Current Commentary

Corticosteroids in the Management of Pregnant Patients With Coronavirus Disease (COVID-19)

Antonio F. Saad, MD, Lucy Chappell, PhD, George R. Saade, MD, and Luis D. Pacheco, MD

Downloaded from https://journals.lww.com/greenjournal by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3SN2oL6kwRjuA0TZGKdCSswkzqFKLhM/RUQneOXZuPe on 08/18/2020

Recent evidence supports the use of an early, short course of glucocorticoids in patients with COVID-19 who require mechanical ventilation or oxygen support. As the number of coronavirus disease 2019 (COVID-19) cases continues to increase, the number of pregnant women with the disease is very likely to increase as well. Because pregnant women are at increased risk for hospitalization, intensive care unit admission, and mechanical ventilation support, obstetricians will be facing the dilemma of initiating maternal corticosteroid therapy while weighing its potential adverse effects on the fetus (or neonate if the patient is postpartum and breastfeeding). Our objective is to summarize the current evidence supporting steroid therapy in the management of patients with acute respiratory distress syndrome and COVID-19 and to elaborate on key modifications for the pregnant patient.

(Obstet Gynecol 2020;00:1–4)
DOI: 10.1097/AOG.0000000000004103

To date, the United States has had the highest number of coronavirus disease 2019 (COVID-19) cases.[1] Although it appears that the death rate is not increased in pregnant patients, recent Centers for Disease Control and Prevention and UK Obstetric Surveillance System[2] data suggest that there is an increased risk for hospitalization, intensive care unit admission, and mechanical ventilation support.[3] The pathogenesis of acute respiratory distress syndrome (ARDS) consists of an excessive pulmonary inflammatory response leading to endothelial injury, in situ thrombosis, and exudative pulmonary edema.[4,5] In severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, a similar picture of an excessive inflammatory response has been described, with elevated markers of both inflammation and coagulation.[6,7] Antiinflammatory agents such as corticosteroids are believed to downregulate this massive inflammatory response.

Recent evidence supports the use of an early, short course of glucocorticoids in patients with COVID-19 who require mechanical ventilation or oxygen support.[8,9] Based on these results, the National Institutes of Health (NIH) COVID-19 Treatment Guidelines Panel recommends dexamethasone 6 mg daily (oral or intravenous) for up to 10 days (or hospital discharge, whichever comes first) in patients with COVID-19 on mechanical ventilation (AI: strong recommendation) or on supplemental oxygen (level of evidence BI: moderate recommendation). The Panel did not recommend using dexamethasone for patients with COVID-19 not requiring supplemental oxygen (level of evidence AI: strong recommendation).[10]

STEROID THERAPY AND ACUTE RESPIRATORY DISTRESS SYNDROME

The role of corticosteroids in the management of ARDS (not related to COVID-19) has been investigated for decades with contradictory findings, with most studies reporting improved oxygenation but limited effect on mortality.[11,12] More recently, the use of daily low-dose methylprednisolone was found to significantly decrease days on mechanical ventilation and mortality among patients with ARDS.[13,14] A

From the Division of Maternal-Fetal Medicine, Department of Obstetrics & Gynecology, and the Division of Surgical Critical Care, Department of Anesthesiology, the University of Texas Medical Branch at Galveston, Galveston, Texas; and the Department of Women and Children's Health, School of Life Course Sciences, King's College London, London, United Kingdom.

Each author has confirmed compliance with the journal's requirements for authorship.

Corresponding author: Antonio F. Saad, MD, the University of Texas Medical Branch at Galveston, Galveston, TX; email: afsaad@utmb.edu.

Financial Disclosure
The authors did not report any potential conflicts of interest.

© 2020 by the American College of Obstetricians and Gynecologists. Published by Wolters Kluwer Health, Inc. All rights reserved.
ISSN: 0029-7844/20

© 2020 by the American College of Obstetricians and Gynecologists. Published by Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

recent individual patient data metanalysis concludes that administration of prolonged methylprednisolone was associated with fewer days on mechanical ventilation and improved survival.[15] Recent guidelines suggest the use of methylprednisolone in patients with moderate ARDS.[16] Methylprednisolone was chosen owing to better lung tissue penetration and longer lung residence time.[17,18] The most recent clinical trial supports the use of intravenous dexamethasone in patients with moderate ARDS.[19] In contrast, the use of glucocorticoids is not recommended in patients with ARDS secondary to community-acquired pneumonia or influenza.[18] In summary, current guidelines recommend their use in patients with moderate ARDS, except if associated with influenza.[20]

STEROID THERAPY AND COVID-19

Until recently, corticosteroid administration in patients with COVID-19 was discouraged because of concerns about potentially delaying viral clearance. Recently, an open-label randomized control trial comparing different treatment modalities with usual care in patients hospitalized with COVID-19 has been completed–the RECOVERY (Randomised Evaluation of COVID-19 Therapy) trial.[8,9] Eligible participants consisted of hospitalized patients with suspected or laboratory-confirmed SARS-Cov-2 infection, including pregnant or breastfeeding women. Patients with a history of diabetes were not excluded. Preliminary evidence from the RECOVERY trial suggests that patients with COVID-19 who received dexamethasone had a significant reduction in 28-day mortality and that this benefit was greatest among patients receiving invasive mechanical ventilation (rate ratio [RR] 0.64; 95% CI 0.51–0.81), followed by patients receiving supplemental oxygen (RR 0.82; 95% CI 0.72–0.94). Patients not requiring oxygen support did not have such benefit (RR 1.19; 95% CI 0.91–1.55).[8,9] In light of these data, the NIH COVID-19 Treatment Guidelines Panel updated their recommendations to include dexamethasone administration in patients with COVID-19 who require oxygen supplementation or ventilatory support.[10]

OBSTETRIC CONSIDERATIONS IN PATIENTS WITH COVID-19 RECEIVING STEROIDS

The neonatal benefit of antenatal glucocorticoids in women at high risk for preterm delivery within 7 days is well established.[21] Of all the corticosteroids, betamethasone and dexamethasone are the only two recommended to induce fetal lung maturity, because they have the highest rate of placental transfer with minimal mineralocorticoid effects.[21] For neonatal benefit, the currently accepted regimen is either dexamethasone or betamethasone. Other corticosteroids (eg, methylprednisolone, prednisone, prednisolone, hydrocortisone) are not suitable alternatives, because they are extensively metabolized by placental 11-b-hydroxylase steroid dehydrogenase-2, leading to reduced placental transfer.[22]

Corticosteroids for fetal lung maturity are not without adverse fetal effects. Exposure to repetitive courses of antenatal glucocorticoids has been associated with adverse neurologic outcomes, small head circumferences, fetal growth restriction,[21] and increased risk of neonatal hypoglycemia.[23] Considering the potential fetal and neonatal side effects associated with repeated doses of glucocorticoids that efficiently cross the placenta, including the one currently recommended by the NIH for patients with COVID-19 requiring oxygen therapy or mechanical ventilation, an alternative approach for pregnant women is needed.

Pregnancy and breastfeeding were not exclusions in the RECOVERY trial, and the protocol recommended prednisolone 40 mg administered by mouth or intravenous hydrocortisone 80 mg twice daily to be used in these patients. However, the trial included only six pregnant women. In their recommendations, the NIH COVID-19 Treatment Guidelines Panel did not address pregnancy or breastfeeding. Recent guidelines from the Royal College of Obstetricians and Gynecologists suggest the use of intravenous hydrocortisone or oral prednisolone in women who are pregnant or breastfeeding.[24] Instead, we suggest using an agent with limited placental transfer and documented efficacy in cases of acute lung injury. Methylprednisolone appears to be the ideal agent.[12–16] A total of 32 mg/d of methylprednisolone orally or intravenously (once a day or in divided doses) would be equivalent to the dexamethasone dose used in the RECOVERY trial. If the woman is not a candidate for corticosteroids for fetal lung maturity (not at increased risk for preterm delivery within the next 7 days or is outside the gestational age window) or is breastfeeding, methylprednisolone can be used for the duration of the steroid course (10 days or up to discharge, whichever is sooner). We suggest that, when the RECOVERY trial criteria are met for the administration of glucocorticoids for COVID-19 management (patient requiring oxygen therapy, mechanical ventilation, or both) and the patient is at increased risk for preterm birth between 24 0/7 and 33 6/7 weeks of gestation, a standard regimen of dexamethasone for neonatal benefit should be administered (6 mg intramuscularly every 12 hours for four doses). We believe

© 2020 by the American College of Obstetricians and Gynecologists. Published by Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

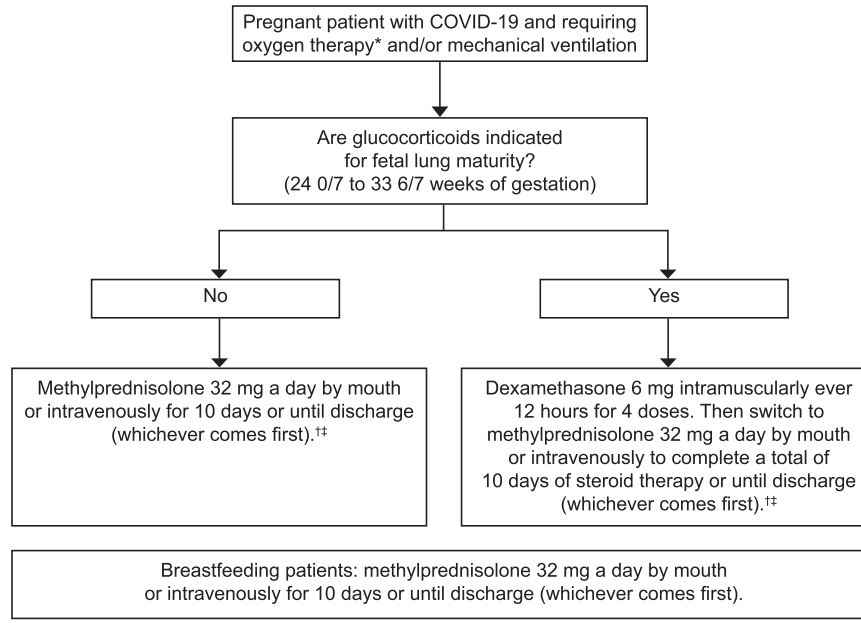

Fig. 1. Use of steroids for pregnant or breastfeeding patients with coronavirus disease 2019 (COVID-19). *Initiated when SpO_2 values fall below 94%. †Alternative regimens: prednisolone 40 mg administered by mouth or intravenous hydrocortisone 80 mg twice daily. ‡Owing to risk of hyperglycemia, close glucose monitoring is indicated, with possible insulin administration.

Saad. Corticosteroids in Pregnant Patients With COVID-19. Obstet Gynecol 2020.

dexamethasone should be used in lieu of betamethasone owing to a lack of evidence of the latter in patients with acute lung injury. We do not recommend dexamethasone for late preterm gestation, because the ALPS (Antenatal Late Preterm Steroids) [25] trial used betamethasone. After the dexamethasone course for lung maturity, we recommend completing the COVID-19 steroid course using methylprednisolone given that 8 additional days of dexamethasone may potentially harm the fetus. The use of short courses of steroids (less than 3 weeks) will not require "stress-dose steroids" at the time of surgery or delivery.[26] The 10-day course does not require steroid taper. Owing to the risk of maternal hyperglycemia, we recommend close glucose monitoring with possible insulin administration, particularly in women who are likely to deliver, putting the neonate at risk for hypoglycemia, and in women with diabetes.

A summary of our suggestions is provided in Figure 1.

In conclusion, pregnant women with COVID-19 who require oxygen therapy or mechanical ventilation or both should be considered for steroid therapy. Because in the RECOVERY trial the use of steroids in patients not on oxygen therapy was consistent with a harmful effect, only pregnant patients with a legitimate indication for oxygen therapy (persistent SpO_2 values below 94%) should be considered for steroid therapy. During pregnancy, we suggest that, when steroids are required for both fetal lung maturity and COVID-19, a four-dose course of dexamethasone over 2 days be used. After this course, dexamethasone should be replaced with methylprednisolone to complete a 10-day course. Limited data are available supporting the use of dexamethasone in the postpartum period and its effect on breastfeeding infants; hence we suggest using methylprednisolone instead. If the patient is not breastfeeding (eg, on mechanical ventilation), dexamethasone may be used.

REFERENCES

1. World Health Organization. Coronavirus disease (COVID-2019) situation reports. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/. Retrieved July 2, 2020.
2. Knight M, Bunch K, Vousden N, Morris E, Simpson N, Gale C, et al. Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: national population based cohort study. BMJ 2020;369:m2107.
3. Ellington S, Strid P, Tong VT, Woodworth K, Galang RR, Zambrano LD, et al. Characteristics of women of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status–United States, January 22–June 7, 2020. MMWR Morb Mortal Wkly Rep 2020;69:769–75.
4. Thompson BT, Chambers RC, Liu KD. Acute respiratory distress syndrome. N Engl J Med 2017;377:562–72.
5. Karakike E, Giamarellos-Bourboulis EJ. Macrophage activation-like syndrome: a distinct entity leading to early death in sepsis. Front Immunol 2019;10:55.
6. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708–20.
7. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020;395:1033–4.
8. RECOVERY: Randomised Evaluation of COVID-19 Therapy. Low-cost dexamethasone reduces death by up to one third in hospitalised patients with severe respiratory complications of

© 2020 by the American College of Obstetricians and Gynecologists. Published by Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

COVID-19. Available at: https://www.recoverytrial.net/news/low-cost-dexamethasone-reduces-death-by-up-to-one-third-in-hospitalised-patients-with-severe-respiratory-complications-of-covid-19. Retrieved July 2, 2020.

9. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson J, Mafham M, Bell J, et al. Dexamethasone in hospitalized patients with Covid-19 - preliminary report. N Engl J Med 2020 Jul 17 [Epub ahead of print].
10. National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. Available at: https://www.covid19treatmentguidelines.nih.gov/. Retrieved July 2, 2020.
11. Confalonieri M, Urbino R, Potena A, Piattella M, Parigi P, Puccio G, et al. Hydrocortisone infusion for severe community-acquired pneumonia: a preliminary randomized study. Am J Respir Crit Care Med 2005;171:242–8.
12. Annane D, Sébille V, Bellissant E; Ger-Inf-05 Study Group. Effect of low doses of corticosteroids in septic shock patients with or without early acute respiratory distress syndrome. Crit Care Med 2006;34:22–30.
13. Meduri GU, Golden E, Freire AX, Taylor E, Zaman M, Carson SJ, et al. Methylprednisolone infusion in early severe ARDS: results of a randomized controlled trial. Chest 2007;131:954–63.
14. Meduri GU, Bridges L, Shih MC, Marik PE, Siemieniuk RAC, Kocak M. Prolonged glucocorticoid treatment is associated with improved ARDS outcomes: analysis of individual patients' data from four randomized trials and trial-level meta-analysis of the updated literature. Intensive Care Med 2016;42:829–40.
15. Lamontagne F, Briel M, Guyatt GH, Cook DJ, Bhatnagar N, Meade M. Corticosteroid therapy for acute lung injury, acute respiratory distress syndrome, and severe pneumonia: a meta-analysis of randomized controlled trials. J Crit Care 2010;25:420–35.
16. Annane D, Pastores SM, Rochwerg B, Arlt W, Balk RA, Beishuizen A, et al. Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017 [published erratum appears in Intensive Care Med 2018 Feb 23]. Intensive Care Med 2017;43:1751–63.
17. Greos LS, Vichyanond P, Bloedow DC, Irvin CG, Larsen GL, Szefler SJ, et al. Methylprednisolone achieves greater concentrations in the lung than prednisolone. A pharmacokinetic analysis. Am Rev Respir Dis 1991;144:586–92.
18. Vichyanond P, Irvin CG, Larsen GL, Szefler SJ, Hill MR. Penetration of corticosteroids into the lung: evidence for a difference between methylprednisolone and prednisolone. J Allergy Clin Immunol 1989;84:867–73.
19. Villar J, Ferrando C, Martínez D, Ambrós A, Muñoz T, Soler JA, et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. Lancet Respir Med 2020;8:267–76.
20. Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med 2019;200:e45–67.
21. Antenatal corticosteroid therapy for fetal maturation. Committee Opinion No. 713. American College of Obstetricians and Gynecologists. Obstet Gynecol 2017;130:e102–9.
22. Murphy VE, Fittock RJ, Zarzycki PK, Delahunty MM, Smith R, Clifton VL. Metabolism of synthetic steroids by the human placenta. Placenta 2007;28:39–46.
23. Saccone G, Berghella V. Antenatal corticosteroids for maturity of term or near term fetuses: systematic review and meta-analysis of randomized controlled trials [published erratum appears in BMJ 2016 Nov 29;355:i6416]. BMJ 2016;355:i5044.
24. Royal College of Obstetricians and Gynaecologists. Coronavirus (COVID-19) infection and pregnancy. Information for healthcare professionals. Available at: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/coronavirus-pregnancy/. Retrieved July 2, 2020.
25. Gyamfi-Bannerman C, Thom EA, Blackwell SC, Tita AT, Reddy UM, Saade GR, et al. Antenatal betamethasone for women at risk for late preterm delivery. N Engl J Med 2016;374:1311–20.
26. Liu MM, Reidy AB, Saatee S, Collard CD. Perioperative steroid management. Anesthesiology 2017;127:166–72.

PEER REVIEW HISTORY

Received July 8, 2020. Received in revised form July 16, 2020. Accepted July 23, 2020. Peer reviews and author correspondence are available at http://links.lww.com/AOG/C33.

© 2020 by the American College of Obstetricians and Gynecologists. Published by Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.