Antenatal corticosteroids (ACS)

IMPORTANT: *Consider individual clinical circumstances. Consult a pharmacopeia for complete drug information. Read the full disclaimer at www.health.qld.gov.au/qcg*

Background

Aspect	Consideration
Relevant to:	• Women at risk of preterm birth (PTB) (less than 37+0 weeks gestation) • Gestational ages including: o 22+0 to 34+6 weeks o Greater than or equal to 35+0 weeks (including elective preterm caesarean section (CS))
Clinical significance	• ACS administration before PTB is an important intervention that improves outcomes for preterm babies[1-4] • Preterm babies often require respiratory support, with some requiring assisted ventilation and treatment due to immature lung development[5,6] o ACS effectively reduces the need for respiratory support[4] • In Queensland in 2017, PTB occurred in 9.4% of all pregnancies[7]
Mode of action	• Betamethasone and dexamethasone for lung maturation pass readily across the placenta[8] • Mechanisms underlying the benefits of ACS include[8]: o Maturation of fetal lungs and increased surfactant production[4] o Improved pulmonary blood flow and adaptation at birth o Increased fluid clearance from the alveolar lumen to the interstitium • Refer to Queensland Clinical Guideline *Respiratory distress and CPAP*[9]

Gestational considerations

Assessment and timing is vital to ensure that ACS use is limited to pregnancies at high risk of PTB and/or transfer to facilities capable of managing PTB occurs.[10] Women with suspected PTB, who are treated with ACS, who go on to delivery at term may have slightly higher rates of small for gestational age (SGA) babies.[11,12]

Aspect	Consideration
Less than 21+6 weeks gestation	• Insufficient evidence to recommend ACS or life sustaining neonatal support • Refer to Queensland Clinical Guideline *Perinatal care of the extremely preterm baby*[13]
22+0 to 23+6 weeks gestation	• After counselling with a multidisciplinary team *recommend* ACS if[14]: o PTB is highly likely within seven days, and life sustaining interventions are planned or may be a possibility (recognising administration of ACS does not mandate resuscitation at birth) o In-utero transfer planned and/or requested by the mother • ACS at this gestation does not impact the ability to provide palliative care at birth should the decision change from planned life sustaining interventions • Refer to Queensland Clinical Guideline *Perinatal care of the extremely preterm baby*[13]
24+0 to 34+6 weeks gestation	• *Recommend* ACS if PTB is highly likely within seven days • ACS in this gestational group associated with significant benefits o Refer to benefits and risks o Beneficial effect demonstrated regardless of whether membranes are ruptured or intact o Refer to Queensland Clinical Guideline *Preterm labour and birth*[15]
Greater than, or equal to, 35+0 weeks gestation	• *Consider* ACS if: o Elective (planned) CS o Fetal lung immaturity is likely or suspected • Use caution with ACS in later gestations as limited evidence about risks vs benefits and long term outcomes[16] o Carefully assess women at risk of late PTB[17] o Refer to benefits and risks

Special circumstances

Aspect	Consideration
Late preterm/near term caesarean section (planned/elective)	• Delay CS until 39+0 weeks gestation or later, when clinically possible[18,19] o The increased risk of respiratory and neurodevelopmental morbidity associated with late PTB or early term CS[18] decreases with advancing gestational age • Babies born by CS (especially planned) may be more susceptible to respiratory distress syndrome (RDS) and transient tachypnoea of the newborn (TTN) than those born vaginally[6,20,21] o Symptoms may be of short duration (minutes to hours) (e.g. TTN) and may be managed, in most cases, with local paediatric team support o Consider ability to manage transient respiratory symptoms and liaise with an expert practitioner, when required o Consider short term vs long term benefits o Counsel women on the potential short term benefits and uncertainty of long term risks of ACS • *Consider* a single course of ACS 48 hours prior when[6,22-25] o CS is clinically indicated at greater than 34+6 weeks and fetal lung immaturity is known or suspected[22] o There are other clinical circumstances that may increase the risk of fetal lung immaturity (e.g. diabetes in pregnancy and/or multiple pregnancy) • ACS for planned CS at gestations greater than 39+0 weeks are not routinely recommended
Pre-existing diabetes, pre-diabetes, or gestational diabetes mellitus (GDM)	• Women with diabetes have a higher risk of: o PTB compared to the general population[20] o Baby having pulmonary immaturity than those without diabetes[20] ▪ Refer to Queensland Clinical Guideline *Preterm labour and birth* and *Respiratory distress and CPAP*[9,15] • ACS are not contraindicated but may affect blood glucose levels (BGLs) o Monitor and manage as per Queensland Clinical Guideline *Gestational diabetes mellitus*[26] • *Consider* ACS based on risk of PTB and other clinical circumstances[22]
Maternal infection	• Insufficient evidence to recommend for, or against, ACS for women with chorioamnionitis[20] • ACS not associated with increased risk of maternal infection[27] o No difference in risk for chorioamnionitis in women treated with ACS vs no ACS [RR 0.90, 95% CI 0.69 to 1.17; 13 trials, n=2525][22] • *Consider* ACS for women with confirmed or suspected chorioamnionitis and at high risk of PTB[22], to mitigate risks associated with PTB[20] o Do not delay birth to administer ACS o Consider individual circumstances
Hypertensive disorders	• For women with hypertension in pregnancy, ACS are o Not indicated unless there is a high risk of PTB within seven days o Associated with reduction in both neonatal mortality and short term morbidities, without evidence of harm[27], for women at risk of PTB • Refer to Queensland Clinical Guideline *Hypertension and pregnancy*[28] • *Consider* ACS based on risk of PTB and other clinical circumstances[22]
Multiple pregnancy	• Multiple pregnancy is a risk factor for PTB, but in isolation is not an indication for ACS[22] • *Consider* ACS based on risk of PTB and other clinical circumstances
Fetal growth restriction	• Limited evidence to recommend for, or against, ACS for women with growth restricted fetus o Population based retrospective studies have demonstrated ACS exposure may result in slightly reduced rates of RDS, neonatal mortality and morbidity[29-31] • *Consider* ACS in pregnancies complicated by fetal growth restriction and PTB is likely within seven days o Assessment and timing of ACS is vital to avoid repeat dosing, where possible • Consider risks vs benefits of *repeat doses* of ACS when there is a growth restricted fetus[22] o Babies exposed to *repeat* ACS doses may have a lower birth weight (mean difference 80 gm) [mean difference -0.12, 95% CI -0.18 to -0.06][5]

Assessment, administration timing and transfer

Aspect	Consideration
Context	• Undertake comprehensive assessment of women with symptoms of PTL (and the likelihood of PTB), to identify optimal timing of ACS administration[6,22] • Both ACS treatment options (betamethasone or dexamethasone) are effective for initial administration (single course)[22] o Betamethasone recommended for repeat administration; however, dexamethasone may be used if betamethasone unavailable
Indications for administration	• May include, but not limited to[2]: o Preterm prelabour rupture of membranes (PPROM) o Preterm labour (with or without intact membranes) o Cervical change and dilation greater than or equal to 2 cm o Positive biochemical preterm birth prediction testing (e.g. fetal fibronectin) o Planned PTB for obstetric causes (e.g. severe FGR with compromise or pre-eclampsia) • Refer to Queensland Clinical Guidelines *Preterm labour and birth*[15], *Standard care*[32] and *Preterm prelabour rupture of membranes (PPROM)*[33]
Timing of administration	• Optimal timing is when PTB is expected or planned within 48 hours[34] • If PTB uncertain commence ACS within seven days, including if anticipated birth within 24 hours[10] o A single dose of ACS, given more than seven days prior to birth is ineffective at reducing RDS[22]
In-utero transfer	• Liaise with Retrieval Services Queensland for advice on administration prior to transfer o Refer to Queensland Clinical Guideline *Preterm labour and birth*[15]
Blood glucose management (maternal and neonatal)	• For women with pre-existing diabetes or GDM, monitor and manage BGLs[22,35] • For babies born to women with diabetes, or, after ACS administration (within the last seven days) plan early and frequent feeding, and screen for neonatal hypoglycaemia [refer to Queensland Clinical Guideline *Gestational diabetes mellitus*[26], *Newborn hypoglycaemia*[36]]

Dosing and administration

Aspect	Consideration
Initial administration	
Indication	• *Recommend* a single course of ACS for women at risk of PTB within the next seven days (including multiple pregnancies[5]), who are[1] 22+0 to 34+6 weeks gestation[10] • *Consider* a single course of corticosteroids for women at high risk of PTB within the next seven days who are[1] o 35+0 weeks or more gestation
Dosing	• The recommended regimens of ACS are[6]: o Two doses of betamethasone 11.4 mg intramuscular injection (IM) 24 hours apart ▪ If PTB likely within 24 hours, consider giving the second dose at 12 hours ***Or*** • Four doses of dexamethasone 6 mg IM injection 12 hours apart
Repeat (rescue) administration	
Indication	• For women at continued risk of PTB following initial administration of ACS[22] o Routine repeat doses of ACS not recommended[37] o Consider based on assessment of risk of ongoing PTB[37]
General considerations	• *Consider* repeat (rescue) dose/s based on[22]: o Gestational age—repeat ACS may be most effective at less than, or equal to, 32+6 weeks but may be considered at any gestation based on individual clinical scenario o PTB is planned or highly likely in the next seven days o Prior dose/s of ACS administered 7 or more days previously, and woman is at continued risk of PTB[1]
Dosing	• Betamethasone 11.4 mg IM injection[22] once: o If after repeat dose the woman has not given birth within seven days a further single dose may be given o Maximum in any one pregnancy is three, single, repeat doses ***Or*** • Two doses of betamethasone 11.4 mg IM injection completed within 24 hours o No further repeat courses recommended

Benefits

Aspect	Consideration
Context	• Women who receive ACS compared to those with no treatment have significantly lower severity or frequency, or both, of serious adverse neonatal outcomes related to prematurity[34]
22+0 to 27+0 weeks and/or weight 401–1000 gm	• Reduced incidence of:[4,38] o Respiratory distress syndrome o Neonatal death o Intracranial haemorrhage (grade 3 or 4) o Neurodevelopmental impairment o Cystic periventricular leukomalacia
Childhood	• Reduced incidence of: o ^Neurodevelopmental impairment[39] o #Cerebral palsy[38]

^18–22 months (corrected age) born at 23+0–25+0 weeks gestation respectively, #18–22 months (corrected age) born at 22+0–27+0 weeks gestation

Gestational age and condition	Treated with ACS	Not treated with ACS	Absolute risk reduction	CI (95%)	NNT
Gestation 24+0 to 35+0 weeks[1,4,34]					
Perinatal death[4]	13.2%	15.6%	2.49%	[1.10 to 3.88]	40
Neonatal death[4]	9.3%	11.9%	2.64%	[1.47 to 3.81]	38
Need for mechanical ventilation/CPAP[4]	16.7%	22.5%	5.73%	[3.42 to 8.04]	17
Systemic infections in the first 48 hours of life[13]	4.4%	7.3%	2.91%	[0.71 to 5.11]	34
Respiratory distress syndrome[4]	10.8%	14.8%	3.96%	[2.73 to 5.20]	23
Intraventricular haemorrhage[4]	2.2%	3.3%	1.3%	[0.61 to 1.99]	77
Necrotising enterocolitis[13]	1.1%	2.2%	1.15%	[0.41 to 1.89]	91
Gestation 35+0 to 36+6 weeks[40]					
Respiratory distress syndrome	5.5%	6.4%	0.9%	[-0.92 to 2.57]	111*
Transient tachypnoea of the newborn	6.7%	9.9%	3.2%	[1.17 to 5.23]	31
Need for surfactant at birth	1.8%	3.1%	1.3%	[0.11 to 2.39]	77
Planned CS at greater than 38+0 weeks[24]					
Need for mechanical ventilation	0.8%	1.8%	0.99%	[-0.28 to 2.26]	100*
Respiratory distress syndrome	0.6%	1.6%	0.99%	[-0.20 to 2.18]	100*
Transient tachypnoea of the newborn	1.3%	3.4%	2.14%	[0.44 to 3.84]	47
Admission to NICU for respiratory morbidity	1.6%	3.9%	2.30%	[0.47 to 4.14]	43

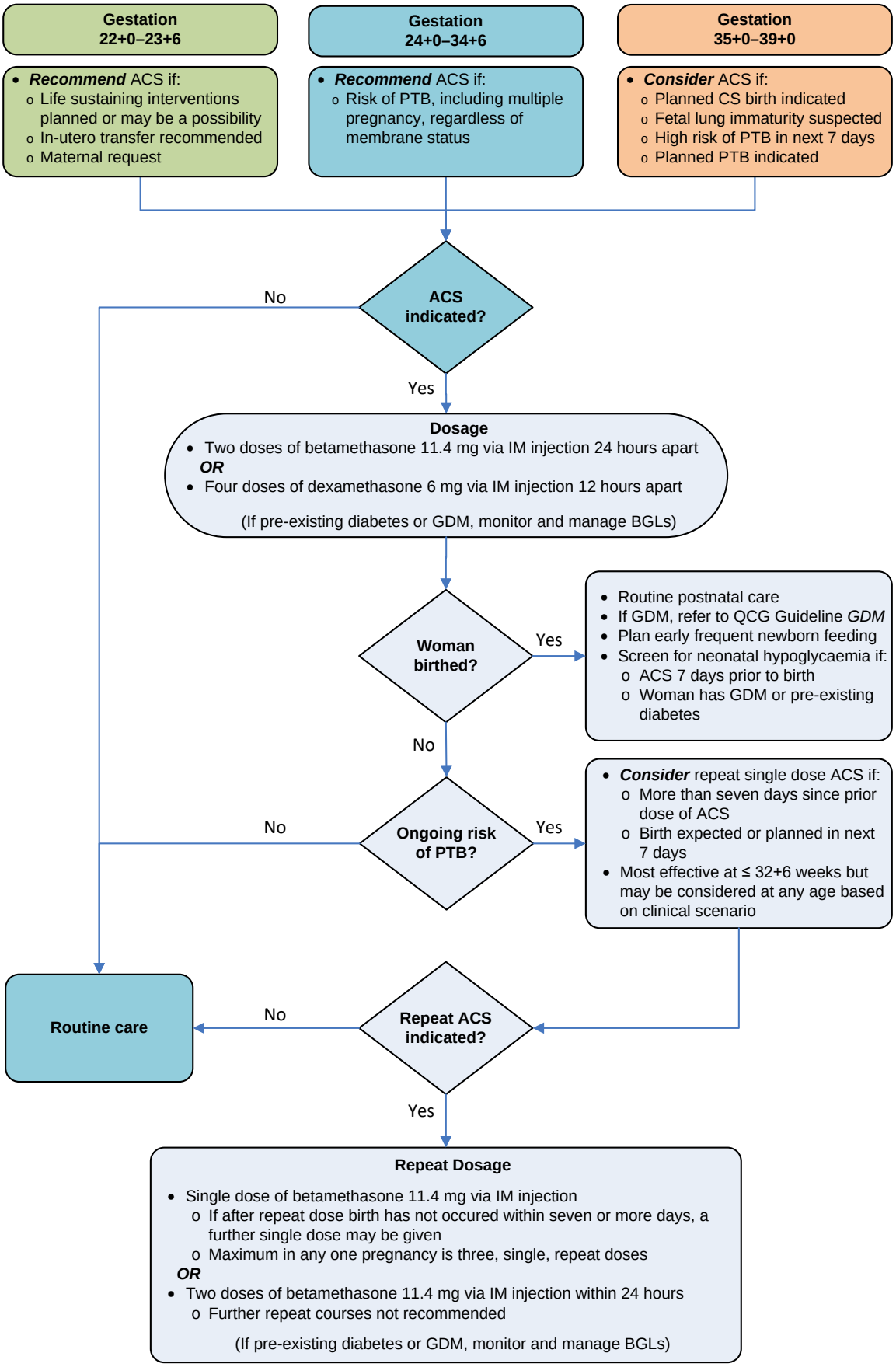
*NS: not statistically significant, NNT: number needed to treat, CI: confidence interval

Risks

Aspect	Consideration
Context	• Long term outcomes for babies exposed to antenatal ACS (for less than 22+0 or greater than 35+0 weeks gestation) are not yet fully known due to limited literature to inform interpretation of risk vs benefit[4,41] • ACS can have an effect on the developing brain and despite the dramatic reductions in mortality for extremely low gestation babies, there is increasing concern about the potential for adverse long term outcomes in more mature babies exposed to ACS[16] • Carefully consider short term vs long term benefits and risks of ACS administration[16]
Hypoglycaemia (neonatal)*	• One study examining ACS for late preterm birth found babies exposed to ACS compared to those not exposed, experienced a higher incidence of neonatal hypoglycaemia (24.0% vs 15.0%)[40]
Adulthood	• Findings in adults at 30 years of age who were given ACS suggest no difference in:[12,27] o Blood pressure o Body size or cardiovascular disease o Fasting plasma concentration of lipids or cortisol • Antenatal exposure to betamethasone may result in:[42] o Increased central insulin resistance measured at 30 minutes for insulin and 120 minutes for glucose response to an oral glucose tolerance test in adults

^5.8 years (corrected age), *born at 34+0–36+6 weeks gestation

Flowchart: Administration of ACS



ACS: antenatal corticosteroids, **BGL:** blood glucose levels, **CS**: caesarean section, **GDM**: gestational diabetes mellitus, **IM:** intramuscular, **PTB**: preterm birth, **QCG:** Queensland Clinical Guidelines, **≤** less than or equal to

Queensland Clinical Guidelines: Antenatal corticosteroids. Flowchart version: F21.64-1-V1-R26

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