

Corticosteroid Guidance for Pregnancy during COVID-19 Pandemic

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Abstract

Keywords

- COVID-19
- corticosteroids
- prematurity
- betamethasone
- dexamethasone

The novel coronavirus disease 2019 (COVID-19) pandemic is causing a necessary, rapid adjustment within the field of obstetrics. Corticosteroid use is a mainstay of therapy for those women delivering prematurely. Unfortunately, corticosteroid use has been associated with worse outcomes in COVID-19 positive patients. Given this information, it is necessary that obstetricians adjust practice to carefully weigh the fetal benefits with maternal risks. Therefore, our institution has examined the risks and benefits and altered our corticosteroid recommendations.

Key Points

- Corticosteroid use is an important part of prematurity treatment because it provides benefit to the fetus.
- Corticosteroid use may be related with increased morbidity and mortality in novel coronavirus disease 2019 (COVID-19).
- Therefore, during the COVID-19 pandemic, an alteration in current corticosteroid practices is necessary to uniquely weigh the maternal risks and fetal benefits.

The field of medicine is facing an unprecedented challenge rapidly adapting current medical practice in caring for novel coronavirus disease 2019 (COVID-19) patients. The field of obstetrics is no different. Current treatment algorithms and protocols must be evaluated and modified to account for what is being learned and already known about COVID-19. One of our common practices in obstetrics is to give corticosteroids for fetal lung maturity to those at risk of delivering prematurely. Unfortunately, corticosteroid use in COVID-19 may be tied to worse patient outcomes, including death. Therefore, it is imperative that our field evaluates our current treatment paradigm and make appropriate modifications to best balance risks and benefits.

Outcomes are worse for patients with COVID-19 with corticosteroid use (→ **Tables 1** and **2**).^{1,2} This was demonstrated in several studies; however, these studies were unable to control for underlying medical comorbidities, ventilation, or intensive care unit (ICU) status. It is therefore

unclear at this time as to whether the steroids were given because the baseline condition was worse or if giving the steroids caused worse outcomes. Additionally, none of the patients were pregnant and the dosing for glucocorticoids in an ICU setting are different than for obstetric indications. The typical obstetrical dosing of betamethasone and dexamethasone in methylprednisolone equivalents is 60 mg. This dosage is similar to that listed in → **Table 2** (40–80 mg/day); however, the duration of treatment is different (4–11 days of treatment).² Therefore, the typical corticosteroids used in pregnant women are roughly one-fourth to one-tenth of the amount used in these publications. While it may seem reasonable to continue our practice of steroids for fetal lung maturity, given its shorter duration, despite similar daily dosages, there is limited evidence at this time to confirm whether this is the case. Therefore, a careful assessment of maternal risk versus neonatal benefit should be undertaken.

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Table 1 Disease severity and adverse composite outcome in COVID-19 patients treated with systemic glucocorticoids¹

Variable	All patients <i>n</i> = 1,099 <i>n</i> (%)	Disease severity		Presence of composite primary end point ^a	
		Nonsevere <i>n</i> (%)	Severe <i>n</i> (%)	Yes <i>n</i> (%)	No <i>n</i> (%)
Systemic glucocorticoids	204 (18.6)	127 (13.7)	77 (44.5)	35 (52.2)	169 (16.4)
Individual aspects of the composite outcomes					
		ICU admission		33 (16.2%)	
		Invasive ventilation		17 (8.3%)	
		ECHMO ^b		5/77 (0.5%)	
		Death		5 (2.5%)	

Abbreviations: COVID-19, novel coronavirus disease 2019; ECHMO, extracorporeal membrane oxygenation; ICU, intensive care unit.

^aPrimary composite endpoint was admission to an ICU, use of mechanical ventilation, or death.

^bECHMO was used in severe patients; % calculated from *n* = 77.

In examining the data, there are numerous studies demonstrating neonatal benefit to corticosteroid use.^{3–7} Because of this, it has become the standard of care to give betamethasone (or dexamethasone) to women at risk for delivering prematurely between 23 and 36 weeks of gestation.^{3,8,9} In fact, corticosteroids are such an ingrained part of obstetric practice, we give them out more than it is truly necessary. In evaluating obstetricians' use of betamethasone, several studies have examined how poorly steroids are timed (<7 days from administration to delivery) for imminent delivery. Two of these studies found that betamethasone was only given within the effective window 45.4 to 80% of the time.^{10,11} In this pandemic, given that obstetricians are faced with two patients, mom and baby, it is necessary to balance the risks and benefits for each patient, which means evaluating how and when it is necessary to give them. In examining corticosteroids by gestational age, the absolute risk of neonatal complications and improved neonatal benefit by gestational

age should be considered. Travers et al demonstrated that the lowest gestations receive the largest benefit from corticosteroids.¹² In this large prospective cohort of 117,941 infants, neonatal death before discharge did not demonstrate a statistically significant reduction at or beyond 31 weeks. Additionally, survival without morbidity also did not reach statistical significance after 28 weeks. Indeed, the number of mothers needed to treat with corticosteroids to prevent one neonatal death is six at 23 to 24 weeks but can increase to 798 women at 34 weeks.¹² Given this delicate balance of choosing between neonatal benefit and possible maternal harm, it is prudent that obstetricians become more cautious with their betamethasone administration during this time. Weighing the risks and benefits, our institution has recommended that no women COVID-19 positive or person under investigation (PUI) receive corticosteroids beyond 32^{0/7} weeks. We acknowledge that it may be difficult to determine whether a maternal fever in labor is chorioamnionitis or COVID-19.

Table 2 Treatment with systemic glucocorticoids by severity²

Survivors	Mild		Severe		Deaths	
	Yes	No	Yes	No	Yes	No
Corticosteroid therapy						
Number (%)	76 (34)	150 (66%)	77 (55)	62 (45)	43 (84)	8 (16)
Usage of corticosteroids						
Dosage (mg/d)	40.0 (32.2–40.0) ^a	–	38.7 (29.7–4.2) ^a	–	65.0 (40.0–80.0)	–
Treatment period (d)	6.0 (4.0–9.0)	–	8.0 (5.5–11.0)	–	7.0 (4.0–9.0)	–
Hospitalization (d)	12.0 (9.0–16.0) ^b	10.0 (8.0–13.0)	14.0 (10.0–18.0) ^b	11.0 (9.0–13.0)	11.0 (7.0–13.0)	11.5 (8.0–16.0)
Days from corticosteroids to temperature restore	2.0 (1.0–4.0) ^a	–	2.0 (1.0–4.0) ^a	–	6.5 (1.0–11.0)	–

Note: All data expressed as *n* (%) or median (interquartile range).

^a*p* < 0.05 vs. death in patients with corticosteroids therapy group.

^b*p* < 0.05 vs. the same group without corticosteroid therapy.

Table 3 Recommendations for corticosteroid use during the COVID-19 pandemic

- We recommend that no women COVID-19 positive or PUI receive corticosteroids beyond 32^{0/7} wk.
- We recommend an MFM consultation for decisions regarding corticosteroid administration for pregnancies <32 wk in women at risk of preterm delivery who are COVID-19 positive or PUI as individualization of care is necessary to take into account the unique risks of corticosteroids for the mother vs the benefit for the fetus.
- We recommend against tocolysis in women who are COVID-19 positive or PUI who are not receiving corticosteroids.

Abbreviations: COVID-19, novel coronavirus disease 2019; MFM, maternal-fetal medicine; PUI, person under investigation.

Given the experience of those in New York with asymptomatic COVID-19 patients at the outset of labor, we recommend treating with antibiotics as is standard for chorioamnionitis, but also treating the patient as a PUI and obtaining a COVID-19 test. We also recommend (→Table 3) a maternal fetal medicine consultation for decisions regarding corticosteroid administration for pregnancies <32 weeks in women at risk of preterm delivery who are COVID-19 positive or PUI as individualization of care is necessary to take into account the unique risks of corticosteroids for the mother versus the benefit for the fetus.

When corticosteroids are not given, tocolysis should also not be undertaken given that the endpoint for tocolysis is to achieve steroid administration. When giving corticosteroids and utilizing tocolysis, consideration for risks and benefits of each tocolytic is prudent. Currently, the most efficacious tocolytic is indomethacin for achieving steroid benefit.¹³ While there was concern about nonsteroidal anti-inflammatory drugs (NSAIDs) in the setting of COVID-19, the Food and Drug Administration (FDA) has recently stated that there are no data to suggest NSAID use should be altered at this time.¹⁴ Other tocolytics, such as nifedipine, would also be reasonable to use, as there is some preliminary suggestions that nifedipine may be beneficial in COVID-19 patients due to its efficacy in the treatment of high-altitude pulmonary edema, which has clinical similarities to the lung manifestations of COVID-19.¹⁵ However, if a woman is already hypotensive or tachycardic, nifedipine should not be used. Magnesium is a less effective tocolytic than indomethacin and nifedipine,¹³ and given the recommendation for conservative fluid management is less than ideal choice. Finally, betamimetics should not be used as they cause significant maternal hypotension, tachycardia, and pulmonary edema which should be avoided in someone who is has COVID-19.¹⁶ The discussions regarding corticosteroid administration and tocolysis should involve a multidisciplinary team including maternal fetal medicine, obstetrics, critical care physician, infectious disease specialists, and neonatologists. These decisions are of critical importance to serve both the interests of the mother and the fetus.

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Conflict of Interest

None declared.

References

- 1 Guan WJ, Ni ZY, Hu Y, et al; China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020
- 2 Shang J, Lu Q, Wu J, et al. The treatment and outcomes of patients with COVID-19 in Hubei, China: a multi-centered, retrospective, observational study. *Lancet* 2020. Doi: 10.2139/ssrn.3546060
- 3 Effect of corticosteroids for fetal maturation on perinatal outcomes. NIH Consens Statement 1994;12(02):1–24
- 4 Roberts D, Dalziel S. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst Rev* 2006;(03):CD004454
- 5 Brownfoot FC, Gagliardi DI, Bain E, Middleton P, Crowther CA. Different corticosteroids and regimens for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst Rev* 2013;(08):CD006764
- 6 Roberts D, Brown J, Medley N, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst Rev* 2017;3:CD004454
- 7 Gyamfi-Bannerman C, Thom EA, Blackwell SC, et al; NICHD Maternal-Fetal Medicine Units Network. Antenatal betamethasone for women at risk for late preterm delivery. *N Engl J Med* 2016;374(14):1311–1320
- 8 Committee on Obstetric Practice. Committee opinion no. 713: antenatal corticosteroid therapy for fetal maturation. *Obstet Gynecol* 2017;130(02):e102–e109
- 9 Obstetric care consensus no. 4: periviable birth. *Obstet Gynecol* 2016;127(06):e157–e169
- 10 Boesveld M, Heida KY, Oudijk MA, Brouwers HA, Koenen SV, Kwee A. Evaluation of antenatal corticosteroid prescribing patterns among 984 women at risk for preterm delivery. *J Matern Fetal Neonatal Med* 2014;27(05):516–519
- 11 Adams TM, Kinzler WL, Chavez MR, Fazzari MJ, Vintzileos AM. Practice patterns in the timing of antenatal corticosteroids for fetal lung maturity. *J Matern Fetal Neonatal Med* 2015;28(13):1598–1601
- 12 Travers CP, Clark RH, Spitzer AR, Das A, Garite TJ, Carlo WA. Exposure to any antenatal corticosteroids and outcomes in preterm infants by gestational age: prospective cohort study. *BMJ* 2017;356:j1039
- 13 Haas DM, Caldwell DM, Kirkpatrick P, McIntosh JJ, Welton NJ. Tocolytic therapy for preterm delivery: systematic review and network meta-analysis. *BMJ* 2012;345:e6226
- 14 Food and Drug Administration. FDA advises patients on use of non-steroidal anti-inflammatory drugs (NSAIDs) for COVID-19. Available at <https://www.fda.gov/drugs/drug-safety-and-availability/fda-advises-patients-use-non-steroidal-anti-inflammatory-drugs-nsaids-covid-19>. Accessed March 20, 2020

- 15 Solaimanzadeh I. Acetazolamide, nifedipine and phosphodiesterase inhibitors: rationale for their utilization as adjunctive countermeasures in the treatment of coronavirus disease 2019 (COVID-19). *Cureus* 2020;12(03):e7343
- 16 Perry KG Jr., Morrison JC, Rust OA, Sullivan CA, Martin RW, Naef RW III. Incidence of adverse cardiopulmonary effects with low-dose continuous terbutaline infusion. *Am J Obstet Gynecol* 1995; 173(04):1273–1277