STUDY PROTOCOL

REVISED Association between intrapartum fetal pulse oximetry and adverse perinatal and long-term outcomes: a systematic review and meta-analysis protocol [version 2; peer review: 2 approved]

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v2 **First published:** 20 Oct 2023, **6**:63
https://doi.org/10.12688/hrbopenres.13802.1
Latest published: 28 Mar 2024, **6**:63
https://doi.org/10.12688/hrbopenres.13802.2

Abstract

Background

Current methods of intrapartum fetal monitoring based on heart rate, increase the rates of operative delivery but do not prevent or accurately detect fetal hypoxic brain injury. There is a need for more accurate methods of intrapartum fetal surveillance that will decrease the incidence of adverse perinatal and long-term neurodevelopmental outcomes while maintaining the lowest possible rate of obstetric intervention. Fetal pulse oximetry (FPO) is a technology that may contribute to improved intrapartum fetal wellbeing evaluation by providing a non-invasive measurement of fetal oxygenation status.

Objective

This systematic review and meta-analysis aims to synthesise the evidence examining the association between intrapartum fetal oxygen saturation levels and adverse perinatal and long-term outcomes in the offspring.

Open Peer Review

Approval Status ✓ ✓

	1	2
version 2 (revision) 28 Mar 2024		✓ view
version 1 20 Oct 2023	✓ view	? view

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Methods

We will include randomised control trials (RCTs), cohort, cross-sectional and case-control studies which examine the use of FPO during labour as a means of measuring intrapartum fetal oxygen saturation and assess its effectiveness at detecting adverse perinatal and long-term outcomes compared to existing intrapartum surveillance methods. A detailed systematic search of PubMed, EMBASE, CINAHL, The Cochrane Library, Web of Science, ClinicalTrials.Gov and WHO ICTRP will be conducted following a detailed search strategy until February 2024. Three authors will independently review titles, abstracts and full text of articles. Two reviewers will independently extract data using a pre-defined data extraction form and assess the quality of included studies using the Risk of Bias tool for RCTs and Newcastle-Ottawa Scale for observational studies. The grading of recommendations, assessment, development, and evaluation (GRADE) approach will be used to evaluate the certainty of the evidence. We will use random-effects meta-analysis for each exposure-outcome association to calculate pooled estimates using the generic variance method. This systematic review will follow the Preferred Reporting Items for Systematic reviews and Meta-analyses and MOOSE guidelines.

PROSPERO registration

CRD42023457368 (04/09/2023)

Keywords
Labour, intrapartum, fetal monitoring, oximetry, oxygen saturation, blood gas monitoring, Sp02

This article is included in the Maternal and Child Health collection.

Any reports and responses or comments on the article can be found at the end of the article.

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Author roles: Mitchell JM: Conceptualization, Investigation, Methodology, Visualization, Writing – Original Draft Preparation; **Walsh S**: Validation, Writing – Review & Editing; **O'Byrne LJ**: Validation, Writing – Review & Editing; **Conrick V**: Investigation, Methodology; **Burke R**: Supervision, Writing – Review & Editing; **Khashan AS**: Conceptualization, Methodology, Supervision, Writing – Review & Editing; **Higgins J**: Conceptualization, Methodology, Supervision, Writing – Review & Editing; **Greene R**: Conceptualization, Methodology, Supervision, Writing – Review & Editing; **Maher GM**: Conceptualization, Methodology, Supervision, Writing – Review & Editing; **McCarthy FP**: Conceptualization, Methodology, Supervision, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: The author(s) declared that no grants were involved in supporting this work.

How to cite this article: Mitchell JM, Walsh S, O'Byrne LJ *et al.* **Association between intrapartum fetal pulse oximetry and adverse perinatal and long-term outcomes: a systematic review and meta-analysis protocol [version 2; peer review: 2 approved]** HRB Open Research 2024, **6**:63 https://doi.org/10.12688/hrbopenres.13802.2

First published: 20 Oct 2023, **6**:63 https://doi.org/10.12688/hrbopenres.13802.1

REVISED **Amendments from Version 1**

We have further defined the review outcomes, for example, we have replaced the term "cord blood acadaemia" with umbilical artery pH less than 7.20, 7.15 or 7.0. We have also defined "low fetal oxygen saturation" as "fetal oxygen saturation less than 30%". We have included 95% prediction intervals as a measure of heterogeneity. We have included an assessment of overall certainty of evidence (i.e. GRADE). We have included Egger's test as a measure of publication bias. We have included clinical trial registers to look for registered studies that may be unpublished but have useable data for inclusion in meta-analysis. Lastly, we have increased the search duration until February 2024.

Any further responses from the reviewers can be found at the end of the article

Introduction

Intrapartum fetal monitoring aims to improve perinatal outcome while avoiding unnecessary operative interventions[1]. The gold standard for assessment of fetal well-being continues to be the auscultation of the fetal heart, along with the interpretation of alterations in the fetal heart rate pattern, as demonstrated through cardiotocography (CTG) to try to predict babies at risk of hypoxic brain injury and adverse perinatal outcomes. Despite its status as the established benchmark in care, employed in approximately 90% of births in the United States (US) and on a global scale, there is a pervasive consensus that current fetal monitoring devices based on heart rate, do not prevent or accurately detect fetal hypoxic brain injury[2–7]. The current use of cardiotocography (CTG) as a method of monitoring intrapartum fetal well‐being during labour is associated with an increased caesarean section rate, compared with intermittent auscultation of the fetal heart rate, resulting in a reduction in neonatal seizures, although no differences in other neonatal outcomes[8]. CTG is complicated by significant inter- and intra-observer variation[2,9,10]. Furthermore, CTG demonstrates a low positive predictive value for fetal hypoxia, meaning that among those fetuses that CTG indicates are at risk for hypoxia, a smaller proportion will truly be hypoxic[2,9,10]. This can lead to an increased frequency of false-positive results, thus potentially prompting unnecessary interventions based on an overestimated risk of fetal hypoxia. Consequently, such misinterpretations could contribute to the escalating rates of caesarean deliveries observed worldwide. For instance, in the US, the caesarean delivery rate has surged, increasing from 20.7% in 1996 to 32.1% in 2021[11]. Similarly in the United Kingdom, the caesarean delivery rate has increased from 14.7% from 1990 to 1999 to 35.21% in 2021–2022[12,13].

Fetal blood sampling (FBS) is widely used as a complementary tool to improve the specificity and sensitivity of CTG[14]. FBS has been shown to reduce operative vaginal delivery rates without affecting neonatal outcomes but it is a complex, invasive procedure[2]. There is a need for more accurate methods of intrapartum fetal surveillance that will decrease the incidence of adverse neonatal and long-term neurodevelopmental outcomes while maintaining the lowest possible rate of obstetric intervention.

Fetal pulse oximetry (FPO) is a technology that may contribute to improved intrapartum fetal wellbeing evaluation by providing a non-invasive measurement of fetal oxygenation status[15–18]. FPO offers a potential dual advantage over traditional fetal heart rate monitoring. It quantifies the percentage of oxygenated haemoglobin directly, thereby assessing fetal oxygenation, which is pivotal in mediating the harmful consequences of hypoxia/ischaemia. Additionally, it utilises a well-established, non-invasive technology, regarded as safe and broadly implemented in all modern intensive care units and operating theatres[8]. Based on data from both human and animal studies, average intrapartum fetal oxygen saturation (FSp02) range from 35% to 65%[19–21]. FSpO2 levels of 30% or higher are generally considered reassuring for the human fetus. However, if FSpO2 levels are less than 30% for a duration of 10 minutes or more, additional evaluation or intervention is warranted[17,19,22–24] A study by McNamara *et al*. (n=100) demonstrated that babies born in poor condition had abnormal fetal oximetry values[25]. FPO is advantageous over FBS in that it is a non-invasive and continuous monitoring technique.

A Cochrane Review published in 2014 compared fetal intrapartum pulse oximetry with other fetal surveillance techniques[8]. This review included seven trials reporting on a total of 8013 pregnancies. The primary outcomes were caesarean section, hypoxic‐ischaemic encephalopathy, neonatal seizures and long‐term neurodevelopmental outcomes. The authors found no significant differences in the overall caesarean delivery rate between those monitored with FPO and those not monitored with FPO or for whom the FPO results were not displayed to the clinician or woman (four studies, n = 4008, risk ratio (RR) 0.99, 95% confidence intervals (CI) 0.86 to 1.13, I^2 = 45). The authors noted a reduction in the number of caesarean sections performed for cases of non-reassuring fetal status in the FPO plus CTG group compared to the CTG only group in two of the four analyses: firstly when considering pregnancies at or beyond 34 weeks where fetal FBS was not required prior to study entry (comprising four studies with 4008 participants, RR 0.65, 95% CI 0.46 to 0.90, I^2 = 63) Secondly, in situations where FBS was a prerequisite before study participation (one study involving 146 participants), the RR was notably low at 0.03, with a 95% confidence interval spanning from 0.00 to 0.44. Additionally, the review reported a reduction in operative births (comprising caesarean sections or operative vaginal births) for non-reassuring fetal status when FPO was combined with CTG monitoring, compared to CTG monitoring alone. This finding was consistent across two studies involving 1610 participants, with a RR of 0.74 (95% confidence interval: 0.62 to 0.89). However, no statistically significant differences were observed in several other outcome measures, including Apgar scores less than four at five minutes or less than seven at five minutes, umbilical arterial pH less than 7.10, neonatal intensive care unit (NICU) admissions, length of hospital stays, mortality, or fetal skin trauma, when comparing the use of FPO in conjunction with CTG to fetal electrocardiography combined with CTG. The results of this review may have been influenced by a large randomised control trial (RCT) by Bloom *et al*.[26] which had several limitations. Namely, that they did not describe the number of caesarean births indicated by the FPO results, nor

did they describe counter-measures, including posture change according to the fetal oxygen saturation values, administration of tocolytic agents, and expedited delivery. Furthermore, observational studies were not included in the previous systematic review. In contrast, our planned review will take a more comprehensive approach, incorporating evidence not just from RCTs, but also from cohort studies, case-control studies, and observational studies.

Uchida *et al*. conducted a narrative review on FPO as a measure of intrapartum fetal condition. They concluded that FPO with fetal heart rate monitoring in selected cases of non-reassuring fetal status may reduce the caesarean section rate[27]. While Uchida and colleagues discussed 31 studies and seven RCTs in their review of previous literature, they did not conduct a systematic review of previous literature. Therefore, we aimed to synthesise the previous literature examining the association between intrapartum fetal oxygen saturation and perinatal and long-term outcomes in the offspring in the form of a systematic review and meta-analysis.

This review has been registered with PROSPERO (CRD42023457368) on 4th September 2023 and follows the PRISMA-P and MOOSE guidelines[28].

Review question
This review will aim to assess the association between intrapartum fetal oxygen saturation less than 30% and the risk of adverse perinatal and long-term neurodevelopmental outcomes. It also aims to investigate whether the addition of the measurement of fetal oxygen saturation by fetal pulse oximetry to established forms of fetal monitoring such as cardiotocographs can reduce the rate of operative delivery without affecting perinatal and long term behavioural outcomes.

Methods
Eligibility criteria
The following PICO criteria will guide this systematic review.

Population
Women in labour with a cephalic baby.

Our search will not exclude multiple pregnancies although we don't expect to find studies where FPO is measured in the non-presenting fetus as it is only technically possible to monitor fetal oxygen saturation using fetal pulse oximetry for the presenting twin using the available technology as the devices are positioned between the fetal cheek or scapula and uterine wall or placed on the fetal scalp[29–34]. This being said, a study is currently ongoing investigating the concurrence of internal and external fetal oxygen sensors using a novel transabdominal fetal pulse oximetry device[35]. However, an inclusion criterion in this study is singleton pregnancy.

Intervention/Exposure
1. Low fetal oxygen saturation defined as less than 30% (exposure).
2. The use of fetal pulse oximetry during labour as a means of measuring intrapartum fetal oxygen saturation (intervention).

Comparison
1. Normal fetal oxygen saturation defined as greater than or equal to 30% (unexposed group).
2. Conventional fetal monitoring e.g. fetal heart rate monitoring by CTG or the use of fetal scalp electrode, fetal blood sampling or fetal electrocardiogram without the measurement of fetal oxygen saturation (control).

Outcomes
The primary outcomes of this review are; umbilical artery pH less than 7.20, 7.15 and 7.0 and 5 minute APGAR Score less than 7. Secondary outcomes include; (i) umbilical artery base excess less then -10mmol/L, (ii) umbilical artery lactate greater than 4.8 mmol/L, correlation between FSp02 and umbilical artery and vein pH, (iii) admission to the neonatal intensive care unit (NICU), (iv) neonatal or intrapartum death, (v) cardiopulmonary resuscitation or intubation required within 24 hours of life, (vi) hypoxic ischaemic encephalopathy, (vii) umbilical vein oxygen saturation less than 55%, (viii) low umbilical artery oxygen saturation less than 30%, (ix) operative delivery for non-reassuring fetal status (as defined by local protocols in each study), (x) operative delivery for dystocia, (xi) fetal scalp pH <7.20, (xii) fetal scalp lactate >4.8mmol/L, (xiii) cerebral palsy and (xiv) severe neurodevelopmental disability. There is no consensus on the specific definition of developmental delay[36]. Multiple different assessment tools exist and the recommended tools have changed over the past 30 years[37,38]. Severe neurodevelopmental disability was defined by a previous Cochrane review[39]; "any one or a combination of the following: non-ambulant cerebral palsy, developmental delay (developmental quotient less than 70), auditory and visual impairment assessed at 12 months of age or more. Development should have been assessed by means of a previously validated tool, such as Bayley Scales of Infant Development (Psychomotor Developmental Index and Mental Developmental Index[40]. See Table 1 for primary and secondary outcome measures.

Studies
Randomised control trials and observational studies including cohort, case-control and cross-sectional studies

We will not exclude studies based on time frame or language.

Review exclusion criteria
- Studies only available in abstract form.
- Non-human studies.
- Review articles, case reports, case series.
- Conference proceedings, letters, commentaries, notes, editorials, dissertations.

Literature search
We will use a two-part search strategy to identify studies meeting the inclusion criteria: (1) we will search electronic bibliographic databases and clinical trial registers for relevant work, using a comprehensive search strategy for fetal intrapartum pulse oximetry and perinatal and long-term outcomes; (2) we will hand-search the reference lists of studies included

Table 1. Review Outcomes.

Primary Outcomes	Perinatal Outcomes	Umbilical artery pH less than 7.20
		Umbilical artery pH less than 7.15
		Umbilical artery pH less than 7.0
		5 minute APGAR Score less than 7
Secondary Outcomes		Umbilical artery base excess less then -10mmol/L
		Umbilical artery lactate greater than 4.8 mmol/L
		Correlation between FSp02 and umbilical artery and vein pH
		Admission to NICU
		Neonatal or intrapartum death
		Cardiopulmonary resuscitation or intubation required within 24 hours of life
		Hypoxic Ischaemic Encephalopathy
		Umbilical vein oxygen saturation less than 55%
		Low umbilical artery oxygen saturation less than 30%
		Operative Delivery for Non-Reassuring Fetal Status (as defined by local protocols in each study)
		Operative Delivery for Dystocia
		Fetal scalp pH <7.20
		Fetal scalp lactate >4.8mmol/L
	Long Term Outcomes	Cerebral Palsy
		Severe Neurodevelopmental Disability*

Perinatal outcomes are defined as outcomes occurring within the first 24 hours of life.

***Severe neurodevelopmental disability was defined by a previous Cochrane review[39]; "any one or a combination of the following: non-ambulant cerebral palsy, developmental delay (developmental quotient less than 70), auditory and visual impairment assessed at 12 months of age or more. Development should have been assessed by means of a previously validated tool, such as Bayley Scales of Infant Development (Psychomotor Developmental Index and Mental Developmental Index"[40].*

in the review and the reference lists of relevant, previously published reviews. The following electronic bibliographic databases will be searched: PubMed, EMBASE, CINAHL, The Cochrane Library and Web of Science ClinicalTrials.Gov and WHO ICTRP until February 2024.

The search strategies for all databases can be found as *Extended data*[41].

Study screening and selection

Titles and abstracts of the studies retrieved from each database search will be stored and managed in the Endnote reference manager and de-duplicated. Three independent reviewers (JM, SW, LOB) will screen all titles and abstracts. Full texts will be obtained where necessary to screen for eligibility. Where consensus on eligibility cannot be achieved, a fourth review author (FMcC) will be involved in the discussion.

Data extraction and management

Two review authors (JM, SW) will independently extract data and discrepancies will be identified and resolved through discussion with a third author (FMcC), where necessary. A standardised, pre-piloted data extraction form will be used to extract data from the included studies. We will extract data including the author and year of publication, study design, country and setting of study, sample size, definition and or assessment of the exposures and outcome(s) of interest, comparison group, length of follow up, confounders adjusted for (if any), crude and adjusted estimates. If additional data is required from an eligible study, the corresponding author will be contacted via email. A reminder email will be sent two weeks later if the corresponding author does not reply.

Quality appraisal of included studies

Articles which meet the selection criteria will be assessed for methodological quality independently by two reviewers using the Risk of Bias tool[42] for randomised controlled trials (RCT) and the Newcastle Ottawa Scale[43] for observational studies. Disagreements between the review authors over the quality assessment of each study will be resolved by discussion, with involvement of a third review author where necessary. The grading of recommendations, assessment, development, and evaluation (GRADE) approach will be used to evaluate the certainty of the evidence by two reviewers independently (J.M. and S.W). The certainty of the evidence was assessed using the GRADEpro software on the basis of the following

domains: the study design, risk of bias, imprecision, inconsistency, indirectness, and publication bias[44].

Data synthesis, including assessment of heterogeneity

We will undertake separate meta-analyses for RCTs and observational studies using RevMan Web. We will also perform separate meta-analyses for each exposure-outcome associations. For example, intrapartum fetal oxygen saturation less than 30% and umbilical artery pH less than 7.20, the addition of FPO as a monitoring method and umbilical artery pH less than 7.0, intrapartum fetal oxygen saturation less than 30% and 5 minute Apgar score less than 7 and intrapartum fetal oxygen saturation less than 30% and admission to NICU. Random effects meta-analyses will be performed to calculate overall pooled estimates where data allow. We will use the generic inverse variance method to display crude and adjusted results where possible. First, we will conduct a meta-analysis of all crude estimates for each exposure-outcome association. We will then conduct a meta-analysis of all adjusted estimates for each exposure-outcome association. We will consider any adjusted estimate as adjusted regardless of the variables adjusted for. When a meta-analysis cannot be conducted because of lack of data, a narrative synthesis of the results will be included. The summary measures will be reported as odds ratio (OR) with 95% confidence interval (CI). We will present the correlation between FSp02 and umbilical artery and vein pH in narrative form.

Heterogeneity will be assessed statistically using the I^2 statistic and explored using subgroup analyses based on the different study designs included in this review. We will perform the subgroup/sensitivity analysis where the data allow, according to the study design (RCT, cohort, case-control and cross-sectional) and study quality/risk of bias (minimal/low versus moderate/high). Where the data allow, we will perform subgroup analyses based on gestational age. Furthermore, for meta-analyses which included at least three studies, 95% prediction intervals were calculated in Microsoft Excel using formulae previously outlined by Borenstein *et al.*[45,46].

The presence of publication bias will be evaluated using a funnel plot, and by conducting an Egger's test for asymmetry of the funnel plot, provided a minimum inclusion of 10 studies or more in the meta-analysis. In instances where additional subgroup/sensitivity analyses are found within the meta-analysis, such as examinations to investigate potential high heterogeneity, these will be labelled as post-hoc analyses.

Presenting and reporting the results

A PRISMA flow diagram will be incorporated to detail the sequential process of study selection, along with explanations for any studies excluded during the full-text review phase. Study characteristics and quality assessment of included studies will be displayed in tables, while pooled estimates will be presented using forest plots. Where data which is unsuitable for meta-analysis, results will be narratively synthesised.

Conclusions

The systematic review and meta-analysis will summarise the existing literature investigating the association between intrapartum fetal oxygen saturation and adverse perinatal and long term outcomes in offspring. This review is of considerable importance as it explores the potential utility of fetal pulse oximetry as a method for intrapartum fetal monitoring. There is a pressing need for innovative and reliable approaches to monitor fetal well-being during labour, and this review could provide pivotal insights in this regard.

Potential strengths and limitations of this study

The robustness of this review is bolstered by the implementation of a thorough search strategy, a prospectively registered protocol, and strict compliance with PRISMA and MOOSE guidelines. Additionally, the engagement of three reviewers in the process of eligibility screening and two reviewers in the process of data extraction, and quality assessment of the included studies serves to substantially mitigate the potential for reviewer-based bias in the systematic review. Furthermore, this review will not have language restrictions, reducing the risk that relevant studies be overlooked. The existence of confounding variables poses a significant challenge in observational research. Possible confounders might encompass the age of the mother, parity, maternal body mass index, heterogenous clinical approaches, different methods of monitoring FSp02 and pregnancy complications such as intrauterine growth restriction, pre-eclampsia and gestational diabetes mellitus. As noted previously, our meta-analyses will present both unadjusted and adjusted outcomes, whenever feasible, using the generic inverse variance approach. This adjustment will be based on the definitions provided in each of the studies we've reviewed. Family wise error rate increases when comparing many secondary outcomes, therefore significant results will be interpreted with caution based on plausibility, theory and uncertainty.

Dissemination

It is anticipated that findings of this review will be disseminated through publication in a peer-reviewed journal and presented at scientific conferences.

Data availability

Underlying data

No data are associated with this article.

Extended data

Fighsare: Search Strategy - Association between Intrapartum Fetal Pulse Oximetry and Adverse Perinatal and Long-term Outcomes- a Systematic Review and Meta-analysis Protocol.docx. *https://doi.org/10.6084/m9.figshare.24049890.v3*[41].

Reporting guidelines

Fighsare: PRISMA-P checklist for 'Association between intrapartum fetal pulse oximetry and adverse perinatal and long-term outcomes: a systematic review and meta-analysis protocol. *https://doi.org/10.6084/m9.figshare.24049899*[28].

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Publisher Full Text

Open Peer Review

Current Peer Review Status: ✔ ✔

Version 2

Reviewer Report 15 April 2024

https://doi.org/10.21956/hrbopenres.15221.r38895

✔ **James X Sotiropoulos**
Evidence Integration, The University of Sydney, Sydney, New South Wales, Australia
Sol Libesman
Evidence Integration, The University of Sydney, Sydney, New South Wales, Australia

Thank you for the opportunity to comment on the revised manuscript.

The authors have addressed all concerns in detail. I have no further comments.

Best wishes with your study.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Systematic Reviews, Meta-analysis, Research Integrity, Neonatal and Perinatal Research

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 27 November 2023

https://doi.org/10.21956/hrbopenres.15101.r37131

James X Sotiropoulos
Evidence Integration, The University of Sydney, Sydney, New South Wales, Australia
Sol Libesman
Evidence Integration, The University of Sydney, Sydney, New South Wales, Australia

We thank you for the opportunity to review this study protocol.

We commend the authors for their practice of open science and publishing the protocol at this stage with pre-registration following PRISMA-P guidelines. We will focus mainly on the methods in this review, as it is most aligned with my experience, and provide some (hopefully) constructive feedback.

Introduction
The introduction is clear and describes the need for this study – with a recent narrative review without systematic review and meta-analysis indicating potential findings.

Methods
Note Table 1 formatting appears odd on the online system – please check
Are there any inclusion/exclusion criteria beyond cephalic, singleton live baby?

The authors' inclusion/exclusion criteria is singleton pregnancies only. Is there a good justification for this? If possible, it may provide future utility in collecting data for multiples, even if only reporting it in stratified analysis separately. If FPO is not feasible/reliable in multiple pregnancies this should be clearly stated and cited.

The authors could consider further specifying the outcomes. For example, the cut-off for “low”, and “abnormal” are not provided. Could you specify how developmental delay will be measured including a cut-off (if this has been established)? Could you also specify the time in which these outcomes are measured (e.g., the primary endpoints), the measurement units (if relevant), and the relative effects that will be used to compare the groups?

In the section “comparator” you mention “We will compare …offspring who had low oxygen saturations in labour versus those who had normal oxygen saturations in labour as measured by…”. Could you specify the cut-off you plan to use for low? For further guidance on the description of treatments and outcomes, the ‘estimand’ framework may help you clarify elements of treatment, population, outcome, population level summaries, and more.

There are two review questions nominated, but the comparator section only appears to address the first review question.

The authors plan to use I^2 as a measure of heterogeneity. I^2 is a flawed measure of heterogeneity, although it permeates systematic review and meta-analysis across all disciplines. Please see this article (https://doi.org/10.1002/jrsm.1230, [1]). Will the authors consider, instead or in addition to I^2, graphically representing heterogeneity with prediction intervals or another measure of between-study variance? The Cochrane Handbook provides some useful guidance.

The authors have not included an assessment of the overall certainty of evidence (e.g., GRADE).

This has also been marked as “NA” in the PRISMA-P document. I strongly recommend the use of GRADE to assess the overall certainty of evidence, or if it is to be omitted for a valid reason that this be explained in the methods and/or discussion. Alternatively, if it is omitted a clear plan as to how the evidence will be evaluated should be provided.
The authors have noted the potential impact of publication bias and plan to use a funnel plot. They may consider a contour-enhanced funnel plot, PET-PEESE, or p-curve analysis to examine publication bias. They might also consider a search of clinical trial registers to look for other registered studies that may be unpublished but have useable data for inclusion in meta-analysis. Guidance for searching clinical trial registers is here https://doi.org/10.1136/bmj-2021-068791 [2].

The authors intend to search only until August 2023. By the time the results of this study are ready for publication the search may be outdated. I note the PROSPERO registration says the search will begin in 2024. This may be a typo. Otherwise, I suggest the search is updated beyond August 2023 prior to the results publication.

The authors have prespecified their outcomes, however, have listed many primary outcomes and stated “Any measure of compromise of neonatal or childhood wellbeing…” will be used. I suggest pre-specifying a single (or at most two) key primary outcomes, and other outcomes be listed as secondary. Mortality and neurodevelopment may be appropriate given the introduction; however, this is beyond my expertise and knowledge of the literature. I also suggest revising the sentence so that the measures of compromised are more specific, and not “any” measure is included.

There are many secondary outcomes. I would recommend a sentence acknowledging the increased family wise error rate when conducting multiple comparisons. E.g., “because family wise error rate increases when comparing many secondary outcomes, significant results will be interpreted with caution based on plausibility, theory and uncertainty.”

Discussion
Strengths and limitations are appropriately noted.

References
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2. Hunter KE, Webster AC, Page MJ, Willson M, et al.: Searching clinical trials registers: guide for systematic reviewers.*BMJ*. 2022; **377**: e068791 PubMed Abstract | Publisher Full Text

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Partly

Are the datasets clearly presented in a useable and accessible format?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Systematic Reviews, Meta-analysis, Research Integrity, Neonatal and Perinatal Research

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.

Author Response 13 Mar 2024

Jill Mitchell

Dear Dr Sotiropoulos and Dr Libesman,
We thank you both for your helpful review of our manuscript entitled "Association between Intrapartum Fetal Pulse Oximetry and Adverse Perinatal and Long-term Outcomes: a Systematic Review and Meta-analysis Protocol".
Please find below an itemized reply addressing each comment in your Reviewer's Report.

1.Introduction
The introduction is clear and describes the need for this study – with a recent narrative review without systematic review and meta-analysis indicating potential findings.

We thank you for your positive comment regarding our Introduction.

2.Methods
Table 1

Table 1. Review Outcomes

https://hrbopenresearch.s3.eu-west-1.amazonaws.com/linked/197134.13802-Author_response_to_Referee_James_X_Sotiropoulos_v1__2.pdf

3. Are there any inclusion/exclusion criteria beyond cephalic, singleton live baby? The authors' inclusion/exclusion criteria is singleton pregnancies only. Is there a good justification for this? If possible, it may provide future utility in collecting data for multiples, even if only reporting it in stratified analysis separately. If FPO is not feasible/reliable in multiple pregnancies this should be clearly stated and cited.
We have removed the word "singleton" from the inclusion criteria so that our search will include multiple pregnancies although we don't expect to find studies where fetal oxygen saturation is measured in both twins as it is therefore only technically possible to monitor fetal oxygen saturation using fetal pulse oximetry for the presenting twin using the available technology. This being said, a study is currently ongoing investigating the concurrence of internal and external fetal oxygen sensors using a novel transabdominal fetal pulse oximetry device (3). However, an inclusion criteria in this study is singleton

pregnancy.

We have updated the manuscript to reflect this, see p9, lines 95 to 111.
"***Population***
Women in labour with a cephalic baby.
Our search will not exclude multiple pregnancies although we don't expect to find studies where FPO is measured in the non-presenting fetus as it is only technically possible to monitor fetal oxygen saturation using fetal pulse oximetry for the presenting twin using the available technology as the devices are positioned between the fetal cheek or scapula and uterine wall or placed on the fetal scalp (4-9). This being said, a study is currently ongoing investigating the concurrence of internal and external fetal oxygen sensors using a novel transabdominal fetal pulse oximetry device (3). However, an inclusion criteria in this study is singleton pregnancy."
We decided not to exclude based on gestational age as we want to include as many relevant studies as possible. Where the data allow, we will perform subgroup analyses based on gestational age. See p14, lines 257-260.

"Where the data allow, we will perform subgroup analyses based on gestational age."

4. The authors could consider further specifying the outcomes. For example, the cut-off for "low", and "abnormal" are not provided.
Thank you for this suggestion. We have updated our protocol and Table 1 to further define the outcomes. See p10-11, lines 124-153;
"The primary outcomes of this review are; (i) umbilical artery pH less than 7.20, (ii) umbilical artery pH less than 7.15 and (iii) umbilical artery pH less than 7.0, (iv) 5 minute APGAR Score less than 7. Secondary outcomes include; (i) umbilical artery base excess less then -10mmol/L, (ii) umbilical artery lactate greater than 4.8 mmol/L, (iii) admission to the neonatal intensive care unit (NICU), (iv) neonatal or intrapartum death, (v) cardiopulmonary resuscitation or intubation required within 24 hours of life, (vi) hypoxic ischaemic encephalopathy, (vii) umbilical vein oxygen saturation less than 55%, (viii) low umbilical artery oxygen saturation less than 30%, (ix) operative delivery for non-reassuring fetal status (as defined by local protocols in each study) (x) operative delivery for dystocia, (xi) fetal scalp pH <7.20, (xii) fetal scalp lactate >4.8mmol/L, (xiii) cerebral palsy and (xiv) severe neurodevelopmental disability. There is no consensus on the specific definition of developmental delay (10). Multiple different assessment tools exist and the recommended tools have changed over the past 30 years (11, 12). Severe neurodevelopmental disability was defined by a previous Cochrane review (1); "any one or a combination of the following: non-ambulant cerebral palsy, developmental delay (developmental quotient less than 70), auditory and visual impairment assessed at 12 months of age or more. Development should have been assessed by means of a previously validated tool, such as Bayley Scales of Infant Development (Psychomotor Developmental Index and Mental Developmental Index (2)."

5. **Could you specify how developmental delay will be measured including a cut-off (if this has been established)?**
We have considered your suggestion and with this in mind have decided to update our objective from "developmental delay" to "severe neurodevelopmental disability" as defined by a previous Cochrane review(1). This is outlined in our on p11, lines 146 to 153, as follows:

"There is no consensus on the specific definition of developmental delay (10). Multiple different

assessment tools exist and the recommended tools have changed over the past 30 years (11, 12). Severe neurodevelopmental disability was defined by a previous Cochrane review (1); "any one or a combination of the following: non-ambulant cerebral palsy, developmental delay (developmental quotient less than 70), auditory and visual impairment assessed at 12 months of age or more. Development should have been assessed by means of a previously validated tool, such as Bayley Scales of Infant Development (Psychomotor Developmental Index and Mental Developmental Index (2)."

6. Could you also specify the time in which these outcomes are measured (e.g., the primary endpoints),the measurement units (if relevant), and the relative effects that will be used to compare the groups?
We have defined the term "perinatal outcomes" as outcomes occurring within the first 24 hours of life (see p19, Table 1, footnote 1) and severe neurodevelopmental disability was defined as any one or a combination of the following: non-ambulant cerebral palsy, developmental delay (developmental quotient less than 70), auditory and visual impairment assessed at 12 months of age (see p19, Table 1, footnote 2).

"**Perinatal outcomes are defined as outcomes occurring within the first 24 hours of life.*
***Severe neurodevelopmental disability was defined by a previous Cochrane review(1); "any one or a combination of the following: non-ambulant cerebral palsy, developmental delay (developmental quotient less than 70), auditory and visual impairment assessed at 12 months of age or more. Development should have been assessed by means of a previously validated tool, such as Bayley Scales of Infant Development (Psychomotor Developmental Index and Mental Developmental Index"(2)."*

The summary measures will be reported as odds ratio with 95% confidence interval. We will present the correlation between FSp02 and umbilical artery and vein pH in narrative form. This has been clarified on p14, lines 242 to 244.

"The summary measures will be reported as odds ratio (OR) with 95% confidence interval (CI). We will present the correlation between FSp02 and umbilical artery and vein pH in narrative form."

7. In the section "comparator" you mention "We will compare …offspring who had low oxygen saturations in labour versus those who had normal oxygen saturations in labour as measured by…". Could you specify the cut-off you plan to use for low? For further guidance on the description of treatments and outcomes, the 'estimand' framework may help you clarify elements of treatment, population, outcome, population level summaries, and more. There are two review questions nominated, but the comparator section only appears to address the first review question.

We have now edited our "intervention/exposure" and "comparison" to incorporate your suggestion. . This is outlined in our manuscript as follows (p10, lines 113 to 122):

"Intervention/Exposure
1. *Low fetal oxygen saturation defined as less than 30% (exposure).*
2. *The use of fetal pulse oximetry during labour as a means of measuring intrapartum fetal*

oxygen saturation (intervention).

Comparison

1. *Normal fetal oxygen saturation defined as greater than or equal to 30% (unexposed group)."*
2. *Conventional fetal monitoring e.g. fetal heart rate monitoring by CTG or the use of fetal scalp electrode, fetal blood sampling or fetal electrocardiogram without the measurement of fetal oxygen saturation (control).*

8. The authors plan to use I^2 as a measure of heterogeneity. I^2 is a flawed measure of heterogeneity, although it permeates systematic review and meta-analysis across all disciplines. Please see this article (https://doi.org/10.1002/jrsm.1230, [1]). Will the authors consider, instead or in addition to I^2, graphically representing heterogeneity with prediction intervals or another measure of between-study variance? The Cochrane Handbook provides some useful guidance.
Thank you for this comment. We have amended methods section to include prediction intervals where meta-analysis include three or more studies, see p14, lines 251 to 253.

"Furthermore, for meta-analyses which include at least three studies, 95% prediction intervals will be calculated in Microsoft Excel using formulae previously outlined by Borenstein et al (13, 14)'

9. The authors have not included an assessment of the overall certainty of evidence (e.g., GRADE). This has also been marked as "NA" in the PRISMA-P document. I strongly recommend the use of GRADE to assess the overall certainty of evidence, or if it is to be omitted for a valid reason that this be explained in the methods and/or discussion. Alternatively, if it is omitted a clear plan as to how the evidence will be evaluated should be provided.
Thank you for this recommendation. We have decided to use an assessment of the overall certainty of evidence using the GRADE approach. This has been added to the manuscript. See p13, lines 216 to 220.

"The grading of recommendations, assessment, development, and evaluation (GRADE) approach will be used to evaluate the certainty of the evidence for primary outcomes by two reviewers independently (J.M. and S.W). The certainty of the evidence was assessed using the GRADEpro software on the basis of the following domains: the study design, risk of bias, imprecision, inconsistency, indirectness, and publication bias(15)."

10. The authors have noted the potential impact of publication bias and plan to use a funnel plot. They may consider a contour-enhanced funnel plot, PET-PEESE, or p-curve analysis to examine publication bias.
Thank you for this suggestion. We have decided to assess publication bias using Egger's test in addition to funnel plots. See p14, lines 254 to 256.

"The presence of publication bias will be evaluated using a funnel plot, and by conducting an Egger's test for asymmetry of the funnel plot, provided a minimum inclusion of 10 studies or more in the meta-analysis."

11. They might also consider a search of clinical trial registers to look for other registered studies that may be unpublished but have useable data for inclusion in meta-analysis. Guidance for searching clinical trial registers is here https://doi.org/10.1136/bmj-2021-068791 [2].

We have decided to include clinical trial registers, namely ClinicalTrials.Gov and WHO ICTRP in our search. We have amended our manuscript to read (p12, lines 185 to 187);
"The following electronic bibliographic databases and clinical trial registers will be searched: PubMed, EMBASE, CINAHL, The Cochrane Library, Web of Science, ClinicalTrials.Gov and WHO ICTRP until February 2024."

12. The authors intend to search only until August 2023. By the time the results of this study are ready for publication the search may be outdated. I note the PROSPERO registration says the search will begin in 2024. This may be a typo. Otherwise, I suggest the search is updated beyond August 2023 prior to the results publication.
Thank you for this suggestion. We have extended our search timeline to February 2024, see p12, lines 185 to 187.
"The following electronic bibliographic databases and clinical trial registers will be searched: PubMed, EMBASE, CINAHL, The Cochrane Library, Web of Science, ClinicalTrials.Gov and WHO ICTRP until February 2024."

13. The authors have prespecified their outcomes, however, have listed many primary outcomes and stated "Any measure of compromise of neonatal or childhood wellbeing…" will be used. I suggest pre-specifying a single (or at most two) key primary outcomes, and other outcomes be listed as secondary. Mortality and neurodevelopment may be appropriate given the introduction; however, this is beyond my expertise and knowledge of the literature. I also suggest revising the sentence so that the measures of compromised are more specific, and not "any" measure is included.
Thank you for this comment. We have taken this suggestion on board and have updated our outcomes accordingly. See p10, lines 124 to 146.

"The primary outcomes of this review are; (i) umbilical artery pH less than 7.20, (ii) umbilical artery pH less than 7.15 and (iii) umbilical artery pH less than 7.0, (iv) 5 minute APGAR Score less than 7. Secondary outcomes include; (i) umbilical artery base excess less then -10mmol/L, (ii) umbilical artery lactate greater than 4.8 mmol/L, (iii) admission to the neonatal intensive care unit (NICU), (iv) neonatal or intrapartum death, (v) cardiopulmonary resuscitation or intubation required within 24 hours of life, (vi) hypoxic ischaemic encephalopathy, (vii) umbilical vein oxygen saturation less than 55%, (viii) low umbilical artery oxygen saturation less than 30%, (ix) operative delivery for non-reassuring fetal status (as defined by local protocols in each study) (x) operative delivery for dystocia, (xi) fetal scalp pH <7.20, (xii) fetal scalp lactate >4.8mmol/L, (xiii) cerebral palsy and (xiv) severe neurodevelopmental disability.

14. There are many secondary outcomes. I would recommend a sentence acknowledging the increased family wise error rate when conducting multiple comparisons. E.g., "because family wise error rate increases when comparing many secondary outcomes, significant results will be interpreted with caution based on

plausibility, theory and uncertainty."
We have included this sentence and will also include it in the limitations section of our review. See p16, page 309 to 311.

"Family wise error rate increases when comparing many secondary outcomes, therefore significant results will be interpreted with caution based on plausibility, theory and uncertainty."

15.Discussion
Strengths and limitations are appropriately noted.
We thank you for your positive comment regarding our Discussion.

We hope these amendments address the suggestions raised. Should any further amendments be necessary, we would be happy to address them accordingly.
Sincerely,
Dr Jill Mitchell
Corresponding author.
Research Fellow
Department of Obstetrics and Gynaecology, University College Cork, Cork, Ireland.

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1. Devane D, Lalor JG, Daly S, McGuire W, Cuthbert A, Smith V. Cardiotocography versus intermittent auscultation of fetal heart on admission to labour ward for assessment of fetal wellbeing. Cochrane Database of Systematic Reviews. 2017(1).
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11. Rosenbaum P. Screening tests and standardized assessments used to identify and characterize developmental delays. Seminars in Pediatric Neurology. 1998;5(1):27-32.
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15. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. Journal of Clinical Epidemiology. 2011;64(4):401-6.

Competing Interests: N/A

Reviewer Report 10 November 2023

https://doi.org/10.21956/hrbopenres.15101.r36909

Maeve Eogan
[1] Rotunda Hospital, Dublin, Ireland
[2] Obstetrics and Gynecology, Royal College of Surgeons in Ireland Faculty of Sports and Exercise Medicine, Dublin, Leinster, Ireland

This protocol for a systematic review & metanalysis synthesising evidence on this relevant topic for parents and practitioners is already registered with Prospero, and is well summarised and detailed in the attached documents. The background to the topic is eloquently described, the review questions are distinct and the methods are described in sufficient detail. Inclusion and exclusion criteria for identified studies are prescribed, and the methodology and proposed reporting of findings appear appropriate.

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?

Yes

Are the datasets clearly presented in a useable and accessible format?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Clinical obstetrics

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.