Peripartum cardiomyopathy and Coronavirus Disease 2019 (COVID-19) associated cardiomyopathy: case series and review of literature

Maryam Dehghan[1], Mohammad Fakhrolmobasheri[2], Tetsuya Kawakita[3], Sadegh Mazaheri-tehrani[1], Aref Rastegar[3], and Leila Mousavi Seresht[1]

[1]Isfahan University of Medical Sciences
[2]Isfahan Cardiovascular Research Center
[3]University of Virginia Department of Obstetrics and Gynecology

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Abstract

Purpose: Peripartum cardiomyopathy (PPCM) is a rare complication of pregnancy manifesting with acute cardiac failure. Coronavirus Disease 2019 (COVID-19) can be complicated by cardiomyopathy, which can be difficult to differentiate from PPCM. The aim of this publication is to investigate different outcomes of cases with cardiomyopathy during pregnancy. **Methods:** Here, we report 4 peripartum cases with COVID-19 and acute cardiac failure due to cardiomyopathy. Moreover, to find previous similar cases, a comprehensive review on PPCM and COVID-19 associated cardiomyopathy was conducted in PubMed, Scopus, Embase, and Google Scholar. **Results:** Out of 4 cases we had, two cases deceased and one became a candidate for heart transplant. Despite advanced diagnostic approaches, differentiating COVID-19 associated cardiomyopathy from PPCM was challenging. According to the literature review, 7 cases with similar conditions were found. **Conclusion:** Pregnant women with COVID-19 may develop acute cardiac failure associated with PPCM or COVID-19 associated cardiomyopathy or both. This condition may be deadly due to rapid disease progression, atypical manifestations, and limited treatment options.

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***Authors**: Maryam Dehghan[1], Mohammad Fakhrolmobasheri[2], Tetsuya Kawakita[3], Sadegh Mazaheri-Tehrani[4], Aref Rastegar[5], Leila Mousavi Seresht[6]**

1. *Assistant professor of gyn & obs, Department of obstetrics and gynecology, Isfahan University of medical science, Isfahan, Iran, ORCID: 0000-0002-7497-7012*
2. *M.D, Heart failure research center, Isfahan cardiovascular research institute, Isfahan University of medical sciences, Isfahan, Iran, ORCID: 0000-0002-6502-376X*
3. *M.D, Department of Obstetrics and Gynecology, Eastern Virginia Medical School, Norfolk, Virginia,United States of America*
4. *M.D, Child Growth and Development Research Center, Research Institute for Primordial Prevention of Non-Communicable Disease, Isfahan University of Medical Sciences, Isfahan, Iran, ORCID: 0000-0002-7199-5696*
5. *Medical student, Department of Obstetrics and Gynecology, Eastern Virginia Medical School, Norfolk, Virginia, United States of America*
6. *Assistant professor of gyn & obs, Fellowship of gynecology oncology, Department of obstetrics and gynecology, Isfahan University of medical science, Isfahan, Iran, ORCID: 0000-0003-3869-4047*

Corresponding authors:

Leila Mousavi Seresht: *Assistant professor of gyn & obs, Fellowship of gynecology oncology, Department of obstetrics and gynecology, Isfahan University of medical science, Isfahan, Iran****Email:****Lmousavi.lm@gmail.com****Tell:*** *+989039078376*

Abstract

Purpose: Peripartum cardiomyopathy (PPCM) is a rare complication of pregnancy manifesting with acute cardiac failure. Coronavirus Disease 2019 (COVID-19) can be complicated by cardiomyopathy, which can be difficult to differentiate from PPCM. The aim of this publication is to investigate different outcomes of cases with cardiomyopathy during pregnancy.**Methods:** Here, we report 4 peripartum cases with COVID-19 and acute cardiac failure due to cardiomyopathy. Moreover, to find previous similar cases, a comprehensive review on PPCM and COVID-19 associated cardiomyopathy was conducted in PubMed, Scopus, Embase, and Google Scholar.**Results:** Out of 4 cases we had, two cases deceased and one became a candidate for heart transplant. Despite advanced diagnostic approaches, differentiating COVID-19 associated cardiomyopathy from PPCM was challenging. According to the literature review, 7 cases with similar conditions were found.**Conclusion:** Pregnant women with COVID-19 may develop acute cardiac failure associated with PPCM or COVID-19 associated cardiomyopathy or both. This condition may be deadly due to rapid disease progression, atypical manifestations, and limited treatment options.**Key words:** Cardiomyopathy, COVID-19, Heart failure, Peripartum Period, Pregnancy**Introduction:** Cardiomyopathies are disorders of the heart characterized by structural or functional abnormalities of myocardium in the absence of other causes for myocardial dysfunction (1). Cardiomyopathies are classified as primary or secondary. In primary cardiomyopathies, the disease is predominantly restricted to the heart and could have been due to genetic and acquired causes while in secondary cardiomyopathies myocardial dysfunction occurs subsequent to a systemic disorder (2). Peripartum Cardiomyopathy (PPCM) is the most common form of acquired cardiomyopathy in pregnancy manifesting as unexplained dilated cardiomyopathy (DCM) during late pregnancy or early postpartum period (1,3). It is known that some viral infections such as Adenovirus, Coxsackie, Epstein-Barr, Parvovirus, and Cytomegalovirus are associated with secondary cardiomyopathy (2,4). Studies suggested that Coronavirus Disease 2019 (COVID-19) is associated with multiple organ dysfunctions particularly the cardiovascular system; manifesting as myocardial injury, cardiac arrhythmia and severe forms of cardiomyopathy (5). Though characteristics of COVID-19 cardiomyopathy (CCM) in non-pregnant patients have been described extendedly, (6–8) there are few reports of cardiomyopathies in pregnant patients with COVID-19 (9–14). Cardiomyopathy in a pregnant patient with COVID-19 may be a consequence of viral infection or PPCM or both. Here, we present 4 cases of pregnant patients with COVID-19, developing cardiomyopathy. We also reviewed the literature surrounding cardiomyopathy in pregnant patients with COVID-19.**Material and methods:**Focusing on the history of 4 pregnant cases with documented COVID-19 and manifestation of cardiomyopathy in the course of their illness, here we sought to explain the characteristic finding in these pregnant patients' presentation and compare them with what has been reported in literature.**Result:**All cases had common clinical manifestations of fever, myalgia and tachycardia and tachypnea. All the cases were positive for severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) polymerase chain reaction (PCR) and had characteristic opaque densities in her chest computerized tomography (CT) or Chest-X-ray. The patients' clinical course which leads to identification of their cardiac dysfunction and prognosis are described.**Case 1**A 26 years old gravida 1 para 0 woman at 17 weeks' gestation was referred to us complaining of vaginal leak and fever for 2 days. Her pregnancy was complicated by gestational diabetes (GDM). Initial physical examination revealed oxygen saturation (O_2-sat) of 94%. Ultra-Sonographic assessment of the uterus showed an intrauterine fetal demise with oligohydramnios. Despite supportive treatment, antibiotics, and spontaneous abortion within 24 hours, her clinical status rapidly deteriorated, making her hemodynamics dependent on vasopressor agents. On the next day she became oliguric while her abdomen was distended. Trans-Thoracic Echocardiography (TTE) revealed severe mitral valve regurgitation, ejection fraction (EF) of 25%, pulmonary arterial pressure (PAP) of 30 mmHg and minimal pericardial effusion. The diagnostic ultrasound guided aspiration reported an intra-abdominal transudative ascites. Within the next 24 hours, despite treatment for heart failure, her condition exacerbated with uremia, bradycardia, and respiratory failure. De-

spite invasive mechanical ventilation (IMV) and hemodialysis she died due to multiple-organ impairment on hospital day 9.**Case 2**A 21 year gravida 2 para 1 previously healthy woman at 21 weeks' gestation presented with symptoms of COVID-19 for the last 3 days. General examination revealed blood pressure (BP) of 80/60 mmHg, tachycardia, and tachypnea (140 beats/min and 30/min respectively), temperature of 39, O_2 sat of 95%, and fetal heart rate of 170 beats/min. Chest CT findings and positive PCR confirmed the diagnosis of COVID-19. According to regional treatment guidelines in early 2020, azithromycin and hydroxychloroquine was first administered for her. Her condition rapidly deteriorated in 24-hour. With clinical and radiological findings in favor of sepsis, broad spectrum antibiotics and vasopressor agents were administered. Initial TTE demonstrated EF of 45% and PAP of 35-40 mmHg. The next morning, acute onset abdominal pain and distention with concurrent anuria and severe respiratory discomfort urged the critical care and surgery teams to start IMV and perform emergent exploratory laparoscopy. Surgery revealed accumulation of transudative ascites. Her cardiac dysfunction exacerbated in the post-operative period. The second TTE revealed EF of 20% suggesting acute left ventricular failure. In the following 12 hours she experienced spontaneous uterine contractions, delivering a non-viable fetus. However, she did not experience any improvement after the delivery. She expired on hospitalization day (HD) 9 with presentation of severe acute cardiac failure.**Case 3**A 36 years old gravida 2 para 2 woman was admitted four days after elective cesarean delivery for twin pregnancy at 38 weeks' gestation. Initial examinations indicated O_2 sat of 68%, temperature of 38.7, respiratory rate of 28/minutes, and pulse rate of 110 beats/min. PCR test for SARS-COV-2 and CT scan established the diagnosis of COVID-19. Prophylactic anticoagulants, piperacillin-tazobactam, high dose corticosteroid, and Remdesivir were administered. Despite all efforts and using non-invasive ventilation, her conditions rapidly deteriorated with progressive dyspnea, O_2 sat of 45% and tachycardia. TTE revealed EF of 30%, Pro-BNP of 36405 pg/ml and pulmonary edema. Laboratory testing indicated high levels of serum IL-6 (61.5pg/ml). Due to worsening respiratory failure, she received mechanical ventilation. Treatment for heart failure and Tocilizumab was started. Tocilizumab was administered only one dose due to suspicion of superinfection. She received bromocriptine since it was difficult to differentiate PPCM from COVID-19 cardiomyopathy. In the following days her respiratory condition ameliorated, and she was extubated on HD 9. After 15 days, she was discharged with favorable conditions.**Case 4**A 34 years old gravida 3 para 2 woman at 24 weeks' gestation presented with severe dyspnea and epigastric pain. She had history of large atrial septal defect (ASD) and GDM, however, she had normal ejection fraction. Initial examination had no significant finding apart from tachycardia. She had COVID-19 infection in 2 weeks before based on positive PCR. Chest CT showed no sign of pulmonary thromboembolism and COVID-19. TTE demonstrated ASD secundum with mild pulmonary insufficiency, EF of 35-40% and PAP of 40 mmHg. She was put on treatment for heart failure and discharged after improvement of her symptoms. She was admitted again at 34 weeks' gestation with symptoms of acute decompensated heart failure. TTE indicated EF of 35%. She underwent an urgent cesarean delivery. Her cardiac function improved after delivery to EF of 45% and she was discharged symptoms free at HD 4.**Discussion**SARS-CoV2 invades human cells by binding to angiotensin-converting enzyme-2 (ACE2) which is mostly expressed in heart and lungs. This interaction could cause alterations in the downstream signaling pathways which leads to severe systemic inflammation and subsequent mitochondrial dysfunction particularly in high metabolic rate organs such as the myocardium (15,16). Accordingly, Cardiomyopathies are one of the frequently reported complications of COVID-19. Serum inflammatory markers including C-reactive protein (CRP), tumor necrosing factor α (TNF-α) and IL-6 reported to be elevated among CCM patients as well as patients with PPCM. Therefore, systemic inflammation and subsequent myocardial dysfunction is hypothesized as a common pathway for PPCM and CCM (17,18). Furthermore, the reports of the presence of different viral genomes in the endomyocardial biopsies (EMB) from patients with PPCM raises the question whether SARS-CoV2 localization in the heart may contribute to the development of PPCM. Mapelli et al (14) reported the presence of SARS-CoV2 and parvovirus b19 in the EMB of their patient with PPCM. Other causes of cardiomyopathy in pregnancy and COVID-19 may be associated with particular nutritional deficiencies such as selenium and Coenzyme Q10 during pregnancy and COVID-19 which are known to be contributing to the development of cardiomyopathies (16,19). The same condition was historically observed in Keshan diseases, which patients in regions with low selenium concentration in soil were more likely to develop cardiomyopathy due to Coxsackie B virus infection ((Fakhrolmobasheri et al., 2021)). Consistently,

among all 11 reported cases, 5 cases were from Iran. This could be explained by the relatively low selenium intake in middle eastern people particularly in people with conditions like pregnancy of which the body needs for micronutrients increases (20). Nevertheless, further research is needed to assess the pathophysiology of cardiomyopathy among pregnant COVID-19 patients. Here, we described 4 cases of cardiomyopathy during or soon after pregnancy of which were associated with poor outcomes in 2 cases. We also reviewed the available literature about this condition. We searched PubMed, Scopus and Embase databases in addition to the Google Scholar search engine using keywords including peripartum cardiomyopathy, pregnancy cardiomyopathy, COVID-19, SARS-COV-2, COVID-19 cardiomyopathy. We also used the indicators of "AND" and "OR" as appropriate. Overall, we found 6 articles, reporting 7 patients (9–14). Juusela et al. (10) reported 2 cases of which both patients were still hospitalized at the time of publication thus their outcome was not clear. Akintayo et al. (12) and Mapelli et al. (14) reported their cases as conference posters. None of the reported cases deceased, however, case 1 reported by Juusela et al. (10) had developed pulseless electrical activities and underwent cardiopulmonary resuscitation for 5 minutes. Notably, as mentioned, the final outcome of the patient was not reported. The patient reported by Akintayo et al. (12) was discharged with left and right ventricular assist devices and became a candidate for heart transplant. In **supplementary Table 1,** we summarized the data from 6 studies. These patients were admitted within the first few months of the pandemic in 2020. At that time we had limited knowledge about COVID-19 and treatment options. Despite the treatment for heart failure and the respiratory distress, two out of four patients did not survive. Also, it is notable that both patients were admitted to hospital with severe disease and unstable hemodynamics. For the third case, regarding that the patient was in postpartum period with lower risk of thromboembolic events and higher suspicion for PPCM we considered bromocriptine as an investigational therapy. Likewise, Mapelli et al. (14) had used bromocriptine, however, Abdulraheem et al. (13) avoided using Bromocriptine considering the risk of adverse vascular events. In this case series, we described cases that were difficult to differentiate PPCM from COVID-19 cardiomyopathy. Cardiac magnetic resonance (CMR) is suggested as the best way to differentiate PPCM from viral myocarditis. Dilated ventricles and hypokinetic myocardium versus tissue edema and inflammation are keys to differentiate PPCM from CCM, however, some studies indicated that tissue inflammation and edema may also be present in PPCM. Moreover, late gadolinium enhancement (LGE) mapping is known as a way to identify tissue scaring that can help to differentiate PPCM from myocarditis (21). Interestingly, from 2 cases that underwent CMR, one had increased LGE values, and one was negative for LGE in the myocardium. Nevertheless, in both cases by Mapelli et al. (14) and De vita et al. (9) finding from CMR were helpful for the diagnosis. CMR is an appropriate way to establish the diagnosis of PPCM or CCM, however, when a patient is receiving the treatment for both heart failure and COVID-19, precise diagnosis may not change the treatment strategies except in cases which bromocriptine is considered as a potential treatment for PPCM (14). The findings from CMR and echocardiography of the 6 patients in the included study are reported in**supplementary Table 2**. CCM may be a complicit or a differential diagnosis for PPCM in the pregnant population with COVID-19. Inflammation and metabolic disturbances in myocardium are common features in both CCM and PPCM thus, these two conditions could aggravate each other and develop severe disease with poor outcomes. Precise cardiac evaluations in pregnant patients with COVID-19 may prevent the occurrence of severe heart failure.**Acknowledgement:** We thank all the researcher and health care provider who will proud of themselves after ending of this unbelievable moment in near future.**Declaration of interest:** The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.**References**

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Table legends:

Table S1. The COVID-19 related cardiomyopathy in pregnancy. Demonstrating the patient characteristic data, clinical finding, disease courses, individualized management, and maternal and perinatal outcomes. Abbreviations: Computed Tomography(CT), Computed Tomography Angiography(CTA), electrocardiography(ECG), Corona Virus Disease 2019(COVID-19), polymerase chain reaction(PCR), alanine aminotransferase(ALT), aspartate aminotransferase(AST), B-type natriuretic peptide(BNP), peripartum cardiomyopathy(PPCM), Covid-19 associated Cardiomyopathy(CCM), Left Ventricular Assist Device(LVAD), Right Ventricular Assist Device(RVAD), Cardiac Magnetic Resonance(CMR), Low Molecular Weight Heparin(LMWH), Chest X-Ray(CXR), C-Reactive Protein(CRP), lactate dehydrogenase(LDH),

Table S2. The echocardiographic and cardiac magnetic resonance findings of patients in studies found in the literature review

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