No. 364, September 2018, (Replaces No. 122, January 2003)

No. 364-Antenatal Corticosteroid Therapy for Improving Neonatal Outcomes

This Clinical Practice Guideline has been prepared by Antenatal Corticosteroid Therapy Working Group and reviewed and approved by the Maternal-Fetal Medicine and Guideline Management and Oversight Committee; and approved by the Board of the Society of Obstetricians and Gynaecologists of Canada.

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Disclosure Statement: Disclosure statements have been received from all authors, and none declared any conflicts of interest.

Key Words: Antenatal corticosteroid therapy, fetal maturation, prematurity, late preterm, pre-labour Caesarean section

J Obstet Gynaecol Can 2018;40(9):1219–1239

https://doi.org/10.1016/j.jogc.2018.04.018

WHAT IS NEW/CHANGED

1. ACS should be routinely administered from 24 + 0 and 34 + 6 weeks gestation when delivery is expected within 7 days.
2. ACS should be administered to women at risk of delivery prior to 24 weeks when delivery is expected within 7 days and intensive care is planned for the baby.
3. Routine use of rescue or repeat courses of ACS is not recommended.
4. Routine use of ACS is not recommended prior to pre-labour Caesarean section at term.

KEY MESSAGES

1. ACS improved neonatal outcomes when administered to women at risk of preterm birth between 24 + 0 and 34 + 6 weeks gestation.
2. ACS should be administered only when preterm delivery is anticipated within 7 days.
3. Possible neonatal benefit should be weighed against possible long-term harm when considering ACS at 35 or 36 weeks gestation.

Abstract

Objective: To assess the benefits and risks of antenatal corticosteroid therapy for women at risk of preterm birth or undergoing pre-labour Caesarean section at term and to make recommendations for improving neonatal and long-term outcomes.

Options: To administer or withhold antenatal corticosteroid therapy for women at high risk of preterm birth or women undergoing pre-labour Caesarean section at term.

Outcomes: Perinatal morbidity, including respiratory distress syndrome, intraventricular hemorrhage, bronchopulmonary dysplasia, infection, hypoglycemia, somatic and brain growth, and neurodevelopment; perinatal mortality; and maternal morbidity, including infection and adrenal suppression.

Intended Users: Maternity care providers including midwives, family physicians, and obstetricians.

Target Population: Pregnant women.

Evidence: Medline, PubMed, Embase, and the Cochrane Library were searched from inception to September 2017. Medical Subject Heading (MeSH) terms and key words related to pregnancy, prematurity, corticosteroids, and perinatal and neonatal mortality and morbidity were used. Statements from professional organizations including that of the National Institutes of Health, the American College of Obstetricians and Gynecologists, the Society for Maternal Fetal Medicine, the Royal College of Obstetricians and Gynaecologists, and the Canadian Pediatric Society were reviewed for additional references. Randomized controlled trials conducted in pregnant women evaluating antenatal corticosteroid therapy and previous systematic reviews on the topic were eligible. Evidence from systematic reviews of non-experimental (cohort) studies was also eligible.

Validation Methods: This Committee Opinion has been reviewed and approved by the Maternal-Fetal Medicine Committee of the SOGC and approved by SOGC Council.

Benefits, Harms, and/or Costs: A course of antenatal corticosteroid therapy administered within 7 days of delivery significantly reduces perinatal morbidity/mortality associated with preterm birth between 24 + 0 and 34 + 6 weeks gestation. When antenatal corticosteroid therapy is given more than 7 days prior to delivery or after 34 + 6 weeks gestation, the adverse effects may outweigh the benefits. Evidence on long-term effects is scarce, and potential neurodevelopment harms are unquantified in cases of late preterm, term, and repeated exposure to antenatal corticosteroid therapy.

Guideline Update: Evidence will be reviewed 5 years after publication to evaluate the need for a complete or partial update of the guideline. If important evidence is published prior to the 5-year time point, an update will be issued to reflect new knowledge and recommendations.

Sponsors: The guideline was developed with resources provided by the Society of Obstetricians and Gynaecologists of Canada with support from the Canadian Institutes of Health Research (APR-126338).

Summary Statements:

1. Trials enrolling pregnant women from 24 + 0 to 34 + 6 weeks gestation at high risk of preterm birth show that antenatal corticosteroid therapy significantly reduces perinatal death, respiratory distress syndrome, and intraventricular hemorrhage (Moderate).
2. Evidence from cohort studies shows a significant reduction in perinatal mortality among infants exposed to antenatal corticosteroid therapy at less than 24 weeks gestation (Low).
3. Antenatal corticosteroid therapy administered to women at risk of preterm delivery between 34 + 0 and 36 + 5 weeks gestation decreases neonatal respiratory morbidity (Moderate).
4. There is an increased risk of neonatal hypoglycemia among infants exposed to antenatal corticosteroid therapy at 34 + 0 to 36 + 5 weeks gestation (Moderate).
5. Administration of antenatal corticosteroid therapy decreases respiratory distress syndrome and need for mechanical ventilation in infants of women undergoing elective pre-labour Caesarean delivery at term (Moderate).
6. Limited evidence is available on long-term outcomes following antenatal corticosteroid therapy in cases of elective pre-labour Caesarean delivery at term gestation. However, there are concerns regarding the cognitive functioning of children exposed to antenatal corticosteroid therapy prior to elective Caesarean section at term gestation (Low).
7. Betamethasone has been more commonly used in studies evaluating the effect of antenatal corticosteroid therapy. In indirect comparisons, betamethasone shows greater reductions in chorioamnionitis, respiratory distress syndrome, and chronic lung disease compared with dexamethasone. In direct comparisons, dexamethasone is associated with a greater reduction in intraventricular hemorrhage and lower length of neonatal intensive care unit stay compared with betamethasone. Effects on other outcomes are generally similar (Low).
8. **The likelihood of preterm delivery and also the gestational age need to be carefully considered** when contemplating the use of antenatal corticosteroid therapy among pregnant women. The efficacy of such therapy is highest when the course is given 24 hours to 7 days prior to delivery. Administration more than 7 days before delivery leads to reduced benefit and potentially unnecessary adverse effects (Low).
9. Repeated courses of antenatal corticosteroid therapy are associated with a reduction in respiratory distress syndrome, mechanical ventilation, and use of surfactant (Moderate).
10. Birth weights and head circumferences are decreased in infants exposed to multiple courses compared with those exposed to a single course of antenatal corticosteroid therapy (High).
11. There is limited evidence on the long-term effects of repeated courses of antenatal corticosteroid therapy. Follow-up from a large trial indicated higher risks of neurosensory disability and of a composite of death or severe disability (neuromotor, neurosensitive, neurocognitive) in children exposed to multiple courses of antenatal corticosteroid therapy and born at term (Moderate).
12. Few trials of antenatal corticosteroid therapy in multifetal pregnancies are available. Subgroup analyses show that effects of antenatal corticosteroid therapy are not different between multifetal pregnancies and singleton pregnancies (Low).
13. Evidence from cohort studies shows benefits of antenatal corticosteroid therapy are greater in multifetal pregnancies when antenatal corticosteroid therapy is administered within 7 days prior to delivery (Low).
14. Evidence on the effects of antenatal corticosteroid therapy in diabetic women is scarce, and no comparative study has been conducted in this subpopulation (Low).
15. Antenatal corticosteroid therapy leads to an increase in maternal blood glucose levels up to 1 week after the initiation of the first dose (Low).
16. There is an absence of evidence on the effects of antenatal corticosteroid therapy among women with obesity, and no comparative study has been conducted in this subpopulation (Low).
17. Responsiveness of growth-restricted fetuses to antenatal corticosteroid therapy remains largely unknown (Low).

18. A lower frequency of major brain lesions, but a higher frequency of body size below the 10th centile at school age is observed in cohort studies of small for gestational age infants exposed to antenatal corticosteroid therapy (Low).
19. Antenatal corticosteroid therapy may induce transient variations in fetal body movements including a potential reduction in fetal movements in the first 3 days following therapy initiation (Low).

Recommendations: Gestational Age Considerations

1. One course of antenatal corticosteroid therapy should be routinely administered to women at 24 + 0 to 34 + 6 weeks gestation who are at high risk for preterm delivery within the next 7 days (Strong, Moderate).
2. Women between 22 + 0 weeks and 23 + 6 weeks gestation at high risk of preterm birth within the next 7 days should be provided with a multidisciplinary consultation regarding the high likelihood for severe perinatal morbidity and mortality and associated maternal morbidity. Antenatal corticosteroid therapy may be considered if early intensive care is requested and planned (Conditional, Low).
3. The balance of risks and benefits does not support routine administration of antenatal corticosteroid therapy for women at 35 + 0 to 35 + 6 weeks gestation who are at high risk for preterm birth in the next 7 days (Conditional, Moderate).
4. Antenatal corticosteroid therapy should not be routinely administered to women at 36 + 0 to 36 + 6 weeks gestation who are at risk for preterm delivery (Conditional, Moderate).
5. Antenatal corticosteroid therapy may be administered between 35 + 0 and 36 + 6 weeks gestation in select clinical situations after risks and benefits are discussed with the woman and the pediatric care provider(s) (Conditional, Moderate).
6. Elective pre-labour Caesarean section should be performed at or after 39 + 0 weeks gestation to minimize respiratory morbidity (Strong, Low).
7. Antenatal corticosteroid therapy should not be routinely administered to women undergoing pre-labour Caesarean section at term gestation (including at 37 and 38 weeks gestation) (Strong, Low).

Agents, Dosage, Regimen, and Target Timing

8. When antenatal corticosteroid therapy is indicated, women should receive a course of antenatal corticosteroid therapy (i.e., either 2 doses of betamethasone 12 mg given by intramuscular injection 24 hours apart or 4 doses of dexamethasone 6 mg given by intramuscular injection 12 hours apart) (Strong, Moderate).
9. Antenatal corticosteroid therapy should be administered to women requiring medically indicated delivery only when the plan to proceed with delivery within 7 days has been finalized and gestational age criteria for antenatal corticosteroid therapy are met (Strong, Low).
10. Antenatal corticosteroid therapy should be routinely administered to women in spontaneous preterm labour characterized by **regular uterine contractions associated with significant cervical dilation or significant cervical change on repeated examination** when gestational age criteria for antenatal corticosteroid therapy are met.
    Regular contractions in the absence of cervical dilation/change, or a short cervical length in the absence of regular contractions, are not indications for antenatal corticosteroid therapy (Strong, Low).
11. Antenatal corticosteroid therapy should be routinely administered at the time of diagnosis to women with preterm premature rupture of membranes, when gestational age criteria are met (Strong, Low).
12. Antenatal corticosteroid therapy should be administered to women with significant antepartum hemorrhage when the risk of delivery within 7 days is high and the gestational age criteria for such therapy are met (Strong, Low).
13. Antenatal corticosteroid therapy should be administered to asymptomatic patients with vasa previa or placenta previa when the risk of delivery within 7 days is high and the gestational age criteria are met (Strong, Low).
14. In cases where the diagnosis of preterm labour has not been firmly established (i.e., no documented cervical change and dilatation <3 cm), and the woman is being transferred to a higher level of care for further assessment, antenatal corticosteroid therapy should not be administered prior to transfer (Strong, Low).
15. If the risk of preterm delivery decreases significantly following administration of the first dose of antenatal corticosteroid therapy, cancellation of the second dose of corticosteroids should be considered. If the second dose is cancelled and a high risk of preterm birth arises subsequently at less than 34 + 6 weeks gestation, 1 dose or 1 course of antenatal corticosteroid therapy should be considered, depending on gestational age and the duration since the first dose (Strong, Low).
16. If the woman remains undelivered beyond 7 days after the first antenatal corticosteroids course, the balance of risks and benefits does not support further routine administration of antenatal corticosteroid therapy even if the risk of preterm delivery increases subsequently. The gestational age and the time interval since the first course of antenatal corticosteroid therapy (at least 14 days) should be taken into account when considering a rescue course. A single rescue course of antenatal corticosteroid therapy may be administered after risks and benefits are discussed with the woman (Conditional, Moderate).

Subpopulations and Special Consideration

17. Antenatal corticosteroid therapy should be administered according to the same indications and in the same gestational age range to women with twin or higher-order multifetal pregnancies as for singleton pregnancies (Conditional, Low).
18. Antenatal corticosteroid therapy should not be administered to women with multifetal pregnancies in the absence of a high risk of preterm birth within the next 7 days (Conditional, Low).
19. Antenatal corticosteroid therapy should be administered to diabetic women at the same dosage, according to the same indications, and in the same gestational age range as that recommended for non-diabetic women (Conditional, Low).
20. Close attention should be paid to control of maternal blood glucose among women with diabetes in the days following antenatal corticosteroid therapy because of anticipated elevations in maternal blood glucose levels (Strong, Low).
21. Because of the transient elevation of blood glucose levels induced by corticosteroids, gestational diabetes screening should be delayed for a minimum of 1 week following antenatal corticosteroid therapy (Strong, Low).
22. Antenatal corticosteroid therapy should be administered to women with obesity at the same dosage as that recommended for women without obesity (according to the same indications and in the same gestational age range) because there is insufficient evidence to guide dosage adjustments by maternal weight (Conditional, Low).
23. There is insufficient evidence to withhold routine antenatal corticosteroid therapy in cases of suspected fetal growth restriction with a high risk of preterm birth. Antenatal corticosteroid therapy should be administered according to the same indications and in the same gestational age range as in normal pregnancies after risks and benefits are discussed with the woman (Conditional, Low).
24. Antenatal corticosteroid therapy should not be administered to women with suspected fetal growth restriction at the time of diagnosis unless there is a high risk of preterm birth within the next 7 days (Conditional, Low).
25. Women should be informed of the potential for a transient reduction in fetal movements and advised to consult with their health care professional if this occurs (Strong, Low).

INTRODUCTION

The rate of preterm birth has remained stable over the last decade in Canada, with 7.3% of live births in 2001 and 7.9% of live births in 2015–2016 delivered at <37 weeks gestation.[1,2] Preterm birth remains a significant cause of perinatal morbidity and mortality,[3–6] with higher risks of RDS, intraventricular hemorrhage, and long-term neurodevelopmental deficits observed in infants born prior to term.[7–9] Such complications have significant long-term health implications and lead to a substantial social and economic burden.[10–14]

Since the first trial of betamethasone for lung maturation in 1972,[15] numerous trials have explored the effect of antenatal corticosteroid therapy for preventing adverse outcomes among infants of women at high risk of preterm birth. These studies showed that antenatal corticosteroid therapy results in a reduction in neonatal mortality and in complications such as intraventricular hemorrhage, necrotizing enterocolitis, and severe RDS.[15–27] The previous guideline by the SOGC on antenatal corticosteroid therapy for women at risk of preterm birth was published in 2003,[28] and currently such treatment is routinely used in women at high risk of birth between 24 and 34 weeks gestation. However, variations in practice are common as uncertainties persist with regard to the benefits and risks of antenatal corticosteroid therapy in specific clinical situations and subpopulations.[29,30] Clinical scenarios where there is uncertainty with regard to the benefits and risks of antenatal corticosteroid therapy include women at high risk of preterm birth at periviable or late preterm gestations, women requiring elective pre-labour Caesarean delivery at term gestations, and women at high risk of preterm birth who have received a first course of antenatal corticosteroid therapy more than 7 days previously. Other areas of uncertainty include the use of antenatal corticosteroid therapy and dose-related issues among women with multifetal pregnancies, women with diabetes, women with obesity, and women with suspected fetal growth restriction. In Canada, antenatal corticosteroid therapy is frequently administered to women who will ultimately deliver at term or more than 2 weeks after treatment,[31] both of which are associated with decreased benefit and potential harms.[32,33] These observations highlight the need for a more rigorous assessment of the risk of preterm delivery before exposing fetuses to antenatal corticosteroid therapy.

This new guideline on antenatal corticosteroid prophylaxis incorporates recent evidence and updates the 2003 SOGC guideline on the topic. As with any intervention, administration of antenatal corticosteroid therapy should always be preceded by a full discussion of benefits and risks with the woman meeting criteria for such treatment.

ABBREVIATIONS

ACS	Antenatal corticosteroid therapy
ALPS	Antenatal Late Preterm Steroids
ASTECS	Antenatal Steroids for Term Caesarean Section
CI	confidence interval
MACS	Multiple Courses of Antenatal Corticosteroids for Preterm Birth Study
OR	odds ratio
RDS	respiratory distress syndrome
RR	risk ratio

GESTATIONAL AGE

Gestational Age Notation

This guideline follows the World Health Organization's notation on gestational age,[34] under which the first day of the last menstrual period is labelled day 0 (of week 0) and days 7 to 13 involve week 1 (or week 1 + 0 to week 1 + 6). A recommendation to administer antenatal corticosteroid therapy to women at high risk of preterm birth between 24 and 34 weeks gestation refers to women at 24 + 0 to 34 + 6 weeks gestation.

Gestational Age: 24 + 0 to 34 + 6 Weeks of Gestation

The 2017 Cochrane review[27] summarized the results of 30 randomized controlled trials that enrolled women from 24 + 0 to 37 + 0 weeks gestation. A majority of studies enrolled women up to a maximum of 34 + 6 weeks (n = 11 studies) or to a lower maximal gestational age (n = 6 studies). The subgroup analyses of studies that recruited women up to 35 + 0 weeks gestation showed a significantly reduced risk of RDS (RR 0.65; 95% CI 0.58–0.73), perinatal death (RR 0.71; 95% CI 0.58–0.87), neonatal death RR 0.67; 95% CI 0.57–0.79), and intraventricular hemorrhage (RR 0.54; 95% CI 0.42–0.68) in the antenatal corticosteroid therapy group compared with the control group. The previous 2006 Cochrane review[32] had shown that RDS was significantly reduced in those who received their first dose of antenatal corticosteroid therapy at 26 + 0 to 29 + 6 weeks gestation, 30 + 0 to 32 + 6 weeks gestation, and 33 + 0 to 34 + 6 weeks gestation compared with the control group.

The evidence presented in the 2017 Cochrane review on the long-term impact of antenatal corticosteroid therapy

Table 1. Summary of studies regarding antenatal corticosteroid therapy administered to women prior to 24 weeks of gestation

Studies		No of patients		Effect		
No. of studies	Study design	ACS	No treatment	Adjusted OR (95% CI)	Certainty	Importance
Mortality before hospital discharge						
4	Observational studies	946/1628 (58.1%)	1423/1982 (71.8%)	OR 0.48 (0.38–0.61)	⨁⨁◯◯ Low	Critical
Respiratory distress syndrome						
2	Observational studies	NA (n = 262)	NA (n = 599)	OR 1.09 (0.69–1.73)	⨁◯◯◯ Very low	Important
Severe intraventricular hemorrhage						
2	Observational studies	NA (n = 261)	NA (n = 598)	OR 0.82 (0.55–1.21)	⨁◯◯◯ Very low	Important

N/A: not available.

Adapted from Park et al.[36]

is limited and shows no significant effects of 1 course of antenatal corticosteroid therapy on childhood developmental delay or cerebral palsy.[27] A review of long-term neurodevelopmental outcomes by Sotiriadis et al. (which included additional observational studies) reported less cerebral palsy and severe disability, and greater intact survival in children whose mothers had received 1 course of antenatal corticosteroid therapy.[35] However, this review documented several limitations with regard to long-term follow-up, and the certainty regarding the long-term effects of antenatal corticosteroid therapy is low. These limitations do not negate the reductions in perinatal mortality and severe neonatal morbidity associated with antenatal corticosteroid therapy, and overall, the available evidence shows significant benefits and limited risks when antenatal corticosteroid therapy is administered between 24 + 0 and 34 + 6 weeks gestation among women at high risk of preterm birth.

Summary Statement

1. Trials enrolling pregnant women from 24 + 0 to 34 + 6 weeks gestation at high risk of preterm birth show that antenatal corticosteroid therapy significantly reduces perinatal death, respiratory distress syndrome, and intraventricular hemorrhage (Moderate).

Recommendation

1. One course of antenatal corticosteroid therapy should be routinely administered to women at 24 + 0 to 34 + 6 weeks gestation who are at high risk for preterm delivery within the next 7 days (Strong recommendation, Moderate certainty of evidence).

Periviable Fetuses: < 24 + 0 Weeks of Gestation

There are limited data on the efficacy of antenatal corticosteroid therapy in the periviable period, specifically from 22 + 0 weeks to 23 + 6 weeks gestation, and no randomized trials have been carried out in women at this gestational age (Table 1).[27,36,37] However, a meta-analysis of cohort studies evaluating antenatal corticosteroid therapy in infants delivered before 24 weeks gestation suggests potential benefit.[36] Such cohort studies show a reduction in perinatal mortality when antenatal corticosteroid therapy is given to women who deliver between 23 + 0 weeks and 23 + 6 weeks gestation, and a possible mortality reduction between 22 + 0 weeks and 22 + 6 weeks. Several national and international groups recommend considering such corticosteroid therapy at a periviable gestation of 23 weeks.[38–42] The recommendation to offer such therapy at 22 + 0 weeks to 22 + 6 weeks is also consistent with Canadian Pediatric Society guidelines.[43] However, the extremely high risk of serious neonatal long-term morbidity and neonatal death associated with delivery before 24 weeks gestation requires that use of antenatal corticosteroid therapy be preceded by an in-depth discussion on prognosis for the infant as well as the mother. Ideally, this should be done in consultation with neonatal care providers. Use of a self-fulfilling line of questioning such as "Do you want everything done for the baby?" should be avoided, as such statements may lead to unintentional moral or emotional coercion. Instead, after the woman (and her partner) has obtained a realistic understanding of prognostic issues, the options of non-intervention versus early intensive care (i.e., active resuscitation) should be provided from a neutral standpoint. Antenatal corticosteroid therapy should only be administered if early intensive care

is requested and planned. If the non-intervention option is chosen, the woman should be reassured that the plan will be revisited and revised with advancing gestation in accordance with the woman's wishes.

Summary Statement

2. Evidence from cohort studies shows a significant reduction in perinatal mortality among infants exposed to antenatal corticosteroid therapy at less than 24 weeks gestation (Low).

Recommendation

2. Women between 22 + 0 weeks and 23 + 6 weeks gestation at high risk of preterm birth within the next 7 days should be provided with a multidisciplinary consultation regarding the high likelihood for severe perinatal morbidity and mortality, and associated maternal morbidity. Antenatal corticosteroid therapy may be considered if early intensive care is requested and planned (Conditional recommendation, Low certainty of evidence).

Late Preterm: 35 + 0 to 35 + 6 and 36 + 0 to 36 + 6 Weeks of Gestation

Recent studies have provided evidence regarding the routine administration of antenatal corticosteroid therapy to women at risk of late preterm delivery (34 + 0 to 36 + 6 weeks gestation).[27] In 2016, Gyamfi-Bannerman et al. published the ALPS study,[26] a randomized, blinded, controlled trial examining 1 course of antenatal betamethasone versus placebo in women with a singleton pregnancy at 34 + 0 to 36 + 5 weeks gestation who were at high risk for delivery during the late preterm period (defined as up to 36 + 6 weeks gestation; N = 2831). According to the ALPS study, a significant reduction in respiratory morbidity (a composite outcome including receipt of continuous positive airway pressure or high-flow nasal cannula for at least 2 consecutive hours, supplemental oxygen of at least 30% for at least 4 continuous hours, extracorporeal membrane oxygenation, mechanical ventilation, or stillbirth or neonatal death within 72 hours after delivery) was observed in the women who received antenatal corticosteroid therapy. Several secondary outcomes including severe respiratory complications (a composite outcome of continuous positive airway pressure or high-flow nasal cannula for at least 12 continuous hours, supplemental oxygen of at least 30% for at least 24 continuous hours, extracorporeal membrane oxygenation or mechanical ventilation, stillbirth, or neonatal death within 72 hours after delivery), transient tachypnea of the newborn, surfactant use, and bronchopulmonary dysplasia were also significantly less frequent following antenatal corticosteroid therapy. There was no significant difference in the rate of RDS in those who received betamethasone versus placebo (RR 0.87; 95% CI 0.65–1.17). However, neonatal hypoglycemia occurred more frequently following antenatal corticosteroid therapy (24% vs. 15%; RR 1.60; 95% CI 1.37–1.87). The study report did not include stratified analyses by gestational week, but a subgroup analysis of women recruited at or after 36 + 0 weeks gestation showed no significant difference in primary outcome (RR 1.00; 95% CI 0.64–1.6) or in the rate of severe respiratory complications (RR 1.28; 95% CI 0.65–2.52). Furthermore, the frequency of the primary outcome and severe respiratory complications was significantly lower among women who delivered at 36 + 0 to 36 + 6 weeks compared with those who delivered at 34 + 0 to 35 + 6 weeks gestation.

A recent meta-analysis summarizing data from the ALPS trial and 5 other randomized controlled trials examining antenatal corticosteroid therapy in women at risk for preterm delivery from 34 + 0 to 36 + 6 weeks gestation showed a significant decrease in severe RDS among those who received antenatal corticosteroid therapy (Table 2).[27] Although these studies demonstrated a reduction in respiratory morbidity with administration of antenatal corticosteroid therapy throughout the late preterm period, the balance of risks and benefits at each gestational week remains unclear.[26,27,44] Previous publications have cautioned against routine use of antenatal corticosteroid therapy at late preterm gestation because of the relatively low baseline rates of respiratory morbidity and concerns regarding an increased risk of hypoglycemia and possible neurodevelopmental morbidity.[45] A meta-analysis of 3 trials of women at risk of late preterm delivery showed that neonatal hypoglycemia occurs significantly more frequently following antenatal corticosteroid therapy.[26,46,47] A recent cohort study documented that neonatal hypoglycemia (i.e., glucose <2.5 mmol/L) in infants between 32 + 0 and 35 + 6 weeks gestation was associated with developmental delay at approximately 4 years of age.[48] However, there is no consensus on the critical threshold of blood glucose level and the period of time the infant is exposed to hypoglycemia for the risk of neurodevelopmental morbidity to increase.[45,49] Previous research has shown an increased risk of neurodevelopmental deficits in children exposed to multiple courses of antenatal corticosteroid therapy prior to term and then subsequently delivered at term.[33] On the other hand, as noted in 2 reviews, follow-up studies have not found an increased risk of neurodevelopmental morbidity in children who were exposed to antenatal corticosteroid therapy and delivered at preterm gestation.[27,35]

The balance of short-term benefits and risks (caused by reductions in respiratory morbidity and increases in

Table 2. Summary of studies regarding antenatal corticosteroid therapy administered to women between 34 + 0 and 36 + 6 weeks of gestation

Studies		No. of patients		Effect			
No. of studies	Study design	ACS	No treatment (or placebo)	RR (95% CI)	Absolute (95% CI)	Certainty	Importance
Perinatal death							
3	RCT	6/1658 (0.4%)	6/1638 (0.4%)	RR 1.03 (0.29–3.67)	0 fewer per 1000 (from 3 fewer to 10 more)	⨁◯◯◯ Very low	Critical
Respiratory distress syndrome							
6	RCT	102/1901 (5.4%)	202/1882 (10.7%)	RR 0.71 (0.56–0.91)	31 fewer per 1000 (from 10 fewer to 47 fewer)	⨁⨁⨁◯ Moderate	Important
Chorioamnionitis							
3	RCT	20/1604 (1.2%)	35/1598 (2.2%)	RR 0.57 (0.33–0.99)	9 fewer per 1000 (from 0 fewer to 15 fewer)	⨁⨁◯◯ Low	Important
Hypoglycemia							
3	RCT	367/1666 (22.0%)	222/1628 (13.6%)	RR 1.62 (1.39–1.88)	85 more per 1000 (from 53 more to 120 more)	⨁⨁⨁◯ Moderate	Important

RCT: randomized controlled trial.

Based on data from Roberts et al.[27] and additional information from original studies.

hypoglycemia) and the absence of evidence regarding the long-term neurodevelopmental effects of antenatal corticosteroid therapy suggest the need for a nuanced approach to antenatal corticosteroid therapy at late preterm gestation. The balance of benefits and risks supports routine antenatal corticosteroid at 34 + 0 to 34 + 6 weeks gestation (when respiratory morbidity is relatively high) but does not support routine antenatal corticosteroid therapy at 35 + 0 to 35 + 6 and especially at 36 + 0 to 36 + 6 weeks gestation (when risks of respiratory morbidity are relatively low). If the anticipated benefit with regard to respiratory morbidity is expected to outweigh potential harms, antenatal corticosteroid therapy may be considered for women at risk of preterm delivery from 35 + 0 to 35 + 6 weeks gestation with close monitoring of the infant's blood glucose levels.

Summary Statements

3. Antenatal corticosteroid therapy administered to women at risk of preterm delivery between 34 + 0 and 36 + 5 weeks gestation decreases neonatal respiratory morbidity (Moderate).
4. There is an increased risk of neonatal hypoglycemia among infants exposed to antenatal corticosteroid therapy at 34 + 0 to 36 + 5 weeks gestation (Moderate).

Recommendations

3. The balance of risks and benefits does not support routine administration of antenatal corticosteroid therapy for women at 35 + 0 to 35 + 6 weeks gestation who are at high risk for preterm birth in the next 7 days (Conditional recommendations, Moderate certainty of evidence).
4. Antenatal corticosteroid therapy should not be routinely administered to women at 36 + 0 to 36 + 6 weeks gestation who are at risk for preterm delivery (Conditional recommendations, Moderate certainty of evidence).
5. Antenatal corticosteroid therapy may be administered between 35 + 0 and 36 + 6 weeks gestation in select clinical situations after risks and benefits are discussed with the woman and the pediatric care provider(s) (Conditional recommendations, Moderate certainty of evidence).

Term Gestation: Pre-Labour Caesarean Section at 37 + 0 Weeks or Later

A number of studies have shown that delivery by elective pre-labour Caesarean section at less than 39 + 0 weeks gestation can lead to respiratory morbidity in infants, requiring admission to the neonatal intensive care unit.[50–53] This has led to recommendations regarding the use of antenatal corticosteroid therapy to reduce the risk of respiratory morbidity in babies delivered by elective pre-labour Caesarean section prior to 39 + 0 weeks gestation.[42] A meta-analysis of 4 randomized controlled trials of antenatal corticosteroid therapy prior to elective Caesarean delivery[54–57] shows some benefits related to respiratory morbidity in infants (Table 3). A decrease in RDS (from 6.7% to 2.7%), transient tachypnea (from 7.0% to 3.0%), and mechanical ventilation (from 3.6% to 0.7%) was observed after antenatal corticosteroid therapy in infants

Table 3. Summary of studies regarding antenatal corticosteroid therapy administered to women prior to elective Caesarean section at term

Studies		No. of patients		Effect			
No. of studies	Study design	ACS	No treatment (or placebo)	RR (95% CI)	Absolute (95% CI)	Certainty	Importance
Neonatal death							
4	RCT	2/1853 (0.1%)	3/1917 (0.2%)	RR 0.67 (0.1–4.10)	0 fewer per 1000 (from 1 fewer to 5 more)	⨁◯◯◯ Very low	Critical
RDS							
4	RCT	41/1853 (2.2%)	96/1917 (5.0%)	RR 0.44 (0.31–0.63)	28 fewer per 1000 (from 19 fewer to 35 fewer)	⨁⨁⨁◯ Moderate	Important
Severe RDS							
2	RCT	1/601 (0.2%)	7/670 (1.0%)	RR 0.22 (0.02–1.31)	8 fewer per 1000 (from 3 more to 10 fewer)	⨁◯◯◯ Very low	Important
Mechanical ventilation							
3	RCT	14/1625 (0.9%)	51/1693 (3.0%)	RR 0.30 (0.14–0.63)	21 fewer per 1000 (from 11 fewer to 26 fewer)	⨁⨁◯◯ Low	Important
Admission to NICU							
4	RCT	51/1853 (2.8%)	89/1917 (4.6%)	RR 0.55 (0.31–1.00)	21 fewer per 1000 (from 0 fewer to 32 fewer)	⨁◯◯◯ Very low	Important

RCT: randomized controlled trial; NICU: neonatal intensive care unit.

Based on data from Saccone et al.[44] and Nooh et al.[57]

of women undergoing elective Caesarean section at term. However, some of these studies were affected by a high risk of bias caused by a lack of blinding and other considerations.[44] Only 1 study[55] included a large number of women with medically indicated Caesarean sections and showed improvements in respiratory morbidity, although these benefits were minimal with increasing gestational age. Furthermore, evidence regarding the safety of antenatal corticosteroid therapy in infants born after 36 + 0 weeks gestation is limited.[44,54] The follow-up study of the ASTECS trial raised concerns regarding the academic ability of children exposed to antenatal corticosteroid therapy at term gestation.[58] The authors concluded that there were no significant behavioural or general health differences at 8 to 15 years between children who received antenatal corticosteroids prior to term elective Caesarean section and those who received a placebo. However, the school assessments of academic ability were significantly lower in children exposed to betamethasone. Importantly, losses to follow-up diminished the validity of this finding.

Elective pre-labour Caesarean section should not be performed until 39 + 0 weeks gestation. Caesarean delivery at or after 39 + 0 weeks gestation is associated with lower rates of respiratory morbidity, and there are limited benefits associated with antenatal corticosteroid therapy at this gestation.[54-57] The benefits of reductions in short-term respiratory morbidity do not justify the risk of antenatal corticosteroid therapy in such cases.[59]

Summary Statements

5. Administration of antenatal corticosteroid therapy decreases respiratory distress syndrome and need for mechanical ventilation in infants of women undergoing elective pre-labour Caesarean section at term (Moderate).
6. Limited evidence is available on long-term outcomes following antenatal corticosteroid therapy in cases of elective pre-labour Caesarean delivery at term gestations. However, there are concerns regarding the cognitive functioning of children exposed to antenatal corticosteroid therapy prior to elective Caesarean section at term gestations (Low).

Recommendations

6. Elective pre-labour Caesarean section should be performed at or after 39 + 0 weeks gestation to minimize respiratory morbidity (Strong recommendation, Low certainty of evidence).
7. Antenatal corticosteroid therapy should not be routinely administered to women undergoing pre-labour Caesarean section at term gestation (including at 37 and 38 weeks gestation) (Strong recommendation, Low certainty of evidence).

Table 4. Summary table of recommendations according to gestational age

Gestational age	Recommendation in case of high risk of delivery within 7 days	Level of evidence	Strength of recommendation
<24 + 0 weeks	Administration based on desire for early intensive care by woman in consultation with health care providers	Low	Conditional
24 + 0 to 34 + 6 weeks	Routine administration	Moderate	Strong
35 + 0 to 35 + 6 weeks	Administration based on discussion of risk and benefits with patients	Moderate	Conditional
36 + 0 to 36 + 6 weeks	Administration restricted to specific clinical situations	Moderate	Conditional
Elective Caesarean delivery at term	Not recommended	Low	Strong

Summary of the Evidence by Gestational Age Category

Gestational age and the associated risk of morbidity need to be carefully considered when contemplating antenatal corticosteroid therapy (Table 4, Figure 1).

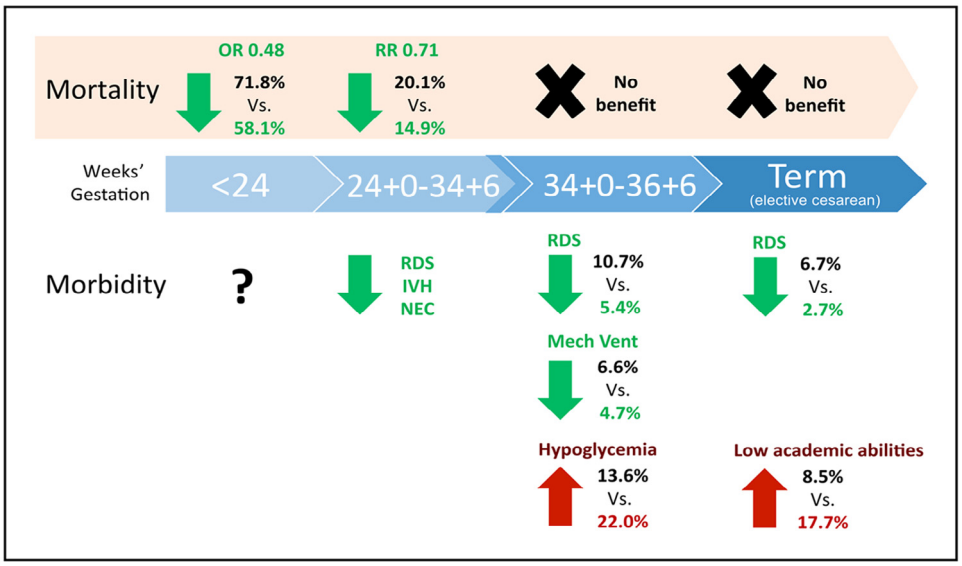
AGENTS, DOSAGE, REGIMEN

Agents and Dosage

In the recent Cochrane review of 30 trials by Roberts et al.,[27] no significant difference was observed between betamethasone and dexamethasone, except for a significantly larger beneficial effect on chorioamnionitis, RDS, and chronic lung disease following betamethasone administration (vs. placebo) compared with studies evaluating dexamethasone administration (vs. placebo). However, this indirect comparison between dexamethasone and betamethasone involved different populations and was potentially confounded.

A recent Cochrane review by Brownfoot et al. examined 12 randomized trials directly comparing different types of corticosteroids and regimens used for accelerating fetal lung maturation.[60] Dexamethasone and betamethasone showed similar effects (Table 5). However, the risk of intraventricular hemorrhage was lower among infants whose mothers were treated with dexamethasone compared with infants whose mothers were treated with betamethasone. Length of neonatal intensive care unit stay was also decreased following dexamethasone prophylaxis compared with betamethasone prophylaxis. There was no other significant difference for comparisons involving perinatal death, RDS and other perinatal outcomes. The upcoming results from the *Australian Antenatal Study To Evaluate the Role Of*

Figure 1. Summary of the evidence.



IVH: intraventricular hemorrhage; Mech Vent: mechanical ventilation; NEC: necrotizing enterocolitis; OR: odds ratio; RR: risk ratio; RDS: respiratory distress syndrome; green arrow: benefit; red arrow: harm. (From S. McDonald, personal communication).

Table 5. Summary of studies comparing dexamethasone and betamethasone

Studies		No. of patients		Effect			
No. of studies	Study design	Dexamethasone	Betamethasone	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Neonatal death							
4	RCT	8/278 (2.9%)	6/318 (1.9%)	RR 1.41 (0.54–3.67)	8 more per 1000 (from 9 fewer to 50 more)	⊕◯◯◯ Very low	Critical
Respiratory distress syndrome							
5	RCT	122/354 (34.5%)	121/399 (30.3%)	RR 1.06 (0.88–1.27)	18 more per 1000 (from 36 fewer to 82 more)	⊕⊕⊕◯ Moderate	Important
Intraventricular hemorrhage							
4	RCT	9/257 (3.5%)	21/292 (7.2%)	RR 0.44 (0.21–0.92)	40 fewer per 1000 (from 6 fewer to 57 fewer)	⊕⊕⊕⊕ High	Important
Birth weight (kg)							
5	RCT	N/A	N/A	N/A	Mean difference 0.01 (–0.11 to 0.12)	⊕⊕⊕◯ Moderate	Important

RCT: randomized controlled trial; N/A: not applicable.

Based on data from Brownfoot et al.[60]

Intramuscular Dexamethasone (A*STEROID) comparing 2 intramuscular 12-mg doses of dexamethasone and 2 doses of 11.4 mg betamethasone both 24 hours apart may shed light on some of the differences observed between the 2 agents.[61]

Only 1 study of 228 women (260 fetuses) compared 12-hourly to 24-hourly dosing of betamethasone.[62] Respiratory distress syndrome was reduced (RR 0.83 [0.69, 0.99]) with the administration of betamethasone 12 hourly compared with 24 hourly when women were enrolled between 23 + 1 and 26 + 0 weeks gestation. Postpartum maternal length of stay was also lower (mean difference −0.73 days [−1.28, −0.18]) in women who received betamethasone every 12 hours. The results of this study have to be interpreted cautiously, considering personnel and participants were not blinded to intervention allocation and no long-term studies have been conducted to evaluate the impact of shorter delays between doses.

Most studies conducted on the use of antenatal corticosteroids have used either 2 doses of betamethasone 12 mg 24 hourly or 4 doses of dexamethasone 6 mg 12 hourly.[27,60]

Summary Statements

7. Betamethasone has been more commonly used in studies evaluating the effect of antenatal corticosteroid therapy. In indirect comparisons, betamethasone shows greater reductions of chorioamnionitis, respiratory distress syndrome, and chronic lung diseases compared with dexamethasone. In direct comparisons, dexamethasone is associated with a greater reduction in intraventricular hemorrhage and lower length of neonatal intensive care unit stay compared with betamethasone. Effects on other outcomes are generally similar (Low).

Recommendation

8. When antenatal corticosteroid therapy is indicated, women should receive a course of antenatal corticosteroid therapy (i.e., either 2 doses of betamethasone 12 mg given by intramuscular injection 24 hours apart or 4 doses of dexamethasone 6 mg given by intramuscular injection 12 hours apart) (Strong recommendation, Moderate certainty of evidence).

Target Timing

The benefits of antenatal corticosteroid therapy are thought to be most pronounced in babies born between 1 and 7 days after the first dose of antenatal corticosteroid therapy.[63–65] However, the majority of patients who receive antenatal corticosteroid therapy remain undelivered beyond this window.[31,66–70] A recent Canadian study shows that 52% of women who receive antenatal corticosteroid therapy deliver at 35 weeks gestation or later.[31] The potential benefits of antenatal steroids as well as their risks are gestational age dependent, with the risks potentially increasing and benefits decreasing with advancing gestational age. Both the likelihood of preterm delivery and the gestational age need

to be considered when contemplating necessity for antenatal corticosteroid therapy.[71]

Antenatal corticosteroid therapy, when not clearly indicated, can lead to at least 2 potential problems. First, the adverse effects of steroids will likely outweigh any potential benefits when the risk of preterm delivery is low. The 2006 Cochrane review did not show benefit of antenatal corticosteroid therapy when the first dose was administered more than 7 days prior to delivery.[32] Second, if the woman remains undelivered beyond the 1-week window of benefit, subsequent preterm labour or other indications may prompt consideration of a rescue course. Administration of multiple courses of antenatal corticosteroids has the potential for adversely affecting neurodevelopment, as seen in the 5-year follow-up of the MACS-5 study.[33] This study reported a higher risk of a composit of death and severe disability in babies exposed to repeated courses of antenatal corticosteroid therapy and delivered at term. In patients with a planned, medically indicated preterm delivery, the decision regarding when to administer antenatal corticosteroid therapy is usually straightforward.[69,70] However, among women at risk of spontaneous preterm delivery or unplanned medically-indicated delivery, the decision and timing of antenatal corticosteroid therapy administration may be more difficult.

The diagnosis of preterm labour is challenging. Antenatal corticosteroid therapy should be considered at the relevant preterm gestation in the presence of regular uterine contractions **associated with significant cervical dilation or significant cervical change on repeated examination.** Women with uterine contractions at preterm gestation who do not have other features supporting a diagnosis of preterm labour (sometimes labelled as having "threatened preterm labour") should be provided clinical oversight, but such a scenario does not warrant antenatal corticosteroid therapy. Incidental findings of a short cervix or a positive fetal fibronectin test result in the absence of uterine contractions are other clinical scenarios that do not warrant administration of antenatal corticosteroid therapy per se. It is a clinically prudent policy to repeat the assessment and ensure that women are in active preterm labour before initiating the administration of antenatal corticosteroid therapy unless the cervix is already dilated to 3 cm or more on first examination.

Women being transferred to a higher level of care need to be assessed on a case-by-case basis to determine whether antenatal corticosteroid therapy should be initiated prior to transfer. If the diagnosis of preterm labour has not been clearly established on the basis of documented cervical change and/or a dilatation ≥3 cm (see earlier text for detail on the diagnosis of preterm labour) and the woman is being transferred for further assessment or observation, initiation of antenatal corticosteroid therapy should be withheld until a reassessment regarding the risk of preterm labour is carried out in the receiving centre. In cases where the first dose of antenatal corticosteroid therapy has been administered and then reassessment suggests that delivery within the next 7 days is unlikely, cancellation of the second dose should be considered.

In cases with "imminent" preterm delivery such as iatrogenic delivery for maternal or fetal indications, or preterm labour with advanced cervical dilation, a dose of corticosteroids can still be given with the understanding that even an interval of a few hours between antenatal corticosteroid therapy administration and delivery could yield some fetal benefit.[32,72] However, depending on the maternal/fetal condition, delivery should not be delayed to allow for this benefit.

Summary Statement

8. **The likelihood of preterm delivery and also the gestational age need to be carefully considered** when contemplating the use of antenatal corticosteroid therapy among pregnant women. The efficacy of such therapy is highest when the course is given 24 hours to 7 days prior to delivery. Administration more than 7 days before delivery leads to reduced benefit and potentially unnecessary adverse effects (Low).

Recommendations

9. Antenatal corticosteroid therapy should be administered to women requiring medically indicated delivery, only when the plan to proceed with delivery within 7 days has been finalized and gestational age criteria for antenatal corticosteroid therapy are met (Strong recommendations, Low certainty of evidence).
10. Antenatal corticosteroid therapy should be routinely administered to women in spontaneous preterm labour characterized by **regular uterine contractions associated with significant cervical dilation or significant cervical change on repeated examination** when gestational age criteria for antenatal corticosteroid therapy are met.
    Regular contractions in the absence of cervical dilation/change, or a short cervical length in the absence of regular contractions, are not indications for antenatal corticosteroid therapy (Strong recommendations, Low certainty of evidence).

11. Antenatal corticosteroid therapy should be routinely administered at the time of diagnosis to women with preterm premature rupture of membranes, when gestational age criteria are met (Strong recommendations, Low certainty of evidence).
12. Antenatal corticosteroid therapy should be administered to women with significant antepartum hemorrhage when the risk of delivery within 7 days is high and the gestational age criteria for such therapy are met (Strong recommendations, Low certainty of evidence).
13. Antenatal corticosteroid therapy should be administered to asymptomatic women with vasa previa or placenta previa when the risk of delivery within 7 days is high and the gestational age criteria are met (Strong recommendations, Low certainty of evidence).
14. In cases where the diagnosis of preterm labour has not been firmly established (i.e., no documented cervical change and dilatation <3 cm), and the woman is being transferred to a higher level of care for further assessment, antenatal corticosteroid therapy should not be administered prior to transfer (Strong recommendations, Low certainty of evidence).

Rescue Course and Repeated Doses

NB. In this section "rescue course" refers specifically to 1 course of antenatal corticosteroid therapy, administered to women who have previously received 1 full course of antenatal corticosteroids but have remained undelivered following completion of this initial course. "Repeat doses" refers to any administration of antenatal corticosteroids at regular intervals after 1 full course of antenatal corticosteroid therapy has been previously administered.

The recent Cochrane review by Roberts et al.[27] showed that weekly administration (n = 9 studies) of antenatal corticosteroid therapy results in a reduction of neonatal and perinatal deaths, RDS, and intraventricular hemorrhage when compared with placebo or no intervention. However, pooled effects from studies evaluating weekly repeats are not significantly different from those of studies evaluating single courses. Weekly repeats of antenatal corticosteroid therapy were not significantly associated with other outcomes in this review.

Another recent Cochrane review of randomized controlled trials evaluating repeated doses (n = 2 studies) or courses (n = 8 studies) of antenatal corticosteroid therapy up until women reached 32 to 34 weeks gestation reported lower risks of RDS, and neonatal interventions such as mechanical ventilation, oxygen supplementation, surfactant, and inotropic support following repeated exposure to antenatal corticosteroid therapy compared with a single course (Table 6).[73] However, the largest study of repeated courses (MACS), which reported similar risks of severe RDS in repeated courses and single-course groups, was not included in the meta-analysis of RDS.[74] The systematic review showed significantly lower birth weights and head circumferences in neonates exposed to repeated courses of antenatal corticosteroid therapy (Table 6). No benefits of repeated courses of antenatal corticosteroid therapy on fetal and neonatal mortality were observed.

The 1- to 2-year follow-up of 1 randomized trial reported in 2017 showed no difference following a rescue course of antenatal corticosteroid therapy versus placebo in pulmonary function tests, asthma, respiratory syncytial virus infection, hospital admission for respiratory illness, weight, length, or head circumference.[75] Similarly, the 6- to 8-year follow-up of the Australasian Collaborative Trial Of Repeat Doses Of Prenatal Steroids (ACTORDS) showed no significant differences in rates of survival free of disability, intellectual quotient, neurosensory disability, cerebral palsy, lung function, use of health services, bone status, or risk factors for cardiovascular and metabolic diseases in those who received weekly repeat doses versus those who received a single course of antenatal corticosteroid therapy.[76–78] However, higher frequency of attention deficit (lower memory and learning score in the Rey Auditory Verbal Learning Test) and a borderline significant increase in behavioural dysfunction (lower Behavioural Regulation Index scores; $P = 0.05$) were observed in the multiple-courses group.[76] Furthermore, the MACS-5 follow-up study showed that 5-year-old children born at term who were exposed to multiple courses of antenatal corticosteroid therapy were at higher risk of neurosensory disability (adjusted OR 3.70; 95% CI 1.57–8.75), and a composite of severe (neuromotor, neurosensory, or neurocognitive) disability or death (adjusted OR 1.69; 95% CI 1.04–2.77).[33]

Use of a single rescue dose or course of antenatal corticosteroid therapy is currently supported by American, British, and Australian guidelines.[79–81] However, evidence supporting such use of a single rescue dose or course is limited. Most studies included in the Cochrane review compared weekly repeated courses to a single course of antenatal corticosteroid therapy, with less than 50% of participants in the weekly repeated courses group receiving a single rescue course.[74,82–85] Most of the studies on multiple doses tested weekly repeats.[82–87]

Three studies compared a single rescue course[88,89] or dose[90] to 1 course of antenatal corticosteroid therapy. Two trials evaluated a single rescue course at least 14 days

Table 6. Summary of studies regarding repeated courses of antenatal corticosteroid therapy

Studies		No. of patients		Effect			
No. of studies	Study design	Repeated courses	single	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Fetal and neonatal mortality							
9	RCT	96/2791 (3.4%)	102/2763 (3.7%)	RR 0.94 (0.71–1.23)	2 fewer per 1000 (from 8 more to 11 fewer)	⨁⨁⨁⨁ High	Critical
Respiratory distress syndrome							
8	RCT	463/1603 (28.9%)	565/1603 (35.2%)	RR 0.83 (0.75–0.91)	60 fewer per 1000 (from 32 fewer to 88 fewer)	⨁⨁⨁◯ Moderate	Important
Birth weight (g)							
9	RCT	NA	NA	NA	Mean difference –75.8 g (–117.6 to –34.0)	⨁⨁⨁⨁ High	Important
Small for gestational age at birth							
7	RCT	191/1996 (9.6%)	163/1979 (8.2%)	RR 1.18 (0.97–1.43)	15 more per 1000 (from 2 fewer to 35 more)	⨁⨁⨁◯ Moderate	Important
Head circumference at birth (cm)							
9	RCT	N/A	N/A	N/A	Mean difference –0.32 cm (–0.49 to –0.15)	⨁⨁⨁⨁ High	Important
Mechanical ventilation							
6	RCT	556/2463 (22.6%)	668/2455 (27.2%)	RR 0.84 (0.71–0.99)	44 fewer per 1000 (from 3 fewer to 79 fewer)	⨁⨁⨁◯ Moderate	Important
Use of surfactant							
9	RCT	514/2772 (18.5%)	643/2753 (23.4%)	RR 0.78 (0.65–0.95)	51 fewer per 1000 (from 12 fewer to 82 fewer)	⨁⨁⨁◯ Moderate	Important
Total mortality up to early childhood follow-up							
4	RCT	96/2190 (4.4%)	90/2180 (4.1%)	RR 1.06 (0.80–1.41)	2 more per 1000 (from 8 fewer to 17 more)	⨁⨁⨁◯ Moderate	Important

RCT: randomized controlled trial; N/A: not applicable.

Based on data from Roberts et al.[27] and Crowther et al.[73]

after the first course;[88,89] and 1 trial evaluated a rescue dose at least 7 days after the first course of antenatal corticosteroid therapy.[90] All administered repeated antenatal corticosteroids before 34 weeks gestation. One trial showed benefits on respiratory morbidity (reduced RDS, surfactant use and composite morbidity)[88]; 1 small trial showed no effect except on respiratory compliance (although the 1- to 2-year follow-up study showed no long-term differences in pulmonary outcomes),[75,89] and another was stopped early because of a significant reduction in intact survival (survival until hospital discharge without RDS or grade III–IV intraventricular hemorrhage) following exposure to a rescue dose of antenatal corticosteroid therapy and delivery within 24 hours.[90] In addition, the largest trial of a single rescue course of antenatal corticosteroid therapy, by Garite et al.,[88] showed that a delay greater than 7 days between rescue course and delivery was associated with no significant short-term benefits.

Overall, the evidence of benefits of rescue or repeated courses of antenatal corticosteroid therapy are limited, no long-term benefit has been shown compared with single course therapy, and concerns regarding potential long-term harms are supported by data from the largest trial.[33]

Summary Statements

9. Repeated courses of antenatal corticosteroid therapy are associated with a reduction in respiratory distress syndrome, mechanical ventilation, and use of surfactant (Moderate).
10. Birth weights and head circumferences are decreased in infants exposed to multiple courses compared with those exposed to a single course of antenatal corticosteroid therapy (High).
11. There is limited evidence on the long-term effects of repeated courses of antenatal corticosteroid therapy.

Follow-up from a large trial indicated higher risks of neurosensory disability and of a composite of death or severe disability (neuromotor, neurosensitive, neurocognitive) in children exposed to multiple courses of antenatal corticosteroid therapy and born at term (Moderate).

Recommendations

15. If the risk of preterm delivery decreases significantly following administration of the first dose of antenatal corticosteroid therapy, cancellation of the second dose of corticosteroids should be considered. If the second dose is cancelled and a high risk of preterm birth arises subsequently at less than 34 + 6 weeks gestation, 1 dose or 1 course of antenatal corticosteroid therapy should be considered, depending on gestational age and the duration since the first dose (Strong recommendations, Low certainty of evidence).
16. If the woman remains undelivered beyond 7 days after the first antenatal corticosteroids course, the balance of risks and benefits does not support further routine administration of antenatal corticosteroid therapy even if the risk of preterm delivery increases subsequently. The gestational age and the time interval since the first course of antenatal corticosteroid therapy (at least 14 days) should be taken into account when considering a rescue course. A single rescue course of antenatal corticosteroid therapy may be administered after risks and benefits are discussed with the woman (Conditional recommendation, Moderate certainty of evidence).

Summary of the Evidence regarding the timing of exposure to antenatal corticosteroid therapy. The risk of delivery within 7 days needs to be carefully assessed when contemplating antenatal corticosteroid therapy (Table 7, Figure 2).

SUBPOPULATIONS AND SPECIAL CONSIDERATION

Multifetal Gestation

The recent review by Roberts et al. 2017 included 11 trials of antenatal corticosteroid therapy in which women with multifetal pregnancies were included, and 4r of these reported RDS rates specifically among the subgroup of women with multifetal pregnancies.[27] There was no significant effect of antenatal corticosteroid therapy observed on RDS, perinatal death, intraventricular hemorrhage, chorioamnionitis, or birth weight in multifetal pregnancies. However, the number of studies and the number of women in these studies were low, leading to limited statistical power. More importantly, there was no significant difference between the effects of antenatal corticosteroid therapy among singleton pregnancies and multifetal pregnancies.

Recent cohort studies show benefits of antenatal corticosteroid therapy in multifetal pregnancies,[91–93] and effects among twins and singletons are similar.[94–96] Palas et al. also report the largest benefits among multifetal pregnancies when antenatal corticosteroid therapy are administered a maximum of 7 days prior to delivery.[93] Furthermore, a study of betamethasone concentration in maternal serum and cord blood shows no significant difference between multifetal and singleton pregnancies after adjustment for gestational age at delivery, number of antenatal corticosteroids courses, days from last course to delivery, and body mass index.[97]

Summary Statements

12. Few trials of antenatal corticosteroid therapy in multifetal pregnancies are available. Subgroup analyses show that effects of antenatal corticosteroid therapy are not different between multifetal pregnancies and singleton pregnancies (Low).
13. Evidence from cohort studies shows benefits of antenatal corticosteroid therapy are greater in multifetal pregnancies when antenatal corticosteroid therapy is administered within 7 days prior to delivery (Low).

Recommendations

17. Antenatal corticosteroid therapy should be administered according to the same indications and in the same gestational age range to women with twin or higher-order multifetal pregnancies as for singleton pregnancies (Conditional recommendation, Low certainty of evidence).
18. Antenatal corticosteroid therapy should not be administered to women with multifetal pregnancies in the absence of a high risk of preterm birth within the next 7 days (Conditional recommendation, Low certainty of evidence).

Women with Pre-Gestational or Gestational Diabetes Mellitus

No randomized controlled trial has been conducted to evaluate the effect of antenatal corticosteroid therapy in diabetic women. In the recent Cochrane review, 10 studies explicitly excluded women with insulin-treated diabetes or other cases of diabetes.[27] Another recent systematic review conducted in 2014 also failed to identify any comparative studies of antenatal corticosteroid therapy in women with pre-existing diabetes or gestational diabetes.[98]

Table 7. Summary table of recommendations for agents, dosage and regimens

Agents, dosage, and regimens	Recommendation when gestational age criteria for antenatal corticosteroid therapy are met	Level of evidence	Strength of recommendation
Agents and dosage	2 × 12 mg doses of betamethasone IM, 24 hours apart **or** 4 × 6 mg doses of dexamethasone IM, 12 hours apart	Moderate	Strong
Timing of antenatal corticosteroid initiation	Administer if medically indicated delivery planned within 7 days	Low	Strong
	Administer if woman is in spontaneous preterm labour (ie, regular uterine contractions associated with significant cervical dilation or significant cervical change on repeated examination)	Low	Strong
	Do not administer in absence of cervical dilation/change or in the absence of regular contractions	Low	Strong
	Administer at the time of diagnosis of preterm premature rupture of membranes	Low	Strong
	Administer in cases of significant antepartum hemorrhage with a high risk of delivery within 7 days	Low	Strong
	Administer in cases of asymptomatic vasa previa or placenta previa with a high risk of delivery within 7 days	Low	Strong
	Do not administer prior to transfer unless a diagnosis of preterm labour has been firmly established	Low	Strong
Repeated dose or course	Consider cancellation of a second dose if the risk of preterm delivery decreases significantly following administration of the first dose After cancellation, consider administration of 1 dose or 1 course if a high risk of preterm birth arises, taking into account gestational age and time interval since the first course	Low	Strong
	Do not administer rescue dose or course routinely Gestational age and time interval since the first course of antenatal corticosteroid therapy (at least 14 days) should be taken into account A single rescue course may be administered after risks and benefits are discussed with the woman	Moderate	Conditional

IM: intramuscularly.

A study of 22 women without diabetes and 11 women with diabetes showed an increase of glucose levels following antenatal corticosteroid therapy administration in both groups, with 97% reaching a blood glucose level of 140 mg/dL or higher at least once over a 48-hour period following the first dose administration.[99] Similar results were obtained in a retrospective study of 55 women with gestational or pre-gestational diabetes, showing an increase in fasting or post-prandial glucose level in the 3 days following administration of a first dose of antenatal corticosteroids.[100] Another smaller prospective cohort study of 9 women showed similar increases in blood glucose among women with and without insulin-requiring diabetes, and the changes lasted up to 72 hours after the first dose of antenatal corticosteroid therapy.[101] In a prospective cohort of 11 non-diabetic women and 4 women with diabetes, blood glucose levels over 110 mg/dL were observed up to 156 hours after initiation of antenatal corticosteroid therapy.[102] Therefore, gestational diabetes screening should not be undertaken until at least 1 week after antenatal corticosteroid therapy administration. However, there is insufficient evidence in the literature to provide guidance on glucose monitoring or insulin dosage following antenatal corticosteroid therapy.

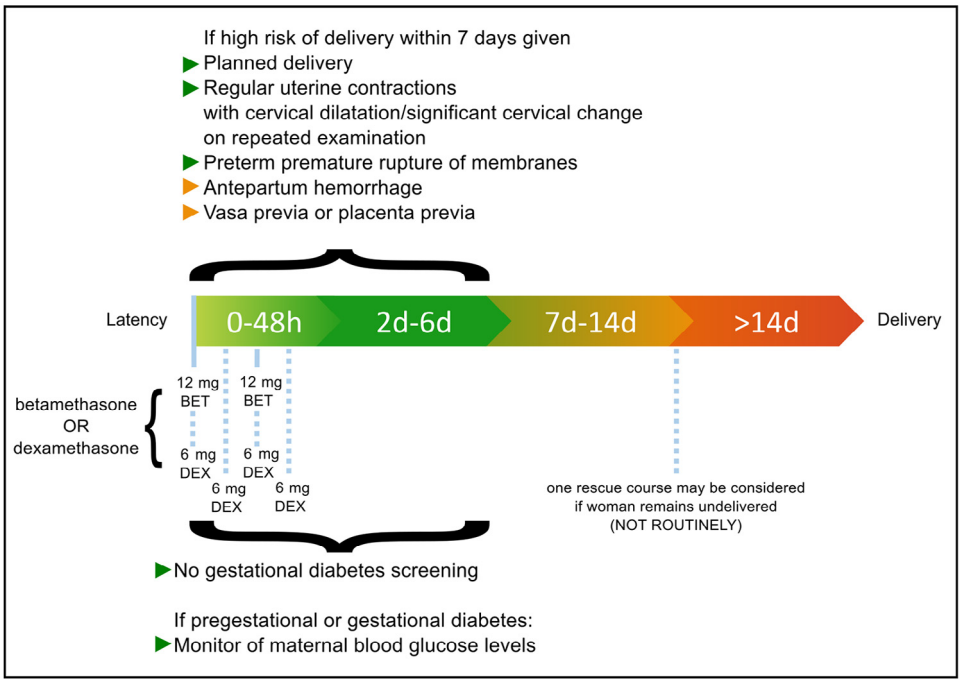
Summary Statements

14. Evidence on the effects of antenatal corticosteroid therapy in diabetic women is scarce, and no comparative study has been conducted in this subpopulation (Low).
15. Antenatal corticosteroid therapy leads to an increase in maternal blood glucose levels up to 1 week after the initiation of the first dose (Low).

Recommendations

19. Antenatal corticosteroid therapy should be administered to diabetic women at the same dosage, according to the same indications, and in the same gestational age range as that recommended for non-diabetic women (Conditional recommendation, Low certainty of evidence).
20. Close attention should be paid to control maternal blood glucose among women with diabetes in the days following antenatal corticosteroid therapy because of anticipated elevations in maternal blood glucose levels (Strong recommendation, Low certainty of evidence).

Figure 2. Summary of the evidence (agents, dosage, and target timing). Note: the same recommendation applies to women with multifetal pregnancies, pre-gestational or gestational diabetes, obesity, or growth-restricted fetuses. See the text for further details.



BET: betamethasone: DEX: dexamethasone.

21. Because of the transient elevation of blood glucose levels induced by corticosteroids, gestational diabetes screening should be delayed for a minimum of 1 week following antenatal corticosteroid therapy (Strong recommendation, Low certainty of evidence).

Women with Obesity

We did not identify any trials evaluating the effect of antenatal corticosteroid therapy on obese women or trials examining the effects of antenatal corticosteroid therapy by obesity status, body mass index, or weight. Current recommendations use a 1-size-fits-all approach in terms of dosage and regimens, although no data are available to evaluate whether such approach is optimal for the subpopulation of women with obesity.

A post hoc analysis[97] of women delivering within 1 week of antenatal corticosteroid therapy in a randomized controlled trial of weekly courses of antenatal corticosteroid therapy[85] showed no significant association between body mass index and cord blood or maternal serum concentrations of betamethasone after adjustment for gestational age at delivery, number of courses, days from last course to delivery, and twin pregnancy. However, the study was based on a small number of participants (n = 55).

Summary Statement

16. There is an absence of evidence on the effects of antenatal corticosteroid therapy among women with obesity, and no comparative study has been conducted in this subpopulation (Low).

Recommendation

22. Antenatal corticosteroid therapy should be administered to women with obesity at the same dosage as that recommended for women without obesity because there is insufficient evidence to guide dosage adjustments by maternal weight (Conditional recommendation, Low certainty of evidence).

Intrauterine Growth Restriction

Responsiveness of growth-restricted fetuses to antenatal corticosteroid therapy remains largely unknown.[103–106] Cortisol levels and risks of hypoglycemia are increased in fetuses displaying growth restriction, and administration of additional exogenous steroids might not lead to the same benefits and harms as expected in normally grown fetuses. Furthermore, a trend towards reduction in birth weight[27] among infants exposed to antenatal corticosteroid therapy has raised concerns regarding their use in growth-restricted foetuses.

Table 8. Summary table of recommendations according to subpopulation

Subpopulation	Recommendation given high risk of delivery within 7 days and if gestational age criteria are met	Level of evidence	Strength of recommendation
Multifetal gestation	Administer according to the same indications and in the same gestational age range as for singleton pregnancies	Low	Conditional
	Do not administer in the absence of a high risk for preterm birth within the next 7 days	Low	Conditional
Pre-gestational or gestational diabetes	Administer at the same dosage, according to the same indications and in the same gestational age range as that recommended for non-diabetic women	Low	Conditional
	Pay close attention to control of maternal blood glucose in the days following antenatal corticosteroid therapy	Low	Strong
	Gestational diabetes screening should be delayed for a minimum of 1 week following antenatal corticosteroid therapy	Low	Strong
Obesity	Administer at the same dosage as that recommended for women without obesity	Low	Conditional
Intrauterine growth restriction	Administer according to the same indications and in the same gestational age range as in normal pregnancies after risks and benefits are discussed with the woman	Low	Conditional
	Do not administer to women with suspected fetal growth restriction at the time of diagnosis unless there is a high risk of preterm birth within the next 7 days	Low	Conditional

Among the trials included in the recent Cochrane review, 3 studies explicitly excluded women with fetuses suspected of intrauterine growth restriction, and no trial evaluated the effect of antenatal corticosteroid therapy in growth-restricted fetuses specifically.[27] A systematic review of comparative studies conducted by Amiya et al. identified 6 retrospective cohort studies, 1 prospective cohort study, and 1 case-control study evaluating the effect of antenatal corticosteroid therapy in women with growth restricted fetuses or who delivered small for gestational age infants.[98] Although intrauterine growth restriction and small for gestational age are not synonymous, the latter population was considered to provide valuable information on the potential impact of antenatal corticosteroid therapy on growth-restricted fetuses. Antenatal corticosteroid therapy in small for gestational age births was associated with a lower frequency of major brain lesions (5 studies; n = 762; OR 0.57; 95% CI 0.41–0.78) but a higher frequency of body size below the 10th centile at school age (1 study; n = 91; OR 5.50; 95% CI 1.38–19.6). No benefit was observed following antenatal corticosteroid therapy exposure on perinatal mortality, respiratory morbidity, neonatal sepsis, or chorioamnionitis in this population. The lack of adjustment for potential confounders limits the validity of these results, thus leaving little evidence to guide the use of antenatal corticosteroid therapy in this population.

Considering the potentially higher risks of harm caused by excess exposure to glucocorticoids, high vigilance is needed regarding the timing (within 7 days of delivery) and gestational age at which antenatal corticosteroid therapy is administered to fetuses with suspected growth restriction.

Summary Statements

17. Responsiveness of growth-restricted fetuses to antenatal corticosteroid therapy remains largely unknown (Low).
18. A lower frequency of major brain lesions, but a higher frequency of body size below the 10th centile at school age is observed in cohort studies of small for gestational age infants exposed to antenatal corticosteroid therapy (Low).

Recommendations

23. There is insufficient evidence to withhold routine antenatal corticosteroid therapy in cases of suspected fetal growth restriction with a high risk of preterm birth. Antenatal corticosteroid therapy should be administered according to the same indications and in the same gestational age range as in normal pregnancies after risks and benefits are discussed with the woman (Conditional recommendation, Low certainty of evidence).
24. Antenatal corticosteroid therapy should not be administered to women with suspected fetal growth restriction at the time of diagnosis unless there is a high risk of preterm birth within the next 7 days (Conditional recommendation, Low certainty of evidence).

Table 8 summarizes the evidence and recommendations regarding specific subpopulations.

Fetal Movements

Antenatal corticosteroid therapy has been shown to induce a temporary disruption of the diurnal rhythm and transient variations in fetal body movements, breathing movements, and heart rate, including a reduction in fetal movements in the first 3 days following antenatal corticosteroid therapy initiation.[107-109] Women should be informed of this potential transient side effect and advised to consult with their health care professional if they notice a reduction of fetal movements.

Summary Statement

19. Antenatal corticosteroid therapy may induce transient variations in fetal body movements including a potential reduction in fetal movements in the first 3 days following therapy initiation (Low).

Recommendation

25. Women should be informed of the potential for a transient reduction in fetal movements and advised to consult with their health care professional if this occurs (Strong recommendation, Low certainty of evidence).

LONG-TERM CONSIDERATIONS

Although evidence supports benefits of antenatal corticosteroid therapy in terms of perinatal mortality and morbidity, few long-term follow-up studies are available to assess potential long-term effects, especially on neurodevelopment. High levels of maternal cortisol[110] and antenatal corticosteroid therapy[111] have been associated with adverse effects on neurological development in cohort studies. Follow-up studies of large randomized controlled trials (albeit with substantial losses to follow-up) show some differences in the academic ability of children exposed to antenatal corticosteroid therapy prior to term Caesarean delivery (ASTECS trial).[58] Higher risks of death and severe disability (including neurosensory disability) have been documented in children born at term exposed to multiple courses of antenatal corticosteroid therapy (MACS-5).[33] The uncertainties surrounding the long-term effects of antenatal corticosteroid therapy should be kept in mind when considering administration of such treatment, especially in the absence of clear short-term benefits. In addition, respiratory morbidity decreases and the number needed to treat increases with advancing gestational age, thus leading to a larger number of fetuses exposed to antenatal corticosteroid therapy without significant benefits and with potential long-term adverse effects. **Gestational age considerations and careful assessment of the risk of preterm birth within 7 days are paramount** when contemplating antenatal corticosteroid therapy.

SUMMARY

A single course of antenatal corticosteroid therapy at 24 + 0 to 34 + 6 weeks gestation among women at high risk for preterm birth reduces perinatal mortality and morbidity. The benefits are maximised by administration within 7 days of delivery. In cases of deliveries beyond this time window, adverse effects may outweigh the expected benefits. A careful assessment of the risk of preterm delivery within 7 days is therefore required prior to administration of antenatal corticosteroid therapy to avoid unnecessary use. There is limited evidence to suggest differential efficacy of antenatal corticosteroid therapy in subpopulations such as multifetal pregnancies, diabetic women, women with obesity, and pregnancies with suspected fetal growth restriction. Dosage regimens that account for maternal weight have also not been evaluated. All such women should be treated with single-course antenatal corticosteroid therapy if indications and gestational age criteria are met. Although many trials have evaluated antenatal corticosteroid therapy, some areas of clinical equipoise persist. For example, studies of the long-term impact of late preterm exposure to antenatal corticosteroid therapy are needed. In situations where the risk of preterm birth is judged to be high, health care providers should discuss the benefits and risks of antenatal corticosteroid therapy with the woman.

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