Post-COVID-19 Peripartum Cardiomyopathy: Experience from a Large Tertiary Referral Center

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ABSTRACT **Background:** Peripartum cardiomyopathy (PPCM) is a rare but potentially devastating complication of pregnancy. Although the pathophysiology of PPCM is not fully understood, there are known risk factors for developing PPCM, which are maternal and gestation related. In the first wave of the coronavirus disease 2019 (COVID-19) pandemic, we witnessed an elevated incidence of PPCM among COVID-19 survivors.

Objectives: To present a single-center case series of three patients diagnosed with peripartum cardiomyopathy after recovered from COVID-19 during the index pregnancy.

Methods: In this single center case study, all patients diagnosed with PPCM at our institute during the examined time frame were included. Electronic medical records were studied.

Results: Three patients previously diagnosed with asymptomatic or mildly symptomatic COVID-19 disease during pregnancy presented with PPCM before or shortly after delivery. Patients underwent testing to rule out residual COVID-19 myocarditis, were treated pharmacologically and with wearable defibrillators as needed, and were examined in follow-up 1–9 months after delivery.

Conclusions: Residual endothelial damage due to COVID-19 disease, even if originally mild in presentation, could predispose pregnant patients to PPCM and should be considered as a risk factor when assessing patients with new onset symptoms of heart failure. Further research is needed to confirm this hypothesis and fully determine the underlying pathophysiology. These preliminary findings warrant a high index of suspicion for PPCM in COVID-19 recoverers.

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KEY WORDS: coronavirus disease 2019 (COVID-19), peripartum cardiomyopathy (PPCM), heart failure

Peripartum cardiomyopathy (PPCM) is defined as idiopathic cardiomyopathy presenting with heart failure secondary to left ventricular systolic dysfunction toward the end of pregnancy or in the months following delivery, where no other cause of heart failure is found [1]. The prevalence of PPCM ranges from 1:100 to 1:4000 pregnancies [2] with significant genetic and geographic variability [1,3]. Recently, there has been a rise in the reported incidence of PPCM, which may be attributed in part to more precise diagnosis but is also a result of increased maternal age and more frequent co-morbidities and multiple gestations [3].

In March 2020, the World Health Organization declared the novel coronavirus outbreak a global pandemic. Coronavirus disease 2019 (COVID-19) infection and its sequelae can range from asymptomatic infection to severe and even fatal disease.

The mechanism and frequency of COVID-19-related myocardial injury remain unclear. While some reports estimated the prevalence of myocardial injury in these patients to be up to 28% [4,5], other studies showed significant sub-clinical left ventricular dysfunction in 80% of patients with cardiac magnetic resonance imaging (CMRI) and strain echocardiography [6,7].

Scant data are available regarding the myocardial consequences of COVID-19 infection in pregnant patients.

We present a single-center case series of three patients diagnosed over a short period with peripartum cardiomyopathy after having apparently recovered from COVID-19 during the index pregnancy.

PATIENTS AND METHODS

This single center case series was conducted in the largest tertiary referral obstetrics and gynecology center in Israel, with 17,000 deliveries per year. The study was approved by the institutions review board. Patient electronic medical records were identified by previous diagnosis of cardiomyopathy (via ICD-9 codes), and all patients were treated by the authors. Data were extracted from the computerized archives. All files were carefully reviewed by authors.

In this case series, all patient data were fully anonymized, and therefore exempt from patient consent by the Institutional Review Board and Soroka Hospital's Helsinki committee.

RESULTS

Three patients with PPCM were admitted to our institution during a 2-month period (December 2020 to January 2021). For comparison, during the whole year of 2020 only two pa-

tients were diagnosed with PPCM at our institution, one of whom is included in this case series.

PATIENT 1

A 21-year-old pregnant woman born in Ethiopia (gravida 2, para 0) presented at 37 weeks of gestation with dyspnea and a progressive dry cough of 1-month duration. Four months prior to admission, the patient was diagnosed as positive for COVID-19 by reverse transcription polymerase chain reaction (rtPCR). Her medical history was otherwise noncontributory, and she was a non-smoker. She was not vaccinated for COVID-19.

On admission, her temperature was 36.8°C, heart rate was 95 beats per minute (bpm), blood pressure was 120/80 mmHg, respiratory rate was 40 breaths per minute, and oxygen saturation was 97% on ambient air.

On examination, bilateral lung crackles were noted, as well as pedal edema (+4) and jugular vein distention. Laboratory findings are presented in Table 1. IgG antibodies for COVID-19 were positive. Work-up for preeclampsia toxemia was unremarkable.

The electrocardiogram showed sinus tachycardia with inverted T waves in leads L1 and aVL. A chest X-ray showed cardiac enlargement. Transthoracic echocardiography (TTE) demonstrated severe Left ventricular (LV) dysfunction, with an estimated LV ejection fraction (EF) of 5–10%, mild aortic regurgitation (AR), mild mitral regurgitation (MR), mildly hypokinetic right ventricle. Fetal assessment was reassuring.

The patient was admitted to the cardiac intensive care unit (CICU) and treated with nitrates and diuretics, with prompt stabilization. An emergency cesarean delivery was performed 2 days later under spinal anesthesia. A subsequent cardiac MRI (CMRI) showed a dilated LV, severe LV systolic dysfunction, mild mitral regurgitation, a small pericardial effusion, and bilateral pleural effusion with no late gadolinium enhancement (LGE).

The patient was given furosemide, spironolactone, bisoprolol, valsartan, bromocriptine, and enoxaparin. After uneventful observation in the CICU and maternity ward, she was released 15 days post-admission in stable condition. Due to her low EF, she was fitted with a wearable cardioverter-defibrillator.

On follow-up one, two, and four months following discharge, the patient was fully compliant with the treatment

Table 1. Laboratory findings for three pregnant women with postpartum cardiomyopathy after recovery from COVID-19

Laboratory tests	Normal range	Patient 1	Patient 2	Patient 3
Hemoglobin	12–16 gr/dl	11.1	8.0	12.0
White blood cells	4.8–0.8 × 10^3/ul	6.2	10.7	7.0
Platelets	130–400 × 10^3/ul	158	227	249
Creatinine	0.51–0.95 mg/dl	0.55	0.7	0.54
Troponin T	< 13 ng/L	**24.56**	**25.17**	**17.8**
N-terminal-pro hormone brain natriuretic peptide	< 550 pg/ml	**4877**	227	**968**
C-reactive protein	< 5 mg/dl	4.59	3.95	2.88
Glutamic oxaloacetic transaminase	0–31 U/L	18	33	78
Glutamic pyruvic transaminase	0–34 U/L	9	21	76
Prothrombin time, international normalized ratio	< 1.1	0.83	1.02	1.01
Activated partial thromboplastin time	26–39 seconds	30.5	23.6	32.2
Fibrinogen	200–500 ng/dl	501	662	587
COVID-19 PCR (at admission)		Not detected	Not detected	–
COVID-19 IgG		Positive (at follow-up)	Negative (at follow-up)	Positive (before admission)
COVID-19 IgG architect	Index (s/CO) positive > 1.4		0.06 (at follow-up)	2.93 (before admission)
COVID-19 IgG liaison	< 12 AU/ml	38.3 (at follow-up)		14.1 (before admission)

COVID-19 = coronavirus disease 2019, IgG = immunoglobulin G, PCR = polymerase chain reaction

Bold indicates abnormal result

and reported dyspnea on exertion (NYHA 2). Repeated echocardiogram still showed an LVEF of 5–10%. An implantable cardioverter-defibrillator (ICD) was placed. Nine months after discharge LVEF was estimated as 20% and she reported a slight improvement of symptoms.

PATIENT 2

A previously healthy 39-year-old woman (gravida 10, para 7) presented with dyspnea and desaturation one day after an uneventful cesarean section (CS) under spinal anesthesia. She was a non-smoker and was not vaccinated for COVID-19. CS was performed electively due to a short interval from previous CS. A healthy female baby, appropriate for gestational age, was delivered. The patient had tested positive for COVID-19 by rtPCR 6 months prior to delivery, following mild symptoms of fatigue and myalgia. She reported dyspnea and cough over the week prior to admission. Physical examination revealed bi-basilar lung crackles. She had impaired fasting glucose.

Her postoperative temperature was 37°C, heart rate was 134 bpm, blood pressure was 120/80 mmHg, respiratory rate was 25 breaths per minute, and oxygen saturation was 92% in ambient air. Laboratory findings included an elevated high sensitivity troponin T level of 25 ng/L (normal 0–14 ng/l). All other laboratory values were within normal range [Table 1].

Electrocardiogram showed sinus tachycardia, with no ST-T wave abnormalities. A chest X-ray showed pulmonary congestion and enlargement of the cardiac silhouette. TTE demonstrated severe LV dysfunction, with global hypokinesis and an estimated LV EF of 5–10%, dilated left atrium (LA) with mild mitral regurgitation (MR), and a dilated inferior vena cava, suggestive of high right atrial (RA) pressure. CMRI showed a dilated LV and severe LV systolic dysfunction with no evidence of LGE.

The patient was admitted to the CICU and was given spironolactone, furosemide, ramipril, bisoprolol, bromocriptine, and enoxaparin. Her course was uneventful, dyspnea resolved and she was discharged 6 days after delivery. She was also fitted with a wearable cardioverter-defibrillator.

One month post-discharge, the patient was asymptomatic; however, a repeat TTE still showed severe LV systolic dysfunction. She was therefore kept on the wearable defibrillator. IgG antibodies for COVID-19 were negative. A repeat TTE 3 months later showed a slight improvement to an EF of 20%, and an ICD was placed. Nine months post-discharge EF was still an estimated 20% and she remained mildly symptomatic.

PATIENT 3

A 27-year-old woman (gravida 4, para 0) presented with dyspnea and orthopnea 4 days after vacuum-assisted delivery at term.

The patient was a healthcare worker, her medical history was noncontributory, and she was a non-smoker. She was not vaccinated for COVID-19. She was found positive for COVID-19 by rtPCR 4 months prior to admission, At the time she had been mildly symptomatic with cough, rhinorrhea, and diarrhea. Serological tests were positive for IgG 2 months prior to the current admission.

Physical examination was notable for bi-basilar diminished breath sounds and jugular vein distention. Her blood pressure was 114/76 mmHg, heart rate 120 bpm, saturation 97–98% in ambient air, and temperature 36.7°C. Laboratory investigation [Table 1] revealed only mildly elevated hepatocellular liver enzymes. Electrocardiogram showed sinus tachycardia, with QS waves in leads V1-3. Computed tomography in pulmonary angiogram protocol ruled out pulmonary embolism. Her TTE showed dilated LV, severe global LV systolic dysfunction, and EF of 35%. CMRI showed a dilated LV, severe LV dysfunction, mild MR, and a dilated LA with no myocardial LGE. The patient was given furosemide, ramipril, metoprolol, bromocriptine, and enoxaparin. Her course was uneventful with full resolution of symptoms. She was discharged 5 days after diagnosis.

On follow-up 1-month postpartum the patient complained of fatigue on mild exertion. TTE showed no change in EF with mild-moderate MR. Nine months post-discharge EF was still 15–20% and she remained symptomatic (NYHA 3) despite full compliance to medication.

DISCUSSION

We reported an unusual cluster of PPCM over a 2-month period (December 2020 to January 2021), among three patients who had confirmed COVID-19 infection earlier during their pregnancy.

The global prevalence of PPCM is variable, but it is a relatively rare complication of pregnancy. Therefore, the appearance of three 3 patients in our institution over the course of 2 months raised concern and warranted further investigation. Of note, during the whole of 2020 only two patients were diagnosed with PPCM at our institution, one of whom is included in this case series.

Peripartum cardiomyopathy is a rare complication of pregnancy. While the exact pathophysiology is unknown, endothelial damage has been implicated as a key factor.

Vasoinhibin, the 16 kDa derivative of prolactin, has been identified as a potential culprit in the pathophysiological mechanism of PPCM via endothelial modulation and dysfunction. It inhibits angiogenesis by inducing endothelial cell cycle arrest and apoptosis and inhibiting endothelial-cell migration. In addition, it attenuates the activation of endothelial nitric oxide synthase, thereby inhibiting vasodilatation, and enhances endothelial inflammation by promoting leukocyte adhesion to endothelial cells.

This theory is supported by the fact that prolactin (and therefore its derivatives) is present mainly in the late gestational and postpartum period, in correlation with the time of

onset of PPCM [8]. Furthermore, the dopamine-receptor agonist bromocriptine, which suppresses prolactin release, was found to prevent PPCM in animal models [9] and may be an effective treatment for PPCM [10].

Endothelial damage appears to be a main component of the pathophysiology of COVID-19 infection, as it appears a likely common pathophysiological pathway for the preexisting co-morbidities predisposing to severe COVID-19, such as cardiovascular disease and hypertension [11], for the adverse manifestations of COVID-19 infection and for significant end-organ damage [12].

COVID-19 infects human cells via the angiotensin converting enzyme 2 (ACE2), found most prominently in the lungs, but also in extrapulmonary tissues and cells, particularly in endothelial cells. Direct infection of endothelial cells by COVID-19 has been demonstrated both in vitro [13] and by pathological post-mortem evidence of viral infection of the endothelium and diffuse endothelial inflammation and apoptosis [14]. Additional endothelial damage is assumed to be mediated by oxidative stress caused by COVID-19 and by the overall systemic inflammatory response [11].

Endothelial inflammation results in endothelial dysfunction, which leads to a proinflammatory, procoagulant, and pro-aggregatory state; increased local oxidative stress; vasoconstriction; and organ ischemia [12].

Single case reports of COVID-19-positive pregnant patients complicated by cardiomyopathy have been published [15,16] as well as the possible overlap between symptoms of PPCM and COVID-19 infection [17]. A recent case series reported myocardial damage in 9.7% of pregnant patients hospitalized with symptomatic COVID-19 disease but did not state whether the diagnosis was COVID-19-related cardiovascular injury or PPCM [18]. Several studies assessed COVID-19 disease progression and complications in pregnant women and found no increase in the incidence of cardiomyopathy [19,20].

To the best of our knowledge, there has been no documentation of potential sequelae in pregnant post COVID-19 patients.

A large meta-analysis found that while pregnant COVID-19 positive patients were less likely to present with symptoms of fever and myalgia, they were more likely to need ICU admission and ventilation than non-pregnant women [20]. Mildly symptomatic pregnant patients may therefore warrant special attention.

Maternal risk factors for PPCM include older age, multiple pregnancies, and history of hypertension [3]. It is worth noting that in this case series, other than advanced maternal age in one patient, patients had no risk factors or predisposing conditions. In addition, all patients had asymptomatic or mildly symptomatic COVID-19 disease and were treated as outpatients with no reported sequelae or cardiac/respiratory symptoms. The most likely alternative diagnosis, residual COVID-19 myocarditis, was ruled out as all patients underwent CMRI that showed no evidence of myocarditis.

In addition to the apparent increase in incidence at our institute, a similar case of post-COVID-19 PPCM was reported by De Vita et al [21]. In their study, a 35-year-old primigravida with no risk factors presented one week after delivery with dyspnea. The authors initially ascribed the symptoms to COVID-19 acute infection, which was ruled out, as PCR was positive, but IgG antibodies were detected, with a weak presence of IgM antibodies. Further diagnostic testing led to the diagnosis of PPCM.

In the first wave of the COVID-19 pandemic, we witnessed an elevated incidence of PPCM among COVID-19 survivors. This phenomena has yet to repeat itself in later variants of COVID-19. It is worth noting that in January 2021 the COVID-19 vaccine became widely available to all pregnant women in Israel.

We hypothesized that some variants of COVID-19 may have predispose pregnant women to PPCM.

CONCLUSIONS

Our observation raises the possibility that a history of COVID-19 infection, even if only mildly symptomatic, predisposes pregnant women to PPCM. We hypothesized that residual endothelial damage/dysfunction in otherwise healthy pregnant patients who have recovered from COVID-19 could serve as a first hit, predisposing these patients to PPCM. Our preliminary hypothesis warrants additional confirmation in the form of larger cohorts and further research on the mechanism of both entities and their synchronic appearance. The reported unforeseen and abrupt increase of incidence in our institute warrants special attention and a high index of suspicion for PPCM among pregnant women who have recovered from COVID-19 and present with signs and symptoms compatible with heart failure.

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Everything you've learned in school as "obvious" becomes less and less obvious as you begin to study the universe. For example, there are no solids in the universe. There's not even a suggestion of a solid. There are no absolute continuums. There are no surfaces. There are no straight lines.

R. Buckminster Fuller (1895–1983, American architect, systems theorist, writer, designer, inventor, philosopher, and futurist

Capsule

Induction of bronchus-associated lymphoid tissue is an early life adaptation for promoting human B cell immunity

Infants and young children are more susceptible to common respiratory pathogens than adults but can fare better against novel pathogens like severe acute respiratory syndrome coronavirus 2. The mechanisms by which infants and young children mount effective immune responses to respiratory pathogens are unknown. Through investigation of lungs and lung-associated lymph nodes from infant and pediatric organ donors aged 0–13 years, **Matsumoto** and colleagues showed that bronchus-associated lymphoid tissue (BALT), containing B cell follicles, $CD4^+$ T cells and functionally active germinal centers, develop during infancy. BALT structures are prevalent around lung airways during the first 3 years of life, and their numbers decline through childhood coincident with the accumulation of memory T cells. Single-cell profiling and repertoire analysis reveals that early life lung B cells undergo differentiation, somatic hypermutation and immunoglobulin class switching and exhibit a more activated profile than lymph node B cells. Moreover, B cells in the lung and lung-associated lymph nodes generate biased antibody responses to multiple respiratory pathogens compared to circulating antibodies, which are mostly specific for vaccine antigens in the early years of life. Together, the findings provide evidence for BALT as an early life adaptation for mobilizing localized immune protection to the diverse respiratory challenges during this formative life stage.

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