

## Identifying and handling potentially untrustworthy trials in Pregnancy and Childbirth Cochrane Reviews

**Alfirevic Z, Kellie FJ, Stewart F, Jones L, Hampson L, on behalf of Pregnancy and Childbirth  
Editorial Board**

### 1. BACKGROUND

Cochrane's mission is to promote evidence-informed health decision-making by producing high-quality, relevant, and accessible systematic reviews. We are increasingly being made aware of the publication of untrustworthy and potentially fraudulent trials in a number of journals within our specialty. Including such trials in our Cochrane Reviews has serious implications – not only for the reputation of Cochrane, our group, and our review authors, but also for the impact on pregnant women and their babies as a result of healthcare decisions informed by our Cochrane Review evidence.

We acknowledge the guidance available to date in the Cochrane Handbook<sup>1</sup> and the Committee on Publication Ethics (COPE) guidelines regarding a journal's responsibilities for retracting fraudulent reports<sup>2</sup>. Cochrane have also recently introduced a new policy for managing potentially problematic studies in systematic reviews – and implementation guidance.

Our Group has developed our own process for identifying untrustworthy (potentially fraudulent) trials, and how to handle them in our group's Cochrane Reviews.

### 2. RETRACTED STUDIES

#### 2.1. Identifying retracted studies

Where a journal publishes a retraction for a study already included in a Cochrane Review, we are well placed to act on this and mitigate any further impact on the Cochrane Review. Our Information Specialist is continually prospectively screening CPC-specific search results in order to populate the [Specialised Register](#). This picks up retractions as they appear in the sources searched. The Information Specialist also receives daily updates from Retraction Watch via email and Twitter.

#### 2.2 Handling retracted studies

In this instance, the editorial office will contact the review team and ask them to move the study from included to excluded, edit all sections of the review accordingly, then resubmit the amended review. Authors will be asked to summarise the changes that they have made to the review and the impact that removing the study has on the review's results/conclusions. We expect authors to act swiftly in addressing the concerns – maximum 6 weeks.

In this scenario, we will add a statement to the main sections of the review to explain what we have done in this amended version of the review, and why. An example statement is provided in **Figure 1**. The amended version should be approved by the Cochrane Pregnancy and Childbirth (CPC) Topic Editor or a Co-ordinating Editor before being re-published in the *Cochrane Library*.

Since publication of this updated review in Issue X, 2018, the Smith 2019 study has now been retracted by the Journal of Made Up Science due to implausible data (link to retraction notice). We have moved this study from included to excluded studies and updated our results and text accordingly.

*Figure 1 – example statement added to Cochrane Review where we remove a retracted study*

### **3. HIGH-RISK STUDIES IN TERMS OF SCIENTIFIC INTEGRITY (TRUSTWORTHINESS)**

Currently, the onus is on peer-reviewers, journal editors, publishers, systematic review authors and institutions where the research was done and/or the authors work to prove that a study is fraudulent. Perhaps the time has come for the onus to be on the authors of primary research to prove that a study is trustworthy.

We are only aware of one very recently published tool to assist us in this endeavour<sup>3</sup>. Another suggested approach might be to include a study only if the study protocol has been prospectively registered. Whilst this is undoubtedly a step in the right direction, an expectation of prospective trial registration is not only relatively recent, but also no guarantee of scientific integrity.

#### **3.1. Cochrane Pregnancy and Childbirth Trustworthiness Screening Tool (CPC-TST)**

We have produced a list of question that could help us flag potentially untrustworthy trials. Criteria that need to be considered when assessing trustworthiness include:

##### **Research governance**

- Are there any retraction notices or expressions of concern listed on the [Retraction Watch Database](#) relating to this study?
- Was the study prospectively registered (for those studies published after 2010) If not, have the authors provided a plausible reason?
- When requested, did the trial authors provide/share the protocol and/or ethics approval letter?
- Did the trial authors engage in communication with Cochrane Pregnancy and Childbirth within the agreed timelines?
- Did the trial authors provide IPD data upon request? If not, was there a plausible reason?

##### **Baseline characteristics**

- Is the study free from characteristics of the study participants that appear too similar (e.g. distribution of the mean (SD) excessively narrow or excessively wide, as noted by [Carlisle 2017](#))?

##### **Feasibility**

- Is the study free from characteristics that could be implausible? (e.g. large numbers of women with a rare condition recruited from a single centre within 12 months);
- In cases with (close to) zero losses to follow-up, is there a plausible explanation?

##### **Results**

- Is the study free from results that could be implausible? (e.g. massive risk reduction for main outcomes with small sample size)?
- Do the numbers randomised to each group suggest that adequate randomisation methods were used (e.g. is the study free from issues such as unexpectedly even numbers of women 'randomised', including a mismatch between the numbers and the methods, equal number of randomised participants when 'no blocking was used', or if the authors say they used 'blocks of 4' but the final numbers differ by 6)?

#### **3.2. Handling CPC-TST 'high risk' studies**

Where a study is classified as 'high risk', the study authors should be contacted to address any possible lack of information/concerns. In cases where it is not possible to obtain contact details for the study authors, or where adequate information has not been provided, the study should remain in 'awaiting classification'. The reasons and communications with the author (or lack of) described in detail. See **Appendix 1** for details of how to apply the CPC-TST.

The CPC-TST has now been added to the CPC data extraction template. Cochrane review authors should use this form to clearly present their trustworthiness assessments against each of the above criteria and detail what, if any, additional information is needed. Where additional information is required, the data extraction sheet should be emailed to Frances Kellie ([f.kellie@liverpool.ac.uk](mailto:f.kellie@liverpool.ac.uk)).

Cochrane Pregnancy and Childbirth Editorial office will contact the trial authors in the first instance with specific requests which, if satisfied, would give reassurance about the trial. If adequate reassurance is not provided, or there is no response to the request, the study, although eligible, will be moved to the "Awaiting classification" where the reasons and communication with authors (or lack of) should be described in detail in 'neutral' language. **Appendix 2** contains a template which can be adapted for use when making initial contact with the trial authors, and if no response is received.

#### **4. WHERE A STUDY IS UNDER INVESTIGATION BY A JOURNAL**

The information regarding possible investigation of a published fraudulent trial may come from various sources. However, we will state this in the Cochrane Review only if we have written confirmation for this to be true. In this scenario, the editorial office will contact the Editor in Chief of the relevant journal (with copies to the journal publisher) to seek clarification regarding the status of investigation and whether any action is currently being taken. An example email is provided in **Appendix 3**.

If the journal editor confirms that a formal investigation is underway, the editorial office will contact the review team asking them to move the study from included to studies awaiting assessment, edit all sections of the review accordingly, then resubmit the amended review. Authors will be asked to summarise the changes that they have made to the review and the impact that removing the study has on the review's results/conclusions. We expect authors to act swiftly in addressing the concerns – within 6 weeks. We will add the statement (as in Figure 2 below) to various sections of the review before publishing a new citation, amended version of the Cochrane Review in the *Cochrane Library*.

The amended version should be approved by the CPC Topic Editor or a Co-ordinating Editor before being re-published in the *Cochrane Library*.

Since publication of this new review in Issue 10, 2017, we have been advised that the [Doe 2016](#) study is currently the subject of an investigation by the Journal of questionable science. We have now moved this study from 'included studies' to 'Studies awaiting classification' until the outcome of the investigation is known.

*Figure 2 – example statement added to Cochrane Review where we are aware of the journal carrying out a formal investigation.*

If, after a reminder, no reply is received from the relevant journal within 2 weeks, we will add the statement in Figure 3 below to various sections of the review before publishing a new citation, amended version of the Cochrane Review in the *Cochrane Library*. If we subsequently receive a reply confirming investigation then we will publish further amendment (not a new citation) updating this information. If journal replies saying that they are aware but don't believe an investigation is warranted then the editorial base discusses with Co-Eds/Topic Editor and makes decision about whether study remains in awaiting assessment, or not.

Since publication of this new review in Issue 10, 2017, we have now moved one study ([Doe 2016](#)) from 'included studies' to 'studies awaiting classification', pending clarification about the study data.

*Figure 3 – example statement added to Cochrane Review where we are aware of the journal carrying out a formal investigation.*

#### **5. THERE ARE SERIOUS CONCERNS RELATING TO A STUDY INCLUDED IN A COCHRANE REVIEW, BUT FOR LEGAL REASONS WE ARE UNABLE TO SHARE DETAILS WITH THE REVIEW TEAM IN THE SHORT TERM**

In this instance, the editorial office will contact the review team informing them that we have been made aware of potentially serious issues, but once we know more we will be in touch and will require them to make urgent edits to the Cochrane Review, if needed.

At this stage, the Cochrane Review is not edited until we have more information. The editorial office maintains lines of communication between whistle-blower, the Cochrane Review Group and the Cochrane Review authors. Any decisions/amended versions should be approved by the Topic Editor or a Co-ordinating Editor.

#### **6. ABSTRACTS**

Data from abstracts will only be included if, in addition to the trustworthiness assessment, the study authors have confirmed in writing that the data to be included in the review have come from the final analysis and will not change. If such information is not available/provided, the study will remain in 'awaiting classification' (as above).

## 7. WHICH SECTIONS OF A REVIEW NEED TO BE EDITED WHEN WE IDENTIFY A PROBLEMATIC INCLUDED STUDY?

Removing an included study from the review is likely to require edits to all sections of the review and may have implications for the overall conclusions of the review. The authors will need to re-assess the relevant trial as 'excluded' or as a study 'awaiting classification'. Data will need to be removed from the data and analysis tables and the GRADE assessments re-done if those analyses were affected by edits to data tables. The results will need to be reconsidered and re-reported in all sections of the review, in light of any changes to the GRADE certainty reassessments. In our experience, even removing one study from a relatively small review will take about one day. When resubmitted, the edited review will need to undergo full checks in the editorial base (including editing the study flow diagram) to ensure that the amended review is correct and internally consistent. We will expect our Cochrane authors to make edits to address these concerns but we will need to make the edits in house if the authors do not do so within 4 weeks. (see **Appendix 4**)

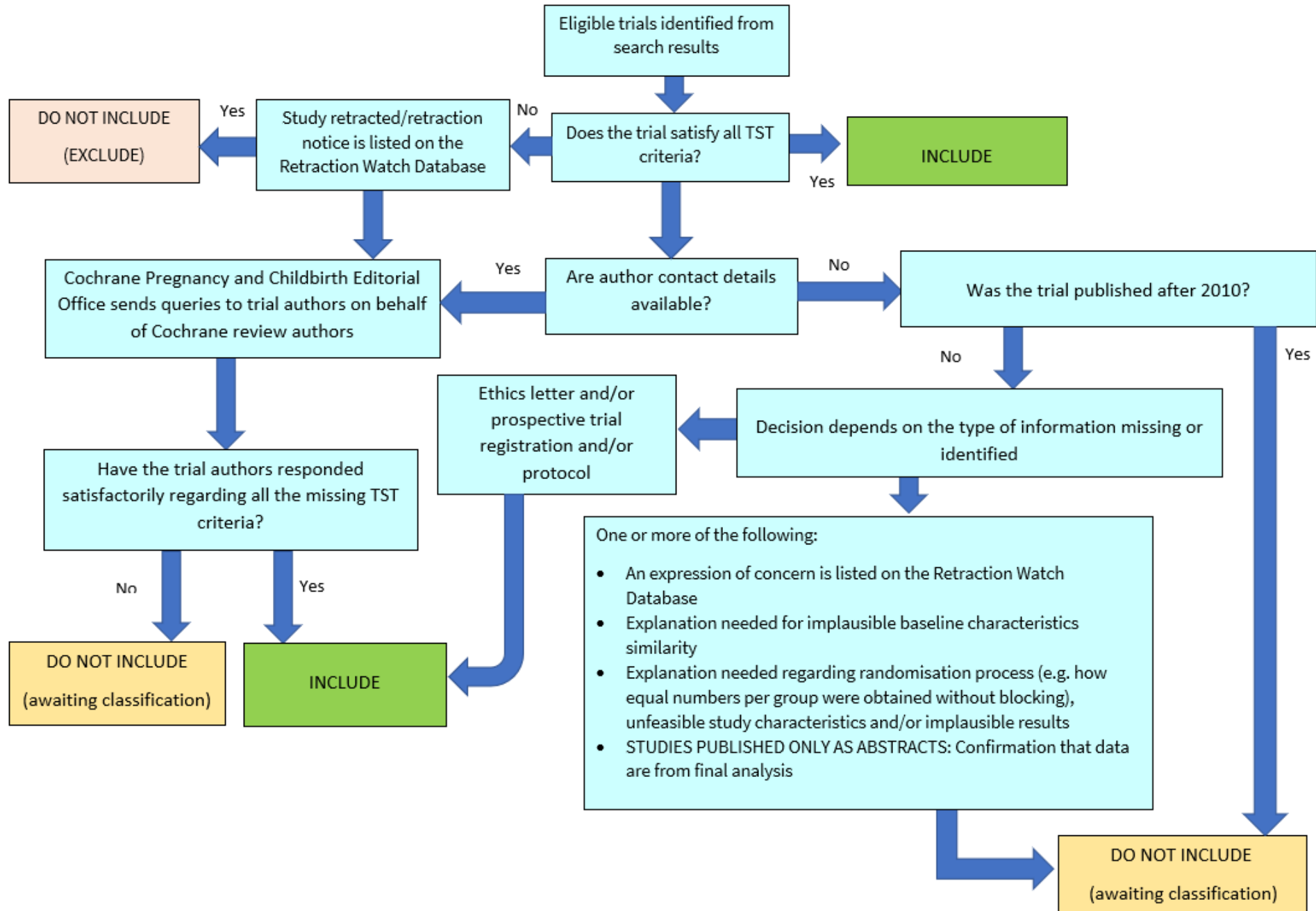
## 8. NOTIFYING STAKEHOLDERS THAT THE COCHRANE REVIEW HAS BEEN AMENDED

A large number of our reviews have been used to inform the clinical care of pregnant women and their babies via national or international guidelines, or policy documents. We have, therefore, a duty of care to inform our key stakeholders that an amended review has been published, especially when removing fraudulent, or potentially-fraudulent trial affected the review's conclusions/and or direction of effect estimates for priority outcomes underpinning corresponding guidelines or policies.

Anne Eisinga at Cochrane UK has spent some years compiling a database of clinical guidelines that have been informed by Cochrane Reviews. For any given review, we will request information about review citations in order to be proactive in contacting stakeholders and alerting them to the amended review.

### References

- <sup>1</sup> Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.0 (updated July 2019). Chapter 4.4.6. Cochrane, 2019. Available from [www.training.cochrane.org/handbook](http://www.training.cochrane.org/handbook)
- <sup>2</sup> COPE. Guidelines: Retraction guidelines 2019. Committee on Publication Ethics, Hampshire, UK. Available at <https://publicationethics.org/files/retraction-guidelines.pdf>, accessed 13 December 2019
- <sup>3</sup> Gray A, Bolland MJ, Avenell A, Klein AA, Gunsalus CK. Check for publication integrity before misconduct. A tool that focuses on papers – not researcher behaviour – can help readers, editors and institutions assess which publication to trust. *Nature* 2020, **577**, 167-169. doi: 10.1038/d41586-019-03959-6
- <sup>4</sup> Carlisle JB. Data fabrication and other reasons for non-random sampling in 5087 randomised, controlled trial in anaesthetic and general medical journals. *Anaesthesia* 2017, **72**, 944-952. doi:10.1111/anae.13938
- <sup>5</sup> Scherer R, Saldanha IJ. How should systematic reviewers handle conference abstracts? A view from the trenches. *Systematic Reviews* 2019 **8**:264



## Appendix 2 – Example email template for use by Cochrane Pregnancy Editorial Office

### Initial email to trial authors

Subject: Query (name of trial) - inclusion in Cochrane review

Dear (lead author),

We are in the process of updating/conducting the Cochrane systematic review entitled (*name of review*) ‘

#### **FOR STUDIES INCLUDED IN PREVIOUS PUBLISHED VERSION OF REVIEW**

Your study (*name of trial*) was included in the last published version of the review but we have some outstanding queries about the trial.

#### **FOR STUDIES IDENTIFIED IN UPDATE SEARCHES**

Your study (*name of trial*) meets the inclusion criteria for the review and we would very much like to include it in our analysis but we have some queries.

We would be very grateful if you could answer the following [*delete and amend as appropriate*]:

1. Clinical trial protocol: was a clinical trial protocol developed prior to the trial being undertaken? If so, please can you provide us with a copy?
2. Trial registration: was the trial prospectively registered? If so, please could you let us know where the trial was registered and the corresponding registration number.
3. Trial registration: we noticed that trial registration was done after all the participants were enrolled. Can you explain the reason why the trial was not registered before enrolment of participants began?
4. Ethics approval: was ethical approval obtained prior to undertaking the trial? If so, please could you let us know from whom (i.e. National, Institutional; Hospital or University) and please send us a copy of the approval letter.
5. Complete data: please can you confirm that the data submitted are the final data used in the analysis of the trial, i.e. the data in the published report are not interim data.
6. Randomisation process: there is an equal number of participants in both groups; what methods did you use (e.g. blocking) to ensure an equal number of women were allocated to each group?
7. Randomisation: a number of participants were excluded from the trial following randomisation. Please can you provide further information/clarification on the reason for these exclusions.
8. Similarities between groups at baseline data: what was done to stratify patients to ensure certain characteristics were equally distributed between groups? [*give details as necessary from trial report, whatever it is that appears to be implausibly similar*]
9. Lack of baseline data: please provide more detail of the baseline characteristics relating to [*whatever it is that you would expect to see in baseline characteristics that hasn't been reported*]
10. Study population: it would appear that no participants withdrew from the study following randomisation and that there were no participants lost to follow up. Is this correct?
11. Results: what explanation or comments do you have about [*whatever results appear to be implausible e.g. the rates of RDS and TTN appear to be unusually high in both groups*].

The information you provide will be extremely valuable for our Cochrane review. We look forward to hearing from you soon.

### For those not contacting us back within two weeks

Dear .....,

We recently contacted you about your study but have not received a reply. Our previous email is copied below, please can you let us have your response within the next two weeks.

If we do not receive a response from you, your study may not be considered for inclusion in our Cochrane review.

Sincerely,

### Appendix 3 – Example email to journal Editor-in-Chief (cc to relevant Institution(s))

**From:** Kellie, Frances

**Sent:** 23 January 2020

**To:** editorinchief@journalofscientificstudies.com

**Cc:** 'Karla Soares-Weiser'; Alfirevic, Zarko; Hampson, Lynn; Jones, Leanne; TLasserson@cochrane.org

**Subject:** Important - re concerns about scientific integrity of Doe 2016

**Importance:** High

Dear [Editor-in Chief's name],

I am contacting you, in your role as Editor-in-chief of the Journal of scientific studies. We have been alerted to very serious concerns about the scientific integrity of the following article published in your journal:

- Doe J, Other AN, Person A. Vaginal progesterone for prevention of preterm labor Journal of scientific studies 2016;14:6–7

Cochrane's mission is to promote evidence-informed health decision-making by producing high-quality, relevant, accessible systematic reviews. Given that the Doe 2016 study is included in a published Cochrane Review, we are keen to resolve this issue as a matter of urgency.

I am aware that your journal is committed to producing high-quality content and that you subscribe to the [Committee on Publication Ethics](#) (COPE) principles on dealing with research misconduct in order to preserve research integrity. Please can you let me know whether you are aware of the concerns relating to the scientific integrity of the Doe 2016 study and whether a formal investigation is currently underway.

I look forward to hearing from you.

Kind regards

Frances

**Dr Frances Kellie**

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## Appendix 4 Information about the edits that have been made in the amendment

- **What's new events**

- Amended - explaining what we have done, why we have done and what is the impact on the overall conclusions
- New citation-conclusions not changed - IF amendment led to no change in review's overall conclusions
- New citation-conclusions changed - IF amendment has led to a change in overall conclusions) [*Internal note – consider whether conclusions changed needs some sort of re-peer review?*]

What's new		
Date	Event	Description
19 November 2019	New citation: conclusions not changed	We are publishing this amended version with a new citation.
14 November 2019	Amended	In this amended version, we have moved one included study ( <a href="#">El-Refaie 2016</a> ) to studies awaiting classification pending clarification about the study data. See <a href="#">Characteristics of studies awaiting classification</a> .  This has resulted in edits to analyses/results for comparison 2, and removal of the comparison of Vaginal progesterone versus no treatment: multiple pregnancy and short cervix - because <a href="#">El-Refaie 2016</a> was the only study contributing data for this comparison.  We have also added this explanation to <a href="#">Published notes</a> .

- **Abstract/background**

### Abstract

### Background

Multiple pregnancy is a strong risk factor for preterm birth, and more than 50% of women with a twin pregnancy will give birth prior to 37 weeks' gestation. Infants born preterm are recognised to be at increased risk of many adverse health outcomes, contributing to more than half of overall perinatal mortality. Progesterone is produced naturally in the body and has a role in maintaining pregnancy, although it is not clear whether administering progestogens to women with multiple pregnancy at high risk of early birth is effective and safe.

Since publication of this new review in Issue 10, 2017, we have now moved one study ([El-Refaie 2016](#)) from included to studies awaiting classification, pending clarification about the study data.

- **Plain language summary**

### Plain language summary

#### Prenatal progestogens for preventing preterm birth in women with a multiple pregnancy

##### What is the issue?

More than half of women with a twin pregnancy give birth before the 37th week of pregnancy (preterm), and women expecting triplets are even more likely to have a preterm birth. Infants born preterm are more likely to die or have health problems compared with babies born at term. Progesterone is produced naturally in the body and is thought to help to maintain pregnancy.

Since publication of this new review in Issue 10, 2017, we have now moved one study ([El-Refaie 2016](#)) from included to studies awaiting classification, pending clarification about the study data.

- **Results/included studies/studies awaiting classification (add new section)**

#### Studies awaiting classification

Since publication of the 2018 update of this review, we have been advised that the [Ismail 2017](#) study is currently the subject of an investigation by the Journal of Maternal-Fetal & Neonatal Medicine. We have now moved this study from 'included studies' to 'studies awaiting classification' until the outcome of the investigation is known.

- **Published notes**

### Published notes

Since publication of this review, one study, previously included ([El-Refaie 2016](#)), has now been moved to [Characteristics of studies awaiting classification](#), pending clarification about the study data. This has resulted in publication of this amended version.

As a result of removing this study from included, we have made edits to analyses/results for comparison 2, and removal of a comparison of Vaginal progesterone versus no treatment: multiple pregnancy and short cervix - because [El-Refaie 2016](#) was the only study contributing data to that comparison.

- **Characteristics of studies awaiting classification**

**El-Refae 2016**

<b>Methods</b>	Randomised controlled study. Mansoura University Hospital and private practice settings in Mansoura, Egypt Participants were recruited from June 2012 until November 2014
<b>Participants</b>	225 women were recruited. Data for 116 intervention group and 108 controls Women with previous preterm birth were included (approximately 25% of each arm) <b>Inclusion criteria:</b> women aged 20 – 35 years old with dichorionic twin pregnancy were selected for measurement of cervical length by transvaginal sonography (TVS) at 20 – 24 weeks of gestation; cervical length of 20 – 25 mm with no symptoms or signs of impending preterm labour <b>Exclusion criteria:</b> known allergy or contraindication (relative or absolute) to progesterone therapy, monochorionic twins, known major fetal structural or chromosomal abnormality, single fetal demise, fetal reduction in current pregnancy, cervical cerclage in current pregnancy, medical conditions that may lead to preterm labour, rupture of membranes, vaginal bleeding
<b>Interventions</b>	<b>Intervention group:</b> received vaginal progesterone suppositories (Cyclogest <sup>®</sup> , Actavis, Barnstaple, EX32 8NS, United Kingdom) in a dose of 400 mg daily, beginning 20 - 24 weeks of gestation until 37 weeks of gestation <b>Contol/comparison group:</b> women received standard antenatal care
<b>Outcomes</b>	<b>Primary outcome:</b> preterm labour before 34 weeks of gestation <b>Secondary outcomes:</b> neonatal RDS, early neonatal death (END) (not defined).
<b>Notes</b>	Funding sources: not reported Declarations of interest: no conflicts of interests This study was listed as an included study in the first published version of this review. We have now removed this study from included studies and placed it in studies awaiting classification pending further clarification about study data.