EDITORIAL

Late Prematurity

Marina Vainder[1], Dan Farine[2]

Donald School Journal of Ultrasound in Obstetrics and Gynecology (2023): 10.5005/jp-journals-10009-1973

This editorial refers to the manuscript entitled "Antenatal corticosteroids for late preterm labor" by the authors Dan Farine, Prakesh Kumar Shah, and Kellie Estelle Murphy, which is published in this issue of DSJUOG (pages 143–148).

Since this manuscript was written in 2019, additional data has been published on the topic of corticosteroid use in the context of late preterm labor (PTL), which will be relevant to the reader. First, there were follow-up studies on the largest randomized controlled trial of the maternal-fetal medicine (MFM) group on the effect of steroids on hypoglycemia.[1] These showed that hypoglycemia was mild, transient, and responded to therapy. Aside from this study and a similar one on the same topic, there were no other long-term studies on the population of this specific paper.

There was a survey that showed that most practitioners in the United States of America (USA) adopted the American College of Obstetricians and Gynecologists and Society for Maternal-Fetal Medicine (SMFM) guidelines.[2] There was also data from a US obstetrics database that showed that the use of corticosteroids in the USA was moderately, but significantly increased after the introduction of the study.

There were four additional retrospective studies looking at the use of corticosteroids in the setting of late prematurity. Their results agreed with previously published work and are not included in this editorial.

There are many recent studies on the effects of administrating corticosteroids to pregnant women. Since they are mainly *in vitro* or *in vivo* animal models, we decided to exclude them from this editorial. The reader is referred to the work of Asztalos et al. on this issue. He shows that corticosteroids modify a variety of pathways in the fetus. There is no proof that corticosteroids alter long-term outcomes. However, the multitude of changes triggered by corticosteroids raises a theoretical concern regarding several possible adverse long-term effects.[3] In addition, in about 50% of cases of PTL, the labor is false, and the baby delivers at term. A recent paper found that with the application of strict criteria, this number is reduced to 15%. However, this implies that 15–50% of these patients may be exposed to the possible risks of corticosteroids without any benefits.

It is interesting to look at the other side of the spectrum. Until about a decade ago, the outcome of extreme prematurity at 22–23 weeks gestation was extremely poor, with a very high neonatal mortality rate and a very low rate of intact survival. As the neonatal care of these infants evolved and outcomes improved, perinatologists began to change their attitudes toward these pregnancies and instituted more aggressive management. One aspect of the more aggressive management is the use of corticosteroids. About 10–20 years ago, there was still a debate regarding the presence of steroid receptors in fetuses at this gestational age. Now, this debate is long over, as there is data not only on the presence of these receptors but also data on the effectiveness of steroids in improving survival among these infants. To the best of our knowledge, there are multiple studies looking at the effect of corticosteroids on perinatal mortality, respiratory distress syndrome, and other outcomes. The overwhelming results of these studies support their use in order to improve survival and early neonatal outcomes, often to the tune of 100%. A recent example of the effects of a full course and one dose of steroids is in a paper with the follow-up of the American MFM network by Chawla et al.[4]

There are currently three guidelines for the administration of corticosteroids for late PTL. These guidelines were issued by:

- The SMFM (USA)—2021.[5]
- The Society of Obstetricians and Gynaecologists of Canada (SOGC).[6]
- International Federation of Gynecology and Obstetrics (FIGO).[7]

[1,2]Department of Obstetrics & Gynaecology, Mount Sinai Hospital, University of Toronto, Ontario, Canada

Corresponding Author: Dan Farine, Department of Obstetrics & Gynaecology, Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada, Phone: 4164189576, e-mail: dan.farine@sinaihealth.ca

How to cite this article: Vainder M, Farine D. Late Prematurity. Donald School J Ultrasound Obstet Gynecol 2023;17(2): 107–108.

Source of support: Nil

Conflict of interest: None

The SMFM issued a new set of guidelines in 2021. The specific guidelines were:

- We recommend offering a single course of antenatal corticosteroids, two doses of 12 mg of intramuscular betamethasone 24 hours apart) to patients who meet the inclusion criteria of the Antenatal Late Preterm Steroids trial, that is, those with a singleton pregnancy between 34 0/7 and 36 6/7 weeks of gestation who are at high risk of preterm birth within the next 7 days and before 37 weeks of gestation (grade 1A).
- We suggest consideration for the use of antenatal corticosteroids in select populations not included in the original Antenatal Late Preterm Steroids trial, such as patients with multiple gestations reduced to a singleton gestation on or after 14 0/7 weeks of gestation, patients with fetal anomalies, or those who are expected to deliver in <12 hours (grade 2C).
- We recommend against the use of antenatal corticosteroids for fetal lung maturity in pregnant patients with a low likelihood of delivery before 37 weeks of gestation (grade 1B).
- We recommend against the use of late preterm corticosteroids in pregnant patients with pregestational diabetes mellitus, given the risk of worsening neonatal hypoglycemia (grade 1C).
- We recommend that patients at risk for late preterm delivery be thoroughly counseled regarding the potential risks and benefits of antenatal corticosteroid administration and be advised that the long-term risks remain uncertain (grade 1C).

The SOGC guidelines recommendations are:

- We continue to strongly recommend antenatal corticosteroid administration up to 336 weeks gestation when delivery is expected within 7 days (strong, high).
- We have changed the upper gestational age boundary to which we strongly recommend antenatal corticosteroid administration from 340 to 336 weeks gestation (conditional, low).
- For pregnant individuals at risk of delivery between 340 and 366 weeks gestation, we recommend considering antenatal corticosteroids based on discussion with patients about absolute harms and benefits specific to the gestational week (strong, moderate).
- Between 340 and 366 weeks gestation, we do not recommend antenatal corticosteroids for pregnancies complicated by pregestational diabetes (strong, low).

The FIGO guidelines: A high-quality US study assessed the effects of corticosteroids in 2831 women at risk of late preterm birth (34 + 0 until 36 + 5 weeks of gestation).[6] The administration of corticosteroids statistically significantly reduced the requirement for respiratory support in the first 72 hours of life [11.6 vs 14.4%; risk ratio (RR) 0.80; 95% confidence interval (CI), 0.66–0.97; number needed to treat = 36]. However, neonatal hypoglycemia was more common in the betamethasone group than in the placebo group (24.0 vs 15.0%; RR 1.6; 95% CI, 1.37–1.87; number needed to harm = 11). While no long-term harms have been proven following corticosteroids at late preterm gestations, there has been no significant follow-up of trials. Observational studies using population data have shown prenatal corticosteroid exposure is associated with increased behavioral and psychiatric diagnoses in children.

Recommendation: Prenatal corticosteroids should not be offered routinely to women in whom late preterm birth is anticipated. Instead, the use of prenatal corticosteroids should be considered in light of the balance of risks and benefits for individual women.

In summary, in the past few years, there has not been any significant additional data published on the use of corticosteroids in the context of late PTL. However, two of the three society guidelines discussed above do not support using corticosteroids in late PTL. The third one, from the SMFM, became more restrictive compared to the previous iteration of the same guideline published in 2017.

References

1. Gyamfi-Bannerman C, Jablonski KA, Blackwell SC et al. Evaluation of hypoglycemia in neonates of women at risk for late preterm delivery: an antenatal late pretermsteroids trial cohort study. Am J Perinatol 2023;40(5):532–538. DOI: 10.1055/s-0041-1729561
2. Battarbee AN, Clapp MA, Boggess KA, et al. Practice variation in antenatal steroid administration for anticipated late preterm birth: a physician survey. Am J Perinatol 2019;36(2):200–204. DOI: 10.1055/s-0038-1667028
3. Asztalos EV, Murphy KE, Matthews SG. A growing dilemma: antenatal corticosteroids and long-term consequences. Am J Perinatol 2022;39(6):592–600. DOI: 10.1055/s-0040-1718573
4. Chawla S, Wyckoff MH, Rysavy MA, et al. Association of antenatal steroid exposure at 21 to 22 weeks of gestation with neonatal survival and survival without morbidities. JAMA Network Open 2022;5(9):e2233331. DOI: 10.1001/jamanetworkopen.2022.33331
5. Society for Maternal-Fetal Medicine (SMFM). Electronic address: pubs@smfm.org; Reddy UM, Deshmukh U, et al. Society for Maternal-Fetal Medicine consult series #58: use of antenatal corticosteroids for individuals at risk for late preterm delivery: replaces SMFM statement #4, implementation of the use of antenatal corticosteroids in the late preterm birth period in women at risk for preterm delivery, August 2016. Am J Obstet Gynecol 2021;225(5):B36–B42. DOI: 10.1016/j.ajog.2021.07.023
6. Liauw J, Hannah Foggin H, Socha P, et al. Technical update no. 439: antenatal corticosteroids at late preterm gestation. J Obstet Gynaecol Can 2023;45(6):445–457. DOI: 10.1016/j.jogc.2022.12.006
7. Norman J, Shennan A, Jacobsson B, et al. FIGO good practice recommendations on the use of prenatal corticosteroids to improve outcomes and minimize harm in babies born preterm. Int J Gynaecol ObstetInt J Gynaecol Obstet 2021;155(1):26–30. DOI: 10.1002/ijgo.13836. Erratum in: 2022;157(2):486.