Review Article

COVID-19 and pregnancy: a narrative review on the use of convalescent plasma

Gianpaolo Grisolia[1], Alessia Pinto[2], Giorgia Pavan[2], Martina Capuzzo[3], Massimo Franchini[4]

[1]Obstetrics and Gynecology Unit, Carlo Poma Hospital, Mantova, Italy; [2]Department of Surgery, Odontostomatology and Maternal and Child Health, University of Verona, Verona, Italy; [3]Department of Medical and Surgical Sciences for Mother, Child and Adult, University of Modena and Reggio Emilia, Modena, Italy; [4]Department of Hematology and Transfusion Medicine, Carlo Poma Hospital, Mantova, Italy

Contributions: (I) Conception and design: G Grisolia, M Franchini; (II) Administrative support: M Franchini; (III) Provision of study materials or patients: G Pavan; (IV) Collection and assembly of data: M Capuzzo; (V) Data analysis and interpretation: A Pinto; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Massimo Franchini, MD. Department of Hematology and Transfusion Medicine, Carlo Poma Hospital, Mantova, Italy.
Email: massimo.franchini@asst-mantova.it.

Abstract: The emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic is a global concern, considering both the severity of the disease, with a high mortality rate compared to that of other influenza-like viral illnesses, and the lack of a specific, effective treatment. Pregnant women with coronavirus disease 2019 (COVID-19) represent a further challenge for clinicians. Indeed, although the majority of them are asymptomatic or their SARS-CoV-2 disease has a mild to moderate course, in some cases this viral infection is accompanied by severe respiratory symptoms. In such a critical clinical setting, the already limited therapeutic armamentarium available for COVID-19 patients is further restricted in pregnant women because of the risk of fetal toxicity especially during the first trimester of gestation. Among the treatment options, the use of convalescent plasma has gained increasing interest from investigators in pregnant women, given the initial positive reports on safety and efficacy aspects of this treatment in critically ill COVID-19 patients. However, the literature data are scanty and almost limited to single case reports, considering that pregnant women are usually excluded from trials on convalescent plasma. In this narrative review, we will critically discuss the current literature evidence on the use of hyperimmune plasma during pregnancies complicated by COVID-19.

Keywords: Coronavirus disease 2019 (COVID-19); severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); pregnancy; convalescent plasma

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Introduction

The year 2020 has been dramatically revolutionized by the global spread of a viral pandemic caused by a novel coronavirus [named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) for its similarity to the coronavirus which caused SARS epidemic in 2003], with the infamously well-known feral consequences. At the time we are writing, more than 1,300,000 people have died from coronavirus disease 2019 (COVID-19) worldwide and circa 16 million of people are currently infected (1).

It has been clear since the beginning of the outbreak that severe forms of the disease could dramatically affect also young patients without comorbidities, including pregnant women (2,3). Pneumonia, which represents the main complication of COVID-19, represents the most important non-obstetric infection in pregnancy, being a significant cause of morbidity and mortality (4). A quarter of the cases of pneumonia in pregnancy needs intensive care treatment with mechanical ventilation (5), and the most frequent

complications which can occur are premature rupture of the membranes (PROM), intrauterine growth restriction (IUGR), preterm labor, intrauterine and neonatal death can occur (6,7). The existing literature on SARS-CoV-2 infection in pregnancy shows similar symptoms for pregnant and non-pregnant patients: common symptoms included fever and cough, whereas less common symptoms were myalgia, malaise, sore throat, diarrhea, and shortness of breath (8). Intrauterine vertical transmission has been excluded (9). At present, there is no evidence of an increased risk of abortion in relation to COVID-19, nonetheless the infection is reported to be associated with a relatively higher rate of preterm birth, preeclampsia, caesarean section, and perinatal death (10).

An intense debate has opened on therapeutic possibilities for COVID-19 infection in pregnancy. Management of the disease is essentially driven by the symptoms. Asymptomatic or pauci-symptomatic women do not require inpatient care or medications, and simply need monitoring of respiratory function for up to 2 weeks for evidence of deterioration. Antiviral treatments such as remdesivir and medications such as hydroxychloroquine and azithromycin have been used but their use is currently not recommended (11). Given the hyperactive inflammatory effects of SARS-CoV-2, agents that modulate the immune response are being explored as adjunctive treatments for the management of moderate to critical illness (12). These agents include human blood-derived products from individuals who have recovered from the infection, such as convalescent plasma and hyperimmune immunoglobulin products. This narrative review is focused on the current evidence of the clinical use of convalescent plasma during pregnancy. We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/aob-2020-cp-02).

Search methods

For this narrative review we analyzed the medical literature for published articles on the use of convalescent plasma in pregnant women with SARS-CoV-2 infection. The Medline and PubMed electronic database was searched for publications during the period January 2020 to November 2020 using English language as a restriction. The Medical Subject Heading and keywords used were: “novel coronavirus disease”, “COVID-19”, “SARS-CoV-2”, “acute respiratory distress syndrome”, “pregnancy”, “pregnant women”, “delivery”, “fetal”, “neonatal”, “obstetric”, “maternal”, “convalescent plasma”, “hyperimmune plasma”, “hyperimmune serum”. We also screened the reference lists of the most relevant review articles for additional studies not captured in our initial literature search.

Use of convalescent plasma during pregnancy

The clinical course of COVID-19 infection during pregnancy shows no substantial differences with the general population as observed in the limited available studies (3,13). However, some studies have shown a worse clinical course in pregnant women (14,15). In a living systematic review by Allotey and colleagues (16) on maternal and perinatal outcomes of COVID-19 and pregnancy, increased maternal age (>35 years), obesity, hypertension and pre-existing diabetes were associated with a severe COVID-19.

To date, there is limited data about the effectiveness of therapies used for COVID-19, particularly in pregnant women. Evidences show that convalescent plasma from patients who have recovered from viral infections was used as a treatment without the occurrence of severe adverse events in general population (17). The main obstacle to the use of convalescent plasma is its limited availability, which is closely linked to the presence of recovered donors and to collection procedures. Convalescent plasma was used in Guinea for Ebola virus disease in pregnant women, among which an increased risk of severe illness and death, with mortality rates from 74–100% has been demonstrated. Six over eight women who were treated survived and didn’t develop complications (18).

Pregnancy is not a contraindication to blood component transfusion. Regarding COVID-19 infection, literature reports six cases of pregnancies managed using convalescent plasma (19-24). In a single report, convalescent plasma was administered in a pregnant woman at 35+2 weeks of pregnancy with survival of the mother but fetal death for endouterine asphyxia (19). In three case reports, convalescent plasma therapy in association with antiviral drugs (remdesivir, lopinavir/ritonavir) successfully managed critically ill obstetric patients at very early gestational age (20,23,24). While in two of these cases neonatal outcome is unknown (20,24), in the remaining case it has been reported the birth of a full term growth restricted fetus (23). In another case report a pregnant patient at 24+2 weeks of gestation was treated with convalescent plasma without antiviral drugs, with a favorable outcome for both mother and fetus (21). We also report the case of a woman with a twin pregnancy at 36 weeks with COVID-19 and

pulmonary involvement, effectively treated with favipiravir and convalescent plasma after cesarean section (22). In some cases convalescent plasma has been used as a last resort to improve the survival rate (19,23), whereas in other cases the infusion occurred when the disease had not yet reached the peak of severity (20,21,24). All in all, although very limited, these data seem to suggest the safety and the potential beneficial effect of convalescent plasma for both maternal and fetal outcome during severe COVID-19 and deserve to be further explored in adequately powered trials.

While treating infected pregnant women it should always be kept in mind that there are two patients, mother and fetus. Maternal hypoxia causes placental vasoconstriction by reducing placental flow and fetal oxygenation. Despite limited human data, animal models suggest that acute maternal hypoxia causes adverse effects on the fetus. In the clinical practice, while treating pregnant women, the aim is to maintain oxygen saturation at least at 95% and oxygen partial pressure (PaO2) at least at 70 mmHg (25,26). The primary goal should be that a positive pregnant patient with COVID-19 remains asymptomatic or, if symptomatic, to avoid progression to ARDS. This is particularly important in the management of pregnancy between 23 and 32 weeks where an emergency delivery will induce severe prematurity in the infant. Pregnant women with COVID-19 critical disease show a high rate of preterm birth (2,10). In the available studies, when specified, the main indication for delivery was the maternal condition (1). In addition, delivery route was cesarean section for the majority of cases (3). The result is a high rate of preterm cesarean sections with all the related maternal known risks (27-29); therefore, it is not already known whether a cesarean section could affect the clinical course of the disease.

Conclusions

Currently, information about the use of convalescent plasma in pregnant patients with COVID-19 is limited to few case reports and concomitant use of other medications may confound the evaluation of plasma effectiveness. In addition, the perinatal outcome of some of pregnancies mentioned above is currently unknown. There are several randomized clinical ongoing trials regarding the use of convalescent plasma in patients with COVID-19, in many of which pregnancy is not considered as an exclusion criterion (30).

In conclusion, further studies on plasma administration during pregnancy should be carried out in order to demonstrate the effectiveness of plasma as a possible therapeutic option in critically ill COVID-19 patients, especially in a gestational age of severe prematurity, with the aim to prolong the course of pregnancy as long as possible.

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