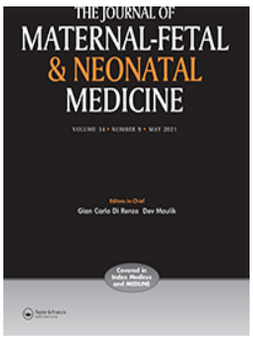

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Zahra Soleimani & Azam Soleimani

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SHORT REPORT

ADRS due to COVID-19 in midterm pregnancy: successful management with plasma transfusion and corticosteroids

Zahra Soleimani[a,b] and Azam Soleimani[c]

[a]Nephrology and Urology Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran; [b]Fetal Health Research Center, Hope Generatin Foundation, Tehran, Iran; [c]Cardiac Rehabilitation Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran

ABSTRACT

Background: Management of acute respiratory distress syndrome (ARDS) in pregnant women infected with new severe acute respiratory syndrome Corona virus 2 (SARS-CoV_2) is a challenging clinical task.

Case: A 30- year-old woman (gravid 3, parity 2) presented at her 21 and 2/7 weeks gestation (pre pregnancy BMI: 36.1 kg/m^2), with ARDS caused by SARS-CoV_2 infection. She received lopinavir/ritonavir and azithromycin as well as early methyl prednisolone therapy. Given the persistent hypoxemia despite oxygen therapy *via* non rebreather face mask (FiO_2:80%), convalescent plasma transfusion was administered that led to a mild clinical improvement as well as decrease in inflammatory markers. Growth of her fetus assessed by obstetric sonography was normal during hospital stay.

Conclusion: Judicious corticosteroid therapy along with convalescent plasma transfusion to suppress viremia and cytokine storm can lead to favorable outcome in the pregnant women with ARDS caused by SARS-CoV_2 infection without superimposed bacterial infection.

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KEYWORDS
Pregnancy; convalescent plasma transfusion; acute respiratory distress syndrome; SARS-CoV_2; corticosteroid

Introduction

In December 2019, a new coronavirus that was later named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV_2) led to epidemic in Wuhan. The disease (coronavirus disease 2019 or COVID-19) turned into pandemic rapidly and was recognized as an emergency situation worldwide by World Health Organization (WHO) [1]. Management of ARDS in the setting of COVID-19 pneumonia is a challenging task and multiple investigational antiviral and antiinflammatory agents have been used to treat it [2–4]. The mechanism of ARDS in this setting has been proposed to be viral related diffuse alveolar injury and immunological insult along with micro thrombus formation [5,6]. Convalescent plasma transfusion as an immune therapy has been reported to improve outcomes in SARS pneumonia, middle east respiratory syndrome (MERS) corona virus and influenza outbreaks as well as recent SARS-CoV_2 infection mainly by suppressing viremia [7–10]. Given these promising results, this treatment was approved by FDA for severe or life-threatening cases of COVID-19 [11]. Corticosteroid is a more challenging adjuvant therapy with apparently no significant benefit in mild COVID-19 disease in a small observational study [11]. On the other hand, pulses of corticosteroid has been reported with less oxygen requirement and more radiographic improvement in SARS pneumonia in 2003 [12]. Opposed to this promising report, a systematic review of corticosteroid therapy in severe ARDS caused by viral influenza pneumonia raised major concerns about increasing mortality, secondary infection and long duration of ICU stay [13]. In this study we report a midterm pregnant woman with severe ARDS due to confirmed COVID-19 that was managed with supportive care, corticosteroid therapy and plasma transfusion.

Case presentation

On 02 April 2020, a 30-year-old Iranian woman (gravid 3, parity 2) at 21 and 2/7 weeks of pregnancy with pre

CONTACT Azam Soleimani asoleimanii@gmail.com Cardiac Rehabilitation Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran

Supplemental data for this article can be accessed here.

Due to the urgent and developing nature of the topic, this paper was accepted after an expedited peer review process. For more information about the process, please refer to the Instructions for Authors.

pregnancy body mass index (BMI) of 36.1 kg/m^2 was referred to our center with complaint of myalgia, dyspnea, fever, chills and dry cough since 7 days. Also, the mentioned symptoms were accompanied by nausea, vomiting and chest pain on the day of admission. Her medical history was unremarkable except for prolonged history of night snoring and day time drowsiness. In the epidemiologic/social history, her husband was a confirmed case of COVID-19 with onset of symptoms one week earlier that was managed in an outpatient setting.

On admission, the patient was found fully conscious, ill with low grade fever (body temperature: 37.8° C), tachypnea (respiratory rate: 24/min) accompanied by hypoxemia (SpO_2 of 76% on room air). Meanwhile, an increased heart rate (HR: 98 bpm) with normal blood pressure (110/70 mmHg) was observed. Emergent bedside obstetric sonography showed a viable cephalic presented fetus with estimated gestational age of 21 weeks and fetal heart rate (FHR) of 144 bpm, posterior placenta and normal level of amniotic fluid.

Due to continuing hypoxemia (SPO_2 of 76–80%) despite nasal cannula oxygen therapy and respiratory distress, the patient was transferred to the intensive care unit (ICU). Standard supportive care, oxygen therapy *via* non rebreather face mask (FiO_2: 80%), prophylactic dose of enoxaparin (60 mg daily by subcutaneous injection) and supplementary obstetric medications were commenced. Standard 12 lead electrocardiogram and bedside transthoracic echocardiography were performed for evaluation of chest pain that showed no abnormality and quantitative troponin assay was reported in normal range. The results of laboratory investigations showed normal leukocyte count, lymphopenia, anemia, elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) despite normal procalcitonin and increased lactate dehydrogenase (LDH) levels. Creatine phosphokinase (CPK), liver enzymes, electrolytes and liver and renal function tests were within normal range.

Due to high clinical suspicion for COVID-19, lymphopenia with absolute lymphocyte count (ALC) of 602 per μL and several peripheral based patchy ground glass opacities in the chest CT scan (Supplementary Figure 1), qualitative RT-PCR assay of oropharyngeal swab for SARS-CoV_2 was performed that confirmed the SARS-CoV_2 infection. Lopinavir/ritonavir (400/100 mg per day) and azithromycin (500 mg loading then 250 mg/day) based on the local hospital protocol for the management of ARDS in the COVID-19 setting were started. The patient became afebrile several hours after admission and due to high load of lung involvement and no clinical and laboratory evidence of bacterial super infection, pulses of methylprednisolone (500 mg bid) for two days, followed by intravenous hydrocortisone in divided doses were administered.

Given low PaO_2/FIO_2 despite full supportive ICU care, antiviral therapy and early corticosteroid therapy, the patient became candidate for the hyperimmune plasma transfusion. Informed written consent was obtained from the patient and her family. The consent was also obtained from a recovered volunteer from COVID-19 who was asymptomatic for 15 days, negative SARS-CoV_2 oropharyngeal swab and negative blood samples for syphilis, hepatitis B, hepatitis C and HIV viruses after ABO blood group matching (approval ID project: IR.TMI.REC.1398.031).

Convalescent plasma transfusion was performed in two sessions (500 cc for each) on consecutive days of hospital day (HD) 10 and 11. Gradual modest increase in PaO_2/FIO_2 was observed as well as decrease in LDH, CRP and ESR levels together with obvious increase in ALC (Supplementary Table 1). Interleukin 6 (IL-6) was not available before transfusion but total immunoglobulin G (Ig G) showed modest increase several days after transfusion. For severe anemia (Hemoglobin $<$8 mg/dl), packed red cells were infused on HD17. The patient became candidate for bi level positive air pressure (BPAP) based on consultation of internist for sleep disorders, nocturnal hypoxemia and referred for evaluation of possible obesity hypoventilation syndrome (OHS) in the future. Fetal health assessment during hospital stay was well and repeat obstetric sonography showed normal fetal growth at discharge day on 02 May 2020 (HD 31). She was advised for regular obstetric and internist visits twice weekly.

The body temperature, PaO_2/FIO_2 and main laboratory data at admission and during hospital stay are presented in Supplementary Table 1. The time course of symptoms with given treatments and respiratory parameters are presented in Figures 1 and 2, respectively.

Discussion

Pregnant women have been reported to be more susceptible to SARS-CoV_2 infection with relatively good obstetric and neonatal outcomes in two recent systematic reviews [14–16]. Management of ARDS due to COVID-19 during pregnancy is challenging and an algorithm in this critical situation has been provided [17]. Several investigational therapies are proposed for

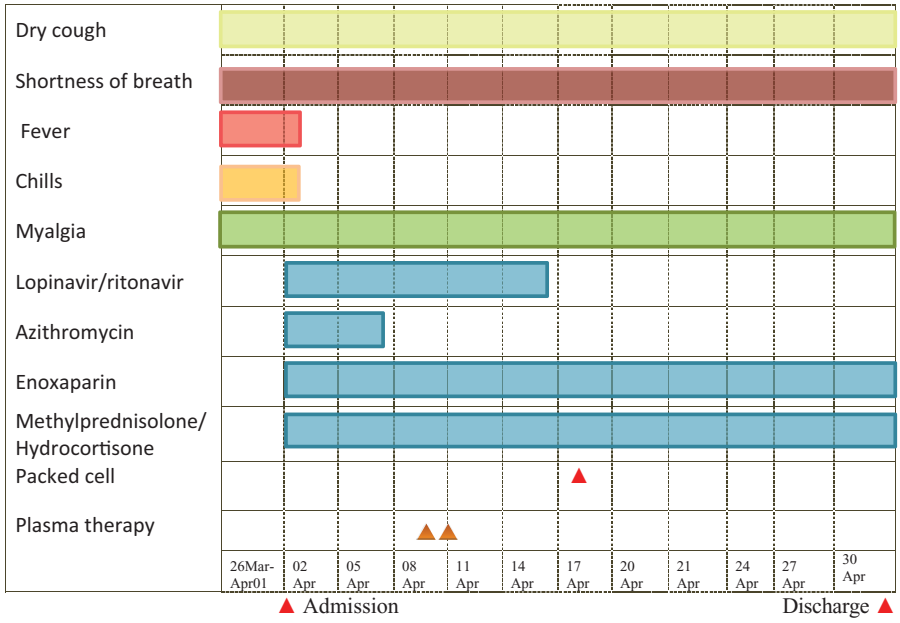

Figure 1. Timeline of symptoms and treatments given to the patient before admission and during hospital stay.

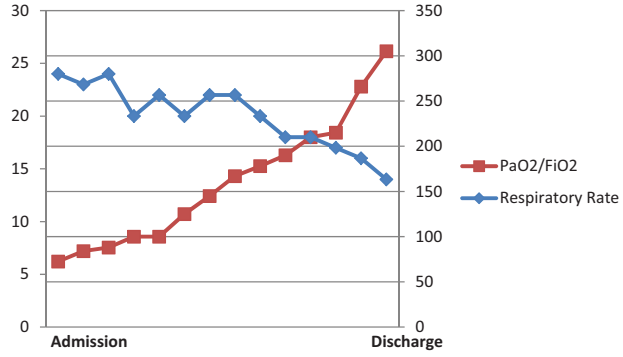

Figure 2. Timeline of respiratory parameters changes during hospital stay.

the management of ARDS due to COVID-19 [2–4]. In a case series of nine pregnant women with COVID19 disease (without severe pneumonia), oxygen therapy *via* nasal cannula and antibiotics were administered to all without corticosteroid and with final good maternal outcome [18]. In another series of seven pregnant women in Wuhan without ARDS, all received antibiotics and five also received methyl prednisolone with promising obstetric results [19].

This pregnant patient received two immunomodulatory treatments. First one was convalescent plasma transfusion that has been reported to improve outcomes in SARS pneumonia, MERS and influenza outbreaks as well as in five critically ill patients infected with new SARS-CoV_2 [7–10]. The last one small case series showed viral load reduction, resolved fever and extubation within 2 weeks in three of five patients after plasma immune therapy [10]. The mechanism may be related to decreased viral load and virus-mediated cellular destruction [20]. Patients with confirmed serious COVID-19 disease namely with "dyspnea, respiratory rate $\geq$ 30/min, $SaO_2 \leq 93\%$, $PaO_2/FIO_2 < 300$, and/or infiltrations in more than half of lung field within 24 to 48 h" or immediately life-threatening patients such as those with "respiratory failure, septic shock, and/or multiple organ dysfunction or failure" are eligible for hyper immune plasma therapy based on recent FDA recommendation [21].

Corticosteroid was the other immunomodulatory adjuvant treatment with significant controversy. In an observational study, 11 of 31 patients with COVID-19 had received corticosteroids. This treatment did not influence virus clearance time, duration of hospital stay or symptoms in patients with mild COVID-19 [11]. High dose pulses of corticosteroids have been associated with less oxygen requirement and more radiographic improvement in SARS pneumonia [12]. This treatment was reported to increase mortality, secondary infection and ICU stay length in a systematic review of ARDS caused by viral influenza pneumonia [13]. Given the role of the inflammatory response and cytokine storm in the pathophysiology of lung damage and ARDS, early administration of corticosteroid therapy in patients without bacterial infection might reduce inflammatory response and lung injury during the initial phase of infection [22].

This woman with severe ARDS became candidate for plasma transfusion after trying antiviral agents, antibiotic, and corticosteroid therapy. Although promising results including resolved lymphopenia, mild improvement in PaO_2/FIO_2 and decrease in most

inflammatory markers together with better fetus growth were achieved, it seems that management of OHS as well as viral and immune mediated established lung injury in this midterm pregnant woman needs long term multidisciplinary approach. Early administration of hyper immune plasma during viremia peak and judicious corticosteroid therapy to suppress cytokine storm may result in better clinical outcome in patients without superimposed bacterial infection. Although this is a case report with its inherent limitations, management of ARDS due to COVID-19 during pregnancy should be performed in a multidisciplinary time saving approach.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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