Cochrane Library

Cochrane Database of Systematic Reviews

Continuation versus discontinuation of intravenous oxytocin in the active phase of labour (Protocol)

Boie S, Uldbjerg N, Bor P, Thornton JG, de Graaf IM, Le Ray C, Glavind J, Goffinet F, Girault A

Boie S, Uldbjerg N, Bor P, Thornton JG, de Graaf IM, Le Ray C, Glavind J, Goffinet F, Girault A.
Continuation versus discontinuation of intravenous oxytocin in the active phase of labour (Protocol).
Cochrane Database of Systematic Reviews 2024, Issue 11. Art. No.: CD015995.
DOI: 10.1002/14651858.CD015995.

www.cochranelibrary.com

Copyright © 2024 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

WILEY

TABLE OF CONTENTS

Copyright © 2024 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

[Intervention Protocol]

Continuation versus discontinuation of intravenous oxytocin in the active phase of labour

Sidsel Boie[1,2], Niels Uldbjerg[2,3], Pinar Bor[2,3], Jim G Thornton[4], Irene M de Graaf[5], Camille Le Ray[6], Julie Glavind[2,3], François Goffinet[6], Aude Girault[6]

[1]Department of Obstetrics and Gynecology, Regional Hospital of Randers, Randers, Denmark. [2]Department of Clinical Medicine, Aarhus University, Aarhus, Denmark. [3]Department of Obstetrics and Gynecology, Aarhus University Hospital, Aarhus N, Denmark. [4]Division of Child Health, Obstetrics and Gynaecology, School of Medicine, University of Nottingham, Nottingham, UK. [5]Department of Obstetrics and Gynaecology, Amsterdam University Medical Centers, Amsterdam, Netherlands. [6]Port Royal Maternity Hospital, Assistance Publique des Hôpitaux de Paris – Université Paris Cité, Paris, France

Contact: Sidsel Boie, sidselboie@clin.au.dk.

Editorial group: Cochrane Central Editorial Service.
Publication status and date: New, published in Issue 11, 2024.

Citation: Boie S, Uldbjerg N, Bor P, Thornton JG, de Graaf IM, Le Ray C, Glavind J, Goffinet F, Girault A. Continuation versus discontinuation of intravenous oxytocin in the active phase of labour (Protocol). *Cochrane Database of Systematic Reviews* 2024, Issue 11. Art. No.: CD015995. DOI: 10.1002/14651858.CD015995.

Copyright © 2024 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the effects of discontinuing intravenous oxytocin stimulation in pregnant women during the active phase of induced or augmented labour.

Copyright © 2024 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

BACKGROUND

Description of the condition

During labour, intravenous oxytocin administration enhances uterine contractions and this synthetic hormone is used in approximately a quarter of all term pregnant women (Bliddal 2018). The indications are either labour augmentation (due to labour dystocia - slow or absent progress during labour) or labour induction. Oxytocin administration is associated with a risk of uterine hyperstimulation (uterine tachysystole defined as ≥ 6 contractions per 10 minutes for a 30-minute period, combined with pathological fetal heart rate), which jeopardises the oxygen supply to the fetus (Simpson 2009). This may lead to the need for immediate birth (caesarean section or instrumental vaginal birth, i.e. unwanted interventions) (Oláh 2015).

Indications for labour induction are either fetal (such as post-term pregnancy and growth restriction), maternal (such as pelvic pain and previous fetal death) or both (such as preeclampsia, spontaneous rupture of membranes, large for gestational age or diabetes). The overall consideration is the potential benefit of delivery versus the potential drawbacks associated with labour induction. These considerations may vary across different populations, including vulnerable and disadvantaged groups. For instance, women with limited access to health care or those from socioeconomically disadvantaged backgrounds may face higher risks and different outcomes from oxytocin use due to disparities in prenatal care and monitoring during labour.

In addition to acceptance by the woman and consideration of indication and contraindications, labour induction includes two technical elements: 1) cervical priming (in the case of an unripe cervix) and 2) stimulation of contractions (under the presumption of a ripe cervix). Cervical priming can be achieved either by prostaglandins (including misoprostol) or by mechanical methods (including balloons and laminaria sticks). Labour contractions may be induced by artificial rupture of membranes and/or by oxytocin administration (Alfirevic 2016; NICE 2021; WHO 2022).

Regarding oxytocin administration, most guidelines recommend a low-dose protocol including a stepwise increase to a maximum of 2.5 mU/min. Furthermore, they recommend continued assessment of fetal wellbeing and continued oxytocin stimulation until birth (Daly 2020). In the case of uterine tachysystole, the infusion should be reduced or discontinued. Approaches for oxytocin stimulation other than continuous stimulation are pulsatile administration (Tribe 2012), an automatic feedback controlled oxytocin infusion system (Steer 1985), high dose (> 2.5 mU/min) (Budden 2014) and discontinuation when the active phase of labour is reached. These alternative approaches aim to reduce the risk of adverse outcomes such as caesarean section, postpartum haemorrhage and instrumental vaginal births by minimising the incidence of uterine hyperstimulation and improving overall fetal and maternal outcomes.

The first stage of labour is divided into the latent and active phases. The latent phase begins with labour contractions and ends when the active phase is reached. One definition of the active phase of labour is a combination of regular contractions with a cervical examination that confirms complete effacement and dilation of at least 6 cm (Caughey 2014). Another definition of the active phase of labour is regular painful contractions combined with progressive cervical dilation of at least 4 cm (NICE 2023).

Since 2018, the Institute for Safe Medication Practice has listed oxytocin as one of the most dangerous medications used in an acute care setting (ISMP 2024). The primary reason for this is the risk of uterine tachysystole causing a traumatic maternal birth experience, as well as a risk of fetal asphyxia, long-term handicap and even perinatal death (Oláh 2015; Simpson 2009). Continuous oxytocin administration, particularly at high doses or over prolonged periods, can potentially increase these risks.

Furthermore, oxytocin stimulation may increase the risk of postpartum haemorrhage (Grotegut 2011), and may hypothetically have an adverse effect on the establishment and duration of breastfeeding (Fernández 2012). Postpartum haemorrhage is a critical concern as it can lead to severe maternal morbidity and mortality, particularly in settings with limited resources. Maternal infections and satisfaction during the birthing process are also significant considerations, as they impact both the immediate and long-term health and wellbeing of the mother. Instrumental vaginal births, another potential outcome, reflect complications that require assisted birth, which can be stressful and risky for both the mother and the newborn.

Neonatal outcomes are critical to understanding the impact of oxytocin on the newborn. Complications such as admission to the neonatal intensive care unit, hypoxic-ischaemic encephalopathy or the need for therapeutic hypothermia, the need for respiratory support and neonatal infections are serious conditions that can arise from the adverse effects of oxytocin-induced labour. These conditions necessitate careful monitoring and timely intervention to ensure the health and safety of the newborn. Adverse effects such as uterine tachysystole during labour directly relate to the safety of oxytocin use, highlighting the importance of managing these risks to prevent severe outcomes like maternal or neonatal death.

Description of the intervention

The intervention is discontinuation of oxytocin stimulation when the active phase of labour is established.

How the intervention might work

The hypothesis is that discontinuation decreases the risk of uterine tachysystole, and the concomitant risk of reduced fetal oxygen supply causing fetal distress and the need for immediate birth, without significantly increasing the risk of dystocia. Thus, the intervention is relevant for women with oxytocin stimulation indicated by labour induction or by dystocia in the latent phase of labour, i.e. oxytocin initiated before establishment of the active phase of labour.

The underlying logic for discontinuation of oxytocin stimulation is that once uterine contractions are established and labour is progressing, the endogenous production of hormone is sufficient to maintain labour progression. Studies demonstrating a reduced myometrial oxytocin receptor mRNA concentration after oxytocin stimulation support this hypothesis (Phaneuf 1998; Phaneuf 2000).

Copyright © 2024 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Why it is important to do this review

The extent of oxytocin use and the potential risk of both maternal and neonatal adverse effects emphasise the need to determine the optimal oxytocin regimen during induction and augmentation of labour. The potential adverse effects of oxytocin correlate with huge social costs, both economic and human (Clark 2009). Reducing the duration of oxytocin stimulation and the total oxytocin dose during labour may lower the number of neonates with neurologic sequelae and the number of adverse events during labour and childbirth, and this in turn will reduce the risk of expensive litigation.

This review protocol overcomes some of the limitations of the 2018 review (Boie 2018), as it includes a broader population of both women who receive oxytocin stimulation for induction of labour and women who receive oxytocin for labour augmentation. The original review from 2018 only included trials on labour induction; the literature search for this review is therefore broader.

OBJECTIVES

To assess the effects of discontinuing intravenous oxytocin stimulation in pregnant women during the active phase of induced or augmented labour.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs, both open-label and blinded) comparing continuous intravenous oxytocin infusion with discontinued administration of oxytocin or placebo in the active phase of labour. Cluster-RCTs will be included. We will exclude quasi-randomised trials and those using a cross-over design. Abstracts without a full-text publication will be included if the corresponding author can provide us with the necessary data.

Types of participants

Term, singleton pregnant women, who received oxytocin stimulation for either:

1. labour induction;
2. labour augmentation during the latent phase of labour.

We will apply no exclusion criteria in terms of parity, definition of the active phase of labour, maternal age, ethnicity, co-morbidities, labour setting or previous caesarean section.

In the case of trials in which participants with induced or accelerated labour are both included, and the two groups are not separated in the original report, we will request data from the authors to enable the participants to be separately included in the subgroups 'induced' or 'accelerated'. If the authors cannot provide such data, we will exclude the trial from the relevant subgroup analysis.

Types of interventions

Intervention

Intended intravenous oxytocin infusion discontinued or replaced by saline when the active phase (as defined by the authors and at least 4 cm) is reached.

Comparison

Intravenous oxytocin stimulation continued until delivery unless tachysystole indicates reduced administration or discontinuation.

We will apply no exclusion criteria in terms of the oxytocin regimen used, co-interventions or combined interventions. If studies with co-interventions or combined interventions are identified and included, we will perform a sensitivity analysis excluding these studies.

Studies evaluating different dosage regimens (high versus low dose) or pulsatile oxytocin dosage regimens, or studies evaluating discontinuation of oxytocin stimulation in the second stage of labour, will not be included in this review.

Types of outcome measures

We will use the core outcome set for induction of labour (Dos Santos 2018) and the pre-specified outcomes defined by the review authors.

Primary outcomes

- Caesarean section

Secondary outcomes

Maternal outcomes

- Instrumental vaginal birth
- Postpartum haemorrhage (as defined by authors; timeframe - postpartum as defined by authors)
- Maternal infection (as defined by authors; timeframe - intrapartal and postpartum during admission)
- Maternal satisfaction (as defined by authors; timeframe - as defined by authors)
- Pre-defined prioritised list of measurement tools:
  - Childbirth Experience Questionnaire (Dencker 2010)
  - Labour Agentry Scale (Hodnett 1987)
  - Edinburgh Postnatal Depression Scale (Cox 1987)
- Duration of the active phase of labour (as defined by authors)
- Uterine tachysystole with normal CTG (cardiotocography) during labour (as defined by authors)

Neonatal outcomes

- Admission to neonatal unit (as defined by authors; timeframe - during admission related to labour, birth and postnatal period)
- Hypoxic ischaemic encephalopathy or need for therapeutic hypothermia (as defined by authors; timeframe - during admission related to labour, birth and postnatal period)
- Neonatal infection (as defined by authors; timeframe - during admission related to labour, birth and postnatal period)
- Death of the baby (intrapartum, neonatal or perinatal) (timeframe - during admission related to labour, birth and postnatal period)

Copyright © 2024 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

- Acidotic cord gasses at birth (arterial umbilical pH < 7.10; if trials only report pH < 7.0, these data will be extracted and included in the analysis) (timeframe in relation to birth)
- Apgar less than seven at five minutes
- Uterine hyperstimulation (uterine tachysystole combined with abnormal CTG (pathological CTG pattern) (as defined by authors; timeframe - in relation to labour and birth)

We will not exclude studies on the basis of reported outcomes. In addition, we will ascertain whether relevant outcomes are available or not by contacting the trial investigators.

Search methods for identification of studies

We will construct and execute the literature search in collaboration with the medical librarian who supported us in the development of the search methods defined in the protocol. We will present the bibliographic database search strategies in an appendix exactly as run and in full, together with the search set numbers and the total number of records retrieved by each search strategy.

Electronic searches

The search strategy has been developed in collaboration with two experienced medical librarians using the PICO search model. We will conduct a comprehensive literature search in the following sources:

1. Cochrane Central Register of Controlled Trials (CENTRAL);
2. PubMed (pubmed.gov);
3. Embase (www.embase.com);
4. Scopus;
5. Web of Science Core Collection, editions A&HCI, ESCI, CPCI-SSH, CPCI-S, SCI-EXPANDED, SSCI;
6. US National Institutes of Health ongoing trials registry (clinical trials.gov [https://clinical trials.gov]);
7. World Health Organization International Clinical Trials Registry Platform (ICTRP) search portal (trialsearch.who.int).

The full draft search strategy for PubMed is available in Appendix 1. We will not apply any language or date restrictions.

The search period will be from the inception date of each database until the search date and will be updated prior to publication to ensure that subsequent relevant studies are included. We will customise the search for each database using both controlled thesaurus terms and natural language terms for synonyms. Following Chapter 4 in the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2024), we will use validated search filters for identifying randomised trials, when available and relevant, and subsequently adapt these to Scopus and Web of Science. In PubMed, we will use the Cochrane highly sensitive search strategy for identifying randomised trials in MEDLINE: sensitivity-maximising version (2008 revision); PubMed format (Glanville 2020) and in Embase.com we will use the Cochrane highly sensitive search strategy for identifying randomised trials in Embase (2023 revision); Embase.com format (Glanville 2019). We will also conduct a follow-up search of references cited in the included studies prior to final publication.

Searching other resources

We will search the reference lists of the retrieved studies and any systematic reviews revealed by the search.

We will contact the corresponding investigator for information if we identify any relevant unpublished trials. We will consider unpublished studies or studies published only as an abstract as eligible for inclusion in the review if the study author can confirm the methods and data.

We will look up each eligible study in the journal of publication in order to capture any published post-publication amendments including expressions of concern, errata, corrigenda and retractions.

Data collection and analysis

Selection of studies

We will identify and remove duplicate reports of individual trials by integrating the search results using Covidence (Covidence). Review authors S Boie and A Girault will independently assess all identified studies for inclusion. We will assess the titles and abstracts of potentially relevant studies and make exclusions. We will then obtain the full text of potentially applicable studies, link multiple communications related to the same study and assess the full text against the eligibility criteria for inclusion in the review. We will resolve any disagreement at each stage through discussion or, if required, we will consult N Uldbjerg. The review authors will not be blinded to study details such as the trial authors' names, institutions and journals of publication or results during the study selection process. Where necessary, we will contact the investigators of potentially eligible studies to provide supplementary information to assist with the final decision regarding the study's inclusion in the review. We will include studies published as abstracts if adequate information is available. We will contact study authors as necessary to supplement the published data. Following this, we will exclude these studies if the information regarding them is inadequate. We will detail the excluded studies and the primary reason for exclusion in the final review.

Studies that have been found to be fraudulent or have been retracted since publication for other reasons will not be included in this review. Errata can reveal important limitations, or even fatal flaws, in eligible studies. All of these may lead to the potential exclusion of a study from the review or the meta-analysis. We will take care to ensure that this information is retrieved in all database searches by downloading the appropriate fields, together with the citation data.

In cases where review authors are investigators on trials that could potentially be included in the review, these authors will not be involved in the selection of those studies. J Thornton and I de Graaf will assess studies where other review authors are investigators.

Data extraction and management

We will pilot a data extraction form. For eligible studies, S Boie and A Girault will extract the data using this form. We will resolve discrepancies through discussion or, if required, we will consult N Uldbjerg. We will enter data into the Review Manager software (RevMan 2024) and check for accuracy. When any of the above-mentioned information is unclear, we will attempt to contact the authors of the original reports to provide further details. For

Copyright © 2024 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

each study, we will extract the following data: setting, dates, participant characteristics, sample size, exclusion criteria, inclusion criteria, cervical dilation at the time of discontinuation, oxytocin dosage, recruited proportion, study completion rates and outcome variables.

In cases where review authors are investigators on trials included in the review, these authors will not be involved in data extraction or assessing the risk of bias for their trials.

Assessment of risk of bias in included studies

S Boie and A Girault will independently assess the risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreement by discussion or by involving N Uldbjerg**.**

(1) Random sequence generation (checking for possible selection bias)

We will describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assess the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We will describe for each included study the method used to conceal allocation to interventions prior to assignment and assess whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assess the methods as:

- low risk of bias (e.g. web or telephone randomisation; consecutively numbered, sealed, opaque envelopes);
- high risk of bias (open list of random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We will describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We will consider that studies are at low risk of bias if they were performed blinded, or if we judge that the lack of blinding would be unlikely to affect results. We will assess blinding separately for the different outcomes or classes of outcomes. We will assess the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We will describe for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We will assess blinding separately for different outcomes or classes of outcomes. We will assess methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

For neonatal outcomes, we will assume that they are not influenced by the lack of blinding and will assess them accordingly.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We will describe for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total number of randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported or can be supplied by the trial authors, we will re-include missing data in the analyses undertaken. We will assess methods as:

- low risk of bias (no more than 10% of missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data; imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We will describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We will assess the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We will describe for each included study any important concerns we have about other possible sources of bias.

(7) Overall risk of bias

We will make explicit judgements about whether studies are at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Copyright © 2024 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

With reference to (1) to (6) above, we will assess the likely magnitude and direction of the bias and whether we consider it likely to impact on the findings. We will explore the impact of the overall level of bias through undertaking sensitivity analyses - see Sensitivity analysis.

Differentiating subjective and objective outcomes

We will consider the nature of the outcomes when assessing the risk of bias. Subjective outcomes (e.g. maternal satisfaction) may be more susceptible to performance and detection bias, whereas objective outcomes (e.g. caesarean section rates, acidotic cord gasses at birth (arterial umbilical pH < 7.10)) are less likely to be influenced by lack of blinding. We will apply stricter criteria for assessing blinding and outcome assessment for subjective outcomes.

Dichotomous data

For dichotomous data, we will present results as a summary risk ratio with 95% confidence intervals.

For rare events, we will apply the Peto method (Higgins 2023).

Continuous data

For continuous data, we will use the mean difference if outcomes are measured in the same way between trials. We will use the standardised mean difference to combine trials that measure the same outcome but use different methods.

Unit of analysis issues

We will include cluster-randomised trials in the analyses along with individually randomised trials. We will adjust their standard errors using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2023) using an estimate of the intra-cluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely. We will also acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of this.

Cross-over trials

It is unlikely that cross-over designs will be a valid study design in pregnancy and childbirth reviews, and so these will be excluded.

Other unit of analysis issues

If we identify trials with more than two treatment groups, we will combine all the results from relevant intervention groups in each individual study into one of two groups for analysis, according to the administration of oxytocin (i.e. continued or discontinued)

Dealing with missing data

For included studies, we will note levels of attrition. We will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, we will carry out analyses, as far as possible, on an intention-to-treat basis, i.e. we will attempt to include all participants randomised to each group in the analyses, and all participants will be analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial will be the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

We will assess statistical heterogeneity in each meta-analysis using the Tau^2, I^2 and Chi^2 statistics. We will regard heterogeneity as substantial if an I^2 is greater than 30% and either a Tau^2 is greater than zero, or there is a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

If there are 10 or more studies in the meta-analysis, we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it (Higgins 2023).

Data synthesis

Where we consider that pooling data from different studies would provide a meaningful result, we will perform meta-analysis. We will carry out statistical analysis using the Review Manager software (RevMan 2024). For the primary analysis, we will use a fixed-effect meta-analysis to combine data, assuming that the studies are estimating the same underlying treatment effect. To explore heterogeneity and the robustness of our findings, we will also conduct a secondary analysis using a random-effects model. This model assumes that the true effect of discontinuing oxytocin during the active phase of labour varies among studies and provides an estimate of the average treatment effect across trials. If there is an indication of funnel plot asymmetry, we will conduct further analyses to explore and address potential biases, such as performing a sensitivity analysis excluding smaller studies or using meta-regression.

We will present the results as the average treatment effect with 95% confidence intervals, along with estimates of Tau^2 and I^2. This dual approach allows us to account for potential heterogeneity while ensuring that the primary analysis minimises the influence of smaller studies.

Where we consider that pooling data from different studies would not provide a meaningful result, we will not carry out a meta-analysis. When meta-analysis is not possible, we will conduct alternative forms of synthesis, including the summary of effect estimates, the combination of P values and vote counting based on the direction of effects, as described in Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2023) and the SWiM guidance (SWiM).

Subgroup analysis and investigation of heterogeneity

If we identify substantial heterogeneity, we will investigate it using subgroup analyses and sensitivity analyses. We will consider

Copyright © 2024 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

whether an overall summary is meaningful and, if it is, we will use random-effects analysis to produce it. We plan to carry out the following subgroup analyses to explore potential sources of heterogeneity:

1. Parity: nulliparous women versus parous women. Parity is a significant factor in labour outcomes. Nulliparous women often experience longer and more complicated labours compared to parous women. This difference could affect the response to oxytocin stimulation and the likelihood of interventions such as caesarean section. We hypothesise that nulliparous women may have a higher risk of requiring a caesarean section due to longer labour duration and potential for dystocia compared to parous women, who may respond more effectively to oxytocin stimulation.
2. Previous caesarean section: women who have not previously had a caesarean section versus women who have had a previous caesarean section. A previous caesarean section can influence the management of subsequent labours due to concerns about uterine rupture and other complications. The response to oxytocin may differ in women with a history of caesarean delivery. We hypothesise that women with a previous caesarean section might have different outcomes, including a higher likelihood of repeat caesarean sections, due to the altered uterine environment and scar tissue compared to women without such history.
3. Indication for oxytocin stimulation: induction of labour versus augmentation of labour. The indication for oxytocin use can impact its effectiveness and the overall labour process. Induction of labour is initiated in women who have not yet begun labour, while augmentation is used to enhance contractions in women already in labour. We hypothesise that the outcomes of oxytocin stimulation may vary between these two groups, with induction possibly leading to higher intervention rates, such as caesarean section, due to the initial lack of labour progression compared to augmentation, which supports already initiated labour.

Subgroup analysis will be restricted to the review's primary outcome. We will assess subgroup differences by interaction tests available within RevMan (RevMan 2024). We will report the results of subgroup analyses, quoting the Chi^2 statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

We will undertake sensitivity analysis on any aspect of the included trials' methodology that could have influenced the results of the meta-analysis. The following components will be specifically considered for sensitivity analysis based on their potential to introduce bias:

1. Participant eligibility criteria: studies with unclear or highly selective participant eligibility criteria may introduce bias due to differences in baseline characteristics. If full details of eligibility criteria are not available or are overly restrictive, we will exclude these studies from a repeat meta-analysis to determine their impact on the overall intervention effect.
2. Random sequence generation: studies rated as having a high risk of bias for random sequence generation (e.g. not truly random methods such as alternation or birthdate) can significantly affect the validity of the results. We will exclude studies with a high risk of bias in this domain from the sensitivity analysis.
3. Allocation concealment: proper allocation concealment prevents selection bias. Studies rated as having a high risk of bias for allocation concealment (e.g. allocation procedures that were not concealed from participants and investigators) will be excluded from the sensitivity analysis.
4. Incomplete outcome data: studies with a high risk of bias due to incomplete outcome data (e.g. high dropout rates or imbalanced missing data between groups) may skew the results. We will include only those studies with a low risk of incomplete outcome data in the repeat analysis to assess the robustness of the findings.

Where components are rated as 'high risk of bias', we will exclude the study from a repeat meta-analysis to determine the impact on the overall intervention effect. We will consider studies with a low risk of incomplete outcome data 'high quality' and include them in the repeat analysis. Sensitivity analysis will only involve the primary outcome. If we identify both cluster-randomised trials and individually randomised trials, we plan to synthesise the relevant information. We will also acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of this.

Summary of findings and assessment of the certainty of the evidence

For this review, we will assess the certainty of the evidence using the GRADE approach as outlined in the *GRADE Handbook* (GRADE Handbook), in order to assess the certainty of the body of evidence relating to the following outcomes for the main comparison: continued versus discontinued oxytocin.

Maternal outcomes

1. Caesarean section
2. Uterine hyperstimulation (uterine tachysystole combined with abnormal/pathological CTG)
3. Instrumental vaginal birth
4. Duration of the active phase of labour

Neonatal outcomes

1. Neonatal: admission to the neonatal unit
2. Neonatal: acidotic cord gasses at birth (arterial umbilical pH < 7.10)
3. Neonatal: Apgar less than seven at five minutes

S Boie and A Girault will use the GRADEpro Guideline Development Tool to import data from RevMan Web in order to create a summary of findings table (GRADEpro GDT). We will produce a summary of the intervention effect and a measure of certainty for each of the above outcomes using the GRADE approach. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the certainty of the body of evidence for each outcome. The evidence can be downgraded from 'high certainty' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias. S Boie and A Girault will resolve any disagreement

Copyright © 2024 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

at each stage through discussion or, if required, we will consult I de Graaf and J Thornton.

ACKNOWLEDGEMENTS

The medical librarians Louise Stenholt and Henrik Laursen, Medical Library, Regional Hospital Central Jutland, Denmark supported the authors in the development of the search methods for this protocol.

Editorial and peer reviewer contributions

The following people conducted the editorial process for this article:

- Sign-off Editor (final editorial decision): Philippa Middleton, Principal Research Fellow, Women and Kids, South Australian Health and Medical Research Institute, Adelaide, Australia;
- Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the article): Leanne Jones and Sara Hales-Brittain, Central Editorial Service;
- Editorial Assistant (conducted editorial policy checks, collated peer reviewer comments and supported the editorial team): Sara Hales-Brittain, Central Editorial Service;
- Copy Editor (copy editing and production): Jenny Bellorini, Cochrane Central Production Service;
- Peer reviewers (provided comments and recommended an editorial decision): Alexis Gimovsky, MD Associate Professor Maternal Fetal Medicine Department of Obstetrics and Gynecology Women and Infants Hospital of Rhode Island Warren Alpert School of Medicine of Brown University Providence, RI, USA (clinical/content review); Jo-Ana Chase, Cochrane Evidence Production and Methods Directorate (methods review); Jo Platt, Central Editorial Information Specialist (search review).

Copyright © 2024 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

REFERENCES

Additional references

Alfirevic 2016

Alfirevic Z, Keeney E, Dowswell T, Welton NJ, Medley N, Dias S, et al. Which method is best for the induction of labour? A systematic review, network meta-analysis and cost-effectiveness analysis. *Health Technology Assessment (Winchester, England)* 2016;**20**(65):1-584. [DOI: 10.3310/hta20650]

Bliddal 2018

Bliddal M, Broe A, Pottegård A, Olsen J, Langhoff-Roos J. The Danish Medical Birth Register. *European Journal of Epidemiology* 2018;**33**(1):27-36. [DOI: 10.1007/s10654-018-0356-1]

Boie 2018

Boie S, Glavind J, Velu AV, Mol BWJ, Uldbjerg N, de Graaf I, et al. Discontinuation of intravenous oxytocin in the active phase of induced labour. *Cochrane Database of Systematic Reviews* 2018, Issue 8. Art. No: CD012274. [DOI: 10.1002/14651858.CD012274.pub2]

Boie 2021

Boie S, Glavind J, Uldbjerg N, Steer PJ, Bor P, CONDISOX trial group. Continued versus discontinued oxytocin stimulation in the active phase of labour (CONDISOX): double blind randomised controlled trial. *BMJ* 2021;**373**:n716. [DOI: 10.1136/bmj.n716]

Bor 2016

Bor P, Ledertoug S, Boie S, Knoblauch NO, Stornes I. Continuation versus discontinuation of oxytocin infusion during the active phase of labour: a randomised controlled trial. *British Journal of Obstetrics and Gynaecology* 2016;**123**(1):129-35. [DOI: 10.1111/1471-0528.13589]

Budden 2014

Budden A, Chen LJY, Henry A. High-dose versus low-dose oxytocin infusion regimens for induction of labour at term. *Cochrane Database of Systematic Reviews* 2014, Issue 10. Art. No: CD009701. [DOI: 10.1002/14651858.CD009701.pub2]

Caughey 2014

Caughey AB, Cahill AG, Guise JM, Rouse DJ. Safe prevention of the primary cesarean delivery. *Obstetrics and Gynecology* 2014;**123**:693-711. [DOI: 10.1097/01.AOG.0000444441.04111.1d]

Clark 2009

Clark SL, Simpson KR, Knox GE, Garite TJ. Oxytocin: new perspectives on an old drug. *American Journal of Obstetrics and Gynecology* 2009;**200**(1):35.e1-e6. [DOI: 10.1016/j.ajog.2008.06.010]

Covidence [Computer program]

Covidence. Version accessed 12 June 2024. Melbourne, Australia: Veritas Health Innovation, 2015. Available at covidence.org.

Cox 1987

Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. *British Journal of Psychiatry* 1987;**150**:782-6. [DOI: 10.1192/bjp.150.6.782]

Daly 2020

Daly D, Minnie KCS, Blignaut A, Blix E, Vika Nilsen AB, Dencker A, et al. How much synthetic oxytocin is infused during labour? A review and analysis of regimens used in 12 countries. *PLOS One* 2020;**15**(7):1-24. [DOI: 10.1371/journal.pone.0227941]

Dencker 2010

Dencker A, Taft C, Bergqvist L, Lilja H, Berg M. Childbirth experience questionnaire (CEQ): development and evaluation of a multidimensional instrument. *BMC Pregnancy Childbirth* 2010;**10**:1-8. [DOI: 10.1186/1471-2393-10-81]

Dos Santos 2018

Dos Santos F, Drymiotou S, Antequera Martin A, Mol BW, Gale C, Devane D, et al. Development of a core outcome set for trials on induction of labour: an international multistakeholder Delphi study. *British Journal of Obstetrics and Gynaecology* 2018;**125**(13):1673-80. [DOI: 10.1111/1471-0528.15397]

Fernández 2012

Olza Fernández I, Marín Gabriel M, Malalana Martínez A, Fernández-Cañadas Morillo A, López Sánchez F, et al. Newborn feeding behaviour depressed by intrapartum oxytocin: a pilot study. *Acta Paediatrica* 2012;**101**:749-54. [DOI: 10.1111/j.1651-2227.2012.02668.x]

Girault 2023

Girault A, Sentilhes L, Desbrière R, Berveiller P, Korb D, Bertholdt C, et al. Impact of discontinuing oxytocin in active labour on neonatal morbidity: an open-label, multicentre, randomised trial. *Lancet* 2023;**402**(10417):2091-100. [DOI: 10.1016/S0140-6736(23)01803-2]

Glanville 2019

Glanville J, Foxlee R, Wisniewski S, Noel-Storr A, Edwards M, Dooley G. Translating the Cochrane EMBASE RCT filter from the Ovid interface to Embase.com: a case study. *Health Information and Libraries Journal* 2019;**36**:264-77. [DOI: 10.1111/hir.12269]

Glanville 2020

Glanville J, Kotas E, Featherstone R, Dooley G. Which are the most sensitive search filters to identify randomized controlled trials in MEDLINE? *Journal of the Medical Library Association* 2020;**108**(1):556-63. [DOI: 10.5195/jmla.2020.912]

GRADE Handbook

Schünemann H, Brożek J, Guyatt G, Oxman A, editors. Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach (updated October 2013). GRADE Working Group, 2013. Available from gdt.guidelinedevelopment.org/app/handbook/handbook.html.

Copyright © 2024 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

GRADEpro GDT [Computer program]

GRADEpro GDT. Version accessed 12 June 2024. Hamilton (ON): McMaster University (developed by Evidence Prime), 2021. Available at gradepro.org.

Grotegut 2011

Grotegut CA, Paglia MJ, Johnson LN, Thames B, James AH. Oxytocin exposure during labor among women with postpartum hemorrhage secondary to uterine atony. *American Journal of Obstetrics and Gynecology* 2011;**204**(1):56.e1-e6. [DOI: 10.1016/j.ajog.2010.08.023]

Higgins 2011

Higgins JPT, Altman DG, Sterne JAC (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from training.cochrane.org/handbook/archive/v5.1/.

Higgins 2023

Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.4 (updated August 2023). Cochrane, 2023. Available from training.cochrane.org/handbook.

Hodnett 1987

Hodnett ED, Simmons-Tropea DA. The Labour Agentry Scale: psychometric properties of an instrument measuring control during childbirth. *Research in Nursing and Health* 1987;**10**(5):301-10. [DOI: 10.1002/nur.4770100503]

ISMP 2024

ISMP Medication Safety Alert. https://www.ismp.org/sites/default/files/attachments/2024-01/20240111.pdf.

Lefebvre 2024

Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf M-I, et al. Chapter 4: Searching for and selecting studies. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.5 (updated September 2024). Cochrane, 2024. Available from training.cochrane.org/handbook.

NICE 2021

National Institute for Health and Care Excellence (NICE). Inducing labour. Available online at www.nice.org.uk/guidance/ng207 (accessed 12 June 2024) 2021. [ISBN: 978-1-4731-4327-2]

NICE 2023

National Institute for Health and Care Excellence (NICE). Intrapartum care. https://www.nice.org.uk/guidance/ng235 (accessed 12 June 2024) 2023. [ISBN: 978-1-4731-5384-4]

Oláh 2015

Oláh Karl SJ, Steer Philip J. The use and abuse of oxytocin. *The Obstetrician & Gynaecologist* 2015;**4**:265-71. [DOI: 10.1111/tog.12222]

Phaneuf 1998

Phaneuf S, Asbóth G, Carrasco MP, Liñares Rodríguez B, Kimura T, Harris A, et al. Desensitization of oxytocin receptors in human myometrium. *Human Reproduction Update* 1998;**4**(5):625-33. [DOI: 10.1093/humupd/4.5.625]

Phaneuf 2000

Phaneuf S, Rodriguez Linares B, TambyRaja RL, MacKenzie IZ, Lopez Bernal A. Loss of myometrial oxytocin receptors during oxytocin-induced and oxytocin-augmented labour. *Journal of Reproduction and Fertility* 2000;**120**(1):91-7.

RevMan 2024 [Computer program]

Review Manager. Version 7.12.0. The Cochrane Collaboration, 2024. Available at revman.cochrane.org.

Simpson 2009

Simpson KR, Knox GE. Oxytocin as a high alert medication: implications for perinatal patient safety. *American Journal of Maternal/Child Nursing* 2009;**34**(1):8-15. [DOI: 10.1097/01.NMC.0000343859.62828.ee]

Steer 1985

Steer PJ, Carter MC, Choong K, Hanson M, Gordon AJ, Pradhan P. A multicentre prospective randomized controlled trial of induction of labour with an automatic closed-loop feedback controlled oxytocin infusion system. *British Journal of Obstetrics and Gynaecology* 1985;**92**(11):1127-33.

SWiM

Synthesis Without Meta-Analysis - SWiM guidelines. Available at https://swim.sphsu.gla.ac.uk/ (accessed 13 June 2024).

Tribe 2012

Tribe RM, Crawshaw SE, Seed P, Shennan AH, Baker PN. Pulsatile versus continuous administration of oxytocin for induction and augmentation of labor: two randomized controlled trials. *American Journal of Obstetrics and Gynecology* 2012;**206**(3):230.e1-e8. [DOI: 10.1016/j.ajog.2011.11.001]

WHO 2022

World Health Organization. WHO recommendations on induction of labour, at or beyond term. Available at https://www.who.int/publications/i/item/9789241501156 (accessed 12 June 2024). [LICENCE: CC BY-NC-SA 3.0 IGO]

APPENDICES

Appendix 1. Search strategy, PubMed

Search	Search Terms

Copyright © 2024 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

(Continued)

#1	delivery, obstetric [mh]
#2	labor, obstetric [mh]
#3	pregnancy outcome [mh]
#4	parturition [mh]
#5	labor [tiab]
#6	labour [tiab]
#7	obstetric* [tiab]
#8	parturition [tiab]
#9	birth* [tiab]
#10	childbirth* [tiab]
#11	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
#12	oxytocin [mh]
#13	oxytocics [mh]
#14	oxytocics [pa]
#15	oxytoci* [tiab]
#16	#12 OR #13 OR #14 OR #15
#17	withholding treatment [mh]
#18	discontinu* [tiab]
#19	withdraw* [tiab]
#20	withhold* [tiab]
#21	cessat* [tiab]
#22	continu* [tiab]
#23	stop* [tiab]
#24	#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23
#25	randomized controlled trial [pt]
#26	controlled clinical trial [pt]
#27	randomized [tiab]
#28	placebo [tiab]

Copyright © 2024 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

(Continued)

#29	drug therapy [sh]
#30	randomly [tiab]
#31	trial [tiab]
#32	groups [tiab]
#33	#25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32
#34	animals [mh] NOT humans [mh]
#35	#33 NOT #34
#36	#11 AND #16 AND #24 AND #35

CONTRIBUTIONS OF AUTHORS

Conceptualisation: SB, AG, JT, NU

Development and design of methodology: SB, AG, NU, JT, PB, JG

Writing - original draft: SB

Writing - review and editing: PB, AG, FG, IG, JG, CLR, JT, NU

DECLARATIONS OF INTEREST

Sidsel Boie is an author/co-author on two of the possibly eligible trials (Boie 2021; Bor 2016). She will not be involved in any decisions relating to this review: eligibility assessment, risk of bias assessment, data extraction and GRADE assessment will be carried out by other members of the team who are not directly involved in the trials.

Niels Ulbjerg is a co-author on one of the possibly eligible trials (Boie 2021). He will not be involved in any decisions relating to this review: eligibility assessment, risk of bias assessment, data extraction and GRADE assessment will be carried out by other members of the team who are not directly involved in the trial.

Jim Thornton has no potential conflicts of interest to declare.

Irene de Graaf has no potential conflicts of interest to declare.

Camille Ray is a co-author on one of the possibly eligible trials (Girault 2023). She will not be involved in any decisions relating to this review: eligibility assessment, risk of bias assessment, data extraction and GRADE assessment will be carried out by other members of the team who are not directly involved in the trial.

Julie Glavind is a co-author on one of the possibly eligible trials (Boie 2021). She will not be involved in any decisions relating to this review: eligibility assessment, risk of bias assessment, data extraction and GRADE assessment will be carried out by other members of the team who are not directly involved in the trial.

Francois Goffinet was involved in one of the possibly eligible trials (Girault 2023). He will not be involved in any decisions relating to this review: eligibility assessment, risk of bias assessment, data extraction and GRADE assessment will be carried out by other members of the team who are not directly involved in the trial.

Aude Girault is an author on one of the possibly eligible trials (Girault 2023). She will not be involved in any decisions relating to this review: eligibility assessment, risk of bias assessment, data extraction and GRADE assessment will be carried out by other members of the team who are not directly involved in the trial.

Pinar Bor is an author/co-author on two of the possibly eligible trials (Boie 2021; Bor 2016). She will not be involved in any decisions relating to this review: eligibility assessment, risk of bias assessment, data extraction and GRADE assessment will be carried out by other members of the team who are not directly involved in the trials.

Copyright © 2024 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

SOURCES OF SUPPORT

Internal sources

- Health Research Foundation of Central Denmark Region, Denmark

  Support for Sidsel Boie's salary

External sources

- No sources of support provided

Copyright © 2024 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.