Antenatal Corticosteroids to Improve Neonatal Outcomes

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• Excluded	
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Contents

Back to Contents

1. Purpose of policy

To provide recommendations for the use of antenatal corticosteroids in women prior to birth to improve neonatal outcomes.

2. Guideline management principles and goals

Antenatal steroids are standard care for women at high risk of birth < 35 weeks gestation.
A single repeat dose may be administered if still at risk of preterm birth, up to 32+6 weeks.

3. Background

Maternal administration of a single course of intramuscular corticosteroids prior to preterm birth has a major role in reducing mortality and major morbidity (including respiratory distress syndrome, intraventricular haemorrhage and necrotising enterocolitis) in babies born very and moderately preterm and is now considered the standard of care for women at high risk of birth < 35 weeks gestation (Crowley, 1990). Evidence from meta-analyses assessing the use of repeat corticosteroids, demonstrates neonatal benefit from repeat dose(s) of corticosteroids to women at on-going risk of preterm birth greater than seven days (and less than 14 days) after the initial course of corticosteroids, with no evidence of adverse effect in follow-up studies of children up to school age (Crowther, 2011; McKinlay 2015).

The evidence lacks clarity regarding the best type, dose, frequency and mode of administration of corticosteroid. There is no evidence of benefit for routes of administration other than intramuscular.

Many have extended the use of antenatal corticosteroids in attempts to improve neonatal outcomes for other groups considered at increased risk of neonatal respiratory morbidity including for late preterm birth at 35-37 weeks gestation, prior to elective caesarean section, in women with diabetes, and in women with multiple pregnancy. In 2015 the Antenatal Corticosteroids Given to Women Prior to Birth to Improve Fetal, Infant, Child and Adult Health: Clinical Practice Guidelines were released. These bi-national guidelines were developed by a multidisciplinary clinical practice guideline panel including several Auckland DHB representatives with all relevant data systematically reviewed and considered. The extensive guideline document provides the best evidence-based recommendations to guide decision-making in clinical practice also highlighting areas of uncertainty requiring further research.

National Women's Health has elected to follow these guidelines for all antenatal corticosteroid use. The full document can be accessed at: http://www.ligginstrials.org/ANC_CPG/

This document provides a summary of the guidelines highlighting practice points of interest. This document should be read in conjunction with:

- Preterm Labour (PTL) - Management of Threatened and Active PTL guideline (see associated Auckland documents) for women at risk of spontaneous preterm birth and

- Magnesium Sulphate for Pre-eclampsia and for Neuroprotection in Pre-Term Births <30 weeks for women at risk of delivery ≤30 weeks gestation

4. Definitions

Term	Definition
Dose	Refers to a quantity of medicine taken at a specific time point
Course	Refers to a series of doses administered over a designated period. In the context of corticosteroid administration the first course includes two doses given 24 (or 12 hours apart).

5. Summary of guidelines

Assessment of the evidence reviewed to provide strength of recommendations for these guidelines included the NHMRC and GRADE (Grading of Recommendations Assessment, Development and Evaluation) systems for guideline review.
Sections A-D below are based on NHMRC level 'A' and GRADE level 'STRONG' evidence. Section E provides direction on best practice points (currently there is insufficient evidence to make stronger recommendations).

5.1 A. In a woman at risk of early preterm birth, use a two dose course of antenatal corticosteroids:

- When gestational age is ≤ 34+6 weeks
- When preterm birth is planned or expected within the next seven days, even if birth is likely within 24 hours
- Regardless of the reason the woman is considered at risk of preterm birth

Practice points of interest:

- There is some benefit even if given <24 hours before delivery
- Effect on perinatal mortality is if delivery occurs within next 48 hours (no effect on mortality if >48 hours but <7 days)
- There is no benefit if delivery occurs >7 days (respiratory distress syndrome or mortality) after first course
- Use adjunct prediction tests to identify those most likely to deliver in 48 hours/next seven days (e.g. for spontaneous preterm labour use fetal fibronectin or transvaginal cervical length, refer to Preterm Labour (PTL) - Management of Threatened and Active PTL guideline in associated Auckland DHB documents).

5.2 B. Type and amount of corticosteroid to use for two dose course:

- Total amount: Betamethasone 24 mg in divided doses, 24 hours apart
- In practical terms = Celestone® two intramuscular doses of 11.4 mg, 24 hours apart
- The following should be charted on the ONCE only section of the medication chart:

Back to Contents

Drug name	Form	Dose	Route	Frequency
Betamethasone sodium phosphate and betamethasone acetate Celestone Chronodose®	5.7mg betamethasone per 1mL injection	11.4mg (2mL)	IM	A total of two doses 24 hours apart
Notes - In practical terms 5.7 mg Celestone Chronodose® = 6 mg betamethasone				

Practice points of interest:

- There is no clear evidence on best interval for divided doses of single course from 12 to 36 hours
- A 12-hour interval may be considered, however, there is no evidence to suggest that if planning 24-hour interval but delivery sooner appears imminent that earlier administration of second dose will improve outcome
- Dexamethasone is a valid alternative if betamethasone is not available. If using Dexamethasone it should be given as 24 mg in divided doses completed between 24 and 40 hours. In practical terms = dexamethasone phosphate intramuscularly, in four doses of 6 mg, 12 hours apart

Drug name	Form	Dose	Route	Frequency
Dexamethasone phosphate (Dexamethasone Hameln®)	4mg dexamethasone per 1mL injection	6mg (1.5mL)	IM	A total of four doses, 12 hours apart
Notes - Dexamethasone is considered a valid alternative if betamethasone is not available. This is an unlicensed indication				

5.3 C. Use repeat antenatal corticosteroids in women still at risk of early preterm, imminent birth following an initial two dose course or single dose repeat of antenatal corticosteroids:

- When gestational age is ≤ 32+6 weeks
- When at least seven days since previous dose of antenatal corticosteroids was administered
- When preterm birth is planned or expected within the next seven days, even if birth is likely within 24 hours
- Regardless of the reason, the woman is considered at risk of preterm birth

Practice points of interest:

- Repeat corticosteroids should not be administered just because a woman who has received a first course remains undelivered. Clinical review must occur to assess whether she is still at risk of preterm birth within the next seven days
- Use adjunct prediction tests to identify those most likely to deliver within the next seven days (e.g. for spontaneous preterm labour use fetal fibronectin or transvaginal cervical length, refer to Preterm Labour (PTL) - Management of Threatened and Active PTL guideline in associated Auckland DHB documents).

5.4 D. Type and amount of corticosteroid to use for repeat dose:

- Use a single repeat betamethasone dose
- In practical terms = Celestone® intramuscular dose of 11.4 mg
- After this dose if a patient has still not given birth ≥7 days and <14 days from previous repeat dose and is still considered to be at risk of preterm birth within the next seven days, a further single repeat dose of betamethasone (Celestone® 11.4mg i.m.) can be administered
- Up **to a total of three single repeat doses** can be given

Drug name	Form	Dose	Route	Frequency
Betamethasone sodium phosphate and betamethasone acetate Celestone Chronodose®	5.7mg betamethasone per 1mL injection	11.4mg (2mL)	IM	Single dose only
Note - In practical terms 5.7mg Celestone Chronodose® = 6 mg betamethasone				

Practice points of interest:

- A single repeat course can be considered (betamethasone 24 mg in divided doses, 24 hours apart), but only be given as a single repeat, no further repeat courses or doses should be administered. This may be considered with representation and when risk of imminent delivery is high but >7 days have already elapsed since first two dose course was given.

5.5 E. Other indications and considerations for antenatal corticosteroid use (with best practice points):

At gestational ages 35+0 to 36+6 weeks:

- A single course of corticosteroids should be considered *only* if there is *known* lung immaturity and preterm birth is planned or expected within the next 7 days, even if birth is likely within 24 hours, and regardless of the reason the woman is considered at risk of preterm birth. There is insufficient evidence on balance of risk/benefit ratio where status of lung immaturity is unknown (i.e. the vast majority).

Evidence published since the 2015 the Antenatal Corticosteroids Given to Women Prior to Birth to Improve Fetal, Infant, Child and Adult Health: Clinical Practice Guidelines were released suggests significant neonatal respiratory benefit when corticosteroids are given prior to late preterm birth (Gyamfi-Bannerman 2016, Saccone 2016) and this has led to some changes in national guidelines (ACOG 2016). However, these clinical trials have also demonstrated a significant increase in rates of neonatal hypoglycaemia associated with maternal corticosteroid use (Gyamfi-Bannerman 2016, Saccone 2016) which may cause long-term harm (Shah 2019). Until further evidence is available to guide practice, avoid routine use of corticosteroids at these gestational ages.

Prior to elective caesarean section (CS):

- Where possible plan for CS ≥39+0 weeks gestation
- If is ≤ 34+6 weeks gestation give a single course of corticosteroids 48 hours prior to planned birth

- If it is ≥35+0 weeks gestation there is insufficient evidence to support standard use of corticosteroids. (If there is *known* lung immaturity it may be considered as a single course of corticosteroids 48 hours prior to planned birth).

Evidence from systematic review and meta-analyses (Saccone 2016) and a Cochrane Review (Sotiriadis 2018) published since the 2015 the Antenatal Corticosteroids Given to Women Prior to Birth to Improve Fetal, Infant, Child and Adult Health: Clinical Practice Guidelines were released suggests significant neonatal respiratory benefit when corticosteroids are given prior to elective CS at 35+0 to 36+6 weeks and >37+0 weeks. However, the GRADE quality of evidence was low (Sotiriadis 2018) indicating that the true effect of corticosteroids may be substantially different than the estimate of effect given, and no trials >37+0 weeks included neonatal hypoglycaemia as an outcome, hence the potential for harm is unknown. Until further evidence is available to guide practice, avoid routine use of corticosteroids for women undergoing elective CS ≥35+0 weeks gestation.

The C*STEROID Feasibility Study has been undertaken at ADHB and the multicentre C*STEROID Trial is being planned by Auckland investigators as a New Zealand-wide randomised placebo-controlled trial of betamethasone prior to planned CS at 35+0 to 39+6 weeks assessing both neonatal benefit and harm. All women meeting inclusion criteria should be offered the opportunity to participate and all healthcare professionals should encourage and endorse participation whilst the trial is active. https://www.auckland.ac.nz/en/liggins/in-the-community/clinical-studies/clinical-studies-pregnancy/c-steroid-feasibility-study/c-steroid-information-for-clinicians-and-midwives.html

In women with diabetes in pregnancy including gestational diabetes:

- Single course and repeat doses of corticosteroids should be given to patients at risk of preterm birth as per guidelines for general use
- Patients with diabetes receiving corticosteroids will require blood glucose monitoring and management of any subsequent hyperglycaemia. This should be done in consultation with the Obstetric Physician service
- Patients with diabetes receiving corticosteroids should be monitored for puerperal sepsis
- There is insufficient evidence to support use of corticosteroids in patients with diabetes greater ≥35+0 weeks gestation, regardless of mode of delivery.

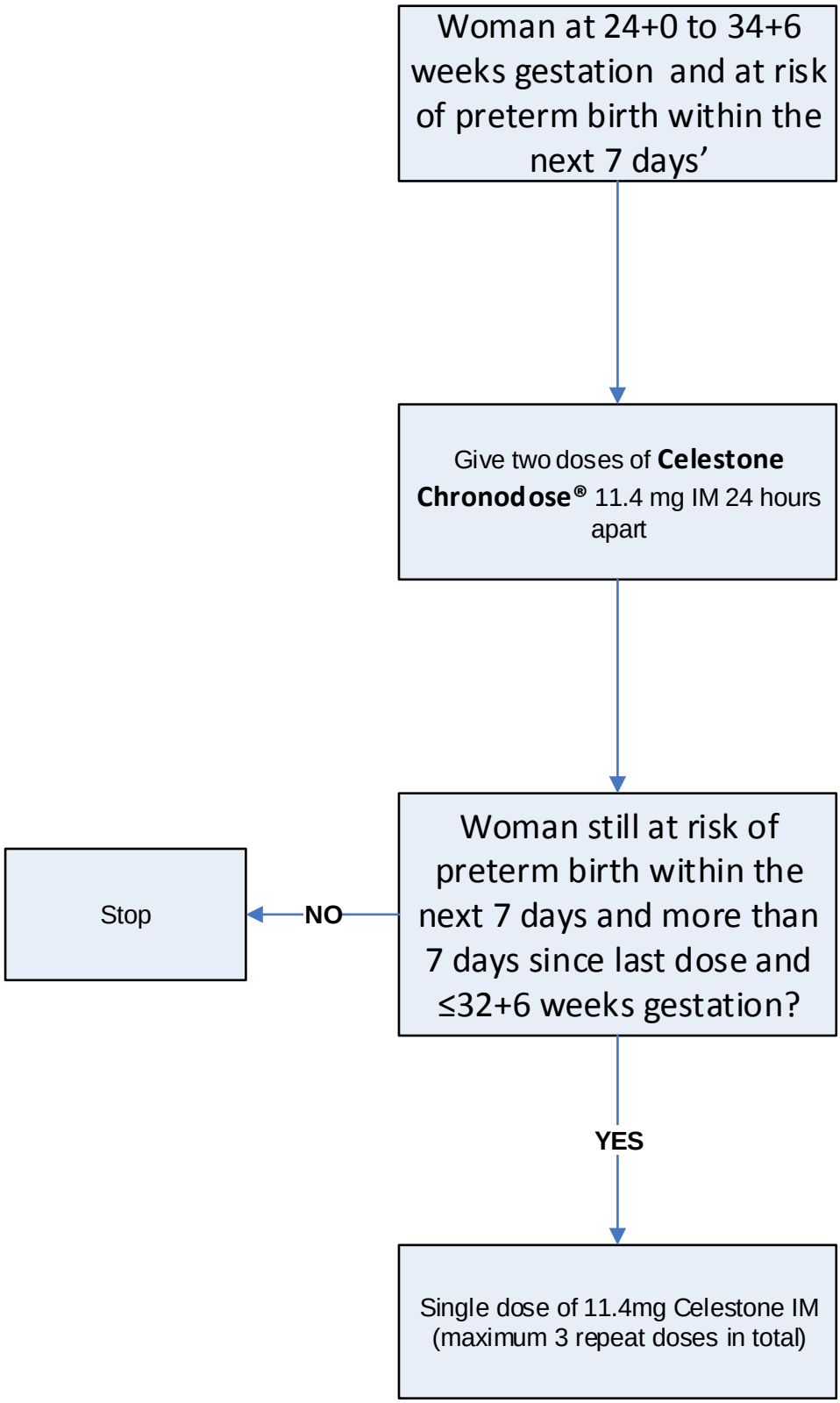
In women with multiple pregnancy:

- Single course and repeat doses of corticosteroids should be given to patients at risk of preterm birth as per guidelines for general use
- Do not use single course and repeat doses of corticosteroids in women with a multiple pregnancy where there is no other identified risk of preterm birth
- Use adjunct prediction tests to identify those most likely to deliver in 48 hours/next seven days (eg for spontaneous preterm labour use fetal fibronectin or transvaginal cervical length, refer to Preterm Labour (PTL) - Management of Threatened and Active PTL guideline in associated Auckland DHB documents.

At gestational age 23+0 – 23+6 weeks:

- Single course of corticosteroids should be considered in women when preterm birth is planned or expected within the next seven days, even if birth is likely within 24 hours, only once a full review has been made and if a plan has been made for 'active intervention' (Refer to section 12 (Threatened and active PTL at <24+0 weeks) in the Preterm Labour (PTL) - Management of Threatened and Active PTL guideline in associated Auckland DHB documents.

6. Flowchart


Woman at 24+0 to 34+6 weeks gestation and at risk of preterm birth within the next 7 days'
Give two doses of **Celestone Chronodose®** 11.4 mg IM 24 hours apart
Woman still at risk of preterm birth within the next 7 days and more than 7 days since last dose and ≤32+6 weeks gestation?
NO
Stop
YES
Single dose of 11.4mg Celestone IM (maximum 3 repeat doses in total)

7. Supporting evidence

Crowley, P., Chalmers, I., & Keirse, M. J. (1990). The effects of corticosteroid administration before preterm delivery: an overview of the evidence from controlled trials. BJOG: *An International Journal of Obstetrics & Gynaecology, 97*(1), 11-25.

Crowther, C. A., McKinlay, C. J., Middleton, P., & Harding, J. E. (2011). Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes. *The Cochrane Library*.

Antenatal Corticosteroid Clinical Practice Guidelines Panel. *Antenatal corticosteroids given to women prior to birth to improve fetal, infant, child and adult health*. Clinical Practice Guidelines. 2015. Liggins Institute, The University of Auckland, Auckland. New Zealand. Retrieved from http://www.ligginstrials.org/ANC_CPG/

McKinlay, C. J., Cutfield, W. S., Battin, M. R., Dalziel, S. R., Crowther, C. A., Harding, J. E., & ACTORDS Study Group. (2015). Cardiovascular risk factors in children after repeat doses of antenatal glucocorticoids: an RCT. *Pediatrics, 135*(2), e405-e415.

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.

Gyamfi-Bannerman C, Thom EA, Blackwell SC, Tita AT, Reddy UM, Saade GR, Rouse DJ, McKenna DS, Clark EA, Thorp JM, Chien EK,, Peaceman AM, Gibbs R, Swamy GK, Norton ME, Casey BM, Caritis SN, Tolosa JE, Sorokin Y, VanDorsten JP, Jain L . Antenatal Betamethasone for Women at Risk for Late Preterm Delivery. *N Engl J Med* 2016; 374(14): 1311-20.

American College of Obstetricians and Gynecologists. Antenatal Therapy for Fetal Maturation Committee Opinion No 677. Obstet Gynecol 2016(128):e187-94.

Shah R, Harding J, Brown J, McKinlay C. Neonatal Glycaemia and Neurodevelopmental Outcomes: A Systematic Review and Meta-Analysis. Neonatology 2019; 115(2): 116-26.

Sotiriadis A, Makrydimas G, Papatheodorou S, et al. Corticosteroids for preventing neonatal respiratory morbidity after elective caesarean section at term. Cochrane Database Syst Rev 2018; 8: CD006614.

8. Associated documents

- Diabetes in Pregnancy
- Fetal Surveillance Policy
- Group B Streptococcus (GBS) – prevention of early – Onset Neonatal Infection
- Intrapartum Care – Normal Labour and Birth
- Magnesium Sulphate for Pre-eclampsia & for Neuroprotection in Pre-Term Births <30 weeks
- Preterm Labour (PTL) - Management of Threatened and Active PTL guideline
- Point of Care Testing Equipment Management – POCT Protocol
- Rupture of Membranes in Pregnancy

Back to Contents

9. Disclaimer

No guideline can cover all variations required for specific circumstances. It is the responsibility of the health care practitioners using this Auckland DHB guideline to adapt it for safe use within their own institution, recognise the need for specialist help, and call for it without delay, when an individual patient falls outside of the boundaries of this guideline.

10. Corrections and amendments

The next scheduled review of this document is as per the document classification table (page 1). However, if the reader notices any errors or believes that the document should be reviewed ***before*** the scheduled date, they should contact the owner or Document Control without delay.