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Title:
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Date:
2021-12-20

Citation:
Tan, A., Wilson, A. N., Eghrari, D., Clark, H., Tse, W. C., Bohren, M. A., Homer, C. S. E. & Vogel, J. P. (2021). Outcomes to measure the effects of pharmacological interventions for pain management for women during labour and birth: a review of systematic reviews and randomised trials. BJOG-AN INTERNATIONAL JOURNAL OF OBSTETRICS AND GYNAECOLOGY, 129 (6), pp.845-854. https://doi.org/10.1111/1471-0528.17031.

Persistent Link:
https://hdl.handle.net/11343/299306

Article type : Systematic Review

Outcomes to measure the effects of pharmacological interventions for pain management for women during labour and birth: A review of systematic reviews and randomised trials

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Short running title: Outcomes for pain management in labour and birth

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/1471-0528.17031

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ABSTRACT

Background: Pharmacological pain management options can relieve women's pain during labour and birth. Trials of these interventions have used a wide variety of outcomes, complicating meaningful comparisons of their effects. In order to facilitate better assessment of the effectiveness of labour pain management in trials and meta-analyses, consensus about key outcomes and the development of a core outcome set is essential.

Objective: To identify all outcomes used in studies of pharmacological pain management interventions during labour and birth.

Design: A review of systematic reviews and their included randomised controlled trials was undertaken.

Search Strategy: Cochrane CENTRAL was searched to identify all Cochrane systematic reviews describing pharmacological pain management options for labour and birth. Search terms included "pain management", "labour" and variants, with no limits on year of publication or language.

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Selection Criteria: Cochrane reviews and randomised controlled trials contained within these reviews were included, provided they compared a pharmacological intervention with other pain management options, placebo or no treatment.

Data Collection and Analysis: All outcomes reported by reviews or trials were extracted and tabulated, with frequencies of individual outcomes reported.

Main Results: Nine Cochrane reviews and 227 unique trials were included. In total, 146 unique outcomes were identified and categorised into maternal, fetal, neonatal, child, health service, provider's perspective, or economic outcome domains.

Conclusions: Outcomes of pharmacological pain management interventions during labour and birth vary widely between trials. The standardisation of trial outcomes would permit the assessment of meta-analyses for best clinical practice.

Funding: No external funding was provided.

Tweetable Abstract:

Pharmacological pain management options during labour are widely studied, yet there is no consensus in the reporting of outcomes. We aimed to identify all outcomes used in studies of pharmacological pain management options during labour and birth. A review of systematic reviews and randomised trials was undertaken using Cochrane CENTRAL - we identified nine systematic reviews and 227 unique trials. In total 146 outcomes were identified, and we found substantial heterogeneity in outcome reporting. The standardisation of trial outcomes would permit meaningful comparisons of interventions. Our findings will support development of a core outcome set for pain management during labour.

INTRODUCTION

Globally, around 140 million women give birth each year and almost all will experience some degree of discomfort or pain during labour and birth.[1, 2] The pain associated with labour and birth has been

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described as one of the most painful experiences that a woman may encounter in her lifetime; a woman's experience with this pain contributes to their overall birth experience.[3, 4] Labour pain is multidimensional, complex and unique to each individual woman.[3,5] It includes pain experienced during the active first stage of labour (due to uterine contractions), as well as somatic pain during the second stage when the baby is born.[6, 7] Labour pain is a physiological pain response that occurs as part of a natural biological process, rather than pathological pain that is a result of a disease process.[8] However, significantly worsening or additional pain may signal labour complications.[3, 9]

Given that individuals experience pain differently, preferences for and responses to pain management interventions are likely to differ, both in terms of benefits and side effects.[10] Pharmacological pain management options during labour - such as nitrous oxide, opioids or epidural analgesia – have been demonstrated to provide effective pain relief for women.[11] However trials of these interventions have used a wide variety of outcomes to measure effects, complicating meaningful comparisons across studies and between different options.[12-15]

A core outcome set is a collection of agreed outcomes, which are consistently used to measure the effects of certain interventions.[15, 16] Core outcome sets have been recognised as critical to reducing research waste, with initiatives such as Core Outcome Measures in Effectiveness Trials (COMET)[17] and the Core Outcomes in Women's and Newborn Health (CROWN)[18] providing a framework by which core outcomes can be developed and disseminated. Currently, no core outcome set exists for research on pharmacological options for pain management during labour. Developing a core outcome set would be advantageous for future research and clinical practice in this area, supporting both clinicians and women to make informed and meaningful decisions on pain management. A first step towards developing a core outcome set is to identify and describe the relevant trial outcomes reported in the literature. In this study, we aim to identify and describe all outcomes reported in studies of pharmacological pain management options for women during labour and birth.

METHODS

The study design is a review of Cochrane systematic reviews and their included randomised controlled trials (RCTs). This study was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[19] and followed a pre-specified protocol that was registered on PROSPERO (registration number: CRD42020168114). Guidance from the Cochrane Handbook of Systematic Reviews of Interventions was also followed.[20] As a systematic review of publicly available literature, no ethical review was required nor sought.

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Eligibility criteria

The population of interest was broadly defined as women experiencing labour and birth who may want or require a pharmacological pain management option. To identify relevant interventions, we conducted an initial scoping search of the literature to identify the range of pharmacological pain management options used in clinical practice (Box 1). This included a review of the 2018 WHO recommendations on intrapartum care for a positive childbirth experience.[1]

Cochrane systematic reviews are considered to be the most reliable source of evidence relating to the effects of interventions, and are generally of higher quality than non-Cochrane reviews.[21-23] Any Cochrane review of a pharmacological pain management option for women during labour and birth was considered eligible, regardless of year of publication – provided they compared any pharmacological pain management option to other options, placebo or no treatment in our population of interest. In addition, any individual randomised controlled trial (RCT) included within these Cochrane reviews was also included in this analysis. For clarity, we have used the term "study" to mean either an included Cochrane review, or a randomised trial included within those Cochrane reviews.

Search strategy and screening

We conducted a search (24th April 2019) of the Cochrane Central Register of Controlled Trials (CENTRAL) database to identify all Cochrane systematic reviews of any pain management option used for women in labour and birth. Search terms included synonyms of "pain management", "labour" and different pain management interventions (Box 1), with no limits on year of publication or language. Where there were multiple versions of the same Cochrane review, only the latest version was included. All RCTs that were reported within the identified Cochrane reviews were also included. In instances where a RCT was reported in more than one Cochrane review, we included it in our database only once, to avoid double-counting of outcomes. At completion of the analysis, we conducted an updated search (25th February 2021) and confirmed that no additional Cochrane reviews had been published or updated on this topic since our initial search.

Two authors (AT, JPV) independently assessed eligibility for the citations identified in the initial search. Firstly, titles and abstracts were screened to identify potentially eligible Cochrane reviews. Full texts were then obtained and read to identify all eligible Cochrane reviews. Where there was disagreement, this was resolved through consensus or discussion with a third author. All trials contained within eligible Cochrane reviews were included.

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Data collection and extraction

The primary author developed an Excel spreadsheet for data extraction, which was pilot tested on three eligible studies and refined. For each included Cochrane review, outcome data were identified from the review's methods section (where primary and secondary review outcomes are pre-specified). For each included trial, we reviewed the methods and results of the trial papers to identify and extract all reported trial outcomes. Data on reported outcomes were systematically extracted, that is, for each study we identified all reported outcomes, regardless of whether they were primary or secondary outcomes. From all included studies, we extracted information on year of publication, intervention of interest and the number of participants. For RCTs, we also extracted information on the trial setting.

The primary author extracted data from all included reviews and trials, with other authors independently verifying extracted data for all included studies. Any discrepancies were resolved through discussion, or a third author was consulted if necessary. If a publication could not be obtained, we contacted the trial authors directly to request the paper. RCTs published in a language other than English were eligible; we sought a person fluent in the language for assistance with data extraction. Where this was not possible, Google Translate was used.

Data Analysis

We produced frequency tables and descriptive statistics for all identified individual outcomes. Through several rounds of discussion and consultation with clinical experts, we organised these outcomes into seven categories: maternal outcomes (pain-related, women's perspectives, physiological, labour and childbirth, infection-related, mental health-related, immediate postpartum, side effects and other maternal outcomes), fetal outcomes, neonatal outcomes (physiological, cardio-respiratory, nutrition, neurological, infection-related, metabolic and other neonatal outcomes), child health outcomes, health service outcomes (maternal and neonatal), provider outcomes and economic outcomes. Additionally, we identified 25 RCTs with the largest sample size to evaluate the outcomes reported across the biggest studies (Figure S1, Figure S2), similar to the approach used by Duffy et al in their analysis of outcomes reported in interventions for pre-eclampsia or eclampsia.[24]

RESULTS

A total of 43 Cochrane reviews were identified through the initial search of the Cochrane CENTRAL database (Figure 1). Ultimately, nine Cochrane reviews met the inclusion criteria and were included

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for extraction.[12-14, 25-30] The nine Cochrane reviews were published between 2012 and 2018, and ranged in size from four to 70 trials. These reviews included the use of epidural, combined spinal-epidural, local anaesthetic nerve blocks, parenteral opioids, non-opioid drugs (such as non-steroidal anti-inflammatory drugs (NSAIDs); paracetamol; antispasmodics; sedatives and antihistamines), inhaled analgesia, patient-controlled analgesia with remifentanil, and analgesia for forceps delivery.[12-14, 25-30]

Within these nine Cochrane reviews, a total of 227 unique trials were identified. These trials were conducted between 1958 and 2018, and sample sizes ranged from eight to 12,793 participants. Of all included RCTs, 38% (N=87) reported the effects of regional analgesia, 37% (N=83) reported the effects of different parenteral opioids, 11% (N=26) reported the effects of inhaled analgesia options, 8% (n=19) reported the effects of non-opioid drugs, and 5% (N=12) reported the effects of local anaesthetic nerve blocks. RCTs of parenteral opioids, regional analgesia, inhaled analgesia, non-opioid drugs and local anaesthetic nerve blocks had been trialled since the mid-1960s, whereas RCTs that studied the effects of patient-controlled analgesia were more recent (2001 onwards). In total, 113 RCTs (N=113/227, 49.8%) reported the setting - these trials were all conducted in high-income countries, typically a medical centre or hospital.

There were 146 unique outcomes reported across all included studies. The majority of the outcomes were maternal (N=92/146, 63.0%) and neonatal (N=34/146, 23.3%) outcomes. The remaining outcomes included health service (N=9/146, 6.1%), fetal (N=7/146, 4.8%), provider's perspective (N=3/146, 2.1%), child (N=1/146, 0.7%) and economic (N=1/146, 0.7%) outcomes. The frequency of outcome categories is provided in Table 1, with the full outcome list in Supplementary Appendix (Box 2).

Maternal outcomes

In total, 92 maternal outcomes were identified across all studies. Maternal outcomes were categorised into nine domains (Box 2); labour and childbirth outcomes (N=22/92, 24%) and maternal side effects (N=28/92, 30.4%) were the most commonly reported. Labour and birth outcomes were reported in 208 (88.1%) studies; the most commonly reported was mode of birth, described in 158 (66.9%) studies. Pain-related outcomes (N=4/92, 4.3%) were reported in 172 (72.9%) studies. Most frequently this was pain intensity, reported in 160 (67.8%) studies, though it was measured using a variety of approaches - visual analogue scale (VAS), numerical rating scale (NRS), verbal rating scale (VRS), the Wong Baker FACES Pain rating scale and others. Amongst the 25 RCTs with the largest sample sizes, 16 measured pain intensity using VAS, and three used a verbal analogue scale (Figure S1).

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Outcomes describing women's perspectives (N=6/92, 6.5%) were reported in 143 (60.6%) studies. A woman's satisfaction with pain relief was the most commonly reported outcome, in 132 (55.9%) studies. This was evaluated using different tools, with considerable overlap with the tools used to measure pain intensity, including descriptive scales (e.g. no pain, mild pain, moderate pain or severe pain), NRS or VAS. When measurements were specified, a descriptive scale was the most common method of measuring a woman's satisfaction with pain relief reported and was used in 48.5% of studies.

At least one maternal side effect was reported in the majority of included studies (194 studies, 82.2%). For example, nausea and vomiting were reported in 127 (53.8%) and 122 (51.7%) studies, respectively. Maternal infections, immediate postpartum outcomes and mental health outcomes were less frequently reported. Other maternal outcomes included the addition of other pain relief interventions reported in 82 (34.7%) studies, and duration and amount of analgesia given, reported in 59 and 55 (25.0%, 23.3%) studies, respectively. The effects of pain management interventions on mother/baby interactions were pre-specified in six Cochrane reviews, but reported in only one RCT.

Fetal outcomes

Seven fetal-related outcomes (N=7/146, 4.8%) were reported in Box 2. Fetal outcomes were reported across 147 (62.3%) studies, with the most frequently reported outcomes being fetal heart rate monitoring reported in 115 (48.7%) studies. Other fetal outcomes included fetal distress, fetal bradycardia and abnormal fetal heart rate reported in 45, 35 and 33 (19%, 14.8%, 14%) studies, respectively. When considering the 25 RCTs with the largest sample size, only two fetal outcomes (fetal heart rate monitoring and bilirubin levels) were reported in nine and three trials, respectively (Figure S2).

Neonatal outcomes

A total of 34 outcomes were reported across 218 (92.4%) studies and categorised into seven domains (Box 2). One or more physiological outcomes (N=8/34, 23.5%), including Apgar score reported in 203 (86%) studies, umbilical cord blood gases reported in 95 (40.3%) studies and acid-base balance reported in 42 (17.8%) studies. Nutrition-related outcomes (N=5/34, 14.7%) were described in 90 (38.1%) studies, including outcomes such as birth weight reported in 76 (32.2%) studies, breastfeeding reported in 17 (7.2%) studies, and feeding behaviours reported in 10 (4.2%) studies. Cardio-respiratory outcomes (N=7/34, 20.6%) such as oxygen and ventilation support (35 studies), respiratory depression (28 studies) and resuscitation (23 studies) were also reported. Newborn neurological outcomes (N=6/34, 17.6%), such as the Neurological Adaptive Capacity Score

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(20 studies) and neuro-behavioural assessments (12 studies) were less frequent. When considering the 25 RCTs with the largest sample size, neonatal resuscitation was reported in four RCTs, acidosis was reported in six studies and infant seizure within 24 hours was reported in two studies (Figure S2).

Child health outcomes

This category included poor infant outcomes at long-term follow-up such as seizures, disability in childhood and neonatal morbidity (Box 2). While four (1.7%) Cochrane reviews pre-defined poor infant outcomes at long-term follow-up[12, 13, 26, 27], no RCTs included in this review reported it.

Provider outcomes

This category included three outcomes (N=3/146, 2.1%) that were reported across 57 (24.2%) studies. Domains included provider's perspectives on labour pain, pain relief or progress of labour; and adverse effects on the healthcare provider, such as occupational exposure (Box 2).

Economic outcomes

Cost was the only economic-related outcome identified (Box 2), reported in 15 (6.4%) studies. Five Cochrane reviews reported cost (defined by individual RCTs) in their pre-defined list of outcomes.[12, 13, 26-28]

DISCUSSION

Pharmacological pain management options during labour have been widely trialled, and we identified 227 unique trials of approximately 49,700 women. While multiple Cochrane reviews have evaluated efficacy and safety of these interventions, the difficulty in comparing studies due to the variation in outcome measures is a consistent finding. This novel analysis has systematically identified the 146 unique outcomes reported across all available Cochrane reviews and RCTs of these interventions to inform future core outcome set development. Consistent with our findings, a 2012 overview of Cochrane reviews on pain management identified inconsistency of pain-related outcome measures, especially when comparing the assessment of pain and its relief, and effects on neonates.[31] Similarly, this review shows substantial heterogeneity of outcome reporting in pain intensity, satisfaction with pain relief and neonatal Apgar scores.

In many clinical settings, the standard method of assessing pain intensity is an unidimensional patient self-report of pain, usually verbal or written.[32-34] The most widely used pain scale is VAS, which is quick to score, more sensitive than other methods (such as VRS), and avoids difficult

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terminologies.[35-37] However, previous literature has highlighted that measurements such as VAS may only be suitable in postoperative contexts; other factors such as the onset of analgesia, stage of labour and the fact that pain is associated with strong physical and emotional effort can affect how pain is perceived.[35, 36, 38] Also, some studies suggest that unidimensional instruments such as VAS and NRS lack the characteristics of more reliable psychometric pain instruments[39, 40] and are often poorly interpreted.[41] A 2018 systematic review by Dualé et al identified the lack of clinical guidelines on how to best assess labour pain, and provide a comprehensive description of measurement and analysis methods to study labour pain.[38] Similar to our findings, Dualé et al report that while the majority of available studies used VAS to measure labour and childbirth pain intensity, there is heterogeneity in measurement methods. Whilst Dualé et al do not make a specific recommendation on the best option to use, they recognised that some studies have adapted VAS/NRS into categories (e.g. mild/moderate/severe) which may be a useful alternative approach, provided that categories adequately identify women with insufficient analgesia. The authors also emphasise that other methods reporting maternal satisfaction,[42] or multidimensional tools such as the Labour Agentry Scale[43] and Angle Labour Pain Questionnaire,[44] can be relevant to measuring pain during labour. Notably, we did not identify any studies using multidimensional tools to measure pain intensity during labour.

Women's satisfaction with pain relief during labour is also a commonly reported outcome in the literature.[10, 45] Only 56% of included studies in our analysis reported on these outcomes, typically using unidimensional scales such as VRS, NRS and VAS. Satisfaction is a complex and multidimensional concept – it comprises both psychological responses to childbirth, and is influenced by previous experiences, pre-birth expectations and prior birth experiences.[45-48] While tools such as VRS, NRS and VAS can be reliable indicators of the effect of treatment for labour pain,[53] they are largely inadequate in measuring the breadth of women's satisfaction with childbirth. There are many methods to measure women's satisfaction with maternity care,[49-51] however few are validated across settings or are underpinned by strong theoretical grounding.[47, 52] A 2002 systematic review by Hodnett et al identified four key factors influencing maternal satisfaction during labour: personal expectations, support from caregivers, direct involvement in the decision-making process and the quality of the relationship between caregiver and patient.[45, 46] A systematic review by Blazquez et al identified 17 tools for evaluating women's satisfaction, typically multidimensional questionnaires that ask women to self-rate their satisfaction with various aspects of labour and childbirth experiences.[47, 54] It is noteworthy that only two of these tools included questions on adequate pain relief.[55, 56] Further research is required on reliable and valid tools for measuring women's satisfaction, both with pain relief and with labour and childbirth more broadly.

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Several core outcome sets in women's and newborn's health have been published in recent years, and consistently reflect the importance of standardising outcome reporting in clinical trials.[57-62] Critical to development of a core outcome set is conducting a systematic review of the literature to identify outcomes used previously, followed by qualitative research and consensus methods (such as Delphi methodology) to engage with stakeholders and patients to identify core outcomes.[15, 63] Similar to those published reviews, this review of systematic reviews utilises robust methods to collect data from previous RCTs and Cochrane reviews to identify outcomes previously used to measure the effects of different pharmacological pain management options during labour and birth. The number of outcomes reported by this review (146 outcomes) is within similar ranges to other systematic reviews supporting core outcome sets, where numbers of outcomes ranged from 9 to 148 outcomes. This review of systematic reviews is the first step towards developing a core outcome set for pain management during labour; further research is planned on this topic.

Strengths and Limitations

This review of systematic reviews and included RCTs used a comprehensive search strategy and design. The review process and data extraction were conducted independently by two authors. Additionally, this study included outcomes identified in individual trials and was not restricted to results from a systematic literature review. An additional search was conducted in February 2021 and confirmed that the identified Cochrane reviews are the latest updates. A possible limitation is the non-inclusion of trials may have been published since the most recent Cochrane review update. Nonetheless, we regard our findings as likely representative of the outcomes used in trials of pharmacological pain management options for labour and birth. We restricted this review to pharmacological pain management options only, though non-pharmacological pain management options (such as transcutaneous nerve stimulation, massage and relaxation therapies) are also important components of pain management in the intrapartum period. Future evidence synthesis for these interventions is warranted, and may identify additional outcomes.

Implications for research and practice

Pain is undoubtedly a subjective measure (and the experience of pain will vary between individuals), therefore evaluating experiences of labour and birth pain in a replicable manner - in RCTs or routine clinical settings - is challenging. However, there is a clear need to ensure standardised measures of pain-related responses and experiences of women to permit meaningful comparisons of pain management options across trials. It is also a high priority amongst consumer groups, to help women understand how to manage their own pain.[28, 64] The outcomes reported by this review can be used to frame a series of questionnaires using Delphi consensus methods to identify a minimum

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set of outcome measures for future trials of pharmacological pain management options in labour and childbirth.

CONCLUSION

This review of systematic reviews and randomised trials is the first step towards the development of a core outcome set in pain management during labour and birth. The variability in outcome reporting between systematic reviews and randomised trials contributes directly to the inability to meaningfully compare the effects of pain management options, therefore restricting informed clinical decision-making by women and providers. A core outcome set in labour pain management will facilitate better assessment of the effectiveness of labour pain management in trials and meta-analyses. This helps ensure the best clinical evidence, counselling and care for pregnant women for a positive childbirth experience.

ACKNOWLEDGEMENTS

None.

DISCLOSURE OF ITERESTS

No authors disclosed any conflicts of interest.

CONTRIBUTION TO AUTHORSHIP

AT and JPV conceptualised the study. AT and JPV wrote the study protocol, and all authors provided feedback. DE, HC, AW, WCT and JPV identified papers and extracted data. AT analysed the data and wrote the initial draft of the manuscript. All authors contributed to the final manuscript.

DETAILS OF ETHICS APPROVAL

None declared, this is a review of publicly available published data.

FUNDING

The authors received no specific funding for this work. JPV is supported by a National Health and Medical Research Council Investigator Grant (GNT1194248). CH is part-funded through a fellowship from the Australian National Health and Medical Research Council (APP137745). AW is part-funded by a Postgraduate Research Scholarship (APP1151585). MAB is supported by an Australian Research Council Discovery Early Career Award (DE200100264).

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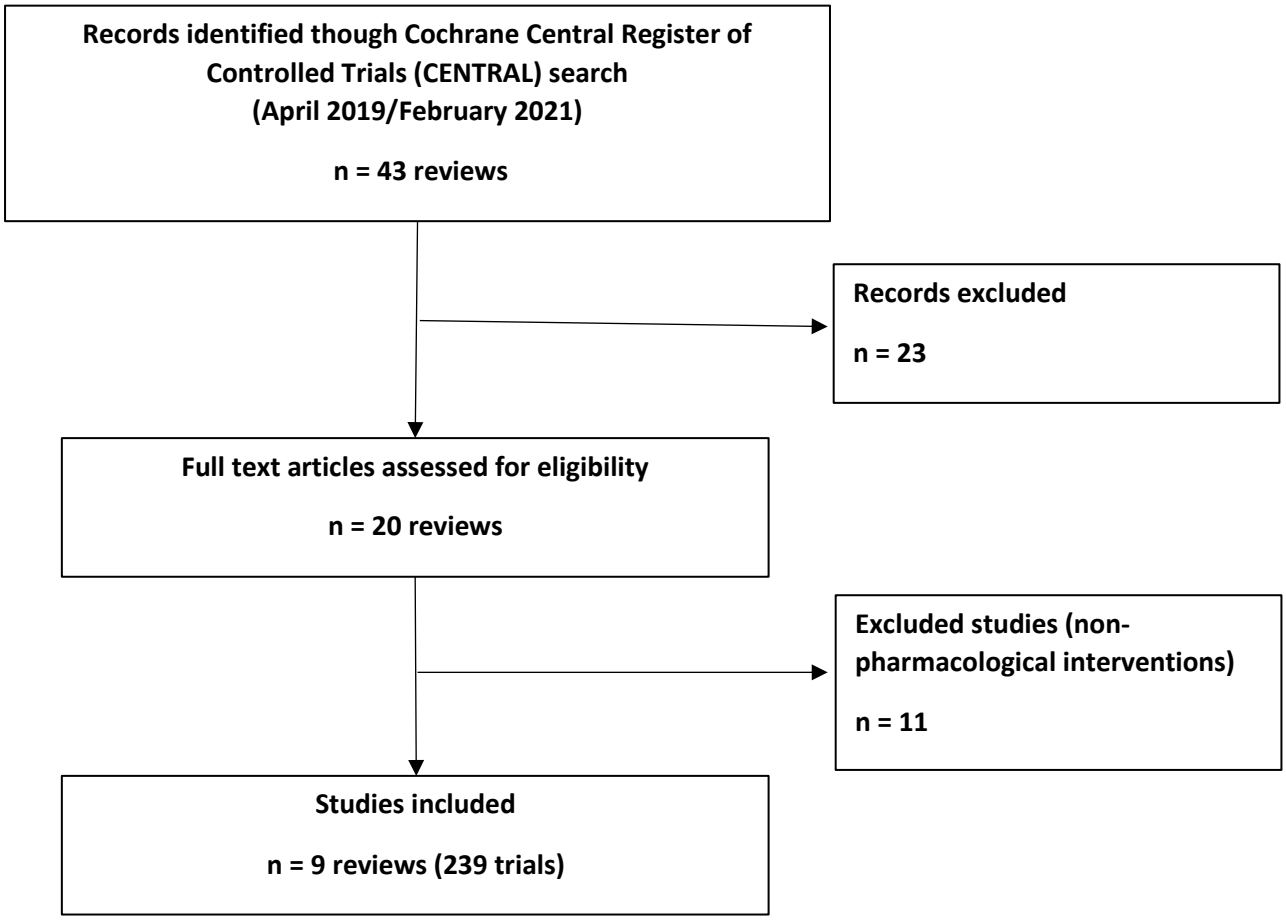
Tables and Figures

Box 1. List of pharmacological pain management options

Pharmacological pain management options:

- Epidural analgesia
- Parenteral opioids, such as fentanyl, diamorphine and pethidine
- Patient-controlled analgesia, such as remifentanil
- Inhaled analgesia, such as nitrous oxide
- Non-opioid drugs, such as diazepam
- Local anaesthetic nerve block, such as paracervical block

Figure 1. PRISMA study flow diagram of included reviews and trials



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Table 1. Frequency of outcomes reported in N=236 studies (Cochrane reviews and RCTs)

Domain	Number of Outcomes N=146	Number of Studies (reviews and trials) N=236
Maternal outcomes	**92/146 (63.0)**	**236/236 (100)**
Pain-related	4/92 (4.3)	172/236 (72.9)
Women's perspectives[1]	6/92 (6.5)	143/236 (60.6)
Labour and childbirth	22/92 (23.9)	208/236 (88.1)
Physiological	12/92 (13.0)	172/236 (72.9)
Infection-related	2/92 (2.2)	20/236 (8.5)
Mental health	3/92 (3.3)	17/236 (7.2)
Immediate postpartum	3/92 (3.3)	39/236 (16.5)
Side effects	28/92 (30.4)	194/236 (82.2)
Other[2]	12/92 (13.0)	186/236 (78.8)
Fetal outcomes	**7/146 (4.8)**	**147/236 (62.3)**
Neonatal outcomes	**34/146 (23.3)**	**218/236 (92.4)**
Physiological	8/34 (23.5)	207/236 (87.7)
Cardio-respiratory	7/34 (20.6)	80/236 (33.9)
Nutrition	5/34 (14.7)	90/236 (38.1)
Neurological	6/34 (17.6)	40/236 (16.9)
Infection	2/34 (5.9)	14/236 (5.9)
Metabolic	3/34 (8.8)	14/236 (5.9)

[1] Examples of women's perspectives include a woman's satisfaction of pain relief and childbirth experience, sense of control in labour and memory of labour, as defined by trialist

[2] This includes but is not limited to the onset, time and duration of analgesia used during labour and childbirth

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Other[3]	3/34 (8.8)	30/236 (12.7)
Child health outcomes	**1/146 (0.7)**	**4/236 (1.7)**
Health service outcomes	**9/146 (6.2)**	**105/236 (44.5)**
Maternal	5/9 (55.6)	49/236 (20.8)
Neonatal	4/9 (44.4)	83/236 (35.2)
Provider outcomes	**3/146 (2.1)**	**57/236 (24.2)**
Provider's perspective	1/3 (33.3)	56/236 (23.7)
Adverse effects on provider	2/3 (66.7)	1/236 (0.4)
Economic outcomes	**1/146 (0.7)**	**15/236 (6.4)**

[3] Includes long-term neonatal complications, morbidity and mortality

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