Milton Keynes University Hospital NHS Foundation Trust

Antenatal Corticosteroids to reduce Neonatal Morbidity and Mortality

Classification :	Guideline
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Authors Division:	Women's and Children's Health
Departments/Group this Document applies to:	Maternity

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Guideline to be followed by (target staff): Doctors, Midwives, Nurses and student Midwives

To be read in conjunction with the following documents:

- Multiple pregnancy guideline
- Diabetes guidelines
- Preterm prelabour rupture of membranes guideline
- Caesarean section guideline

Are there any eCARE implications? No

CQC Fundamental standards:
Regulation 9 – person centred care
Regulation 10 – dignity and respect
Regulation 11 – Need for consent
Regulation 12 – Safe care and treatment
Regulation 13 – Safeguarding service users from abuse and improper treatment

Disclaimer

Since every patient's history is different, and even the most exhaustive sources of information cannot cover every possible eventuality, you should be aware that all information is provided in this document on the basis that the healthcare professionals responsible for patient care will retain full and sole responsibility for decisions relating to patient care; the document is intended to supplement, not substitute for, the expertise and judgment of physicians, pharmacists or other healthcare professionals and should not be taken as an indication of suitability of a particular treatment for a particular individual.
The ultimate responsibility for the use of the guideline, dosage of drugs and correct following of instructions as well as the interpretation of the published material **lies solely with you** as the medical practitioner.

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Guideline Statement

The aim of this guideline is to provide up-to-date information on the appropriate use of antenatal corticosteroid therapy in women whose babies are at risk of complications owing to either preterm birth or elective caesarean at term

Executive Summary

- Antenatal steroids are associated with a significant reduction in rates of neonatal death by 31%, RDS (respiratory distress syndrome) by 44% and intraventricular haemorrhage by 46% and are safe for the mother.
- Antenatal corticosteroid use is also associated with a reduction in necrotising enterocolitis, respiratory support, intensive care admissions and systemic infections in the first 48 hours of life compared with no treatment or treatment with placebo.
- Antenatal corticosteroids have no known benefits for the mother.

Definitions

RDS Respiratory Distressed Syndrome
IVH Intraventricular haemorrhage
PVL Periventricular leukomalacia

1.0 Roles and Responsibilities

Doctors – decision making, discussion, planning care

Midwives - discussion, planning midwifery care and administration of steroids

2.0 Implementation and dissemination of document

This guideline is available on the Trust intranet and has followed the full guideline review process prior to publication.

3.0 Processes and Procedures

There is evidence to suggest that antenatal corticosteroids are effective not only in reducing respiratory distress syndrome (RDS) but also in reducing other complications of prematurity such as intraventricular haemorrhage (IVH), neonatal death, necrotising enterocolitis, need for mechanical ventilation and systemic infections in the first 48 hours of life (Devender R et al 2017). Women may be advised that the use of a single course of antenatal corticosteroids does not appear to be associated with any significant short-term maternal or fetal adverse effects.

Antenatal corticosteroids are most effective in reducing RDS in pregnancies that birth 24 hours after and up to 7 days following administration of the second dose of antenatal corticosteroids.

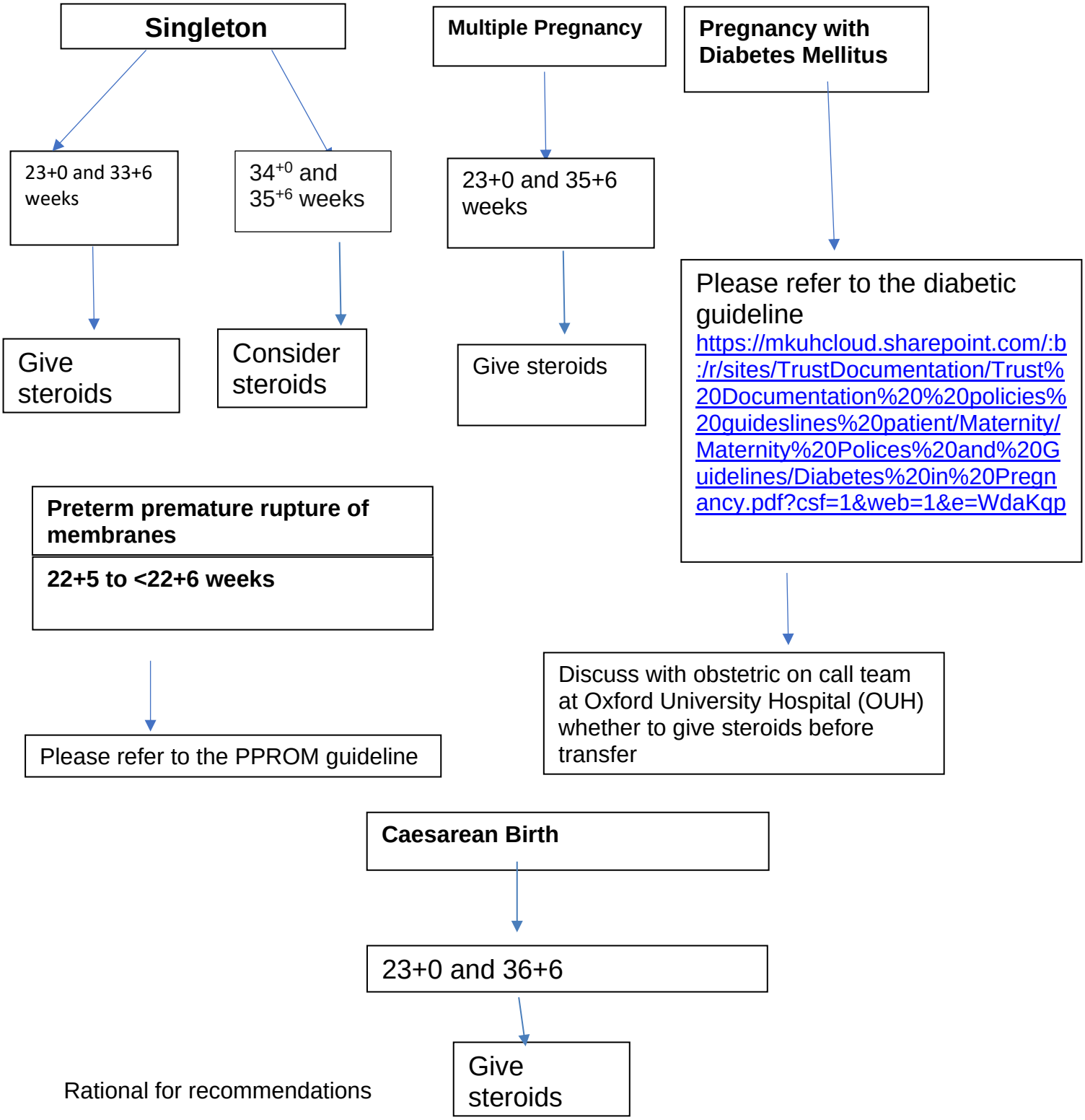
Antenatal corticosteroid use reduces neonatal morbidity and mortality within the first 24 hours of life and therefore should still be given even if birth is expected within this time.

3.1 Drugs and Doses

First line:

Injection **Betamethasone 12 mg IM as 2 doses 12 to 24 hours**

3.2 Women at risk of iatrogenic or spontaneous preterm birth



Rational for recommendations

Singleton Pregnancies

- Antenatal corticosteroids should be given to all women at risk of iatrogenic or spontaneous preterm birth between 23 weeks & 34 weeks of gestation

- Consider maternal corticosteroids for women between 34^{+0} and 35^{+6} weeks of pregnancy who are in suspected, diagnosed or established preterm labour, are having a planned preterm birth or have PPROM. (NICE guidance on ***Preterm labour & birth August 2019)***

- The effect of treatment is optimal if the baby is delivered more than 24 hours after administration of corticosteroids and less than 7 days after the start of treatment

- Corticosteroids should be considered to reduce the risk of respiratory morbidity in all babies delivered by elective caesarean prior to 36+6 weeks of gestation

- The predicted probability of admission to NNU decreases with steroid treatment. At 37 weeks it decreases from 11.4% to 5.2%, at 38 weeks it decreases from 6.2% to 2.8% and at 39 weeks it decreases from 1.5% to 0.6% with antenatal steroid treatment

- When offering or considering maternal corticosteroids, discuss with the woman (and her family members or carer as appropriate): how corticosteroids may help the potential risks associated with them

Multiple Pregnancy

Clinicians should continue to offer a single course of antenatal corticosteroid treatment to women with multiple pregnancy at risk of imminent iatrogenic or spontaneous preterm birth between 23+0 and 35+6 weeks of gestation.
There is little data regarding risks and benefits of antenatal corticosteroids in multiple pregnancies and other high-risk obstetric groups (Roberts et al 2017).

Women at risk of Late Preterm birth (LPT) (34-36+6 weeks' gestation)

Infants who are born at 34 to 36 weeks of gestation (late preterm) are at greater risk for adverse respiratory and other complication than those born at 37 weeks of gestation or later. Administration of steroids to women at risk for late preterm birth significantly reduced the rate of neonatal respiratory complications.

Clinicians should consider offering women who are at risk of imminent iatrogenic or spontaneous late preterm birth (34 to 35+6) a single course of antenatal corticosteroids. Long term safety of antenatal corticosteroids at late preterm or term is still not well known.

Antenatal steroids at ≥34 weeks' gestation reduce neonatal respiratory morbidity. A single course of corticosteroids can be considered for women at risk of imminent late premature delivery 34^{0}-36^{6} weeks' gestation, as well as for women undergoing planned cesarean delivery at ≥37 weeks' gestation (Saccone, G et al 2016).

Gyamfi-Bannerman investigated the role of ACS in the Antenatal Late Preterm Steroids (ALPS) trial, a multicentre randomised trial of 2,800 women at high risk of LPT birth.
Notably, there were no stillbirths or neonatal deaths in the study and the major benefit of ACS derived from a reduction in transient tachypnoea of the newborn and bronchopulmonary dysplasia (0.1% vs. 0.6%) rather than in RDS. The extremely stringent inclusion criteria, with only 11% of screened women eligible to participate, means this evidence may not be easily translatable to

clinical practice. Furthermore, this short-term benefit came at a cost of increased neonatal hypoglycaemia (24% vs. 15%) defined as a glucose level of 40 mg/dl or < 2.2mmol/l, a concern as neonatal hypoglycaemia in an independent risk factor for developmental delay.

Pregnancy with Diabetes Mellitus

Diabetes mellitus is not a contraindication to antenatal corticosteroid treatment for fetal lung maturation.

Women with impaired glucose tolerance or diabetes who receive steroids should be closely monitored and additional insulin given according to an agreed protocol and monitoring (please refer to the Diabetes in Pregnancy guideline).

There is at present no clear evidence for the benefit or harm of steroids between 37 and 38 weeks gestation prior to elective caesarean section. A systematic review of antenatal corticosteroids for maturity of term or near term fetuses noted that more research is needed in groups not well studied, including women with pregestational diabetes.

Fetal Growth Restriction

Overall, there is thus insufficient evidence to conclude on the benefits or harms of antenatal corticosteroids therapy in women whose infants were growth-restricted in-utero or who are likely to deliver SGA preterm infants. Routine use of antenatal corticosteroids in growth-restricted infants should thus be re-evaluated, as the potential detrimental side effects of steroids on growth are specifically unwarranted in this already growth-restricted group. An RCT is merited to clarify whether treatment brings any added benefit in growth-restricted infants and to address further questions regarding antenatal corticosteroids treatment of SGA infants. (Amiya et al 2016)

Antenatal corticosteroids administration is associated with umbilical artery vasodilation in both appropriate for gestational age and growth restricted fetuses and with an increase in right myocardial performance index in the latter group. This suggests a worsening in cardiac function in growth restricted fetuses (Marchi et al, 2020).

Preterm premature rupture of membranes - Please refer to PPROM guideline

Single Course and Rescue Course

Weekly repeat courses are not recommended. Though repeat courses of antenatal corticosteroids reduce the occurrence and severity of neonatal respiratory disease, the short-term benefits are associated with a reduction in weight and head circumference.

A single rescue course may be considered with caution in pregnancies where the initial course was given at less than 26+0 weeks gestation. Consultant opinion should be sought if a rescue course is to be considered.

Cautious Use

Caution should be exercised when giving corticosteroid therapy to women with systemic infection including tuberculosis or sepsis.

Consultant opinion should be sought when contemplating delaying birth for steroid prophylaxis in cases of overt chorioamnionitis.

22+5 to <22+6 weeks

Oxford AHSN guidance advises to offer antenatal corticosteroids to all women in pre-term labour from >= 22+5 weeks to < 34 gestation in established preterm labour and in those with threatened pre-term labour who have a positive Fibronectin test. Neonatal teams at MKUH do not attend deliveries < 23 weeks. Therefore if the pregnancy is between 22+5 to <23 weeks, not imminently delivering and suitable for inutero transfer (IUT), discuss with obstetric on call team at Oxford University Hospital (OUH) whether to give steroids before transfer**.**

Before 25weeks, there is a study that support the benefits of antenatal corticosteroids for mortality, severe IVH/ PVL for neonates born. The NNT for these benefits was small (mortality: 5, IVH/PVL: 13). Antenatal corticosteroids was associated with significantly reduced neonatal mortality at 22, 23 and 24 weeks. However, it had no effect on ≥stage II necrotizing enterocolitis. The benefit for severe IVH/PVL was significant only at 23 and 24 weeks (Deshmukh & Patole, 2017)

Caesarean Birth

Corticosteroids should only be given to reduce the risk of respiratory morbidity in all babies delivered by elective caesarean prior to 36+6 weeks of gestation.

Elective cesarean birth before 39 weeks of gestation is common and is associated with respiratory and other adverse neonatal outcomes. The rates of adverse respiratory outcomes, mechanical ventilation, newborn sepsis, hypoglycemia, admission to the neonatal ICU, and hospitalization for 5 days or more were increased by a factor of 1.8 to 4.2 for births at 37 weeks and 1.3 to 2.1 for births at 38 weeks.[4]

Infants of mothers undergoing planned cesarean delivery at ≥37 weeks' gestation who received prophylactic antenatal corticosteroids 48 hours before delivery had a significantly lower risk of RDS, transient tachypnea of the newborn, and mechanical ventilation, significantly less time receiving oxygen, shorter stay in neonatal intensive care, and a higher APGAR score at one and at five minutes (Saccone G & Berghella V, 2016).

The ASTECS study randomised almost 1,000 women at 37 weeks' gestation or beyond to receive betamethasone 48 hours before elective caesarean section. Of the 942 neonates, 24 (5.1%) control babies and 11 (2.4%) treated babies were admitted to intensive care for respiratory distress, including five control babies and one treated baby diagnosed with severe RDS. The number needed to treat to prevent one admission to the neonatal intensive care unit (NICU) was 37. (Stutchfield P et al 2005)

There has not yet been a longer-term follow-up of the LPT ALPS trial. However, the ASTECS trial of early term caesarean section has reported data from a questionnaire returned by half their 8–15-year-old offspring. This revealed a possible subtle difference in neurodevelopment: there were no differences in behaviour or standardised tests of academic achievement, but children exposed to ACS were more likely to be in the lower quarter of academic ability as reported by their school (17.7% vs. 8.5%).

Should steroids be given to babies born by elective caesarean at term (>39 weeks)?

Results from metanalysis of four trials are promising, but more high-quality studies with larger sample sizes that are adequately powered to detect the effect of prophylactic antenatal corticosteroids on outcomes of respiratory morbidity are needed (Sortiriadis et al, 2018).

Are there any maternal risks with antenatal corticosteroids administration?

A meta-analysis has established the expected temporal leukocytosis in healthy, non-infected pregnant women after administration of antenatal corticosteroids based on the available literature. The total leukocyte count increases and reaches a peak upper bound at 20.7 × 10^9/L within 24 hours after steroid administration and returns to a mean of 11.5 ± 2.9 × 10^9/L by 72 hours after administration. (Bauer ME et al 2018)
Clinicians may wish to consider further investigation into the clinical cause, whether infectious or non-infectious, for persistent elevation, absolute values and changes outside this range

3.3 Rationale for main recommendations

To ensure that the correct response and effective communication has been adopted by staff who are dealing with a case of administering antenatal steroids

3.4 Record keeping

Good record keeping in the maternity records as well as the prescription chart is an integral part of practice and is essential to the provision of safe and effective care.

All staff should make clear, accurate and immediate records of all medication prescribed and administered in both the maternity records and the prescription chart, as well as any medication intentionally withheld or refused by the woman.

4.0 Statement of evidence/references

Please note that although Milton Keynes University Hospital NHS Foundation Trust may include links to external websites, the Trust is not responsible for the accuracy or content therein.

Alexandros Sotiriadis [1], George Makrydimas, Stefania Papatheodorou, John Pa Ioannidis, Emma McGoldrick (2018) **Corticosteroids for Preventing Neonatal Respiratory Morbidity After Elective Caesarean Section at Term** Cochrane Database Syst Rev 2018 Aug 3;8(8):CD006614.

Amiya RM, Mlunde LB, Ota E, Swa T, Oladapo OT, Mori R.PLoS One. 2016 Feb **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.
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Devender Roberts[1] Julie Brown [2], Nancy Medley [3], Stuart R Dalziel 2017)[2] Antenatal Corticosteroids for Accelerating Fetal Lung Maturation for Women at Risk of Preterm Birth Cochrane Database Syst Rev 2017 Mar 21;3(3):CD004454. doi: 10.1002/14651858.CD004454.pub3. 26841022

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Marchi L, et al. Ultraschall Med. 2020. Cardiovascular Hemodynamic Changes After Antenatal Corticosteroids in Growth Restricted and Appropriate for Gestational Age Fetuses PMID: 30366353 English. https://pubmed.ncbi.nlm.nih.gov/30366353/

NICE 2008 Diabetes in pregnancy. Management of diabetes and its complications from pre-conception to the postnatal period.

NICE Preterm labour and birth guideline (update August 2019)

NMC (2007) Standards for medicines management. London.

NMC (2009) Record keeping: Guidance for nurses and midwives. London.

RCOG (2006) Preterm prelabour rupture of membranes. Guideline no 44.

RCOG (2010) Antenatal Corticosteroids to Reduce Neonatal Morbidity and Mortality Green-top Guideline No.7 accessed via http://www.rcog.org.uk/womens-health/clinical-guidance/antenatal-corticosteroids-prevent-respiratory-distress-syndrome-gree

Roberts D, Brown J, Medley N, Dalziel SR. (2017) **Antenatal corticosteroids** for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev. Mar 21;3(3):CD004454. doi: 10.1002/14651858.CD004454.pub3.

Saccone G & Berghella V. Antenatal corticosteroids for maturity of term or near term fetuses: systematic review and meta-analysis of randomized controlled trials. BMJ 2016; 355 :i5044

Stutchfield P, Whitaker R, Russell I; (2005) Antenatal Steroids for Term Elective Caesarean Section (ASTECS) Research Team. Antenatal betamethasone and incidence of neonatal respiratory distress after elective caesarean section: pragmatic randomised trial. *BMJ* 331:662.

Tita ATN, Landon MB, Spong CY, Lai Y, Leveno KJ, Varner MW et al (2009). Timing of elective repeat cesarean delivery at term and neonatal outcomes. *New Engl J Med* 2009;360:111–20.

5.0 Governance

5.1 Document review history

Version number	Review date	Reviewed by	Changes made
6	08/2021	J Elliot	Full review and update
5	07/2020	J Elliot	Full review and update
4	11/2019	F Nizami	Changes to gestational age limits Change of first line corticosteroid to betamethasone

5.2 Consultation History

Stakeholders Name/Board	Area of Expertise	Date Sent	Date Received	Comments	Endorsed Yes/No
Julie Cooper	Head of Midwifery	13/07/2020	14/07/2020		
Cath Hudson	Lead Midwife for risk and QI	13/07/2020	13/07/2020		
Natalie Lucas	Audit and guidelines Midwife	13/07/2020	13/07/2020		
Women's health guidelines group		25/07/2021	25/07/2021	Minor comments and amendments	Yes
Women's health CIG		01/09/2021	01/09/2021	Approved	N/A

5.3 Audit and Monitoring Criteria

Audit Criteria	Tool	Audit Lead	Frequency of Audit	Responsible Committee
Clinical practice 1) Antenatal corticosteroids were given to all	Pharmacy statistics	Midwives and doctors as designated	Annually	Maternity CIG

women at risk of iatrogenic or spontaneous preterm birth between 23 weeks & 34 weeks of gestation 2) Clinicians offered a single course of antenatal corticosteroid treatment to women with multiple pregnancy at risk of imminent iatrogenic or spontaneous preterm birth between 23+0 and 35+6 weeks of gestation 3) Pregnancy between 22+5 to <23 weeks, not imminently delivering and suitable for inutero transfer (IUT), is discuss with obstetric on call team at Oxford University Hospital (OUH) whether to give steroids before transfer. 4) Planned caesarean section performed prior to 39 weeks of gestation, antenatal intramuscular corticosteroids was considered .		by audit leads		

Appendix 1: Comparison of national guidelines on when to give steriods

Table 1. Current recommendations for the administration of antenatal corticosteroids in pregnancy.

	RCOG; NICE guidelines	ACOG	RANZCOG (Liggins Institute)	FIGO Working Group on Good Clinical Practice in Maternal–Fetal Medicine	World Health Organization
Title	Preterm labour and birth (1.9.1–1.9.9)	Committee Opinion Number 713, Antenatal Corticosteroid Therapy for Fetal Maturation	Antenatal corticosteroids given to women prior to birth to improve fetal, infant, child, and adult health Clinical Practice Guidelines	Good Clinical practice advice: antenatal corticosteroids for fetal lung maturation	WHO recommendations on interventions to improve preterm birth outcomes (1.0–1.10)
Year of publication	2015	2017	2015	2019	2015
Gestational age	24+0 to 33+9 weeks of gestation Consider in patients between 23+0 and 23+6 weeks of gestation and between 34+0 and 35+6 weeks of gestation	24+0 to 36+6 weeks of gestation at risk of birth within 7 days Consider in patients between 23+0 and 23+6 weeks of gestation upon family's decision	24+0 to 34+6 weeks of gestation Up to 39+0 weeks when lung immaturity known, e.g. amniocentesis for lecithin sphingomyelin	24–34 weeks of gestation <24 weeks of gestation in discussion with family and clinician Consider in patients 34+0 to 36+6 weeks of gestation	24+0 to 34+0 weeks of gestation if there is no evidence of maternal infection and there is available childbirth and neonatal care
Steroid given	Not specified	Betamethasone or dexamethasone	Betamethasone or dexamethasone	Betamethasone or dexamethasone	Betamethasone or dexamethasone
Dosing regimen	Not specified	Betamethasone two 12 mg doses (IM) 24 hours apart OR dexamethasone four 6 mg doses (IM) every 12 hours	Betamethasone 24 mg in divided doses, completed between 12 and 36 hours (as betamethasone sodium phosphate 7.8 mg and betamethasone acetate 6 mg) OR dexamethasone phosphate 24 mg in divided doses completed between 24 and 40 hours	Betamethasone two 12 mg doses (IM) 24 hours apart OR dexamethasone four 6 mg doses (IM) 12 hours apart	Betamethasone (total 24 mg in divided doses) OR dexamethasone (total 24 mg in divided doses)
Recommended dosing interval prior to birth	Not specified	0–7 days prior to birth (2–7 days ideal). Therapy should not be withheld if delivery is anticipated prior to second dose (12 hours after first dose)	0–48 hours prior to birth (up to 7 days), even if birth is likely within 24 hours	Most effective when birth occurs 24 hours after (and up to 7 days) administration of the second dose	Within 7 days of birth, including within 24 hours of birth

5.4 Equality Impact Assessment

As part of its development, this Guideline and its impact on equality has been reviewed. The purpose of the assessment is to minimise and if possible remove any disproportionate impact on the grounds of race, gender, disability, age, sexual orientation, religion or belief, pregnancy and maternity, gender reassignment or marriage and civil partnership. No detriment was identified. Equality Impact assessments will show any future actions required to overcome any identified barriers or discriminatory practice.

Equality Impact Assessment			
Division	Women's and Children's Health	Department	Maternity
Person completing the EqIA	J Elliot	Contact No.	
Others involved:		Date of assessment:	07/2020
Existing policy/service	Yes	New policy/service	No

Will patients, carers, the public or staff be affected by the policy/service?	Yes
If staff, how many/which groups will be affected?	*Doctors, Midwives and student midwives working in maternity*

Protected characteristic	Any impact?	Comments
Age	NO	Positive impact as the policy aims to recognise diversity, promote inclusion and fair treatment for patients and staff
Disability	NO	
Gender reassignment	NO	
Marriage and civil partnership	NO	
Pregnancy and maternity	NO	
Race	NO	
Religion or belief	NO	
Sex	NO	
Sexual orientation	NO	

What consultation method(s) have you carried out?
Circulation via email and MS Teams. Discussion at guidelines meeting and WH CIG.
How are the changes/amendments to the policies/services communicated?
Via email, discussion at guidelines meeting and WH CIG
What future actions need to be taken to overcome any barriers or discrimination?

What?	Who will lead this?	Date of completion	Resources needed
Review date of EqIA			