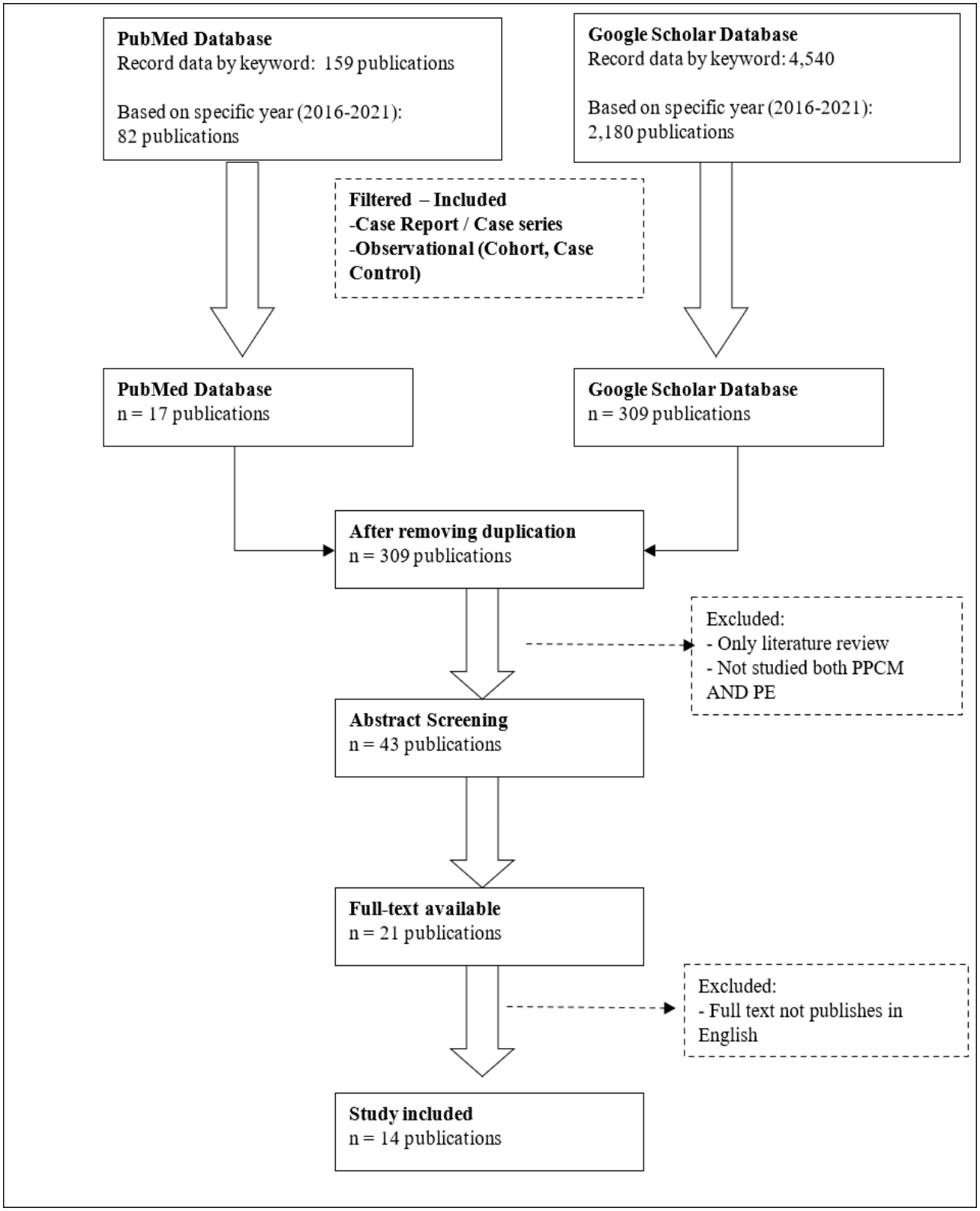

Figure 1. Flowchart of included studies

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.[2-10] 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.[3] 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.[6,14] 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.[5] 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.[16,17]

Careful assessment of the risk factors in pregnant women could help prevent PPCM.[18] 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.[19] Delayed time to diagnosis is associated with lower rates of LV recovery.[20] 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 mode fractional shortening of < 30% or LVEF < 45% or both, and an end-diastolic dimension of > 2.7 cm/m^2. 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.[2,11-15]

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 (SpO_2 < 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 micro vascularization.[11-15] PE as comorbid PPCM is treated as common PE management, including the management in BP control and MgSO4 therapy.[2] Almost all studies reported that the majority of the patients experienced gradual recovery of LV systolic function.[1-15] Lindley et al. reported a higher mortality risk among women with concomitant PE and PPCM than those with PPCM without PE.[6]

Table 1. Information of included studies evaluating peripartum cardiomyopathy and preeclampsia

Authors, Year	Type of Study Number of sample/ Region (Period)/ Age	Result and Reported Data
Malhamé et al., 2019[1]	Cohort n = 1,024,035 pregnancies U.S.A (2011 – 2014) 15–55 years (31.8 ± 6.8)	-64,503 (6.3%) had PE -874 had PPCM (283 with PE; 591 without PE) -Cumulative incidence of PPCM was 1:1172 deliveries -Cumulative incidence of PPCM among PE was 1:228 deliveries - Women with PE-PPCM had a higher risk of major adverse cardiovascular events (MACE) than women PPCM without PE (adjusted RR 1.29, 95% CI [1.06, 1.57])
Ersbøll et al., 2016[2]	Cohort n = 619 084 deliveries Denmark (2005-2014) ≥18 years (31.7 ± 6.3)	-61 women (1:10,149 deliveries) meet EORP PPCM registry's criteria. -33 / 61 PPCM patients have hypertensive disorder of pregnancy -Mean duration from delivery to diagnosis: 25±44 days -Majority recovered LVEF within one year
Ersbøll, et al., 2018[3]	Cohort n = 84 women Denmark (2005-2014) ≥18 years (30.7 ± 6.0)	-3 groups age-matched: PPCM, severe PE, uncomplicated pregnancy - In 91 months median time follow-up, 85% PPCM group have no heartfailure symptoms - PPCM group's mean LVEF was normal (62%), but significantly (P< 0.0001) lower than uncomplicated pregnancies group (67%) andPE group (69%)
Krishnamoorthyet al., 2016[4]	Cohort n = 4859 USA (2009-2010) 15–60 years (30.3±0.2)	-Prevalence of PPCM was 0.04% (1:2367) -78% diagnose at postpartum, 18% in peripartum, 4% antepartum -PE found in 9.9% PPCM patient -PPCM was more common in African-Americans (43.9%)
Lindley et al., 2017[6]	Cohort n = 39 patient PPCM Barnes (2004-2014) 27.4±7.4 years	-44% women (17/39) with PPCM had PE -During one-year follow up, patients with PE had worse event-freesurvival (4/15 with vs. 1/17 without PE, p= 0.16)
Behrens et al., 2019[8]	Cohort n = 1,088,063 women / 2,078,822 pregnancies Denmark (1978-2012)	-39/126 (30%) PPCM women had gestational hypertension -Risks of PPCM were significantly higher in women with gestational hypertension than in women with normotensive pregnancies

PE=preeclampsia ; PPCM=peripartum cardiomyopathy; SC= sectio-caesarian; LVEF=left ventricular ejection fraction

CONCLUSION

Epidemiologic studies show significant overlap between PE and PPCM patients. However, there are not enough data of good quality to fully draw conclusions about the relationship between PE and PPCM, whether PE is the independent risk factor of PPCM or an early predictor of PPCM development. The diagnosis by exclusion and high index of suspension is the key to identifying this rapidly progressing condition. 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

Acknowledgment

The author thanks dr. Made Aryana for helping and supporting in the making of this paper.

Conflict of Interest

The authors declare there is no conflict of interest.

Funding Disclosure

This research has received no external funding.

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.

REFERENCES

1. Malhamé I, Dayan N, Moura CS, et al. Peripartum cardiomyopathy with co-incident preeclampsia: A cohort study of clinical risk factors and outcomes among commercially insured women. Pregnancy Hypertens. 2019;17:82-8. doi: 10.1016/j.preghy.2019.05.014. Epub 2019 May 9. PMID: 31487662.
2. Ersbøll AS, Damm P, Gustafsson F, et al. Peripartum cardiomyopathy: a systematic literature review. Acta Obstet Gynecol Scand. 2016;95(11):1205-19. doi: 10.1111/aogs.13005. PMID: 27545093.
3. Ersbøll AS, Bojer AS, Hauge MG, et al. Long-term cardiac function after peripartum cardiomyopathy and preeclampsia: A Danish nationwide, clinical follow-up study using maximal exercise testing and cardiac magnetic resonance imaging. J Am Heart Assoc. 2018;7(20):e008991. doi: 10.1161/JAHA.118.008991. PMID: 30371259; PMCID: PMC6474952.
4. Krishnamoorthy P, Garg J, Palaniswamy C, et al. Epidemiology and outcomes of peripartum cardiomyopathy in the United States: findings from the Nationwide Inpatient Sample. J Cardiovasc Med (Hagerstown). 2016;17(10):756-61. doi: 10.2459/JCM.0000000000000222. PMID: 25943626.
5. Gammill HS, Chettier R, Brewer A, et al. Cardiomyopathy and preeclampsia: shared genetics? Circulation. 2018;138(21):2359-66. doi: 10.1161/CIRCULATIONAHA.117.031527
6. Lindley KJ, Conner SN, Cahill AG, et al. Impact of preeclampsia on clinical and functional outcomes in women with peripartum cardiomyopathy. Circ Heart Fail. 2017;10(6):e003797. doi: 10.1161/CIRCHEARTFAILURE.116.003797. PMID: 28572214; PMCID: PMC5520674.
7. Bello N, Rendon ISH, Arany Z. The relationship between preeclampsia and peripartum cardiomyopathy: a systematic review and meta-analysis. J Am Coll Cardiol. 2013;62(18):1715-23. doi: 10.1016/j.jacc.2013.08.717. Epub 2013 Sep 4. PMID: 24013055; PMCID: PMC3931606.
8. Behrens I, Basit S, Lykke JA, et al. Hypertensive disorders of pregnancy and peripartum cardiomyopathy: A nationwide cohort study. PLoS One. 2019;14(2):e0211857. doi: 10.1371/journal.pone.0211857. PMID: 30785920; PMCID: PMC6382119.
9. Chaitra S, Kumar S, Malapure P, et al. Peripartum cardiomyopathy: A 5-year retrospective study in a tertiary care center, India. Int J Clin Obstet Gynaecol 2019;3(2):206-9. DOI: 10.33545/gynae.2019.v3.i2d.35
10. Isogai T, Matsui H, Tanaka H, et al. In-hospital management and outcomes in patients with peripartum cardiomyopathy: a descriptive study using a national inpatient database in Japan. Heart Vessels. 2017;32(8):944-51. doi: 10.1007/s00380-017-0958-7. Epub 2017 Feb 23. PMID: 28233090.
11. Karaye KM, Ishaq NA, Sa'idu H, et al; PEACE Registry Investigators. Incidence, clinical characteristics, and risk factors of peripartum cardiomyopathy in Nigeria: results from the PEACE Registry. ESC Heart Fail. 2020;7(1):235-43. doi: 10.1002/ehf2.12562. Epub 2020 Jan 28. PMID: 31990449; PMCID: PMC7083508.
12. Hoy M, Flavin K, Prasad V. A complex obstetric case. J Intensive Care Soc. 2017;18(3):239-43. doi: 10.1177/1751143717700910. Epub 2017 Apr 3. PMID: 29118838; PMCID: PMC5665137.
13. Hakata S, Umegaki T, Soeda T, et al. Bromocriptine use for sudden peripartum cardiomyopathy in a patient with preeclampsia: a case report. JA Clin Rep. 2019;5(1):38. doi: 10.1186/s40981-019-0256-8. PMID: 32026046; PMCID: PMC6966983.
14. Sethi D, Kumar N. Peripartum cardiomyopathy with preeclampsia in a parturient: A case report with literature review. Turk J Emerg Med. 2020;20(4):202-5. doi: 10.4103/2452-2473.297467. PMID: 33089031; PMCID: PMC7549512.
15. Chou MH, Huang HH, Lai YJ, et al. Cardiac arrest during emergency cesarean section for severe preeclampsia and peripartum cardiomyopathy. Taiwan J Obstet Gynecol. 2016;55(1):125-7. doi: 10.1016/ j.tjog.2015.12.010. PMID: 26927264.
16. Espinoza-Lewis RA, Wang DZ. MicroRNAs in heart development. Curr Top Dev Biol. 2012;100:

279-317. doi: 10.1016/B978-0-12-387786-4.00009-9. PMID: 22449848; PMCID: PMC4888772.
17. Pang JKS, Phua QH, Soh BS. Applications of miRNAs in cardiac development, disease progression and regeneration. Stem Cell Res Ther. 2019;10(1):336. doi: 10.1186/s13287-019-1451-2. PMID: 31752983; PMCID: PMC6868784.
18. Scardovi AB, De Maria R. Peripartum cardiomyopathy: Challenges and solutions. 2017; 8: 31-40. doi: 10.2147/RRCC.S103577
19. Fett JD. Promoting full recovery and improved relapse-free prognosis in the diagnosis and treatment of peripartum cardiomyopathy. J Am Coll Cardiol. 2020;76(20):2365-7. doi: 10.1016/j.jacc.2020.09.599. PMID: 33183510.
20. Lewey J, Levine LD, Elovitz MA, et al. Importance of Early Diagnosis in Peripartum Cardiomyopathy. Hypertension. 2020;75(1):91-7. doi: 10.1161/HYPERTENSIONAHA.119.13291. Epub 2019 Nov 11. PMID: 31707840; PMCID: PMC6906246.