National Institute for Health and Care Excellence

Final

Intrapartum care

[F] Evidence reviews for use of oxytocin in the first or second stage of labour

NICE guideline NG235

Evidence reviews underpinning recommendations 1.8.47 to 1.8.51, 1.8 53 and 1.9.32 and research recommendations in the NICE guideline

September 2023

Final

These evidence reviews were developed by NICE

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Contents

This evidence report contains information on 2 reviews relating to oxytocin in the first or second stage of labour.

- What is the effectiveness of altering the dose of intravenous oxytocin to reduce excessive frequency of uterine contractions?
- What is the optimum dose at which oxytocin should be restarted if stopped due to an abnormality in the cardiotocography (CTG)?

Oxytocin in the first or second stage of labour

Review questions

- What is the effectiveness of altering the dose of intravenous oxytocin to reduce excessive frequency of uterine contractions?
- What is the optimum dose at which oxytocin should be restarted if stopped due to an abnormality in the cardiotocography (CTG)?

Introduction

Oxytocin can be used for induction of labour or for delay in the first or second stage of labour to increase the frequency and strength of uterine contractions. Women who are given oxytocin can experience uterine tachysystole and hyperstimulation, which can lead to adverse outcomes for the baby. In addition, the use of oxytocin necessitates continuous monitoring of the baby with CTG. There is currently wide variation and uncertainty in practice about the optimum dosage at which oxytocin should be altered to reduce excessive frequency of uterine contractions. There is also uncertainty in practice over what dose to restart oxytocin if stopped due to an abnormality in the CTG.

This review aims to identify the optimal method of reducing the dose of oxytocin and restarting oxytocin when stopped due to tachysystole or CTG abnormalities, and so to provide guidance to clinicians on the safe use of oxytocin.

Summary of the protocol

See Table 1 and Table 2 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of these reviews.

Table 1: Summary of the protocol (PICO table) – reducing the dose of oxytocin

Population	• Women in labour who are pregnant with a single baby, who go into labour at term (37 to 42 weeks of pregnancy) and who do not have any pre-existing medical conditions or antenatal conditions that predispose to a higher risk birth • Women whose baby has not been identified before labour to be at high risk of adverse outcomes • Women who have been started on intravenous oxytocin for induction or delay in the first or second stage of labour • Singleton babies born at term (37 to 42 weeks of pregnancy) with no previously identified problems (for example congenital malformations, genetic anomalies, intrauterine growth restriction, placental problems)
Intervention	Any method of reducing the dose of oxytocin (for example, in magnitude or frequency of dose reductions, as defined by the study)
Comparison	Any other method of reducing the dose of oxytocin (for example, a different magnitude or frequency of dose reductions, as defined by the study)
Outcome	**Critical:** • Uterine hyperstimulation, or uterine tachysystole, or 5 or more contractions per 10 minutes (with or without changes in CTG) • Mode of birth (for example spontaneous vaginal, instrumental, caesarean birth) • Length of labour **Important:** • Non-reassuring, abnormal, suspicious or pathological CTG • Neonatal death, intrapartum stillbirth, or hypoxic ischaemic encephalopathy (grade 2/3) • Apgar score below 7 at 5 minutes • Women's experience of labour and birth

CTG: cardiotocography

Table 2: Summary of the protocol (PICO table) – restarting oxytocin

Population	• Women in labour who are pregnant with a single baby, who go into labour at term (37 to 42 weeks of pregnancy) and who do not have any pre-existing medical conditions or antenatal conditions that predispose to a higher risk birth • Women whose baby has not been identified before labour to be at high risk of adverse outcomes • Women who have been started on oxytocin but it had to be stopped due to an abnormality in the CTG • Singleton babies born at term (37 to 42 weeks of pregnancy) with no previously identified problems (for example congenital malformations, genetic anomalies, intrauterine growth restriction, placental problems)
Intervention	• Restart using the same dose as the dose when oxytocin was switched off • Restart using a lower dose than the dose when oxytocin was switched off
Comparison	• Any of the above interventions compared to each other
Outcome	**Critical:** • Uterine hyperstimulation or uterine tachysystole, or 5 or more contractions per 10 minutes (with or without changes in CTG) • Non-reassuring, abnormal, suspicious or pathological CTG • Length of labour **Important:** • Mode of birth (for example spontaneous vaginal, instrumental, caesarean birth) • Neonatal death, intrapartum stillbirth, or severe hypoxic ischemic encephalopathy (grade 2/3) • Apgar score below 7 at 5 minutes • Women's experience of labour and birth

CTG: cardiotocography

For further details see the review protocols in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document (supplementary document 1).

Declarations of interest were recorded according to NICE's conflicts of interest policy.

The committee agreed that only studies conducted in high-income countries (as defined by the Organisation for Economic Co-operation and Development [OECD]) should be considered for inclusion because low and middle income countries are likely to have a significantly different monitoring.

Effectiveness evidence

Included studies

A systematic review of the literature was conducted but no studies were identified which were applicable to these review questions.

See the literature search strategies in appendix B and study selection flow charts in appendix C.

Excluded studies

Studies not included in these reviews are listed, and reasons for their exclusion are provided in appendix J.

Summary of included studies

No studies were identified which were applicable to these review questions (and so there are no evidence tables in appendix D). No meta-analysis was conducted for this review (and so there are no forest plots in appendix E).

Summary of the evidence

No studies were identified which were applicable to these review questions (and so there are no GRADE tables in appendix F).

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to these review questions.

Economic model

No economic modelling was undertaken for these reviews because the committee agreed that other topics were higher priorities for economic evaluation.

The committee's discussion and interpretation of the evidence

The outcomes that matter most

Dose of oxytocin

For this review, uterine hyperstimulation was prioritised as a critical outcome by the committee as they agreed this would be an indicator of whether reducing the dose of oxytocin would reduce excessive frequency of uterine contractions. The committee also prioritised mode of birth and length of labour as they wanted to find out whether a reduction in the dose of oxytocin would have a negative impact on mode of birth (for example requiring more interventions) or a prolonged labour.

The committee agreed that as well as the critical outcomes, a non-reassuring, abnormal, suspicious or pathological CTG should be an important outcome. This would provide information on the condition of the neonate. The committee also agreed that other neonatal outcomes such as neonatal death, intrapartum stillbirth, severe hypoxic ischaemic encephalopathy and Apgar score below 7 at 5 minutes, would also be indicators of the wellbeing of the neonate, and also provide some information on potential long-term impact to the child, as hypoxic ischemic encephalopathy can lead to ongoing neurological deficits. They agreed that it was important to look at neonatal outcomes because inappropriate oxytocin use can have negative consequences for the baby.

The committee agreed that women's experience of labour and birth should be an important outcome as needing oxytocin, developing hyperstimulation, and going through the process of trying to reverse this with dose reduction while not leading to cessation of labour can make a woman feel her labour is more complicated or out of her control. Other outcomes such as length of labour and mode of birth will also impact on women's experience, and reducing the

dose of oxytocin should be considered together with safety and women's experience. Although the committee recognised the great importance of this outcome, they were aware that the data identified may be sparse and so was less likely to inform decision-making in a meaningful way, so they prioritised this outcome as an important rather than a critical outcome.

Restarting oxytocin

For this review, uterine hyperstimulation was prioritised as a critical outcome by the committee as they agreed this would be an indicator of whether the restarting dose was appropriate, as uterine hyperstimulation is a consequence of too high a dose of oxytocin for the woman. The committee also prioritised a non-reassuring, abnormal, suspicious or pathological CTG as a critical outcome as an indicator of the condition of the neonate following restarting oxytocin, and thus provide information on whether the restarting dose is safe for the neonate. The committee also prioritised the outcome length of labour as a critical outcome as it is important to consider whether the restarting dose results in prolonged labour.

The committee agreed that as well as the critical outcomes, mode of birth should be an important outcome. This was because it is important to know whether the restarting dose leads to the need for more interventions. The committee also agreed that outcomes for the neonate such as, neonatal death, intrapartum stillbirth, severe hypoxic ischemic encephalopathy and Apgar score below 7 at 5 minutes, would all be indicators of the safety of the restarting dose, and would provide some information on whether there was likely to be a long-term impact on a child's health.

The committee agreed that women's experience of labour and birth should be an important outcome, as women whose oxytocin has been stopped due to hyperstimulation may be anxious about it being restarted again. The committee recognised the great importance of women's experience of labour and birth, but they were aware that data on this outcome was likely to be sparse and unlikely to inform decision-making in a meaningful way, so they prioritised other outcomes as critical. Also, other outcomes such as length of labour and mode of birth could have an impact on women's experience.

The quality of the evidence

No studies were identified which were applicable to these review questions.

Benefits and harms

No evidence was identified for these review questions, therefore recommendations are based on committee experience and informal consensus agreement. The committee agreed that this was an important area in which to make recommendations to reduce variation in practice and improve the way oxytocin is used. Firstly, the committee agreed that oxytocin use should always be discussed with women, along with an explanation of its effects and possible adverse effects such as hyperstimulationand that a shared decision about its use should be made. This applied both when starting oxytocin initially and if considering restarting it, and so the committee amended existing recommendations about starting oxytocin and added a new recommendations about restarting oxytocin to state this.

The committee used, as a starting point to guide their discussions about the dose, the 2007 recommendations for oxytocin in the first stage of labour in the previous version of the Intrapartum care for healthy women and babies guideline and the summary of product characteristics (SPC) for oxytocin. The committee agreed to amend the recommended number of contractions to 3-4 contractions every 10 minutes in line with the SPC, which was a reduction from previous guidance, which advised 4 to 5 contractions in 10 minutes. The

committee agreed that 4 to 5 contractions in 10 minutes were excessive and was more likely to predispose to hyperstimulation. The 2007 recommendations also gave guidance on the time between dose increments of oxytocin and stated that dose increments should be every 30 minutes, despite the fact that the SPC advised that the dose could be increased every 20 minutes. The committee discussed that the SPC wording suggested that the dose could be increased every 20 minutes but did not mandate that it should be increased every 20 minutes. They therefore agreed that they would not amend the existing recommendations to match the shorter time frame given in the SPC, as they were concerned about the risks of hyperstimulation due to too rapid a dose increase, and agreed that keeping the time increments at 30 minutes, and erring on the side of caution, would ensure safe use of oxytocin and avoid a big change in practice.

The committee noted that oxytocin is a very powerful drug and agreed that it should be used with caution due to the increased risk of adverse outcomes, particularly hypoxic ischaemic encephalopathy in the baby if used at a dose causing too frequent contractions. The committee discussed the lack of evidence about how the dose of oxytocin should be reduced if women experience excessive (above 4 in 10 minutes) contractions and agreed that this would depend on the cardiotocography (CTG) trace.

In keeping in line with the recommendation for aiming for 3-4 contractions every 10 minutes, the committee agreed to make a recommendation that if contractions reach more than 4 in 10 minutes, oxytocin should either be reduced or stopped until contractions were not more than 4 in 10 minutes. However, the committee discussed that in the case of a pathological CTG trace oxytocin should be discontinued immediately. The committee noted that the SPC for oxytocin states oxytocin should be discontinued immediately if there is fetal distress, and they agreed that a pathological CTG trace would be an indication of fetal distress. The committee also used their knowledge and experience of situations where oxytocin had not been discontinued following a pathological CTG and resulted in fetal death. The committee agreed that as these recommendations were based on SPC guidance in addition to their knowledge of the possible adverse effects of oxytocin, they could make this a strong recommendation. The committee also discussed the importance of highlighting the need for an obstetrician or senior midwife to review the woman and fetus in cases of a pathological CTG, as this may be an indication for birth to be expedited. The committee also referred to the NICE guideline on fetal monitoring as they agreed that this would ensure best practice and safety of the baby. Finally, as there was a lack of evidence to inform the best method of reducing the dose of oxytocin, the committee were not able to recommend any specific dose reductions.

The committee were aware that there were also recommendations in the guideline about starting oxytocin in the second stage of labour and agreed that the recommendations on how to titrate the dose would be relevant for women on oxytocin in the first and second stages of labour, and so they replicated this recommendation in the section of the guideline on delay in the second stage of labour.

The committee discussed that there was also no evidence on the best dose to restart oxytocin, once it had been stopped due to an abnormality in the CTG. They agreed that it was important to make recommendations in this area using committee expertise to ensure safe use of oxytocin in practice, as there is currently no guidance in this area. They discussed that a safe option to take could be to restart the oxytocin using the starting dose (as recommended in the SPC) and gradually increase the dose every 30 minutes to obtain 3 to 4 contractions in 10 minutes. However they agreed that this could mean it would take a longer time to rebuild contractions, and would increase the length of labour and potentially lead to more interventions. This led the committee to discuss that, when restarting oxytocin, careful consideration should be given to the full clinical picture, including the initial reasons for discontinuation, and the previous dose that was being administered.

The committee discussed that there were benefits of speeding up labour using oxytocin for both labour wards in terms of capacity, and for the woman regarding her experience with length of labour. The committee agreed that prior to restarting oxytocin obstetricians and midwives should assess the safety of continuing oxytocin and the full clinical picture for each individual woman and her labour and discuss this with the woman. However, they agreed that not all women would be comfortable or want to speed up their labour if there were risks associated with restarting oxytocin, and that the decision to restart should be made with the woman. Due to lack of evidence, the committee were unable to specify a particular dose in the recommendation if the decision to restart oxytocin was reached, but they were comfortable that clinicians would be in a better position to take a sensible and reasonable approach, once the clinical picture and the woman's choice had been carefully considered.

The committee were aware that oxytocin acts as an antidiuretic and its use in labour, especially if given in conjunction with intravenous fluids, can lead to water retention, fluid overload and hyponatremia. Based on their clinical experience and knowledge the committee therefore made a recommendation to highlight this and advise monitoring of fluid balance.

As there was a lack of evidence for both reducing the dose and restarting oxytocin the committee made 2 research recommendations.

Cost effectiveness and resource use

The committee considered that the recommendations are likely to reinforce and clarify best current practice. As oxytocin is inexpensive, the recommendations which relate to reducing the dose of or restarting oxytocin infusions are unlikely to have resource implications for the NHS especially as the new recommendations stress the need for caution in its use. The committee considered their recommendations would mitigate the risk of adverse effects potentially saving NHS resources and improving the cost-effective use of oxytocin in labour.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.8.47 to 1.8.51, 1.8.53 and 1.9.32, and research recommendations.

References – included studies

Effectiveness

No studies were identified which were applicable to these review questions.

Economic

No studies were identified which were applicable to this review question.

Appendices

Appendix A Review protocols

Review protocol for review question: What is the effectiveness of altering the dose of intravenous oxytocin to reduce excessive frequency of uterine contractions?

Table 3: Review protocol – dose of oxytocin

Field	Content
PROSPERO registration number	CRD42021266233
Review title	Effectiveness of altering the dose of intravenous oxytocin to reduce excessive frequency of uterine contractions
Review question	What is the effectiveness of altering the dose of intravenous oxytocin to reduce excessive frequency of uterine contractions?
Objective	To update the recommendations in CG190 (2014) on titration of intravenous oxytocin. HSIB has identified that women receiving IV oxytocin have uterine contractions over the 4-5 contractions in 10 minutes, especially in the later stages of labour and that guidance is required on how the dose should be reduced
Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE & MEDLINE In-Process • International Health Technology Assessment (IHTA) database Searches will be restricted by: • No date limitations • English language studies • Human studies Other searches:

Field	Content
	• Inclusion lists of systematic reviews The full search strategies for the MEDLINE database will be published in the final review. For each search, the principal database search strategy is quality assured by a second information scientist using an adaptation of the PRESS 2015 Guideline Evidence-Based Checklist.
Condition or domain being studied	Labour and birth
Population	Women in labour who are pregnant with a single baby, who go into labour at term (37 to 42 weeks of pregnancy) and who do not have any pre-existing medical conditions or antenatal conditions that predispose to a higher risk birth Women whose baby has not been identified before labour to be at high risk of adverse outcomes Women who have been started on intravenous oxytocin for induction or delay in the first or second stage of labour Singleton babies born at term (37 to 42 weeks of pregnancy) with no previously identified problems (for example congenital malformations, genetic anomalies, intrauterine growth restriction, placental problems)
Intervention	Any method of reducing the dose of oxytocin (for example, in magnitude or frequency of dose reductions, as defined by the study)
Comparator	Any other method of reducing the dose of oxytocin (for example, a different magnitude or frequency of dose reductions, as defined by the study)
Types of study to be included	Include published full-text papers: • Systematic reviews of RCTs • Parallel RCTs (individual, cluster) If insufficient RCTs: • Systematic reviews of observational studies • Cohort studies with > 100 women in each arm Note: studies must make adjustment for confounding factors in their analysis

Field	Content
	Conference abstracts will not be included because these do not typically have sufficient information to allow full critical appraisal.
Other exclusion criteria	Population: • Women in labour who are identified before labour to be at high risk, or whose baby is at high risk, of complications or adverse outcomes • Women with babies in non-cephalic presentation • Women in preterm labour • Women with an intrauterine fetal death • Women pregnant with multi-fetal pregnancies • Women who have had a previous caesarean birth or who are having a planned caesarean birth Setting: • Countries other than high income countries (as defined by the OECD) because LMIC would use oxytocin, but the monitoring would vary If any study or systematic review includes <1/3 of women with the above characteristics/ who received care in the above setting, it will be considered for inclusion but, if included, the evidence will be downgraded for indirectness.
Context	This guideline will partly update the following: Intrapartum care for healthy women and babies (CG190)
Primary outcomes (critical outcomes)	• Uterine hyperstimulation, or uterine tachysystole, or 5 or more contractions per 10 minutes (with or without changes in CTG) • Mode of birth (for example spontaneous vaginal, instrumental, caesarean birth) • Length of labour
Secondary outcomes (important outcomes)	• Non-reassuring, abnormal, suspicious or pathological CTG • Neonatal death, intrapartum stillbirth, or hypoxic ischaemic encephalopathy (grade 2/3) • Apgar score below 7 at 5 minutes • Women's experience of labour and birth **Amendment:** A change to the outcome Apgar score was made to more accurately reflect measures of poor outcome. Previous measurement: Apgar score below 6 at 5 minutes

Field	Content
Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Duplicate screening will not be undertaken for this question. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs • Cochrane RoB tool v.2 for cluster-randomized trials • Cochrane ROBINS-I tool for non-randomised (clinical) controlled trials and cohort studies The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
Strategy for data synthesis	Quantitative findings will be formally summarised in the review. Where multiple studies report on the same outcome for the same comparison, meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios if possible or odds ratios when required (for example, if only available in this form in included studies) for dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes. Heterogeneity in the effect estimates of the individual studies will be assessed using the I2 statistic. Alongside visual inspection of the point estimates and confidence intervals, I2 values of greater than 50% and 80% will be considered as significant and very significant heterogeneity, respectively. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through subgroup analysis then a random effects model will be used for meta-analysis, or the data will not be pooled. The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/ Minimally important differences:

Field	Content
	• Length of labour: 1 day • Neonatal death, intrapartum stillbirth, or severe hypoxic ischemic encephalopathy (grade 2/3): statistical significance • Validated scales/continuous outcomes: published MIDs where available • All other outcomes & where published MIDs are not available: 0.8 and 1.25 for all relative dichotomous outcomes ; +/- 0.5x control group SD for continuous outcomes
Analysis of subgroups	Evidence will be stratified by: • Reason for administration of intravenous oxytocin in labour • Induction of labour • Delay in first stage • Delay in second stage • Pre-labour rupture of membranes • BMI thresholds on booking: ○ Underweight range: <18.5 kg/m^2 ○ Healthy weight range: 18.5 to 24.9 kg/m^2 ○ Overweight range: 25 to 29.99 kg/m^2 ○ Obesity range 1: 30 to 34.99 kg/m^2 ○ Obesity range 2: 35 to 39.99 kg/m^2 • Parity (nulliparous vs mixed parity vs multiparous) Stratifications will be dealt with in a hierarchy (this is, by reasons for administration of intravenous oxytocin in labour, then by BMI and then by parity) Evidence will be subgrouped by the following only in the event that there is significant heterogeneity in outcomes: • Age of woman (<35 vs >/= 35) • Ethnicity ○ White ○ Asian/Asian British ○ Black/African/Caribbean/Black British

Field	Content	
	○ Mixed/Multiple ethnic groups ○ Other ethnic group • Women with disability vs not • Deprived socioeconomic group vs not Where evidence is stratified or subgrouped the committee will consider on a case by case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.	
Type and method of review	☒	Intervention
	☐	Diagnostic
	☐	Prognostic
	☐	Qualitative
	☐	Epidemiologic
	☐	Service Delivery
	☐	Other (please specify)
Language	English	
Country	England	
Anticipated or actual start date	22/06/2021	
Anticipated completion date	22/03/2023	
Named contact	5a. Named contact Guideline Development Team National Guideline Alliance (NGA) 5b. Named contact e-mail IPCupdate@nice.org.uk 5c. Organisational affiliation of the review Guideline Development Team NGA, Centre for Guidelines, National Institute for Health and Care Excellence (NICE)	

Field	Content
Review team members	From the Guideline Development Team NGA: • Senior Systematic Reviewer • Systematic Reviewer
Funding sources/sponsor	Guideline Development Team NGA, Centre for Guidelines, which is part of the National Institute for Health and Care Excellence (NICE)
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/cg190
Other registration details	None
URL for published protocol	https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=266233
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: notifying registered stakeholders of publication publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
Keywords	Oxytocin; birth; contractions
Details of existing review of same topic by same authors	Not applicable

Field	Content
Additional information	None
Details of final publication	www.nice.org.uk

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; CTG: cardiotocography; GRADE: Grading of Recommendations Assessment, Development and Evaluation; (I)HTA: (International) Health Technology Assessment; LMIC: low and middle income countries; MID: minimally important difference; NGA: National Guideline Alliance; NHS: National health service; NICE: National Institute for Health and Care Excellence; OECD: Organisation for Economic Co-operation and Development; RCT: randomised controlled trial; RoB: risk of bias; SD: standard deviation

Review protocol for review question: What is the optimum dose at which oxytocin should be restarted if stopped due to an abnormality in the CTG?

Table 4: Review protocol - restarting oxytocin

Field	Content
PROSPERO registration number	CRD42021266237
Review title	Optimum dose at which oxytocin should be restarted if stopped due to an abnormality in the CTG
Review question	What is the optimum dose at which oxytocin should be restarted if stopped due to an abnormality in the CTG?
Objective	To provide clarity in practice regarding the optimum dose at which oxytocin should be restarted if stopped due to an abnormality in the CTG
Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • International Health Technology Assessment database (IHTA) Searches will be restricted by: • No date limitations • English language only

Field	Content
	• Human studies only Other searches: • Inclusion lists of systematic reviews The full search strategies for MEDLINE database will be published in the final review. For each search, the principal database search strategy is quality assured by a second information scientist using an adaptation of the PRESS 2015 Guideline Evidence-Based Checklist.
Condition or domain being studied	Labour and birth
Population	• Women in labour who are pregnant with a single baby, who go into labour at term (37 to 42 weeks of pregnancy) and who do not have any pre-existing medical conditions or antenatal conditions that predispose to a higher risk birth • Women whose baby has not been identified before labour to be at high risk of adverse outcomes • Women who have been started on oxytocin but it had to be stopped due to an abnormality in the CTG • Singleton babies born at term (37 to 42 weeks of pregnancy) with no previously identified problems (for example congenital malformations, genetic anomalies, intrauterine growth restriction, placental problems)
Intervention	• Restart using the same dose as the dose when oxytocin was switched off • Restart using a lower dose than the dose when oxytocin was switched off
Comparator	• Any of the above interventions compared to each other
Types of study to be included	Include published full-text papers: • Systematic reviews of RCTs • Parallel RCTs • If insufficient RCTs: ○ Systematic reviews of observational studies

Field	Content
	○ Cohort studies with > 100 women in each arm Note: studies must make adjustment for confounding factors in their analysis Conference abstracts will not be included because these do not typically have sufficient information to allow full critical appraisal.
Other exclusion criteria	Population: • Women in labour who are identified before labour to be at high risk, or whose baby is at high risk, of complications or adverse outcomes • Women with breech presentation • Women in preterm labour • Women with an intrauterine fetal death • Women with multi-fetal pregnancies • Women who have had a previous caesarean birth or who are having a planned caesarean birth Setting: • Countries other than high income countries (as defined by the OECD) because LMIC would use oxytocin, but the monitoring would vary *If any study or systematic review includes <1/3 of women with the above characteristics/ who received care in the above setting, it will be considered for inclusion but, if included, the evidence will be downgraded for indirectness.*
Context	This guideline will partly update the following: Intrapartum care for healthy women and babies (CG190)
Primary outcomes (critical outcomes)	• Uterine hyperstimulation or uterine tachysystole, or 5 or more contractions per 10 minutes (with or without changes in CTG) • Non-reassuring, abnormal, suspicious or pathological CTG • Length of labour

Field	Content
Secondary outcomes (important outcomes)	• Mode of birth (for example spontaneous vaginal, instrumental, caesarean birth) • Neonatal death, intrapartum stillbirth, or severe hypoxic ischemic encephalopathy (grade 2/3) • Apgar score below 7 at 5 minutes • Women's experience of labour and birth **Amendment:** A change to the outcome Apgar score was made to more accurately reflect measures of poor outcome. Previous measurement: Apgar score below 6 at 5 minutes
Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Duplicate screening will not be undertaken for this question. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs • Cochrane RoB tool v.2 for cluster-randomized trials • Cochrane ROBINS-I tool for non-randomised (clinical) controlled trials and cohort studies The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
Strategy for data synthesis	Quantitative findings will be formally summarised in the review. Where multiple studies report on the same outcome for the same comparison, meta-analyses will be conducted using Cochrane Review Manager software.

Field	Content
	A fixed effect meta-analysis will be conducted and data will be presented as risk ratios if possible or odds ratios when required (for example, if only available in this form in included studies) for dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes. Heterogeneity in the effect estimates of the individual studies will be assessed using the I2 statistic. Alongside visual inspection of the point estimates and confidence intervals, I2 values of greater than 50% and 80% will be considered as significant and very significant heterogeneity, respectively. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through subgroup analysis then a random effects model will be used for meta-analysis, or the data will not be pooled. The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/ **Minimally important differences:** • Length of labour: 1 day • Neonatal death, intrapartum stillbirth, or severe hypoxic ischemic encephalopathy (grade 2/3): statistical significance • Validated scales/continuous outcomes: published MIDs where available • All other outcomes & where published MIDs are not available: 0.8 and 1.25 for all relative dichotomous outcomes ; +/- 0.5x control group SD for continuous outcomes
Analysis of subgroups	Evidence will be stratified by: • Difference in reduction of oxytocin dose (if restarting dose is reduced) • BMI thresholds on booking: ○ Underweight range: <18.5 kg/m^2 ○ Healthy weight range: 18.5 to 24.9 kg/m^2 ○ Overweight range: 25 to 29.99 kg/m^2 ○ Obesity 1: 30 to 34.99 kg/m^2

Field	Content	
	○ Obesity 2: 35 to 39.99 kg/m^2 • Parity (nulliparous vs mixed parity vs multiparous) Stratifications will be dealt with in a hierarchy (this is, by difference in reduction of oxytocin dose, then by BMI and then by parity) Evidence will be subgrouped by the following only in the event that there is significant heterogeneity in outcomes: • Age of woman (<35 vs >/= 35) • Ethnicity ○ White ○ Asian/Asian British ○ Black/African/Caribbean/Black British ○ Mixed/Multiple ethnic groups ○ Other ethnic group • Women with disability vs not • Deprived socioeconomic group vs not Where evidence is stratified or subgrouped the committee will consider on a case by case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.	
Type and method of review	☒	Intervention
	☐	Diagnostic
	☐	Prognostic
	☐	Qualitative
	☐	Epidemiologic
	☐	Service Delivery

Field	Content	
	☐	Other (please specify)
Language	English	
Country	England	
Anticipated or actual start date	22/06/2021	
Anticipated completion date	22/03/2023	
Named contact	5a. Named contact Guideline Development Team National Guideline Alliance (NGA) 5b. Named contact e-mail IPCupdate@nice.org.uk 5c. Organisational affiliation of the review Guideline Development Team NGA, Centre for Guidelines, National Institute for Health and Care Excellence (NICE)	
Review team members	From the Guideline Development Team NGA: • Senior Systematic Reviewer • Systematic Reviewer	
Funding sources/sponsor	This systematic review is being completed by the Guideline Development Team NGA, Centre for Guidelines, which is part of the National Institute for Health and Care Excellence (NICE).	
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	

Field	Content
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/cg190
Other registration details	None
URL for published protocol	https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=266237
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: notifying registered stakeholders of publication publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
Keywords	Oxytocin; CTG
Details of existing review of same topic by same authors	Not applicable
Additional information	None
Details of final publication	www.nice.org.uk

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; CTG: cardiotocography; ; GRADE: Grading of Recommendations Assessment, Development and Evaluation; (I)HTA: International Health Technology Assessment; LMIC: low and middle income countries; MID: minimally important difference; NGA: National Guideline Alliance; NHS: National health service; NICE: National Institute for Health and Care Excellence; OECD: Organisation for Economic Co-operation and Development; RCT: randomised controlled trial; RoB: risk of bias; SD: standard deviation

Appendix B Literature search strategies

Literature search strategies for review question: What is the effectiveness of altering the dose of intravenous oxytocin to reduce excessive frequency of uterine contractions?

Review question search strategies

Database: Medline OVID interface

Date of last search: 07/12/2022

#	Searches
1	OXYTOCIN/
2	(ocytocin or oxytocin or pitocin or syntocinon).mp.
3	or/1-2
4	((excess$ or elevat$) adj3 (uterine or uterus$) adj3 (activit$ or contracti$)).ti,ab.
5	((uterine or uterus$) adj3 (hyperstimulat$ or tachysystole)).ti,ab.
6	or/4-5
7	3 and 6
8	limit 7 to english language
9	LETTER/
10	EDITORIAL/
11	NEWS/
12	exp HISTORICAL ARTICLE/
13	ANECDOTES AS TOPIC/
14	COMMENT/
15	CASE REPORT/
16	(letter or comment*).ti.
17	or/9-16
18	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
19	17 not 18
20	ANIMALS/ not HUMANS/
21	exp ANIMALS, LABORATORY/
22	exp ANIMAL EXPERIMENTATION/
23	exp MODELS, ANIMAL/
24	exp RODENTIA/
25	(rat or rats or mouse or mice).ti.
26	or/19-25
27	8 not 26
28	META-ANALYSIS/
29	META-ANALYSIS AS TOPIC/
30	(meta analy* or metanaly* or metaanaly*).ti,ab.
31	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
32	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
33	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
34	(search* adj4 literature).ab.
35	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
36	cochrane.jw.
37	or/28-36
38	randomized controlled trial.pt.
39	controlled clinical trial.pt.
40	pragmatic clinical trial.pt.
41	randomi#ed.ab.
42	placebo.ab.
43	randomly.ab.
44	CLINICAL TRIALS AS TOPIC/
45	trial.ti.
46	or/38-45
47	COHORT STUDIES/
48	FOLLOW-UP STUDIES/
49	LONGITUDINAL STUDIES/
50	PROSPECTIVE STUDIES/
51	RETROSPECTIVE STUDIES/

#	Searches
52	((cohort* or follow-up or follow?up or longitudinal* or prospective* or retrospective*) adj1 (stud* or research or analys*)).tw.
53	(incidence? adj (stud* or research or analys*)).tw.
54	(longitudinal* adj1 (survey* or evaluat*)).tw.
55	(prospective* adj method*).tw.
56	(retrospective* adj design*).tw.
57	or/47-56
58	27 and 37
59	27 and 46
60	27 and 57
61	or/58-60

Database: Embase – OVID interface

Date of last search: 07/12/2022

#	Searches
1	OXYTOCIN/
2	(ocytocin or oxytocin or pitocin or syntocinon).mp.
3	or/1-2
4	((excess$ or elevat$) adj3 (uterine or uterus$) adj3 (activit$ or contracti$)).ti,ab.
5	((uterine or uterus$) adj3 (hyperstimulat$ or tachysystole)).ti,ab.
6	or/4-5
7	3 and 6
8	limit 7 to english language
9	letter.pt. or LETTER/
10	note.pt.
11	editorial.pt.
12	CASE REPORT/ or CASE STUDY/
13	(letter or comment*).ti.
14	or/9-13
15	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
16	14 not 15
17	ANIMAL/ not HUMAN/
18	NONHUMAN/
19	exp ANIMAL EXPERIMENT/
20	exp EXPERIMENTAL ANIMAL/
21	ANIMAL MODEL/
22	exp RODENT/
23	(rat or rats or mouse or mice).ti.
24	or/16-23
25	8 not 24
26	SYSTEMATIC REVIEW/
27	META-ANALYSIS/
28	(meta analy* or metanaly* or metaanaly*).ti,ab.
29	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
30	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
31	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
32	(search* adj4 literature).ab.
33	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
34	((pool* or combined) adj2 (data or trials or studies or results)).ab.
35	cochrane.jw.
36	or/26-35
37	random*.ti,ab.
38	factorial*.ti,ab.
39	(crossover* or cross over*).ti,ab.
40	((doubl* or singl*) adj blind*).ti,ab.
41	(assign* or allocat* or volunteer* or placebo*).ti,ab.
42	CROSSOVER PROCEDURE/
43	SINGLE BLIND PROCEDURE/
44	RANDOMIZED CONTROLLED TRIAL/
45	DOUBLE BLIND PROCEDURE/
46	or/37-45
47	COHORT ANALYSIS/
48	FOLLOW UP/
49	LONGITUDINAL STUDY/

#	Searches
50	PROSPECTIVE STUDY/
51	RETROSPECTIVE STUDIES/
52	((cohort* or follow-up or follow?up or longitudinal* or prospective* or retrospective*) adj1 (stud* or research or analys*)).tw.
53	(incidence? adj (stud* or research or analys*)).tw.
54	(longitudinal* adj1 (survey* or evaluat*)).tw.
55	(prospective* adj method*).tw.
56	(retrospective* adj design*).tw.
57	or/47-56
58	25 and 36
59	25 and 46
60	25 and 57
61	or/58-60

Databases: Cochrane Central Register of Controlled Trials; and Cochrane Database of Systematic Reviews – Wiley interface

Date of last search: 07/12/2022

#	Searches
#1	MeSH descriptor: [Oxytocin] this term only
#2	(ocytocin or oxytocin or pitocin or syntocinon):ti,ab
#3	#1 or #2
#4	((excess* or elevat*) near/3 (uterine or uterus*) near/3 (activit* or contracti*)):ti,ab
#5	((uterine or uterus*) near/3 (hyperstimulat* or tachysystole)):ti,ab
#6	#4 or #5
#7	#3 and #6

Database: International Health Technology Assessment

Date of last search: 07/12/2022

#	Searches
	MeSH Search: OXYTOCIN
	OR All: ocytocin or oxytocin or pitocin or syntocinon

Health economics search strategies

Database: Medline – OVID interface

Date of last search: 07/12/2022

#	Searches
1	OXYTOCIN/
2	(ocytocin or oxytocin or pitocin or syntocinon).mp.
3	or/1-2
4	((excess$ or elevat$) adj3 (uterine or uterus$) adj3 (activit$ or contracti$)).ti,ab.
5	((uterine or uterus$) adj3 (hyperstimulat$ or tachysystole)).ti,ab.
6	or/4-5
7	3 and 6
8	limit 7 to english language
9	LETTER/
10	EDITORIAL/
11	NEWS/
12	exp HISTORICAL ARTICLE/
13	ANECDOTES AS TOPIC/
14	COMMENT/
15	CASE REPORT/
16	(letter or comment*).ti.
17	or/9-16
18	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.

#	Searches
19	17 not 18
20	ANIMALS/ not HUMANS/
21	exp ANIMALS, LABORATORY/
22	exp ANIMAL EXPERIMENTATION/
23	exp MODELS, ANIMAL/
24	exp RODENTIA/
25	(rat or rats or mouse or mice).ti.
26	or/19-25
27	8 not 26
28	ECONOMICS/
29	VALUE OF LIFE/
30	exp "COSTS AND COST ANALYSIS"/
31	exp ECONOMICS, HOSPITAL/
32	exp ECONOMICS, MEDICAL/
33	exp RESOURCE ALLOCATION/
34	ECONOMICS, NURSING/
35	ECONOMICS, PHARMACEUTICAL/
36	exp "FEES AND CHARGES"/
37	exp BUDGETS/
38	budget*.ti,ab.
39	cost*.ti,ab.
40	(economic* or pharmaco?economic*).ti,ab.
41	(price* or pricing*).ti,ab.
42	(financ* or fee or fees or expenditure* or saving*).ti,ab.
43	(value adj2 (money or monetary)).ti,ab.
44	resourc* allocat*.ti,ab.
45	(fund or funds or funding* or funded).ti,ab.
46	(ration or rations or rationing* or rationed).ti,ab.
47	ec.fs.
48	or/28-47
49	27 and 48

Database: Embase – OVID interface

Date of last search: 07/12/2022

#	Searches
1	OXYTOCIN/
2	(ocytocin or oxytocin or pitocin or syntocinon).mp.
3	or/1-2
4	((excess$ or elevat$) adj3 (uterine or uterus$) adj3 (activit$ or contracti$)).ti,ab.
5	((uterine or uterus$) adj3 (hyperstimulat$ or tachysystole)).ti,ab.
6	or/4-5
7	3 and 6
8	limit 7 to english language
9	letter.pt. or LETTER/
10	note.pt.
11	editorial.pt.
12	CASE REPORT/ or CASE STUDY/
13	(letter or comment*).ti.
14	or/9-13
15	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
16	14 not 15
17	ANIMAL/ not HUMAN/
18	NONHUMAN/
19	exp ANIMAL EXPERIMENT/
20	exp EXPERIMENTAL ANIMAL/
21	ANIMAL MODEL/
22	exp RODENT/
23	(rat or rats or mouse or mice).ti.
24	or/16-23
25	8 not 24
26	HEALTH ECONOMICS/
27	exp ECONOMIC EVALUATION/
28	exp HEALTH CARE COST/
29	exp FEE/
30	BUDGET/

#	Searches
31	FUNDING/
32	RESOURCE ALLOCATION/
33	budget*.ti,ab.
34	cost*.ti,ab.
35	(economic* or pharmaco?economic*).ti,ab.
36	(price* or pricing*).ti,ab.
37	(financ* or fee or fees or expenditure* or saving*).ti,ab.
38	(value adj2 (money or monetary)).ti,ab.
39	resourc* allocat*.ti,ab.
40	(fund or funds or funding* or funded).ti,ab.
41	(ration or rations or rationing* or rationed).ti,ab.
42	or/26-41
43	25 and 42

Database: Cochrane Central Register of Controlled Trials - Wiley interface

Date of last search: 07/12/2022

#	Searches
#1	MeSH descriptor: [Oxytocin] this term only
#2	(ocytocin or oxytocin or pitocin or syntocinon):ti,ab
#3	#1 or #2
#4	((excess* or elevat*) near/3 (uterine or uterus*) near/3 (activit* or contracti*)):ti,ab
#5	((uterine or uterus*) near/3 (hyperstimulat* or tachysystole)):ti,ab
#6	#4 or #5
#7	#3 and #6
#8	MeSH descriptor: [Economics] this term only
#9	MeSH descriptor: [Value of Life] this term only
#10	MeSH descriptor: [Costs and Cost Analysis] explode all trees
#11	MeSH descriptor: [Economics, Hospital] explode all trees
#12	MeSH descriptor: [Economics, Medical] explode all trees
#13	MeSH descriptor: [Resource Allocation] explode all trees
#14	MeSH descriptor: [Economics, Nursing] this term only
#15	MeSH descriptor: [Economics, Pharmaceutical] this term only
#16	MeSH descriptor: [Fees and Charges] explode all trees
#17	MeSH descriptor: [Budgets] explode all trees
#18	budget*:ti,ab
#19	cost*:ti,ab
#20	(economic* or pharmaco?economic*):ti,ab
#21	(price* or pricing*):ti,ab
#22	(financ* or fee or fees or expenditure* or saving*):ti,ab
#23	(value near/2 (money or monetary)):ti,ab
#24	resourc* allocat*:ti,ab
#25	(fund or funds or funding* or funded):ti,ab
#26	(ration or rations or rationing* or rationed):ti,ab
#27	#8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26
#28	#7 and #27

Database: International Health Technology Assessment

Date of last search: 07/12/2022

#	Searches
	MeSH Search: OXYTOCIN
	OR All: ocytocin or oxytocin or pitocin or syntocinon

Literature search strategies for review question: What is the optimum dose at which oxytocin should be restarted if stopped due to an abnormality in the CTG?

Review question search strategies

Database: Medline – OVID interface

Date of last search: 07/12/2022

#	Searches
1	OXYTOCIN/ad [Administration & Dosage]
2	((ocytocin or oxytocin or pitocin or syntocinon) adj5 (dose? or dosage? or dosing or regimen?)).mp.
3	or/1-2
4	CARDIOTOCOGRAPHY/
5	(cardiotocogra* or CTG or electronic* f?etal monitor* or EFM).ti,ab.
6	or/4-5
7	3 and 6
8	((ocytocin or oxytocin or pitocin or syntocinon) adj10 (start* or stop* or initiat* or initial* or introduc* or begin* or commenc* or inaugurat* or launch* or instigat* or establish*) adj10 (dose? or dosage? or dosing or regimen*)).mp.
9	((ocytocin or oxytocin or pitocin or syntocinon) adj10 (restart* or re-start*)).mp.
10	((ocytocin or oxytocin or pitocin or syntocinon) adj10 interrupt*).mp.
11	((ocytocin or oxytocin or pitocin or syntocinon) adj10 (optimum or optimal or optimi* or same or maintain* or maintenance or lower* or decreas* or reduc*) adj10 (dose? or dosage? or dosing or regimen*)).mp.
12	or/7-11
13	limit 12 to english language
14	LETTER/
15	EDITORIAL/
16	NEWS/
17	exp HISTORICAL ARTICLE/
18	ANECDOTES AS TOPIC/
19	COMMENT/
20	CASE REPORT/
21	(letter or comment*).ti.
22	or/14-21
23	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
24	22 not 23
25	ANIMALS/ not HUMANS/
26	exp ANIMALS, LABORATORY/
27	exp ANIMAL EXPERIMENTATION/
28	exp MODELS, ANIMAL/
29	exp RODENTIA/
30	(rat or rats or mouse or mice).ti.
31	or/24-30
32	13 not 31
33	META-ANALYSIS/
34	META-ANALYSIS AS TOPIC/
35	(meta analy* or metanaly* or metaanaly*).ti,ab.
36	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
37	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
38	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
39	(search* adj4 literature).ab.
40	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
41	cochrane.jw.
42	or/33-41
43	randomized controlled trial.pt.
44	controlled clinical trial.pt.
45	pragmatic clinical trial.pt.
46	randomi#ed.ab.
47	placebo.ab.
48	randomly.ab.
49	CLINICAL TRIALS AS TOPIC/
50	trial.ti.
51	or/43-50
52	COHORT STUDIES/
53	FOLLOW-UP STUDIES/

#	Searches
54	LONGITUDINAL STUDIES/
55	PROSPECTIVE STUDIES/
56	RETROSPECTIVE STUDIES/
57	((cohort* or follow-up or follow?up or longitudinal* or prospective* or retrospective*) adj1 (stud* or research or analys*)).tw.
58	(incidence? adj (stud* or research or analys*)).tw.
59	(longitudinal* adj1 (survey* or evaluat*)).tw.
60	(prospective* adj method*).tw.
61	(retrospective* adj design*).tw.
62	or/52-61
63	32 and 42
64	32 and 51
65	32 and 62
66	or/63-65

Database: Embase – OVID interface

Date of last search: 07/12/2022

#	Searches
1	OXYTOCIN/do [Drug Dose]
2	((ocytocin or oxytocin or pitocin or syntocinon) adj5 (dose? or dosage? or dosing or regimen?)).mp.
3	or/1-2
4	CARDIOTOCOGRAPHY/
5	(cardiotocogra* or CTG or electronic* f?etal monitor* or EFM).ti,ab.
6	or/4-5
7	3 and 6
8	((ocytocin or oxytocin or pitocin or syntocinon) adj10 (start* or stop* or initiat* or initial* or introduc* or begin* or commenc* or inaugurat* or launch* or instigat* or establish*) adj10 (dose? or dosage? or dosing or regimen*)).mp.
9	((ocytocin or oxytocin or pitocin or syntocinon) adj10 (restart* or re-start*)).mp.
10	((ocytocin or oxytocin or pitocin or syntocinon) adj10 interrupt*).mp.
11	((ocytocin or oxytocin or pitocin or syntocinon) adj10 (optimum or optimal or optimi* or same or maintain* or maintenance or lower* or decreas* or reduc*) adj10 (dose? or dosage? or dosing or regimen*)).mp.
12	or/7-11
13	limit 12 to english language
14	letter.pt. or LETTER/
15	note.pt.
16	editorial.pt.
17	CASE REPORT/ or CASE STUDY/
18	(letter or comment*).ti.
19	or/14-18
20	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
21	19 not 20
22	ANIMAL/ not HUMAN/
23	NONHUMAN/
24	exp ANIMAL EXPERIMENT/
25	exp EXPERIMENTAL ANIMAL/
26	ANIMAL MODEL/
27	exp RODENT/
28	(rat or rats or mouse or mice).ti.
29	or/21-28
30	13 not 29
31	SYSTEMATIC REVIEW/
32	META-ANALYSIS/
33	(meta analy* or metanaly* or metaanaly*).ti,ab.
34	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
35	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
36	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
37	(search* adj4 literature).ab.
38	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
39	((pool* or combined) adj2 (data or trials or studies or results)).ab.
40	cochrane.jw.
41	or/31-40
42	random*.ti,ab.
43	factorial*.ti,ab.
44	(crossover* or cross over*).ti,ab.

#	Searches
45	((doubl* or singl*) adj blind*).ti,ab.
46	(assign* or allocat* or volunteer* or placebo*).ti,ab.
47	CROSSOVER PROCEDURE/
48	SINGLE BLIND PROCEDURE/
49	RANDOMIZED CONTROLLED TRIAL/
50	DOUBLE BLIND PROCEDURE/
51	or/42-50
52	COHORT ANALYSIS/
53	FOLLOW UP/
54	LONGITUDINAL STUDY/
55	PROSPECTIVE STUDY/
56	RETROSPECTIVE STUDIES/
57	((cohort* or follow-up or follow?up or longitudinal* or prospective* or retrospective*) adj1 (stud* or research or analys*)).tw.
58	(incidence? adj (stud* or research or analys*)).tw.
59	(longitudinal* adj1 (survey* or evaluat*)).tw.
60	(prospective* adj method*).tw.
61	(retrospective* adj design*).tw.
62	or/52-61
63	30 and 41
64	30 and 51
65	30 and 62
66	or/63-65

Databases: Cochrane Central Register of Controlled Trials; and Cochrane Database of Systematic Reviews – Wiley interface

Date of last search: 07/12/2022

#	Searches
#1	MeSH descriptor: [Oxytocin] this term only and with qualifier(s): [administration & dosage - AD]
#2	((ocytocin or oxytocin or pitocin or syntocinon) near/5 (dose* or dosage* or dosing or regimen or regimens)):ti,ab
#3	#1 or #2
#4	MeSH descriptor: [Cardiotocography] this term only
#5	(cardiotocogra* or CTG or "electronic* fetal monitor*" or "electronic* foetal monitor*" or EFM):ti,ab
#6	#4 or #5
#7	#3 and #6

Databases: International Health Technology Assessment

Date of last search: 07/12/2022

#	Searches
	MeSH Search: OXYTOCIN
	OR All: ocytocin or oxytocin or pitocin or syntocinon

Health economics search strategies

Database: Medline – OVID interface

Date of last search: 07/12/2022

#	Searches
1	OXYTOCIN/ad [Administration & Dosage]
2	((ocytocin or oxytocin or pitocin or syntocinon) adj5 (dose? or dosage? or dosing or regimen?)).mp.
3	or/1-2
4	CARDIOTOCOGRAPHY/
5	(cardiotocogra* or CTG or electronic* f?etal monitor* or EFM).ti,ab.
6	or/4-5

#	Searches
7	3 and 6
8	((ocytocin or oxytocin or pitocin or syntocinon) adj10 (start* or stop* or initiat* or initial* or introduc* or begin* or commenc* or inaugurat* or launch* or instigat* or establish*) adj10 (dose? or dosage? or dosing or regimen*)).mp.
9	((ocytocin or oxytocin or pitocin or syntocinon) adj10 (restart* or re-start*)).mp.
10	((ocytocin or oxytocin or pitocin or syntocinon) adj10 interrupt*).mp.
11	((ocytocin or oxytocin or pitocin or syntocinon) adj10 (optimum or optimal or optimi* or same or maintain* or maintenance or lower* or decreas* or reduc*) adj10 (dose? or dosage? or dosing or regimen*)).mp.
12	or/7-11
13	limit 12 to english language
14	LETTER/
15	EDITORIAL/
16	NEWS/
17	exp HISTORICAL ARTICLE/
18	ANECDOTES AS TOPIC/
19	COMMENT/
20	CASE REPORT/
21	(letter or comment*).ti.
22	or/14-21
23	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
24	22 not 23
25	ANIMALS/ not HUMANS/
26	exp ANIMALS, LABORATORY/
27	exp ANIMAL EXPERIMENTATION/
28	exp MODELS, ANIMAL/
29	exp RODENTIA/
30	(rat or rats or mouse or mice).ti.
31	or/24-30
32	13 not 31
33	ECONOMICS/
34	VALUE OF LIFE/
35	exp "COSTS AND COST ANALYSIS"/
36	exp ECONOMICS, HOSPITAL/
37	exp ECONOMICS, MEDICAL/
38	exp RESOURCE ALLOCATION/
39	ECONOMICS, NURSING/
40	ECONOMICS, PHARMACEUTICAL/
41	exp "FEES AND CHARGES"/
42	exp BUDGETS/
43	budget*.ti,ab.
44	cost*.ti,ab.
45	(economic* or pharmaco?economic*).ti,ab.
46	(price* or pricing*).ti,ab.
47	(financ* or fee or fees or expenditure* or saving*).ti,ab.
48	(value adj2 (money or monetary)).ti,ab.
49	resourc* allocat*.ti,ab.
50	(fund or funds or funding* or funded).ti,ab.
51	(ration or rations or rationing* or rationed).ti,ab.
52	ec.fs.
53	or/33-52
54	32 and 53

Database: Embase – OVID interface

Date of last search: 07/12/2022

#	Searches
1	OXYTOCIN/do [Drug Dose]
2	((ocytocin or oxytocin or pitocin or syntocinon) adj5 (dose? or dosage? or dosing or regimen?)).mp.
3	or/1-2
4	CARDIOTOCOGRAPHY/
5	(cardiotocogra* or CTG or electronic* f?etal monitor* or EFM).ti,ab.
6	or/4-5
7	3 and 6
8	((ocytocin or oxytocin or pitocin or syntocinon) adj10 (start* or stop* or initiat* or initial* or introduc* or begin* or commenc* or inaugurat* or launch* or instigat* or establish*) adj10 (dose? or dosage? or dosing or regimen*)).mp.

#	Searches
9	((ocytocin or oxytocin or pitocin or syntocinon) adj10 (restart* or re-start*)).mp.
10	((ocytocin or oxytocin or pitocin or syntocinon) adj10 interrupt*).mp.
11	((ocytocin or oxytocin or pitocin or syntocinon) adj10 (optimum or optimal or optimi* or same or maintain* or maintenance or lower* or decreas* or reduc*) adj10 (dose? or dosage? or dosing or regimen*)).mp.
12	or/7-11
13	limit 12 to english language
14	letter.pt. or LETTER/
15	note.pt.
16	editorial.pt.
17	CASE REPORT/ or CASE STUDY/
18	(letter or comment*).ti.
19	or/14-18
20	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
21	19 not 20
22	ANIMAL/ not HUMAN/
23	NONHUMAN/
24	exp ANIMAL EXPERIMENT/
25	exp EXPERIMENTAL ANIMAL/
26	ANIMAL MODEL/
27	exp RODENT/
28	(rat or rats or mouse or mice).ti.
29	or/21-28
30	13 not 29
31	HEALTH ECONOMICS/
32	exp ECONOMIC EVALUATION/
33	exp HEALTH CARE COST/
34	exp FEE/
35	BUDGET/
36	FUNDING/
37	RESOURCE ALLOCATION/
38	budget*.ti,ab.
39	cost*.ti,ab.
40	(economic* or pharmaco?economic*).ti,ab.
41	(price* or pricing*).ti,ab.
42	(financ* or fee or fees or expenditure* or saving*).ti,ab.
43	(value adj2 (money or monetary)).ti,ab.
44	resourc* allocat*.ti,ab.
45	(fund or funds or funding* or funded).ti,ab.
46	(ration or rations or rationing* or rationed).ti,ab.
47	or/31-46
48	30 and 47

Database: Cochrane Central Register of Controlled Trials – Wiley interface

Date of last search: 07/12/2022

#	Searches
#1	MeSH descriptor: [Oxytocin] this term only and with qualifier(s): [administration & dosage - AD]
#2	((ocytocin or oxytocin or pitocin or syntocinon) near/5 (dose* or dosage* or dosing or regimen or regimens)):ti,ab
#3	#1 or #2
#4	MeSH descriptor: [Cardiotocography] this term only
#5	(cardiotocogra* or CTG or "electronic* fetal monitor*" or "electronic* foetal monitor*" or EFM):ti,ab
#6	#4 or #5
#7	#3 and #6
#8	MeSH descriptor: [Economics] this term only
#9	MeSH descriptor: [Value of Life] this term only
#10	MeSH descriptor: [Costs and Cost Analysis] explode all trees
#11	MeSH descriptor: [Economics, Hospital] explode all trees
#12	MeSH descriptor: [Economics, Medical] explode all trees
#13	MeSH descriptor: [Resource Allocation] explode all trees
#14	MeSH descriptor: [Economics, Nursing] this term only
#15	MeSH descriptor: [Economics, Pharmaceutical] this term only
#16	MeSH descriptor: [Fees and Charges] explode all trees
#17	MeSH descriptor: [Budgets] explode all trees
#18	budget*:ti,ab
#19	cost*:ti,ab
#20	(economic* or pharmaco?economic*):ti,ab

#	Searches
#21	(price* or pricing*):ti,ab
#22	(financ* or fee or fees or expenditure* or saving*):ti,ab
#23	(value near/2 (money or monetary)):ti,ab
#24	resourc* allocat*:ti,ab
#25	(fund or funds or funding* or funded):ti,ab
#26	(ration or rations or rationing* or rationed):ti,ab
#27	#8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26
#28	#7 and #27

Database: International Health Technology Assessment

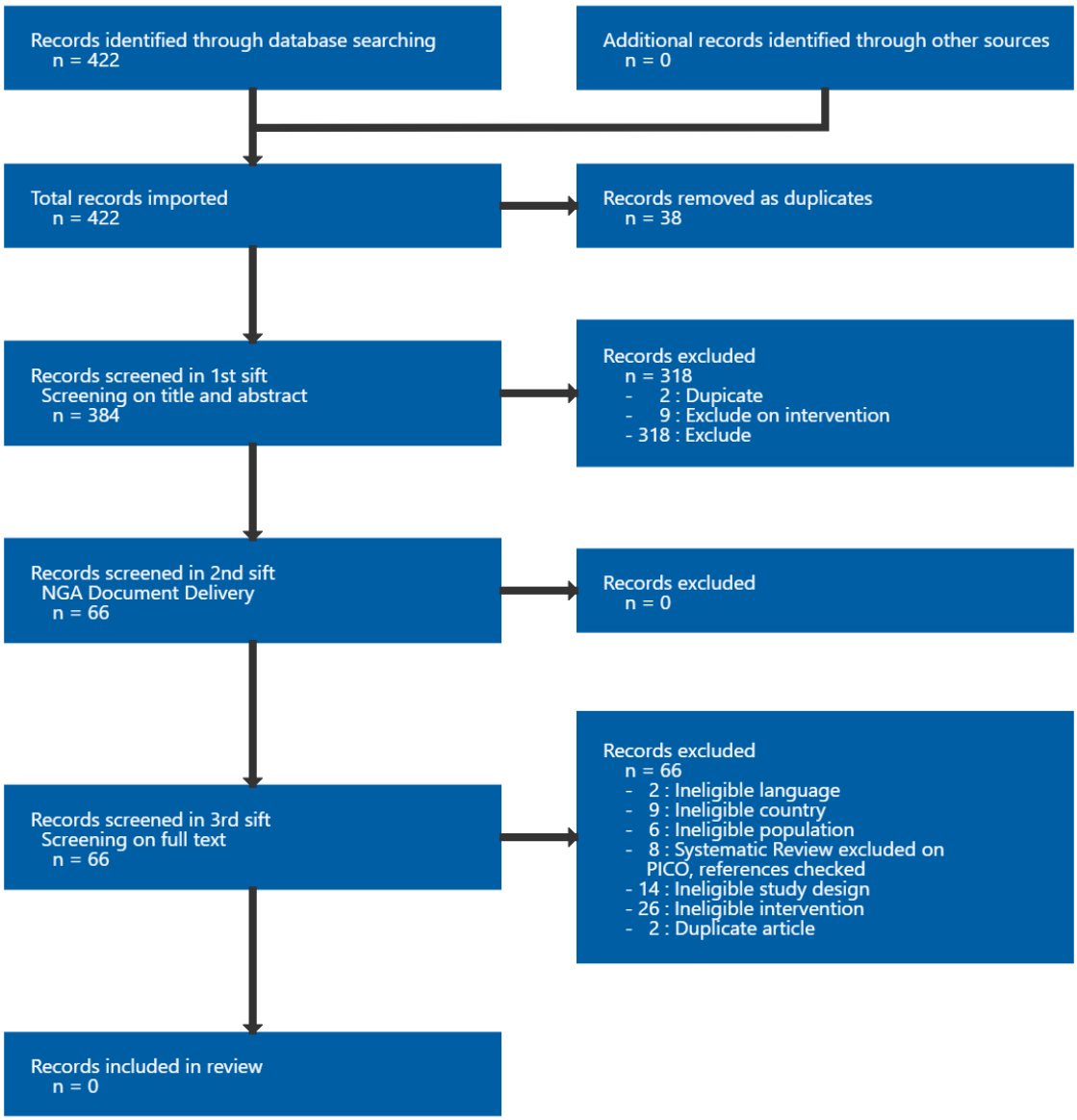
Date of last search: 07/12/2022

#	Searches
	MeSH Search: OXYTOCIN
	OR All: ocytocin or oxytocin or pitocin or syntocinon

Appendix C Effectiveness evidence study selection

Study selection for: What is the effectiveness of altering the dose of intravenous oxytocin to reduce excessive frequency of uterine contractions?

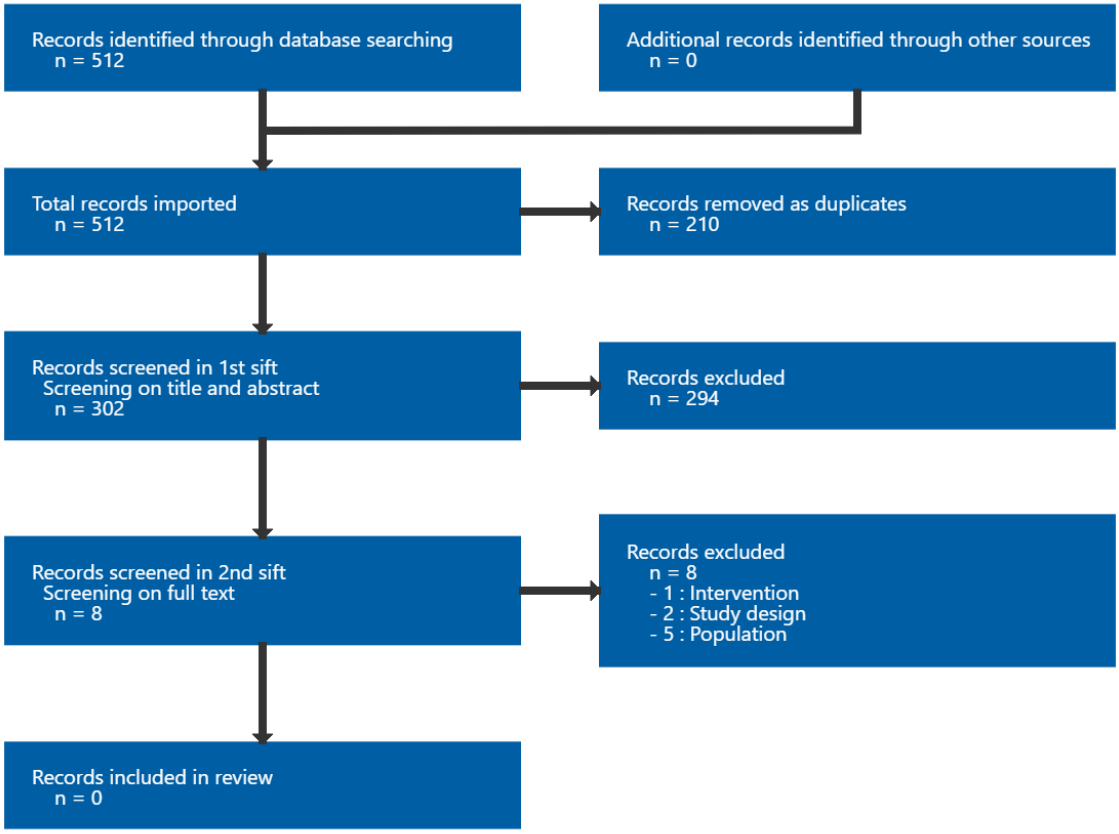
Figure 1: Study selection flow chart – dose oxytocin



Note: for this review, de-duplication was done outside of EPPI in EndNote for practical reasons, therefore the study selection flowchart does not accurately reflect the records removed as duplicates

Study selection for: What is the optimum dose at which oxytocin should be restarted if stopped due to an abnormality in the CTG?

Figure 2: Study selection flow chart – restarting oxytocin



Note: for this review, de-duplication was done outside of EPPI in EndNote for practical reasons, therefore the study selection flowchart does not accurately reflect the records removed as duplicates

Appendix D Evidence tables

Evidence tables for review question: What is the effectiveness of altering the dose of intravenous oxytocin to reduce excessive frequency of uterine contractions?

Evidence tables for review question: What is the optimum dose at which oxytocin should be restarted if stopped due to an abnormality in the CTG?

No evidence was identified which was applicable to these review questions.

Appendix E Forest plots

Forest plots for review question: What is the effectiveness of altering the dose of intravenous oxytocin to reduce excessive frequency of uterine contractions?

Forest plots for review question: What is the optimum dose at which oxytocin should be restarted if stopped due to an abnormality in the CTG

No meta-analysis was conducted for these review questions and so there are no forest plots.

Appendix F GRADE tables

GRADE tables for review question: What is the effectiveness of altering the dose of intravenous oxytocin to reduce excessive frequency of uterine contractions?

GRADE tables for review question: What is the optimum dose at which oxytocin should be restarted if stopped due to an abnormality in the CTG?

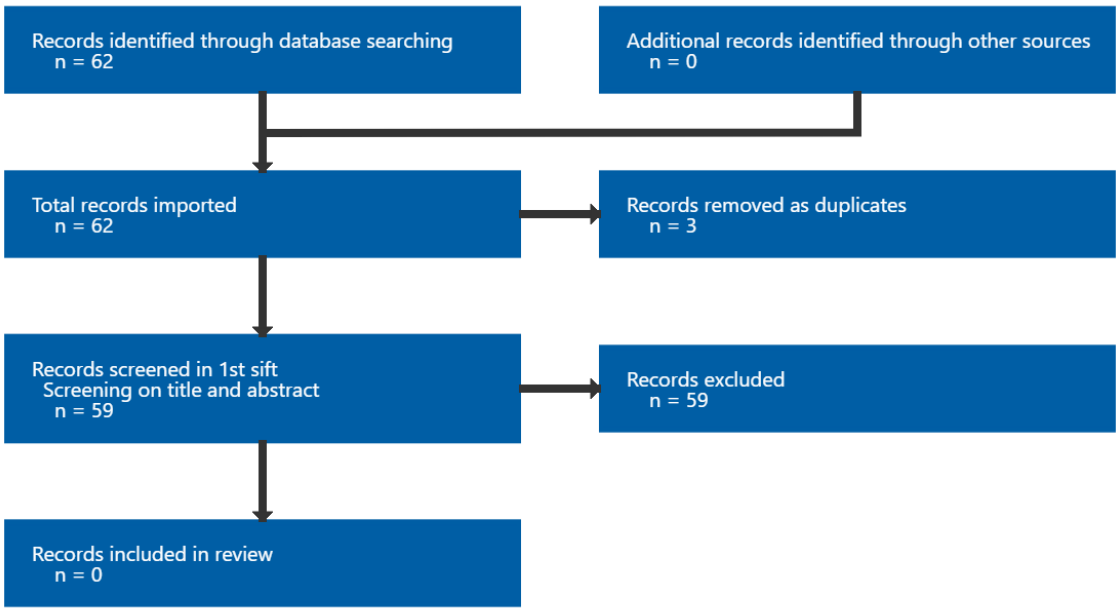
No evidence was identified which was applicable to these review questions.

Appendix G Economic evidence study selection

Study selection for: What is the effectiveness of altering the dose of intravenous oxytocin to reduce excessive frequency of uterine contractions?

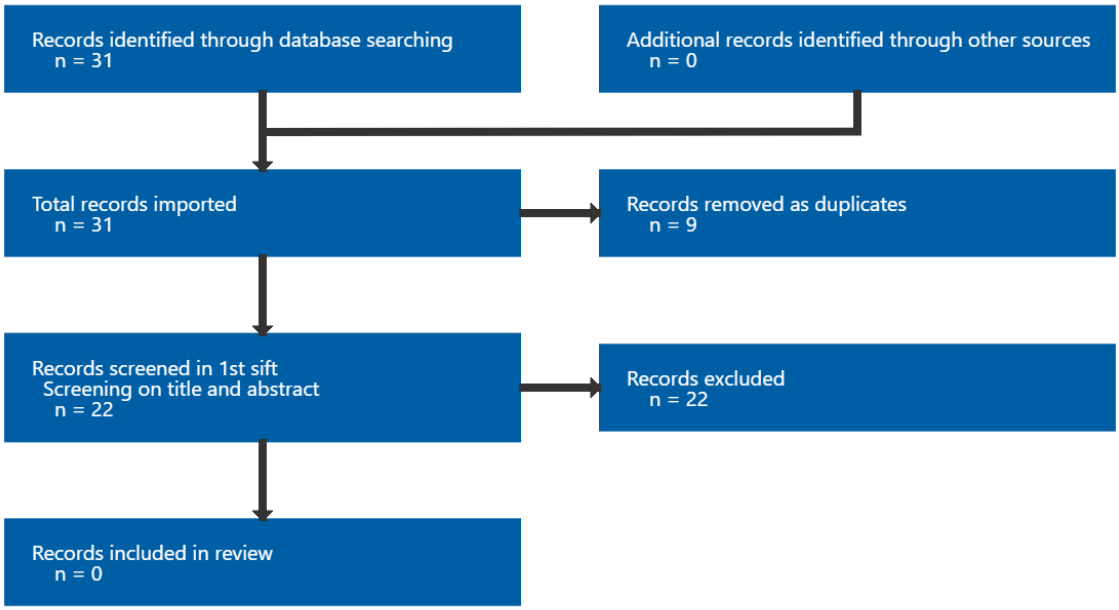
No economic evidence was identified which was applicable to this review question.

Figure 3: Study selection flow chart - dose oxytocin



Study selection for: What is the optimum dose at which oxytocin should be restarted if stopped due to an abnormality in the CTG?

Figure 4: Study selection chart - restarting oxytocin



Appendix H Economic evidence tables

Economic evidence tables for review question: What is the effectiveness of altering the dose of intravenous oxytocin to reduce excessive frequency of uterine contractions?

Economic evidence tables for review question: What is the optimum dose at which oxytocin should be restarted if stopped due to an abnormality in the CTG?

No evidence was identified which was applicable to these review questions.

Appendix I Economic model

Economic model for review question: What is the effectiveness of altering the dose of intravenous oxytocin to reduce excessive frequency of uterine contractions?

Economic model for review question: What is the optimum dose at which oxytocin should be restarted if stopped due to an abnormality in the CTG?

No economic analysis was conducted for these review questions.

Appendix J Excluded studies

Excluded studies for review question: What is the effectiveness of altering the dose of intravenous oxytocin to reduce excessive frequency of uterine contractions?

Excluded effectiveness studies

Table 5: Excluded studies and reasons for their exclusion – dose oxytocin

Study	Reason for exclusion
(2021) High Or Low Dose Syntocinon for delay in labour (HOLDS).	- Duplicate article No dose reduction – high vs low dose increments
(2018) High-dose versus low-dose of oxytocin for labour augmentation: a randomised controlled trial. Women and birth	- Ineligible intervention No dose reduction – High (6.6 mU oxytocin/min) vs low dose (3.3 mU oxytocin/min), increments every 20 min
Aboshama, Rehab Abdelhamid, Abdelhakim, Ahmed Mohamed, Shareef, Mohammad Abrar et al. (2021) High dose vs. low dose oxytocin for labor augmentation: a systematic review and meta-analysis of randomized controlled trials. Journal of perinatal medicine 49(2): 178-190	- Ineligible intervention No dose reduction, high vs low dose increments
Actrn (2019) Does the use of oxytocin in a pulsatile fashion (intermittent boluses), when compared to the use of continuous oxytocin, for the commencement and/or assistance of labour, result in a reduction in the number of caesarean sections that are required?. http://www.who.int/trialsearch/Trial2.aspx?TrialID=ACTRN12619000588190	- Ineligible study design Abstract only, no published results
Alomari, S. (2021) Oxytocin in active labour, should we maintain, break or discontinue the dose?. BJOG: An International Journal of Obstetrics and Gynaecology 128(suppl2): 138-139	- Ineligible study design Abstract only, no published results
Boie, S., Glavind, J., Uldbjerg, N. et al. (2021) Continued versus discontinued oxytocin stimulation in the active phase of labour (CONDISOX): double blind randomised controlled trial. BMJ (Clinical research ed.) 373: n716	- Ineligible intervention No dose reduction – 5 vs 10 IU oxytocin at 3.3 mIU/min every 20 min by 3.3 mIU/min until regular contractions (3-5 contractions every 10 minutes)
Boie, S., Glavind, J., Velu, A. V. et al. (2018) Discontinuation of intravenous oxytocin in the active phase of induced labour. Cochrane Database of Systematic Reviews	- Systematic Review excluded on PICO, references checked Systematic Review excluded on PICO, references checked [ineligible population (any gestational age eligible), references checked no eligible studies identified]
Boie, Sidsel, Bor, Pinar, Glavind, Julie et al. (2019) CONDISOX-continued versus discontinued oxytocin stimulation of induced labour in a double-blind randomised controlled trial. BMC Pregnancy and Childbirth 19(1): 320	- Systematic Review excluded on population, references checked Ineligible population (any gestational age eligible), references checked no eligible studies identified
Bor, P., Ledertoug, S., Boie, S. et al. (2016) Continuation versus discontinuation of oxytocin infusion during the active phase of labour: a randomised	- Ineligible population includes gestation less than 37 weeks

Study	Reason for exclusion
controlled trial. BJOG : an international journal of obstetrics and gynaecology 123(1): 129-35	
Budden, A.; Chen, L.; Henry, A. (2015) High-dose versus low-dose oxytocin infusion for induction of labour: A systematic review. BJOG: An International Journal of Obstetrics and Gynaecology 122(suppl2): 163	- Duplicate article
Budden, Aaron; Chen, Lily J. Y.; Henry, Amanda (2014) High-dose versus low-dose oxytocin infusion regimens for induction of labour at term. The Cochrane database of systematic reviews: cd009701	- Systematic Review excluded on study designs, references checked Ineligible study designs included, references checked no eligible studies identified
Bugg, George J.; Siddiqui, Farah; Thornton, Jim G. (2013) Oxytocin versus no treatment or delayed treatment for slow progress in the first stage of spontaneous labour. The Cochrane database of systematic reviews: cd007123	- Systematic Review excluded on comparator, references checked Ineligible intervention: comparator is no treatment/placebo
Chua, S., Arulkumaran, S., Kurup, A. et al. (1991) Oxytocin titration for induction of labour: a prospective randomized study of 15 versus 30 minute dose increment schedules. The Australian & New Zealand journal of obstetrics & gynaecology 31(2): 134-7	- Ineligible intervention No dose reduction (30 minute dose increments versus 15 minute dose increments)
Chua, S., Kurup, A., Arulkumaran, S. et al. (1990) Augmentation of labor: does internal tocography result in better obstetric outcome than external tocography?. Obstetrics and gynecology 76(2): 164-7	- Ineligible intervention Oxytocin was titrated in the same way for all women, and the intervention group had internal tocography whereas the comparison group had external tocography
Coleman, F. H., Rayburn, W. F., Burks, L. S. et al. (1997) Patterns of uterine activity. Using oxytocin after intracervical PGE2. The Journal of reproductive medicine 42(1): 44-8	- Ineligible population Includes women with medical complications
Ctri (2019) Study to see if discontinuation of oxytocin in active phase of induced labours has an effect on the maternal and fetal outcomes. http://www.who.int/trialsearch/Trial2.aspx?TrialID=CTRI/2019/08/020657	- Ineligible study design Conference abstract, no published results
Cummiskey, K. C. and Dawood, M. Y. (1990) Induction of labor with pulsatile oxytocin. American journal of obstetrics and gynecology 163(6pt1): 1868-74	- Ineligible intervention No dose reduction – 10-second pulse of oxytocin was delivered IV every 8 minutes vs continuous IV of 1 mU/minute continuous IV every 30 mins
Daniel-Spiegel, Etty, Weiner, Zeev, Ben-Shlomo, Izhar et al. (2004) For how long should oxytocin be continued during induction of labour?. BJOG : an international journal of obstetrics and gynaecology 111(4): 331-4	- Ineligible population Includes patients with medical complications: "oligohydroamnios (amniotic fluid index <5 cm), intrauterine growth restriction, diabetes and a sporadic non-reassuring fetal heart rate pattern"
de Aquino, M. M. and Cecatti, J. G. (2003) Misoprostol versus oxytocin for labor induction in term and post-term pregnancy: randomized controlled trial. Sao Paulo medical journal 121(3): 102-106	- Ineligible country Study conducted in Brazil
Dupont, C., Carayol, M., Fischer, C. et al. (2017) Oxytocin administration during spontaneous labour:	- Ineligible study design Guideline

Study	Reason for exclusion
Guidelines for clinical practice. Guidelines short text. Gynecologie Obstetrique Fertilite et Senologie 45(1): 56-61	
Durie, Danielle, Campbell, Nigel, Sato, Holly et al. (2009) Two low dose oxytocin induction protocols: Effects on tachysystole, fetal heart rate patterns and mode of delivery. American Journal of Obstetrics and Gynecology 201(6suppl1): 106	- Ineligible study design Abstract, no published results
Durodola, A., Kuti, O., Orji, E. O. et al. (2005) Rate of increase in oxytocin dose on the outcome of labor induction. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 90(2): 107-11	- Ineligible country Study conducted in Nigeria
Escudero, F. and Contreras, H. (1997) A comparative trial of labor induction with misoprostol versus oxytocin. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 57(2): 139-43	- Ineligible country Study conducted in Peru
Fitzpatrick, C. Brennan, Grotegut, Chad A., Bishop, Tammy S. et al. (2012) Cervical ripening with foley balloon plus fixed versus incremental low-dose oxytocin: a randomized controlled trial. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians 25(7): 1006-10	- Ineligible intervention No dose reduction, Incremental dose increase 2 vs 1 mUs/min every 30 mins
Foster, T. C.; Jacobson, J. D.; Valenzuela, G. J. (1988) Oxytocin augmentation of labor: a comparison of 15- and 30-minute dose increment intervals. Obstetrics and gynecology 71(2): 147-9	- Ineligible intervention No dose reduction, incremental dose increases every 30 vs 15 min
Gilson, George J. (2017) A randomized control trial of low dose oral liquid misoprostol versus foley balloon-oxytocin for induction of labor. American Journal of Obstetrics and Gynecology 216(1supplement1): 511	- Ineligible intervention Ineligible intervention & comparator, low dose oral liquid misoprostol versus foley balloon-oxytocin
Girard, Benedicte, Vardon, Delphine, Creveuil, Christian et al. (2009) Discontinuation of oxytocin in the active phase of labor. Acta obstetricia et gynecologica Scandinavica 88(2): 172-7	- Ineligible population includes women with/without a previous caesarean birth
Goni, S.; Sawhney, H.; Gopalan, S. (1995) Oxytocin induction of labor: a comparison of 20- and 60-min dose increment levels. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 48(1): 31-6	- Ineligible country Study conducted in India
Hernandez-Martinez, Antonio, Arias-Arias, Angel, Morandeira-Rivas, Antonio et al. (2019) Oxytocin discontinuation after the active phase of induced labor: A systematic review. Women and birth : journal of the Australian College of Midwives 32(2): 112-118	- Systematic Review excluded on intervention, references checked No dose reduction, oxytocin continuation/discontinuation
Hourvitz, A., Alcalay, M., Korach, J. et al. (1996) A prospective study of high- versus low-dose oxytocin for induction of labor. Acta obstetricia et gynecologica Scandinavica 75(7): 636-41	- Ineligible intervention no dose reduction - 1.25 vs 2.5 mU/minute every 20 mins
Irct20100414003706N (2018) Comparison of Effect of Early and Delayed Oxytocin Infusion on Some Maternal	- Ineligible study design Abstract, no published results

Study	Reason for exclusion
and Neonatal Outcomes in Prolonged Labor. http://www.who.int/trialsearch/Trial2.aspx?TrialID=IRCT20100414003706N32	
Kenyon, Sara, Tokumasu, Hironobu, Dowswell, Therese et al. (2013) High-dose versus low-dose oxytocin for augmentation of delayed labour. The Cochrane database of systematic reviews: cd007201	- Ineligible population Compares a starting dose and increment dose of oxytocin for augmentation
Kunz, Marguerite K.; Loftus, Rebecca J.; Nichols, Amy A. (2013) Incidence of uterine tachysystole in women induced with oxytocin. Journal of obstetric, gynecologic, and neonatal nursing : JOGNN 42(1): 12-8	- Ineligible intervention No does reduction or comparison between Oxytocin dose/regimen
Lazor, L. Z., Philipson, E. H., Ingardia, C. J. et al. (1993) A randomized comparison of 15- and 40-minute dosing protocols for labor augmentation and induction. Obstetrics and gynecology 82(6): 1009-12	- Ineligible intervention No dose reduction - 1mU/minute increments every 15 vs 40 mins
Legardeur, Helene, Kayem, Gilles, Blanc-Petitjean, Pauline et al. (2014) Is a restrictive use of oxytocin during spontaneous labor associated with a change in obstetric or neonatal outcomes?. American Journal of Obstetrics and Gynecology 210(1suppl1): S270-S271	- Ineligible study design Abstract, no published results
Mercer, B.; Pilgrim, P.; Sibai, B. (1991) Labor induction with continuous low-dose oxytocin infusion: a randomized trial. Obstetrics and gynecology 77(5): 659-63	- Ineligible intervention No dose reduction, study compares oxytocin increments every 20 minutes versus every 60 minutes
Mozurkewich, Ellen L., Chilimigras, Julie L., Berman, Deborah R. et al. (2011) Methods of induction of labour: a systematic review. BMC pregnancy and childbirth 11: 84	- Ineligible intervention No dose reduction, various induction methods Includes various induction methods, not specific to oxytocin
Muller, P. R.; Stubbs, T. M.; Laurent, S. L. (1992) A prospective randomized clinical trial comparing two oxytocin induction protocols. American journal of obstetrics and gynecology 167(2): 373-1	- Ineligible population Population includes women with no more than one prior lower segment caesarean birth
Nct (2019) Continuous Versus Intermittent Oxytocin Infusion for Induction of Labor. https://clinicaltrials.gov/show/NCT04017247	- Ineligible study design Protocol, no published results
Nct (2009) Induction of Labor With Oxytocin: when Should Oxytocin be Held?. https://clinicaltrials.gov/show/NCT00957593	- Ineligible intervention No relevant comparison group: oxytocin was fully discontinued once women were deemed to be in active labour
Nct (2019) Reducing Neonatal Morbidity by Discontinuing Oxytocin During the Active Phase of 1st Stage of Labor. https://clinicaltrials.gov/show/NCT03991091	- Ineligible study design Protocol, no published results
Nct (2021) Effect of Increased Oxytocin Doses on the Mode of Delivery in Obese Primiparous Women With Spontaneous Labour. https://clinicaltrials.gov/show/NCT04760496	- Ineligible study design Protocol, no published results
Nct (2015) Continued Versus Discontinued Oxytocin Stimulation of Labour. https://clinicaltrials.gov/show/NCT02553226	- Ineligible study design Protocol, published results ineligible (see Boie 2021)
Nguyen, V. T., Do, D. V., Tran, T. S. et al. (2012) Labor induction using sub-lingual misoprostol for prelabor rupture of membranes at term: a randomized controlled	- Ineligible study design Abstract, no published results

Study	Reason for exclusion
trial. International journal of gynaecology and obstetrics 119: S802	
Odem, R. R.; Work, B. A., Jr.; Dawood, M. Y. (1988) Pulsatile oxytocin for induction of labor: a randomized prospective controlled study. Journal of perinatal medicine 16(1): 31-7	- Ineligible intervention No dose reduction – 10/40 units of oxytocin increments in pulsatile boluses every 8 minutes vs 1 mU/minute continuous IV every 30 mins
Omoigiafo, O.; Adeniyi, A.; Bakare, A. (2021) Comparison of two different oxytocin incremental intervals for induction of labour. BJOG: An International Journal of Obstetrics and Gynaecology 128(suppl2): 138	- Ineligible study design Conference abstract, no published results
Orhue, A. A. (1993) A randomized trial of 30-min and 15-min oxytocin infusion regimen for induction of labor at term in women of low parity. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 40(3): 219-25	- Ineligible country Study conducted in Nigeria
Orhue, A. A. (1994) Incremental increases in oxytocin infusion regimens for induction of labor at term in primigravidas: a randomized controlled trial. Obstetrics and gynecology 83(2): 229-33	- Ineligible country Study conducted in Nigeria
Pacheco, L. D., Rosen, M. P., Gei, A. F. et al. (2006) Management of uterine hyperstimulation with concomitant use of oxytocin and terbutaline. American journal of perinatology 23(6): 377-380	- Ineligible intervention No dose reduction - oxytocin discontinuation versus administration of subcutaneous terbutaline while maintaining the oxytocin infusion
Pactr (2018) Obstetric outcomes following immedicate versus delayed intravenous Oxytocin after amniotomy among parturients: a randomized clinical trial. http://www.who.int/trialsearch/Trial2.aspx?TrialID=PACTR201803003123163	- Ineligible country Study conducted in Kenya
Perales, A. J., Blasco, N., Domingo, S. et al. (1995) Oxytocin challenge test: use of dosis increases at 20 and 40 minutes interval. Progresos en obstetricia y ginecologia 38(4): 239-243	- Ineligible language Spanish
Reid, G. J. and Helewa, M. E. (1995) A trial of pulsatile versus continuous oxytocin administration for the induction of labor. Journal of perinatology : official journal of the California Perinatal Association 15(5): 364-8	- Ineligible intervention No dose reduction – 4 mU per pulse and the pulse dose was increased after every third pulse vs 1 mU/minute continuous IV every 30 mins
Rosenzweig, B. A., Levy, J. S., Schipiour, P. et al. (1989) Comparison of the nipple stimulation and exogenous oxytocin contraction stress tests. A randomized, prospective study. The Journal of reproductive medicine 34(12): 950-4	- Ineligible intervention Nipple stimulation and exogenous oxytocin contraction stress tests
Saccone, Gabriele, Ciardulli, Andrea, Baxter, Jason K. et al. (2017) Discontinuing Oxytocin Infusion in the Active Phase of Labor: A Systematic Review and Meta-analysis. Obstetrics and gynecology 130(5): 1090-1096	- Systematic Review excluded on PICO, references checked No dose reduction, oxytocin continuation/discontinuation
Sanchez-Ramos, L., Kaunitz, A. M., Del Valle, G. O. et al. (1993) Labor induction with the prostaglandin E1 methyl analogue misoprostol versus oxytocin: a randomized trial. Obstetrics and gynecology 81(3): 332-6	- Ineligible intervention Misoprostol versus oxytocin

Study	Reason for exclusion
Satin, A. J.; Hankins, G. D.; Yeomans, E. R. (1991) A prospective study of two dosing regimens of oxytocin for the induction of labor in patients with unfavorable cervices. American journal of obstetrics and gynecology 165(4pt1): 980-4	- Ineligible intervention No dose reduction – initial dose of 2 mU/min oxytocin with 1 mU/min at 30-min vs 2 mU/min at 15-min
Satin, A. J., Leveno, K. J., Sherman, M. L. et al. (1992) High- versus low-dose oxytocin for labor stimulation. Obstetrics and gynecology 80(1): 111-6	- Ineligible intervention No dose reduction - Incremental dose 1 vs 2 mUs/min every 20 mins
Satin, A. J., Leveno, K. J., Sherman, M. L. et al. (1994) High-dose oxytocin: 20- versus 40-minute dosage interval. Obstetrics and gynecology 83(2): 234-8	- Ineligible intervention No dose reduction - oxytocin infusion was immediately after amniotomy vs 4 h post-amniotomy
Selo-Ojeme, Dan O., Pisal, Pradnya, Lawal, Olalekan et al. (2009) A randomised controlled trial of amniotomy and immediate oxytocin infusion versus amniotomy and delayed oxytocin infusion for induction of labour at term. Archives of gynecology and obstetrics 279(6): 813-20	- Ineligible intervention No dose reduction – no dose reduction, oxytocin infusion was immediately after amniotomy vs 4 h post-amniotomy
Sengupta, S. K., Jain, V., Chopra, S. et al. (2014) Oxytocin discontinuation in active phase: The effects. BJOG: An International Journal of Obstetrics and Gynaecology 121(suppl2): 88	- Ineligible study design Conference abstract
Tan, Peng Chiong; Daud, Siti Aishah; Omar, Siti Zawiah (2009) Concurrent dinoprostone and oxytocin for labor induction in term premature rupture of membranes: a randomized controlled trial. Obstetrics and gynecology 113(5): 1059-1065	- Ineligible country Study conducted in Malaysia
Ustunyurt, Emin, Ugur, Mustafa, Ustunyurt, Basak Ozlem et al. (2007) Prospective randomized study of oxytocin discontinuation after the active stage of labor is established. The journal of obstetrics and gynaecology research 33(6): 799-803	- Ineligible country Study conducted in Turkey
Vlachos, Dimitrios-Efthymios G., Pergialiotis, Vasilios, Papantoniou, Nikolaos et al. (2015) Oxytocin discontinuation after the active phase of labor is established. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians 28(12): 1421-7	- Systematic Review excluded on PICO, references checked No dose reduction, oxytocin continuation/discontinuation
Vroman, S.; Thiery, M.; Yo Le Sian, A. (1972) A double blind comparative study of prostaglandin F(2alpha) and oxytocin for the elective induction of labor. Eur. J. Obstet. Gynecol. 2(4): 115-123	- Ineligible intervention No does reduction or eligible comparator (Prostaglandin F(2 alpha) vs oxytocin)
Wei, S., Wo, B. L., Qi, H. P. et al. (2013) Early amniotomy and early oxytocin for prevention of, or therapy for, delay in first stage spontaneous labour compared with routine care. Cochrane Database of Systematic Reviews	- Systematic Review excluded on intervention, references checked No dose reduction, amniotomy and oxytocin versus usual treatment
Yazdani, S., Bouzari, Z., Farahi, S. et al. (2012) Oral misoprostol with oxytocin versus oxytocin alone for labor induction in pre-labor rupture of membranes (PROM) at term pregnancy. Journal of babol university of medical sciences 14(3): 7-11	- Ineligible language Farsi

Excluded economic studies

No economic evidence was identified for this review.

Excluded studies for review question: What is the optimum dose at which oxytocin should be restarted if stopped due to an abnormality in the CTG?

Excluded effectiveness studies

Table 6: Excluded studies and reasons for their exclusion – restarting oxytocin

Study	Reason for exclusion
(2010) High-dose vs low-dose oxytocin for labor augmentation: A systematic review. American Journal of Obstetrics and Gynecology 203(4): 296-304	- Intervention Not women who have been started on oxytocin but stopped due to abnormality on CTG
Aboshama, Rehab Abdelhamid, Abdelhakim, Ahmed Mohamed, Shareef, Mohammad Abrar et al. (2021) High dose vs. low dose oxytocin for labor augmentation: a systematic review and meta-analysis of randomized controlled trials. Journal of perinatal medicine 49(2): 178-190	- Population Not women who have been started on oxytocin but had to be stopped due to abnormality on CTG
Alomari, S. (2021) Oxytocin in active labour, should we maintain, break or discontinue the dose?. BJOG: An International Journal of Obstetrics and Gynaecology 128(suppl2): 138-139	- Study design Abstract only, full text not located as not women who have been started on oxytocin but stopped due to CTG abnormality
Blakemore, K. J., Qin, N. G., Petrie, R. H. et al. (1990) A prospective comparison of hourly and quarter-hourly oxytocin dose increase intervals for the induction of labor at term. Obstetrics and gynecology 75(5): 757-61	- Population Not women who have been started on oxytocin but it had to be stopped due to abnormality on CTG
Chopra, Seema, SenGupta, Sandip K., Jain, Vanita et al. (2015) Stopping Oxytocin in Active Labor Rather Than Continuing it until Delivery: A Viable Option for the Induction of Labor. Oman medical journal 30(5): 320-5	- Population Not women who have been started on oxytocin but it had to be stopped due to abnormality on CTG
Durie, Danielle, Campbell, Nigel, Sato, Holly et al. (2009) Two low dose oxytocin induction protocols: Effects on tachysystole, fetal heart rate patterns and mode of delivery. American Journal of Obstetrics and Gynecology 201(6suppl1): 106	- Study design Abstract only, full text not location, but not women who have been started on oxytocin but it had to be stopped due to abnormality on CTG
Legardeur, Helene, Kayem, Gilles, Blanc-Petitjean, Pauline et al. (2014) Is a restrictive use of oxytocin during spontaneous labor associated with a change in obstetric or neonatal outcomes?. American Journal of Obstetrics and Gynecology 210(1suppl1): S270-S271	- Population Not women who have been started on oxytocin but it had to be stopped due to abnormality on CTG
Pan, Ho-Yu, Heine, R. Phillip, Brown, Haywood L. et al. (2014) Labor and pregnancy outcomes after adoption of a more conservative oxytocin labor protocol. Obstetrics and Gynecology 123(suppl1): 66s	- Population Not women who have been started on oxytocin but it had to be stopped due to abnormality on CTG

Excluded economic studies

No economic evidence was identified for this review.

Appendix K Research recommendations – full details

Research recommendations for review question: What is the effectiveness of altering the dose of intravenous oxytocin to reduce excessive frequency of uterine contractions?

K.1.1 Research recommendation

What is the effectiveness of altering the dose of intravenous oxytocin to reduce excessive frequency of uterine contractions?

K.1.2 Why this is important

The use of oxytocin in labour to increase the frequency and strength of the uterine contractions can cause uterine hyperstimulation with or without CTG abnormalities. Oxytocin is titrated against uterine contractions aiming for 3-4 contractions in 10 minutes, with dose increments being made not more frequently than every 30 minutes. However, in some women tachysystole and hyperstimulation can occur requiring an alteration in the dosage of the oxytocin.

There is wide variation and uncertainty in practice on the effectiveness of altering the dosage of oxytocin to reduce excessive frequency of uterine contractions, and what dose reductions are optimal. This study aims to address this question and provide guidance to clinicians.

K.1.3 Rationale for research recommendation

Table 7: Research recommendation rationale

Importance to 'patients' or the population	Despite oxytocin being commonly used in labour, little is known on the effectiveness of dose alteration in reducing the frequency and strength of uterine contractions.
Relevance to NICE guidance	The research question was considered in this guidance and there is lack of evidence to support any recommendations
Relevance to the NHS	The outcome would provide clarity and guidance to maternity service providers and minimise wide variations in practice
National priorities	High. Improving maternity outcomes is a national priority
Current evidence base	None
Equality considerations	None known

Insert abbreviations

K.1.4 Modified PICO table

Table 8: Research recommendation modified PICO table

Population	• Women in labour who are pregnant with a single baby, who go into labour at term (37 to 42 weeks of pregnancy) and who do not have any pre-existing medical conditions or

	antenatal conditions that predispose to a higher risk birth • Women whose baby has not been identified before labour to be at high risk of adverse outcomes • Women who have been started on intravenous oxytocin for induction or delay in the first or second stage of labour • Singleton babies born at term (37 to 42 weeks of pregnancy) with no previously identified problems (for example congenital malformations, genetic anomalies, intrauterine growth restriction, placental problems)
Intervention	• Any method of reducing the dose of oxytocin (for example, in magnitude or frequency of dose reductions, as defined by the study)
Comparator	• Any other method of reducing the dose of oxytocin (for example, a different magnitude or frequency of dose reductions, as defined by the study)
Outcome	**Critical** • Uterine hyperstimulation, or uterine tachysystole, or 5 or more contractions per 10 minutes (with or without changes in CTG) • Mode of birth (for example spontaneous vaginal, instrumental, caesarean birth) • Length of labour **Important** • Non-reassuring, abnormal, suspicious or pathological CTG • Neonatal death, intrapartum stillbirth, or hypoxic ischaemic encephalopathy (grade 2/3) • Apgar score below 6 at 5 minutes • Women's experience of labour and birth
Study design	Cross-sectional study design
Timeframe	Follow-up to 6 months
Additional information	None

CTG: cardiotocography

Research recommendations for review question: What is the optimum dose at which oxytocin should be restarted if stopped due to an abnormality in the CTG?

K.1.5 Research recommendation

What is the most effective dosage at which oxytocin should be recommenced once stopped in labour due to an abnormal CTG?

K.1.6 Why this is important

Oxytocin is widely used in labour to increase frequency and strength of contractions. It can also cause hyperstimulation leading to abnormalities of the fetal heart rate and may need to be stopped because of this. There is uncertainty and lack of guidance about the dosage at which should oxytocin be restarted and it is important to provide clarity and guidance to clinicians to reduce wide variations in practice.

K.1.7 Rationale for research recommendation

Table 9: Research recommendation rationale

Importance to 'patients' or the population	There is lack of evidence on what is the safe optimum dosage to recommence oxytocin when it has been stopped in labour due to hyperstimulation and/or an abnormal CTG. There are wide variations in practice among clinicians
Relevance to NICE guidance	The review question was considered in this guidance and there is lack of evidence to support any recommendations.
Relevance to the NHS	The outcome would provide clarity and guidance to maternity service providers and minimise wide variations in practice
National priorities	High. Improving maternity outcomes is a national priority
Current evidence base	None
Equality considerations	None known

CTG: cardiotocography; NHS: national health service; NICE: National Institute for Health and Care Excellence

K.1.8 Modified PICO table

Table 10: Research recommendation modified PICO table

Population	• Women in labour who are pregnant with a single baby, who go into labour at term (37 to 42 weeks of pregnancy) and who do not have any pre-existing medical conditions or antenatal conditions that predispose to a higher risk birth • Women whose baby has not been identified before labour to be at high risk of adverse outcomes

	• Women who have been started on oxytocin, but it had to be stopped due to an abnormality in the CTG • Singleton babies born at term (37 to 42 weeks of pregnancy) with no previously identified problems (for example congenital malformations, genetic anomalies, intrauterine growth restriction, placental problems)
Intervention	• Restart using the same dose as the dose when oxytocin was switched off • Restart using a lower dose than the dose when oxytocin was switched off
Comparator	• Any of the above interventions compared to each other
Outcome	**Critical** • Uterine hyperstimulation or uterine tachysystole, or 5 or more contractions per 10 minutes (with or without changes in CTG) • Non-reassuring, abnormal, suspicious or pathological CTG • Length of labour **Important** • Mode of birth (for example spontaneous vaginal, instrumental, caesarean birth) • Neonatal death, intrapartum stillbirth, or severe hypoxic ischemic encephalopathy (grade 2/3) • Apgar score below 6 at 5 minutes • Women's experience of labour and birth
Study design	RCT
Timeframe	Follow-up to 6 months
Additional information	None

CTG: cardiotocography; RCT: randomised controlled trial