CLINICAL GUIDELINES

DOSING REGIMENS FOR ANTENATAL GLUCOCORTICOID THERAPY IN SINGAPORE

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INTRODUCTION

Worldwide there are three exogenous glucocorticoids in clinical use as antenatal steroid (ANS) therapy in the setting of imminent preterm birth: dexamethasone sodium phosphate, betamethasone sodium phosphate, and betamethasone acetate[1]. Herein, imminent preterm birth is defined as being within seven (7) days. Betamethasone acetate is used clinically only in combination with betamethasone sodium phosphate. The dose of a single course of antenatal glucocorticoids is approximately 24 mg. Worldwide, ANS therapy regimens are generally delivered as four 6 mg maternal intramuscular injections of dexamethasone given at a 12-hour interval, or two (approximately) 12 mg maternal intramuscular injections of betamethasone given at a 24-hour interval. Dexamethasone and betamethasone vary significantly in pharmacokinetics and duration of action, making them non-interchangeable between regimens.[1, 2]

The purpose of this document is to recommend two antenatal glucocorticoid dosing regimens for clinical use as ANS therapy in Singapore. Associated clinical considerations, including gestational age range, repeat dosing, plurality, infection and potential contraindications are outside the scope of this document.

AIM OF GUIDELINE

Target audience: This guideline is intended for obstetricians, maternal–fetal medicine specialists, neonatologists, general practitioners, midwives, and other healthcare professionals involved in the care of pregnant women at risk of preterm birth.

Aims: By standardising dosing regimens for antenatal glucocorticoid therapy, these guidelines aim to reduce the morbidity and mortality associated with preterm birth in Singapore, improve both short- and long-term outcomes for mothers and their children, and align practice in Singapore with robust trials-based evidence.

Commissioned by the Academy of Medicine, Singapore and developed using GRADE-ADOLOPMENT methodology (Adopt - Adapt - Develop).[3]

EXECUTIVE SUMMARY OF RECOMMENDATIONS

Good Practice Point: A related Clinical Guideline, Management of Preterm Birth (January 2026), provides an authoritative treatment of associated clinical considerations.

Key Recommendation: This document recommends that clinicians in Singapore adopt a standardised approach to antenatal glucocorticoid dosing for imminent preterm birth and select a single preferred regimen. Details of recommendations can be found in the main text.

- The first regimen recommended for use is dexamethasone sodium phosphate 6 mg intramuscular injections every 12 hours for four doses (24 mg total), given to the mother (eight trials, moderate to high-certainty evidence).[4]
- The second regimen recommended for use is betamethasone sodium phosphate and acetate 11.4 mg intramuscular injections every 24 hours for two doses (22.8 mg total), given to the mother. (sixteen trials, moderate to high-certainty evidence).[4]

The above recommendations are made based on moderate to high-certainty published evidence demonstrating the safety and efficacy of these two regimens.[4] Pragmatic and logistical considerations unique to Singapore were given secondary consideration. Therapy cost was not used as a primary decision factor in regimen selection. In Singapore, dexamethasone sodium phosphate is readily available at low cost. A combined preparation of betamethasone sodium phosphate and acetate is less readily available and is more costly.

STATEMENT OF INTENT

This guideline is not intended to serve as a standard of medical care. Standards of medical care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge advances and patterns of care evolve. The contents of this publication is a guideline to clinical practice, based on the best available evidence at the time of development. Adherence to this guideline may not ensure a successful outcome in every case, nor should it be construed as including all proper methods of care or excluding other acceptable methods of care. Each physician is ultimately responsible for the management of his/her unique patient in the light of the clinical data presented by the patient and the diagnostic and treatment options available.

1. PRETERM BIRTH AND ANTENATAL GLUCOCORTICOIDS

Preterm birth, defined as delivery prior to 37 weeks' gestational age, impacts an estimated 15 million pregnancies and results in over 1 million newborn deaths every year.[5, 6] Survivors of preterm birth are at an elevated risk of acute (i.e. respiratory distress syndrome, RDS) and long-term (i.e. sub-optimal growth, neurological deficit, renal impairment, hypertension) diseases, with risk proportional to the degree to which infants are born preterm.[5-8] In Singapore, the preterm birth rate is approaching 10%.[9] Moreover, maternal factors associated with preterm birth and poor infant respiratory outcomes are also increasingly prevalent in the Singapore population (e.g. advanced maternal age, use of assisted reproductive technologies, gestational diabetes). Accordingly, the use of effective treatments for preterm respiratory disease is an area of priority. Although the aetiology of preterm risk is multifactorial, respiratory immaturity remains a primary cause of both death and life-long disease risk. Accordingly, significant attention has been devoted to the development of antenatal and neonatal care strategies to assist the preterm infant to safely transition from placental to pulmonary respiration.[5, 6, 10-12]

In obstetric medicine, the antenatal administration of exogenous glucocorticoids (antenatal steroid therapy; ANS) in anticipation of imminent preterm birth constitutes one of the most important, albeit poorly understood and inconsistently applied interventions to improve preterm lung function and neonatal survival.[1, 10, 11] The use of exogenous glucocorticoids to accelerate maturation of the human preterm lung is primarily attributed to a clinical trial reported by Drs Graham Liggins and Ross Howie in New Zealand.[13] Informed by studies performed in the pregnant sheep (wherein fetal glucocorticoid infusions elicited preterm parturition and an apparent improvement in lung compliance in some, but not all, lambs studied),[14, 15] this trial compared two 12 mg maternal intramuscular injections of betamethasone phosphate and acetate spaced by 24 hours, to identically-timed injections with placebo (cortisone acetate) in an initial cohort of 287 patients, and was published in 1972.[13] In this study, antenatal exposure to betamethasone phosphate and acetate was associated with a statistically significant reduction in RDS and neonatal death in infants born below 32 weeks' gestation.

The full study cohort (n=1115 mothers, which included 211 subjects receiving a double dose of 48 mg betamethasone phosphate and acetate) was not reported in its entirety until 2023[16]. Analysis of the complete data set showed that there was no survival benefit deriving from ANS exposure, but there was a reduction in the risk of RDS (adjusted risk ratio (RR) and 95% confidence interval (CI) 0.62, 0.45 – 0.86). In addition, there was no benefit derived from doubling the dose of betamethasone administered. Due to concerns regarding the effects of high-dose glucocorticoid exposure on the developing fetus (and perhaps a near absence of ANS dose and regimen optimisation data) the clinical uptake of ANS therapy was slow prior to the publication of a 1994 National Institutes of Health (NIH) Consensus Statement. This statement concluded that ANS therapy conveyed a wide range of benefits to the preterm infant across a broad gestational age (24 – 34 weeks) range, including reductions in mortality, RDS and intraventricular haemorrhage (IVH).[17]

Despite this NIH Consensus Statement, and the endorsement of professional bodies, ANS therapy remains an 'off-label' (i.e. not formally assessed and approved by a regulatory agency such as the US Federal Drug Administration) use of betamethasone or dexamethasone.[1] A large number of ANS clinical trials have been undertaken over the past 50 years, with the

majority replicating the original protocol used by Liggins and Howie (two maternal intramuscular injections of betamethasone phosphate and acetate 12 mg spaced by 24 hours) or the so named 'WHO regimen', being four maternal intramuscular injections of dexamethasone phosphate 6 mg spaced by 12 hours.[4]

The most recent Cochrane meta-analysis of ANS therapy for accelerating fetal lung maturation for women at risk of preterm birth assessed studies undertaken in 20 countries.[4] The meta-analysis concluded that a single course of ANS reduces the risk of perinatal/neonatal death and RDS. Authored by McGoldrick and colleagues it provides an analysis of the clinical trials literature as of September 3, 2020. This systematic review included 27 studies (11,272 women and 11,925 neonates) from 20 countries, with 19 involving the use of a single course of ANS.

Fifteen trials were assessed as being at low risk of bias, two had a high risk of bias in at least two domains and ten trials were assessed as being at high risk of bias due to a lack of placebo blinding.[4] Evidence certainty overall was assessed as moderate to high but was downgraded for neonatal IVH (moderate certainty due to indirectness), developmental delay (moderate certainty due to risk of bias) and maternal adverse outcomes including death, chorioamnionitis and endometriosis (moderate certainty due to imprecision). 26 of 27 trials reporting on outcomes at study entry less than or equal to 35 weeks' gestation were historical (i.e. >20 years old). Of the three included studies reported since 01 January 2016, two were performed in late-preterm pregnancy populations (one in a high resource setting, one in a low and middle income country (LMIC) setting) and the third was performed in an extremely to moderately (26 – 33^{+6} weeks' gestation) preterm pregnancy populations across five LMIC jurisdictions.[4]

Eight studies included in the McGoldrick systematic review reported the sole use of dexamethasone sodium phosphate. Most reported using a course of 24 mg although two reported using 20 mg in a single course. All but one (the Dexiprom Trial, which used two 12 mg doses of dexamethasone phosphate at a 24-hour interval in the setting of preterm pre-labour rupture of the membranes and failed to demonstrate benefit) administered a single course as four equal doses given at 12-hour intervals.[4]

Sixteen studies included in the McGoldrick systematic review reported the sole use of betamethasone, either as betamethasone phosphate (alone), betamethasone phosphate and acetate, or did not specify the betamethasone ester/s used. Of these studies, most used a single course of 24 mg given as two equal doses spaced by a 24-hour interval. Gamsu *et al.* reported the use of six 4 mg doses of betamethasone phosphate given at an 8-hour interval. Mansouri *et al.* reported the administration of two 12mg/kg/maternal body weight doses of betamethasone – although this is highly unlikely given the very high dose of drug and volume of injections required.[4]

One study reported using either betamethasone or dexamethasone (Shanks, *et al.*), two reported using methylprednisolone (Block *et al*., Schmidt *et al*.) or hydrocortisone (Morrison *et al.*, Schmidt *et al*.). Methylprednisolone administration was not shown to be beneficial. Interestingly, an intravenous hydrocortisone regimen (four 500 mg intravenous injections given 12 hourly) adopted by Morrison *et al.* appeared to have more beneficial lung maturation effect than the intramuscular (two 250 mg intramuscular injections given 24 hourly) hydrocortisone regimen utilized by Schmidt and colleagues.[4]

Twenty-nine identified studies were excluded from the review, including the ACT cluster randomised trial (Althabe *et al.*), which reported increased ANS use did not decrease neonatal

mortality in low-birth weight infants, was associated with an excess 3.5 neonatal deaths per 1000 women treated and may have increased maternal infection.[18] This trial was excluded as its design aimed to assess the feasibility, effectiveness and safety of multicomponent interventions to improve the use of ANS in LMIC jurisdictions.[4]

The headline findings of the McGoldrick review were that antenatal steroids reduced the risk of:

(i) **perinatal death**, RR 0.85, 95% CI 0.77 to 0.93; 9833 infants; 14 studies; high-certainty evidence;

(ii) **neonatal death**, RR 0.78, 95% CI 0.70 to 0.87; 10,609 infants; 22 studies; high-certainty evidence; and

(iii) **respiratory distress syndrome**, RR 0.71, 95% CI 0.65 to 0.78; 11,183 infants; studies 26; high-certainty evidence.[4]

These analyses were based principally on trials utilising either 24 mg dexamethasone sodium phosphate given as four 6 mg maternal intramuscular injections spaced by 12 hours, or approximately 24 mg betamethasone (phosphate or phosphate and acetate) given as two approximately 12 mg maternal intramuscular injections spaced by 24 hours. In summary, there is high certainty evidence from multiple trials in high resource countries, as well as LMICs, that the use of these two regimens conveys substantial benefit to the preterm infant.

2. ANTENATAL GLUCOCORTICOIDS – AGENT CONSIDERATIONS

A key unresolved question in relation to ANS therapy dosing regimens is the choice of agent: either betamethasone sodium phosphate, betamethasone acetate, or dexamethasone sodium phosphate. Other than the use of approximately 24 mg of drug in a single course (given as two or four doses), there is limited global consensus regarding the optimal choice of drug and dosing regimen used for ANS therapy.

RCOG Green Top Guideline 74 recommends that 24 mg of dexamethasone phosphate is given intramuscularly in two divided doses of 12 mg 24 hours apart or four divided doses of 6 mg 12 hours apart.[19] An alternative recommendation of 24 mg betamethasone sodium phosphate/acetate mix given intramuscularly in two divided doses of 12 mg 24 hours apart is also made. The New Zealand and Australian and Clinical Practice Guidelines 2015 (Antenatal Corticosteroids given to women prior to preterm birth to improve fetal, infant, child and adult health) recommends the use of betamethasone 24 mg in divided doses, completed between 12 and 36 hours (11.4 mg betamethasone sodium phosphate and acetate as two intramuscular doses, 24 hours apart) or dexamethasone 24 mg in divided doses completed between 24 and 40 hours (dexamethasone phosphate intramuscularly, four doses of 6 mg, 12 hours apart).[20] The FIGO good practice recommendations on the use of prenatal corticosteroids to improve outcomes and minimise harm in babies born preterm advises that appropriate ANS regimens include two 12 mg intramuscular doses of betamethasone phosphate 24 h apart, or two intramuscular doses of dexamethasone phosphate 12 mg 24 hours apart.[21]

Despite being used somewhat interchangeably,[22, 23] betamethasone phosphate and dexamethasone phosphate have very different pharmacokinetic profiles[2] and potentially distinctive signaling effects[24]. Two major lines of evidence inform decision making in this

regard: pharmacokinetic and pharmacodynamic studies, and human randomised control trial data.

Firstly, with regard to pharmacokinetic and pharmacodynamic assessments, there is now strong evidence from large animal models of pregnancy to show that maturation of the preterm fetal lung is principally a function of maintaining a fetal plasma betamethasone or dexamethasone concentration of approximately 2 ng/ml, with the duration of exposure required being dependent upon eventual treatment to delivery interval.[1, 10, 25-27] This concept is consistent with 1995 data from Ballard and Ballard showing that maintenance of glucocorticoid in *in vitro* systems is necessary for the sustained expression of lung maturation-associated factors.[24]

In the preterm fetal sheep (approximately equivalent to 32 weeks' human gestation with regard to lung maturation), a 12-hour fetal plasma concentration targeting 2 ng/ml was insufficient to achieve robust functional lung maturation at a 48-hour treatment to delivery interval.[26] In contrast, robust maturation at a 48-hour treatment to delivery interval was achieved with exposures of 36-48 hours in duration.[28, 29] A similar pattern holds at extended durations; at an 8 day treatment to delivery interval, fetal plasma concentrations of approximately 2 ng/ml for at least 72 hours achieved clinically beneficial lung maturation[30]. Maturation benefit degraded with reduced durations of fetal exposure, and was almost lost entirely if fetal exposure was pulsed or interrupted.[30] These data are of importance given the sizable difficulties that exist in accurately predicting timing of delivery in cases of preterm labour.

The human plasma half-life of dexamethasone phosphate is around 5.2 hours, being half of that of betamethasone phosphate at 10.2 hours.[2] A study of non-pregnant women undertaken in Bangalore, India, showed that betamethasone acetate (used in combination with betamethasone phosphate) has an extremely long half-life, at around 59 hours.[2] The use of betamethasone acetate thus conveys a particular advantage in achieving a very extended duration of fetal glucocorticoid plasma concentration within the projected therapeutic range of 1-4 ng/ml. However, aside from it not being clinically available as a sole preparation, a particular draw-back of using betamethasone acetate is the persistence of drug in the plasma at levels sub-therapeutic for fetal lung maturation, but still at sufficiently high levels to suppress the maternal and fetal hypothalamic pituitary adrenal axis and perturb immunocyte populations.[2] Whether or not this extended sub-therapeutic exposure conveys material adverse risk to the mother or the fetus remains to be established.

Secondly, with regard to clinical trials data, the picture is more complex. Not only have there been limited efforts made to directly compare the efficacy and safety of betamethasone and dexamethasone clinically, interpreting these existing data is made challenging by a lack of information relating potential confounders such as treatment-to-delivery intervals, differences in gestational ages, differences in co-morbidities (i.e. chorioamnionitis), the historical nature of many studies, and differences in patient populations and care strategies (i.e. high resource *vs.* LMIC settings).

One study attempting to address this question, the 2019 ASTEROID randomised control trial publication (Crowther *et al.*) was not included in the 2020 McGoldrick Cochrane review.[22] This study used a standard betamethasone regimen (two maternal intramuscular injections of 11.4mg betamethasone phosphate and acetate administered at a 24-hour interval) and a non-standard (two maternal intramuscular injections of 12mg dexamethasone sodium phosphate

at a 24-hour interval) dexamethasone regimen. The only other example of this regimen reported in the McGoldrick review is found in the Dexiprom study (South Africa, 1999).[31]

The primary hypothesis of the Crowther *et al.* study was that, compared with betamethasone, dexamethasone reduces the risk of death or any neurosensory disability in their children at two years' corrected age (primary study endpoint). The incidence rate of death or neurosensory disability in children at 2 years of age for mothers treated with antenatal dexamethasone and betamethasone was 33% and 32%, respectively. This difference was not statistically significant (Adjusted RR = 0.97, 95% CI 0.83 – 1.13. p=0.66). Accordingly, there was not enough evidence to show that dexamethasone reduced the risk of death or any neurosensory disability compared to betamethasone.[22]

A 2021 systematic review by Ciapponi and colleagues (evaluating the comparative clinical effectiveness and safety of betamethasone *vs.* dexamethasone for preterm birth) concluded no statistically significant differences between the use of these agents for neonatal death (moderate-certainty evidence) , neurodevelopmental disability (moderate-certainty evidence), intraventricular haemorrhage (low-certainty evidence), or birthweight (high-certainty evidence). Although not statistically significant, the authors reported potentially clinically important effects between dexamethasone and betamethasone for the following outcomes: chorioamnionitis (OR 0.70; 95% CI, 0.45-1.06; moderate-certainty evidence), fetal death (OR 0.81; 95% CI 0.24-2.41; low-certainty evidence), and respiratory distress syndrome (OR 1.34; 95% CI 0.96-2.11; moderate-certainty evidence).[32]

A 2022 Cochrane systematic review investigated the effects of betamethasone or dexamethasone, and different dosing regimens, on neonatal and maternal morbidity and mortality. The majority of analyses performed were based on outcomes from one or two trials per category, with the bulk of subjects deriving from a single trial (Crowther *et al.*). The authors noted that evidence for different regimens was limited and concluded that, overall, it was unclear if there are important differences between betamethasone and dexamethasone for mother or infant.[33]

Evidence from animal and human studies suggesting a transient, ill-defined period of ANS treatment benefit serves to emphasise the importance of accurately identifying imminent preterm birth risk in deciding to administer ANS therapy. Given the pharmacokinetic differences between betamethasone and dexamethasone, and strong evidence regarding the mode of ANS action for preterm lung maturation, it is reasonable to conclude that betamethasone-based regimens (especially those including the use of betamethasone acetate) may convey a longer duration of benefit than those employing dexamethasone sodium phosphate. Irrespective, based on the available clinical data, there is no evidence to suggest that the maternal or infant outcomes associated with the use of a regimen of four 6 mg maternal intramuscular injections of dexamethasone sodium phosphate administered at 12 hourly intervals will differ from the use of a regimen of two 11.4 mg maternal intramuscular injections of betamethasone sodium phosphate and acetate

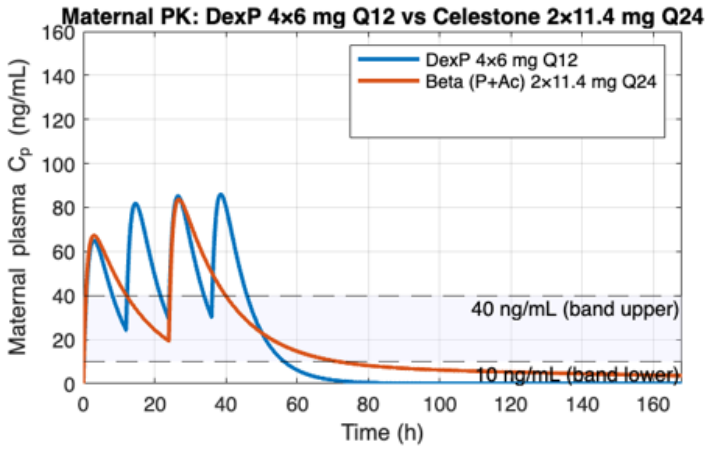


Figure 1. Pharmacokinetic (PK) projection of maternal compartment (plasma) glucocorticoid concentrations over time deriving from two dosing regimens recommended for use in Singapore. **i)** (blue line), 4 x 6 mg maternal intramuscular injections of dexamethasone sodium phosphate given at a 12-hour interval; **ii)** (orange line), 2 x 11.4 mg maternal intramuscular injections of betamethasone sodium phosphate and betamethasone acetate given at a 24-hour interval. Note the substantially (approximately 20 hours) longer time at which the maternal plasma glucocorticoid concentration is above 10 ng/ml (3 x lower bound of projected efficacious range in the fetus) in the projection for a regimen comprised of 2 x 11.4 mg maternal intramuscular injections of betamethasone sodium phosphate and betamethasone acetate given at a 24-hour interval. Projections based on non-pregnant human female data from Jobe *et al*[2].

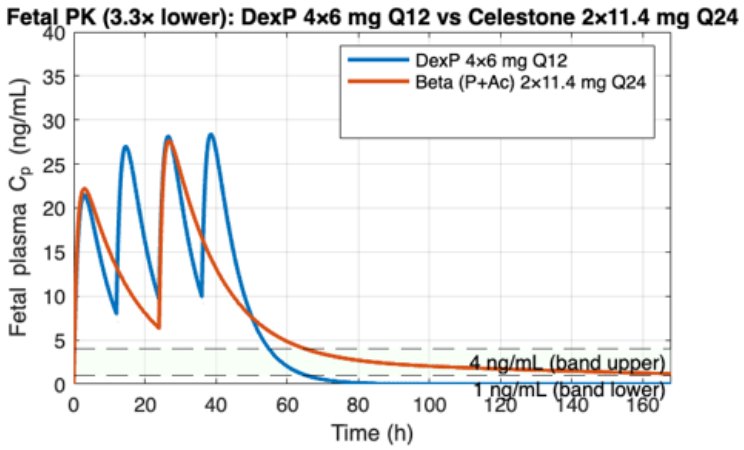


Figure 2. Projection of fetal compartment (plasma) glucocorticoid concentrations over time deriving from two dosing regimens recommended for use in Singapore. **i)** (blue line), 4 x 6 mg maternal intramuscular injections of dexamethasone sodium phosphate given at a 12-hour interval; **ii)** (orange line), 2 x 11.4 mg maternal intramuscular injections of betamethasone sodium phosphate and betamethasone acetate given at a 24-hour interval. Note the substantially (~100 hours) longer time at which fetal plasma glucocorticoid is above 1.0 ng/ml (lower bound of projected efficacious range in the fetus) in the projection for a regimen comprised of 2 x 11.4 mg maternal intramuscular injections of betamethasone sodium phosphate and betamethasone acetate given at a 24-hour interval. Projections based on non-pregnant human female data from Jobe *et al*[2].

3. ANTENATAL GLUCOCORTICOIDS – USE CONSIDERATIONS

The ANS regimen used historically in Singapore was based around the 12 hourly administration of two 12 mg maternal intramuscular injections of dexamethasone sodium phosphate.[9] Consistent with international variation in ANS dosing regimens, not all public or

private providers employed this regimen. Some Government Restructured Hospitals have adopted the use of a regimen based on two 12 mg maternal intramuscular injections of dexamethasone sodium phosphate given at a 24-hour interval. Others have previously adopted a regimen based on two 12 mg maternal intramuscular injections of betamethasone sodium phosphate given at a 24-hour interval. A regimen of four 6 mg maternal intramuscular injections of dexamethasone sodium phosphate given at 12-hour intervals has also been used in private obstetric practice. Given on-going clinical trials of low-dose ANS regimens, it is reasonable to conclude that reassessment of recommended dosing regimens in Singapore will be required in the future.

As outlined above, betamethasone sodium phosphate, dexamethasone sodium phosphate and betamethasone acetate each have very distinct pharmacokinetic profiles.[2] Accordingly, altering the dose of these drugs or the schedule over which they are administered will materially alter both maternal and fetal drug exposures. This is a very important consideration because of data showing that lung maturation benefit from ANS therapy requires achieving and then maintaining a minimum (1-4 ng/ml plasma betamethasone in the preterm sheep) therapeutic glucocorticoid concentration in the fetal compartment.[25, 27, 29] The required exposure duration is a function of the eventual treatment to delivery interval, with longer latencies predicted to need extended periods of therapeutic-concentration glucocorticoid exposure. Accordingly, current data do not support the concept that truncated dosing regimens (i.e. 12 hourly administration of 12 mg betamethasone or dexamethasone) will achieve outcomes equivalent to those reported by trials using longer dosing intervals (i.e. standard 24-hourly administration of 12 mg betamethasone). Nor do these data support the interchangeability of glucocorticoids between treatment protocols (i.e. administering two 12 mg maternal intramuscular injections of dexamethasone sodium phosphate using the 24-hour dosing interval tested clinically with a combined betamethasone sodium phosphate and acetate preparation, which has a substantially longer half-life).

In Singapore, dexamethasone sodium phosphate is a fully subsidized drug for citizens and its use in an ANS therapy regimen conveys negligible cost to the patent. Costs for a full course of betamethasone sodium phosphate and acetate are higher, but still modest in comparison to the cost of preterm infant care. Drug cost was not considered to be an important factor for the purposes of regimen recommendation.

Reliable access to exogenous glucocorticoids poses several challenges in Singapore. Betamethasone sodium phosphate and combined preparations of betamethasone sodium phosphate and acetate are not registered with the Health Sciences Authority of Singapore (HSA) and need to be imported and used under an exemption / special access route. Implications of this arrangement are that order volumes may be limited, supply contracts need to be renewed on an annual basis, and individual health clusters may need to negotiate their own contracts. It is also likely that private providers will similarly need to negotiate their own supply agreements.

4. REGIMEN RECOMMENDATIONS

This document focuses exclusively on the choice of agent, dose, and administration schedule for ANS dosing. It does not address topics such as gestational age ranges, repeated doses, or contraindications. The present document recommends that, where possible, Singapore

adopts a uniform approach to antenatal glucocorticoid dosing in the setting of imminent preterm birth. Herein, imminent preterm birth is defined as being within seven (7) days.

Two antenatal glucocorticoid regimens are recommended, with the intent that one be selected as a preferred regimen. Given likely pharmacokinetic-based differences in ANS regimen efficacy, and pragmatic challenges regarding drug supply, effort should be made to establish the feasibility of obtaining reliable supplies of combined betamethasone sodium phosphate and acetate prior to a preferred regimen being selected.

- The first regimen recommended for use is dexamethasone sodium phosphate 6 mg intramuscular injections every 12 hours for four doses (24 mg total), given to the mother (eight trials, moderate to high-certainty evidence).[4]
- The second regimen recommended for use is betamethasone sodium phosphate and acetate 11.4 mg intramuscular injections every 24 hours for two doses (22.8 mg total), given to the mother. (sixteen trials, moderate to high-certainty evidence).[4]

There is a larger body of high certainty trials evidence for the use of betamethasone (16 trials as per McGoldrick *et al.*)[4] over dexamethasone sodium phosphate (8 trials as per McGoldrick *et al.*).[4] Trials of uncertain quality and potential bias are included in both agent analyses, notably Mansouri *et al*. for betamethasone.[4]

Based on pharmacokinetic and pharmacodynamic data, the combined betamethasone sodium phosphate and acetate regimen may have a longer efficacy window than that of the dexamethasone sodium phosphate regimen. This projection is consistent with data showing a larger relative risk benefit for respiratory distress syndrome in betamethasone (phosphate, phosphate and acetate) exposed preterm infants than that reported for dexamethasone sodium phosphate (0.63 [0.55 - 0.72] vs. 0.80 [0.70 - 0.92]) exposed infants.[4]

However, it is important to note that there are no high-certainty data showing a statistically significant difference in maternal or newborn clinical outcomes between the use of these two glucocorticoids for ANS therapy. It is also important to note that there is also no high-certainty evidence that doses and regimens for dexamethasone sodium phosphate and betamethasone (phosphate or phosphate and acetate) may be used interchangeably. It will be important to revisit recommendations for ANS dosing regimens in light of on-going work at specific gestational ages to identify an optimal glucocorticoid and dose for maturation of the preterm fetal lung.

5. SUMMARY OF GUIDELINE DEVELOPMENT METHODOLOGY

A proposal to develop a new clinical practice guideline (CPG) for Singapore on the matter of ANS therapy dosing regimens was submitted to the Academy of Medicine, Singapore in 2025. On acceptance of the proposal, a Core Working Group led by a Two Co-Chairs (one representing Obstetrics, one representing Neonatology) and supported by a Deputy Chair was established.

The Core Working Group comprised an Obstetrics & Gynaecology representative and a Neonatology representative from each of the three major maternity services (KK Women's and Children's Hospital, Singapore General Hospital, National University Hospital) in Singapore, an Obstetrics & Gynaecology representative and a Neonatology representative

from the private sector, and a Science representative from National University of Singapore (NUS). The Core Working Group was supported by a secretary. A Terms of Reference and Operating Manual was established for the Core Working Group. The Core working group consulted widely but had ultimate responsibility for drafting and approving the CPG. Pharmacy representatives from each of the above three major maternity services and NUS were invited to join meetings by standing invitation from December 2025 onwards.

To ensure the efficient function of the Core Working Group, whilst considering a wide range of perspectives, three Discipline Advisory Panels (one for Obstetrics & Gynaecology, one for Neonatology, one for Science) were created to provide advice and feedback to the Core Working Group. The Discipline Advisory Panels each reported to a member of the Core Working Group. The Co-Chairs nominated two discipline representatives from the Core Working Group to Chair and manage the respective Discipline Advisory Panels. The workflow adopted by the Core Working Group is summarised below.

Having identified and refined the subject area (antenatal steroid dosing in Singapore) the Core Working Group proposed to:

Convene a series of meetings representing public and private sector expertise in obstetrics and neonatology;

Draw on existing guideline,[12, 17, 19-21] individual trial,[13, 16, 18, 22, 31, 34] systemic review,[4, 32, 33] and experimental data[1, 2, 6, 10, 24, 25, 29, 35] to assesses the evidence informing the choice of antenatal steroid dose to be used in Singapore in anticipation of imminent preterm birth;

Seek Discipline Advisory Panel, wider stakeholder, community and health sector input on issues pertaining to the CPG;

Consider, adapt or adopt the available evidence, with reference to Core Working Group, Disciplinary Panel stakeholder and community input as relevant, to develop a recommendation within a CPG; and

Arrange for external review of the guideline drawing on the Discipline Advisory Panels, national and international expertise.

Lastly, the Core Working Group arranged for CPG publication, dissemination, continuing education regarding practice change.

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8. LIST OF ABBREVIATIONS

- Antenatal Steroid Therapy, ANS.
- Confidence Interval, CI.
- Clinical Practice Guideline, CPG.
- Intraventricular Haemorrhage, IVH.
- Low- and Middle-Income Country, LMIC.
- Ministry of Health Singapore, MoH.
- National Institutes of Health, NIH.
- National University of Singapore, NUS.
- Respiratory Distress Syndrome, RDS.
- Risk Ratio, RR.
- Royal College of Obstetricians and Gynaecologists (UK), RCOG.
- World Congress of Obstetrics and Gynaecology, FIGO.
- World Health Organisation, WHO.

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