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Case Report

Challenges Associated with Convalescent Plasma Infusion Therapy During Pregnancy, a Case Report

Antonio Mastroianni[1]*, MD; Sonia Greco[1], MD; Luciana Chidichimo[1], MD; Maria Vittoria Mauro[2], MD; Francesca Greco[2], MD; Filippo Urso[3], MD; Valeria Vangeli[1], MD

[1]Infectious and Tropical Diseases Unit, "Annunziata" Hospital, Azienda Ospedaliera di Cosenza, Cosenza, Italy
[2]Microbiology and Virology Unit, "Annunziata" Hospital, Azienda Ospedaliera di Cosenza, Cosenza, Italy
[3]Hospital Pharmacy, "Annunziata" Hospital, Azienda Ospedaliera di Cosenza, Cosenza, Italy

Corresponding author:* Antonio Mastroianni, MD; Infectious and Tropical Diseases Unit, "Annunziata" Hub Hospital, Viale della Repubblica s.n.c. 87100 Cosenza, Italy. **Tel: +39-984-681833; **Email:** antoniomastroianni@yahoo.it

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Abstract

Introduction: The Covid-19 pandemic has so far been characterized by significant morbidity and a high mortality rate worldwide. People who are frail due to age and / or the presence of comorbidities, including pregnant women, are exposed to a greater risk of developing a very serious disease. However, only recently, certain experimental studies have focused on the role of anti-Covid-19 drugs during pregnancy. Convalescent plasma (CP), derived from the people who recover from Covid-19, can represent an interesting therapeutic option for improving the antiviral immune response, owing to its specific neutralizing content and different immune mediators against SarsCov-2. It can also improve the survival of the patients who are diagnosed with the disease early and treated in the primary stages of the disease.
Case Presentation: We reported the case of a pregnant patient safely treated with CP at our hospital and conducted a comprehensive literature search using extensive database for similar case reports published from February 12, 2020 to May 31, 2021.
Conclusions: An extensive literature search documented the publication of a limited number of case reports concerning Covid-19 hyperimmune plasma treatment (CPT) during pregnancy. The available results are not homogeneous; however, a very early use of CPT may possibly be effective in pregnancy. The evolution of Covid-19-related pneumonia, due to a reduction in both viremia and the concentration of proinflammatory cytokines, can be positively influenced by CPT, together with the standards of care treatment.

Keywords: COVID-19, Plasma, Pregnancy, Pneumonia

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1. Introduction

The COVID-19 pandemic has to date involved about 49,000 pregnant women in the United States. The information reported by the largest databases lead experts to believe that pregnant women may contract a more severe pneumonia. An updated analysis of 400,000 symptomatic patients showed that pregnant patients may develop severe hypoxia, or failing noninvasive ventilation. Pregnant women hospitalized for COVID-19 may have high rates of preeclampsia and cesarean delivery compared with the general population, with perinatal mortality of 10%.

Epidemiological data has documented an increase in COVID-19 cases in women during various stages of the pandemic worldwide. Currently, the information on the efficacy of the therapies available in pregnancy is not so extensive because only a limited number of randomized studies have been carried out on pregnant patients. Our analysis aimed to share the very encouraging results of the use of CPT in a pregnant patient at our hospital, with a brief discussion of the possible perspectives for the use of CPT in pregnancy derived from published case reports, to stimulate a new clinical research interest on this topic.

2. Case Presentation

A 31-year-old Somalian pregnant woman at 24th week of gestation (Gravida 2, Para 1), who had been living in Italy for five years, presented at the Emergency Department of "Annunziata" Hospital in Cosenza on November 9th, 2020, 04.00 A.M. presenting with fever and dyspnea. She was transferred to the Infectious Diseases and Tropical Diseases Unit with suspicion of COVID-19. The diagnostic test, based on real time polymerase chain reaction (qRT-PCR), from a nasopharyngeal swab, was positive for SARS-CoV-2: ct gene E=22/45, ct gene N=25/45, ct gene RdRp=25/45. She was diagnosed with COVID-19 pneumonia and acute hypoxemic respiratory failure. At admission, her temperature was 38.2°C, her pulse rate was 106 per minute, and her blood pressure was 125/75 mm Hg. She

was noted to be hypoxic to 88% breathing ambient air and was tachypneic to 36 breaths/minute. She required intravenous fluids, and supplemental oxygen by nasal cannula at a flow of 6 L/min, with the goal of oxygen saturation >95% to support adequate fetal oxygenation. Ultrasound was performed, showing active fetal movements, normal fetal morphology, and normal amniotic fluid quantity. In 2016, she had a normal vaginal delivery in Italy. Her medical history was normal. The body mass index on admission to prenatal care was 47 kg/m 2 with a length of 163 centimetres (cm) and weight of 126 kg (kg), and her pregnancy had been without complications. On admission, the patient described a five-day history of shortness of breath, dry cough, myalgia, nausea, abdominal pain, dyarrhea, and fever. She had a great deal of abdominal pain on admission, but the surgeon did not find any signs of an acute abdominal event. Obstetric examination, including cardio-tocography (CTG) and an abdominal ultrasound, showed no significant evidence of abnormalities. Fetal ultrasound examination was normal with normal doppler flows.

A computerized tomography chest scan revealed multiple and extended ground-glass areas, mainly with sub-pleuric distribution, some of which were associated with thickness of the interlobular interstitium and parenchymal consolidations in the lower lobes. Common trunk of the pulmonary artery presented a maximum diameter of about 29 mm. CT chest scan framework was compatible with COVID-19 interstitial pneumonitis.

Laboratory tests revealed significantly increased inflammatory markers: CRP 390 mg/L, procalcitonin 81 ng/mL, leucocytosis WBC>20 G/l. Moreover, peripheral blood count demonstrated microcytic anaemia with low iron levels and thrombocytopenia 90 g/L, vitamin D 15 ng/mL (20-60), IL-6 38.6 pg/mL, and d-dimer 1.95 mg/L. The patient received 2 units of convalescent plasma collected from an ABO-compatible donor who had recovered from COVID-19, with a SARS-CoV-2–specific antibody (IgG) binding titer greater than 1:1000 (end point dilution titer, by enzyme-linked immunosorbent assay[ELISA]) and a neutralization titer greater than 40 (end point dilution titer). The first CP unit was transfused on day one and the second unit was transfused on the following day, in addition to standard of care. There was no contraindication to transfusion (severe volume overload, history of severe allergic reaction to blood products), as judged by the physicians. The patient also received a standard-of-care treatment, including dexamethasone, ceftriaxone, and enoxaparin.

The patient underwent a series of safety, efficacy, and laboratory evaluations on a daily basis while hospitalized, and clinical status assessment was made using the National Early Warning Score (NEWS).

Hypoxia improved with supplemental oxygen by nasal cannula. After 7 days, the patient's evolution was marked by a full clinical recovery; her last blood panel showed a decreased serum level of CRP to 37.42 mg/L with a white blood cell count of 10.16×10 9/L. Following a full recovery from COVID-19, the patient had an uncomplicated vaginal delivery at term.

3. Discussion

The CP obtained from patients recovered from COVID-19 can represent a valid therapeutic option to transfer an effective passive immunity against Sars-Cov-2 infection and faster viral clearance, as it has been previously documented in patients with other viral diseases (Ebola virus, Junin virus, H1N1, and H5N1). CP acts through neutralizing viral constituents, antibody-dependent cellular cytotoxicity, and phagocytosis, along with controlling an overactive immune system.

It has been suggested that earlier administration of CP yields a better outcome; as a matter of fact, the time of initiating the CP therapy may be an important factor affecting its efficacy.

A substantial increase in the spread of new SARS-CoV-2 variants has raised concerns; however, experts have suggested that patients recovered from COVID-19 variant infection may develop effective neutralizing antibodies to these strains. There are currently only two ongoing randomized controlled trials evaluating the effects of CP use in pregnant women (ClinicalTrials.gov Identifier: NCT04388527, NCT04397757, 2020).

Currently, the literature does not always suggest concordant results of CPT on the prognosis and clinical improvement of hospitalized patients although the safety of CPT has been confirmed. The results of various papers have suggested that pregnancy can be considered as a state characterized by a modulated immune response that could increase the exposure to risk conditions, including some infections, especially when an infectious diseases is acquired in the third quarter of pregnancy. During pregnancy, the immune response is characterized by a physiological functional modification in the cellular effectors, particularly in reference to the humoral, T-cellular response, and the release of some cytokines (↑ IL-4 and IL10, ↓IL-2,

and IFN-γ), specifically in the third trimester. Real life clinical medicine has shown healthcare professionals the high risk that pregnant women can experience in case of SarsCov-2 infection, including the possibility of maternal mortality, preeclampsia, and stillbirth risks.

The guideline group agreed there is some overall uncertainty about the ineffectiveness of CPT in patients with COVID-19; however, they do not rule out that CPT may be effective in selected patients if given early (preferably within three days of diagnosis) and if CP contains high neutralizing titers (1).

Furthermore, it is important to identify its efficacy in unique subpopulations of patients, such as patients who are immunosuppressed due to chronic diseases, or from therapies that cause immunoglobulin deficiencies; pregnant patients are also included in these subgroups of frail patients.

We analyzed the studies published in the literature through the PubMed database in order to investigate the characteristics described by other authors for similar cases, in the period from February 12, 2020 to May 31, 2021. There were four reports on Mers-CoV and 5 SARS-CoV describing CPT during pregnancy. A 28-year-old pregnant woman with SARS was treated with two bags of 250 ml of CP; there was an impressive record of recovery in this case (2). In a different report, six out of eight CP-treated pregnant women in Africa survived (3). In a phase II study, two pregnant women were enrolled so that the safety and efficacy of influenza CPT could be assessed (4).

We analyzed the data provided by the current literature, mainly using the PubMed database, to evaluate the experiences regarding the use of a CPT for the treatment of diseases caused by coronavirus in pregnancy. There were 12 COVID-19 reports describing CP use in pregnancy (5-7). An analysis of the previous reports published in the literature showed heterogeneous data. Unfortunately, most of the reports do not indicate the titer of neutralizing antibodies in each of the plasma units administered, which limits the judgment on the efficacy of the plasma units used. The dosage of CP used appears to be not homogeneous. Additionally, the timing of the administration did not follow a precise schedule although the limited data available have also confirmed that in these case series, it is advisable to administer CP as early as possible.

All pregnant patients transfused with CP had no adverse events. The majority of patients presented with severe ARDS that required mechanical ventilation. The patients described in some reports presented a dramatic response immediately after plasma administration (5). In other reports, the CPT seems to have determined only a mild clinical improvement and / or in the oxygen therapy requirements. Meanwhile, in some papers, there is evidence of a mild clinical response (6), or no evidence of effective CPT was highlighted (7). In their report, Grisolia and colleagues (5) described clinical improvement after administration of a second unit of CP in a 29-year-old gravida who developed an acute respiratory failure. A recent Cochrane review argued that the use of CPT may not affect mortality and / or improve the clinical condition of hospitalized patients (8).

Currently, only one RCT has documented an influence on the progression of COVID-19 with the early use of CPT containing a high neutralizing titer in elderly patients with a non-severe disease (9). Publication of further studies might resolve some of the uncertainties around CPT beacuse the current reports cannot state with absolute certainty whether CTP may be the cause of risky conditions for the health status of critically ill patients. An extensive program on the use of CPT has shown only a low percentage of adverse events among the 22,000 patients treated (10).

Our experiment documented an evident success, especially in our patient who, within 24 hours of CP transfusion, presented an important clinical improvement, no longer requiring additional oxygen supplements and no longer having fever. The second patient also presented a favorable course; nonetheless, she was also treated with intravenous remdesivir, which may have helped to improve her clinical conditions.

4. Conclusions

The administration of CPT may be considered as an important therapeutic option, without adverse effects on pregnant patients even though the results of larger randomized studies are needed. It is advisable to utilize plasma units with a high concentration of specific immunoglobulins and to use the CPT as soon as possible in order to reach the best clinical and virological outcome. In order to increase the effectiveness of CPT, it is likely that an antiviral treatment should also be used. CPT, as a supportive treatment in pregnant COVID-19 women, has not been systematically evaluated in large clinical trials. Nevertheless, it is important to stress the merits of its use in the immediate onset of the disease in pregnant patients with severe pneumonia through a

reduction in the viraemic titer and the concentration of pro-inflammatory cytokines, in combination with other drugs characterized by antiviral activity, anti-inflammatory properties, and anticoagulant characteristics.

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