National Institute for Health and Care Excellence

Final

Intrapartum care for women with existing medical conditions or obstetric complications and their babies

[E] Evidence review for long-term systemic steroids

NICE guideline NG121

Evidence reviews for women at high risk of adverse outcomes for themselves and/or their baby because of existing maternal medical conditions

March 2019

Final

Developed by the National Guideline Alliance hosted by the Royal College of Obstetricians and Gynaecologists

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The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

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Contents

Intrapartum care for women on long-term systemic steroid medication

Review question

What steroid replacement regimen should be used during the peripartum period for women on long-term systemic steroid medication?

Introduction

The aim of this review is to determine what kind, if any, of steroid replacement regimen should be used during labour and birth for women who are on long-term steroid medication. This is important because although women with an underlying condition requiring long-term systemic steroid therapy can usually continue using oral corticosteroid medication (such as prednisone) during pregnancy (because prednisone does not cross the placenta), during the highly stressful events of labour and birth, a temporary increase in steroid therapy (that is, a stress dose of steroids) might be needed.

Summary of the protocol

See Table 1 for a summary of the population, intervention, comparison and outcomes (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO) table

Population	Women in spontaneous or induced labour (or who have a caesarean section) who are or have been on long-term systemic steroid therapy for at least 2 weeks

Intervention	Intervention 1:
	• Continuation of antenatal steroid medication
	Intervention 2:
	• Variation of or addition to antenatal steroid therapy regimen, including the following elements:
	  ○ dose (mg)
	  ○ mode of administration (intramuscular [IM], intravenous [IV] bolus, IV infusion)
	  ○ timing and interval of administration (when and how often)
	  ○ type of corticosteroid

Comparison	Comparison 1:
	• No steroid medication
	Comparison 2:
	• Different dosages
	Comparison 3:
	• Different modes of administration
	  ○ IM versus IV bolus
	  ○ IM versus IV infusion
	  ○ IV bolus versus IV infusion

	Comparison 4: • Different timings and intervals of administration Comparison 5: • Different corticosteroids (for example, hydrocortisone versus prednisolone versus dexamethasone)
Outcomes	For the woman: • mortality • acute adrenal insufficiency (hypotension, cardiovascular collapse, hypoglycaemia, disorientation, weakness, or hyponatremia) • women's satisfaction with labour and birth (including psychological wellbeing) • adverse effects For the baby: • mortality • acute adrenal insufficiency (hypotension, cardiovascular collapse, hypoglycaemia, disorientation, weakness, or hyponatremia) • long-term neurodevelopmental outcomes (for example, cerebral palsy, or developmental delay) • admission to a neonatal unit

IM: intramuscular; IV: intravenous

For further details see the full review protocol in Appendix A. The search strategies are presented in Appendix B.

Clinical evidence

Included studies

One retrospective cohort study was included in this review (see 'Summary of clinical studies included in the evidence review').

This study compared additional high dose hydrocortisone (100 mg) and low dose hydrocortisone (50 mg) in labour (Owa 2017).

Evidence from the studies included in the review is summarised below (see 'Quality assessment of clinical studies included in the evidence review').

Data was reported on the critical outcome, acute adrenal insufficiency for the woman, long-term neurodevelopmental outcomes for the baby, and the important outcome, adverse effects for the woman. There was no evidence identified for the following outcomes for the woman, mortality (critical outcome) and women's satisfaction with labour and birth (important outcome). There was no evidence identified for the following outcomes for the baby, mortality (critical outcome), acute adrenal insufficiency (critical outcome) and admission to a neonatal unit (of limited importance).

There was no evidence available for other interventions, continuation of antenatal steroid medication, or variation of or addition to antenatal steroid therapy regimen, including variation in dose, mode of administration, timing and interval of administration or type of corticosteroid.

There was no evidence available for other comparisons, no steroid medication, different modes of administration, different timings and intervals of administration or different corticosteroids.

See also the study selection flow chart in Appendix C.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in Appendix D.

Summary of clinical studies included in the evidence review

Table 2 provides a brief summary of included studies.

Table 2: Summary of included studies

Study	Population	Intervention/Comparison	Outcomes	Comments
Owa 2017 Retrospective cohort study Japan	N=102 women taking oral corticosteroid therapy during their pregnancy ART: 54.5% Average oral prednisolone: 9.3 mg/day Oral steroid therapy for ≥1year: 90% Underlying medical conditions: SLE 29.3%, ITP 12.5%, renal transplant 11.5%, RA 11.5%, MCTD 6.9%, Aortitis syndrome 5.6%, others 23.5%	• High dose (HD): 100 mg hydrocortisone at onset of labour and then 8 hourly until birth. After birth, some received 50 mg hydrocortisone 8 hourly for 1 day. (n=47) • Low dose (LD): 50 mg hydrocortisone at onset of labour and then 8 hourly until birth. After birth, all received 25 mg hydrocortisone 8 hourly for 1 day. (n=55)	For the woman: • Adrenal insufficiency* • Major side-effects For the baby: • Congenital anomalies	• There were more women with ITP in HD than in LD group. • HD and LD were those having babies during 2008-2012 and 2012-2016, respectively.

Study	Population	Intervention/Comparison	Outcomes	Comments
		Note – All women continued their regular oral corticosteroids throughout labour, birth and after birth in both groups.		

ART: Assisted reproductive technology; HD: High dose; ITP: Idiopathic thrombocytopenia; LD: Low dose; MCTD: Mixed connective tissue disease; RA: Rheumatoid arthritis; SLE: Systemic lupus erythematosus
**hypotension, cardiovascular collapse, hypoglycaemia, disorientation, weakness, hyponatremia*

See also the study evidence tables in Appendix E. No meta-analysis was undertaken for this review (and so there are no forest plots in Appendix F).

Quality assessment of clinical studies included in the evidence review

The clinical evidence profiles for this review question are presented in Appendix G.

Economic evidence

Included studies

No economic evidence was identified for this review.

See the study selection flow chart in Supplement 2 (Health economics).

Excluded studies

No full-text copies of articles were requested for this review and so there is no excluded studies list (see Supplement 2 (Health economics)).

Summary of studies included in the economic evidence review

No economic evidence was identified for this review (and so there are no economic evidence tables in Supplement 2 (Health economics)).

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation (see Supplement 2 (Health economics)).

Evidence statements

Comparison: High dose hydrocortisone versus low dose hydrocortisone

Outcomes for the woman

Acute adrenal insufficiency: adrenal insufficiency

Very low quality evidence from one retrospective cohort study (N=102) reported that there was no case of adrenal insufficiency in either the group of women who received high dose hydrocortisone or those who had low dose hydrocortisone.

Adverse effects: endometriosis or hyperglycaemia or wound infection

Very low quality evidence from one retrospective cohort study (N=102) reported that there was no clinically important difference in the risk of adverse effects (endometriosis or hyperglycaemia or wound infection) between the group of women who received high dose and those who received low dose hydrocortisone.

Outcomes for the baby

Long-term neurodevelopmental outcomes: oesophageal atresia or cleft lip or congenital cystic adenomatoid malformations

Very low quality evidence from one retrospective cohort study (N=102) reported that there was no clinically important difference in the risk of long-term neurodevelopmental outcomes of babies (oesophageal atresia or cleft lip or congenital cystic adenomatoid malformations) between the group of women who received high dose hydrocortisone and those who received low dose hydrocortisone.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

Maternal and neonatal outcomes were prioritised for review, as the committee considered these important and believed that steroids could influence them.

Mortality and acute adrenal insufficiency (hypotension, cardiovascular collapse, hypoglycaemia, disorientation, weakness and hyponatremia) were considered as critically important outcomes for women and babies because these are disastrous and fatal consequences for both the woman and the baby if there is failure to give adequate steroids to women who require them. Long-term neurodevelopmental outcomes such as cerebral palsy and developmental delay were regarded as being of critical importance to the baby because these are serious and lifelong complications.

Women's satisfaction with labour and birth (including psychological wellbeing) and incidence of adverse effects were considered to be important outcomes for women because these would act as proxy measures for successful control of adrenaline levels during labour.

The quality of the evidence

The quality of the evidence was very low and it came from a single retrospective cohort study. The study considered only women who took steroid therapy orally during pregnancy. There was an increased proportion of women with idiopathic thrombocytopenic purpura (ITP) in the high dose (HD) hydrocortisone group compared to the low dose (LD) hydrocortisone group and the study authors did not perform any adjustment in their analysis. The study periods for the HD and LD groups were also different and thus, there is a possibility that pregnancy and labour care other than hydrocortisone treatment could have differed between the groups. There was no clinically important difference in the reported outcomes, with the

confidence intervals being very wide. Thus, it was considered that no definite conclusion could be drawn from this very low quality evidence, and so the committee based their recommendations on their knowledge and experience.

Benefits and harms

The committee discussed that taking a smaller dose of prednisolone for a defined period of time would not suppress adrenal function and thus, supplementary steroids during labour would not be recommended in these circumstances. They explained that recommendations would be beneficial for women taking 5 mg or more of daily oral prednisolone for more than 3 weeks or the equivalent amount of other form of steroids. Thus, the committee made their recommendations based on preventing adrenal crisis (which could be fatal) while attempting to limit the woman's dose of steroids as far as possible. As the committee believed that the physiological stress of labour was lower than for caesarean section, they made separate recommendations for the 2 situations.

In the case of women with adrenal insufficiency, or taking 5 mg or more of daily oral prednisolone for more than 3 weeks or the equivalent amount of other forms of steroids, and planning a vaginal birth, regular oral steroids should be continued. The committee explained that the risk in discontinuing the steroids to more accurately gauge dose of supplementary steroids was that this might cause problems for the woman in restarting steroids after the birth, and that continuing oral medication would not make a significant difference to outcomes for the woman or the baby (since oral medication is not well absorbed during labour). In addition, 6-hourly intravenous or intramuscular hydrocortisone of 50 mg or more should be added in the established first stage of labour and this dosage should be continued until 6 hours after the baby is born.

The committee recommended that supplementary steroids be given by the intravenous or intramuscular route, since oral medication is not well absorbed during labour (blood is required by the uterus and so the bowel receives less supply) and vomiting is not uncommon. This means the intravenous or intramuscular route is likely to be a more reliable method of medication delivery. The committee recommended hydrocortisone, because a smaller amount of hydrocortisone crosses the placenta than beta- or dexa-methasone and this minimises the risk of fetal toxicity. The committee recommended that a minimum of 50 mg of hydrocortisone should be given per dose if the woman is in established labour. This was based on clinical consensus. The committee explained that existing guidelines (such as the Scottish Intercollegiate Guidelines Network (SIGN) guideline on the management of asthma, Addison's disease self-help group (ADSHG) surgical guidelines, Bancos 2015) recommended doses of between 50 mg and 100 mg with the dosage interval of 6-8 hourly. Thus, these were important cut-off points for use in clinical practice. The committee noted that there was no evidence for either threshold, and also that an extended duration of increased steroid dose carried potential risks, but the committee was unable to recommend how to respond in this situation as it would depend on many factors specific to the individual woman. However, they explained that using the lower 50 mg dose would minimise the side effects of acute administration of high- dose steroids.

In the case of women giving birth through caesarean section and who have adrenal insufficiency or who have been taking long-term oral steroids, the committee recommended continuing with regular oral steroids and adding hydrocortisone, but they added that the dose would depend on whether the woman had already been in labour. The committee intended for the total dose for a woman having a caesarean section to be 100 mg (the upper end of

clinical consensus), with a supplementary 50 mg 6 hours after the baby is born. In order to reach this dose, either 100 mg should be given outright if the woman has not already had any hydrocortisone for labour (as above) and 50 mg if she has already had a 50 mg dose in labour. The committee discussed how this could mean the woman might have as little as 75 mg overall (if the last 50 mg dose she received in labour was around 6 hours prior to the 50 mg caesarean section dose) but they concluded that there was insufficient evidence that the added benefit of the remaining 25 mg hydrocortisone justified more invasive blood monitoring, which could make the woman anxious. The risks associated with this higher dose were greatly reduced by the fact that caesarean section could be completed much faster than labour and so the total dose (that is, the number of doses times the amount per dose) was relatively small. The committee recommended giving the dose every 6 hours since they knew this to be the half-life of steroids in the body (and this would therefore give better control over the dose). They recommended giving a final dose 6 hours after the baby was born in order to prevent adrenal collapse in the immediate postpartum period.

The committee discussed how most women taking inhaled or topical steroids do not require supplemental hydrocortisone in the intrapartum period, because the bioavailability of steroids in this form is known to be poor and so these women would be unlikely to be receiving a high dose of steroids from an inhaled or topical dose alone. This would prevent such women from being exposed to the harmful side-effects of steroids, without increasing their risk of adrenal crisis. However the committee explained that this was not always the case, and a specialist may be required to determine whether the dose was high enough to be treated as being 5 mg or more prednisolone daily for more than 3 weeks or an equivalent amount of another steroid.

The committee explained that antenatal steroids given for fetal lung maturation should be treated as for any other steroid for the purpose of determining intrapartum dosing; although they agreed that stopping the dose during the intrapartum period did not carry the same risk as stopping the dose for a condition that would persist after the birth (since the dose would be stopping anyway). The committee considered that the high levels of steroids used for fetal lung maturation might mean that suddenly stopping them could have a negative effect on the woman's health, for example provoking an adrenal crisis. For the sake of continuing the dose for a few extra hours the committee believed the risk was balanced by the likely benefits.

Cost effectiveness and resource use

No evidence was found for this review and the committee made a qualitative assessment of cost effectiveness.

The committee noted that steroids are relatively inexpensive and so they reasoned that recommendations that minimised the risk of an adrenal crisis, which can be fatal, were likely to be cost effective. The committee believed that recommending a higher dose of additional steroids for women having a caesarean section would be cost effective as this procedure is more stressful physiologically than labour.

The committee believed that there is variation in practice and that steroids are likely to be overprescribed for women in labour. Therefore the recommendations might reduce the amount of steroids given, particularly for women using inhaled or topical steroids. However, because steroids are inexpensive, this is unlikely to have a significant impact on resource use within the NHS in England.

Other factors the committee took into account

As only very low quality evidence from one study was identified, the committee made a research recommendation on whether supplemental steroids are required in the intrapartum period for women taking regular antenatal steroids. See Appendix L for further details.

References

Bancos 2015

Bancos, Irina, Hahner, Stefanie, Tomlinson, Jeremy, Arlt, Wiebke, Diagnosis and management of adrenal insufficiency, The Lancet Diabetes & Endocrinology, 3, 216-226, 2015

Owa 2017

Owa, Takao, Mimura, Kazuya, Kakigano, Aiko, Matsuzaki, Shinya, Kumasawa, Keiichi, Endo, Masayuki, Tomimatsu, Takuji, Kimura, Tadashi, Pregnancy outcomes in women with different doses of corticosteroid supplementation during labor and delivery, The journal of obstetrics and gynaecology research, 43, 1132-1138, 2017

Appendices

Appendix A – Review protocol

Intrapartum care for women on long-term systemic steroid medication

Item	Details	Working notes
Area in the scope	Women at high risk of adverse outcomes for themselves and/or their baby because of existing maternal medical conditions – intrapartum care for women on long-term systemic steroid medication - steroid replacement regimens	
Review question in the scope	What steroid replacement regimen should be used during birth and the peripartum period for women on long-term systemic steroid medication?	
Review question for the guideline	What steroid replacement regimen should be used during the peripartum period for women on long-term systemic steroid medication?	
Objective	The aim of this review is to determine what kind, if any, of steroid replacement regimen should be used during labour and birth for women who are on long-term steroid medication. This is important because although women with an underlying condition requiring long-term systemic steroid therapy can usually continue using oral corticosteroid medication (such as prednisone) during pregnancy (because prednisone does not cross the placenta), during the highly stressful events of labour and birth, a temporary increase in steroid therapy (that is, a stress dose of steroids) might be needed	
Population and directness	Women in spontaneous or induced labour (or who have a caesarean section) who are or have been on long-term systemic steroid therapy for at least 2 weeks. Long-term systemic steroid therapy includes the following oral tablet medications: • prednisone • prednisolone • hydrocortisone • dexamethasone. Conditions that might require long-term steroid therapy include (but are not limited to): • asthma • systemic lupus erythematosus (SLE) • Addison's disease (primary adrenal insufficiency, primary adrenocortical insufficiency, chronic adrenal insufficiency, hypocortisolism, hypoadrenalism)	

Item	Details	Working notes
	• chronic obstructive pulmonary disease (COPD) • inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis • polymyalgia rheumatica • autoimmune thrombocytopenia, including idiopathic thrombocytopenic purpura (ITP) • arthritis, including rheumatic arthritis/rheumatoid arthritis • atopic eczema • multiple sclerosis (MS) • polymorphic eruption of pregnancy (PEP) Women who have had an organ transplant may also be on long-term systematic steroid therapy	
Intervention	Continuation of antenatal steroid medication Variation of or addition to antenatal steroid therapy regimen, including the following potential elements: • dose (mg) • mode of administration (intramuscular [IM], intravenous [IV] bolus, IV infusion) • timing and interval of administration (when and how often) • type of corticosteroid (this could be any steroid, but is expected to be prednisone, fluprednisolone, methylprednisolone, prednimustine, hydrocortisone, fludrocortisone or dexamethasone)	
Comparison	No steroid medication (stopping steroids during the intrapartum period) Different dosages Different modes of administration o IM versus IV bolus o IM versus IV infusion o IV bolus versus IV infusion Different timings and intervals of administration Different corticosteroids (for example, hydrocortisone versus prednisolone versus dexamethasone)	
Outcomes	Critical outcomes: • for the woman: o mortality o acute adrenal insufficiency (hypotension, cardiovascular collapse, hypoglycaemia, disorientation, weakness, or hyponatremia) • for the baby: o mortality o acute adrenal insufficiency (hypotension, cardiovascular collapse, hypoglycaemia, disorientation, weakness, or hyponatremia) o long-term neurodevelopmental outcomes (for example, cerebral palsy, or developmental delay)	

Item	Details	Working notes

	Important outcomes:
	• for the woman:
	  ○ women's satisfaction with labour and birth (including psychological wellbeing)
	  ○ adverse effects
	
	Outcomes of limited importance:
	• for the baby:
	  ○ admission to a neonatal unit	

Importance of outcomes	Preliminary classification of the outcomes for decision making: • critical (up to 3 outcomes) • important but not critical (up to 3 outcomes) • of limited importance (1 outcome)	Given the small volume of evidence available for inclusion overall, the committee agreed to consider more than the nominal maximum of 7 outcomes for this question
Setting	All settings	
Stratified, subgroup and adjusted analyses	Groups that will be reviewed and analysed separately: • women having steroids for fetal lung maturity • mode of birth In the presence of heterogeneity, the following subgroups will be considered for sensitivity analysis: • women with different underlying health conditions for which they are taking systemic steroids (see Population and directness above) • women on different doses and/or types of long-term steroid medication • women with different durations of long-term steroid medication prior to the peripartum period Potential confounders: • obesity • kidney and liver disease	
Language	English	

Item	Details	Working notes
Study design	• Published full-text papers only • Systematic reviews • RCTs • Only if RCTs unavailable or there is limited data to inform decision making: ○ prospective or retrospective comparative cohort studies • Prospective study designs will be prioritised over retrospective study designs • Conference abstracts will not be considered	
Search strategy	Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA and Embase. Limits (e.g. date, study design): All study designs. Apply standard animal/non-English language filters. No date limit. Supplementary search techniques: No supplementary search techniques were used. See appendix B for full strategies	
Review strategy	Appraisal of methodological quality: • the methodological quality of each study will be assessed using checklists recommended in the NICE guidelines manual 2014 (for example, AMSTAR or ROBIS for systematic reviews, and Cochrane RoB tool for RCTs) and the quality of the evidence for each outcome (that is, across studies) will be assessed using GRADE • if studies report only p-values, this information will be recorded in GRADE tables without an assessment of imprecision Synthesis of data: • meta-analysis will be conducted where appropriate • default MIDs will be used; 0.8 and 1.25 for dichotomous outcomes; 0.5 times the SD of the measurement in the control arm (or median score across control arms if multiple studies are included) for continuous outcomes • for continuous data, change scores will be used in preference to final scores for data from non-RCT studies; final and change scores will not be pooled; if any study reports both, the method used in the majority of studies will be adopted	Review questions selected as high priorities for health economic analysis (and those selected as medium priorities and where health economic analysis could influence recommendations) will be subject to dual weeding and study selection; any discrepancies will be resolved through discussion between

Item	Details	Working notes
		the first and second reviewers or by reference to a third person. This review question was not prioritised for health economic analysis and so no formal dual weeding, study selection (inclusion/ exclusion) or data extraction into evidence tables will be undertaken. However, internal (NGA) quality assurance processes will include consideration of the outcomes of weeding, study selection and data extraction and the committee will review the results

Item	Details	Working notes
		of study selection and data extraction
Equalities	Equalities considerations will be considered systematically in relation to the available evidence and draft recommendations. The guideline scope includes women with cognitive or physical disability as populations for whom there may be equalities issues. Women who have received no antenatal care will be considered as a subgroup for all systematic reviews performed within the medical conditions work stream and a specific question has been included in the obstetric complications work stream for this population	
Notes/additional information	• SIGN British guideline on the management of asthma, p120: "Women receiving steroid tablets at a dose exceeding prednisolone 7.5 mg per day for > more than two weeks prior to delivery should receive parenteral hydrocortisone 100 mg 6–8 hourly during labour." Reference: https://www.brit-thoracic.org.uk/document-library/clinical-information/asthma/btssign-asthma-guideline-2014/ • Nelson-Piercy C. Asthma in pregnancy. In: Respiratory diseases in pregnancy 1. Thorax 2001;56:325–328: "Those on oral steroids (>7.5 mg prednisolone daily for more than 2 weeks) at the onset of labour or delivery should receive parenteral steroids (hydrocortisone 100 mg 6–8 hourly) during labour, and until they are able to restart their oral medication." Reference: http://thorax.bmj.com/content/56/4/325.full.pdf+html • Pandey D, Pai M, Kumar P. Systemic lupus erythematosus and pregnancy: Today's scenario. The Internet Journal of Gynecology and Obstetrics. 2008 Volume 11 Number 2: "…stress dose of glucocorticoids should be given during labor or cesarean, to all patients who have been treated with chronic steroids within the previous year. Hydrocortisone, in three doses of 100 mg, 8 hourly IV is an acceptable regimen." Reference: http://ispub.com/IJGO/11/2/7581 • Surgical literature includes some studies on stress dose steroid therapy, however, evidence is somewhat limited and the common recommendations are being questioned by new evidence. In a review by Kelly and Domajnko (2013), they conclude that "Based on the existing evidence, it is recommended that patients on long-term exogenous steroids do not require the high-dose corticosteroids that were once the standard of care. Rather, patients should remain on their baseline maintenance doses, throughout the perioperative period and be treated for hypotension that is otherwise unresponsive or unexplained with a rescue dose of steroids." (Kelly K. N., Domajnko B. Perioperative Stress-Dose Steroids. Clin Colon Rectal Surg 2013;26:163-167.) • Below are two examples of guidelines for perioperative steroid therapy for patients on long-term steroid therapy from the UK. It should be noted, that surgery and labour and delivery cannot be compared as such. ○ Guidelines for perioperative steroids By Dr N Loh, Senior House Officer, and Dr M Atherton, Consultant, Department of Anaesthesia, Arrowe Park Hospital, Wirral CH49 5PE:	

Item	Details	Working notes
	"Suggested steroid treatment regimen for patients who have received a regular daily dose of more than 10mg prednisolone or equivalent in the last three months: Minor Surgery: 25mg Hydrocortisone at induction (hernias, hands) Moderate Surgery: Usual pre-op steroids (hysterectomy) + 25mg Hydrocortisone at induction +100mg hydrocortisone/day Major Surgery: Usual pre-op steroids + 25mg Hydrocortisone at induction +100mg hydrocortisone/day for 2-3 days. Resume normal oral therapy when gastrointestinal function has returned." Reference: http://www.e-safe-anaesthesia.org/sessions/02_02/pdf/Perioperative-Steroids.pdf ○ Clinical Guideline for the Perioperative Steroid Replacement Royal Cornwall Hospital (NHS Trust): "Patients currently taking steroids: <10 mg day-1 Additional steroid cover not required. >10 mg day-1 - Minor surgery - 25 mg hydrocortisone at induction - Moderate surgery - Usual pre-operative steroids + 25 mg hydrocortisone at induction + 100 mg day-1 for 24 h. - Major surgery - Usual pre-operative steroids + 25 mg hydrocortisone at induction + 100 mg day-1 for 48-72 h. - Patients stopped taking steroids - <3 months - Treat if on steroids - >3 months - No peri-operative steroids necessary" Reference: http://www.rcht.nhs.uk/DocumentsLibrary/RoyalCornwallHospitalsTrust/Clinical/Anaesthetics/PeriOperativeSteroidReplacement.pdf	
Key papers	Lebbe M, Arlt W. What is the best diagnostic and therapeutic management strategy for an Addison patient during pregnancy? Clin Endocrinol (Oxf). 2013 Apr;78(4):497-502. doi: 10.1111/cen.12097. Adonakis G, Georgopoulos NA, Michail G, Spinos N, Papadopoulos V, Kourounis GS, Kyriazopoulou V. Successful pregnancy outcome in a patient with primary Addison's disease. Gynecol Endocrinol. 2005 Aug;21(2):90-2. Kristin N. Kelly and Bastian Domajnko. Perioperative Stress-Dose Steroids. Clin Colon Rectal Surg. 2013 Sep; 26(3): 163–167. doi: 10.1055/s-0033-1351132	

AMSTAR: Assessing the Methodological Quality of Systematic Reviews; CCTR: Cochrane Central Register of Controlled Trials; CDSR: Cochrane Database of Systematic Reviews; COPD: chronic obstructive pulmonary

disease; DARE: Database of Abstracts of Reviews of Effects; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; IBD: inflammatory bowel disease; IM: intramuscular; ITP: idiopathic thrombocytopenic purpura; IV: intravenous; MID: minimally important difference; MS: multiple sclerosis; NGA: National Guideline Alliance; NICE: National Institute for Health and Care Excellence; PEP: polymorphic eruption of pregnancy; RCT: randomised controlled trial; RoB: risk of bias; ROBIS: Risk of Bias in Systematic Reviews; SD: standard deviation; SLE: systemic lupus erythematosus

Appendix B – Literature search strategies

Intrapartum care for women on long-term systemic steroid medication

Database: Medline; Medline EPub Ahead of Print; and Medline In-Process & Other Non-Indexed Citations

#	Searches
1	PERIPARTUM PERIOD/
2	PARTURITION/
3	exp LABOR, OBSTETRIC/
4	exp DELIVERY, OBSTETRIC/
5	OBSTETRIC LABOR, PREMATURE/
6	(labo?r or childbirth or partu$ or intra?part$ or peri?part$).ti,ab.
7	((during or giving or give) adj3 birth?).ti,ab.
8	(c?esar#an$ or c section$ or csection$ or (deliver$ adj3 abdom$) or ((vagina$ or cephalic$ or forcep? or induc$ or extract$ or ventouse? or spontaneous$) adj3 (birth$ or born or deliver$))).ti,ab.
9	or/1-8
10	exp STEROIDS/
11	exp ADRENAL CORTEX HORMONES/
12	PREDNISONE/
13	exp PREDNISOLONE/
14	exp HYDROCORTISONE/
15	exp DEXAMETHASONE/
16	steroid$.mp.
17	corticosteroid?.mp.
18	prednisone.mp.
19	(prednisolone or fluprednisolone or methylprednisolone or prednimustine).mp.
20	(hydrocortisone or fludrocortisone).mp.
21	dexamethasone.mp.
22	or/10-21
23	((stress or rescue or maintenance or increment$ or boost$ or supplement$ or additional$ or added$ or increas$) adj3 (dose? or dosag$)).ti,ab.
24	((Temporar$ or short term or physiological$) adj3 increase$).ti,ab.
25	or/23-24
26	((steroid$ or corticosteroid? or prednisone or fluprednisolone or methylprednisolone or prednimustine or Hydrocortisone or fludrocortisone or Dexamethasone) adj3 (stress or rescue

#	Searches
	or maintenance or increment$ or boost$ or supplement$ or additional$ or added$ or increas$)).mp.
27	((steroid$ or corticosteroid? or prednisone or fluprednisolone or methylprednisolone or prednimustine or Hydrocortisone or fludrocortisone or Dexamethasone) adj3 (high$ adj2 (dose? or level?))).mp.
28	((steroid$ or corticosteroid? or prednisone or fluprednisolone or methylprednisolone or prednimustine or Hydrocortisone or fludrocortisone or Dexamethasone) adj3 replace$).mp.
29	((steroid$ or corticosteroid? or prednisone or fluprednisolone or methylprednisolone or prednimustine or Hydrocortisone or fludrocortisone or Dexamethasone) adj3 (regimen$ or long term)).mp.
30	9 and 22 and 25
31	9 and 26
32	9 and 27
33	9 and 28
34	9 and 29
35	or/30-34
36	limit 35 to english language
37	LETTER/
38	EDITORIAL/
39	NEWS/
40	exp HISTORICAL ARTICLE/
41	ANECDOTES AS TOPIC/
42	COMMENT/
43	CASE REPORT/
44	(letter or comment*).ti.
45	or/37-44
46	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
47	45 not 46
48	ANIMALS/ not HUMANS/
49	exp ANIMALS, LABORATORY/
50	exp ANIMAL EXPERIMENTATION/
51	exp MODELS, ANIMAL/
52	exp RODENTIA/
53	(rat or rats or mouse or mice).ti.
54	or/47-53
55	36 not 54

Database: Cochrane Central Register of Controlled Trials

#	Searches
1	PERIPARTUM PERIOD/
2	PARTURITION/
3	exp LABOR, OBSTETRIC/

#	Searches
4	exp DELIVERY, OBSTETRIC/
5	OBSTETRIC LABOR, PREMATURE/
6	(labo?r or childbirth or partu$ or intra?part$ or peri?part$).ti,ab,kw.
7	((during or giving or give) adj3 birth?).ti,ab.
8	(c?esar#an$ or c section$ or csection$ or (deliver$ adj3 abdom$) or ((vagina$ or cephalic$ or forcep? or induc$ or extract$ or ventouse? or spontaneous$) adj3 (birth$ or born or deliver$))).ti,ab.
9	or/1-8
10	exp STEROIDS/
11	exp ADRENAL CORTEX HORMONES/
12	PREDNISONE/
13	exp PREDNISOLONE/
14	exp HYDROCORTISONE/
15	exp DEXAMETHASONE/
16	steroid$.mp,kw.
17	corticosteroid?.mp,kw.
18	prednisone.mp,kw.
19	(prednisolone or fluprednisolone or methylprednisolone or prednimustine).mp,kw.
20	(hydrocortisone or fludrocortisone).mp,kw.
21	dexamethasone.mp,kw.
22	or/10-21
23	((stress or rescue or maintenance or increment$ or boost$ or supplement$ or additional$ or added$ or increas$) adj3 (dose? or dosag$)).ti,ab.
24	((Temporar$ or short term or physiological$) adj3 increase$).ti,ab.
25	or/23-24
26	((steroid$ or corticosteroid? or prednisone or fluprednisolone or methylprednisolone or prednimustine or Hydrocortisone or fludrocortisone or Dexamethasone) adj3 (stress or rescue or maintenance or increment$ or boost$ or supplement$ or additional$ or added$ or increas$)).mp.
27	((steroid$ or corticosteroid? or prednisone or fluprednisolone or methylprednisolone or prednimustine or Hydrocortisone or fludrocortisone or Dexamethasone) adj3 (high$ adj2 (dose? or level?))).mp.
28	((steroid$ or corticosteroid? or prednisone or fluprednisolone or methylprednisolone or prednimustine or Hydrocortisone or fludrocortisone or Dexamethasone) adj3 replace$).mp.
29	((steroid$ or corticosteroid? or prednisone or fluprednisolone or methylprednisolone or prednimustine or Hydrocortisone or fludrocortisone or Dexamethasone) adj3 (regimen$ or long term)).mp.
30	9 and 22 and 25
31	9 and 26
32	9 and 27
33	9 and 28
34	9 and 29
35	or/30-34

Database: Cochrane Database of Systematic Reviews

#	Searches
1	PERIPARTUM PERIOD.kw.
2	PARTURITION.kw.
3	LABOR, OBSTETRIC.kw.
4	DELIVERY, OBSTETRIC.kw.
5	OBSTETRIC LABOR, PREMATURE.kw.
6	(labo?r or childbirth or partu$ or intra?part$ or peri?part$).ti,ab.
7	((during or giving or give) adj3 birth?).ti,ab.
8	(c?esar#an$ or c section$ or csection$ or (deliver$ adj3 abdom$) or ((vagina$ or cephalic$ or forcep? or induc$ or extract$ or ventouse? or spontaneous$) adj3 (birth$ or born or deliver$))).ti,ab.
9	or/1-8
10	STEROIDS.kw.
11	ADRENAL CORTEX HORMONES.kw.
12	PREDNISONE.kw.
13	PREDNISOLONE.kw.
14	HYDROCORTISONE.kw.
15	DEXAMETHASONE.kw.
16	steroid$.ti,ab.
17	corticosteroid?.ti,ab.
18	prednisone.ti,ab.
19	(prednisolone or fluprednisolone or methylprednisolone or prednimustine).ti,ab.
20	(hydrocortisone or fludrocortisone).ti,ab.
21	dexamethasone.ti,ab.
22	or/10-21
23	((stress or rescue or maintenance or increment$ or boost$ or supplement$ or additional$ or added$ or increas$) adj3 (dose? or dosag$)).ti,ab.
24	((Temporar$ or short term or physiological$) adj3 increase$).ti,ab.
25	or/23-24
26	((steroid$ or corticosteroid? or prednisone or fluprednisolone or methylprednisolone or prednimustine or Hydrocortisone or fludrocortisone or Dexamethasone) adj3 (stress or rescue or maintenance or increment$ or boost$ or supplement$ or additional$ or added$ or increas$)).ti,ab.
27	((steroid$ or corticosteroid? or prednisone or fluprednisolone or methylprednisolone or prednimustine or Hydrocortisone or fludrocortisone or Dexamethasone) adj3 (high$ adj2 (dose? or level?))).ti,ab.
28	((steroid$ or corticosteroid? or prednisone or fluprednisolone or methylprednisolone or prednimustine or Hydrocortisone or fludrocortisone or Dexamethasone) adj3 replace$).ti,ab.
29	((steroid$ or corticosteroid? or prednisone or fluprednisolone or methylprednisolone or prednimustine or Hydrocortisone or fludrocortisone or Dexamethasone) adj3 (regimen$ or long term)).ti,ab.
30	9 and 22 and 25
31	9 and 26

#	Searches
32	9 and 27
33	9 and 28
34	9 and 29
35	or/30-34

Database: Database of Abstracts of Reviews of Effects

#	Searches
1	PERIPARTUM PERIOD.kw.
2	PARTURITION.kw.
3	LABOR, OBSTETRIC.kw.
4	DELIVERY, OBSTETRIC.kw.
5	OBSTETRIC LABOR, PREMATURE.kw.
6	(labo?r or childbirth or partu$ or intra?part$ or peri?part$).tw,tx.
7	((during or giving or give) adj3 birth?).tw,tx.
8	(c?esar#an$ or c section$ or csection$ or (deliver$ adj3 abdom$) or ((vagina$ or cephalic$ or forcep? or induc$ or extract$ or ventouse? or spontaneous$) adj3 (birth$ or born or deliver$))).tw,tx.
9	or/1-8
10	STEROIDS.kw.
11	ADRENAL CORTEX HORMONES.kw.
12	PREDNISONE.kw.
13	PREDNISOLONE.kw.
14	HYDROCORTISONE.kw.
15	DEXAMETHASONE.kw.
16	steroid$.tw,tx.
17	corticosteroid?.tw,tx.
18	prednisone.tw,tx.
19	(prednisolone or fluprednisolone or methylprednisolone or prednimustine).tw,tx.
20	(hydrocortisone or fludrocortisone).tw,tx.
21	dexamethasone.tw,tx.
22	or/10-21
23	((stress or rescue or maintenance or increment$ or boost$ or supplement$ or additional$ or added$ or increas$) adj3 (dose? or dosag$)).tw,tx.
24	((Temporar$ or short term or physiological$) adj3 increase$).tw,tx.
25	or/23-24
26	((steroid$ or corticosteroid? or prednisone or fluprednisolone or methylprednisolone or prednimustine or Hydrocortisone or fludrocortisone or Dexamethasone) adj3 (stress or rescue or maintenance or increment$ or boost$ or supplement$ or additional$ or added$ or increas$)).tw,tx.
27	((steroid$ or corticosteroid? or prednisone or fluprednisolone or methylprednisolone or prednimustine or Hydrocortisone or fludrocortisone or Dexamethasone) adj3 (high$ adj2 (dose? or level?))).tw,tx.

#	Searches
28	((steroid$ or corticosteroid? or prednisone or fluprednisolone or methylprednisolone or prednimustine or Hydrocortisone or fludrocortisone or Dexamethasone) adj3 replace$).tw,tx.
29	((steroid$ or corticosteroid? or prednisone or fluprednisolone or methylprednisolone or prednimustine or Hydrocortisone or fludrocortisone or Dexamethasone) adj3 (regimen$ or long term)).tw,tx.
30	9 and 22 and 25
31	9 and 26
32	9 and 27
33	9 and 28
34	9 and 29
35	or/30-34

Database: Health Technology Assessment

#	Searches
1	PERIPARTUM PERIOD/
2	PARTURITION/
3	exp LABOR, OBSTETRIC/
4	exp DELIVERY, OBSTETRIC/
5	OBSTETRIC LABOR, PREMATURE/
6	(labo?r or childbirth or partu$ or intra?part$ or peri?part$).tw.
7	((during or giving or give) adj3 birth?).tw.
8	(c?esar#an$ or c section$ or csection$ or (deliver$ adj3 abdom$) or ((vagina$ or cephalic$ or forcep? or induc$ or extract$ or ventouse? or spontaneous$) adj3 (birth$ or born or deliver$))).tw.
9	or/1-8
10	exp STEROIDS/
11	exp ADRENAL CORTEX HORMONES/
12	PREDNISONE/
13	exp PREDNISOLONE/
14	exp HYDROCORTISONE/
15	exp DEXAMETHASONE/
16	steroid$.tw.
17	corticosteroid?.tw.
18	prednisone.tw.
19	(prednisolone or fluprednisolone or methylprednisolone or prednimustine).tw.
20	(hydrocortisone or fludrocortisone).tw.
21	dexamethasone.tw.
22	or/10-21
23	((stress or rescue or maintenance or increment$ or boost$ or supplement$ or additional$ or added$ or increas$) adj3 (dose? or dosag$)).tw.
24	((Temporar$ or short term or physiological$) adj3 increase$).tw.
25	or/23-24

#	Searches
26	((steroid$ or corticosteroid? or prednisone or fluprednisolone or methylprednisolone or prednimustine or Hydrocortisone or fludrocortisone or Dexamethasone) adj3 (stress or rescue or maintenance or increment$ or boost$ or supplement$ or additional$ or added$ or increas$)).tw.
27	((steroid$ or corticosteroid? or prednisone or fluprednisolone or methylprednisolone or prednimustine or Hydrocortisone or fludrocortisone or Dexamethasone) adj3 (high$ adj2 (dose? or level?))).tw.
28	((steroid$ or corticosteroid? or prednisone or fluprednisolone or methylprednisolone or prednimustine or Hydrocortisone or fludrocortisone or Dexamethasone) adj3 replace$).tw.
29	((steroid$ or corticosteroid? or prednisone or fluprednisolone or methylprednisolone or prednimustine or Hydrocortisone or fludrocortisone or Dexamethasone) adj3 (regimen$ or long term)).tw.
30	9 and 22 and 25
31	9 and 26
32	9 and 27
33	9 and 28
34	9 and 29
35	or/30-34

Database: Embase

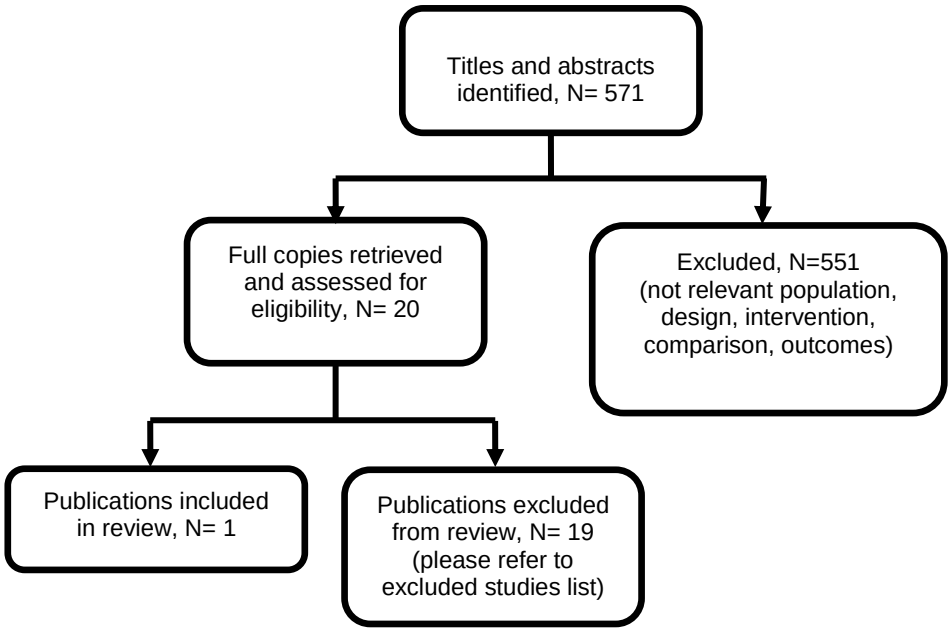
#	Searches
1	*PERINATAL PERIOD/
2	exp *BIRTH/
3	exp *LABOR/
4	exp *DELIVERY/
5	*PREMATURE LABOR/
6	*INTRAPARTUM CARE/
7	(labo?r or childbirth or partu$ or intra?part$ or peri?part$).ti,ab.
8	((during or giving or give) adj3 birth?).ti,ab.
9	(c?esar#an$ or c section$ or csection$ or (deliver$ adj3 abdom$) or ((vagina$ or cephalic$ or forcep? or induc$ or extract$ or ventouse? or spontaneous$) adj3 (birth$ or born or deliver$))).ti,ab.
10	or/1-9
11	exp *STEROID/
12	exp *CORTICOSTEROID/
13	*PREDNISONE/
14	*PREDNISOLONE/
15	*HYDROCORTISONE/
16	*DEXAMETHASONE/
17	steroid$.mp.
18	corticosteroid?.mp.
19	prednisone.mp.
20	(prednisolone or fluprednisolone or methylprednisolone or prednimustine).mp.

#	Searches
21	(hydrocortisone or fludrocortisone).mp.
22	dexamethasone.mp.
23	or/11-22
24	((stress or rescue or maintenance or increment$ or boost$ or supplement$ or additional$ or added$ or increas$) adj3 (dose? or dosag$)).ti,ab.
25	((Temporar$ or short term or physiological$) adj3 increase$).ti,ab.
26	or/24-25
27	((steroid$ or corticosteroid? or prednisone or fluprednisolone or methylprednisolone or prednimustine or Hydrocortisone or fludrocortisone or Dexamethasone) adj3 (stress or rescue or maintenance or increment$ or boost$ or supplement$ or additional$ or added$ or increas$)).mp.
28	((steroid$ or corticosteroid? or prednisone or fluprednisolone or methylprednisolone or prednimustine or Hydrocortisone or fludrocortisone or Dexamethasone) adj3 (high$ adj2 (dose? or level?))).mp.
29	((steroid$ or corticosteroid? or prednisone or fluprednisolone or methylprednisolone or prednimustine or Hydrocortisone or fludrocortisone or Dexamethasone) adj3 replace$).mp.
30	((steroid$ or corticosteroid? or prednisone or fluprednisolone or methylprednisolone or prednimustine or Hydrocortisone or fludrocortisone or Dexamethasone) adj3 (regimen$ or long term)).mp.
31	10 and 23 and 26
32	10 and 27
33	10 and 28
34	10 and 29
35	10 and 30
36	or/31-35
37	limit 36 to english language
38	letter.pt. or LETTER/
39	note.pt.
40	editorial.pt.
41	CASE REPORT/ or CASE STUDY/
42	(letter or comment*).ti.
43	or/38-42
44	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
45	43 not 44
46	ANIMAL/ not HUMAN/
47	NONHUMAN/
48	exp ANIMAL EXPERIMENT/
49	exp EXPERIMENTAL ANIMAL/
50	ANIMAL MODEL/
51	exp RODENT/
52	(rat or rats or mouse or mice).ti.
53	or/45-52
54	37 not 53

Appendix C – Clinical evidence study selection

Intrapartum care for women on long-term steroid medication

Figure 1: Flow diagram of clinical article selection for intrapartum care for women on long-term systemic steroid medication



Appendix D – Excluded studies

Intrapartum care for women on long-term systemic steroid medication

Clinical studies

Study	Reason for Exclusion
Anonymous,, Systemic lupus erythematosus in pregnancy, Annals of Internal Medicine, 94, 667-77, 1981	Study design; non-comparative study
Bar, J., Fisch, B., Wittenberg, C., Gelerenter, I., Boner, G., Hod, M., Prednisone dosage and pregnancy outcome in renal allograft recipients, Nephrology Dialysis Transplantation, 12, 760-3, 1997	Study design; non-comparative study
Beck, J. C., Johnson, J. W. C., Maternal administration of glucocorticoids, Clinical Obstetrics and Gynecology, 23, 93-113, 1980	Study design; non-systematic review
Centre for, Reviews, Dissemination,, Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies (Structured abstract), Database of Abstracts of Reviews of Effects, 2015	Population outside of scope; women using hydrocortisone during pregnancy
Daskalakis, G., Mole, I., Ntomali, A., Papantoniou, N., Antsaklis, P., Mesogitis, S., Pregnancy in a patient with eosinophilic granulomatosis with polyangiitis (churg-strauss syndrome), Journal of Maternal-Fetal and Neonatal Medicine, 27, 302-303, 2014	Conference proceedings
Fawzy,M., Shokeir,T., El-Tatongy,M., Warda,O., El-Refaiey,A.A., Mosbah,A., Treatment options and pregnancy outcome in women with idiopathic recurrent miscarriage: a randomized placebo-controlled study, Archives of Gynecology and Obstetrics, 278, 33-38, 2008	Population outside of scope; women with idiopathic recurrent miscarriage
Foocharoen, C., Nanagara, R., Salang, L., Suwannaroj, S., Mahakkanukrauh, A., Pregnancy and disease outcome in patients with systemic lupus erythematosus (SLE): a study at Srinagarind Hospital, Journal of the Medical Association of Thailand, 92, 167-74, 2009	Comparison outside of scope
Goetzl,L., Zighelboim,I., Badell,M., Rivers,J., Mastrangelo,M.A., Tweardy,D., Suresh,M.S., Maternal corticosteroids to prevent intrauterine exposure to hyperthermia and inflammation: a randomized, double-blind, placebo-controlled trial, American Journal of Obstetrics and Gynecology, 195, 1031-1037, 2006	Population outside of scope; women not on long-term steroid medication
Kuprys-Lipinska, I., Tworek, D., Kuna, P., Omalizumab in pregnant women treated due to	Study design; case report

Study	Reason for Exclusion
severe asthma: two case reports of good outcomes of pregnancies, Postepy Dermatologii I Alergologii, 31, 104-7, 2014	
Lebbe, M., Arlt, W., What is the best diagnostic and therapeutic management strategy for an Addison patient during pregnancy?, Clinical Endocrinology, 78, 497-502, 2013	Study design; non-systematic review
Leung, Y. P. Y., Kaplan, G. G., Coward, S., Tanyingoh, D., Kaplan, B. J., Johnston, D. W., Barkema, H. W., Ghosh, S., Panaccione, R., Seow, C. H., Field, C. J., Dewey, D., Bell, R. C., Bernier, F. P., Cantell, M., Casey, L. M., Eliasziw, M., Farmer, A., Gagnon, L., Giesbrecht, G. F., Goonewardene, L., Kooistra, L., Letourneau, N., Leung, B. M., Manca, D. P., Martin, J. W., McCargar, L. J., O'Beirne, M., Pop, V. J., Singhal, N., Intrapartum corticosteroid use significantly increases the risk of gestational diabetes in women with inflammatory bowel disease, Journal of Crohn's and Colitis, 9, 223-230, 2015	Population outside of scope; mixed population (18.1% of women used intrapartum corticosteroid therapy)
Lockshin, M. D., Sammaritano, L. R., Corticosteroids during pregnancy, Scandinavian Journal of Rheumatology - Supplement, 107, 136-8, 1998	Study design; non-systematic review
Petersen, E., Frey, H., Benninger, C., Phillips, G., Shellhaas, C., McCallister, J. W., Comparison of the emergency department with labor and delivery in the treatment of pregnant women with acute asthma exacerbations, American Journal of Respiratory and Critical Care Medicine. Conference: American Thoracic Society International Conference, ATS, 185, 2012	Conference proceedings
Plauborg, A. V., Hansen, A. V., Garne, E., Use of azathioprine and corticosteroids during pregnancy and birth outcome in women diagnosed with inflammatory bowel disease, Birth Defects Research, 106, 494-9, 2016	Study design; non-comparative study
Plauborg, Anne Veie, Hansen, Anne Vinkel, Garne, Ester, Use of azathioprine and corticosteroids during pregnancy and birth outcome in women diagnosed with inflammatory bowel disease, Birth defects research. Part A, Clinical and molecular teratology, 106, 494-9, 2016	Comparison outside of scope; women with ulcerative colitis vs. women with Crohn's disease vs. women with no IBD diagnosis
Pollard,J.K., Scott,J.R., Branch,D.W., Outcome of children born to women treated during pregnancy for the antiphospholipid syndrome, Obstetrics and Gynecology, 80, 365-368, 1992	Comparison outside of scope; women in the control group did not have any medical condition indicated for long-term steroid therapy

Study	Reason for Exclusion
Powrie,R.O., Larson,L., Miller,M., Managing asthma in expectant mothers, Treatments in Respiratory Medicine, 5, 1-10, 2006	Full text unavailable
Ravenscraft, S. A., Lupo, V. R., Asthma: Management during pregnancy, Seminars in Respiratory and Critical Care Medicine, 19, 221-230, 1998	Study design; non-systematic review
Ruiz-Irastorza, G., Khamashta, M. A., Managing lupus patients during pregnancy, Best Practice & Research in Clinical Rheumatology, 23, 575-82, 2009	Study design; non-systematic review

IBD: inflammatory bowel disease

Economic studies

See Supplement 2 (Health economics) for details of economic evidence reviews and health economic modelling.

Appendix E – Clinical evidence tables

Intrapartum care for women on long-term systemic steroid medication

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Full citation

Owa, Takao, Mimura, Kazuya, Kakigano, Aiko, Matsuzaki, Shinya, Kumasawa, Keiichi, Endo, Masayuki, Tomimatsu, Takuji, Kimura, Tadashi, Pregnancy outcomes in women with different doses of corticosteroid supplementation during labor and</td>
<td>Sample size
n=102

Characteristics
Average age: 33.3 years

Assisted reproductive technology (ART): 54.5%

Average oral prednisolone: 9.3 mg/day

Note - No difference in baseline characteristics were observed between the high-dose and low-dose group in age, ART, oral prednisolone dose, primipara.
<table>
<tr><td></td><td>HD (%)</td><td>LD (%)</td></tr>
<tr><td>SLE</td><td>13(27.7%)</td><td>17(30.9%)</td></tr>
<tr><td>ITP*</td><td>9(19.1%)</td><td>3(5.5%)</td></tr>
</table>
</td>
<td>Interventions
High dose (HD) group (n=47) (from January 2008 to May 2012, women receiving corticosteroid therapy were administered a high dose of corticosteroid supplementation): Women were given 100 mg hydrocortisone at the onset of labour and every 8 hours until birth. After birth, some women were given 50 mg hydrocortisone every 8 hours for 1 day. The tapering</td>
<td>Details
During January 2008 and May 2012, there were a total of 54 women receiving corticosteroid therapy of which 7 were excluded (reasons for exclusion were not reported).

Similarly, during June 2012 and December 2016, a total</td>
<td>Results
<table>
<tr><td></td><td>HD</td><td>LD</td></tr>
<tr><td>Adrenal insufficiency</td><td>0</td><td>0</td></tr>
<tr><td>Major side effects</td><td>Endometriosis:3
Hyperglycemia:2
Wound infection:1</td><td>Endometriosis:1</td></tr>
<tr><td>Congenital anomalies</td><td>Oesophageal atresia:1</td><td>Cleft lip:1
CCAM:1</td></tr>
<tr><td>pH (umbilical cord)</td><td>7.28±0.07</td><td>7.30±0.06</td></tr>
</table>
</td>
<td>Limitations
Quality Assessment: Newcastle-Ottawa Assessment Scale for Cohort Studies

Selection:

1) Representativeness of the exposed cohort
a) representative

2) Selection of the non-exposed cohort
a) drawn from the same community as the exposed cohort</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
delivery, The journal of obstetrics and gynaecology research, 43, 1132-1138, 2017 **Ref Id** 834498 **Country/ies where the study was carried out** Japan **Study type** Retrospective cohort study **Aim of the study** To examine the pregnancy outcomes of women receiving	<table><tr><td>Renal transplant</td><td>4(8.5%)</td><td>8(14.5%)</td></tr><tr><td>RA</td><td>4(8.5%)</td><td>8(14.5%)</td></tr><tr><td>MCTD</td><td>3(6.4%)</td><td>4(7.3%)</td></tr><tr><td>Aortitis Syndrome</td><td>1(2.1%)</td><td>5(9.1%)</td></tr><tr><td>Others</td><td>13(27.7%)</td><td>10(18.2%)</td></tr></table>*p=0.06; <table><tr><td rowspan="2">Prednisolone (mg/day)</td><td colspan="3">HD</td><td colspan="3">LD</td></tr><tr><td><1 year</td><td>≥1-<10 years</td><td>≥10 years</td><td><1 year</td><td>≥1-<10 years</td><td>≥10 years</td></tr><tr><td><5</td><td>1</td><td>4</td><td>1</td><td>0</td><td>5</td><td>3</td></tr><tr><td>>/=5-<10</td><td>0</td><td>12</td><td>7</td><td>1</td><td>18</td><td>8</td></tr><tr><td>>/=10-<20</td><td>3</td><td>7</td><td>4</td><td>1</td><td>8</td><td>6</td></tr><tr><td>>/=20</td><td>3</td><td>3</td><td>2</td><td>2</td><td>1</td><td>2</td></tr></table>	method was not fixed. Low dose (LD) group (n=55) (from June 2012 to December 2016, women receiving corticosteroid therapy were administered a low dose of corticosteroid supplementation): Women were given 50 mg hydrocortisone at the onset of labour and every 8 hours until birth. After birth, they were given 25 mg hydrocortisone ev ery 8 hours for 1 day. All women took their regular oral corticosteroids throughout labour,	of 60 women receiving steroids of which 5 were excluded (reasons for exclusion were not reported). The characteristi cs of these women were not different from those included.		*3) Ascertainment of exposure* a) secure records and the study reported significant difference in hydrocortisone dose taken *4) Demonstration that outcome of interest was not present at start of study* a) yes **Comparability:** *1) Comparability of cohorts on the basis of the design or analysis* None **Outcome:**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
steroid therapy during labour **Study dates** January 2008 to December 2016 **Source of funding** Grants-in-Aid for Scientific Research	HD = high-dose group, LD = low-dose group **Inclusion criteria** • Pregnant women who received oral corticosteroid therapy **Exclusion criteria** • Pregnant women who used inhaled or topical steroids	birth and after birth in both groups.			*1) Assessment of outcome* b) record linkage *2) Was follow-up long enough for outcomes to occur?* a) yes *3) Adequacy of follow-up of cohorts* *a) complete follow-up* **Overall score: 7/9** **Other information** None

ART: assisted reproductive technology; CCAM: congenital cystic adenomatoid malformations; HD: high dose; ITP: idiopathic thrombocytopenic purpura; LD: low dose; MCTD: mixed connective tissue disease; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus

Appendix F – Forest plots

Intrapartum care for women on long-term systemic steroid medication

No meta-analysis was undertaken for this review and so there are no forest plots

Appendix G – GRADE tables

Intrapartum care for women on long-term systemic steroid medication

Table 3: Clinical evidence profile for high dose versus low dose of top-up hydrocortisone therapy during labour, outcomes for the women

Quality assessment							Number of women		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High dose	Low dose	Relative (95% CI)	Absolute	Quality	Importance
Acute adrenal insufficiency: adrenal insufficiency												
1 (Owa 2017)	Retrospective cohort study	Very serious[1]	Not applicable	No serious indirectness	Not estimable due to 0 events	None	0/47 (0%)	0/55 (0%)	Not calculable[2]	Not calculable[2]	⨁⊖⊖⊖ VERY LOW	CRITICAL
Adverse effects: endometriosis or hyperglycaemia or wound infection												
1 (Owa 2017)	Retrospective cohort study	Very serious[1]	Not applicable	No serious indirectness	Serious[3]	None	6/47 (12.7%)	1/55 (1.8%)	RR 7.02 (0.88, 56.25)	109 more per 1000 (from 2 fewer to 1000 more)	⨁⊖⊖⊖ VERY LOW	IMPORTANT

CI: confidence interval; HD: high dose; LD: low dose; RR: risk ratio
[1]There were more women with ITP in HD than LD group and no adjustment was done in the analysis
[2]This was not calculable as there were zero events
[3] The quality of the evidence was downgraded by 1 level because the 95% CI crosses 1 default MID threshold

Table 4: Clinical evidence profile for high dose versus low dose of top-up hydrocortisone therapy during labour, outcomes for the baby

Quality assessment							Number of babies		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High dose	Low dose	Relative (95% CI)	Absolute	Quality	Importance
Long-term neuro-developmental outcomes: oesophageal atresia or cleft lip or congenital cystic adenomatoid malformations												
1 (Owa 2017)	Retrospective cohort study	Very serious[1]	Not applicable	No serious indirectness	Very serious[2]	None	1/47 (2.1%)	2/55 (3.6%)	RR 0.59 (0.05, 6.25)	15 fewer per 1000 (from 35 fewer to 191 more)	⨁⊖⊖⊖ VERY LOW	IMPORTANT

CI: confidence interval; HD: high dose; LD: low dose; RR: risk ratio
[1]There were more women with ITP in HD than LD group and no adjustment was done in the analysis
[2] The quality of the evidence was downgraded by 2 levels because the 95% CI crosses 2 default MID thresholds

Appendix H – Economic evidence study selection

Intrapartum care for women on long-term systemic steroid medication

See Supplement 2 (Health economics) for details of economic evidence reviews and health economic modelling.

Appendix I – Economic evidence tables

Intrapartum care for women on long-term systemic steroid medication

See Supplement 2 (Health economics) for details of economic evidence reviews and health economic modelling.

Appendix J – Health economic evidence profiles

Intrapartum care for women on long-term systemic steroid medication

See Supplement 2 (Health economics) for details of economic evidence reviews and health economic modelling.

Appendix K – Health economic analysis

Intrapartum care for women on long-term systemic steroid medication

See Supplement 2 (Health economics) for details of economic evidence reviews and health economic modelling.

Appendix L – Research recommendations

Intrapartum care for women on long-term systemic steroid medication

Are supplemental steroids required in the intrapartum period for women taking regular antenatal steroids?

Why this is important

Pregnant women who require long-term anti-inflammatory steroids are expected to have suppressed production of endogenous steroids from their adrenal glands. This would make them less able to mount a natural steroid response to stress, such as that experienced at the time of child birth.

Based on the committee's experience and expertise, this guideline has recommended that pregnant women receiving long-term oral steroids (equivalent to a low anti-inflammatory dose of 5mg or more prednisolone daily, for more than 3 weeks) should receive a minimum of 50mg of hydrocortisone every 6 hours from the onset of established labour until 6 hours postpartum.

There has been no clinical study to determine at what regular dose of prednisolone or any other steroid formulation, is a pregnant woman unable to mount an adrenal steroid response

to stress. Furthermore, it is unknown what dose of intrapartum hydrocortisone supplementation is required to protect the woman with chronically suppressed adrenal glands from adrenal crisis. It is unknown what effects antenatal hydrocortisone have on peripartum outcome for woman and neonate.

This research question aims to evaluate the effectiveness and safety of current NICE recommendation of steroid supplementation during childbirth.

Research recommendation rationale

Research question	Are supplemental steroids required in the intrapartum period for women taking regular antenatal steroids?
Importance to 'patients' or the population	Current treatment recommendations are not based on evidence from studies in pregnancy. Supplementation with hydrocortisone for all pregnant women taking 5mg prednisolone or more, may lead to a large number of women being treated unnecessarily and their intrapartum experience being unnecessarily over medicalised. Benefits and harms to woman and neonate have not been assessed.
Relevance to NICE guidance	High Priority: Recommendations are based on clinical consensus. A clinical trial to assess endogenous adrenal function in women on different doses of prednisolone and the necessary hydrocortisone supplementation will give evidence to guide a NICE recommendation in this area.
Relevance to NHS	Ensuring appropriate evidence-based treatment of pregnant women during the intrapartum period.
National priorities	This research will guide clinical practise.
Current evidence base	No clinical trials informed current NICE recommendations which were based on the guideline committee's experience and expertise.
Equalities	N/A

N/A: not applicable; NICE: National Institute for Health and Care Excellence

Research recommendation PICO

Criterion	Explanation
Population	Pregnant women taking regular steroid treatment shortly before childbirth
Intervention	Offering intrapartum steroid supplementation to those with evidence of suppressed endogenous adrenal function (determined by endogenous adrenal function in pregnant women taking regular steroid treatment shortly before childbirth)
Comparator	Care guided by new NICE recommendation
Outcomes	• Number of women in each group receiving intrapartum hydrocortisone supplementation • Acceptability of both regimes to women • Pregnancy and neonatal outcomes.
Study design	RCT
Timeframe	3 years

NICE: National Institute for Health and Care Excellence; RCT: randomised controlled trial