National Women & Infants Health Programme

National Clinical Practice Guideline

Antenatal Corticosteroids to Reduce Neonatal Morbidity and Mortality

INSTITUTE OF OBSTETRICIANS & GYNAECOLOGISTS

ROYAL COLLEGE OF PHYSICIANS OF IRELAND

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National Clinical Guideline: antenatal corticosteroids to reduce neonatal morbidity and mortality

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This Guideline aims to provide evidence-based recommendations for the administration of antenatal corticosteroids, over a variety of pre-defined gestational ranges and clinical circumstances.
Description:
This National Clinical Practice Guideline provides an evidence-based framework for antenatal corticosteroid administration to reduce neonatal morbidity and mortality. It specifies indications, gestational-age thresholds, dosage regimens and timing where preterm birth is anticipated, including at the threshold of viability. It also addresses late-preterm and term caesarean birth, multiple pregnancy, diabetes, preterm prelabour rupture of membranes, infection and repeat courses, emphasising individualised counselling and the balance between neonatal benefit and potential maternal or neonatal harms.

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Key Recommendations

1. A course of antenatal corticosteroids should be strongly recommended, where pre-term birth is anticipated between 24+0 and 34+6 weeks' gestation. *1A*
2. A course of antenatal corticosteroids should be offered to women where preterm birth is likely in the next 7 days from 23+0 weeks' gestation. This should be at the judgement of the senior treating Obstetric and Neonatal teams and in consultation with the woman/couple. This should occur even if it is anticipated that the full course of corticosteroids (two doses) may not be complete prior to delivery. *1B*
3. In certain circumstances it may be appropriate to offer antenatal corticosteroids from 22+5 weeks' gestation in anticipation of active neonatal management at 23+0 weeks. *1C*
4. For regional centres transferring to tertiary units for management of threatened preterm labour and/or for anticipated preterm birth under 28 weeks, commencement of antenatal corticosteroids should ideally be discussed with the receiving hospital. *Best Practice*
5. A course of antenatal corticosteroids should not be routinely recommended between 35+0 and 36+6 weeks' gestation. *1C*
6. If late pre-term birth is likely to occur between 35+0 and 36+6 weeks' gestation, the potential risks and benefits of administration of antenatal corticosteroids should be discussed with the pregnant woman, to allow her to come to an informed decision with regards to their administration. *Best Practice*
7. Routine administration of antenatal corticosteroids is not recommended before planned caesarean section from 37+0 weeks to 38+6 weeks' gestation. *1C*
8. Healthcare professionals should be aware that the knowledge base around antenatal corticosteroids is limited in some clinical scenarios. *Best Practice*
9. Healthcare professionals and professional bodies have a responsibility to keep themselves informed on the changing evidence base and the balance between intended short-term benefits versus potential long-term harms of antenatal corticosteroids. *Best Practice*
10. A course of antenatal corticosteroids should be strongly recommended, where pre-term birth in a multiple pregnancy is anticipated between 24+0- and 34+6-weeks' gestation. This is line with the recommendations for singleton pregnancy. *1C*
11. It should be explained to pregnant women that most of the evidence available examines the role of antenatal corticosteroids in singleton pregnancies, but data available for multiple pregnancy are very promising and suggest the benefits are similar. *Best Practice*
12. Women with pre-existing diabetes or gestational diabetes should be offered antenatal corticosteroids within the same gestational ranges as to women without diabetes. *1C*
13. Close monitoring of blood glucose levels should take place in the days following administration of antenatal corticosteroids in women with pre-existing or gestational diabetes, and additional insulin administered if required, according to local protocols. *Best Practice*

14. Women presenting with preterm prelabour rupture of membranes between 23+0- and 34+6-weeks' gestation should be offered antenatal corticosteroids as part of a bundle of obstetric care including prophylactic antibiotics. *1C*
15. Where there is evidence of clinical chorioamnionitis a course of antenatal corticosteroids may be started but should not delay delivery if indicated by maternal or fetal condition. *1C*
16. A course of antenatal corticosteroids consisting of 24 mg of dexamethasone phosphate administered intramuscularly, in two divided doses of 12 mg, given 24 hours apart, is recommended where antenatal corticosteroid administration is considered clinically appropriate. Administration of the second dose after a 12-hour interval may be considered where delivery is imminent. *1C*
17. An alternative course consists of 24 mg of betamethasone phosphate in two divided doses of 12 mg, given intramuscularly 24 hours apart. Administration of the second dose after a 12-hour interval may be considered where delivery is imminent. *1C*
18. In the presence of systemic infection, the potential beneficial effects of antenatal corticosteroids intended for the infant must be balanced against the effects of exacerbating the severity of infection for both the woman and her infant. Delivery should not be delayed to administer antenatal corticosteroids when there are serious concerns about the maternal or fetal condition that will be alleviated by expedited birth.*1C*
19. Where preterm birth is likely within 7 days, antenatal corticosteroid therapy should be initiated. *1A*
20. If preterm birth is imminent within the next 24 hours, it is still of benefit to initiate antenatal corticosteroids, even if treatment (the course) is incomplete. *1C*
21. Women should be counselled on the risks of neonatal hypoglycaemia where there is a shorter interval between corticosteroid administration and birth. *Best Practice*
22. A single repeated dose (i.e., 12 mg) of antenatal corticosteroid may be considered on an individual basis for women at risk of imminent preterm birth greater than 7-14 days from the initial completed antenatal corticosteroid course (up to 34+6 weeks' gestation). *1C*
23. Women should be counselled on the risk of lower birth weight, length, or head circumference with repeated antenatal corticosteroid therapy. *2B*

Chapter 1: Initiation

The National Clinical Effectiveness Committee (NCEC) and Health Information and Quality Authority (HIQA) define clinical guidelines as systematically developed statements, based on a thorough evaluation of the evidence, to assist practitioner and patient decisions about appropriate healthcare for specific clinical circumstances, across the entire clinical spectrum.[1]

1.1 Purpose

The purpose of this Guideline was to develop and provide a comprehensive evidence-based guide for all healthcare professionals on the use of antenatal corticosteroids to reduce rates of neonatal morbidity and mortality. The Guideline provides guidance for the administration of antenatal corticosteroids at pre-term and term gestations as well as their use in a variety of specific clinical circumstances.

The content of this Guideline is also intended to provide information relating to the benefits and safety of antenatal corticosteroids in different clinical circumstances, while acknowledging there is still a paucity of evidence in some clinical scenarios.

1.2 Scope

Target Users

Healthcare staff, doctors, advanced midwifery practitioners[2], midwives, nurses, health and social care professionals involved in the care of pregnant women.

The Guideline is a resource for all healthcare professionals working in maternity and neonatology services, including all allied healthcare professionals who may be involved in providing care to women during the antenatal period.

Target Population

Pregnant women in the antenatal period, and also their partners and families.

1.3 Objective

To provide evidence-based recommendations for the administration of antenatal corticosteroids, over a variety of pre-defined gestational ranges and clinical circumstances.

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1 National Clinical Effectiveness Committee (NCEC) and Health Information and Quality Authority (HIQA) (2015) National quality assurance criteria for clinical guidelines. Version 2. Dublin: NCEC and HIQA. https://www.hiqa.ie/sites/default/files/2017-01/National-Quality-Assurance-Criteria.pdf

2 Nursing and Midwifery Board of Ireland (NMBI) (2018) Advanced Practice (Midwifery) Standards and Requirements. Dublin. www.nmbi.ie/NMBI/media/NMBI/Advanced-Practice-(Midwifery)-Standards-and-Requirements-2018-final.pdf

1.4 Guideline development process

The Guideline Developers agreed to undertake this work under the direction of the Guideline Programme Team (GPT). An Expert Advisory Group (EAG) was commissioned by the GPT. Their role was to critically review the Guideline prior to submission to the National Women and Infants Health Programme (NWIHP) for final approval. See Appendix 1 for EAG membership and Appendix 2 for Guideline Programme Process.

This Guideline was developed by:

- Dr Sarah Murphy, Specialist Registrar Obstetrics and Gynaecology, Royal College of Physicians Ireland
- Dr Elizabeth Murphy, Specialist Registrar Paediatrics, Royal College of Physicians Ireland
- Ms Alana Dineen, Clinical Pharmacist, Cork University Maternity Hospital
- Ms Joan Ryan, Chief Pharmacist Maternity Services, Cork University Maternity Hospital
- Prof. Eugene Dempsey, Consultant Neonatologist, Cork University Maternity Hospital
- Prof. Keelin O'Donoghue, Consultant Obstetrician and Gynaecologist, Cork University Maternity Hospital

Maria Mulrooney, Clinical Pharmacist CUMH, worked with the Guideline developers and wrote the Patient Information Leaflet.

1.5 Stakeholder involvement

Stakeholders are people who have a common interest in improving health services. This includes persons that are responsible for delivering and those who receive services related to the Clinical Guideline.

The Expert Advisory Group has representatives from obstetrics, midwifery, neonatology as well as pharmacy.

The following additional stakeholders were consulted regarding this Guideline and reviewed the Guideline drafts:

- *Pharmacists working clinically with both maternity and neonatology services.*
- *Irish Neonatal Health Alliance: A collaborative network to represent the interests of preterm infants and their families.*
- *Professor Jan Miletin, Consultant Neonatologist, Coombe Women's Hospital, Dublin.*
- *Dr. Donough J. O'Donovan, Director Neonatal Intensive Care Unit. Consultant Neonatologist/ Paediatrician, University College Hospital Galway.*

1.6 Disclosure of interests

Guideline developers and reviewers bring a range of experiences and perspectives to the work of the national Guideline Programme. It is likely that both Guideline developers and stakeholders/reviewers will have a variety of interests, arising from different contexts and activities done in a professional or personal capacity. These can include employment and other sources of income, speaking engagements, publications and research, and membership of professional or voluntary organisations. The involvement of individuals with relevant content expertise is essential for enhancing the value of Guideline recommendations, but these individuals may also have interests that can lead to conflicts of interest, as may peer reviewers, patient representatives and researchers.

All interests should be declared if, in the view of a reasonable person, they are relevant, or could be perceived to be relevant, to the work of the Clinical Practice Guideline in question.[3] Declaring an interest does not mean there is a conflict of interest.

It is important that interests are openly declared so they can be appropriately managed. Conflicts of interest can bias recommendations and ultimately be harmful to women and the health system. Disclosures of interests and appropriate management of conflicts of interest, when identified, are therefore essential to producing high-quality, credible health guidelines.[4]

The Guidelines International Network (GIN), a global network of Guideline developers that aims to promote best practices in the development of high-quality guidelines, developed a set of 9 principles to provide guidance on how financial and non-financial conflicts of interest should be both disclosed and managed. It is recommended that Guideline developers follow the GIN principles.[5]

For this National Clinical Practice Guideline, all Guideline developers are asked to complete a conflict of interest declaration form. The response to declared interests will be managed by the Guideline programme team, in accordance with GIN principles. Conflicts of interest may be reported in the published Guideline (word doc) and declarations of interest can be made available.

Professor Keelin O'Donoghue is Clinical Lead for Guideline Development in Maternity and Gynaecology at the National Women and Infants Health Programme (NWIHP), HSE (2021-) and leads implementation for the HSE's National Standards for Bereavement Care following Pregnancy Loss and Perinatal Death (2017-). In the last five years, she has received research funding for projects related to pregnancy loss, perinatal death and maternal-fetal medicine from Science Foundation Ireland, the Health Research Board, the Irish Research Council, the Department of Children and Youth Affairs, the Irish Hospice Foundation, the MPS Foundation and Féileacáin. Prof O'Donoghue served/serves on the following Committees/Groups (in non-remunerated roles): Institute of Obstetricians and Gynaecologists (IOG) Speciality Training Committee (2014-); IOG Executive Council (2018-2022); Royal Irish Academy Life and Health Sciences Multidisciplinary Committee (2022-); Department of Health National Screening Advisory Committee (2019-2023); Termination of Pregnancy (Review Recommendations National Implementation Group (2023-); Perinatal Mortality National Clinical Audit Governance Committee (2014-); Clinical Advisory Group, NWIHP (2017-); International Stillbirth Alliance Advocacy Working Group (2022-).

3 NICE (2019) Policy on declaring and managing interests for NICE advisory committees https://www.nice.org.uk/Media/Default/About/Who-we-are/Policies-and-procedures/declaration-of-interests-policy.pdf

4 Traversy G, Barnieh L, Akl EA, Allan GM, Brouwers M, Ganache I, Grundy Q, Guyatt GH, Kelsall D, Leng G, Moore A, Persaud N, Schünemann HJ, Straus S, Thombs BD, Rodin R, Tonelli M. CMAJ. 2021, 193(2):E49-E54. DOI: 10.1503/cmaj.200651 https://www.cmaj.ca/content/193/2/E49

5 Holger J. Schünemann, Lubna A. Al-Ansary, Frode Forland, *et al.*; for the Board of Trustees of the Guidelines International Network. Guidelines International Network: Principles for disclosure of interests and management of conflicts in guidelines. Ann Intern Med. 2015;163:548-553. doi:10.7326/M14-1885. https://www.acpjournals.org/doi/10.7326/m14-1885

Prof. Dempsey the inaugural Horgan Chair in Neonatology at University College Cork, a Consultant Neonatologist at Cork University Maternity Hospital and Neonatal Clinical lead at the INFANT Research Centre, UCC. In the last five years he has received funding for projects related to the care of preterm infants from funding agencies including Science Foundation Ireland, the Health Research Board and Horizon Europe. He is a member of a number of Trial Steering Committees for ongoing international clinical trials and is a member of a number of Data Monitoring Committees for a number of ongoing neonatal trials. He is a member of the National Research Ethics Committee CT A (2021-), a member of National Office of Clinical Audit (2023-) and a member of a National Clinical Trials Office Stakeholder & Management Committee (2021-). He is a member of a number of subgroups of the European Society of Paediatric Research, including the European Neonatal Echo Working group, European NIRS Working group and Pharmacology section of the European Society for Paediatric Research.

1.7 Disclaimer

These guidelines have been prepared to promote and facilitate standardisation and consistency of good clinical practice, using a multidisciplinary approach. Information in this Guideline is current at the time of publication.

The ultimate judgement regarding a particular clinical procedure or treatment plan must be made by the Clinician in light of clinical data presented by the woman and the diagnostic and treatment options available.

Clinical material offered in this Guideline does not replace or remove clinical judgment or the professional care and duty necessary for each specific woman.

Clinical care carried out in accordance with this Guideline should be provided within the context of locally available resources and expertise. This Guideline does not address all elements of standard practice and assumes that individual clinicians are responsible for:

- Discussing care with women in an environment that is appropriate and which enables respectful confidential discussion. This includes the use of interpreter services where necessary
- Advising women of their choices and ensure informed consent is obtained
- Provide care with professional scope of practice, meeting all legislative requirements and maintaining standards of professional conduct
- Applying standard precautions and additional precautions, as necessary, when delivering care
- Documenting all care in accordance with local and mandatory requirements

1.8 Use of language

Within this guidance we use the terms 'woman' and 'women's health'. However, it is important to acknowledge that people who do not identify as cis-gender women are excluded from this descriptor, including people who identify as transgender, gender diverse and gender non-binary.[6] We also appreciate that there are risks to desexing language when describing female reproduction.[7] [8] Services and delivery of care must be appropriate, inclusive and sensitive to the needs of people whose gender identity does not align with the sex they were assigned at birth. This includes training and education regarding diverse pathways to pregnancy and the use of practices which affirm the sexual and gender identities of all people using Obstetrics and Gynaecology services.

Language use is key to effectively communicate options, recommendations, and respectfully accept a woman's fully informed decision[9]. With this in mind, the use of birth is preferable to the term delivery in all circumstances and is used consistently where possible throughout the guidelines. It is acknowledged that in some circumstances (e.g., in the case of a medically indicated intervention or surgery) and in some contexts, substituting with the term delivery is considered appropriate and this term may be used instead.

6 Moseson H, Zazanis N, Goldberg E, *et al.* The Imperative for Transgender and Gender Nonbinary Inclusion. Obstet Gynecol. 2020;135(5):1059-1068. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7170432/

7 Brotto LA, Galea LAM. Gender inclusivity in women's health research. BJOG: An International Journal of Obstetrics and Gynaecology. https://obgyn.onlinelibrary.wiley.com/doi/full/10.1111/1471-0528.17231

8 Gribble KD, Bewley S, Bartick MC, *et al.* Effective Communication About Pregnancy, Birth, Lactation, Breastfeeding and Newborn Care: The Importance of Sexed Language. *Frontiers in Global Women's Health*. 2022;3. Accessed June 9, 2022. https://www.frontiersin.org/article/10.3389/fgwh.2022.818856

9 https://blogs.bmj.com/bmj/2018/02/08/humanising-birth-does-the-language-we-use-matter/

Chapter 2: Clinical Practice Guideline

Background

Preterm birth (PTB), that is birth before 37 weeks' gestation, is a leading cause of early childhood morbidity and mortality. It results in one million deaths globally each year.[1] Preterm birth is associated with adverse effects on a variety of organ systems in the neonate, including neurological, gastrointestinal, and respiratory complications. Respiratory distress syndrome (RDS) is one of the leading causes of morbidity in the neonate[2], affecting up to 50% of neonates born before 28 weeks' gestation and up to one third of those born before 32 weeks' gestation.[3]

Respiratory disease in the preterm neonate is caused by both anatomical and biochemical immaturity of the fetal lungs, which are insufficiently developed to safely support the transition to *ex-utero* life. The final stage of fetal lung development is known as the alveolar stage; from 28 to 35 weeks' gestation alveoli increase in number and maturity and demonstrate a curvilinear increase with gestational age. The alveoli are the functional unit of the lung and produce surfactant, which is stored in lamellar bodies. Surfactant is a complex biochemical mixture of lipids and a variety of apoproteins. It is surfactant which allows the alveoli to maintain stability during expiration and avoid collapse of these units. Without adequate levels of surfactant the lungs are predisposed to intrapulmonary shunting and ventilation/perfusion mismatch, which is turn can lead to respiratory failure.[4] Endogenous glucocorticoids are required for adequate fetal lung development and maturation. It is now known that glucocorticoids increase surfactant production, increase lung compliance and volume and decrease vascular permeability, which in turn improve respiratory maturation and function.[5]

Liggins *et al.* first noted the link between glucocorticoid administration and fetal lung development in 1969, following exogenously administered dexamethasone to pregnant sheep. They found that sheep, born to mothers who had received dexamethasone, had lung inflation at gestations where this was not expected.[6] It was then in 1972 that Liggins and Howie carried out the first randomised control trial (RCT), studying the effect of corticosteroids administration in humans prior to preterm birth.[7] This seminal study, which included 282 women, reported a reduction in RDS (from 25.8% in the control group to 9% in the treatment group, p 0.003) and in neonatal mortality (from 15% in the control group to 3.2% in the treatment group, p 0.01) in infants whose mothers' received corticosteroids in pregnancy.

Since 1972, numerous studies have confirmed Liggins and Howie's findings, that antenatal administration of corticosteroids decreases RDS and mortality in infants born preterm.[8, 9] Perhaps most notable was the publication of a large meta-analysis of 15 RCTs published between 1972-1994 by Crowley *et al.* in 1995[8], reaffirming the original findings of Liggins and Howie. The use of corticosteroids in suspected preterm birth also increased in popularity following a National Institutes of Health (NIH) sponsored meeting; 'Effects of Corticosteroids for Fetal Maturation and Perinatal Outcomes' in 1994.[10] Since then, evidence continues to support the use of corticosteroid administration prior to suspected pre-term birth before 34 weeks' gestation. Internationally amongst obstetric and perinatal professional bodies and societies a single course of antenatal corticosteroid administration is recommended consistently for suspected pre-term labour before 34 weeks in an effort to prevent neonatal morbidity and mortality. [14, 15, 18]

Despite this, and even though it is over 50 years since Liggins and Howie's first human RCT, a number of controversies still exist with regard to the use of corticosteroids in the antenatal period. Discrepancies still exist with regards to choice of corticosteroid along with the dosing, timing and interval, with uncertainty surrounding balancing the maturation of the preterm lung with unwanted off-target effects. Recent data from animal studies show that current dosing regimens see both mother and fetus exposed to unnecessarily high doses of corticosteroids, with no further lung benefit to the preterm fetus.[11] Elevated steroid exposures may disrupt (suppress) the maternal hypothalamic pituitary-adrenal (HPA) axis[12] and increase the risk of placental dysfunction[13], reducing transport capacity and negatively impacting fetal growth.

It is known that antenatal corticosteroid exposure can increase the risk of short-term effects including neonatal hypoglycaemia; long-term data have linked antenatal corticosteroid exposure to potential developmental delays in childhood, with concerns that these could persist into adulthood. Controversies exist with regards to repeat doses of corticosteroid, administration of corticosteroids at other gestations including peri-viable gestations, late pre-term gestations and early term gestations.

There is a paucity of data pertaining to the use and benefits of corticosteroids for specific populations, including in multiple pregnancy and women with diabetes in pregnancy. More recent data suggests that the administration of corticosteroids is not without potential harm. These concerns relate to neurocognitive morbidity when administered at later gestations and concerns with regards to fetal growth post-administration. This follows animal- and human-based studies showing that infants exposed to corticosteroids have lower birth weights, smaller head circumference, and shorter overall length than those not exposed to corticosteroids.[13]

There is considerable variation in use of antenatal corticosteroids to prevent neonatal morbidity and mortality, with little uniformity internationally. While robust evidence supports their use prior to suspected pre-term birth before 34 weeks, there remain large areas of uncertainty and controversy. High quality, reproducible studies with long-term longitudinal follow-up are still needed to explore these areas of controversy.

Recommendations relevant to this Guideline will also be found in other guidelines currently under preparation (and due in 2024-25):

- National Clinical Guideline: Fetal Growth Restriction
- National Clinical Guideline: Preterm Birth
- National Clinical Guideline: Monochorionic Twin Pregnancy
- National Clinical Guideline: Dichorionic Twin Pregnancy

Section 1: Antenatal Corticosteroids between 24+0 and 34+6 Weeks

Clinical Question 2.1: What are the benefits of antenatal corticosteroids in pre-term labour and/or with anticipated preterm birth between 24+0 and 34+6 weeks' gestation?

Evidence Statement

There is a strong body of evidence to support the use of antenatal corticosteroids for women at high risk of pre-term birth between 24+0 and 34+6 weeks' gestation. Administration of corticosteroids prior to pre-term birth is associated with a reduction in both neonatal morbidity and mortality. A recent update of a Cochrane systematic review in 2020, which included 27 studies, found a high certainty of benefit for the neonate when corticosteroids are administered prior to anticipated pre-term birth.[4] This included a reduction in perinatal death (RR 0.85; 95% CI 0.77-0.93), respiratory distress syndrome (RR 0.71; 95% CI 0.65-0.78) and neonatal death (RR 0.78, 95% CI 0.70-0.87). It found moderate certainty evidence that corticosteroids reduce intraventricular haemorrhage (RR 0.58; 95% CI 0.45-0.75) and developmental delay in childhood (RR 0.51; 95% CI 0.27-0.97). This systematic review did not show a reduction in cerebral palsy following the administration of antenatal corticosteroids. They also found that administration of corticosteroids at this gestation had no effect on birth weight (mean difference – 14.02g, 95% CI – 33.79-5.76), maternal death (RR 1.19, 95% CI 0.36-3.89), chorioamnionitis (RR 0.86, 95% CI 0.69-1.08) and endometritis (RR 1.14; 95% CI 0.82-1.58). The review found that this evidence base was robust across all resource settings, from low to high income countries.

The use and benefits of antenatal corticosteroids in this setting is supported by the National Institute for Health and Care Excellence (NICE) guideline (NG25) which notes that 'evidence for benefit over harm is strongest for babies born between 24+0 and 34+0 gestation'.[14]

The Royal College of Obstetricians and Gynaecologists (RCOG) recommend antenatal corticosteroids be offered to all women with expected pre-term birth up to 34+6 gestation.[15] Most studies included in the Cochrane review used this upper limit, however the most recent randomised control trial (RCT) included, which was commissioned by The World Health Organisation (WHO) used 33+6 weeks' gestation as the upper limit.[16] Unlike the RCOG[15], European Guidelines published in the Journal of Maternal-Fetal and Neonatal Medicine[17], The International Federation of Gynaecology and Obstetrics (FIGO) [18] and the American College of Obstetrics and Gynaecology (ACOG) use 33+6 weeks as the upper gestational limit for which antenatal corticosteroids should be offered.[19] For the purpose of this guideline and from review of the literature, it has been difficult to determine from the evidence available the upper limit of gestation in which neonatal benefit is evident, however the Cochrane review primarily included studies which used 34+6 weeks as their upper gestational limit.

No studies have identified evidence of benefit to the pregnant woman upon receiving antenatal corticosteroids. However, exposure to corticosteroids has not been shown to impact maternal outcomes, including sepsis, endometritis, and maternal death.[4]

Clinical Practice

If pre-term birth is anticipated between 24+0 to 34+6 weeks' gestation, a course of antenatal corticosteroids should be strongly recommended to the pregnant woman, to reduce both neonatal morbidity and mortality.

Antenatal corticosteroids should be offered in both the setting of iatrogenic and spontaneous pre-term birth. The woman should be informed of the neonatal benefits associated with corticosteroid exposure in these settings.

Recommendations

1. **A course of antenatal corticosteroids should be strongly recommended, where pre-term birth is anticipated between 24+0 and 34+6 weeks' gestation.**

Section 2: Antenatal Corticosteroids at the Threshold of Viability

Clinical Question 2.2: What are the benefits of antenatal corticosteroids at the threshold of viability? (23-25 weeks' gestation)

Evidence Statement

As described in section 1, the numerous benefits of antenatal corticosteroids for the preterm neonate are well established: reduced mortality, respiratory distress syndrome (RDS), intraventricular haemorrhage (IVH), necrotising enterocolitis (NEC) and developmental delay are well established >26 weeks. The evidence of benefit to babies at the limits of viability (less than 25 weeks) is less clearly demonstrated.[4] Performing studies in this group is challenging. Thus, the majority of available existing research for this cohort of extreme preterm infants arises predominantly from observational cohort studies, each with their own inherent limitations. These include greater risk of selection bias and lack of a defined control group. Despite the relatively limited evidence base, many national guidelines have extended practice to recommend antenatal corticosteroid administration for this group of extreme preterm infants.

There are no RCTs available for inclusion in this cohort of infants. Three systematic reviews and meta-analysis of observational studies are reviewed below. Deshmukh *et al.* published a 2016 systematic review and meta-analysis to evaluate the effectiveness of antenatal corticosteroids vs placebo or no treatment in less than 25 weeks' gestation.[20] They subsequently published an updated meta-analysis to include a further observational study. Nine observational studies yielded 3334 patients. Meta-analysis showed that among infants born <25 weeks and antenatal corticosteroid exposed, there was reduced odds of mortality, (n=13 443; OR=0.48 (95% CI 0.42 to 0.55) P<0.00001) and IVH or periventricular leuocmalacia (PVL) (n=8418; OR=0.70 (95% CI 0.63 to 0.79), P<0.00001). No difference was seen for other morbidities such as necrotising enterocolitis, while the incidence of chronic lung disease (CLD) was higher (n=7983; OR=1.32 (95% CI 1.04 to 1.67), P=0.02; LOE: low) in antenatal corticosteroid group. A composite outcome of death or major morbidities were reduced amongst the antenatal corticosteroid exposed group.[21]

A 2018 systematic review and meta-analysis by Park *et al.* similarly demonstrated a reduction in mortality in neonates born 22-24 weeks in receipt of antenatal corticosteroids. The adjusted odds of mortality before discharge was reduced by 52% in the antenatal corticosteroid group compared with the control group (aOR 0.45, 95% CI 0.36-0.56; a OR 0.48, 95% CI 0.38-0.61; mortality to discharge 58.1% in the antenatal corticosteroid arm vs 71.8% in control). There was no significant difference for severe morbidities. There was a reduction in the composite outcome of IVH/PVL among antenatal corticosteroid exposed infants born at 23 and 24 weeks that was not replicated <23 weeks. No difference in rates of CLD or NEC was demonstrated.[22] Numerous publications have arisen from the NIH Neonatal Research network database which have contributed substantially to the above meta-analyses.[23, 24]

In 2008, data from the Neonatal Research Network (NRN) cohort of 4446 infants between 22+0 and 25+0 weeks of gestation found a reduced risk of death among those who received intensive care, were exposed to antenatal corticosteroids, were of female sex, were from singleton pregnancies and of higher birth weight. The risk of death or any neurodevelopmental impairment at 18-22 months corrected age was reduced in survivors who were in receipt of antenatal corticosteroid.[25] Ehret *et al.*, using data from the Vermont-Oxford Network of neonates born 22-25 weeks GA, demonstrated that a combination of antenatal corticosteroids with proactive neonatal management is associated with improved survival to discharge and survival without "major" morbidity.[26] A more recent NRN cohort of 431 infants born between 22-23+6 weeks found that, among antenatal corticosteroid exposed, there was greater survival to discharge and survival without major morbidities. Exposure to complete antenatal corticosteroid course resulted in higher adjusted odds of survival to discharge (adjusted odds ratio [aOR], 1.95 [95% CI, 1.07-3.56]) and survival without major morbidity (aOR, 2.74 [95% CI, 1.19-6.30]).[27] Another 2022 retrospective cohort from the US Natality Live Birth Database CDC registry 2016-2017 showed that antenatal corticosteroid treatment was associated with decreased mortality and decreased odds of 5-minute Apgar score <7 in infants at 23-27 weeks' gestation.[28]

More recent publications have explored the benefit at 22 weeks as neonatal practice has evolved to active intervention at this gestation in a number of centres internationally. A 2020 systematic review and meta-analysis of pooled US data examined outcomes of proactive treatment at 22 weeks and observed once again a survival advantage (236/605 [39.0%]) among infants who were provided comprehensive treatment (antenatal corticosteroid and neonatal treatment) compared with among infants who were solely provided neonatal treatment (104/534 [19.5%]; P<.01).[29]

Rossi *et al.*'s large US population based study of 10,627 infants born between 22+0-23+6 weeks who received postnatal resuscitation during years 2009-2014 showed that survival to 1 year for extremely premature infants at 22 week and 23 weeks was more likely if exposed to antenatal corticosteroid than not (survival 45.2% versus 27.8% (adjusted relative risk [aRR]: 1.6, 95% confidence interval [CI]: 1.2-2.1) and 57.9 versus 47.7% (aRR: 1.3, 95% CI: 1.1-1.5) at 23 weeks.[30]

We have reviewed and summarised the recommendations from similar guidelines from relevant international bodies in the associated summary table (Appendix 3). However, additional international perinatal care bodies have issued statements relevant to this question. The British Association of Perinatal Medicine (BAPM) document on management of extreme preterm birth 2019 advises active neonatal management may be considered from 22+0 weeks and antenatal corticosteroid administration <24 weeks should be included when active obstetric and neonatal care is planned.[31] The Australian "Queensland" guideline published in 2021 advises to give antenatal corticosteroids for all >24 weeks if PTB likely within 7 days. Between 22+0 and 23+6 weeks, it advises antenatal corticosteroid after sufficient counselling if PTB is likely within the next 7 days and life sustaining measures are possible (even if decision on active management is not final) or if in-utero transfer is planned.

In 2016, 2017 and 2018, survival at 23-23+6 weeks was 37%, 47%, 33% respectively in Ireland, while in the 2020 National Perinatal Epidemiology Centre (NPEC) report on VLBW infants in Ireland, survival at 23 weeks was 25% (5/20). There remains no published survival below 23 weeks' gestation in Ireland although it is not clear if active measures have been instituted in any cases. The absolute numbers of births at these gestations in Ireland remain small and so year on year variation also impacts these rates.

Decisions around initiation of active management is complex and relies on more than gestational age alone. Numerous factors such as estimated weight, fetal growth restriction, fetal risk factors, e.g. anomalies, obstetric risk factors, umbilical arterial Dopplers, chorioamnionitis, in addition to parents' views must be considered in decision making. As obstetric and neonatal care continues to improve, it is likely that the threshold for active intervention will fall below 23 +0 weeks and as discussed above, antenatal corticosteroid will contribute to perinatal optimisation of these infants.[32, 33] In addition, it seems unlikely that RCTs could now take place in this cohort of preterm infants, given the available evidence, the evidence from other gestations and the lack of clinician equipoise.

Clinical Practice

This Guideline is written in agreement with the 2020 HSE Framework for Practice Document that initiation of resuscitation is not recommended below 23 weeks.[33] This framework is under review in 2024.

In light of this framework, we suggest antenatal corticosteroids should be given when preterm birth is likely in the following 7 days from 23+0 weeks' gestation. Provision of antenatal corticosteroids can be considered in anticipation of active neonatal management before 23 weeks, e.g. at 22+5 weeks' gestation.

We recognise decision making in these cases can be challenging and that these clinical situations are dynamic. It may be reasonable to commence antenatal corticosteroids when extreme preterm birth is likely and when any decision regarding active resuscitation of the neonate at birth is not yet finalised.

In cases of threatened preterm birth less than 28 weeks in level I and II maternity units referring to a tertiary centre, the referring unit may administer antenatal corticosteroids in preparation of an in-utero transfer if delivery is likely even if a definite decision on active management has not been reached. Ideally this should be discussed between the transferring clinicians.

Recommendations

2. **A course of antenatal corticosteroids should be offered to women where preterm birth is likely in the next 7 days from 23+0 weeks' gestation. This should be at the judgement of the senior treating Obstetric and Neonatal teams and in consultation with the woman/couple. This should occur even if it is anticipated that the full course of corticosteroids (two doses) may not be complete prior to delivery.**
3. **In certain circumstances it may be appropriate to offer antenatal corticosteroids from 22+5 weeks' gestation in anticipation of active neonatal management at 23+0 weeks.**
4. **For regional centres transferring to tertiary units for management of threatened preterm labour and/or for anticipated preterm birth under 28 weeks, commencement of antenatal corticosteroids should ideally be discussed with the receiving hospital.**

Section 3: Antenatal Corticosteroids between 35+0 and 36+6 Weeks' Gestation

Clinical Question 2.3: What are the benefits and risks of antenatal corticosteroids in late pre-term labour and/or with anticipated preterm birth before between 35+0 and 36+6 weeks' gestation?

Evidence Statement

Data has also suggested that a course of antenatal corticosteroids is beneficial in the late pre-term period between 35+0 to 36+6 weeks' gestation. A single, large trial within the Cochrane review examined the effect of antenatal corticosteroids in this specific birth period. The 'Antenatal Late Preterm Steroids' trial by The Maternal Fetal Medicine Units in the UK specifically compared the effects of antenatal corticosteroids to placebo between 34+0-36+6 weeks and included 2,831 women.[34] It found a significant decrease in the overall primary outcome (defined as need for respiratory support within 72 hours after birth and consisting of one or more of the following: the use of continuous positive airway pressure (CPAP) or high-flow nasal cannula for at least 2 consecutive hours, supplemental oxygen with a fraction of inspired oxygen of at least 0.30 for at least 4 continuous hours, extracorporeal membrane oxygenation (ECMO), or mechanical ventilation)with a RR 0.80, 95% CI 0.66-0.97. It also found a reduction in severe respiratory complications, including transient tachypnoea of the newborn (TTN). However, it did not demonstrate a decrease in the incidence of respiratory distress syndrome (RDS) itself, neonatal mortality or length of hospital stay. Furthermore, this study identified harm, with higher rates of neonatal hypoglycaemia in the infant group exposed to corticosteroids; the number needed to harm was 11 (RR 1.61; 95%, 1.38-1.88). Evidence of benefit was also demonstrated within a further meta-analysis carried out in 2016 of six trials which also found a decrease in neonatal morbidity, specifically respiratory, with a decrease of TTN (0.38, 95% CI, 0.25-0.57) and the need for mechanical ventilation (0.19, 95% CI 0.08-0.43).[35]

While there is clear evidence of benefit at this gestation, there is also emerging evidence of potential harm, with a lack of large, high-quality studies examining long-term neurodevelopmental outcomes. Neonates at risk of pre-term birth at this late pre-term gestation need to be considered separately given the fetal brain is at a crucial and vulnerable point of development between 34 and 36 weeks' gestation.

During this period, the fetal brain undergoes rapid growth with 25% of cerebellar volume yet to form and 50% of cortical volume. Secondary to growth factors, specifically neurotrophins, oligodendrocytes are stimulated to undergo rapid growth and myelin synthesis. Within very pre-term gestations, corticosteroids have been found to increase neurotrophin levels, however amongst late pre-term fetuses, corticosteroid exposure has been shown to down-regulate neurotrophin-3.[36] This in turn has raised concerns with regards to possible adverse neurodevelopmental outcomes in the long-term. This concern is evident within both the RCOG Guideline and the European guideline on perinatal care: corticosteroids for women at risk of preterm birth, neither of which recommend routine administration of corticosteroids beyond 34+6 and 34+0 weeks' gestation, respectively.[15, 17] This is in contrast to a 2021 Society for Maternal-Fetal Medicine Consult Series which recommended offering a course of corticosteroids to those at risk of pre-term birth up to 36+6 weeks' gestation.[37]

While data from RCTs with regards to long-term developmental outcomes is lacking, an additional body of evidence is emerging suggesting adverse neurodevelopmental outcomes for neonates exposed to corticosteroids at late pre-term and term gestations. In 2020, a Finish population-based, retrospective study also gave rise to concerns with regards to neurodevelopmental outcomes post-corticosteroids exposure. This study compared neurodevelopmental outcomes of children exposed to corticosteroids in utero to peers who had not been exposed. They found a higher hazard ratio for mental and behavioural disorders for those children exposed to corticosteroids. This finding was of statistical significance for neonates born at term and not for those born pre-term. The number needed to harm for this population was found to be 33.8.[38] In a follow up analysis of this cohort, the authors found a higher hazard ratio for speech and language disorders (aHR, 1.38 [95% CI, 1.27-1.50]; $P<.001$), motor function disorders (aHR, 1.32 [95% CI, 1.18-1.49]; $P<.001$) and pervasive developmental disorder (aHR, 1.35 [95% CI, 1.17-1.56]; $P<.001$) in term-born children who had been exposed antenatally to corticosteroids.[39]

In 2022, a meta-analysis of 30 studies found that neonates exposed to corticosteroids in the late pre-term period have an increased rate of neurocognitive disorders (OR 1.12, 95% 1.05, 1.20). This is compared to exposure to corticosteroids in the early pre-term period, in which exposure is associated with a decreased incidence of neurodevelopmental impairment. It should be acknowledged that the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool rates this finding as 'low', primarily due to the observational nature of the studies included.[40]

Clinical Practice

While there is clear evidence of benefit at this later preterm gestation (35+0 to 36+6 weeks), there is also emerging evidence of potential harm, with a lack of large, high-quality studies examining long-term neurodevelopmental outcomes.

Neonates at high risk of pre-term birth at this late pre-term gestation need to be considered separately given (a) corticosteroids decrease the risk of what is for the majority a short-term and self-limiting complication and (b) the fetal brain is at a crucial and vulnerable point of development between 34 and 36 weeks' gestation.

If late pre-term birth is anticipated between 35+0 and 36+6 weeks' gestation, a discussion should take place between the clinician and the woman, and partner, if applicable. This discussion should include conversation about the short-term benefits of corticosteroids at this gestation, as well as the potential long-term harms. It should be acknowledged that further studies are needed with regards to long term outcomes after antenatal corticosteroids.

Recommendations

5. **A course of antenatal corticosteroids should not be routinely recommended between 35+0 and 36+6 weeks' gestation.**
6. **If late pre-term birth is likely to occur between 35+0 and 36+6 weeks' gestation, the potential risks and benefits of administration of antenatal corticosteroids should be discussed with the pregnant woman, to allow her to come to an informed decision with regards to their administration.**

Section 4: Antenatal Corticosteroids before Planned Caesarean Section at Term

Clinical Question 2.4: What are the benefits and risks of antenatal corticosteroids before planned caesarean section at term, 37+0 to 39+6 weeks' gestation?

Evidence Statement

Infants born by caesarean section at term are at a greater risk of respiratory morbidity, compared to infants born via vaginal birth, including risk of RDS and TTN.[41] Overall, the risk of respiratory morbidity is low and decreases with gestational age. At 37-37+6 8.4% of infants born by caesarean are at risk of respiratory morbidity. This is compared to 4.4% risk at 38-38+6 and just 1.2% at 39+0.[42] This decrease is particularly noticeable for respiratory distress syndrome, with an incidence of 39/1000 at 37+0-37+6 and 8/1000 when born after 39+0.[43] For this reason, NICE NG192 recommends that planned caesarean sections should not routinely be performed before 39+0 weeks' gestation.[44] Despite this, a proportion of planned caesarean sections are still performed before this recommended threshold, with an Irish study reporting that 15% of planned caesarean sections took place between 37+0-38+6 weeks' gestation.[45]

A Cochrane review, which originally included data from four trials when published in 2018, suggested that antenatal corticosteroids may decrease respiratory morbidity in this cohort.[46] However, in an updated version of this review, three of these four studies (Ahmed 2015, Nada 2016 and Nooh 2018) were removed due to the trials 'not meeting pre-specified trustworthiness criteria'.[47] The authors of this Cochrane review were concerned with regards to the conduct of these three studies, particularly with regards to queries about data integrity and a lack of prospective trial registration, which is a requirement for all studies published after 2010.The authors of the review reached out to the authors of Ahmed, Nada and Nooh but at the time of publication in 2021, were still awaiting response. The integrity of the trials included was also questioned by Mol *et al.* in 2021 when they highlighted deficiencies in the four trials included in the original Cochrane review published in 2018.[48] One of the studies included in the 2018 review, Nada *et al.*, which was originally published in The European Journal of Obstetrics and Gynaecology in 2016, has since been retracted. This study, which was the largest included in the 2018 review, was retracted by the journal in 2022, after concerns were raised by the journal's editorial board. The journal reached out to the authors to offer a response and provide the original dataset, however they failed to return a satisfactory response.[49]

Following this, the updated Cochrane review published in 2021 now contains one multi-centre RCT, with data from 943 infants. This trial was not placebo controlled, nor blinded. It found that the administration of antenatal corticosteroids in this cohort probably reduced neonatal admission to the NICU for respiratory morbidity (RR 0.45, 95% CI 0.49-1.33). However, it was uncertain if rates of RDS or TTN were reduced and uncertain if overall rates of NNU admission were reduced, with data pertaining to these parameters considered to be 'low certainty evidence'.[35] Given this updated Cochrane review we have not considered the findings of the retracted studies in this Guideline.

A separate systematic review included three RCTs of 2,498 women who were undergoing a planned caesarean section after 37+0 weeks' gestation.[34] Infants whose mothers received antenatal corticosteroids prior to the planned caesarean were found to have a significantly lower risk of mild RDS (RR 0.43, 95% 0.26-0.72), moderate RDS (RR 0.40, 95% CI 0.18-0.88), TTN (RR 0.38, 95% CI 0.25-0.57) and the need for mechanical ventilation (RR 0.19, 95% CI 0.08-0.43). There was no significant

difference in overall admission to the NICU or the incidence of neonatal death. It should be noted that two of these three studies were not included in the aforementioned Cochrane review due to concerns with regards to 'trustworthiness', as per the Cochrane Pregnancy and Childbirth Study Trustworthiness Screening Tool.

As with the late pre-term group, antenatal corticosteroid administration at this gestation is also associated with neonatal hypoglycaemia.[50] In one observational study, infants born to women with diabetes who had been exposed to antenatal corticosteroids at term were significantly more likely to require admission for hypoglycaemia, compared to those who had not been exposed (24.2% vs. 4.4% $P = 0.003$).[51] In another retrospective, cohort study authors found that over 1/3 (38%) of infants exposed to antenatal corticosteroids would become hypoglycaemic after birth.[52] It is known that hypoglycaemia in the neonatal period can be detrimental, with prolonged periods associated with brain injury. It is therefore concerning to routinely apply an intervention which may increase the risk of this insult.[53]

Similarly, to the 'late-pre-term' group (see clinical question 2.3), there are also concerns about adverse effects with respect to neonatal neurodevelopment post-antenatal corticosteroid exposure. A follow up of the Antenatal Steroid for Term Elective Caesarean Section (ASTECS) trial found that children exposed to antenatal corticosteroids were more likely to have lower academic ability at school, compared to children who has not been exposed in utero. Their findings suggested that children exposed were more likely to be ranked by teachers in the 'lower quartile for academic ability', as well as have reduced proficiency in English.[17] It should be noted that the long-term follow up of this study was low, at 46%.

Respiratory morbidity post-term caesarean section overall has a low prevalence and is usually mild and short-term, if it does occur. The evidence to support the use of antenatal corticosteroids to reduce this risk further is not clear and it is emerging that it may also be associated with harm, both in the short-term and long-term settings. With all of this considered, the European Guidelines for antenatal corticosteroids, explicitly recommend that antenatal corticosteroids should not be considered in the setting of planned caesarean section at term.[17] Similarly, FIGO and SOGC guidelines suggest 'they should not be given routinely' to this population.[18, 54] This is in contrast to the RCOG green-top guidelines which suggest 'an informed discussion should take place between the woman and doctor about the potential risks and benefits' of corticosteroids administered at this gestation.[15]

Clinical Practice

Planned caesarean section, in the absence of specific maternal or fetal concerns, should ideally be performed after 39+0 weeks' gestation, in order to reduce the risk of neonatal respiratory morbidity.

Administration of corticosteroids after 37+0 weeks' gestation in these scenarios should not be considered given the generally mild and transient risk of respiratory morbidity, the paucity of evidence of benefit and the emerging evidence of potential neonatal harm.

Recommendations

7. **Routine administration of antenatal corticosteroids should not be considered, even before planned caesarean section from 37+0 weeks to 38+6 weeks' gestation.**

Clinical Question 2.5: What are the risks of antenatal corticosteroids?

Evidence statement

Much of long-term implications for neonates exposed to in-utero antenatal corticosteroids is unknown. Some areas of controversy exist. In particular, the risk of adverse neurological and metabolic effects in the exposed infant, effects on fetal growth and the debate over optimal dose and timing. The latter concern is explored in detail in section 6.

Animal studies have suggested glucocorticoids delay myelination in sheep, reduce cell proliferation and result in apoptosis in rodents among other neurotoxic effects.[55] In vivo, there remains concern that antenatal corticosteroids have a negative impact on cerebral development, particularly with repeated exposure. However, there remains a paucity of long-term outcome data.

A systematic review and meta-analysis published in 2022 among babies born at term and antenatal corticosteroids exposed suggests an increased risk of some neurocognitive disorders including cerebral palsy.[40] However, the data included was from a limited number of observational cohort studies. A population-based cohort in Finland over 11 years reported increased risk of any mental or behavioural disorder in the whole cohort of children (12.01% vs 6.45%; adjusted Hazards Ratio, 1.33 [95% CI, 1.26-1.41]), in term-born children (8.89% vs 6.31%; HR, 1.47 [95% CI, 1.36-1.69]).[38] In a similar Canadian population cohort of children aged five years who were born at term but antenatal corticosteroids exposed, the cumulative rate of a composite of proven or suspected neurodevelopmental problems was higher among infants exposed to antenatal corticosteroids compared with non-exposed infants: 61.7% (3346/5423) vs 57.8% (302 520/523 782), respectively (p<0.001,(aHR) 1.12 95% CI 1.08-1.16).[56] Definitions of neurodevelopmental impairment are heterogeneous in many of these studies. As part of the ACTORDS study involving 1085 children, two year follow up showed children whose mothers received weekly repeated antenatal corticosteroids doses were more likely to have problems with attention than those who received a single course (6% vs 3.2% aRR 1.87, 95% CI 1.03-3.42 p=0.04).[57] The most recent Cochrane meta-analysis report a probable overall reduction in developmental delay in childhood for those born preterm (RR 0.51, 95% CI 0.27-0.97; 600 children, 3 studies) but insufficient data exists to comment on individual domains of developmental impairment.[4] This is consistent with the known reduced risk of IVH and other significant neonatal morbidities.

We know from a number of studies that antenatal corticosteroids infer an increased risk of neonatal hypoglycaemia.[4] A 2014 cohort of 6675 deliveries between 32-37 weeks from 1997-2007 reported higher neonatal hypoglycaemia in antenatal corticosteroids exposed vs not exposed (5.7% and 4.2% respectively, p<0.05) resulting in an adjusted OR of 1.6 (95% CI 1.24-2.07).

Hyperbilirubinemia is also significantly more frequent in antenatal corticosteroids-exposed (45.9% vs 24.1%, p<0.05).[55] Cord blood samples of newborns born close to term exposed to betamethasone have increased glucose, c-peptide, cortisol and insulin like growth factor levels. While this explains hyperinsulinemia leading to hypoglycaemia risk, the long term metabolic impacts are unknown.[58] A 30-year follow-up of the cohort from the original Liggins' RCT showed higher insulin resistance in the antenatal corticosteroids-exposed group but no other differences in cardiovascular risk factors.

While there is evidence, particularly with repeated antenatal corticosteroids doses, of negative impact on anthropometric measurements at birth, this was not demonstrated in the overall meta-analysis in the 2020 Cochrane analysis. There was no significant difference in mean birth weight (mean difference -14.02, 95% CI -33.79 to 5.76; 19 studies, 9551 infants), mean birth length (MD 0 cm, 95% CI -0.37 to 0.37 cm, 1 study 2766 infants) and mean head circumference at birth (MD 0.00 cm, 95% CI -0.22-0.22 cm; 1 study, 2766 infants).

Clinical practice

On balance, as we have discussed in several sections of this Guideline, for babies born preterm, the benefits of antenatal corticosteroids for reducing important morbidities outweighs the potential risks.

However, we should continue to seek the optimum strategy to maximise benefit while minimising exposure to excessive doses. Close to term, this balance shifts and the potential short-term benefits are not necessarily offset by the potential risks of excessive exposure. These potential impacts should be considered if preterm birth is less likely. It is the challenge of the treating perinatal team to consider this and to judge the likelihood of preterm birth. Healthcare professionals therefore need to keep up to date on the changing evidence base and the balance between intended short-term benefits versus potential long-term harms of antenatal corticosteroids.

Further when offering or considering corticosteroids a discussion should always take place with the woman about how corticosteroids may help, and the potential risks associated with their administration.

Recommendations

8. **Healthcare professionals should be aware that the knowledge base around antenatal corticosteroids is limited in some clinical scenarios.**
9. **Healthcare professionals and professional bodies have a responsibility to keep themselves informed on the changing evidence base and the balance between intended short-term benefits versus potential long-term harms of antenatal corticosteroids.**

Section 5: Specific Clinical Scenarios

Clinical Question 2.6: Should antenatal corticosteroids be offered in multiple pregnancy?

Evidence Statement

There remains a degree of uncertainty about the effectiveness of antenatal corticosteroids in the setting of expected pre-term birth amongst multiple pregnancies including twins, triplets, and higher order multiples. This is because the majority of antenatal corticosteroid trials excluded women with multiple pregnancies. However, the Cochrane review of antenatal corticosteroids, twelve trials included multiples.[4] Of these, only five reported data separately for multiple pregnancies. From this data, subgroup analysis did not find a statistically significant difference in rates of perinatal, neonatal and fetal death nor in respiratory distress syndrome or IVH between singletons and multiples. There was insufficient data to perform analysis with respect to moderate and severe RDS individually. This would suggest that the evidence available for the role of antenatal corticosteroids in singletons, should be applicable to multiples. However, this should be interpreted with caution, given the limited volume of data available.

Not included in this Cochrane review was a retrospective cohort study from Canada in 2016.[56] This study compared rates of neonatal morbidity and mortality in twins born at a pre-term gestation in those who had been exposed to antenatal corticosteroids, compared to those that had not. For twins whose mother received antenatal corticosteroids prior to birth there was a decreased odds ratio of neonatal death (OR 0.42, 95% CI 0.24-0.76), the need for mechanical ventilation (OR 0.47, 95% 0.35-0.63) and of respiratory distress syndrome (OR 0.53, 95% CI 0.40-0.69). The EPIPAGE-2 cohort study found that twins exposed to antenatal corticosteroids within seven days before pre-term birth had a decreased odds of neurological morbidity, namely via decreased IVH grade III/IV (aOR 0.2, 95% 0.1-0.5).[59]

Since the publication of the most recent Cochrane update, two further studies have specifically compared outcomes for twin pregnancies born at pre-term gestation that were exposed to antenatal corticosteroids to those who were not. Kong *et al.* demonstrated a decreased risk of RDS in the treatment group (aOR 0.0661, 95% CI 0.506-0.863) but did not find infant mortality rates to be significantly reduced.[60] This is in contrast to Ushida *et al.*, which demonstrated a reduction in short-term neurological morbidity in twin pregnancies exposed to antenatal corticosteroids, but no decrease in rates of RDS.[61]

NICE[14], The Royal College of Obstetricians and Gynaecologists[15], The American College of Obstetricians and Gynaecologists[19], The European Guidelines for Corticosteroids[17], The Royal Australian and New Zealand College of Obstetricians and Gynaecologists[62] and The Society of Obstetricians and Gynaecologists Canada[54] all support offering antenatal corticosteroids in multiple pregnancy in line with the settings for which they are offered for singletons. See summary table in Appendix 3.

Clinical Practice

If pre-term birth is expected to occur over the next seven days, women with multiple pregnancies should be offered a single course of antenatal corticosteroids in line with the settings in which they are offered to women with singleton pregnancies.

It should be explained to women that the primary evidence base for the use of antenatal corticosteroids comes from studies which examine their use in singleton pregnancies. However, from the data available at present and possibly into the future, given challenges with conducting any type of RCT now in this group, the benefits appear to be applicable to multiple pregnancy. Ideally, further studies are needed to focus on this specific subgroup.

Recommendations

10. **A course of antenatal corticosteroids should be strongly recommended, where pre-term birth in a multiple pregnancy is anticipated between 24+0 and 34+6 weeks' gestation. This is line with the recommendations for singleton pregnancy.**
11. **It should be explained to pregnant women that the majority of evidence available examines the role of antenatal corticosteroids in singleton pregnancies, but data available for multiple pregnancy are very promising and suggest the benefits are similar.**

Clinical Question 2.7: Should antenatal corticosteroids be offered to women with diabetes mellitus or gestational diabetes?

Evidence Statement

There is a paucity of data specifically pertaining to the use of antenatal corticosteroids in women with pre-existing and gestational diabetes. In fact, within Cochrane review, published in 2020[4], which contained 27 studies, ten of these specifically excluded women with a diagnosis of diabetes, both insulin dependent and otherwise treated. A separate systematic review published in 2016, examined the use of antenatal corticosteroids in special populations of women at risk of pre-term birth, but failed to identify any studies on outcomes of antenatal corticosteroid use in women with diabetes.[63]

Despite this, it is known that the administration of antenatal corticosteroids in pregnancy can give rise to hyperglycaemia, both in the case of the woman with diabetes and without. One study, published in Diabetes Research and Clinical Practice in 2016 looked at the effect of antenatal corticosteroid administration on both women with and without diabetes in pregnancy. They found that blood sugar levels remained elevated for 48 hours post-antenatal corticosteroid administration.[64] A separate prospective study of both women with and without diabetes found blood sugar levels to be elevated even at 156 hours after administration.[65] With this in mind, careful monitoring of glucose levels should take place in cases of antenatal corticosteroid of administration to women with both pre-existing and gestational diabetes in pregnancy. This should take place alongside appropriate management of hyperglycaemia where needed. This is in keeping with the recommendations given by NICE with regards to the management of diabetes in pregnancy.[66]

The NICE guideline for the management of diabetes in pregnancy agrees that diabetes itself is not a contra-indicated to antenatal corticosteroid administration, but that their use in pregnancy should be followed with monitoring and the administration of additional insulin if required.[66] The RCOG, SOGC and RANZCOG guidelines also agree that a diagnosis of maternal diabetes is not a contraindication to the use of antenatal corticosteroids, if needed. [15, 54, 62]

Clinical Practice

Diabetes in pregnancy is not a contraindication to the administration of antenatal corticosteroids. Corticosteroids should be administered if pre-term birth is suspected to occur in women with both pre-existing and gestational diabetes. They should be administered in the same gestational ranges as those recommended for women without diabetes in pregnancy.

Women should be informed of the likelihood of hyperglycaemia and should be counselled about the need for extra glucose monitoring and the potential for extra treatment. Monitoring and additional insulin should occur based on agreed local protocols, as suggested by the clinical diabetes team in the hospital/unit.

Recommendations

12. **Women with pre-existing or gestational diabetes should be offered antenatal corticosteroids within the same gestational ranges they are offered to women without diabetes.**
13. **Close monitoring of blood glucose levels should take place in the days following administration of antenatal corticosteroids in women with pre-existing or gestational diabetes, and additional insulin administered if required, according to local protocols.**

Clinical Question 2.8: Should antenatal corticosteroids be offered in the scenarios of Preterm Prelabour Rupture of Membranes (PPROM) and/or chorioamnionitis?

Evidence Statement

The provision of antenatal corticosteroids in cases of preterm prelabour rupture of membranes (PPROM) has been a particular area of controversy over the years. There has been doubt that the benefits are attenuated in this group compared with other indications for preterm birth.[10] In addition, concern exists that there is potential for increased risk of chorioamnionitis or sepsis in the neonate. Some early trials added to the concern for increased infection, however this was prior to the integration of prophylactic antibiotics into obstetric management of PPROM.[67]

Few trials have explored this scenario as a distinct clinical question or separated this from other indications for preterm birth. The original Liggins trial on antenatal steroids for fetal lung maturation in 1972 included women with PPROM.[7] Harding *et al.* in 2001 published data from the subgroup of cases with preterm rupture of membranes from the original trial by Liggins with a meta-analysis on the subject. Among 318 women with PPROM from the 1972 trial, there was a non-statistically significant trend towards reduction in RDS. In a meta-analysis of 15 trials with > 1400 women with PROM, including the above RCT, they did not demonstrate an increase in risk of overall infection in the mother (relative risk (RR) 0.86; 95% CI 0.61-1.20) or baby (relative risk, 1.05; 95% confidence interval, 0.66-1.68).[68]

A small retrospective cohort compared antenatal corticosteroid exposed 32-33+6 weeks' gestation with PPROM. Among the 191 cases, antenatal corticosteroids did not appear to increase the risk of chorioamnionitis in 150 exposed vs 41 unexposed (12.8% vs 10.0%, p50.43).[69]

In an RCT of antenatal corticosteroids in 2831 women with late prematurity 34-35+6, a prespecified subgroup analysis was performed on 620 women with PPROM. They reported no effect of indication for premature delivery and effect on antenatal corticosteroids on the primary outcome of a composite respiratory support (11.7% v 13.2%, CI 0.89 (0.59-1.53) p=0.83) and severe respiratory morbidity (5.1% v 4.6%, CI 1.10 (0.55-2.21) p=0.38).[34]

A review of 17 RCTs comparing women with PPROM receiving antenatal corticosteroids vs no antenatal corticosteroid combined data of 1900 women. Antenatal corticosteroids reduced risk of intraventricular haemorrhage (IVH) grade 3 or 4 (RR = 0.49, 95% CI 0.25-0.96), IVH grade 1-4 (RR = 0.52, 95% CI 0.37-0.72) and respiratory distress syndrome (RR = 0.81, 95% CI 0.67-0.98). No differences were observed between corticosteroid exposed vs non-exposed for neonatal sepsis, perinatal mortality and maternal chorioamnionitis.[70]

Among the 27 studies of antenatal corticosteroids that contributed to the most recent Cochrane meta-analysis, 10 of the antenatal corticosteroid trials reported specifically on outcomes for women with ruptured membranes while 10 reported on cases with intact membranes. The remaining studies included in this metanalysis did not distinguish membrane status in their reporting. In terms of chorioamnionitis, subgroup testing did not suggest a difference in effect on chorioamnionitis (P = 0.51, I2 = 0%, overlapping confidence intervals) neonatal mortality (P= 0.29, I2 = 20%, overlapping confidence intervals) or respiratory distress syndrome (P = 0.08, I2 = 60%, overlapping confidence intervals) in cases of preterm rupture of membranes receiving antenatal corticosteroids.[4]

There is very limited evidence on antenatal corticosteroid treatment in cases of established chorioamnionitis as this is an exclusion criterion in many studies. A review of outcomes in specific groups following antenatal steroids summarised 8 publications on outcomes among chorioamnionitis diagnosed histologically (4 studies), clinically (2 studies) or either (2 studies). Among cases of histological chorioamnionitis in 1193 infants from 6 studies, antenatal corticosteroids may reduce neonatal mortality (OR 0.4 OR 0.49, 95% CI (0.33 to 0.74)) and IVH (658 babies, OR 0.41, 95% CI 0.23 to 0.726). In clinical chorioamnionitis, there may be a reduction in IVH (OR 0.39, 95% CI 0.15 to 0.99). There is insufficient evidence on other morbidities such as respiratory distress syndrome and insufficient data in maternal outcomes.[63]

Many international clinical guidelines do not specifically address the administration of antenatal corticosteroids to women with chorioamnionitis.[15, 17, 53, 18, 52] The WHO does not recommend administration where women with chorioamnionitis are likely to give birth preterm.[71] RANZCOG guidelines recommend a single course for women with chorioamnionitis at risk of preterm birth with the proviso that delivery should not be delayed to administer a course if clinically indicated.[61]

A 2020 evidence based review of the management of clinical chorioamnionitis concluded that the administration of a course, or of at least a single dose, of antenatal corticosteroids to women with clinical chorioamnionitis between 24+0 and 33+6 weeks of gestation, and possibly between 23+0 and 23+6 weeks, has an overall beneficial effect on the infant. However, delivery should not be delayed in order to complete the full course of corticosteroids. Once the diagnosis of clinical chorioamnionitis has been established, delivery should be considered, regardless of the gestational age. This evidence based review stated that, as over 90% of women with clinical chorioamnionitis would be expected to be delivered within 12 hours of diagnosis, most would receive only one dose of antenatal corticosteroid. Nonetheless, the review concluded that there is evidence from observational studies showing that infants exposed to an incomplete course of antenatal corticosteroids had a significantly lower risk of death and/or other adverse neonatal or neurodevelopmental outcomes compared to infants not exposed to antenatal corticosteroids.[72]

Considering this existing evidence, antenatal corticosteroids appear to be safe with probable benefit for fetal maturation in cases of threatened preterm birth with preterm prelabour rupture of membranes (PPROM). To reflect this, existing international guidelines do not distinguish PPROM from other indications. Antibiotics and antenatal corticosteroids have been integrated into guidance on management of preterm prelabour rupture of membranes.[73, 74]

Current available evidence suggests that the administration of at least one single dose of antenatal corticosteroids to patients with clinical chorioamnionitis has an overall beneficial effect on the neonate.[72]

Clinical practice

Preterm prelabour rupture of membranes (PPROM) is not a contraindication to antenatal corticosteroid therapy. Evidence suggests it is safe at the range of gestational ages discussed in the previous sections of this Guideline.

Antenatal corticosteroids together with antibiotics are recommended as part of the bundle of obstetric management of PPROM during the latency period. Women should be counselled on the potential of increased infection in scenarios of PPROM.

Where there is evidence of clinical chorioamnionitis a course of antenatal corticosteroids may be started, but completion of the course should not delay delivery if this is indicated by either the maternal or fetal condition.

Recommendations

14. **Women presenting with preterm prelabour rupture of membranes between 23+0 and 34+6 weeks' gestation should be offered antenatal corticosteroids as part of a bundle of obstetric care including prophylactic antibiotics**
15. **Where there is evidence of clinical chorioamnionitis a course of antenatal corticosteroids may be started but should not delay delivery if indicated by maternal or fetal condition.**

Section 6: Dosing, Dose Interval and Regimens of Antenatal Corticosteroids

Clinical Question 2.9: What antenatal corticosteroid agent and dosage should be used?

Evidence Statement

The most widely studied antenatal corticosteroids are betamethasone and dexamethasone, both fluorinated, synthetic glucocorticoids with minimal mineralocorticoid activity. They have similar molecular structures and possess the ability to cross the human placenta from mother to fetus with high affinities for the corticosteroid receptor.[75] All current international guidelines[15, 17, 19, 54, 62, 71] and best practice statements[18, 76] include both agents in their recommendations, with the 2022 WHO guideline stating there is currently no evidence on the comparative efficacy of dexamethasone and betamethasone that would support a recommendation of one over the other.[71]

Guidelines are in agreement that an antenatal corticosteroid course consists of a total corticosteroid dose of 24 mg, of either dexamethasone or betamethasone, administered intramuscularly in divided doses, either 12 or 24 hours apart. This total corticosteroid dose of 24 mg corresponds to a high occupancy of steroid receptors in fetal tissues.[77] Intramuscular administration (IM) is the preferred route with maximum maternal serum concentration occurring after 1 hour.[75] Intravenous administration is not recommended as it exposes mother and fetus to higher initial serum concentrations than IM administration.[5, 78]

Gaps in knowledge persist however on the optimal drug choice and regimen to maximise fetal benefits and limit excessive fetal exposure.[79] Studies over the last 50 years have largely been based on the relatively high doses used by Liggins and Howie in their seminal studies.[7] There has been limited research on the complex pharmacokinetics and pharmacodynamics of antenatal corticosteroid treatment[80, 81] and on optimising regimens for human pregnancy, with research primarily focussed on neonatal and maternal outcomes.[82] There is insufficient evidence to support the use of other corticosteroids that may cross the placenta including hydrocortisone which is extensively metabolised by placental enzymes [83] the use of oral corticosteroid preparations [84] or for direct fetal administration.[85]

A 2022 Cochrane Intervention Review[77] identified all published and unpublished randomised controlled trials (RCT) or quasi-randomised controlled trials comparing any two corticosteroids (dexamethasone or betamethasone or any corticosteroid that crosses the placenta), and different regimens (dose, frequency, interval), in women at risk of preterm birth. Eleven trials were identified for inclusion.[77]

Nine trials [86-94] (2096 women, 2319 infants) compared IM dexamethasone versus IM betamethasone. Total corticosteroid dose per course (22.8 mg or 24 mg) was consistent, but trials varied in terms of individual doses, dosing interval, number of doses, and the betamethasone formulation studied. The most widely studied betamethasone formulation was a mixed formulation of betamethasone phosphate (short-acting) and betamethasone acetate (long-acting) but the exact betamethasone formulation studied was not specified in all trials. Doses were administered either 12 hours or 24 hours apart, with four doses of dexamethasone 6 mg 12 hours apart, or 2 doses of betamethasone 12 mg 24 hours apart, the most commonly studied regimens.

Three trials compared different regimens, or preparations, of either dexamethasone or betamethasone: oral dexamethasone 32 mg versus IM dexamethasone 24 mg;[84] betamethasone acetate/betamethasone phosphate versus betamethasone phosphate;[89] and 12-hourly betamethasone versus 24-hourly betamethasone.[81]

The Cochrane Review concluded that "it remains unclear whether there are important differences between dexamethasone and betamethasone, or between one regimen and another. While for most infant and early childhood outcomes there may be no difference between these drugs, for several important outcomes for the mother, infant and child, the evidence was inconclusive and did not rule out significant benefits or harms". The authors commented that evidence about optimal doses, timing, dosage interval and preparation of specific antenatal corticosteroids was sparse and does not support the use of one particular corticosteroid regimen over another.[77]

The 2019 Asteroid RCT randomised 1346 women to two IM injections of either 12 mg dexamethasone phosphate or 11.4 mg betamethasone phosphate/acetate given 24 hours apart and found no differences in two-year outcomes between the two groups.[86]

Administration is ideally timed so optimal efficacy is achieved before delivery, timing of which is challenging in the setting of pre-term labour. An optimal administration-to-birth interval likely exists, however a recently published systematic review concluded that variations in study design limit identification of this interval from available evidence.[95] WHO guidelines state there is sufficient evidence to support benefit when the interval between antenatal corticosteroid administration and birth is 1-7 days and acknowledges there is also evidence to indicate there may be benefits within the first 24 hours, and benefit which continues beyond 7 days after the first dose.[71] This is considered reassuring by the WHO Guideline Development Group in the context of the challenges of accurately predicting spontaneous preterm labour.

Currently, a standard dosing regimen is utilised for all women irrespective of body mass index (BMI). The Society of Obstetricians and Gynaecologists of Canada (SOGC) 2018 review did not identify any trials evaluating the effect of antenatal corticosteroid therapy on women with obesity, or trials examining the effects of antenatal corticosteroid therapy by obesity status, body mass index, or weight.[54] There is no specific discussion of the management of women with a raised BMI or obesity in the majority of guidelines with the exception of the SOCG, who recommend antenatal corticosteroid therapy be administered to women with obesity at the same dosage as that recommended for women without obesity.[54]

Dexamethasone phosphate injection is available in Ireland as a Health Products Regulatory Authority (HPRA) licensed product. The most extensively studied betamethasone preparation, the betamethasone phosphate/acetate mixed formulation, is in use in most European countries, and in the US, Canada, Australia and New Zealand, but is not available in Ireland or the UK. Betamethasone phosphate injection is licensed in the UK and is available in Ireland as an unauthorised medicine[10] or Exempt Medicinal Product.[96] The difference between the two formulations of betamethasone injection and their different pharmacokinetics has not been widely studied, with the Royal College of Obstetricians and Gynaecologists (RCOG) noting in their 2022 Guideline (15) that there is little direct evidence from studies to guide the effective dosage regimen of the betamethasone phosphate formulation.

10 An unauthorised medicine is considered 'exempt' from authorisation by the HPRA when it is supplied to the order/prescription of a registered doctor for use by his/her individual patients on his/her direct responsibility in order to fulfil the special needs of those patients.

Based on a review of the published evidence, and on the preparations of dexamethasone and betamethasone injections currently available in Ireland, our recommendations broadly align with those of the RCOG 2022 Guideline.[15] However, where two regimens for dexamethasone phosphate (two doses of 12 mg, 24 hours apart, or four doses of 6 mg, 12 hours apart) are included in the RCOG guideline, our preferred regimen is two 12 mg doses of dexamethasone phosphate administered 24 hours apart, a regimen which also aligns with WHO[71], FIGO[18] and EAPM[17] recommendations.

A two-dose regimen gives consideration to likely patient preference for fewer injections (local adverse effects are commonly reported with antenatal corticosteroid intramuscular injections, including a sensation of heat and relatively persistent pain[97], and to ensuring the woman completes the full course, or receives a substantial amount of the total dose before delivery.[71]

The RCOG guideline[15] includes the betamethasone sodium phosphate/acetate mixed product in their recommendations as an alternative but notes that this product is not marketed in the UK. The RCOG guideline comments that, as the available betamethasone phosphate product in the UK is a soluble form of betamethasone structurally similar to dexamethasone, with a similar half-life (36-72 hours)[97], a dosage schedule in line with that of dexamethasone phosphate is considered pragmatic.[15]

Clinical Practice

The optimal drug, dose, regimen and timing of antenatal corticosteroids continues to be investigated.[79, 98] The majority of current international guidelines recommend administration of a total antenatal corticosteroid dose of 24 mg, in two divided doses, at a 24-hour interval.

Variation in clinical practice with regard to the timing of the second dose in maternity units in Ireland and the UK is recognised, with a 12-hour interval between doses utilised by some to achieve earlier course completion where delivery is considered imminent.

Following review of the available scientific evidence and the injection formulations available in Ireland, a course consisting of dexamethasone phosphate 24 mg administered intramuscularly in two doses of 12 mg, 24 hours apart, is recommended for women for whom antenatal corticosteroid administration is considered clinically appropriate. Administration of the second dose after a 12-hour interval may be considered where delivery is imminent.

An alternative course is betamethasone phosphate 24 mg administered intramuscularly in two divided doses of 12 mg, 24 hours apart. Administration of the second dose after a 12-hour interval may be considered where delivery is imminent.

Recommendations

16. **A course of antenatal corticosteroids consisting of 24 mg of dexamethasone phosphate administered intramuscularly, in two divided doses of 12 mg, given 24 hours apart, is recommended where antenatal corticosteroid administration is considered clinically appropriate. Administration of the second dose after a 12-hour interval may be considered where delivery is imminent.**
17. **An alternative course consists of 24 mg of betamethasone phosphate in two divided doses of 12 mg, given intramuscularly 24 hours apart. Administration of the second dose after a 12-hour interval may be considered where delivery is imminent.**

Clinical Question 2.10: In which clinical situations should caution be exercised when considering antenatal corticosteroids?

Evidence Statement

Corticosteroids are contraindicated in women with a known hypersensitivity to any component of the injection formulation, active or excipient; such cases are rare.[97]

Women with sickle cell disease (SCD) are at high risk of maternal and neonatal morbidity. There is limited research on the administration of antenatal corticosteroids to women with SCD and no specific guidance on the management of this patient cohort in current international guidelines. Wang *et al.* recently published one of the first studies to examine the tolerance of antenatal corticosteroids in sickle cell patients.[99] They concluded that antenatal corticosteroids were associated with more severe vaso-occlusive crises, suggesting that they should be avoided and restricted to cases at very high risk of extreme prematurity.

In the presence of systemic infection, the potential beneficial effects of antenatal corticosteroids intended for the infant must be balanced against the effect of exacerbating the severity of the systemic infection both for the woman and her infant.[15] Where there is evidence of ongoing systemic infection, including; systemic bacterial infection; systemic fungal infection; acute viral infection, e.g., varicella; or latent tuberculosis; corticosteroid therapy should be considered only when strictly necessary and with additional targeted anti-infective therapy.[15, 73]

Clinical Practice

Corticosteroids are contraindicated in the rare patient with a known hypersensitivity to any component of the injection formulation, active or excipient.

Where antenatal corticosteroids are under consideration for a woman with sickle cell disease, consultation with a senior Obstetrician and consultant Haematologist is recommended to individualise care.

In the context of preterm birth, clinical judgement is necessary where there is evidence of systemic infection with the potential beneficial effects of antenatal corticosteroids intended for the infant being balanced against the effects of exacerbating the severity of the systemic infection for both the woman and her infant. Birth should not be delayed to administer antenatal corticosteroids when there are serious concerns about the maternal or fetal condition that will be alleviated by expedited birth.[15]

Recommendations

18. **In the presence of systemic infection, the potential beneficial effects of antenatal corticosteroids intended for the infant must be balanced against the effects of exacerbating the severity of infection for both the woman and her infant. Delivery should not be delayed to administer antenatal corticosteroids when there are serious concerns about the maternal or fetal condition that will be alleviated by expedited birth.**

Clinical Question 2.11: After what length of time are antenatal corticosteroids most effective?

Evidence Statement

Concern regarding decline in effect of antenatal corticosteroid with increased interval to delivery has been evident since the initial trial on corticosteroids for fetal maturation by Liggins *et al.*[7] Animal research has also contributed to this clinical question demonstrating diminished effect after seven days in preterm lambs. Concentrations of corticosteroids in cord blood samples peak around one hour after administration and are not detectable after two days from the last dose.[5] The timing of effects on the fetal lung including induction of beta-receptor reception, accelerated lung tissue and surfactant production among others are challenging to measure. We below summarise the best available evidence on this question.

The 2006 Cochrane review by Roberts *et al.* reviewed outcomes according to duration between trial entry and birth. This meta-analysis found a reduction in the composite outcome of fetal and neonatal death in those born less than 24 hours (293 infants, 3 studies RR 0.60, 95% CI 0.39- 0.94) and less than 48 hours (373 infants in 1 study RR 0.59, 95% CI 0.41- 0.8*)* from the first dose of corticosteroid given to the pregnant woman. However, this was not found between 1-7 days (RR 0.59, 95% CI 0.41- 0.86, 373 infants in 1 study) or after 7 days (RR 1.42, 95% CI 0.91- 2.23, 598 infant, 3 studies*)*.[100] In terms of respiratory distress syndrome, there was a reduction in RDS in antenatal corticosteroid-exposed babies born after 48 hours from first dose (RR 0.63, (95% CI 0.43-0.93, 374 infants 3 studies) and between 1 and 7 days from first dose (RR 0.46 95% CI 0.35-0.60 1110, 9 studies). Similar benefit was not demonstrated in infants born before 24 hours or after 7 days from the first dose.[100] The more recent Cochrane reviews of antenatal corticosteroids did not analyse this question. This review, now archived, may be prone to bias given variable gestational ages, heterogeneous outcomes, and corticosteroid dosing regimens in the included studies.

A number of cohort studies have endeavoured to further clarify the optimal time from initiation of antenatal corticosteroids to birth. A prospective Swedish population cohort of 591 infants exposed to antenatal corticosteroid showed better survival in those exposed between 1-7 days after antenatal corticosteroid administration compared with <24 hours or >7 days.[101]

The Effective Perinatal Intensive Care in Europe (EPICE) study was a retrospective cohort of 4594 infants <32 weeks' gestation across 11 countries in Europe in 2011-2012. They divided infants into four categories of exposure interval from antenatal corticosteroids to delivery. Antenatal corticosteroid administration at any time prior to birth was associated with lower mortality. This effect was greatest between 24 hours and 7 days (adj. risk ratio: 0.5; 95% CI 0.4-0.6). However, there was a significant reduction in mortality <12 hours after initiation of antenatal corticosteroid. Similar risk reduction was seen at this interval for the composite outcome of infant mortality or severe neonatal morbidity (IVH grade 3 or 4, cystic PVL, surgical NEC, RoP >stage 3). They did not report on RDS or other respiratory morbidity in this cohort.[102]

Another retrospective cohort study from the Canadian Neonatal Network between 2010-2012 reported 6,870 infants born from 24-34 weeks. Their findings were consistent with other studies; those who did not receive antenatal corticosteroid and those who received treatment less than 24 hours or after 7 days were more likely to experience the composite outcome of neonatal mortality and morbidity, BPD, severe IVH. This association between dosing interval and birth was more evident in infants born <28 weeks.[103]

In Cincinnati, a retrospective cohort of 736 infants exposed to antenatal corticosteroid at variable intervals was reviewed. This study focused on anthropometry, and metabolic effects on glucose and thyroid homeostasis. Among infants born within the window of 107 days, measurements of weight, length and head circumference were significantly lower ($p<0.05$). Lower blood sugars were found in infants born <24 hours from initiation of antenatal corticosteroid but there was no significant difference in incidence of other neonatal morbidities (IVH, NEC, CPAP or need for surfactant, ventilation, BPD or PVL).[104] A secondary analysis of two prospective studies of 2259 women who delivered between 23 and 34 gestation and received antenatal corticosteroid at variable intervals was published in 2020. The likelihood of RDS in this group was least in those born between 2 and 7 days after administration of antenatal corticosteroids (51.3%) compared to other intervals (<2 days 62.7% 7-14 days 57.6% or >14 days 57.6% $p<0.001$).[105]

In the above European cohort, 50% failed to receive a course of antenatal corticosteroid between two and seven days prior to delivery as per recommendations. Also, in the Canadian cohort, 20% received no antenatal corticosteroid with 19% receiving treatment >7 days before birth. A recent small prospective study of 120 women in Germany receiving antenatal corticosteroids for impending preterm birth from found that only 20.8% gave birth within 1-7 days after giving corticosteroids. Similar observations were noted in many of the above publications.[106] This highlights the ongoing challenge of accurately predicting preterm birth.

Clinical practice

In summary, it appears benefit for respiratory morbidity likely peaks approximately 24 hours to 7 days from completion of antenatal corticosteroids, however some benefit especially for neonatal mortality may be evident within hours of initiation.

It is likely that benefit diminishes from 7 to 14 days after the completion of the antenatal corticosteroid course, however it is not clear from the available evidence to what degree this happens.

Women should be counselled regarding the likely maximal benefit after 24 hours of antenatal corticosteroid therapy and that a shorter interval to birth may be associated with increased risk of neonatal hypoglycaemia.

Recommendations

19. **Where preterm birth is likely within 7 days antenatal corticosteroid therapy should be initiated.**
20. **If preterm birth is imminent within the next 24 hours, it is still of benefit to initiate antenatal corticosteroids, even if treatment (the course) is incomplete.**
21. **Women should be counselled on the risks of neonatal hypoglycaemia with a shorter interval between corticosteroid administration and birth.**

Clinical Question 2.12: Should a dose of antenatal corticosteroid treatment be repeated?

Evidence Statement

From the early trials of antenatal corticosteroids suggesting diminished benefit after 7 days, administration of repeat courses evolved into clinical practice despite lack of supporting evidence. Concerns have grown regarding the effect of multiple doses of antenatal corticosteroids on fetal growth and an increased risk of neurodevelopmental impairment. This in part arose from animal studies suggesting dose-dependent adverse effects. Although lamb studies on repeating antenatal corticosteroids showed benefit in terms of respiratory distress syndrome,[107] they also demonstrated delayed myelination[108] as well as dose-dependent reduction in birth weight.[107] This translated to smaller human studies raising concern regarding HPA suppression in repeated doses.[109] Given this uncertainty, we reviewed a number of studies attempting to clarify if repeated courses of antenatal corticosteroids are beneficial.

The NIH NCHD designed an RCT administering weekly doses of antenatal corticosteroid versus a single course and no benefit was demonstrated for RDS or other clinical outcomes, although better lung function (less need for surfactant, non-invasive ventilation, ventilation) and reduced incidence of pneumothorax was demonstrated in infants born <32 weeks' gestation. They also reported an increased chance of birth weight below 5th and 10th centiles with repeated antenatal corticosteroid doses.[110]

Similar effects were seen in the 2006 RCT from Australia of 982 women at risk of PTB <32 weeks receiving weekly doses of betamethasone or placebo following first course. They demonstrated a reduction in "severe lung disease" and RDS (33%vs 41%; relative risk 0.82, 95% CI 0.71-0.95, p=0.01) in the repeat corticosteroid group.[111]

Follow up of the US National Institutes of Health "MUFU" trial showed that Bayley neurodevelopmental assessment at a mean corrected gestational age (CGA) of two to three years was not significantly different. However, a non-statistically significant increase in diagnosis of cerebral palsy was noted in the repeat doses group (six compared with one child, relative risk, 5.7; 95% confidence interval, 0.7 to 46.7; P=0.12). Loss to follow up was 13% and 14% in the intervention and control groups respectively. Although not statistically significant, this finding raises concern. Suggested effects of antenatal corticosteroid on neurodevelopment domains such as attention or cognition may not be evident at this stage and longer term follow up outcomes are of interest.[112]

Repeat BM trial was an RCT that administered a single dose of prenatal betamethasone to those >7 days from completing a primary course of antenatal corticosteroid, and at imminent risk of delivery <34 weeks. 249 women were enrolled with 150 receiving an additional betamethasone dose. This study demonstrated increased need for surfactant for RDS in the group receiving additional betamethasone.[113] Two-year neurodevelopmental follow up of this group did not demonstrate a difference in risk of severe neurodevelopmental impairment or growth.[114]

The 2006 "ACTORDS" RCT randomised 982 women to receive weekly additional one dose betamethasone or placebo while <32 weeks' gestation at risk of preterm delivery. They demonstrated a reduction in RDS (33%vs 41%; relative risk 0.82, 95% CI 0.71-0.95, p=0.01) and severe respiratory disease, and less need for oxygen among additional corticosteroid dose-exposed babies.[111] In a subgroup of 145 babies from this study, follow-up growth measurements demonstrated a more rapid increase in weight, length, and head circumference approximately. 3-5 weeks after birth.[115] Secondary analysis of follow up data looked at cardiac and growth outcomes in the subpopulation of growth

restricted fetuses at 6-8 years. They did not demonstrate an impact of repeated doses on cardiac or metabolic function, however reported a small positive impact on height.[116] Follow up of these babies in mid childhood was also performed; 963 participants at 6-8 years neurocognitive follow up of the growth restricted subgroup did not demonstrate a difference between repeated corticosteroid course exposed infants and the placebo group.[117]

In 2010, follow up cognitive assessments were performed on a prospective Swedish cohort of children exposed to repeated antenatal corticosteroid courses. The original cohort of 94 infants were exposed to variable numbers of repeated antenatal corticosteroid doses (between two and nine). They reported a dose dependant decrease in fetal weight, length and head circumference.[118] Long term follow- up included 58 adolescents and 36 young adults were exposed to multiple antenatal corticosteroid courses compared with non-exposed controls and a group exposed to one course. There was no significant difference in cognitive or psychological functioning, although they demonstrated consistently lower scores in measures of attention in infants exposed to repeated doses versus no antenatal corticosteroid.[119]

Walters *et al.* in 2022 published the most recent Cochrane meta-analysis on repeat doses of antenatal corticosteroids for improving neonatal outcomes. This included 11 randomised controlled trials totalling 5975 women at risk of preterm birth >/= 7 days from the initial completed corticosteroid course. Nine studies were included for the primary outcome of RDS to show a reduction in risk of RDS in the repeat corticosteroids group (total 3540 infants RR 0.82, CI 0.74- 0.90) but little effect on “severe” RDS. There was a probable reduction in risk of “severe lung disease” (RR 0.83, CI 0.72-0.97) but definitions are heterogenous between the included studies. For other outcomes, e.g. CLD, IVH or severe IVH, NEC, there was either insufficient evidence or a lack of demonstrated benefit. Repeat doses were found to be associated with an increase in small-for- gestational age births (RR 1.25, 95% CI 1.08-1.44,7 trials, 4013 fetuses) and an overall reduction in birthweight for gestational age. There was no impact on mean weight at discharge. There was little effect of repeated doses on proven neonatal infection during admission or early systemic infection. This review did not demonstrate an effect of repeated courses on risk of neurodevelopmental impairment (4 trials, n= 3616 RR 0.98, CI 0.85-1.10) and there was little to no effect on survival free of neurodevelopmental impairment at early childhood follow up. In terms of late follow up, only two trials were included that look at this outcome. Benefit or harm could not be excluded for the risk of cerebral palsy. One trial reported on neurocognitive outcomes 5-18 years and the authors concluded that benefit or harm cannot be excluded. Walters *et al.* concluded that both weekly repeated doses and single rescue doses of antenatal corticosteroid reduce the relative risk of RDS by 18% (NNT 16, 95% CI 11-29 women) and of “serious infant outcome” by 12% (NNTB 39, 95% CI 24-158 women). In terms of neurodevelopmental effects, they concluded with moderate certainty little to no effect of repeat doses on neurodevelopmental impairment.[119] There was heterogeneity between dosing strategies, interval to birth and gestational ages among the included trials.

A more recent systematic review published in 2023 examined long-term outcomes in children born term and preterm who were exposed to multiple courses of antenatal corticosteroid versus a single course (3 trials, 6 publications). There was no benefit or adverse neurodevelopmental outcome among children born preterm randomised to multiple courses of antenatal corticosteroid, but data was lacking on outcomes in single repeat dose or course. However, among infants born at term exposed to multiple (212) vs single course (247) antenatal corticosteroid, there was a significant association with increased odds of neurosensory impairment (adjusted odds ratio = 3.70, 95% CI 1.57-8.75) This review is limited however by small numbers and variable antenatal corticosteroid regimens.[120]

Clinical Practice

Limitations of many of these studies and meta-analysis are the variable outcome measures studied, since the potential effects on the neonate and mother are broad.

Although the Cochrane meta-analysis concludes overall benefit, the results of individual trials as explored above are at times conflicting.

It is likely that benefit diminishes from 7 to 14 days after the completion of the antenatal corticosteroid course, however it is not clear from the available evidence to what degree this happens.

A single repeat dose of antenatal corticosteroids is probably of benefit in terms of reduction in risk of RDS and other in-hospital morbidities (mortality, severe IVH, NEC, PVL).

In terms of multiple repeated doses, however, the long-term effects in particular if the infant is born at term, remain incompletely understood and the short-term benefits may not outweigh risks of fetal growth impairment and the potential but unknown risks of neurodevelopmental impairment.

Recommendations

22. **A single repeated dose (i.e., 12 mg) of antenatal corticosteroid may be considered on an individualised basis for women at risk of imminent preterm birth greater than 7-14 days from the initial completed antenatal corticosteroid course.**
23. **Women should be counselled on the risk of lower birth weight, length, or head circumference with repeated antenatal corticosteroid therapy.**

Chapter 3: **Development of Clinical Practice Guideline**

3.1 Literature search strategy

A comprehensive literature review was undertaken which included national and international publications. The Cochrane Library and electronic databases (EMBASE, Trip, MEDLINE, Web of Science and PubMed) were searched, looking for relevant systematic reviews, meta-analyses, intervention, and observational studies. The following search terms were reviewed; 'steroid', 'corticosteroid', 'glucocorticoid', 'adrenal cortex hormone', 'fetal lung maturation', 'foetal lung maturation'. The search was restricted to papers published between January 2008 and January 2023. We included relevant publications outside this timeline when identified from references. Searches were further limited to humans and restricted to the titles of English language articles. See Appendix 4 for a full list of search terms and the search strategy.

This Guideline also comprehensively reviewed and referenced relevant international guidelines including; the Royal College of Obstetricians and Gynaecologists (RCOG)[15], the American College of Obstetricians and Gynaecologists (ACOG)[19], the International Federation of Gynaecology and Obstetrics (FIGO)[18], the National Institute for Health and Care Excellence (NICE)[14], the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG)[62], the Society of Obstetricians and Gynaecologists of Canada (SOGC)[54], and the Society for Maternal-Fetal Medicine (SMFM) guidelines.[37] See Appendix 3 – Table of guidelines.

3.2 Appraisal of evidence

Following a comprehensive literature review the quality, validity and relevance of the evidence gathered were critically appraised by the Guideline developers under the following headings:

- Study design
- Relevance of primary and secondary outcomes
- Consistency of results across studies
- Magnitude of benefit versus magnitude of harm
- Applicability to practice context

The applicability and strength of the evidence based on the principles of 'hierarchy of evidence', formed the basis for this Guideline.

A number of evidence-based recommendations for the National Clinical Practice Guideline: "antenatal corticosteroids to reduce neonatal morbidity and mortality" were agreed upon. They have been adapted to reflect care in the Irish healthcare setting.

3.3 AGREE II process

While being developed, the Guideline was assessed using the AGREE II checklist (Appendix 5) as recommended by the Department of Health in the 'How to Develop a National Clinical Guideline: a manual for guideline developers', 2019.[11]

The purpose of AGREE II is to provide a framework to:

1. Assess the quality of guidelines;
2. Provide a methodological strategy for the development of guidelines; and
3. Inform what information and how information ought to be reported in guidelines

3.4 Literature review

Details of supportive evidence-based literature for this Guideline are reported in chapter two.

The following steps were taken to ensure a comprehensive review of the literature with continuous input and discussion between committee members:

- The search strategy was agreed by the Guideline Committee members.
- The search was undertaken by one Reviewer (AD) on the 30th and 31st of March 2023.
- The Cochrane Library and electronic databases (EMBASE, Trip, MEDLINE, Web of Science and PubMed) were searched, looking for relevant systematic reviews, meta-analyses, intervention, and observational studies.
- The search was restricted to papers published between January 2008 and January 2023. Searches were further limited to humans and restricted to the titles of English language articles. See Appendix 4 for a full list of search terms used and the search strategy.
- There was a comprehensive review of relevant international guidelines including; the Royal College of Obstetricians and Gynaecologists (RCOG)[15], the American College of Obstetricians and Gynaecologists (ACOG)[19], the International Federation of Gynaecology and Obstetrics (FIGO)[18], the National Institute for Health and Care Excellence (NICE)[14], the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG)[62], the Society of Obstetricians and Gynaecologists of Canada (SOGC)[54], and the Society for Maternal-Fetal Medicine (SMFM) guidelines.[37] See Appendix 3 – Table of guidelines.
- Quality of the evidence was assessed using the GRADE approach for network meta-analysis.
- A volume of evidence is available on this topic, but there are also limitations due to variations in international practice and recommendations. Considerations were given to the Irish setting and the application of the evidence to this specific cohort.
- Systematic reviews and meta-analyses provided a higher level of evidence than cohort or case-control studies. The latter were omitted from the Guideline due to the volume and strength of systematic reviews and meta-analyses available on this subject.

11 Department of Health (2019). How to develop a National Clinical Guideline: a manual for guideline developers. Available at: https://www.gov.ie/en/collection/cd41ac-clinical-effectiveness-resources-and-learning/

The Guideline committee met to consider the clinical questions to be addressed; these were divided into 7 sections as described in chapter 2.

Committee members were then assigned sections based on their specialities and areas of expertise:

- Obstetrics and Gynaecology: K. O'Donoghue, S. Murphy
- Neonatology: G. Dempsey, E. Murphy
- Pharmacy: J. Ryan, A. Dineen
- Literature Search: A. Dineen

The Guideline committee met regularly, every 2 weeks, to discuss the evidence and recommendations for each clinical question, to facilitate discussion and to provide an update on progress.

- Completed chapters were distributed to all committee members for review and analysis.
- Where there was no or limited evidence to support certain recommendations or variations in recommendations, these were made based on group consensus and committee expertise.
- The final draft of the Guideline was reviewed by all committee members, with a further meeting to discuss the final recommendations and evidence presented.

3.5 Grades of recommendation

GRADE offers a transparent and structured process for developing and presenting evidence summaries and for carrying out the steps involved in developing recommendations.[12]

While we acknowledge that for this particular work an extensive GRADE approach is not possible, we have used the suggested language set out in the GRADE table when making recommendations.[13] (Appendix 6)

3.6 Future research

An important outcome of the Guideline development process is in highlighting gaps in the evidence base.

Considerations for future research include the following;

- The optimum gestational age range at which antenatal corticosteroids provide benefit and should therefore be considered or offered.
- Safety and effectiveness of antenatal corticosteroids in particular groups such as, multiple pregnancies, women with diabetes, women with chorioamnionitis, women with obesity.
- Long-term outcomes and impact of antenatal corticosteroids on; neonatal cardiovascular function, neurodevelopment, infection rates.

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12 Guyatt, Gordon, *et al.* "GRADE Guidelines: 1. Introduction – GRADE Evidence Profiles and Summary of Findings Tables." *Journal of Clinical Epidemiology*, vol. 64, no. 4, 2011, pp. 383-94, https://doi.org/10.1016/j.jclinepi.2010.04.026.

13 SMFM adopts GRADE (Grading of Recommendations Assessment, Development, and Evaluation) for clinical guidelines. Society for Maternal-Fetal Medicine (SMFM), Chauhan SP, Blackwell SC. Am J Obstet Gynecol. 2013 Sep;209(3):163-5. doi: 10.1016/j.ajog.2013.07.012. PMID: 23978245 https://pubmed.ncbi.nlm.nih.gov/23978245/

- Assessment of benefits and risks of antenatal corticosteroids prior to elective caesarean section at later gestations.
- Sexual dimorphism in response to antenatal corticosteroids.
- Pharmacokinetic and pharmacodynamics studies to investigate differences between betamethasone phosphate and betamethasone phosphate/acetate mixed formulation.
- Comparative studies of pharmacokinetic profiles of dexamethasone phosphate and betamethasone phosphate to establish if significant differences.
- Establishment of a minimum effective dose and optimal regimen for dexamethasone phosphate and for betamethasone phosphate to maximise benefits and minimise excessive fetal exposure.

Chapter 4: Governance And Approval

4.1 Formal governance arrangements

This Guideline was written by the Guideline developers under the direction of the Guideline Programme Team (GPT). An Expert Advisory Group was formed to review the Guideline prior to submission for final approval with the National Women and Infants Health Programme. The roles and responsibilities of the members of each group and their process were clearly outlined and agreed.

4.2 Guideline development standards

This Guideline was developed by the Guideline Developer Group (GDG) within the overall template of the HSE National Framework[14] for developing Policies, Procedures, Protocols and Guidelines (2016) (Appendix 7) and under supervision of the Guideline Programme Team.

A review was conducted by a group of experts, specialists and advocates (the EAG) prior to approval by the Clinical Advisory Group (CAG) of the National Women and Infants Health Programme (NWIHP) with final sign off for publication by CAG Co-Chairs, the Clinical Director of NWIHP and the Chair of the IOG. See Appendix 8 for list of CAG members.

14 Health Service Executive (2016). National Framework for developing Policies, Procedures, Protocols and Guidelines (PPPGs). Available from: https://www.hse.ie/eng/about/who/qid/nationalframeworkdevelopingpolicies/

Chapter 5: Communication And Dissemination

A communication and dissemination plan for this Guideline has been developed by the GPT and endorsed by NWIHP.

Effective ongoing clear communication is essential in explaining why the Guideline is necessary and securing continued buy-in. It provides an opportunity to instil motivation within staff, helps overcome resistance to change and gives an opportunity for feedback.[15]

The Clinical Guideline will be circulated and disseminated through the Guideline Programme Team as well as through the professional networks who participated in developing and reviewing the document.

Senior management within the maternity units are responsible for the appropriate dissemination of new and updated guidelines. Local hospital groups including Guideline committees are also instrumental in the circulation of new and updated guidelines and promoting their use in the relevant clinical settings.

The HSE will make this Guideline available to all employees through standard networks such as the Neonatal Clinical Advisory Group and Faculty Of Paediatrics, as well as storing it in the online PPPG repository. Electronic versions available on the NWIHP https://www.hse.ie/eng/about/who/acute-hospitals-division/woman-infants/clinical-guidelines/ and RCPI websites (https://www.rcpi.ie/faculties/obstetricians-and-gynaecologists/national-clinical-guidelines-in-obstetrics-and-gynaecology/) and other communication means can be used to maximise distribution. The NWIHP website will also provide a training webinar introducing each Guideline and where relevant a downloadable version of the recommended algorithm will be available.

15 Department of Health (2018). NCEC Implementation Guide and Toolkit. Available at: https://health.gov.ie/national-patient-safety-office/ncec/

Chapter 6: Implementation

6.1 Implementation plan

Implementation was considered at the beginning, and throughout the Guideline development process. The local multidisciplinary clinical team, senior executive and clinical management in each maternity and gynaecology unit are ultimately responsible for the appropriate structured adoption and implementation of the Guideline within their area of responsibility. They must ensure that all relevant personnel under their supervision have read and understood the Guideline and monitor both its effectiveness and adoption.

Within each site, local multidisciplinary teams are responsible for the clinical implementation of Guideline recommendations, and ensuring that their local clinical practices and processes reflect and are aligned with the Guideline recommendations

The following have been put in place to help facilitate the implementation of this Guideline.

- Quick Summary Document (QSD) for clinical staff (includes key recommendations, auditable standards, algorithms and recommended reading)
- Clinical Guideline mobile application
- Plain language summary
- Patient information leaflet (Appendix 9)

6.2 Education plans required to implement the Guideline

Healthcare professionals and professional bodies have a responsibility to keep themselves informed on the changing evidence base and the balance between intended short-term benefits versus potential long-term harms of antenatal corticosteroids.

It is acknowledged that this Guideline should be complemented by ongoing education, training and assessment where required.

While antenatal corticosteroids are currently used in all maternity hospitals/units in Ireland this Guideline's recommendations involve some changes for many in dosing, dosing intervals and specific indications. This will need a specific education piece around change in practice and ongoing monitoring to be sure this has taken place.

6.3 Barriers and facilitators

To ensure successful implementation of guidelines, it is first necessary to look at potential barriers and facilitators. Taking these into account when developing the implementation plan should improve levels of support from relevant users. (DOH 2018, 2019)

Barriers may be categorised as internal (specific to the Guideline itself) or external (specific to the clinical environment).

The Guideline Development Group has aimed to address any internal barriers during the development of this Guideline.

Potential external barriers include:

- Structural factors (e.g. budget or service redesign)
- Organisational factors (e.g. lack of facilities or equipment)
- Individual factors (e.g. knowledge, skills, training)
- Woman's perceptions.

In the case of this Guideline it will be necessary to examine possible barriers and consider implementation strategies to address them. By example, this may include discussion with relevant management groups with regards budgetary impact or providing training to the relevant staff.

6.4 Resources necessary to implement recommendations

The implementation of this Guideline should be undertaken as part of the quality improvement of each hospital. Hospitals should review existing service provision against this Guideline, identifying necessary resources required to implement the recommendations in this Guideline.

Antenatal corticosteroids are currently used in all maternity hospitals/units in Ireland. So while this Guideline's recommendations involve some changes for many in dosing, dosing intervals and specific indications, this is not expected to lead to any specific change in or need for additional resources.

Chapter 7: Audit and Evaluation

7.1 Introduction to audit

It is important that both implementation of the Guideline and its influence on outcomes are audited to ensure that this Guideline positively impacts on the care of the woman. Institutions and health professionals are encouraged to develop and undertake regular audits of Guideline implementation. Personnel tasked with the job of conducting the audit should be identified on receipt of the most recent version of the Guideline.

7.2 Auditable standards

Audit using the key recommendations as indicators should be undertaken to identify where improvements are required and to enable changes as necessary. Audit should also be undertaken to provide evidence of continuous quality improvement initiatives.

Auditable standards for this Guideline include:

- Number of women giving birth between 23 and 25 weeks who receive a full course of antenatal corticosteroids as defined in the guidelines, which is two doses of 12 mg, administered 24 hours apart.
- For women giving birth between 23 and 25 weeks, the number who receive any dose of antenatal corticosteroids and the interval between this and the preterm birth.
- Number of women giving birth before 34+6 weeks who receive a full course of antenatal corticosteroids, as defined in the guidelines, which is two doses of 12 mg, administered 24 hours apart.
- Number of women with threatened preterm labour before 35 weeks who receive antenatal steroids but who deliver beyond 35 weeks' gestation.
- Number of women giving birth before 34+6 weeks who have received more than one course of antenatal corticosteroids.
- Number of women who have an elective caesarean birth before 39 weeks' gestation and who have received a course of antenatal corticosteroids from 35 weeks onwards.

7.3 Evaluation

Evaluation is defined as a formal process to determine the extent to which the planned or desired outcomes of an intervention are achieved.[16] Implementation of this Guideline will be audited periodically at national level, with standards for this set by the NWIHP. Evaluation of the auditable standards should also be undertaken locally by senior hospital clinical management to support implementation.

16 Health Information Quality Authority (2012). National Standards for Safer Better Healthcare [Internet]. Available from: https://www.hiqa.ie/reports-and-publications/standard/national-standards-safer-better-healthcare

Chapter 8: Revision Plan

8.1 Procedure for the update of the Guideline

It may be a requirement to amend, update or revise this Guideline as new evidence emerges. This Guideline will be reviewed at national level every three years, or earlier if circumstances require it, and updated accordingly.[17]

The Guideline Development Group will be asked to review the literature and recent evidence to determine if changes are to be made to the existing Guideline. If the Guideline Development Group are unavailable, the GPT along with the NWIHP senior management team will select a suitable expert to replace them.

If there are no amendments required to the Guideline following the revision date, the detail on the revision tracking box must still be updated which will be a new version number and date.

The recommendations set out in this Guideline remain valid until a review has been completed.

8.2 Method for amending the Guideline

As new evidence become available it is inevitable that Guideline recommendations will fall behind current evidence based clinical practice. It is essential that clinical guidelines are reviewed and updated with new evidence as it becomes available.

In order to request a review of this Guideline one of the following criteria must be met:

- 3 years since the Guideline was published
- 3 years since last review was conducted
- Update required as a result of new evidence
- Correspondence requesting a review of the Guideline should be submitted to the National Women and Infants Health. Any such requests should be dealt with in a timely manner.

17 Health Service Executive (2016). National Framework for developing Policies, Procedures, Protocols and Guidelines (PPPGs). Available from: https://www.hse.ie/eng/about/who/qid/nationalframeworkdevelopingpolicies/

Chapter 9: References

1. Blencowe H, Cousens S, Chou D, Oestergaard M, Say L, Moller AB, *et al.* Born too soon: the global epidemiology of 15 million preterm births. Reprod Health. 2013;10 Suppl 1(Suppl 1):S2.

2. Millman G. Fanaroff and Martin's neonatal-perinatal medicine diseases of the fetus and infant, 8th Edn. 2006;Vols I and II.

3. Hintz SR, Van Meurs KP, Perritt R, Poole WK, Das A, Stevenson DK, *et al.* Neurodevelopmental outcomes of premature infants with severe respiratory failure enrolled in a random*is*ed controlled trial of inhaled nitric oxide. J Pediatr. 2007 Jul;151(1):16-22, 22.e1-3.

4. McGoldrick E, Stewart F, Parker R, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev. 2020;12(100909747):CD004454.

5. Ballard PL, Ballard RA. Scientific basis and therapeutic regimens for use of antenatal glucocorticoids. Am J Obstet Gynecol. 1995 Jul;173(1):254-62.

6. Liggins GC. Premature delivery of foetal lambs infused with glucocorticoids. J Endocrinol. 1969 Dec;45(4):515-23.

7. Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. Pediatrics. 1972 Oct;50(4):515-25.

8. Crowley P, Chalmers I, Keirse MJ. The effects of corticosteroid administration before preterm delivery: an overview of the evidence from controlled trials. Br J Obstet Gynaecol. 1990 Jan;97(1):11-25.

9. Effect of antenatal dexamethasone administration on the prevention of respiratory distress syndrome. Am J Obstet Gynecol. 1981 Oct 1;141(3):276-87.

10. Effect of corticosteroids for fetal maturation on perinatal outcomes. NIH Consens Statement. 1994 Mar 28;12(2):1-24.

11. Kemp M, Saito M, Usuda H, Watanabe S, Sato S, Hanita T, *et al.* The efficacy of antenatal steroid therapy is dependent on the duration of low-concentration fetal exposure: evidence from a sheep model of pregnancy. Am J Obstet Gynecol. 2018 Sep;219(3).

12. Duthie L, Reynolds RM. Changes in the maternal hypothalamic-pituitary-adrenal axis in pregnancy and postpartum: influences on maternal and fetal outcomes. Neuroendocrinology. 2013;98(2):106-15.

13. Audette MC, Challis JRG, Jones RL, Sibley CP, Matthews SG. Synthetic Glucocorticoid Reduces Human Placental System A Transport in Women Treated With Antenatal Therapy. J Clin Endocrinol Metab. 2014 Nov 1;99(11):E2226-33.

14. National Institutefor Health and Care Excellence. Preterm labour and birth (NICE Guideline NG25) [Internet]. 2022. Available from: https://www.nice.org.uk/guidance/ng25

15. Stock S, Thomson A, Papworth S, the Royal College of Obstetricians and Gynaecologists. Antenatal corticosteroids to reduce neonatal morbidity and mortality. BJOG Int J Obstet Gynaecol. 2022;129(8):e35-60.

16. Antenatal Dexamethasone for Early Preterm Birth in Low-Resource Countries. N Engl J Med. 2020 Dec 24;383(26):2514-25.

17. Daskalakis, George. European guidelines on perinatal care: corticosteroids for women at risk of preterm birth, The Journal of Maternal-Fetal and Neonatal Medicine, 36:1, 2160628 Dec 2023. 2022.

18. Norman J, Shennan A, Jacobsson B, Stock SJ, Birth the FWG for P. FIGO good practice recommendations on the use of prenatal corticosteroids to improve outcomes and minim*ise* harm in babies born preterm. Int J Gynecol Obstet. 2021;155(1):26-30.

19. The American College of Obstetricians and Gynecologists (ACOG). Antenatal Corticosteroid Therapy for Fetal Maturation. 2017;130(2).

20. Deshmukh M, Patole S. Antenatal corticosteroids for neonates born before 25 Weeks-A systematic review and meta-analysis. PloS One. 2017;12(5):e0176090.

21. Park CK, Isayama T, McDonald SD. Antenatal Corticosteroid Therapy Before 24 Weeks of Gestation: A Systematic Review and Meta-analysis. Obstet Gynecol. 2016 Apr;127(4):715-25.

22. Deshmukh M, Patole S. Antenatal corticosteroids in impending preterm deliveries before 25 weeks' gestation. Arch Dis Child Fetal Neonatal Ed. 2018 Mar;103(2):F173-6.

23. Manktelow BN, Lal MK, Field DJ, Sinha SK. Antenatal corticosteroids and neonatal outcomes according to gestational age: a cohort study. Arch Dis Child Fetal Neonatal Ed. 2010 Mar;95(2):F95-98.

24. Carlo WA, McDonald SA, Fanaroff AA, Vohr BR, Stoll BJ, Ehrenkranz RA, *et al.* Association of antenatal corticosteroids with mortality and neurodevelopmental outcomes among infants born at 22 to 25 weeks' gestation. JAMA. 2011 Dec 7;306(21):2348-58.

25. Tyson JE, Parikh NA, Langer J, Green C, Higgins RD. Intensive care for extreme prematurity--moving beyond gestational age. N Engl J Med. 2008 Apr 17;358(16):1672-81.

26. Ehret DEY, Edwards EM, Greenberg LT, Bernstein IM, Buzas JS, Soll RF, *et al.* Association of Antenatal Steroid Exposure With Survival Among Infants Receiving Postnatal Life Support at 22 to 25 Weeks' Gestation. JAMA Netw Open. 2018 Oct 5;1(6):e183235.

27. Chawla S, Wyckoff MH, Rysavy MA, Patel RM, Chowdhury D, Natarajan G, *et al.* Association of Antenatal Steroid Exposure at 21 to 22 Weeks of Gestation With Neonatal Survival and Survival Without Morbidities. JAMA Netw Open. 2022 Sep 1;5(9):e2233331.

28. Gulersen M, Grunebaum A, Lenchner E, Chervenak FA, Bornstein E. Antenatal corticosteroids and neonatal outcomes in preterm birth in the United States. J Perinat Med. 2022 Jun 27;50(5):573-80.

29. Backes CH, Rivera BK, Pavlek L, Beer LJ, Ball MK, Zettler ET, *et al.* Proactive neonatal treatment at 22 weeks of gestation: a systematic review and meta-analysis. Am J Obstet Gynecol. 2021 Feb;224(2):158-74.

30. Rossi RM, DeFranco EA, Hall ES. Association of Antenatal Corticosteroid Exposure and Infant Survival at 22 and 23 Weeks. Am J Perinatol. 2021 Nov 28;

31. Mactier H, Bates SE, Johnston T, Lee-Davey C, Marlow N, Mulley K, *et al.* Perinatal management of extreme preterm birth before 27 weeks of gestation: a framework for practice. Arch Dis Child Fetal Neonatal Ed. 2020 May;105(3):232-9.

32. Leitao S, Corcoran P, Greene R, Murphy B, Twomey A, on behalf of NICORE Republic of Ireland. Very Low Birth Weight Infants in the Republic of Ireland Annual Report 2020. Cork: National Perinatal Epidemiology Centre, 2022.

33. The Clinical Programme in Neonatology The Neonatal Clinical Advisory Group The Faculty of Paediatrics The Institute of Obstetricians and Gynaecologists The National Women and Infants Health Programme. Perinatal Management of Extreme Preterm Birth at the Threshold of Viability A Framework for Practice. 2020;

34. Gyamfi-Bannerman C, Thom EA, Blackwell SC, Tita ATN, Reddy UM, Saade GR, *et al.* Antenatal Betamethasone for Women at Risk for Late Preterm Delivery. N Engl J Med. 2016 Apr 7;374(14):1311-20.

35. 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 Oct 12;355:i5044.

36. Kugelman A, Colin AA. Late preterm infants: near term but still in a critical developmental time period. Pediatrics. 2013 Oct;132(4):741-51.

37. Reddy UM, Deshmukh U, Dude A, Harper L, Osmundson SS. Society for Maternal-Fetal Medicine Consult Series #58: Use of antenatal corticosteroids for individuals at risk for late preterm delivery: Replaces SMFM Statement #4, Implementation of the use of antenatal corticosteroids in the late preterm birth period in women at risk for preterm delivery, August 2016. Am J Obstet Gynecol. 2021 Nov;225(5):B36-42.

38. Räikkönen K, Gissler M, Kajantie E. Associations Between Maternal Antenatal Corticosteroid Treatment and Mental and Behavioral Disorders in Children. JAMA. 2020 May 19;323(19):1924-33.

39. Räikkönen K, Gissler M, Tapiainen T, Kajantie E. Associations Between Maternal Antenatal Corticosteroid Treatment and Psychological Developmental and Neurosensory Disorders in Children. JAMA Netw Open. 2022 Aug 1;5(8):e2228518.

40. Ninan K, Liyanage SK, Murphy KE, Asztalos EV, McDonald SD. Evaluation of Long-term Outcomes Associated With Preterm Exposure to Antenatal Corticosteroids: A Systematic Review and Meta-analysis. JAMA Pediatr. 2022 Jun 1;176(6):e220483.

41. Levine EM, Ghai V, Barton JJ, Strom CM. Mode of delivery and risk of respiratory diseases in newborns. Obstet Gynecol. 2001 Mar;97(3):439-42.

42. van den Berg A, van Elburg RM, van Geijn HP, Fetter WP. Neonatal respiratory morbidity following elective caesarean section in term infants. A 5-year retrospective study and a review of the literature. Eur J Obstet Gynecol Reprod Biol. 2001 Sep;98(1):9-13.

43. Zanardo V, Simbi AK, Franzoi M, Soldà G, Salvadori A, Trevisanuto D. Neonatal respiratory morbidity risk and mode of delivery at term: influence of timing of elective caesarean delivery. Acta Paediatr Oslo Nor 1992. 2004 May;93(5):643-7.

44. National Institute for Health and Care Excellence (NICE). Caesarean Birth: NICE Guideline ng192. [Internet]. 2021. Available from: https://www.nice.org.uk/guidance/ng192/resources/caesarean-birth-pdf-661

45. Finn D, O'Neill SM, Collins A, Khashan AS, O'Donoghue K, Dempsey E. Neonatal outcomes following elective caesarean delivery at term: a hospital-based cohort study. J Matern-Fetal Neonatal Med Off J Eur Assoc Perinat Med Fed Asia Ocean Perinat Soc Int Soc Perinat Obstet. 2016 Mar;29(6):904-10.

46. Sotiriadis A, Makrydimas G, Papatheodorou S, Ioannidis JP, McGoldrick E. Corticosteroids for preventing neonatal respiratory morbidity after elective caesarean section at term. Cochrane Database Syst Rev. 2018 Aug 3;8(8):CD006614.

47. Sotiriadis A, McGoldrick E, Makrydimas G, Papatheodorou S, Ioannidis JP, Stewart F, *et al.* Antenatal corticosteroids prior to planned caesarean at term for improving neonatal outcomes. Cochrane Database Syst Rev. 2021 Dec 22;12(12):CD006614.

48. Mol BW, Li W, Lai S, Stock S. Effectiveness of antenatal corticosteroids at term: Can we trust the data that 'inform' us? Eur J Obstet Gynecol Reprod Biol. 2021 Jun;261:144-7.

49. Nada AM, Shafeek MM, El Maraghy MA, Nageeb AH, Salah El Din AS, Awad MH. RETRACTED: Antenatal corticosteroid administration before elective caesarean section at term to prevent neonatal respiratory morbidity: a randomized controlled trial. Eur J Obstet Gynecol Reprod Biol. 2016 Apr 1;199:88-91.

50. Gupta K, Rajagopal R, King F, Simmons D. Complications of Antenatal Corticosteroids in Infants Born by Early Term Scheduled Cesarean Section. Diabetes Care. 2020 Apr;43(4):906-8.

51. di Pasquo E, Saccone G, Angeli L, Dall'Asta A, Borghi E, Fieni S, *et al.* Determinants of neonatal hypoglycemia after antenatal administration of corticosteroids (ACS) for lung maturation: Data from two referral centers and review of the literature. Early Hum Dev. 2020 Apr;143:104984.

52. Burns CM, Rutherford MA, Boardman JP, Cowan FM. Patterns of cerebral injury and neurodevelopmental outcomes after symptomatic neonatal hypoglycemia. Pediatrics. 2008 Jul;122(1):65-74.

53. Stutchfield PR, Whitaker R, Gliddon AE, Hobson L, Kotecha S, Doull IJM. Behavioural, educational and respiratory outcomes of antenatal betamethasone for term caesarean section (ASTECS trial). Arch Dis Child Fetal Neonatal Ed. 2013 May;98(3):F195-200.

54. Skoll A, Boutin A, Bujold E, Burrows J, Crane J, Geary M, *et al.* No. 364-Antenatal Corticosteroid Therapy for Improving Neonatal Outcomes. J Obstet Gynaecol Can. 2018 Sep 1;40(9):1219-39.

55. Pettit KE, Tran SH, Lee E, Caughey AB. The association of antenatal corticosteroids with neonatal hypoglycemia and hyperbilirubinemia. J Matern-Fetal Neonatal Med Off J Eur Assoc Perinat Med Fed Asia Ocean Perinat Soc Int Soc Perinat Obstet. 2014 May;27(7):683-6.

56. Melamed N, Asztalos E, Murphy K, Zaltz A, Redelmeier D, Shah BR, *et al.* Neurodevelopmental disorders among term infants exposed to antenatal corticosteroids during pregnancy: a population-based study. BMJ Open. 2019 Sep 30;9(9):e031197.

57. Crowther CA, Doyle LW, Haslam RR, Hiller JE, Harding JE, Robinson JS. Outcomes at 2 years of age after repeat doses of antenatal corticosteroids. N Engl J Med. 2007 Sep 20;357(12):1179-89.

58. Sifianou P, Thanou V, Karga H. Metabolic and hormonal effects of antenatal betamethasone after 35 weeks of gestation. J Pediatr Pharmacol Ther JPPT Off J PPAG. 2015 Apr;20(2):138-43.

59. Palas D, Ehlinger V, Alberge C, Truffert P, Kayem G, Goffinet F, *et al.* Efficacy of antenatal corticosteroids in preterm twins: the EPIPAGE-2 cohort study. BJOG Int J Obstet Gynaecol. 2018 Aug;125(9):1164-70.

60. Kong X, Xu F, Wang Z, Zhang S, Feng Z. Antenatal corticosteroids administration on mortality and morbidity in premature twins born at 25~34 gestational weeks: A retrospective multicenter study. Eur J Obstet Gynecol Reprod Biol. 2020 Oct;253:259-65.

61. Ushida T, Kotani T, Sadachi R, Hirakawa A, Hayakawa M, Moriyama Y, *et al.* Antenatal Corticosteroids and Outcomes in Preterm Twins. Obstet Gynecol. 2020 Jun;135(6):1387-97.

62. 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.

63. Amiya RM, Mlunde LB, Ota E, Swa T, Oladapo OT, Mori R. Antenatal Corticosteroids for Reducing Adverse Maternal and Child Outcomes in Special Populations of Women at Risk of Imminent Preterm Birth: A Systematic Review and Meta-Analysis. PloS One. 2016;11(2):e0147604.

64. Jolley JA, Rajan PV, Petersen R, Fong A, Wing DA. Effect of antenatal betamethasone on blood glucose levels in women with and without diabetes. Diabetes Res Clin Pract. 2016 Aug;118:98-104.

65. Langen ES, Kuperstock JL, Sung JF, Taslimi M, Byrne J, El-Sayed YY. Maternal glucose response to betamethasone administration. Am J Perinatol. 2015 Feb;30(2):143-8.

66. National Institute for Health and Care Excellence (NICE); (NICE Guideline,. Diabetes in pregnancy: management from preconception to the postnatal period. London:No. 3 [Internet]. 2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK555331/

67. Garite TJ, Freeman RK, Linzey EM, Braly PS, Dorchester WL. Prospective randomized study of corticosteroids in the management of premature rupture of the membranes and the premature gestation. Am J Obstet Gynecol. 1981 Nov 1;141(5):508-15.

68. Harding JE, Pang J, Knight DB, Liggins GC. Do antenatal corticosteroids help in the setting of preterm rupture of membranes? Am J Obstet Gynecol. 2001 Jan;184(2):131-9.

69. Sheibani L, Fong A, Henry DE, Norton ME, Truong YN, Anyikam A, *et al.* Maternal and neonatal outcomes after antenatal corticosteroid administration for PPROM at 32 to 33 6/7 weeks' gestational age. J Matern-Fetal Neonatal Med Off J Eur Assoc Perinat Med Fed Asia Ocean Perinat Soc Int Soc Perinat Obstet. 2017 Jul;30(14):1676-80.

70. Magann EF, Haram K, Ounpraseuth S, Mortensen JH, Spencer HJ, Morrison JC. Use of antenatal corticosteroids in special circumstances: a comprehensive review. Acta Obstet Gynecol Scand. 2017 Apr;96(4):395-409.

71. WHO recommendations on antenatal corticosteroids for improving preterm birth outcomes. – NLM Catalog – NCBI [Internet]. [cited 2023 May 18]. Available from: https://www.ncbi.nlm.nih.gov/nlmcatalog/101396

72. Conde-Agudelo A, Romero R, Jung EJ, Garcia Sanchez AJ. Management of clinical chorioamnionitis: an evidence-based approach. Am J Obstet Gynecol. 2020;223(6):848-69.

73. Prelabor Rupture of Membranes: ACOG Practice Bulletin, Number 217. Obstet Gynecol. 2020 Mar;135(3):e80-97.

74. Thomson AJ. Care of Women Presenting with Suspected Preterm Prelabour Rupture of Membranes from 24(+0) Weeks of Gestation: Green-top Guideline No. 73. BJOG Int J Obstet Gynaecol. 2019 Aug;126(9):e152-66.

75. Kemp MW, Newnham JP, Challis JG, Jobe AH, Stock SJ. The clinical use of corticosteroids in pregnancy. Hum Reprod Update. 2016 Mar 1;22(2):240-59.

76. Dagklis T, Sen C, Tsakiridis I, Villalaín C, Allegaert K, Wellmann S, *et al.* The use of antenatal corticosteroids for fetal maturation: clinical practice guideline by the WAPM-World Association of Perinatal Medicine and the PMF-Perinatal Medicine foundation. J Perinat Med. 2022 May 25;50(4):375-85.

77. Williams MJ, Ramson JA, Brownfoot FC. Different corticosteroids and regimens for accelerating fetal lung maturation for babies at risk of preterm birth. Cochrane Database Syst Rev. 2022;8(100909747):CD006764.

78. Berger R, Kyvernitakis I, Maul H. Administration of Antenatal Corticosteroids: Current State of Knowledge. Geburtshilfe Frauenheilkd. 2022 Mar;82(3):287-96.

79. Shanks AL, Grasch JL, Quinney SK, Haas DM. Controversies in antenatal corticosteroids. Semin Fetal Neonatal Med. 2019 Jun;24(3):182-8.

80. Elimian A, Figueroa R, Spitzer AR, Ogburn PL, Wiencek V, Quirk JG. Antenatal corticosteroids: are incomplete courses beneficial? Obstet Gynecol. 2003 Aug;102(2):352-5.

81. Khandelwal M, Chang E, Hansen C, Hunter K, Milcarek B. Betamethasone dosing interval: 12 or 24 hours apart? A randomized, noninferiority open trial. Am J Obstet Gynecol. 2012 Mar;206(3):201.e1-11.

82. Vidaeff AC, Belfort MA, Kemp MW, Saade GR, Caughey AB, Wapner RJ, *et al.* Updating the balance between benefits and harms of antenatal corticosteroids. Am J Obstet Gynecol. 2023 Feb;228(2):129-32.

83. Antenatal corticosteroid therapy for reduction of neonatal respiratory morbidity and mortality from preterm delivery – UpToDate [Internet]. [cited 2023 May 18]. Available from: https://www.uptodate.com/contents/antenatal-corticosteroid-therapy-for-reduction-of-neonatal-respiratory-morbidity-and-mortality-from-preterm-delivery?search=antenatal%20corticosteroids&source=search_result&selectedTitle=1~127&usage_type=default&display_rank=1

84. Egerman RS, Mercer BM, Doss JL, Sibai BM. A randomized, controlled trial of oral and intramuscular dexamethasone in the prevention of neonatal respiratory distress syndrome. Am J Obstet Gynecol. 1998 Nov;179(5):1120-3.

85. Utama DP, Crowther CA. Transplacental versus direct fetal corticosteroid treatment for accelerating fetal lung maturation where there is a risk of preterm birth. Cochrane Database Syst Rev. 2018;6(100909747):CD008981.

86. Crowther CA, Ashwood P, Andersen CC, Middleton PF, Tran T, Doyle LW, *et al.* Maternal intramuscular dexamethasone versus betamethasone before preterm birth (ASTEROID): a multicentre, double-blind, randomised controlled trial. Lancet Child Adolesc Health. 2019 Nov;3(11):769-80.

87. Elimian A, Garry D, Figueroa R, Spitzer A, Wiencek V, Quirk JG. Antenatal betamethasone compared with dexamethasone (betacode trial): a randomized controlled trial. Obstet Gynecol. 2007 Jul;110(1):26-30.

88. Rotmensch S, Liberati M, Vishne TH, Celentano C, Ben-Rafael Z, Bellati U. The effect of betamethasone and dexamethasone on fetal heart rate patterns and biophysical activities. A prospective randomized trial. Acta Obstet Gynecol Scand. 1999 Jul;78(6):493-500.

89. Subtil D, Tiberghien P, Devos P, Therby D, Leclerc G, Vaast P, *et al.* Immediate and delayed effects of antenatal corticosteroids on fetal heart rate: a randomized trial that compares betamethasone acetate and phosphate, betamethasone phosphate, and dexamethasone. Am J Obstet Gynecol. 2003 Feb;188(2):524-31.

90. Urban R, Lemancewicz A, Przepieść J, Urban J, Kretowska M. Antenatal corticosteroid therapy: a comparative study of dexamethasone and betamethasone effects on fetal Doppler flow velocity waveforms. Eur J Obstet Gynecol Reprod Biol. 2005 Jun 1;120(2):170-4.

91. Magee LA, Dawes GS, Moulden M, Redman CW. A randomised controlled comparison of betamethasone with dexamethasone: effects on the antenatal fetal heart rate. Br J Obstet Gynaecol. 1997 Nov;104(11):1233-8.

92. Mushkat Y, Ascher-Landsberg J, Keidar R, Carmon E, Pauzner D, David MP. The effect of betamethasone versus dexamethasone on fetal biophysical parameters. Eur J Obstet Gynecol Reprod Biol. 2001 Jul;97(1):50-2.

93. Senat MV, Minoui S, Multon O, Fernandez H, Frydman R, Ville Y. Effect of dexamethasone and betamethasone on fetal heart rate variability in preterm labour: a randomised study. Br J Obstet Gynaecol. 1998 Jul;105(7):749-55.

94. Mulder EJ, Derks JB, Visser GH. Antenatal corticosteroid therapy and fetal behaviour: a randomised study of the effects of betamethasone and dexamethasone. Br J Obstet Gynaecol. 1997 Nov;104(11):1239-47.

95. McDougall ARA, Aboud L, Lavin T, Cao J, Dore G, Ramson J, *et al.* Effect of antenatal corticosteroid administration-to-birth interval on maternal and newborn outcomes: a systematic review. EClinicalMedicine. 2023 Apr;58:101916.

96. Medicinal Products (Control of Placing on the Market) Regulations 2007 (S.I.No. 540 of 2007), as amended.

97. Pinewood Laboratories Ltd. Dexamethasone phosphate 4 mg/ml Solution for Injection or Infusion. Summary of Product Characteristics [Internet]. Health Products Regulatory Authority; Available from: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0281-237-002_01042022112836.pdf

98. Schmitz T, Alberti C, Ursino M, Baud O, Aupiais C, for the BETADOSE study group and the GROG (Groupe de Recherche en Gynécologie Obstétrique). Full versus half dose of antenatal betamethasone to prevent severe neonatal respiratory distress syndrome associated with preterm birth: study protocol for a randomised, multicenter, double blind, placebo-controlled, non-inferiority trial (BETADOSE). BMC Pregnancy Childbirth. 2019 Feb 12;19(1):67.

99. Wang F, Mandelbrot L, Affo L, Galacteros F, Bounan S, Fernandez H, *et al.* Impact of prenatal corticosteroid therapy on sickle cell disease in pregnant women. Int J Gynecol Obstet. 2023 Oct;163(1):243-55.

100. Roberts D, Brown J, Medley N, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev. 2017;3(100909747):CD004454.

101. Norberg H, Kowalski J, Maršál K, Norman M. Timing of antenatal corticosteroid administration and survival in extremely preterm infants: a national population-based cohort study. BJOG Int J Obstet Gynaecol. 2017 Sep;124(10):1567-74.

102. Norman M, Piedvache A, Børch K, Huusom LD, Bonamy AKE, Howell EA, *et al.* Association of Short Antenatal Corticosteroid Administration-to-Birth Intervals With Survival and Morbidity Among Very Preterm Infants: Results From the EPICE Cohort. JAMA Pediatr. 2017 Jul 1;171(7):678-86.

103. Melamed N, Shah J, Soraisham A, Yoon EW, Lee SK, Shah PS, *et al.* Association Between Antenatal Corticosteroid Administration-to-Birth Interval and Outcomes of Preterm Neonates. Obstet Gynecol. 2015 Jun;125(6):1377-84.

104. Taleghani AA, Bhriguvanshi A, Kamath-Rayne BD, Liu C, Narendran V. Timing of Antenatal Steroid Administration and Effects on the Newborn Infant: A Retrospective Study. Am J Perinatol. 2022 Jul;39(10):1065-73.

105. Battarbee AN, Ros ST, Esplin MS, Biggio J, Bukowski R, Parry S, *et al.* Optimal timing of antenatal corticosteroid administration and preterm neonatal and early childhood outcomes. Am J Obstet Gynecol MFM. 2020 Feb;2(1):100077.

106. Humbeck C, Jonassen S, Bringewatt A, Pervan M, Rody A, Bossung V. Timing of antenatal steroid administration for imminent preterm birth: results of a prospective observational study in Germany. Arch Gynecol Obstet. 2023 Sep;308(3):839-47.

107. Ikegami M, Jobe AH, Newnham J, Polk DH, Willet KE, Sly P. Repetitive prenatal glucocorticoids improve lung function and decrease growth in preterm lambs. Am J Respir Crit Care Med. 1997 Jul;156(1):178-84.

108. Dunlop SA, Archer MA, Quinlivan JA, Beazley LD, Newnham JP. Repeated prenatal corticosteroids delay myelination in the ovine central nervous system. J Matern Fetal Med. 1997 Dec;6(6):309-13.

109. Ashwood PJ, Crowther CA, Willson KJ, Haslam RR, Kennaway DJ, Hiller JE, *et al.* Neonatal adrenal function after repeat dose prenatal corticosteroids: a randomized controlled trial. Am J Obstet Gynecol. 2006 Mar;194(3):861-7.

110. Wapner RJ, Sorokin Y, Thom EA, Johnson F, Dudley DJ, Spong CY, *et al.* Single versus weekly courses of antenatal corticosteroids: evaluation of safety and efficacy. Am J Obstet Gynecol. 2006 Sep;195(3):633-42.

111. Crowther CA, Haslam RR, Hiller JE, Doyle LW, Robinson JS. Neonatal respiratory distress syndrome after repeat exposure to antenatal corticosteroids: a randomised controlled trial. Lancet Lond Engl. 2006 Jun 10;367(9526):1913-9.

112. Wapner RJ, Sorokin Y, Mele L, Johnson F, Dudley DJ, Spong CY, *et al.* Long-term outcomes after repeat doses of antenatal corticosteroids. N Engl J Med. 2007 Sep 20;357(12):1190-8.

113. Peltoniemi OM, Kari MA, Tammela O, Lehtonen L, Marttila R, Halmesmäki E, *et al.* Randomized trial of a single repeat dose of prenatal betamethasone treatment in imminent preterm birth. Pediatrics. 2007 Feb;119(2):290-8.

114. Peltoniemi OM, Kari MA, Lano A, Yliherva A, Puosi R, Lehtonen L, *et al.* Two-year follow-up of a randomised trial with repeated antenatal betamethasone. Arch Dis Child Fetal Neonatal Ed. 2009 Nov;94(6):F402-406.

115. Battin M, Bevan C, Harding J. Growth in the neonatal period after repeat courses of antenatal corticosteroids: data from the ACTORDS randomised trial. Arch Dis Child Fetal Neonatal Ed. 2012 Mar;97(2):F99-105.

116. Cartwright RD, Harding JE, Crowther CA, Cutfield WS, Battin MR, Dalziel SR, *et al.* Repeat Antenatal Betamethasone and Cardiometabolic Outcomes. Pediatrics. 2018 Jul;142(1):e20180522.

117. Cartwright RD, Crowther CA, Anderson PJ, Harding JE, Doyle LW, McKinlay CJD. Association of Fetal Growth Restriction With Neurocognitive Function After Repeated Antenatal Betamethasone Treatment vs Placebo: Secondary Analysis of the ACTORDS Randomized Clinical Trial. JAMA Netw Open. 2019 Feb 1;2(2):e187636.

118. Norberg H, Stålnacke J, Diaz Heijtz R, Smedler AC, Nyman M, Forssberg H, *et al.* Antenatal corticosteroids for preterm birth: dose-dependent reduction in birthweight, length and head circumference. Acta Paediatr Oslo Nor 1992. 2011 Mar;100(3):364-9.

119. Walters A, McKinlay C, Middleton P, Harding JE, Crowther CA. Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes. Cochrane Database Syst Rev. 2022 Apr 4;4(4):CD003935.

120. Ninan K, Liyanage SK, Murphy KE, Asztalos EV, McDonald SD. Long-Term Outcomes of Multiple versus a Single Course of Antenatal Steroids: A Systematic Review. Am J Perinatol. 2023 Feb 1;

Bibliography

Health Information Quality Authority (2012). National Standards for Safer Better Healthcare [Internet]. Available from: https://www.hiqa.ie/reports-and-publications/standard/national-standards-safer-better-healthcare

Scottish Intercollegiate Guidelines Network (SIGN). A guideline developer's handbook. Edinburgh: SIGN; 2019. (SIGN publication no. 50). [November 2019]. Available from URL: http://www.sign.ac.uk

Society of Maternal-Fetal Medicine. SMFM Clinical Practice Guidelines Development Process [Internet]. Available from: https://www.smfm.org/publications

Department of Health (2018). NCEC Implementation Guide and Toolkit. Available at: https://health.gov.ie/national-patient-safety-office/ncec/

Department of Health (2019). How to develop a National Clinical Guideline. Available at: https://www.gov.ie/en/collection/cd41ac-clinical-effectiveness-resources-and-learning/

Department of Health (2015). NCEC Standards for Clinical Practice Guidance. Available at: https://www.nmbi.ie/NMBI/media/NMBI/Forms/standards-for-clinical-practice-guidance-ncec.pdf

Health Service Executive (2016). National Framework for developing Policies, Procedures, Protocols and Guidelines (PPPGs). Available from: https://www.hse.ie/eng/about/who/qid/nationalframeworkdevelopingpolicies/

Health Service Executive (2019). National Review of Clinical Audit. Available from: https://www.hse.ie/eng/services/publications/national-review-of-clinical-audit-report-2019.pdf

National Clinical Effectiveness Committee (NCEC) and Health Information and Quality Authority (HIQA) (2015) National quality assurance criteria for clinical guidelines. Version 2. Dublin: NCEC and HIQA. https://www.hiqa.ie/sites/default/files/2017-01/National-Quality-Assurance-Criteria.pdf

Health Service Executive (2022), National Centre for Clinical Audit Nomenclature – Glossary of Terms, National Quality and Patient Safety Directorate. Available from: https://www.hse.ie/eng/about/who/nqpsd/ncca/

Supporting Evidence

GRADE: http://www.gradeworkinggroup.org/

AGREE: http://www.agreetrust.org/agree-ii/

HSE: https://www.hse.ie/eng/about/who/qid/use-of-improvement-methods/nationalframeworkdevelopingpolicies/

Glossary

ACOG American College of Obstetricians and Gynaecologists

AGREE Appraisal of Guidelines for Research and Evaluation

BAPM British Association of Perinatal Medicine

BPD Bronchopulmonary Dysplasia

CAG Clinical Advisory Group

CDC Centres for Disease Control and Prevention

CGA Corrected Gestational Age

CI Confidence Interval

CLD Chronic Lung Disease of Prematurity

CP Cerebral Palsy

CPAP Continuous Positive Airway pressure

EAG Expert Advisory Group

EAPM European Association of Perinatal Medicine

ECMO Extracorporeal Membrane Oxygenation

ELBW Extremely Low Birth Weight (<1000g)

FIGO International Federation of Gynaecology and Obstetrics

GA Gestational age

GPT Guideline Programme Team

GRADE Grading of Recommendations, Assessments, Developments and Evaluations

HIQA Health Information and Quality Authority

HPA Hypothalamic Pituitary Axis

HPRA Health Products Regulatory Authority (Ireland)

HR Hazards Ratio

HSE Health Service Executive

IM Intramuscular

IOG Institute of Obstetricians and Gynaecologists

IVH Intraventricular haemorrhage

LBW Low Birth Weight (<2500g)

MD Mean Difference

MV Mechanical ventilation

NCEC National Clinical Effectiveness Committee

NDI Neurodevelopmental Impairment

NEC Necrotising enterocolitis

NICE The National Institute for Health and Care Excellence

NICU Neonatal Intensive Care Unit

NIH National Institutes of Health

NIV Non-Invasive Ventilation

NNU Neonatal Unit

NNT Number-needed-to-treat

NPEC National Perinatal Epidemiology Centre (Ireland)

NWIHP National Women and Infants Health Programme

OR Odds ratio

PPPG Policy, Procedures, Protocols and Guidelines

PPROM Preterm Prelabour Rupture of Membranes

PTB Preterm Birth

PVL Periventricular Leucomalacia

RANZCOG Royal Australian and New Zealand College of Obstetricians and Gynaecologists

RCOG Royal College of Obstetricians and Gynaecologists

RCPI Royal College of Physicians of Ireland

RCT Randomised Control Trial

RDS Respiratory Distress Syndrome

RoP Retinopathy of Prematurity

RR Relative Risk

SCD Sickle Cell Disease

SGOC Society of Obstetricians and Gynaecologists of Canada

TTN Transient Tachypnoea of the Newborn)

VLBW Very Low Birth Weight (< 1500g)

WHO World Health Organisation

Terminology

Antenatal – Occurring before birth

Antenatal corticosteroids – "Betamethasone" and "dexamethasone" are examples of corticosteroids or glucocorticoids, which are given to pregnant women before birth to to improve lung development in the unborn premature infant.

Antepartum haemorrhage – Bleeding from the vagina during pregnancy before birth

Apgar score – A measure of the physical condition of a newborn infant at birth and 5 minutes of life out of 10. The score is obtained by adding points for heart rate, respiratory effort, muscle tone, response to stimulation, and skin colour.

Applicability – The relevance of research findings to a health care context.

Bias – Systematic error in a study that can encourage a result that deviates from the truth. Can be related to the researcher or study design and can lead to false conclusions.

Blinding – concealment of treatment allocation to one or more parties involved in a research study. "Double- blind" is concealment of allocation to both the participant and the experimenters.

Cerebral Palsy – A group of disorders affecting movement and posture diagnosed in childhood that does not progress.

Chronic Lung Disease – A lung condition primarily of infants born preterm where there is a prolonged need for breathing support or oxygen. Often used interchangeably with Bronchopulmonary Dysplasia which is the pattern of damage to the airways and small air sacs of the lung.

Clinical impact – The effect of making a change in practice in the relevant population

Cochrane Review/Cochrane Systematic Review – A systematic review of the evidence usually from randomised controlled trials relating to a particular health problem or healthcare intervention, produced by the Cochrane Collaboration. Available electronically as part of the Cochrane Library.

Cognitive dysfunction – Impairment in mental ability or potential for example lack of attention, memory and problem-solving issues.

Confidence interval – A range of values for a specified outcome estimated from a study. It will depend on the number of people in the study and the variation in the outcome data. A 95% confidence interval (CI) means that if the study was repeated 100 times with a different sample of recruits and a CI calculated each time, the interval would contain the 'true' value of the population outcome 95 times.

Control – An element that remains unchanged in an experiment, used as a comparison with a treatment to measure an outcome. A "fake" treatment.

Course – A number of doses included in a specified treatment

Developmental delay – A lag in a child's motor, behavioural, cognitive, emotional or social

Development compared with the population average.

Dose – A quantity of a medicine taken at a specific time point

Eclampsia – Seizures (convulsions) in a pregnant woman related to hypertensive disease in pregnancy.

Evidence statement – A summary of the findings of a group of studies that represents the evidence supporting a particular recommendation in a guideline.

Fetal – Pertaining to an unborn child at the fetal stage of development

Gestational age – The period of time between last menstrual period and birth.

Harms – Unintended or adverse effects

Individual patient data – The central collection, validation and re-analysis of 'raw' data from existing trials addressing the same research question to allow further exploration of patient factors or groups that are more or less likely to benefit from treatment.

Intellectual impairment – A condition where powers of comprehension and information processing abilities are affected to the point where it impairs a persons' ability to perform.

Intraventricular haemorrhage – A condition primarily of preterm newborns of bleeding inside the cerebral ventricles, the fluid filled spaces in the brain. It is graded 1-4 with 4 bring the most severe.

Meta-Analysis – A statistical analysis that combines the results of multiple scientific studies. This involves the examination of data from a number of independent studies of the same subject, in order to determine overall trends.

Mechanical Ventilation – Using a machine or ventilator to assist breathing

Necrotising enterocolitis – A condition primarily seen in premature infants, where areas of the intestine become inflamed and can undergo tissue death (necrosis).

Neonatal – Pertaining to the neonatal period which is the first four weeks after birth.

Neurologic impairment – A range of disorders that relate to the central nervous system (brain and spinal cord). Among the more common diagnostic categories for children are cerebral palsy, epilepsy, blindness, deafness, and developmental delay.

Number needed to treat – How many people would need to be receive a new intervention or treatment for one patient to benefit from the new treatment.

Periventricular leukomalacia – A form of brain injury most commonly in premature infants characterised by injury of white matter near the cerebral ventricles.

Placebo – An inactive substance used as a control or comparison in an experiment or test to determine the effectiveness of a medicinal drug.

Pre-eclampsia – A pregnancy induced condition which can occur in the second half of pregnancy. It is characterised by high blood pressure, swelling that happens suddenly along with rapid weight gain due to fluid retention, and protein in the urine.

Preterm birth – The birth of a baby of less than 37 weeks' gestation.

Preterm labour – Labour before 37 weeks of gestation.

p-value – The probability that the difference seen between two treatments in a study occurred by chance. This is a used in hypothesis testing where initially it is assumed that there is no difference between two treatments. Small p-values support evidence against an assumption of no difference. Large p-values indicate insufficient evidence against the assumption of no difference between treatments, NOT that there is actually no difference between treatments. P-values will depend on study size; large studies can detect small differences for example.

Randomised Control Trial – A design of study in which participants are randomly allocated to an intervention or control and are followed up after to examine differences in outcomes between the groups.

Regimens – A pattern of treatment such as dose or frequency of a drug.

Respiratory distress syndrome – Breathing difficulty usually in preterm babies, caused by lack of surfactant and structural immaturity of the lungs.

Respiratory distress – The presence of cyanosis, grunting, inspiratory stridor, nasal flaring and tachypnoea.

Risk – The probability of an outcome which is given by the number with the outcome divided by the number with and without the outcome.

Relative risk or risk ratio (RR) – The ratio of risks in two treatment groups. In intervention studies, it is the ratio of the probability of an outcome in an intervention group to the probability in the control group. A relative risk of one indicates no difference between comparison groups and a risk ratio that is less than one indicates that the intervention is effective in reducing the risk of that outcome.

Retinopathy of Prematurity – An eye disease of premature infants involving abnormal blood vessel growth at the back of the eye.

Sample size – The number of participants in a population of a study. The sample size should be big enough to be able to detect a true difference between two groups.

Singleton – A single baby.

Stillbirth – Death in a fetus ≥500 g or at least 24 weeks' gestational age.

Systematic review – A review of a specific research question that uses exact methods to identify, select and critically assess available relevant research, and to collect and analyse data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyse and summarise the results of the included studies.

Transient tachypnoea of the newborn – Rapid breathing or respiratory distress after birth that resolves over 24-48 hours.

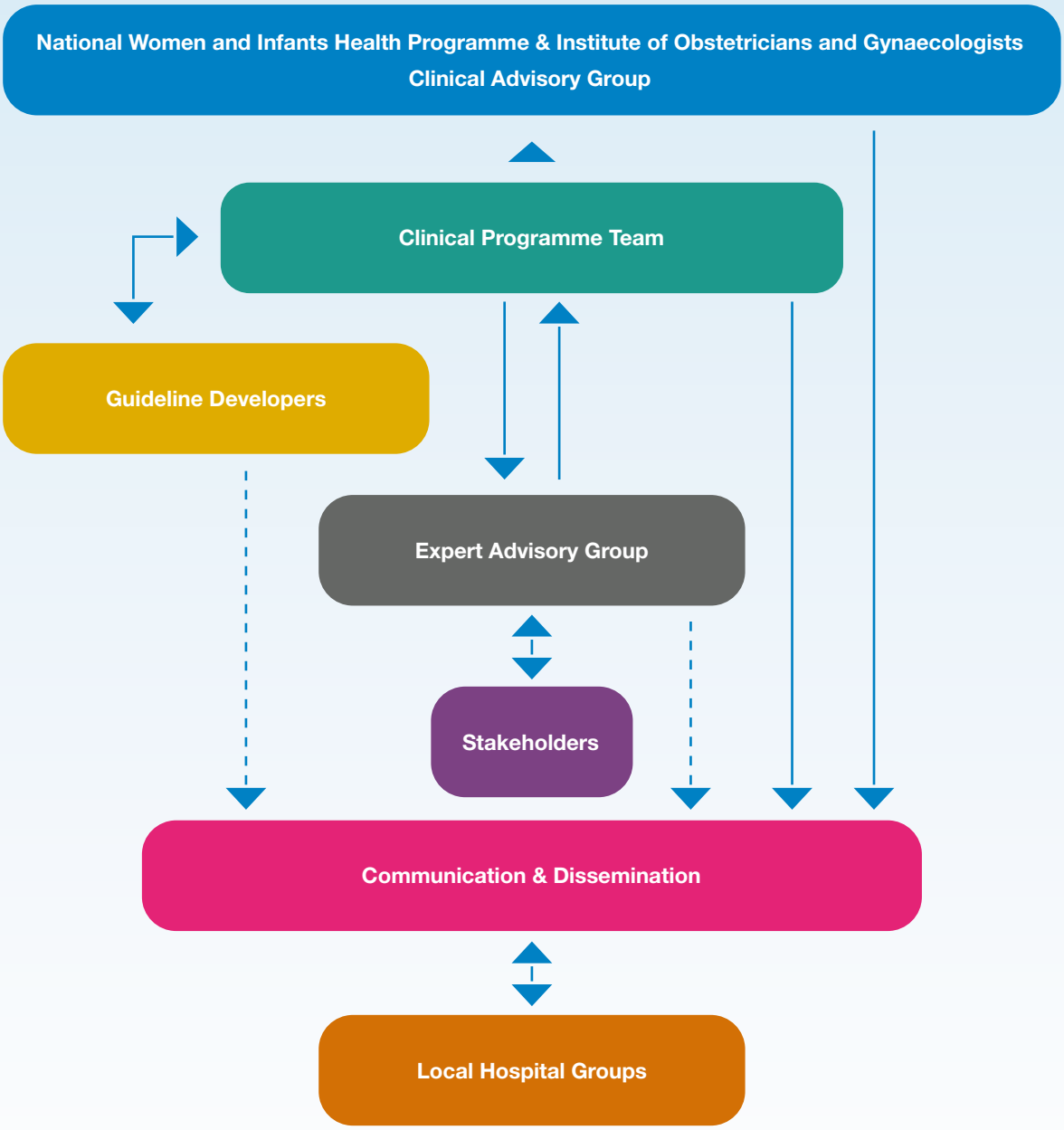
Appendix 1:
Expert Advisory Group Members 2021-

Attendee	Profession	Location (2021)
Dr Fergus McCarthy	Consultant Obstetrician, Gynaecologist, Senior Lecturer and Maternal-Fetal Medicine Sub-specialist	Cork University Maternity Maternity unit, University College Cork
Dr Mairead Butler	Consultant Obstetrician and Gynaecologist	University Maternity unit Waterford
Prof. Declan Keane	Professor of Obstetrics and Gynaecology	National Maternity Maternity unit Dublin, Royal College of Surgeons in Ireland
Dr Katherine Astbury	Consultant Obstetrician and Gynaecologist Gynaecology Oncology Sub-specialist	University Maternity unit Galway
Dr Cathy Monteith	Consultant Obstetrician and Gynaecologist	Our Lady of Lourdes Hospital Drogheda
Dr Sarah Petch	Specialist Registrar, Obstetrics and Gynaecology	National Maternity Maternity unit Dublin
Dr Orla Donohoe	Specialist Registrar, Obstetrics and Gynaecology	Sligo University Maternity unit
Dr Aisling McDonnell	Specialist Registrar, Obstetrics and Gynaecology	Mater Misericordiae University Hospital Dublin
Prof. John Murphy	Consultant Neonatologist and Clinical Lead for the National Clinical Programme for Paediatrics and Neonatology	National Women and Infants Health Programme
Ms Siobhan Canny	Group Director of Midwifery	Saolta University Health Care Group
Ms Fiona Hanrahan	Director of Midwifery and Nursing	Rotunda Maternity unit Dublin
Ms Margaret Quigley	National Lead for Midwifery	Office of Nursing and Midwifery Services Director
Prof. Valerie Smith	Professor of Midwifery	School of Nursing and Midwifery, Trinity College Dublin

Attendee	Profession	Location (2021)
Ms Triona Cowman	Director of the Centre for Midwifery Education	Centre for Midwifery Education, Coombe Women & Infants University Maternity unit
Ms Janet Murphy	Advanced Midwifery Practitioner	University Maternity unit Waterford
Dr Ciara McCarthy	General Practitioner and ICGP Women's Health Lead	Irish College of General Practitioners
Mr Fergal O' Shaughnessy *And* Dr Brian Cleary *(Shared nomination)*	Senior Pharmacist, Honorary Lecturer *And* Chief Pharmacist, Honorary Clinical Associate Professor and Medications Lead, Maternal & Newborn Clinical Management System	Rotunda Maternity unit Dublin Royal College of Surgeons in Ireland
Ms Marie Finn	Medical Social Work Counsellor	Saolta University Health Care Group
Ms Áine Kelly	Physiotherapy Manager	Coombe Women & Infants University Hospital, Dublin
Ms Marie Culliton	Scientific Lead	National Clinical Programme for Pathology
Ms Marita Hennessy	Post-Doctoral Researcher	Pregnancy Loss Research Group, INFANT Centre, University College Cork
Ms Niamh Connolly-Coyne *And* Ms Mandy Daly *(Shared nomination)*	Board of Directors	Irish Neonatal Health Alliance
Ms Caroline Joyce	Principal Clinical Biochemist PhD Candidate	Cork University Maternity unit University College Cork
Dr Richard Duffy	Consultant Perinatal Psychiatrist	Rotunda Maternity unit Dublin
Ms Sinéad Curran	Dietician Manager	National Maternity Maternity unit
Dr Nicholas Barrett	Lead for Obstetric Anaesthesiology services	Limerick University Maternity unit
Dr Brendan Fitzgerald	Consultant Perinatal Pathologist	Cork University Maternity unit
Dr Niamh Conlon	Consultant Histopathologist	Cork University Maternity unit
Ms Georgina Cruise	National Manager	Patient Advocacy Service

Appendix 2: Guideline Programme Process

Guideline Programme Process



Appendix 3:
Summary of Antenatal Corticosteroid Guidelines

	RCOG[15] Guideline	WHO[71] Recommendations	EAPM[17] Guidelines	SOCG[54] Guidelines	RANZCOG[62] Guidelines	ACOG[19] Committee Opinion / recommendations	FIGO[18] Good practice recommendations
Guideline	**Green-top Guideline** No 74 Antenatal corticosteroids to reduce neonatal morbidity and mortality	**WHO recommendations** Antenatal corticosteroids for improving preterm birth outcomes	**European guidelines** on perinatal care Corticosteroids for women at risk of preterm birth	**Clinical Practice Guideline** No. 364 Antenatal Corticosteroid Therapy for Improving Neonatal Outcomes	**Clinical Practice Guidelines** on the use of antenatal corticosteroids given to women prior to birth to improve fetal, infant and child and adult health.	**ACOG Committee Opinion / recommendations** Antenatal Corticosteroid Therapy for Fetal Maturation	**FIGO good practice recommendations** on the use of prenatal corticosteroids to improve outcomes and minimize harm in babies born preterm
Publication Date	July 2022	January 2022	23 Jan 2023	2018	2015	August 2017 Reaffirmed 2020	2021

	RCOG[15] Guideline	WHO[71] Recommendations	EAPM[17] Guidelines	SOCG[54] Guidelines	RANZCOG[62] Guidelines	ACOG[19] Committee Opinion / recommendations	FIGO[18] Good practice recommendations
Search Strategy	Cochrane Library and electronic databases (DARE, EMBASE, Trip, MEDLINE and PubMed). Searched looking for following terms in title or abstract: 'corticosteroids', 'glucocorticoids', 'pregnancy', 'obstetrics', 'antenatal', 'fetal'.	WHO Steering Group, in collaboration with -external team of systematic reviewers and guideline methodologists, retrieved evidence on the effectiveness of interventions from systematic reviews of randomized controlled trials (RCTs) and non-randomized studies as needed. Cochrane systematic reviews were the primary source of effectiveness evidence for the recommendations.	PubMed, EMBASE, Cochrane Library, Ovid, UpToDate. Limited to studies involving humans and published in English bet. Jan 1988 and April 2022. Randomized trials and observational studies considered eligible. Search terms: corticosteroids, betamethasone, dexamethasone, antenatal, pregnancy, preterm birth, prematurity, twin pregnancies, cesarean section, diabetes mellitus, intrauterine growth restriction, repeat doses, interval to delivery.	Medline, PubMed, Embase, and the Cochrane Library searched from inception to September 2017. MeSH terms and key words: pregnancy, prematurity, corticosteroids, and perinatal and neonatal mortality and morbidity. Randomized controlled trials and previous systematic reviews eligible. Evidence from systematic reviews of non-experimental (cohort) studies also eligible.	Medline, Embase, CENTRAL, Cochrane Database, HTA database, National Guideline Clearing House, Guidelines International Network, Clinical Trials Register, Specialised register of Pregnancy and Childbirth Cochrane Group. Not date limited. Evidence restricted to clinical guidelines, systematic reviews and randomised controlled trials. Excluded: case series studies, editorials and commentaries, book chapters, personal communications or news items.	ACOG Committee Opinion developed to help guide timing and frequency of corticosteroid administration under various clinical contexts before preterm birth. Designed as an educational resource to aid clinicians in providing obstetric and gynecologic care and use of the information is voluntary.	The purpose of this document is to review the evidence and provide good practice recommendations for the use of prenatal corticosteroids to improve outcomes in babies likely to be born preterm
Years looked at	Start date: 2018 End date: Jan 2021	1972- 2021	January 1988 to April 2022	Up to September 2017	Searches took place in October 2012 and were re-run in September 2014.	Includes references up to and including 2016	Includes references up to and including 2020

	RCOG[15] Guideline	WHO[71] Recommendations	EAPM[17] Guidelines	SOCG[54] Guidelines	RANZCOG[62] Guidelines	ACOG[19] Committee Opinion / recommendations	FIGO[18] Good practice recommendations
Structure of Guideline Working Group	**Produced on behalf of the RCOG** by: Dr SJ Stock FRCOG, Edinburgh; Dr A J Thomson MRCOG, Paisley and Dr S Papworth FRCPCH, Newport. **Committee lead reviewers** were: Dr A McKelvey MRCOG, Norwich and Dr S Karavolos MRCOG, Manchester **Peer reviewed** **Co-Chairs of Guidelines Committee** were: Dr MA Ledingham FRCOG, Glasgow and Dr B Magowan FRCOG, Melrose	**Executive Guideline Steering Group** independent panel of 14 external experts **WHO Steering Group:** drafted key questions in PICO format. Supervised retrieval and syntheses of evidence, finalized recommendations. **Guideline Development Group (GDG):** 18 external experts and relevant stakeholders **External Review Group** **Evidence Synthesis Group**	**European Association of Perinatal Medicine** **Writing group** **Guideline panel Members = co-authors** An evidence-based guideline intended to assist practitioners in the optimal use of corticosteroids for women at risk of imminent spontaneous preterm birth, and those planned for iatrogenic preterm birth due to maternal or fetal pathology.	Antenatal Corticosteroid Therapy Working Group Reviewed and approved by the Maternal-Fetal Medicine and Guideline Management and Oversight Committee. Approved by Board of the Society of Obstetricians and Gynaecologists of Canada.	Multidisciplinary expert advisory **Clinical Practice Guidelines Panel** **Executive Group** guided overall preparation of the guidelines **Management Group** identified and synthesised the evidence presented in these guidelines Endorsement has been received from The Perinatal Society of Australia and New Zealand, New Zealand College of Midwives, Neonatal Nurses College of Aotearoa, Australian College of Neonatal Nurses and Royal Australasian College of Physicians.	Committee Opinion developed by the **ACOG Committee on Obstetric Practice**	**FIGO Working Group for Preterm Birth 2018-2021**

	RCOG[15] Guideline	WHO[71] Recommendations	EAPM[17] Guidelines	SOCG[54] Guidelines	RANZCOG[62] Guidelines	ACOG[19] Committee Opinion / recommendations	FIGO[18] Good practice recommendations
Steroid regimen	**RCOG July 2022** Dexamethasone phosphate 24mg intramuscularly in two divided doses of 12 mg 24 hours apart or four divided doses of 6 mg 12 hours apart Alternative: betamethasone sodium phosphate/ acetate mix 24mg given intramuscularly in two divided doses of 12 mg 24 hours apart Acknowledgement that betamethasone sodium phosphate / acetate mix not available in UK. Betamethasone phosphate only available in UK. Similar situation in ROI.	**WHO Jan 2022** Either intramuscular (IM) dexamethasone or IM betamethasone Total 24 mg in divided doses 12 hours or 24 hours apart. The GDG reviewed the important differences in the type and preparation of antenatal corticosteroids across settings and emphasized that local protocols on the type and dosing regimen should be informed by the preparations that are readily available in their setting.	**EAPM Jan 2023** Betamethasone 12 mg administered intramuscularly twice 24-h apart or dexamethasone 6 mg administered intramuscularly in four doses, 12-h apart, or 12 mg administered intramuscularly twice 24-h apart Doesn't specify the betamethasone salt. Existing evidence suggests both betamethasone and dexamethasone have similar effects on survival & long-term neurodevelopmental disability, and that minor differences are seen in short-term morbidity and mortality. These are insufficient to judge the superiority of either regimen, or of alternative doses.	**SOCG 2018** 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) Betamethasone sodium phosphate/ acetate mix formulation marketed in Canada	**RANZCOG 2015** Either betamethasone sodium phosphate/ acetate mix 24mg in divided doses, completed between 12 and 36 hours or dexamethasone phosphate 24 mg in divided doses completed between 24 and 40 hours Celestone® Chronodose® Injection, available in New Zealand and Australia: sterile aqueous suspension containing betamethasone sodium phosphate and betamethasone acetate.	**ACOG 2020** Either two 12mg doses of betamethasone given intramuscularly twenty four hours apart or four 6mg doses of dexamethasone administered intramuscularly every 24 hours Betamethasone sodium phosphate/ acetate mix formulation marketed in US	**FIGO 2021** Appropriate regimens include two doses of betamethasone acetate/phosphate 12 mg (=one course) IM 24 h apart, or two doses of dexamethasone phosphate 12mg (=one course) IM 24 h apart Most studies have used betamethasone acetate/phosphate or dexamethasone phosphate as prenatal steroid

	RCOG[15] Guideline	WHO[71] Recommendations	EAPM[17] Guidelines	SOCG[54] Guidelines	RANZCOG[62] Guidelines	ACOG[19] Committee Opinion / recommendations	FIGO[18] Good practice recommendations
	Suggests similar betamethasone phosphate dose to dexamethasone phosphate dose as both soluble salts.				A single dose provided in 2 mL contains betamethasone 11.4 mg, as betamethasone sodium phosphate 7.8 mg (in solution) and betamethasone acetate 6 mg (in suspension).		
Threshold of viability <24 weeks	Concludes that benefits are evident <24 weeks. Recommend ANS can be considered >22 weeks when perinatal team+ woman have made informed decision for active care	Insufficient evidence to recommend AN administration prior to 24 weeks GA	At GA 22+0 - 23+6 weeks: ANS should be considered when preterm birth is anticipated in the next seven days and active newborn life-support is indicated, taking into account parental wishes. Survival benefit has been observed, but the impact on short-term neurological and respiratory function, as well as long-term neurodevelopmental outcome is still unclear	Concludes reduction in perinatal mortality <24 week in ACS exposed. 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 and ACS may be considered if early intensive care is planned	Recommend administration when preterm birth anticipated within 7 days at GA<34+6 weeks, lower GA limit not specified	2017 guideline recommended single course of ANS from 24 weeks where at risk of PTB within 7 days, although active neonatal care be provided at lower gestations. Most recent addendum to the guideline recommends ANS may be considered 22-22+6 if neonatal resuscitation is planned.	States that the evidence for benefit of ANS is greatest between 24-34 weeks, therefore they recommend ANS for anticipated preterm birth between 24-34 weeks.

	RCOG[15] Guideline	WHO[71] Recommendations	EAPM[17] Guidelines	SOCG[54] Guidelines	RANZCOG[62] Guidelines	ACOG[19] Committee Opinion / recommendations	FIGO[18] Good practice recommendations
Early pre-term birth	Corticosteroids should be offered to women between 24+0 and 34+6 weeks' gestation in whom imminent pre-term birth is anticipated	Antenatal corticosteroid therapy is recommended for women with a high likelihood of preterm birth from 24 weeks to 34 weeks of gestation	Corticosteroids should be administered to a woman at a gestational age between 24+0 and 33+6 weeks, when preterm birth is anticipated in the next seven days, as these have been consistently shown to reduce neonatal mortality and morbidity. In selected cases, extension of this period up to 34+6 weeks may be considered.	One course of antenatal corticosteroids should be routinely administered to women at 24+0 to 34+6 weeks' gestation who are at high risk of preterm delivery within the next seven days.	In women at risk of early preterm imminent birth, use a single course of antenatal corticosteroids when the gestational age is 34 weeks and 6 days or less.	A single course of corticosteroids is recommended for pregnant women between 24+0 and 33+6 weeks of gestation who are at risk of preterm delivery within 7 days.	For women with singleton pregnancies where active neonatal care is appropriate, for whom preterm birth is anticipated between 24+0 and 34+0 weeks of gestation, prenatal corticosteroids should be offered to improve outcomes for the baby.

	RCOG[15] Guideline	WHO[71] Recommendations	EAPM[17] Guidelines	SOCG[54] Guidelines	RANZCOG[62] Guidelines	ACOG[19] Committee Opinion / recommendations	FIGO[18] Good practice recommendations
Late pre-term birth	Clinicians and women should consider the balance of risks and benefits of corticosteroids in women in whom imminent preterm birth is anticipated from 35+0 to 36+6 weeks' gestation	Antenatal corticosteroid therapy is not recommended for women undergoing planned caesarean section at 34+0 to 36+6 weeks	Administration between 35+0 and 36+6 should be restricted to prospective randomised control trials.	The balance of risks and benefits does not support routine administration of corticosteroid therapy for women at 35=0 to 35+6 weeks' gestation who are at high risk for preterm birth. Antenatal corticosteroid therapy should not be routinely administered to women at 36=0 to 36+6 weeks' gestation who are at risk pf preterm delivery.	**N/A**	A single course of betamethasone is recommended for pregnant women between 34+0 weeks and 36+6 weeks' gestation at risk of preterm birth within 7 days, and who have not received a previous course of antenatal corticosteroids.	Prenatal corticosteroids should not be offered routinely to women in whom late preterm birth is anticipated (34+0 to 36+6). Instead the use of prenatal corticosteroids should be considered in light of the balance of risks and benefits of individual women.
Before planned caesarean at term	An informed discussion should take place with a woman if undergoing a planned caesarean birth between 37+0 and 38=6 weeks' gestation about the potential risks and benefits of a course of antenatal corticosteroids	**N/A**	Administration in pregnancies beyond 37+0 weeks is not indicated, even for scheduled caesarean delivery.	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)	Use antenatal corticosteroids 48 hours prior to caesarean birth planned beyond 36 weeks and 6 days if there is known fetal lung immaturity.	**N/A**	Prenatal corticosteroids should not be given routinely before caesarean section at term.

	RCOG[15] Guideline	WHO[71] Recommendations	EAPM[17] Guidelines	SOCG[54] Guidelines	RANZCOG[62] Guidelines	ACOG[19] Committee Opinion / recommendations	FIGO[18] Good practice recommendations
In multiple pregnancy	Women with twins and triplets should be offered targeted antenatal corticosteroids for early birth in line with recommendations for singletons. Uncertainties around the benefits and risks of antenatal corticosteroids in twins and triplets should be discussed with women	Antenatal corticosteroid therapy is recommended for women with a high likelihood of preterm birth, irrespective of whether single or multiple birth is anticipated	Administration should be given in twin pregnancies, with the same indication and doses as singletons.	Antenatal corticosteroid therapy should be administered according to the same indication and in the same gestational age range to women with twin or higher-order multifetal pregnancies as for singleton pregnancies.	Use of single course of antenatal corticosteroids for women with a multiple pregnancy at risk of preterm birth.	A single course of corticosteroids is recommended for pregnant women between 24+0 weeks and 33+6 weeks of gestation who are risk of delivery within 7 days, including those with multiple gestations.	For women with multiple pregnancy where active neonatal care is appropriate, for whom preterm birth is anticipated between 24+0 and 34+0 weeks of gestation, prenatal corticosteroids should be offered to improve outcomes for baby,

	RCOG[15] Guideline	WHO[71] Recommendations	EAPM[17] Guidelines	SOCG[54] Guidelines	RANZCOG[62] Guidelines	ACOG[19] Committee Opinion / recommendations	FIGO[18] Good practice recommendations
Women with diabetes mellitus	Diabetes should not be considered an absolute contraindication to antenatal corticosteroids for fetal lung maturation. In women with diabetes who are receiving corticosteroids, additional insulin should be given according to an agreed protocol and close monitoring should be undertaken.	Antenatal corticosteroid therapy is recommended for women with pre-gestational and gestational diabetes when there is a high likelihood of preterm birth, and this should be accompanied by interventions to optimise maternal blood glucose levels.	**N/A**	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. Close attention should be paid to control of maternal blood glucose among women with diabetes in the days following administration.	Use a single course of antenatal corticosteroids for women with diabetes in pregnancy or gestational diabetes at risk for preterm birth, Women will require blood glucose monitoring and management of any hyperglycaemia.	**N/A**	**N/A**

	RCOG[15] Guideline	WHO[71] Recommendations	EAPM[17] Guidelines	SOCG[54] Guidelines	RANZCOG[62] Guidelines	ACOG[19] Committee Opinion / recommendations	FIGO[18] Good practice recommendations
Chorio-amnionitis	Not specifically addressed Future research section: The safety and effectiveness of steroids in multiple pregnancy, women with diabetes and in women with chorioamnionitis requires further investigation.	Antenatal corticosteroid therapy is not recommended for women with chorioamnionitis who are likely to give birth preterm. What is the overall certainty of the evidence on effects of antenatal corticosteroids, considering presence of chorioamnionitis? Rated: very low It was not possible to use trial evidence to assess the effects of antenatal corticosteroids in women with chorioamnionitis, as the 2020 Cochrane review on antenatal corticosteroid efficacy did not conduct a subgroup analysis in women with and without chorioamnionitis. Any such subgroup analysis is unlikely to be informative, as chorioamnionitis was generally an exclusion criterion in these trials.	Not specifically addressed	Not specifically addressed	Use a single course of antenatal corticosteroids for women with chorioamnionitis at risk of preterm birth. Do not delay birth in women with chorioamnionitis to administer a single course of antenatal corticosteroids. Where appropriate, monitor women with chorioamnionitis for signs of puerperal sepsis when antenatal corticosteroids have been given. Strength of Recommendation: Weak - Practice point (PP) Lowest grade of recommendation	Late preterm administration of ACS is not indicated in women diagnosed with clinical chorioamnionitis. No grade of evidence given.	Not specifically addressed

Appendix 4: Search Strategy and Terms

National HSE Antenatal Corticosteroids – Search Strategy

Literature search carried out by Alana Dineen

Start date: January 2008

End date: January 2023

ECRI Trust (https://guidelines.ecri.org/)

Date: 30 March 2023

Search terms: steroid, steroids, corticosteroid, corticosteroids, glucocorticoid, glucocorticoids, adrenal cortex hormones, foetal lung maturation, fetal lung maturation

0 results

No longer available when reviewed 30 March 2023

NICE Evidence Search (http://www.evidence.nhs.uk/)

0 results

RCOG website (http://www.rcog.org.uk/)

Green-Top Guideline No. 74: Antenatal corticosteroids to reduce neonatal morbidity and mortality

Cited as: Stock SJ, Thomson AJ, Papworth S; the Royal College of Obstetricians, Gynaecologists. Antenatal corticosteroids to reduce neonatal morbidity and mortality. BJOG 2022;

Date: 30 March 2023

Search terms: steroid, steroids, corticosteroid, corticosteroids, glucocorticoid, glucocorticoids, adrenal cortex hormones, foetal lung maturation, fetal lung maturation

1 result

NICE website (https://www.nice.org.uk/guidance)

NICE guideline [NG25] Preterm labour and birth

Section 1.9 Maternal corticosteroids

Last updated 10 June 2022

Date: 31 March 2023

Search terms: steroid, steroids, corticosteroid, corticosteroids, glucocorticoid, glucocorticoids, adrenal cortex hormones, foetal lung maturation, fetal lung maturation

1 result

RANZCOG website (https://ranzcog.edu.au/womens-health/)

'Women's Health'

Antenatal Corticosteroids Given to Women Prior to Birth to Improve Fetal, Infant, Child and Adult Health

Citation: 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.

Date: 31 March 2023

Search terms: steroid, steroids, corticosteroid, corticosteroids, glucocorticoid, glucocorticoids, adrenal cortex hormones, foetal lung maturation, fetal lung maturation corticosteroids, steroids, glucocorticoids, foetal lung maturation

1 result

FIGO website (https://www.figo.org/)

FIGO good practice recommendations on the use of prenatal corticosteroids to improve outcomes and minimise harm in babies born preterm

Citation: Norman J, Shennan A, Jacobsson B, Stock SJ; on behalf of the FIGO Working Group for Preterm Birth. FIGO good practice recommendations on the use of prenatal corticosteroids to improve outcomes and minimise harm in babies born preterm. *Int J Gynecol Obstet*. 2021;155:

26-30. https://doi.org/10.1002/ijgo.13836

Date: 31 March 2023

Search terms: steroid, steroids, corticosteroid, corticosteroids, glucocorticoid, glucocorticoids, adrenal cortex hormones, foetal lung maturation, fetal lung maturation

1 result

SOGC website (https://sogc.org/)

User Login required

No.364 – Antenatal Corticosteroid Therapy for Improving Neonatal Outcomes. No. 364, September 2018 (Replaces No.122, January 2003)

Citation: J Obstet Gynaecol Can 2018;40(9):1219-1239 https://doi.org/10.1016/j.jogc.2018.04.018

Date: 31 March 2023

Search terms: steroid, steroids, corticosteroid, corticosteroids, glucocorticoid, glucocorticoids, adrenal cortex hormones, foetal lung maturation, fetal lung maturation

1 result

SMFM website (https://www.smfm.org/)

SMFM Consult Series #58: Use of antenatal corticosteroids for individuals at risk for late preterm delivery

Date: 31 March 2023

Search terms: steroid, steroids, corticosteroid, corticosteroids, glucocorticoid, glucocorticoids, adrenal cortex hormones, foetal lung maturation, fetal lung maturation

1 result

ACOG website (https://www.acog.org/)

ACOG Committee Opinion Number 713, August 2017. Reaffirmed 2020. Volume 130, No.2. This update replaces Committee Opinion No.677, October 2016.

Antenatal Corticosteroid Therapy for Fetal Maturation.

Date: 31 March 2023

Search terms: steroid, steroids, corticosteroid, corticosteroids, glucocorticoid, glucocorticoids, adrenal cortex hormones, foetal lung maturation, fetal lung maturation

1 result

Trip (http://www.tripdatabase.com/)

Date: 30 March 2023

The furthest refinement of year from the Trip Database was 2014.

Search terms:

1. foetal lung maturation or fetal lung maturation (1896)
2. pregnancy or obstetrics or antenatal or prenatal or fetus or foetus or fetal or foetal (390392)
3. adrenal cortex hormones (1128)
4. corticosteroids or glucocorticoids (88088)
5. #1 and #2 and #3 and #4 (68456)
6. limited to guidelines (1415)
7. limited to 'OB-GYN' order by relevance (131)
8. limit to 'since 2014' (120)

Amended 'clinical area' search

1. foetal lung maturation or fetal lung maturation (1896)
2. pregnancy or obstetrics or antenatal or prenatal or fetus or foetus or fetal or foetal (390392)
3. adrenal cortex hormones (1128)
4. corticosteroids or glucocorticoids (88088)
5. #1 and #2 and #3 and #4 (68456)
6. limited to guidelines (1415)
7. **limited to 'Women's Health' order by relevance (122)**
8. **limit to 'since 2014' (116)**

Amended 'clinical area' search

1. foetal lung maturation or fetal lung maturation (1896)
2. pregnancy or obstetrics or antenatal or prenatal or fetus or foetus or fetal or foetal (390392)
3. adrenal cortex hormones (1128)
4. corticosteroids or glucocorticoids (88088)
5. #1 and #2 and #3 and #4 (68456)
6. limited to guidelines (1415)
7. **limited to 'Pediatrics' order by relevance (215)**
8. **limit to 'since 2014' (190)**

Guidelines International Network (https://guidelines.ebmportal.com/)

Date: 30 March 2023

Search terms: steroid, steroids, corticosteroid, corticosteroids, glucocorticoid, glucocorticoids, adrenal cortex hormones, foetal lung maturation, fetal lung maturation

0 results

Medline (OVID)

Date: 30 March 2023

Database: Ovid MEDLINE(R) < 2008 to 2023>

Search Strategy:

Multi-Field Search > All fields = *Abstract, Abstract Label, Anatomy Supplementary Concept, Anatomy Supplementary Concept Word, Article Identifier, Author Last Name, Author NameID, Authors, Authors Full Name, Beginning Date, Book Accession, Book Authors, Book Authors Full Name, Book Edition, Book Editors, Book Part, Book Title, Book Volume, Cited Reference DOI, Cited Reference Date, Cited Reference Issue, Cited Reference PMCID, Cited Reference Page, Cited Reference Publisher Identifer, Cited Reference Source, Cited Reference UI, Cited Reference Volume, Collection Title, Comments, Conflict of Interest, Contribution Date, Copyright Index, Corporate Author, Country of Publication, Create Date, Date of Publication, Digital Object Identifier, Editor Last Name, Editors, Editors Full Name, Electronic Date of Publication, Ending Date, Entrez Date, Entry Date, Equal Contributor, Exploded Sub-Heading, Floating Sub-Heading, Floating Sub-Heading Word, Gene Symbol, Gene Symbol Word, General Note, Grant Acronym, Grant Country, Grant Information, Grant Number, Grant Organisation, ISBN, ISO Journal Abbreviation, ISSN Linking, ISSN Print, Indexing Method, Institution, Investigator, Investigator Affiliation, Investigator NameID, Issue/Part, Journal Abbreviation, Journal Name, Journel Subset, Journal Word, Keyword Heading, Keyword Heading Owner, Keyword Heading Word, Language, MeSH Date, MeSH Subject Heading, Media Type, NLM Category, NLM Journal Code, NLM Journal Name, NLM Journal Word, Name of Substance Word, Object ID, Organism Supplementary Concept, Organism Supplementary Concept Word, Primary Author, Protocol Supplementary Concept, Protocol Supplementary Concept Word, Pubmed Central Release, Publication History Status, Publication Status, Publication Type, Publisher Item Identifier, Rare Disease Supplementary Concept, Rare Disease Supplementary Concept Word, Record Owner, Reference Title Index, Registry Number/Name of Substance, Report Number, Revision Date, Season, Secondary Source AN, Secondary Source ID, Secondary Source Link, Section, Space Flight Mission, Status, Subject Heading Word, Synonyms, Text Word, Title, Title Comment, Unique Identifier, Update Date, Version Date, Version ID, Volume, Volume Book Title, Year of Publication*

1. All fields: adrenal cortex hormone* or glucocorticoid* or corticosteroid* (266006)
2. All fields: pregnancy or obstetrics or antenatal or prenatal or fetus or foetus or fetal or foetal (1563543)
3. All fields: fetal lung maturation or foetal lung maturation (690)
3. #1 and #2 and #3 (338)
4. limit #3 to ‘English language’ (312)
5. limit #4 to ‘Humans’ (179)
6. limit #5 to ‘Publication Year’ 2008- 2023 (90)

Embase (OVID)

Date: 30 March 2023

Database: Embase <2008 to 2023>

Search Strategy:

Multi-Field Search > All fields = *Abstract, Accession Number, Article Number, Associated PUI, Author NameID, Author, Author Email, Book Series, Book Title, CAS Registry Numbers, CODEN, Candidate Term Word, Candidate Terms, Clinical Trial Number, Collaboration, Conference Editor, Conference End Date, Conference Information, Conference Location, Conference Name, Conference Paper Count, Conference Publication, Conference Start Date, Contributors, Copyright, Correspondence Address, Country of Publication, Date Created, Date Delivered, Date of Publication, Digital Object Identifier, Device Index Terms, Device Index Terms Word, Device Manufacturer, Device Trade Name, Drug Index Terms, Drug Index Terms Word, Drug Manufacturer, Editors, Electronic ISSN, Embase Accession Number, Embase Section Headins, Entry Week, Enzyme Commission Numbers, Figure Information, Floating Subheading, Floating Subheading Word, Grant Acronym, Grant Country, Grant Abstract, Grant Number, Grant Organisation, Grant Organisation Number, Heading Word, ISBN, ISSN, Indexing Status, Institution, Journal Abbreviation, Journal Name, Journal Word, Journal Issue, Journal Translated Name,*

Keyword Heading, Keyword Heading Word, Language, Molecular Sequence Number, NLM Status, Number of References, Original Title, Other Index Terms Word, PMID, Page, Parent Book Title, Part Number, Preferred Journal Name, Publication Type, Publisher, Publisher Copyright, Related Accession Number, Related Article Number, Related Book Series, Related Book Title, Related Conference Information, Related Date of Publication, Related Figure Information, Related Issue Part, Related Item CODEN, Related Item Contributor, Related Item Country, Related Item DOI, Related Item Editor, Related Item ISBN, Related Item ISSN, Related Item Publisher, Related Item Title, Related Item URL, Related Journal Name, Related Page, Related Part Number, Related Publication Type, Related Publisher Identifier, Related Source Type, Related Volume, Related Volume Title, Related Year, Revised Date, Source Type, Status, Subject Headings, Summary Language, Text Word, Title, Triple Subheading, Triple Subheading Word, URL, Volume, Year of Publication, arXiv Identifier

Multi-field Search

1. All fields: adrenal cortex hormone* or glucocorticoid* or corticosteroid* (515358)
2. All fields: pregnancy or obstetrics or antenatal or prenatal or fetus or foetus or fetal or foetal (1762097)
3. All fields: foetal lung maturation or fetal lung maturation (1015)
4. #1 and #2 and #3 (502)
5. limit #4 to ‘English language’ (448)
6. limit #5 to *Subject*: ‘Humans’ (267)
7. limit #6 to ‘Publication Year’ 2008- 2023 (182)

Pubmed

Date: 31 March 2023

Database: Pubmed <01 Jan 2008 to 01 Jan 2023>

Search Strategy:

1. All fields: adrenal cortex hormone*or glucocorticoid* or corticosteroid* (124747)
2. All fields: pregnancy or obstetrics or antenatal or prenatal or fetus or foetus or fetal or foetal (1565630)
3. #1 and #2 (8730)
4. All fields: foetal lung maturation or fetal lung maturation (4580)
5. #3 and #4 (522)
6. limit 5 to *Species*: 'humans' (315)
7. limit 6 to *Article Language*: 'English' (274)
8. limit 7 to Publication Date: 'Custom Range' > 'Start Date' 01-01-2008 – 01-01-2023 (121)

Web of Science

Date: 30 March 2023

Database: Web of Science <2008 to 2022>

1. All fields: adrenal cortex hormone* or glucocorticoid*or corticosteroid*(211993)
2. All fields: pregnancy or obstetrics or antenatal or prenatal or fetus or foetus or fetal or foetal (1361469)
3. #1 and #2 (14795)
4. All fields: foetal lung maturation or fetal lung maturation (2445)
5. #3 and #4 (711)
6. limit 5 to *Languages:* 'English' (693)
7. limit 6 to *Web of Science Categories:* 'obstetrics gynaecology' and 'pediatrics' (338)
8. limit 7 to *Citation Topics Micro*: '1.72.924 preterm labour' and '1.72.748 Preterm Infants' (166)
9. limit 8 to *Publication Years*: '2008-2023' (86)

Cochrane Library		
Date: 31 March 2023 Date Run: 31/03/2023 10:50		
ID	**Search**	**Hits**
#1	MeSH descriptor: [“adrenal cortex hormones “] explode all trees	16845
#2	MeSH descriptor: [glucocorticoids] explode all trees	5314
#3	MeSH descriptor: [hydrocortisone] explode all trees	6728
#4	(foetal lung maturation or fetal lung maturation)	132
#5	{or #1-#4}	376
#6	(pregnan* or obstet* or antenatal* or ante natal* or prenatal* or pre-natal* or maternal* or mother* or fetus or foetus or fetal or foetal)	127606
#7	{#5 and #6}	302
#8	#7 with Cochrane Library publication date Between Jan 2008 and Jan 2023	256
#9	Limit ‘Topics’ to ‘Pregnancy and Childbirth’	57

Appendix 5: AGREE II Checklist[18]

AGREE Reporting Checklist 2016

This checklist is intended to guide the reporting of Clinical Practice Guidelines.

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	Page #
DOMAIN 1: SCOPE AND PURPOSE		
1. OBJECTIVES *Report the overall objective(s) of the guideline. The expected health benefits from the guideline are to be specific to the clinical problem or health topic.*	☐ Health intent(s) (i.e., prevention, screening, diagnosis, treatment, etc.) ☐ Expected benefit(s) or outcome(s) ☐ Target(s) (e.g., patient population, society)	
2. QUESTIONS *Report the health question(s) covered by the guideline, particularly for the key recommendations.*	☐ Target population ☐ Intervention(s) or exposure(s) ☐ Comparisons (if appropriate) ☐ Outcome(s) ☐ Health care setting or context	
3. POPULATION *Describe the population (i.e., patients, public, etc.) to whom the guideline is meant to apply.*	☐ Target population, sex and age ☐ Clinical condition (if relevant) ☐ Severity/stage of disease (if relevant) ☐ Comorbidities (if relevant) ☐ Excluded populations (if relevant)	
DOMAIN 2: STAKEHOLDER INVOLVEMENT		
4. GROUP MEMBERSHIP *Report all individuals who were involved in the development process. This may include members of the steering group, the research team involved in selecting and reviewing/ rating the evidence and individuals involved in formulating the final recommendations.*	☐ Name of participant ☐ Discipline/content expertise (e.g., neurosurgeon, methodologist) ☐ Institution (e.g., St. Peter's hospital) ☐ Geographical location (e.g., Seattle, WA) ☐ A description of the member's role in the guideline development group	

18 AGREE Reporting Checklist is available on the AGREE Enterprise website, a free and open access resource to support the practice guideline field (www. agreetrust.org).

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	Page #
5. TARGET POPULATION PREFERENCES AND VIEWS *Report how the views and preferences of the target population were sought/considered and what the resulting outcomes were.*	☐ Statement of type of strategy used to capture patients'/publics' views and preferences (e.g., participation in the guideline development group, literature review of values and preferences) ☐ Methods by which preferences and views were sought (e.g., evidence from literature, surveys, focus groups) ☐ Outcomes/information gathered on patient/public information ☐ How the information gathered was used to inform the guideline development process and/or formation of the recommendations	
6. TARGET USERS *Report the target (or intended) users of the guideline.*	☐ The intended guideline audience (e.g. specialists, family physicians, patients, clinical or institutional leaders/administrators) ☐ How the guideline may be used by its target audience (e.g., to inform clinical decisions, to inform policy, to inform standards of care)	
DOMAIN 3: RIGOUR OF DEVELOPMENT		
7. SEARCH METHODS *Report details of the strategy used to search for evidence.*	☐ Named electronic database(s) or evidence source(s) where the search was performed (e.g., MEDLINE, EMBASE, PsychINFO, CINAHL) ☐ Time periods searched (e.g., January 1, 2004 to March 31, 2008) ☐ Search terms used (e.g., text words, indexing terms, subheadings) ☐ Full search strategy included (e.g., possibly located in appendix)	
8. EVIDENCE SELECTION CRITERIA *Report the criteria used to select (i.e., include and exclude) the evidence. Provide rationale, where appropriate.*	☐ Target population (patient, public, etc.) characteristics ☐ Study design ☐ Comparisons (if relevant) ☐ Outcomes ☐ Language (if relevant) ☐ Context (if relevant)	

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	Page #
9. STRENGTHS & LIMITATIONS OF THE EVIDENCE *Describe the strengths and limitations of the evidence. Consider from the perspective of the individual studies and the body of evidence aggregated across all the studies. Tools exist that can facilitate the reporting of this concept.*	☐ Study design(s) included in body of evidence ☐ Study methodology limitations (sampling, blinding, allocation concealment, analytical methods) ☐ Appropriateness/relevance of primary and secondary outcomes considered ☐ Consistency of results across studies ☐ Direction of results across studies ☐ Magnitude of benefit versus magnitude of harm ☐ Applicability to practice context	
10. FORMULATION OF RECOMMENDATIONS *Describe the methods used to formulate the recommendations and how final decisions were reached. Specify any areas of disagreement and the methods used to resolve them.*	☐ Recommendation development process (e.g., steps used in modified Delphi technique, voting procedures that were considered) ☐ Outcomes of the recommendation development process (e.g., extent to which consensus was reached using modified Delphi technique, outcome of voting procedures) ☐ How the process influenced the recommendations (e.g., results of Delphi technique influence final recommendation, alignment with recommendations and the final vote)	
11. CONSIDERATION OF BENEFITS AND HARMS *Report the health benefits, side effects, and risks that were considered when formulating the recommendations.*	☐ Supporting data and report of benefits ☐ Supporting data and report of harms/side effects/risks ☐ Reporting of the balance/trade-off between benefits and harms/side effects/risks ☐ Recommendations reflect considerations of both benefits and harms/side effects/risks	
12. LINK BETWEEN RECOMMENDATIONS AND EVIDENCE *Describe the explicit link between the recommendations and the evidence on which they are based.*	☐ How the guideline development group linked and used the evidence to inform recommendations ☐ Link between each recommendation and key evidence (text description and/or reference list) ☐ Link between recommendations and evidence summaries and/or evidence tables in the results section of the guideline	

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	Page #
13. EXTERNAL REVIEW *Report the methodology used to conduct the external review.*	☐ Purpose and intent of the external review (e.g., to improve quality, gather feedback on draft recommendations, assess applicability and feasibility, disseminate evidence) ☐ Methods taken to undertake the external review (e.g., rating scale, open-ended questions) ☐ Description of the external reviewers (e.g., number, type of reviewers, affiliations) ☐ Outcomes/information gathered from the external review (e.g., summary of key findings) ☐ How the information gathered was used to inform the guideline development process and/or formation of the recommendations (e.g., guideline panel considered results of review in forming final recommendations)	
14. UPDATING PROCEDURE *Describe the procedure for updating the guideline.*	☐ A statement that the guideline will be updated ☐ Explicit time interval or explicit criteria to guide decisions about when an update will occur ☐ Methodology for the updating procedure	
DOMAIN 4: CLARITY OF PRESENTATION		
15. SPECIFIC AND UNAMBIGUOUS RECOMMENDATIONS *Describe which options are appropriate in which situations and in which population groups, as informed by the body of evidence.*	☐ A statement of the recommended action ☐ Intent or purpose of the recommended action (e.g., to improve quality of life, to decrease side effects) ☐ Relevant population (e.g., patients, public) ☐ Caveats or qualifying statements, if relevant (e.g., patients or conditions for whom the recommendations would not apply) ☐ If there is uncertainty about the best care option(s), the uncertainty should be stated in the guideline	
16. MANAGEMENT OPTIONS *Describe the different options for managing the condition or health issue.*	☐ Description of management options ☐ Population or clinical situation most appropriate to each option	

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	Page #
17. IDENTIFIABLE KEY RECOMMENDATIONS *Present the key recommendations so that they are easy to identify.*	☐ Recommendations in a summarized box, typed in bold, underlined, or presented as flow charts or algorithms ☐ Specific recommendations grouped together in one section	
DOMAIN 5: APPLICABILITY		
18. FACILITATORS AND BARRIERS TO APPLICATION *Describe the facilitators and barriers to the guideline's application.*	☐ Types of facilitators and barriers that were considered ☐ Methods by which information regarding the facilitators and barriers to implementing recommendations were sought (e.g., feedback from key stakeholders, pilot testing of guidelines before widespread implementation) ☐ Information/description of the types of facilitators and barriers that emerged from the inquiry (e.g., practitioners have the skills to deliver the recommended care, sufficient equipment is not available to ensure all eligible members of the population receive mammography) ☐ How the information influenced the guideline development process and/or formation of the recommendations	
19. IMPLEMENTATION ADVICE/TOOLS *Provide advice and/or tools on how the recommendations can be applied in practice.*	☐ Additional materials to support the implementation of the guideline in practice. For example: • Guideline summary documents • Links to check lists, algorithms • Links to how-to manuals • Solutions linked to barrier analysis (see Item 18) • Tools to capitalize on guideline facilitators (see Item 18) • Outcome of pilot test and lessons learned	

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	Page #
20. RESOURCE IMPLICATIONS *Describe any potential resource implications of applying the recommendations.*	☐ Types of cost information that were considered (e.g., economic evaluations, drug acquisition costs) ☐ Methods by which the cost information was sought (e.g., a health economist was part of the guideline development panel, use of health technology assessments for specific drugs, etc.) ☐ Information/description of the cost information that emerged from the inquiry (e.g., specific drug acquisition costs per treatment course) ☐ How the information gathered was used to inform the guideline development process and/or formation of the recommendations	
21. MONITORING/ AUDITING CRITERIA *Provide monitoring and/or auditing criteria to measure the application of guideline recommendations.*	☐ Criteria to assess guideline implementation or adherence to recommendations ☐ Criteria for assessing impact of implementing the recommendations ☐ Advice on the frequency and interval of measurement ☐ Operational definitions of how the criteria should be measured	
DOMAIN 6: EDITORIAL INDEPENDENCE		
22. FUNDING BODY *Report the funding body's influence on the content of the guideline.*	☐ The name of the funding body or source of funding (or explicit statement of no funding) ☐ A statement that the funding body did not influence the content of the guideline	
23. COMPETING INTERESTS *Provide an explicit statement that all group members have declared whether they have any competing interests.*	☐ Types of competing interests considered ☐ Methods by which potential competing interests were sought ☐ A description of the competing interests ☐ How the competing interests influenced the guideline process and development of recommendations	

From: Brouwers MC, Kerkvliet K, Spithoff K, on behalf of the AGREE Next Steps Consortium. The AGREE Reporting Checklist: a tool to improve reporting of clinical practice guidelines. BMJ 2016;352:i1152. doi: 10.1136/bmj.i1152.

For more information about the AGREE Reporting Checklist, please visit the AGREE Enterprise website at http://www.agreetrust.org.

Appendix 6: Grades of Recommendations[19]

Grade of recommendation	Clarity of risk/ benefit	Quality of supporting evidence	Implications	Suggested Language
1 A. Strong recommendation, high-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Consistent evidence from well-performed randomised, controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk	Strong recommendations can apply to most patients in most circumstances without reservation. Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present	We strongly recommend… We recommend that …should be performed/ administered… We recommend that … is indicated/ beneficial/ effective….
1 B. Strong recommendation, moderate-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Evidence from randomised, controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence of some other research design. Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate	Strong recommendation and applies to most patients. Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present	We recommend… We recommend that … should be performed/ administered… We recommend that … is (usually) indicated/ beneficial/ effective…

19 SMFM adopts GRADE (Grading of Recommendations Assessment, Development, and Evaluation) for clinical guidelines. Society for Maternal-Fetal Medicine (SMFM), Chauhan SP, Blackwell SC. Am J Obstet Gynecol. 2013 Sep;209(3):163-5. https://pubmed.ncbi.nlm.nih.gov/23978245/

Grade of recommendation	Clarity of risk/ benefit	Quality of supporting evidence	Implications	Suggested Language
1 C. Strong recommendation, low-quality evidence	Benefits appear to outweigh risk and burdens, or vice versa	Evidence from observational studies, unsystematic clinical experience, or from randomised, controlled trials with serious flaws. Any estimate of effect is uncertain	Strong recommendation that applies to most patients. Some of the evidence base supporting the recommendation is, however, of low quality	We recommend… We recommend that … should be performed/ administered… We recommend that … Is (maybe) indicated/ beneficial/ effective…
2A. Weak recommendation, high-quality evidence	Benefits closely balanced with risks and burdens	Consistent evidence from well-performed randomised, controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk	Weak recommendation: best action may differ depending on circumstances or patients or societal values	We suggest… We suggest that … may/might be reasonable…
2B. Weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burdens, some uncertainty in the estimates of benefits, risks and burdens	Evidence from randomised, controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence of some other research design. Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate	Weak recommendation; alternative approaches likely to be better for some patients under some circumstances	We suggest… We suggest that … may/might be reasonable…

Grade of recommendation	Clarity of risk/ benefit	Quality of supporting evidence	Implications	Suggested Language
2C. Weak recommendation, low-quality evidence	Uncertainty in the estimates of benefits, risks, and burdens; benefits may be closely balanced with risks and burdens	Evidence from observational studies, unsystematic clinical experience, or from randomised, controlled trials with serious flaws. Any estimate of effect is uncertain	Very weak recommendation: other alternatives may be equally reasonable.	We suggest… is an option We suggest that … may/might be reasonable.
Best practice	A recommendation that is sufficiently obvious that the desirable effects outweigh undesirable effects, despite the absence of direct evidence, such that the grading of evidence is unnecessary			We recommend… We recommend that … should be performed/ administered… We recommend that … Is usually) indicated/ beneficial/effective

Appendix 7: Policies, Procedures, Protocols and Guidelines Checklist

The PPPG Checklists were developed to assist staff to meet standards when developing Clinical PPPGs.

Standards for developing clinical PPPG	
Stage 1 initiation	**Checklist**
The decision making approach relating to the type of PPPG guidance required (policy, procedure, protocol, guideline), coverage of the PPPG (national, regional, local) and applicable settings are described.	☐
Synergies/co-operations are maximised across departments/organisations (Hospitals/ Hospital Groups/Community Healthcare Organisations (CHO)/National Ambulance Service (NAS)), to avoid duplication and to optimise value for money and use of staff time and expertise.	☐
The scope of the PPPG is clearly described, specifying what is included and what lies outside the scope of the PPPG.	☐
The target users and the population/patient group to whom the PPPG is meant to apply are specifically described.	☐
The views and preferences of the target population have been sought and taken into consideration (as required).	☐
The overall objective(s) of the PPPGs are specifically described.	☐
The potential for improved health is described (e.g. clinical effectiveness, patient safety, quality improvement, health outcomes, quality of life, quality of care).	☐
Stakeholder identification and involvement: The PPPG Development Group includes individuals from all relevant stakeholders, staff and professional groups.	☐
Conflict of interest statements from all members of the PPPG Development Group are documented, with a description of mitigating actions if relevant.	☐
The PPPG is informed by the identified needs and priorities of service users and stakeholders.	☐
There is service user/lay representation on PPPG Development Group (as required).	☐
Information and support is available for staff on the development of evidence-based clinical practice guidance.	☐

Stage 2 development	**Checklist**
The clinical question(s) covered by the PPPG are specifically described.	☐
Systematic methods used to search for evidence are documented (for PPPGs which are adapted/ adopted from international guidance, their methodology is appraised and documented).	☐
Critical appraisal/analysis of evidence using validated tools is documented (the strengths, limitations and methodological quality of the body of evidence are clearly described).	☐
The health benefits, side effects and risks have been considered and documented in formulating the PPPG.	☐
There is an explicit link between the PPPG and the supporting evidence.	☐
PPPG guidance/recommendations are specific and unambiguous.	☐
The potential resource implications of developing and implementing the PPPG are Identified e.g. equipment, education/training, staff time and research.	☐
There is collaboration across all stakeholders in the planning and implementation phases to optimise patient flow and integrated care.	☐
Budget impact is documented (resources required).	☐
Education and training is provided for staff on the development and implementation of evidence- based clinical practice guidance (as appropriate).	☐
Three additional standards are applicable for a small number of more complex PPPGs:	☐
Cost effectiveness analysis is documented.	☐
A systematic literature review has been undertaken.	☐
Health Technology Assessment (HTA) has been undertaken.	☐
Stage 3 governance and approval	**Checklist**
Formal governance arrangements for PPPGs at local, regional and national level are established and documented.	☐
The PPPG has been reviewed by independent experts prior to publication (as required).	☐
Copyright and permissions are sought and documented.	☐
Stage 4 communication and dissemination	**Checklist**
A communication plan is developed to ensure effective communication and collaboration with all stakeholders throughout all stages.	☐
Plan and procedure for dissemination of the PPPG is described.	☐
The PPPG is easily accessible by all users e.g. PPPG repository.	☐

Stage 5 implementation	**Checklist**
Written implementation plan is provided with timelines, identification of responsible persons/ units and integration into service planning process.	☐
Barriers and facilitators for implementation are identified, and aligned with implementation levers.	☐
Education and training is provided for staff on the development and implementation of evidence- based PPPG (as required).	☐
There is collaboration across all stakeholders in the planning and implementation phases to optimise patient flow and integrated care.	☐
Stage 6 monitoring, audit, evaluation	**Checklist**
Process for monitoring and continuous improvement is documented.	☐
Audit criteria and audit process/plan are specified.	☐
Process for evaluation of implementation and (clinical) effectiveness is specified.	☐
Stage 7 revision/update	**Checklist**
Documented process for revisions/updating and review, including timeframe is provided.	☐
Documented process for version control is provided.	☐

To view in full refer to website: https://www.hse.ie/eng/about/who/qid/nationalframeworkdevelopingpolicies/

Appendix 8: **NWIHP/IOG CAG (2023-)**

Dr Cliona Murphy (Chair, 2023-). Consultant Obstetrician and Gynaecologist, Coombe Women and Infants University Hospital. Clinical Director, National Women and Infants Health Programme.

Dr Sam Coulter-Smith (2023-). Consultant Obstetrician and Gynaecologist, Rotunda Hospital. Chair, Institute of Obstetricians and Gynaecologists.

Dr Venita Broderick (2024-). Clinical Lead Gynaecology, National Women and Infants Health Programme.

Dr Brian Cleary (2023-). Chief Pharmacist, Rotunda Hospital. Medications Lead, Maternal and Newborn Clinical Management System Project.

Angela Dunne (2023-). Director of Midwifery, National Women and Infants Health Programme.

Prof. Seán Daly (2023-). Master, Consultant Obstetrician and Gynaecologist, Rotunda Hospital.

Prof. Maeve Eogan (2023-). Consultant Obstetrician and Gynaecologist, Rotunda Hospital. Clinical Lead, Sexual Assault Treatment Units, National Women and Infants Health Programme.

Prof. Richard Greene (2023-). Consultant Obstetrician and Gynaecologist, Cork University Maternity Hospital. Clinical Director, National Perinatal Epidemiology Centre, University College Cork.

Prof. John Higgins (2023-). Cork University Maternity Hospital, Consultant Obstetrician and Gynaecologist, Clinical Director, Ireland South Women and Infants Directorate.

Prof. Shane Higgins (2023-). Master, Consultant Obstetrician and Gynaecologist, National Maternity Hospital.

Dr Mendinaro Imcha (2023-). Clinical Director, Consultant Obstetrician and Gynaecologist, University Maternity Hospital Limerick.

Prof. John Murphy (2023-). Clinical Lead Neonatology, National Women and Infants Health Programme.

Dr Aoife Mullaly (2023-). Consultant Obstetrician and Gynaecologist, Coombe Women and Infants University Hospital. Clinical Lead, Termination of Pregnancy Services, National Women and Infants Health Programme.

Prof. John Morrison (2023-). Consultant Obstetrician and Gynaecologist, University Hospital Galway. Clinical Director, Saolta Maternity Directorate.

Kilian McGrane (2023-). Director, National Women and Infants Health Programme.

Dr Peter McKenna (2023-). Clinical Lead, Obstetric Event Support Team, National Women and Infants Health Programme.

Prof. Keelin O'Donoghue (2023-). Consultant Obstetrician and Gynaecologist, Cork University Maternity Hospital. Clinical Lead, National Guidelines, National Women and Infants Health Programme.

Dr Suzanne O'Sullivan (2023-). Consultant Obstetrician and Gynaecologist, Cork University Maternity Hospital. Director of Education and Training, Obstetrics and Gynaecology, Institute of Obstetricians and Gynaecologists.

Prof. Mike O'Connell (2023-). Master, Consultant Obstetrician and Gynaecologist, Coombe Women and Infants University Hospital.

Dr Vicky O'Dwyer (2023-). Consultant Obstetrician and Director of Gynaecology, Rotunda Hospital.

Prof. Nóirín Russell (2023-). Consultant Obstetrician and Gynaecologist, Cork University Maternity Hospital. Clinical Director, Cervical Check.

Dr Orla Shiel (2024-). Consultant Obstetrician and Gynaecologist, National Maternity Hospital

Ms Clare Thompson (2023-). Consultant Gynaecological Oncologist, The Mater, Dublin.

Prof. Mary Wingfield (2024-). Clinical Lead Fertility, National Women and Infants Health Programme.

Appendix 9: Patient Information Leaflet

Corticosteroids in Pregnancy to Improve Preterm Birth Outcomes – Patient Information Leaflet

Who is this information for?

Corticosteroids may be recommended for you by your doctor if there is a possibility that your baby could be born early. This information leaflet aims to answer some questions you may have.

What are corticosteroids?

Corticosteroids, or steroids, are a medication that may be offered to you to benefit your baby if there is a chance that your baby may be born early.

A single course of corticosteroids consists of two injections given 24 hours apart. Steroid injections are given into a muscle, usually in your thigh or upper arm.

Why have corticosteroids been advised?

Premature babies (born before 35 weeks of pregnancy) may have an increased risk of health problems including breathing problems, which are more serious the earlier the baby is born.

Steroid injections have been given for many years to women who are thought to have a high chance of having their baby early. Steroids help improve a baby's lung development which means they are less likely to have problems with their breathing after they are born.

A single course of steroids has also been shown to reduce the risks of other serious problems in babies that are born early, including bleeding into the brain, bowel inflammation and infection, and developmental delay in childhood. (Developmental delay means that a child might take a bit more time to learn and do things like talking, walking or playing, compared to other children their age.)

Who should be given corticosteroids in pregnancy?

Corticosteroids are recommended as a single course of two injections to women at risk of delivery at, or over, 23 weeks of pregnancy, and before 35 weeks of pregnancy.

This includes:

- If you are in active or suspected premature (also known as preterm) labour
- If your waters have broken early (even if you are not having contractions)
- If it may benefit your baby to be delivered early, e.g. if your baby is not growing well
- If it may benefit you to deliver your baby early, e.g. if you are seriously unwell, are experiencing heavy bleeding or have been diagnosed with severe pre-eclampsia (high blood pressure) in pregnancy.

If your baby is at risk of being born around 23 weeks of pregnancy a senior doctor will discuss the benefits and risks of a course of corticosteroids with you. The evidence that they will be helpful for your baby at this stage of pregnancy is less clear.

What are the potential side effects for my baby and me?

Lots of research has been done around the world to ensure corticosteroids are a safe and beneficial treatment for you and your baby. Your healthcare team will discuss this fully with you.

Research teams continue to study this treatment to ensure safety for mothers and babies. There is no evidence that steroids cause any long-term health problems in either babies or mothers.

Some studies suggest steroids may affect a baby's brain growth and behaviour, but this mostly is in studies where multiple courses of steroids were used and more research is needed to clarify this.

You may experience some short-term side-effects after your injections which could include:

- Soreness at the site of injection
- Flushing of face and chest
- Glucose appearing in your urine for 1-2 days
- Difficulty sleeping at night for 1-2 days
- Some reduction in your baby's movements for around 24 hours.

If you have been diagnosed with gestational diabetes during your pregnancy, or if you have a pre-existing diagnosis of diabetes, your blood sugar levels will be closely monitored by your healthcare team while you are receiving a course of corticosteroids as corticosteroids may increase your blood sugar level. If you are taking insulin, you may require a higher or additional dose following your steroid injection. Your healthcare team will advise you on this.

How long are corticosteroids effective for?

Steroids are of most benefit if the last dose is given to you between 24 hours and 1 week before the birth of your baby. There may still be some benefit even if your baby is born within 24 hours of the first dose.

Can I have more than one course of corticosteroids in this pregnancy?

If you do not give birth in the next 7 days after receiving a single course of steroids, a second dose may be considered by your doctor if your baby is still expected to be born prematurely, but the evidence to support the benefits of a second course is limited. Your doctor will discuss the potential benefits and risks of a second dose of steroids with you based on your individual situation.

When are corticosteroids not necessary?

It is not necessary to receive corticosteroids if you are unlikely to give birth within the next 7 days.

Steroids are not usually given after 35 weeks.

Steroids are no longer considered to be of enough benefit for babies if given after 37 weeks in the case of a planned Caesarean section.

Further Information:

The full guideline link

The Irish Neonatal Health Alliance https://www.inha.ie/