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Discontinuation of intravenous oxytocin in the active phase of induced labour (Protocol)

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[Intervention Protocol]

Discontinuation of intravenous oxytocin in the active phase of induced labour

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

The aim of this review is to assess whether discontinuation of intravenous oxytocin infusion used for induction of labour, once active labour is established, will improve birth outcomes.

BACKGROUND

Description of the condition and the intervention

Oxytocin (*Syntocinon*® - Orphan Biovitrum) was first synthesised in 1954 (den Hertog 2001). Since then it has become one of the most widely used medications in obstetrics for induction and acceleration of labour (Simpsons 2009), affecting approximately one in four women (Oscarsson 2006; Selin 2009).

The use of oxytocin however, may result in a number of maternal and neonatal adverse effects. A common complication of the use of oxytocin is uterine tachysystole, which is defined as a contraction frequency of more than five in 10 minutes (ACOG 2009). When the contractions are too frequent or too long, the relaxation period between contractions is too short for the neonate to recover sufficient oxygen, which can lead to fetal distress, presenting as non-reassuring fetal heart rate (FHR). Hyperstimulation (uterine tachysystole due to oxytocin use (Oláh 2015)) may require immediate delivery by caesarean section or delivery with forceps or ventouse.

Use of oxytocin almost doubles the likelihood of uterine tachysystole with FHR changes and triples the likelihood of hyperstimulation leading to an immediate intervention (Bakker 2007). Oxytocin use also increases the risk of uterine rupture, postpartum haemorrhage, and unsuccessful breastfeeding (Fernandez 2012). One study found a inverse association between oxytocin use and urine stress incontinence (Svare 2014). The use of oxytocin during labour may result in a number of maternal adverse effects including hypotension (low blood pressure), tachycardia (heart rate > 100),

arrhythmias (irregular heart rhythm), nausea, vomiting, headache, and flushing (Dansereau 1999). Furthermore, a longer duration of oxytocin use decreases the efficacy of labour induction and increases maternal complication rates, due to down-regulation of oxytocin receptors in the myometrium (Oscarsson 2006; Phaneuf 2000). Rarely, large doses of oxytocin may cause water retention, hyponatraemia (an electrolyte disturbance with low concentration of sodium in the serum), myocardial ischaemia, seizures, and coma (Begum 2009).

Furthermore, recent research states that synthetic oxytocin given during labour crosses the placental barrier and thereby prevents the child from producing its own endogenous oxytocin, which it has been suggested, causes long-term effects on behavioural development of the child (Dahlen 2013).

There is a growing concern about the use of oxytocin infusion for labour induction and acceleration (Oláh 2015). According to a survey of liability cases, approximately 50% of paid liability claims affecting maternity services involve alleged misuse of oxytocin (Clark 2008). For these reasons, oxytocin is considered one of the 12 most dangerous medications used in a hospital (ISMP List 2014).

Despite the fact that oxytocin is widely used, there is no consensus on whether it should be continued until delivery or stopped at the onset of the active phase (Daniel-Spiegel 2004; Diven 2012; Girard 2009; Ustunyurt 2007).

Discontinuation of oxytocin when active stage of labour is established may have advantages over continuous oxytocin. Theoretically, once labour contractions are established, the endogenous production of hormone from the endometrium disrupted by the contractions may be enough to maintain appropriate uterine activity without further stimulation with oxytocin. Discontinuation of intrapartum-administered oxytocin would shorten the duration of oxytocin infusion, reducing the oxytocin receptor desensitisation, and stimulate production of endogenous oxytocin, thereby enabling oxytocin to retain its potency and effective uterine activity to be maintained and the stages of labour to progress. The sum of these factors could increase the chance of full cervical dilatation in women and achieve a vaginal birth without numerous adverse effects.

The comparison of interest is continued oxytocin (standard care) versus discontinued oxytocin or placebo.

Intravenous oxytocin is discontinued once active labour is established. A common definition of active labour is a combination of regular contractions with a cervical examination that confirms complete effacement and dilatation of > 4 cm. We will use the definition of active phase of labour as described by the trial authors. Resumption of oxytocin will be accepted, in the case of slow progression of labour, as defined by the trial authors.

The trial authors' definitions of oxytocin solutions and dosage will be used.

How the intervention might work

Small trials have been published that support the experience in clinical practice that labour can progress when the active phase is established without further oxytocin stimulation and thus reduce maternal and neonatal complications (Daniel-Spiegel 2004; Diven 2012; Girard 2009; Ustunyurt 2007). A policy to discontinue the oxytocin infusion once active labour is achieved allows mother and child to produce endogenous oxytocin and enables the possibility for a more natural birth mechanism after an artificial induction of labour with synthetic oxytocin. Thus, in theory, discontinued administration could prove more effective and safer than conventional continuous administration.

Why it is important to do this review

The extent of use and the potential risk of adverse effects to both mother and child emphasise the need for determining the optimal oxytocin regimen during induction of labour. The potential adverse effects of oxytocin are correlated with huge social costs, both economic and human. Reducing the duration of oxytocin stimulation during labour may lower the number of neonates with asphyxial sequelae and the number of adverse events during labour and delivery, and this in turn will reduce the risk of expensive litigation.

OBJECTIVES

The aim of this review is to assess whether discontinuation of intravenous oxytocin infusion used for induction of labour, once active labour is established, will improve birth outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised control trials (RCTs) comparing continuous intravenous oxytocin infusion with discontinued administration of oxytocin for the induction of labour. Cluster-RCTs will also be included. We will exclude quasi-randomised RCTs and trials using a cross-over design.

Abstracts, without full-text publication, will only be included if the corresponding author can provide us with the necessary data.

Types of participants

This review will include studies on pregnant women who receive oxytocin stimulation for induction of labour during the latent phase of labour. No exclusion criteria will be applied in terms of parity, maternal age, ethnicity, co-morbidities, labour setting, gestational age, or previous caesarean section.

Types of interventions

Intravenous oxytocin stimulation replaced by saline and/or discontinued when the active phase of labour is established (as defined by the individual investigators) versus intravenous oxytocin stimulation continued until delivery, regardless of the oxytocin regimen used.

Studies evaluating different dosage regimens or pulsatile oxytocin dosage regimens will not be included in this review.

Types of outcome measures

Primary outcomes

1. Caesarean delivery

Secondary outcomes

Maternal

1. Duration of the active phase of labour (as defined by author)
2. Postpartum haemorrhage of 1000 mL or more
3. Uterine hyperstimulation
4. Uterine tachysystole
5. Chorioamnionitis
6. Maternal mortality
7. Maternal intensive care unit admission
8. Analgesia and epidural usage during labour
9. Uterine rupture/scar dehiscence
10. Episiotomy
11. Third- or fourth-degree perineal tear
12. Retained placenta/manual removal
13. Postnatal blood transfusion
14. Duration of hospital stay
15. Breastfeeding
16. Maternal satisfaction

Fetal

1. Intrapartum fetal death
2. Intrapartum cardiotocograph (CTG) abnormalities (suspicious/pathological CTGs)
3. Apgar score less than seven at five minutes
4. Acidotic cord gasses at birth pH < 7.00
5. Need for intubation within the first 24 hours postpartum
6. Neonatal morbidity (e.g. seizures, birth asphyxia, neonatal encephalopathy, infection requiring antibiotics), excluding malformations
7. Neonatal death within the first 24 hours postpartum
8. Childhood disability

Search methods for identification of studies

The following methods section of this protocol is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Electronic searches

We will search the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting their Information Specialist.

The Register is a database containing over 21,000 reports of controlled trials in the field of pregnancy and childbirth. For full search methods used to populate the Pregnancy and Childbirth Group's Trials Register including the detailed search strategies for CENTRAL, MEDLINE, Embase and CINAHL; the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service, please follow this link to the editorial information about the Cochrane Pregnancy and Childbirth Group in the Cochrane Library and select the '***Specialized Register***' section from the options on the left side of the screen.

Briefly, the Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by their Information Specialist and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE (Ovid);
3. weekly searches of Embase (Ovid);
4. monthly searches of CINAHL (EBSCO);
5. handsearches of 30 journals and the proceedings of major conferences;
6. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Search results are screened by two people and the full text of all relevant trial reports identified through the searching activities described above is reviewed. Based on the intervention described, each trial report is assigned a number that corresponds to a specific Pregnancy and Childbirth Group review topic (or topics), and is then added to the Register. The Information Specialist searches the Register for each review using this topic number rather than keywords. This results in a more specific search set that will be fully accounted for in the relevant review sections (Included, Excluded, Awaiting Classification or Ongoing).

In addition, we will search SCOPUS, and also ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) for unpublished, planned and ongoing trial reports (see Appendix 1 for planned search terms. We will document the search process in full in the review).

Searching other resources

We will search the reference lists of retrieved studies.
We will not apply any language or date restrictions.

Data collection and analysis

Selection of studies

We will identify and remove duplicate reports of individual trials by integrating the search results with a reference management package. Review author S Boie and a second review author will independently assess for inclusion all the potential studies we identify. The titles and abstracts of potentially relevant studies will be assessed and exclusions made. We will then obtain the full text of potentially applicable studies, link multiple communications relating to the same study and will 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 a third person. The review authors will not be blinded to the study details such as the trial authors' names, institution, and journal 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.

Data extraction and management

We will design a data extraction form. For eligible studies, S Boie and a second review author will extract the data using this form. We will resolve discrepancies through discussion or, if required, we will consult review author J Bakker. We will enter data into Review Manager software (RevMan 2014) and check for accuracy. When information regarding any of the above-mentioned information is unclear, we will attempt to contact authors of the original reports to provide further details.
For each study, the following data will be extracted: setting, dates, sample size, exclusion criteria, inclusion criteria, cervical dilatation at the time of establishing the intervention, oxytocin dosage regimens used, recruited proportion, study completion rates, outcome measurements, and a list of adjusted confounders.

Assessment of risk of bias in included studies

S Boie and a second review author will independently assess 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 J Bakker.

(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 will 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 will assess whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.
We will assess the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes);
- 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.

(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.

We will assess whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other 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 *Handbook* (Higgins 2011). 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 level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

Assessment of the quality of the evidence using the GRADE approach

For this review the quality of the evidence will be assessed using the GRADE approach as outlined in the GRADE handbook in order to assess the quality of the body of evidence relating to the following outcomes for the main comparisons continued versus discontinued oxytocin, plus gestation, previous caesarean delivery, and parity subgroups continued versus discontinued oxytocin and gestation and parity subgroups.

1. Caesarean delivery
2. Maternal: uterine hyperstimulation
3. Maternal chorioamnionitis
4. Maternal: analgesia and epidural usage during labour
5. Neonatal: Apgar score less than seven at five minutes
6. Neonatal acidotic cords gases pH < 7.00
7. Intrapartum cardiotocograph (CTG) abnormalities (suspicious/pathological CTGs)

We will use the GRADEpro Guideline Development Tool to import data from Review Manager 5.3 (RevMan 2014) in order to create 'Summary of findings' tables. A summary of the intervention effect and a measure of quality for each of the above outcomes will be produced using the GRADE approach. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence can be downgraded from 'high quality' 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.

Measures of treatment effect

Dichotomous data

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

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

Cluster-randomised trials

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 2011) using an estimate of the intracluster 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 the randomisation unit.

Cross-over trials

It is unlikely that cross-over designs will be a valid study design for Pregnancy and Childbirth reviews, and so 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 T^2, I^2 and Chi^2 statistics. We will regard heterogeneity as substantial if an I^2 is greater than 30% and either a T^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.

Data synthesis

We will carry out statistical analysis using the Review Manager software (RevMan 2014). We will use fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are estimating the same underlying treatment effect: i.e. where trials are examining the same intervention, and the trials' populations and methods are judged sufficiently similar. If there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity is detected, we will use random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials is considered clinically meaningful. The random-effects summary will be treated as the average range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful, we will not combine trials.
If we use random-effects analyses, we will present the results as the average treatment effect with 95% confidence intervals, and the estimates of T^2 and I^2.

Subgroup analysis and investigation of heterogeneity

If we identify substantial heterogeneity, we will investigate it using subgroup analyses and sensitivity analyses. We will consider whether an overall summary is meaningful, and if it is, use random-effects analysis to produce it.
We plan to carry out the following subgroup analyses.

1. Parity: nulliparous women versus multiparous women.
2. Gestational age: term (> 37 weeks) versus preterm (< 37 weeks).
3. Previous caesarean delivery: women who have not previously had a caesarean section versus women who have had a previous caesarean section.

Subgroup analysis will be restricted to the review's primary outcome.

We will assess subgroup differences by interaction tests available within RevMan (RevMan 2014). 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, such as participant eligibility criteria for inclusion in each study, random sequence generation and allocation concealment. Where full details of eligibility criteria are not available or where components are rated as "high risk of bias", we will exclude the study from a repeat meta-analysis to determine their 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 the randomisation unit.

ACKNOWLEDGEMENTS

As part of the pre-publication editorial process, this protocol has been commented on by four peers (an editor and three referees who are external to the editorial team), a member of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search terms

Planned search terms

SCOPUS

MesH terms: Oxytocin AND ("Labor, induced" OR "obstetric labor complications" OR "delivery, obstetrics")

Free text term: discontinu*

ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP)

oxytocin AND labo(u)r AND discontinu*

We will work with a librarian experienced in performing systematic literature search to perform this search and will document the full search in the review

CONTRIBUTIONS OF AUTHORS

Designing the protocol: Sidsel Boie wrote the original protocol. Julie Glavind, Pinar Bor and Jannet Bakker worked collaboratively in the development of the protocol and gave feedback on the draft of the protocol.

DECLARATIONS OF INTEREST

Sidsel Boie: none known.

Adeline V Velu receives salary from the Academic Medical Center, Amsterdam.

Julie Glavind: Trygfonden Denmark provided post doctoral salary support at Aarhus University Hospital from April-September 2014. Julie now receives salary support (as a registrar) from Central Denmark Region.

Ben Willem J Mol and his institution have received payment for consultancy from ObsEva Geneva. Ben has also received payment for review preparation from Eur J Obste Gynaecol from ESHRE Munich and Prebic Geneva in respect of travel/accommodation/meeting expenses.

Niels Uldbjerg: none known.

Irene de Graaf: none known.

Pinar Bor: none known.

Jannet JH Bakker: none known.