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MINIREVIEWS

Antenatal corticosteroids in COVID-19 perspective

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Abstract

The aim of this manuscript is to discuss the practice of antenatal corticosteroids administration for fetal maturation in severe acute respiratory syndrome coronavirus 2 positive pregnant women. Recent high-quality evidence supports the use of dexamethasone in the treatment of hospitalized patients with coronavirus disease 2019 (COVID-19). Randomized disease outcome data have identified an association between disease stage and treatment outcome. In contrast to patients with more severe forms who benefit from dexamethasone, patients with mild disease do not appear to improve and may even be harmed by this treatment. Therefore, indiscriminate usage of fluorinated corticosteroids for fetal maturation, regardless of disease trajectory, is unadvisable. Obstetrical care needs to be adjusted during the COVID-19 pandemic with careful attention paid to candidate selection and risk stratification.

Key Words: Antenatal corticosteroids; COVID-19; Dexamethasone; Pregnancy; SARS-CoV-2; Preterm delivery

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Core Tip: Evidence from the randomized evaluation of coronavirus disease 2019 therapy trial supports the use of dexamethasone in the setting of maternal respiratory disease requiring either invasive mechanical ventilation or oxygen alone but not for patients receiving no respiratory support. Dexamethasone will have the added benefit of promoting fetal maturity at < 34 wk gestation in cases at risk for preterm delivery. Fetal indications for antenatal corticosteroids should be limited to obstetrical indications resulting in a high probability of preterm delivery and indiscriminate usage of fluorinated corticosteroids for fetal maturation, regardless of disease stage, is unadvisable.

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INTRODUCTION

Early in the pandemic, the use of corticosteroids as a means of immune-modulatory therapy among patients with coronavirus disease 2019 (COVID-19) was considered relatively contraindicated based on limited data suggesting adverse outcomes in the previous coronavirus outbreaks (severe acute respiratory syndrome coronavirus 1 and Middle East respiratory syndrome coronavirus)[1]. This position was supported by a 2019 meta-analysis of 6548 patients with influenza pneumonia, demonstrating that the use of corticosteroids was associated with increased mortality and duration of intensive care unit stay[2].

Notwithstanding such concerns, during the current severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, methylprednisolone, and less frequently dexamethasone (DXM), have been used globally in as great as 50% of patients with COVID-19[3].A resultant systematic review on the role of corticosteroids in the management of COVID-19 identified 5 studies (4 retrospective and 1 prospective study) with mixed findings: 3 studies have shown benefit, while 2 studies failed to demonstrate benefit with one suggesting harm from a sub-study[3].

Renewed interest in the use of corticosteroid adjunct therapy in COVID-19 followed the recent publication of the randomized evaluation of COVID-19 therapy (RECOVERY) trial, which presented preliminary compelling evidence of benefit with the use of DXM[4]. The American College of Obstetricians and Gynecologists (ACOG) and several other national and international organizations shortly thereafter reversed their initial recommendations, now prioritizing DXM as the steroid of choice in pregnant women with COVID-19. It is worth shining a light on the RECOVERY trial with a critical lens at the available data emerging from it.

BENEFICIAL EFFECT OF CORTICOSTEROIDS IS DEPENDENT ON PATIENT SELECTION

The RECOVERY trial, which is still ongoing in the United Kingdom, is an open-label, multi-center, randomized controlled study, with several arms. The study design is pragmatic, and allows for the potential differentiation between several therapeutic agents (DXM, hydroxychloroquine, lopinavir-ritonavir, azithromycin, tocilizumab, and convalescent plasma) in hospitalized patients with COVID-19. In the arm assigned to DXM treatment (6 mg daily, orally or intravenously for 10 days, or until hospital discharge), a total of 2104 patients were randomized to receive the corticosteroid and they were compared with 4324 patients randomized to the standard of care. The primary outcome (28-d mortality) was significantly reduced from 25.7% to 22.9% (rate ratio 0.83, 95%CI: 0.75-0.93; $P < 0.001$). The therapeutic effect was directly proportional to the severity of illness. In patients receiving mechanical ventilation, mortality was reduced by about one third (29.3% *vs* 41.4%; rate ratio 0.64; 95%CI: 0.51-0.81) while in those receiving oxygen without invasive mechanical ventilation, the reduction in mortality was about one fifth (23.3% *vs* 26.2%; rate ratio 0.82; 95%CI: 0.72-0.94). A striking finding occurred among patients who did not require any respiratory support to maintain adequate oxygen saturation at the time of randomization; among them, mortality was 17.8% with DXM *vs* 14.0% without DXM (non-significant difference with a rate ratio 1.19; 95%CI: 0.91-1.55). Other small observational studies have also shown a lack of benefit with corticosteroids among patients with mild COVID-19[5], and we believe that the trend towards harm with the absence of benefit warrants ongoing consideration and caution with use. Specifically, while we concur that the RECOVERY trial supports the use of DXM among hospitalized COVID-19 patients with moderate to severe respiratory disease (*i.e.*, requiring mechanical ventilation or oxygen therapy), inferring benefit in the absence of harm for patients with mild or asymptomatic disease would be premature. Our perspective is shared by the authors of the RECOVERY trial themselves, as they stated that "It is likely that the beneficial effect of glucocorticoids…is dependent on a selection of the right dose, at the right time, in the

right patient"[4].Other guiding entities have reiterated this point, including the expert consensus opinion of the Chinese Thoracic Society that stated: "Corticosteroid treatment is a double-edged sword…we oppose liberal use of corticosteroids"[6].The take-home message from the frontlines is that appropriate and judicious patient selection for potential benefit is key[4],and that corticosteroids should not be administered indiscriminately[7] nor in the outpatient setting[8].

Recognizing that every day brings better understanding of the biologic underpinnings to COVID-19, it is generally accepted that while the viral dynamics are predictable, there is marked heterogeneity among patients as to if and when they will experience clinical disease[9]. Administering DXM during early phases of disease hallmarked by viral replication may actually impair the host's functional immune response, including dampening of innate immunity, disrupting T-cell dependent initiation of humoral immunity and inhibiting requisite cognate interactions with antigen presenting cells[9,10].The net effect of disrupting initiation of functional immunity includes the potential to not only increase the circulating viral load and promote transmissibility, but also hindrance of crucial interactions within the immune system necessary for the production of lasting immunity (inclusive of the production of neutralizing antibodies, critical for immunity on re-exposure). This is not merely a theoretical consideration, as early corticosteroid administration was shown to delay viral clearance and result in higher plasma viral loads in the SARS epidemic[11].

With respect to disease severity and clinical heterogeneity, we know that COVID-19 not only presents with cardiopulmonary symptoms ranging from mild to severe but, in a subgroup of patients, is also associated with systemic autoimmune inflammation as evidenced by elevated inflammatory markers (C-reactive protein, ferritin, D-dimer, IL-1, IL-2, IL-6, IL-7, tumor necrosis factor α, granulocyte-macrophage colony-stimulating factor, macrophage inflammatory protein 1-α; the so-called "cytokine storm")[12].This dysregulated systemic inflammation is thought to be a key contributor to the COVID-19-associated fatality rate and will typically lag behind active viral replication[13].In contrast to periods with high viral replication, it is both logical and evidence-based to anticipate that corticosteroids would be of benefit amongst this subset of patients in their course of clinically evident disease. For the better part of 6 decades we have understood that corticosteroids downregulate proinflammatory cytokine transcription, consequently preventing an over-extended cytokine response and accelerating the resolution of pulmonary and systemic inflammation[14,15].

In keeping with the RECOVERY findings, DXM, a widely available and inexpensive therapeutic agent, is recommended by the World Health Organization for the treatment of patients with severe and critical COVID-19, but not in the treatment of patients with non-severe COVID-19 (www.who.int/publications/i/item/therapeutics-and-covid-19-living-guideline). Similarly, the National Institutes of Health in the US recommend against using DXM in patients with COVID-19 who do not require supplemental oxygen (www.covid19treatmentguidelines.nih.gov).

BENEFICIAL EFFECT OF CORTICOSTEROIDS IS DEPENDENT ON THE DOSE

An emerging and common pattern arising from the aggregated analysis of the experience with the use of corticosteroids in the management of COVID-19 patients is the potential for benefit with low dose corticosteroids when compared to high dose protocols[3].It is considered that a low dose of corticosteroids should not exceed 1 mg/kg per day of methylprednisolone or equivalent (Table 1). The dose of DXM used in the RECOVERY trial (6mg daily) was carefully selected to be in the low dosage range. Although high doses may exert a more rapid anti-inflammatory effect, the associated risks of secondary infections, hyperglycemia, or psychosis are also increased. High dose corticosteroids concomitantly increase the neutrophil/lymphocyte ratio and D-dimer levels. The WAYFARER Study has identified an increased risk of thromboembolism with high doses of corticosteroids, a very concerning trend since COVID-19 itself may increase the risk of coagulopathy[16].

BENEFICIAL EFFECT OF CORTICOSTEROIDS IN PREGNANCY

In the RECOVERY trial, a small number of pregnant women were enrolled, but instead

Table 1 Synthetic corticosteroids – comparative chart

Compound	Equivalent dose	Anti-inflammatory activity	Mineralocorticoid activity
Dexamethasone	0.8 mg	25	0
Betamethasone	0.8 mg	25	0
Cortisone	25 mg	0.8	0.8
Hydrocortisone	20 mg	1	1
Prednisone	5 mg	4	0.6
Prednisolone	5 mg	4	0.6
Methylprednisolone	4 mg	5	0.25

of DXM they received either prednisolone or hydrocortisone at an equivalent dosage. Prednisolone, which is inactivated by placental 17alpha-hydroxylase, as well as hydrocortisone which is rapidly inactivated by fetal enzymes, are not expected to have fetal effects and the treatment was intended exclusively for maternal benefit. Only 6 pregnant women were such treated and their number is too small to allow for valid interpretations. With the same goal, of limiting the fetal exposure, methylprednisolone, which has very limited transplacental passage, has been recommended by some to replace at least partially the DXM in the treatment of pregnant women[17].The use of methylprednisolone in COVID-19 has been studied in several small controlled trials, with a mixture of positive and negative results[18-21].Given that the sample size of many of these trials was insufficient to assess efficacy, it is reasonable to conclude that the evidence to support the use of methylprednisolone is not as robust as that demonstrated for DXM. The effectiveness of methylprednisolone or lack thereof has not been established yet and several randomized trials are currently underway or in development. Moreover, DXM may be preferable to methylprednisolone because of its higher anti-inflammatory properties and lower mineralocorticoid activity (Table 1), being therefore less likely to cause sodium and fluid retention, a concern in these critically ill patients.

The RECOVERY trial did not address the administration of antenatal corticosteroids for the purpose of fetal maturation among pregnant women with COVID-19 and it is our opinion that ACOG (www.acog.org/clinical-information/physician-faqs/covid-19-faqs-for-ob-gyns-obstetrics) and a number of other guiding bodies did not exercise sufficient caution when extrapolating the results of the RECOVERY trial to the pregnant population. Evidence from the RECOVERY trial supports the use of DXM in the setting of maternal respiratory disease, and will have the added benefit of promotion of fetal maturity at < 34 wk gestation in cases at risk for preterm delivery. Even in cases not expected to deliver prematurely, given the potential benefit of decreased maternal mortality, it is ethically acceptable to expose the fetus to a short course of low-dose DXM. In consideration here, however, is the maternal risk of morbidity and death following corticosteroid exposure in asymptomatic or mild COVID-19 cases. Indeed, the great majority of pregnant women infected with SARS-CoV-2 are not candidates for DXM by virtue of failing to meet RECOVERY criteria[22]. In a single institution study from the United States, 95% of pregnant women infected with SARS-CoV-2 remained asymptomatic or had mild disease[23].The use of antenatal corticosteroids for fetal benefit should be judiciously considered and weighed against any potential harm to the pregnant patient based on her clinical status. It has been said that in a pandemic-adjusted clinical practice, the decisions must be precisely delineated based on level of risk rather than a reflexive "one size fits all" approach[24].

CONCLUSION

Based on the above evidence and considerations, with regard to the administration of antenatal corticosteroids for fetal maturation in SARS-CoV-2 infected pregnant women, we urge consideration of the following.

The safety signal of possibly increased mortality elicited in the RECOVERY trial among patients with mild COVID-19 receiving DXM should not discourage the appropriate use of a single course of fluorinated corticosteroids (betamethasone 12 mg

daily for 2 d or dexamethasone 4 doses of 6 mg 12 h apart) for mothers with impending (within 7 d) anticipated delivery at 24 to 34 wk. The fetal indications for antenatal corticosteroids should be limited to obstetrical indications resulting in a high probability of preterm delivery. Unfortunately, the track record of antenatal corticosteroids utilization in clinical practice is inviting concern. There is a tendency to give out antenatal corticosteroids more than it is truly necessary and several studies have reported on how poorly antenatal corticosteroids are timed; 30 to 80% of women receiving them for threatened preterm birth deliver at or after 34 wk[25]. A rigorous application of the existent guidelines is necessary, promoting minimally necessary exposure and elimination of indiscriminate usage.

Contrary to the well justified, standard of care use of antenatal corticosteroids for infants delivered at 24 to 34 wk, when the anticipated benefits of antenatal corticosteroids are minimal, potential maternal adverse effects become a highly relevant concern and assuming the risk of corticosteroids administration in asymptomatic or mild COVID-19 cases is no longer warranted. Rescue corticosteroid courses are not advisable and the administration of antenatal corticosteroids after 34 wk (late preterm) may be associated with an unfavorable risk/benefit ratio. The late preterm administration of corticosteroids does not reduce neonatal mortality, overall RDS, NICU admissions or need for mechanical ventilation[26].The benefit is primarily a reduction in transient tachypnea of the newborn, a typically mild and self-limited condition. Such a modest benefit pales when weighed against maternal risks. After 34 wk, the risk of antenatal corticosteroids administered to the SARS-CoV-2 positive mothers with asymptomatic or mild disease, in our opinion, outweighs the expected modest benefit to the neonate.

The decision to use (or not use) antenatal corticosteroids is best made in consultation with a multidisciplinary team that includes maternal fetal medicine and intensive care specialists who consider the phase of the disease and the potential for maternal harm. Corticosteroids should be used prudently and withheld when maternal comorbidities pose increased risk. One such example is heart failure secondary to ischemia, where corticosteroids should be avoided since they may potentiate infarction[27].

As on so many other times before in obstetrics, our decisions have to be based on extrapolation of data from non-pregnant populations. It is hoped that in the future, pregnant and lactating women will be included in therapeutic clinical trials of COVID-19. Moreover, recognition of the further disproportionality of underserved populations and the impact of social determinants of health on both acquisition and severity of disease should prompt ardent efforts at recruiting and retaining underserved populations of reproductive age and pregnant or lactating women.

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