REVIEW ARTICLE

Antenatal Corticosteroids for Late Preterm Labor

Dan Farine[1], Prakeshkumar Shah[2], Kellie E Murphy[3]

Received on: 24 March 2023; *Accepted on:* 30 April 2023; *Published on:* 30 June 2023

Abstract

This article reviews several different aspects of corticosteroids in preterm labor (PTL). After a short review of the history of the administration of corticosteroids for preterm labor, we review the overall data on PTL.

The next paragraph is on repeated courses of corticosteroids in PTL. Most of the literature does not show benefits from such repeated dosages. Furthermore, some like the large multiple courses of antenatal corticosteroids (MACS) study showed that repeated dosages resulted in smaller babies. What was probably more important was that it resulted in small head conferences, most likely reflecting smaller head sizes.

There is ample literature on the effect of corticosteroids on different organ systems. We do not have good data on the long-term outcomes of this effect. A very long-term study on the original study of Liggins showed some effect on glucose tolerance but no effect on frank diabetes. It is difficult to use these issues in determining the need for corticosteroids as there is always a concern that a long-term effect may be found years later (look at the ORACLE study mentioned here).

There is limited information on the effect of corticosteroids in the late preterm labor. The data is summarized in a table. Two of these papers are on administrating corticosteroids prior to a cesarean section (CS) and are discussed separately. Of the studies on the administration of corticosteroids for late PTL, one stands out. It was done by the maternal fetal medicine (MFM) network in the US, it is large and well-designed. It showed a decrease in both respiratory distress syndrome (RDS) by close to 50% and shortened the stay in the neonatal intensive care unit (NICU) by an average of 8 days. The price was an increase in GDM.

These were the reasons that both the society of maternal fetal medicine (SMFM) and American College of Obstetricians and Gynecologists (ACOG) recommended the use of corticosteroids in late preterm. No other society came forward with such recommendations probably because of the concern for long-term effects.

Keywords: Corticosteroids, Gestational diabetes, Late preterm labor, Preterm labor.

Donald School Journal of Ultrasound in Obstetrics and Gynecology (2023): 10.5005/jp-journals-10009-1975

History and Background

The story of corticosteroids for the management of prematurity is quite interesting and educational. Sir Liggins was working on the induction of labor when he started his experiments with corticosteroids.[1] He found that corticosteroids had no tocolytic effect. He also noticed that the drug had a pronounced effect on the respiratory systems of the kids and improved survival. Once he confirmed his observations in the sheep model, he performed a randomized controlled study (RCT) on humans. He found, as he expected by now, that the therapy improved neonatal outcomes, especially respiratory status, significantly.[2] His work was replicated with several other RCTs and the results were confirmed again and again. The results of these RCTs have been seen by most of us repeatedly as they are now the famous logo of the Cochrane database. Interestingly, there were few researchers who changed his dose and schema of therapy so we know a lot about this specific dose and very little about lower doses that may have the same effect. It is likely that lower doses may have clinical effects as it has been shown that a partial course with only one dose still has therapeutic effects. There were other puzzling results in the initial set of studies. For example, the outcomes of women with preeclampsia/hypertension were worse as the perinatal mortality rate was 31.6 vs 15.4%. It was found later that this was a result of trying not to deliver these patients despite worsening clinical status and not because of the corticosteroids *per se*. Another area was the twins' pregnancy. There was a trend for improvement but until recently it

[1,3]Department of Obstetrics and Gynecology, Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada

[2]Department of Pediatrics, Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada

Corresponding Author: Dan Farine, Department of Obstetrics and Gynecology, Mount Sinai Hospital and University of Toronto, Toronto, Ontario, Canada, Phone: 1-416-586-8592, e-mail: dan.farine@sinaihealth.ca

How to cite this article: Farine D, Shah P, Murphy KE. Antenatal Corticosteroids for Late Preterm Labor. Donald School J Ultrasound Obstet Gynecol 2023;17(2):143–148.

Source of support: Nil

Conflict of interest: None

was not proven beyond doubt.[2,3] Many years ago some questioned if the dose has to be increased but most authors and guidelines that have followed accepted that although the statistics are not strong the clinical information suggests using it. One good aspect of all these trials that repeated the same dose and scheme from the mid-70s to 40 years later is that we know that it works in the evolving clinical management of prematurity. The most important aspect of the changed management was the administration of surfactants. We know now, thanks to these repeated studies, that antenatal corticosteroids (ACS) worked in both the pre and postsurfactant eras.

Repeated Administration of Steroids

By 1990 there was data that the effect of corticosteroids lasts for about 1 week.[4] As a result many clinicians started administrating repeated courses of corticosteroids, usually on a weekly basis. The research on this practice followed later. A detailed account of this research is beyond the scope of this chapter. It is important to notice that most of the RCTs done on this topic showed no major benefit from repeat administration and[5–7] some like the MACS study[5] showed that repeated doses of steroids resulted in a reduction of fetal weight and what may be more important reduction was a reduction in the infant head circumference that reflected smaller brain size. Only one earlier study or repeated corticosteroids[8] showed that repeated ACS could be useful. It may be important to mention that in a study we did >20 years ago we found that repeated large doses of steroids administrated daily in pregnancy aiming at reducing recurrent pregnancy losses resulted in slightly stunted fetal growth.[9]

Effects of Steroids on the Fetus

Adverse fetal effects of multiple doses of ACS have been repeatedly documented in different species and have recently been the subject of a systematic review.[10] Multiple courses have been associated with a decrease in birth weight in nine out of the 11 studies reviewed (sheep, rabbits, and mice). A delay in the maturation or development of the fetal nervous system was found in six studies published (sheep, monkeys) while in one murine study, no effect was found on behavioral outcomes. In addition, multiple doses of ACS have been associated with permanent changes in the expression of glucocorticoid receptors in the hippocampus and limbic system, suggestive of a decrease in central glucocorticoid feedback (rats and guinea pigs).[11,12] Few studies have been undertaken to establish the long-term effects of fetal exposure to synthetic glucocorticoids on hippocampal pituitary axis (HPA) function in the primate. Pregnant rhesus monkeys were treated daily with dexamethasone (4 × 1.25 mg/kg) commencing on 132 days of gestation. Basal and stress-stimulated cortisol levels were elevated in the offspring (10 months of age) born to dexamethasone-treated mothers.[13] It is also known that the HPA programming effect of maternal ACS administration differs between male and female offspring.[14] Collectively, these studies demonstrate that short-term fetal exposure to glucocorticoids can effectively program HPA function in different species of animals. This is of relevance to the development of metabolic syndrome, as exaggerated cortisol secretion has been linked to obesity, insulin resistance, and hypertension. Despite this large body of evidence, extrapolation of these findings to humans is problematic due to inherent differences between humans and animals in the timing of brain development, sensitivity to glucocorticoid receptors, and transfer of glucocorticoids to the fetal central nervous system. Nunham from Perth had data pertaining mainly to possible lung and brain effects similar to the MAC study mentioned above.[15] A finding that was common to several animal models was a major reduction of the volume of the prelimbic area of the brain. This reduction in volume was in the range of up to 40%. Of note, this area is involved in memory regulation.

Long-term Effect of ACS

There is data on the long-term effect of ACS. Such data includes the longest follow-up by the group of Dalziel et al. that evaluated the original cohort of the Liggins study.[16–18] They found that the offspring of both arms did well and the only significant difference was some glucose intolerance (but not diabetes) in the subjects who were exposed to ACS. In a meta-analysis of 14 studies looking at ACS administration for preterm labor (PTL) with the standard dose there was no indication of poor outcomes.[19] Of note the EPIPAGE cohort study showed a decrease in white matter lesions at the age of 5.[20] In contrast, the data on long-term outcomes in the late preterm period is limited.

General Concerns about the Long-term Effect of Therapy

Whenever recommending therapy one has to be concerned about the long-term effect of such a therapy. There are two good examples of this specific issue. The first is the ORACLE-II study. In this study, women with preterm birth were randomized to therapy with antibiotics or a placebo. The initial study did not show any difference between the two groups. However, a follow-up of the children exposed to the therapy showed that 1/64 of babies receiving antibiotics developed cerebral palsy.[21] The study was done in the UK and it affected the British guidelines that now look for long-term outcomes,[22] prior to adopting new therapy.

The other example is cesarean delivery. The risks of bleeding, infection, and damage to other organs have been known for >100 years. The risk for placenta accreta has become evident about 15–20 years ago. The association between cesarean delivery and a higher incidence of diseases with an inflammatory component in the infant has become known about 10–20 years ago. These conditions include type I diabetes; asthma, obesity, etc.[23] There is no proof of causation at this time, however, the consent for a CS probably

should include a short description of these late outcomes. However, the risk for stillbirths following cesarean delivery was described by Gordon Smith only in this decade.[24]

Randomized Controlled Study (RCT) on Late Use of ACS

There are six RCTs evaluating the administration of ACS in the late preterm period and at term. These RCTs are outlined in Table 1 below—modified from Saccone and Berghella.[25] Most of the studies were quite small and their results were not significant. Two of these studies were large enough and had significant results—these studies were by Gyamfi-Bannerman[26] and Stutchfield et al.[27,28] We will expand on these studies below. Only one study had significant results for RDS although the meta-analysis showed a benefit [risk ratio (RR) = 0.55 (0.33–0.91)]; There were similar results for RDS (RR = 0.74 (0.61–0.91)). The length of stay in the NICU was significantly shorter and translated to 8 days on average. The neonate had a significantly shorter stay in the NICU–8 days on average! The rate of neonatal infection and mortality was not different.

The paper Gyamfi-Bannerman[26] was a large study that was properly designed and executed. It is the key paper for the recent guidelines by both the SMFM[29] and ACOG.[30] The major problem in this study is that the follow-up is only for 3 days. The frequency of hypoglycemia was more than twice that of the benefit which was a composite outcome (9 vs 4% of added risk). However, the outcomes that were improved were more important clinically than the hypoglycemia which could be easily monitored. There were two neonatal mortalities in the ACS group. One was due to a cardiac anomaly but the other was due to sepsis. It is well known that steroids may mask the clinical presentation of sepsis. If this was the case it is a reason for major concern, however, there is a good chance this was just a coincidence.

The two papers by Stutchfield et al.[27,28] are related to ACS given prior to a CS and not too late prematurity. However, these studies may provide further insight into the use of ACS. In the initial study, both RDS and transient tachypnea of the newborn (TTN) were reduced but not significantly (RR = 0.21 (0.03–1.32) and RR = 0.54 (0.26–1.12), respectively. The rate of admissions to the NICU for RDS was significantly reduced [RR = 0.46 (0.23–0.93)]. However, a similar effect would have been achieved by delaying the cesarean delivery to 39 weeks. This paper was criticized for exposing the fetus to a potent hormone with long-term outcomes for a benefit that was minimal.[31] The Astecs study had a follow-up study using a questionnaire.[28] The study found no adverse effect was seen on the health, behavior, and academic achievement of children born following a single course of antenatal betamethasone at term. Antenatal betamethasone did not reduce the prevalence of asthma and allergy following elective cesarean section. However, the ACS group is 2x likely to be identified as being in the lowest achievement group at school 17.7 vs 8.5%; RR 2.1 (1.1–3.7); $p = 0.01$. Of note, these results need to be interpreted with caution as these were secondary outcomes and data was missing for more than half of the study participants.

Another study that deals with early PTL therapy may still be relevant to this chapter. This study was performed by Althabe et al.[32] The study was done in low resources countries. It was large with 51 intervention and 50 control clusters, with approximately 100,000 births. This was a negative study showing worse results in the ACS group. These included:

- Infants <5%th centile: 45% in the ACS group and 10% in the control clusters.
- Suspected maternal infection ACS group: 10% 6% in the control group (odds ratio [OR] 1.67, 1.33–2.09, and $p < 0.0001$.
- The 28-day neonatal mortality was 27.4/1,000 live births for the intervention and 23.9 per 1,000 live births for the control group (RR 1.12, 1.02–1.22, and $p = 0.0127$).
- Suspected maternal infection, 1,207 (3%) in the intervention and 867 (2%) in the control group (OR 1.45, 1.33–1.58, and $p < 0.0001$).

This study is quite different than all previous studies not only in size but many of the elements that exist in high resources countries such as ultrasound. One of the concerns expressed following these results was that the lack of accurate dating that stemmed from the low use of ultrasound scanning caused these results. The major impact of the lack of ultrasound would be the inclusion of patients with late preterm birth in the population studied. In addition, there are concerns about very high baseline rates of sepsis in both maternal and neonatal cohorts and results which may not be applicable to high-income countries.

Guidelines and Conclusion

Most obstetrical societies have guidelines for the use of ACS in PTL. This intervention has been studied extensively and was shown again and again to be of benefit. In addition to these guidelines, there were two National institution of health consensus documents supporting this intervention.[33,34] In contrast, there are only two guidelines on late preterm birth and ACS and these are both American (SMFM and ACOG). One of the reasons is that the leaders of these two societies are proud of this high-quality research that came from the American MFM network. Another reason may be that in the United States, the NICU costs are at times carried by individual families. These costs become an individual and not a societal burden. The NICU cost in the United States is probably one of the highest in the world and 8 days of NICU stay would be costly anywhere. The opposite question is why other societies do not rush to produce similar guidelines. There could be several reasons for that approach. These include:

- Lack of data–there are only three RCTs on the topic and two of them are relatively small.
- The outcome of the large study is not really clear-cut in terms of sepsis and hypoglycemia.

Table 1: Randomized controlled studies (RCTs) evaluating the administration of ACS in the late preterm period and at term

Characteristics	*Stutchfield et al. 2005*[27]	*Balci et al. 2010*[36]	*Porto et al. 2011*[37]	*Ahmed et al. 2015*[38]	*Gyamfi-Bannerman et al. 2016*[26]	*Nada et al. 2016*[39]
Study location	United Kingdom	Turkey	Brazil	Egypt	United States	Egypt
Study design	Open label RCT	Open label RCT	Double blind RCT	Open label RCT	Double blind RCT	Double blind RCT
No. of centers	10	1	1	1	17	1
Duration of study (months)	48	28	26	17	51	37
Lost to follow-up (%)	2.9	0	12.5	0	0.1	N/R
No. of participants*	819 (373 vs 446)	100 (50 vs 50)	273 (143 vs 130)	452 (228 vs 224)	2831 (1427 vs 1400)	1227 (616 vs 611)
Inclusion criteria	Women undergoing planned cesarean delivery	Women at risk of imminent late premature delivery	Women at risk of imminent late premature delivery	Women undergoing planned cesarean delivery	Women at risk of imminent late premature delivery	Women undergoing planned cesarean delivery
Women with diabetes*	10 (4 vs 6)	Excluded	5 (3 vs 2)	N/R	Excluded	N/R
Corticosteroids used	Betamethasone	Betamethasone	Betamethasone	Dexamethasone	Betamethasone	Dexamethasone
Dose (mg) and route	48 hours before delivery. Two 12 mg IM doses separated by 24 hours. Around 48 hours before the planned cesarean delivery	One 12 mg IM dose	Two 12 mg IM doses were separated by 24 hours at the time of admission to the hospital	48 hours before delivery, two 12 mg IM doses separated by 24 hours. 48 hours before planned cesarean delivery	Two 12 mg IM doses were separated by 24 hours at the time of admission to the hospital	Four 8 mg IM doses separated by 8 hours. Around 48 hours before the planned cesarean delivery
Control	No treatment	No treatment	Placebo	No treatment	Placebo	Placebo
Gestational age at randomization (weeks^{days})	≥37^0	34^0–36^6	34^0–36^6	***** 0.3	34^0–36^6	38^0–38^6
Primary outcome	Admission to NICU	Incidence of RDS	Incidence of RDS	Incidence of RDS	Composite neonatal outcomet	Admission to NICU for respiratory morbidity
Definition of RDS	Tachypnea with grunting, recession, or nasal flaring with diffuse reticulogranular infiltrate and oxygen requirement	Respiratory difficult with diffuse reticulogranular infiltrate and oxygen requirement	Tachypnea with grunting, recession, or nasal flaring with diffuse reticulogranular infiltrate and oxygen requirement	Tachypnea with grunting, recession, or nasal flaring with diffuse reticulogranular infiltrate and oxygen requirement	Tachypnea with grunting, recession, or nasal flaring with diffuse reticulogranular infiltrate and oxygen requirement	Tachypnea with grunting, recession, or nasal flaring with diffuse reticulogranular infiltrate and oxygen requirement
Definition of mild RDS	<30% oxygen	N/R	N/R	<30% oxygen	<30% oxygen	N/R
Definition of moderate RDS	30–70% oxygen	N/R	N/R	30–70% oxygen	N/R	N/R
Definition of severe RDS	>70% oxygen or ventilator support	N/R	N/R	>70% oxygen or ventilator support	>30% oxygen for ≥24 continuous hours	N/R
Definition of TTN	Respiratory distress resolved by 72 hours of age without diffuse reticulogranular infiltrate	N/R	Respiratory distress resolved by 72 hours of age without diffuse reticulogranular infiltrate	Respiratory distress resolved by 72 hours of age without diffuse reticulogranular infiltrate	Respiratory distress resolved by 72 hours of age without diffuse reticulogranular infiltrate	Respiratory distress resolved by 72 hours of age without diffuse reticulogranular infiltrate

- The impact of the therapy could be perceived by some as not that clinically important.
- Antenatal corticosteroids (ACS) involve the administration of a pharmacological dose of a hormone that may have a major impact on the developing fetus in at least the three known axes of its effect.
- The major one is the lack of long-term follow-up.

A recent Canadian paper,[35] suggested these points and recommended not implementing this therapy yet. Another issue that has not been studied at all is the fact that ACS may have different therapeutic effects at 34 vs 36 weeks. It may be also the case for side effects and long-term outcomes. This needs to be analyzed as part of a large RCT in this area.

On the contrary, one also needs to ask a question if steroids are not harmful to preterm neonates <34 weeks gestational age (GA) in 30 years follow-up, what is the likelihood of them causing harm in relatively mature neonates? Preterm neonates of 34–36 weeks GA are at lower risk of complications and thus

one would need to follow a very large cohort of neonates, who are routinely not assessed in neurodevelopmental follow-up clinics, to get the answer, which appears to be highly infeasible. In this situation, one could wait for this evidence to come up or discuss the benefits and potential lack of data on harms with parents and make a joint decision as to what families value most: reduced likelihood of respiratory issues, lower length of admission to NICU, a chance to bond with their neonates, early initiation of skin to skin and breastfeeding and take child home vs the risk of hypoglycemia and the very remote and unproven possibility of affecting neurodevelopment.

References

1. Liggins GC. Premature parturition after infusion of corticotrophin or cortisol into foetal lambs. J Endocrinol 1968;42(2):323–329. DOI: 10.1677/joe.0.0420323
2. Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. Pediatrics 1972;50(4):515–525.
3. Melamed N, Shah J, Yoon EW, et al. The role of antenatal corticosteroids in twin pregnancies complicated by preterm birth. Am J Obstet Gynecol 2016;215(4):482.e1–482.e9. DOI: 10.1016/j.ajog.2016.05.037
4. Crowley P, Chalmers I, Keirse MJ. The effects of corticosteroid administration before preterm delivery: an overview of the evidence from controlled trials. Br J Obstet Gynaecol 1990;97(1):11–25. DOI: 10.1111/j.1471-0528.1990.tb01711.x
5. Murphy KE, Hannah ME, Willan AR, et al. Multiple courses of antenatal corticosteroids for preterm birth (MACS): a randomised controlled trial. Lancet 2008;372(9656):2143–2151. DOI: 10.1016/S0140-6736(08)61929-7
6. Wapner RJ, Sorokin Y, Thom EA, et al. Single versus weekly courses of antenatal corticosteroids: evaluation of safety and efficacy. Am J Obstet Gynecol 2006;195(3):633–642. DOI: 10.1016/j.ajog.2006.03.087
7. Crowther CA, Haslam RR, Hiller JE, et al. Neonatal respiratory distress syndrome after repeat exposure to antenatal corticosteroids: a randomised controlled trial. Lancet 2006;367(9526):1913–1919. DOI: 10.1016/S0140-6736(06)68846-6
8. Guinn DA, Atkinson MW, Sullivan L, et al. Single vs weekly courses of antenatal corticosteroids for women at risk of preterm delivery: a randomized controlled trial. JAMA 2001;286(13):1581–1587. DOI: 10.1001/jama.286.13.1581
9. Laskin C, Bombardier C, Hannah ME, et al. Prednisone and aspirin in women with autoantibodies and unexplained recurrent fetal loss. N Engl J Med 1997;337(3):148–153. DOI: 10.1056/NEJM199707173370302
10. Aghajafari F, Murphy K, Matthews S, et al. Repeated doses of antenatal corticosteroids in animals: a systematic review. Am J Obstet Gynecol 2002;186(4):843–849. DOI: 10.1067/mob.2002.121624
11. Dean F, Matthews SG. Maternal dexamethasone treatment in late gestation alters glucocorticoid and mineralocorticoid receptor mRNA in the fetal Guinea pig brain. Brain Res 1999;846(2):253–259. DOI: 10.1016/s0006-8993(99)02064-8
12. Levitt NS, Lindsay RS, Holmes MC, et al. Dexamethasone in the last week of pregnancy attenuates hippocampal glucocorticoid receptor gene expression and elevates blood pressure in the adult offspring in the rat. Neuroendocrinology 1996;64(6):412–418. DOI: 10.1159/000127146
13. Uno H, Eisele S, Sakai A, et al. Neurotoxicity of glucocorticoids in the primate brain. Horm Behav 1994;28(4):336–348. DOI: 10.1006/hbeh.1994.1030
14. Liu L, Li A, Matthews SG. Maternal glucocorticoid treatment programs HPA regulation in adult offspring: sex-specific effects. Am J Physiol Endocrinol Metab 2001;280(5):E729–E739. DOI: https://doi.org/10.1152/ajpendo.2001.280.5.E729
15. Newnham JP, Evans SF, Godfrey M, et al. Maternal, but not fetal, administration of corticosteroids restricts fetal growth. J Matern Fetal Med 1999;8(3):81–87. DOI: 10.1002/(SICI)1520-6661(199905/06)8:3<81::AID-MFM3>3.0.CO;2-N
16. Dalziel SR, Walker NK, Parag V, et al. Cardiovascular risk factors after antenatal exposure to betamethasone: 30-year follow-up of a randomised controlled trial. Lancet 2005;365(9474):1856–1862. DOI: 10.1016/S0140-6736(05)66617-2
17. Dalziel SR, Lim VK, Lambert A, et al. Antenatal exposure to betamethasone: psychological functioning and health related quality of life 31 years after inclusion in randomised controlled trial. BMJ 2005;331(7518):665. DOI: 10.1136/bmj.38576.494363.E0
18. Harding JE, Dalziel antenatal glucocorticoids: where are we after forty years? BJOG 2016;123(10):1707–1708.
19. Sotiriadis A, Tsiami A, Papatheodorou S, et al. Neurodevelopmental outcome after a single course of antenatal steroids in children born preterm: a systematic review and meta-analysis. Obstet Gynecol 2015;125(6):1385–1396. DOI: 10.1097/AOG.0000000000000748
20. Foix-L'Hélias L, Marret S, Ancel PY, et al. Impact of the use of antenatal corticosteroids on mortality, cerebral lesions and 5-year neurodevelopmental outcomes of very preterm infants: the EPIPAGE cohort study. BJOG 2008;115(2):275–282. DOI: 10.1111/j.1471-0528.2007.01566.x
21. Kenyon S, Pike K, Jones DR, et al. Childhood outcomes after prescription of antibiotics to pregnant women with spontaneous preterm labor: 7-year follow-up of the ORACLE II trial. Lancet 2008;372(9646):1319–1327. DOI: 10.1016/S0140-6736(08)61203-9
22. The Royal College of Obstetricians and Gynaecologists: The Use of. Progesterone to Prevent Preterm Delivery Published: 10/02/2010https://www.rcog.org.uk/en/guidelines-research-services/guidelines/the-us
23. Darmasseelane K, Hyde MJ, Santhakumaran S, et al. Mode of delivery and offspring body mass index, overweight and obesity in adult life: a systematic review and meta-analysis. PLoS One 2014;9(2):e87896. DOI: 10.1371/journal.pone.0087896
24. Flenady V, Koopmans L, Middleton P, et al. Major risk factors for stillbirth in high-income countries: a systematic review and meta-analysis. Lancet 2011;377(9774):1331–1340. DOI: 10.1016/S0140-6736(10)62233-7
25. Saccone G, Berghella V. Antenatal corticosteroids for maturity of term or near term fetuses: systematic review and meta-analysis of randomized controlled trials. BMJ 2016;355:i5044. DOI: 10.1136/bmj.i5044. Erratum in: BMJ. 2016 Nov 29;355:i6416
26. Gyamfi-Bannerman C, Thom EA, Blackwell SC, et al. Antenatal betamethasone for women at risk for late preterm delivery. N Engl J Med 2023;388(18):1728.
27. Stutchfield P, Whitaker R, Russell I, et al. Antenatal betamethasone and incidence of neonatal respiratory distress after elective caesarean section: pragmatic randomised trial. BMJ 2005;331(7518):662. DOI: 10.1136/bmj.38547.416493.06

28. Stutchfield PR, Whitaker R, Gliddon AE, et al. Behavioural, educational and respiratory outcomes of antenatal betamethasone for term caesarean section (ASTECS trial). Arch Dis Child Fetal Neonatal Ed 2013;98(3):F195–F200. DOI: 10.1136/archdischild-2012-303157
29. SMFM Statement: Implementation of the use of antenatal corticosteroids in the late preterm birth period in women at risk for preterm delivery. August 2016.
30. ACOG Committee Opinion. Antenatal Corticosteroid. Therapy for Fetal Maturation. #713 August 2017
31. Aiken CE, Fowden AF, Smith GC. Antenatal glucocorticoids prior to Cesarean section at term. JAMA Pediatr 2014;168(6): 507–508. DOI: 10.1001/jamapediatrics.2014.9
32. Althabe F, Belizán JM, McClure EM, et al. A population-based, multifaceted strategy to implement antenatal corticosteroid treatment versus standard care for the reduction of neonatal mortality due to preterm birth in low-income and middle-income countries: the ACT cluster randomised trial. Lancet 2015;385(9968):629–639. DOI: 10.1016/S0140-6736(14)61651-2
33. Effect of corticosteroids for fetal maturation on perinatal outcomes. NIH Consensus Statement. 1994;12(2):1–24.
34. Effect of corticosteroids for fetal maturation on perinatal outcomes. NIH Consensus Development Panel on the Effect of Corticosteroids for Fetal Maturation on Perinatal Outcomes. JAMA 1995;273(5):413–418. DOI: 10.1001/jama.1995.03520290065031
35. Nowik CM, Davies GA, Smith GN. We should proceed with caution when it comes to antenatal corticosteroids after 34 weeks. J Obstet Gynaecol Can 2017;39(1):49–51. DOI: 10.1016/j.jogc.2016.05.011
36. Balci O, Ozdemir S, Mahmoud AS et al. The effect of antenatal steroids on fetal lung maturation between the 34th and 36th week of pregnancy. Gynecol Obstet Invest 2010;70(2):95–99.
37. Porto AM, Coutinho IC, Correia JB, et al. Effectiveness of antenatal corticosteroids in reducing respiratory disorders in late preterm infants: randomised clinical trial. BMJ 2011;342:d1696.
38. Ahmed MR, Sayed Ahmed WA, Mohammed TY. Antenatal steroids at 37 weeks, does it reduce neonatal respiratory morbidity? A randomized trial. J Matern Fetal Neonatal Med 2014;22:1–5.
39. Nada AM, Shafeek MM, Maraghy MA, et al. Antenatal corticosteroid administration before elective caesarean section et term to prevent neonatal respiratory morbidity: a randomized controlled trial. Eur J Obstet Gynecol Reprod Biol 2016;199:88–91.