Cochrane
Library

Cochrane Database of Systematic Reviews

Thyrotropin-releasing hormone added to corticosteroids for women at risk of preterm birth for preventing neonatal respiratory disease (Review)

Crowther CA, Alfirevic Z, Han S, Haslam RR

Crowther CA, Alfirevic Z, Han S, Haslam RR.

Thyrotropin-releasing hormone added to corticosteroids for women at risk of preterm birth for preventing neonatal respiratory disease.

Cochrane Database of Systematic Reviews 2013, Issue 11. Art. No.: CD000019.

DOI: [10.1002/14651858.CD000019.pub3](https://doi.org/10.1002/14651858.CD000019.pub3).

www.cochranelibrary.com

Thyrotropin-releasing hormone added to corticosteroids for women at risk of preterm birth for preventing neonatal respiratory disease (Review)

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

WILEY

TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	3
OBJECTIVES	3
METHODS	3
RESULTS	6
Figure 1.	7
Figure 2.	7
DISCUSSION	10
AUTHORS' CONCLUSIONS	11
ACKNOWLEDGEMENTS	11
REFERENCES	12
CHARACTERISTICS OF STUDIES	15
DATA AND ANALYSES	30
Analysis 1.1. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 1 Death prior to hospital discharge.	32
Analysis 1.2. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 2 Chronic lung disease.	33
Analysis 1.3. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 3 Respiratory distress syndrome.	33
Analysis 1.4. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 4 Chronic lung disease or death.	33
Analysis 1.5. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 5 Need for oxygen therapy.	34
Analysis 1.6. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 6 Severe respiratory distress syndrome.	34
Analysis 1.7. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 7 Use of respiratory support. ...	34
Analysis 1.8. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 8 Admission to neonatal intensive care unit.	35
Analysis 1.9. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 9 Intraventricular haemorrhage.	35
Analysis 1.10. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 10 Severe intraventricular haemorrhage.	36
Analysis 1.11. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 11 Air leak syndrome.	36
Analysis 1.12. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 12 Pulmonary haemorrhage. .	36
Analysis 1.13. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 13 Necrotising enterocolitis. ..	37
Analysis 1.14. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 14 Patent ductus arteriosus. ..	37
Analysis 1.15. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 15 Low Apgar score at 5 minutes.	37
Analysis 1.16. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 16 Use of surfactant.	38
Analysis 1.17. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 17 Gestational age at birth. ...	38
Analysis 1.18. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 18 Motor delay at follow-up. ..	38
Analysis 1.19. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 19 Motor impairment at follow-up.	39
Analysis 1.20. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 20 Fine motor delay at follow-up.	39
Analysis 1.21. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 21 Sensory impairment at follow-up.	39
Analysis 1.22. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 22 Language delay at follow-up.	39
Analysis 1.23. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 23 Social delay at follow-up. ..	40
Analysis 1.24. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 24 Any neurodevelopmental abnormality at follow-up.	40
Analysis 1.25. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 25 Bayley Mental Developmental Index.	40

Analysis 1.26. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 26 Bayley Psychomotor Developmental Index.	41
Analysis 1.27. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 27 Bayley Behavioural Rating Scales (18 months).	41
Analysis 1.28. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 28 Bayley Language Developmental Age (18 months).	42
Analysis 1.29. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 29 Bayley Cognitive Developmental Age (18 months).	42
Analysis 1.30. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 30 Serious neurological abnormality at follow-up.	42
Analysis 1.31. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 31 Ophthalmological or hearing abnormalities at follow-up.	42
Analysis 1.32. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 32 Maternal nausea.	43
Analysis 1.33. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 33 Maternal vomiting.	43
Analysis 1.34. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 34 Maternal light headedness.	43
Analysis 1.35. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 35 Urgency of micturition.	44
Analysis 1.36. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 36 Maternal facial flushing. ...	44
Analysis 1.37. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 37 Maternal systolic blood pressure rise ≥ 25 mmHg.	44
Analysis 1.38. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 38 Maternal diastolic blood pressure rise ≥ 15 mmHg.	44
Analysis 2.1. Comparison 2 TRH + steroids versus steroids alone (dose of TRH subgroups), Outcome 1 Death prior to hospital discharge.	46
Analysis 2.2. Comparison 2 TRH + steroids versus steroids alone (dose of TRH subgroups), Outcome 2 Chronic lung disease. ...	46
Analysis 2.3. Comparison 2 TRH + steroids versus steroids alone (dose of TRH subgroups), Outcome 3 Respiratory distress syndrome.	47
Analysis 2.4. Comparison 2 TRH + steroids versus steroids alone (dose of TRH subgroups), Outcome 4 Chronic lung disease or death.	48
Analysis 2.5. Comparison 2 TRH + steroids versus steroids alone (dose of TRH subgroups), Outcome 5 Need for oxygen therapy.	49
Analysis 2.6. Comparison 2 TRH + steroids versus steroids alone (dose of TRH subgroups), Outcome 6 Severe respiratory distress syndrome.	49
Analysis 2.7. Comparison 2 TRH + steroids versus steroids alone (dose of TRH subgroups), Outcome 7 Use of respiratory support.	50
Analysis 3.1. Comparison 3 TRH + steroids versus steroids alone (timing of delivery subgroups), Outcome 1 Death prior to hospital discharge.	52
Analysis 3.2. Comparison 3 TRH + steroids versus steroids alone (timing of delivery subgroups), Outcome 2 Chronic lung disease.	52
Analysis 3.3. Comparison 3 TRH + steroids versus steroids alone (timing of delivery subgroups), Outcome 3 Respiratory distress syndrome.	53
Analysis 3.4. Comparison 3 TRH + steroids versus steroids alone (timing of delivery subgroups), Outcome 4 Chronic lung disease or death.	54
Analysis 3.5. Comparison 3 TRH + steroids versus steroids alone (timing of delivery subgroups), Outcome 5 Need for oxygen therapy.	55
Analysis 3.6. Comparison 3 TRH + steroids versus steroids alone (timing of delivery subgroups), Outcome 6 Severe respiratory distress syndrome.	56
Analysis 3.7. Comparison 3 TRH + steroids versus steroids alone (timing of delivery subgroups), Outcome 7 Use of respiratory support.	57
Analysis 4.1. Comparison 4 TRH + steroids versus steroids alone (optimally treated variously defined), Outcome 1 Death prior to hospital discharge.	58
Analysis 4.2. Comparison 4 TRH + steroids versus steroids alone (optimally treated variously defined), Outcome 2 Chronic lung disease.	59
Analysis 4.3. Comparison 4 TRH + steroids versus steroids alone (optimally treated variously defined), Outcome 3 Respiratory distress syndrome.	60
Analysis 4.4. Comparison 4 TRH + steroids versus steroids alone (optimally treated variously defined), Outcome 4 Chronic lung disease or death.	60

Analysis 4.5. Comparison 4 TRH + steroids versus steroids alone (optimally treated variously defined), Outcome 5 Need for oxygen therapy.	61
Analysis 4.6. Comparison 4 TRH + steroids versus steroids alone (optimally treated variously defined), Outcome 6 Severe respiratory distress syndrome.	61
Analysis 4.7. Comparison 4 TRH + steroids versus steroids alone (optimally treated variously defined), Outcome 7 Use of respiratory support.	62
Analysis 5.1. Comparison 5 TRH + steroids versus steroids alone (high-quality trials), Outcome 1 Death prior to hospital discharge.	63
Analysis 5.2. Comparison 5 TRH + steroids versus steroids alone (high-quality trials), Outcome 2 Chronic lung disease.	63
Analysis 5.3. Comparison 5 TRH + steroids versus steroids alone (high-quality trials), Outcome 3 Respiratory distress syndrome.	64
Analysis 5.4. Comparison 5 TRH + steroids versus steroids alone (high-quality trials), Outcome 4 Chronic lung disease or death.	64
Analysis 5.5. Comparison 5 TRH + steroids versus steroids alone (high-quality trials), Outcome 5 Need for oxygen therapy.	64
Analysis 5.6. Comparison 5 TRH + steroids versus steroids alone (high-quality trials), Outcome 6 Severe respiratory distress syndrome.	65
Analysis 5.7. Comparison 5 TRH + steroids versus steroids alone (high-quality trials), Outcome 7 Use of respiratory support. ...	65
APPENDICES	65
WHAT'S NEW	65
HISTORY	66
CONTRIBUTIONS OF AUTHORS	66
DECLARATIONS OF INTEREST	66
SOURCES OF SUPPORT	66
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	66
INDEX TERMS	67

[Intervention Review]

Thyrotropin-releasing hormone added to corticosteroids for women at risk of preterm birth for preventing neonatal respiratory disease

Caroline A Crowther^{1,2}, Zarko Alfrevic³, Shanshan Han², Ross R Haslam⁴

¹Liggins Institute, The University of Auckland, Auckland, New Zealand. ²ARCH: Australian Research Centre for Health of Women and Babies, The Robinson Institute, Discipline of Obstetrics and Gynaecology, The University of Adelaide, Adelaide, Australia. ³Department of Women's and Children's Health, The University of Liverpool, Liverpool, UK. ⁴Department of Perinatal Medicine, The University of Adelaide, Adelaide, Australia

Contact address: Caroline A Crowther, Liggins Institute, The University of Auckland, Private Bag 92019, 85 Park Road, Auckland, New Zealand. caroline.crowther@adelaide.edu.au.

Editorial group: Cochrane Pregnancy and Childbirth Group.

Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 11, 2013.

Citation: Crowther CA, Alfrevic Z, Han S, Haslam RR. Thyrotropin-releasing hormone added to corticosteroids for women at risk of preterm birth for preventing neonatal respiratory disease. *Cochrane Database of Systematic Reviews* 2013, Issue 11. Art. No.: CD000019. DOI: [10.1002/14651858.CD000019.pub3](https://doi.org/10.1002/14651858.CD000019.pub3).

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

Thyrotropin-releasing hormones (TRH) added to prenatal corticosteroids has been suggested as a way to further reduce breathing problems and neonatal lung disease in infants born preterm.

Objectives

To assess the effects of giving prenatal TRH in addition to corticosteroids to women at risk of preterm birth for the prevention of neonatal respiratory disease.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (30 June 2013) and reference lists of retrieved studies. We also contacted trial authors.

Selection criteria

Randomised controlled trials in women at sufficient risk of preterm birth to warrant the use of prenatal corticosteroids to promote lung maturity. TRH and corticosteroids were compared with corticosteroids, with or without placebo.

Data collection and analysis

All assessments of trial eligibility, risk of bias and data extractions were independently carried out by at least two review authors.

Main results

Over 4600 women were recruited into the 15 trials included in the review, however two trials did not contribute any outcome data to the review. The trials had a moderate risk of bias. Overall, prenatal TRH, in addition to corticosteroids, did not reduce the risk of death prior to hospital discharge (risk ratio (RR) 1.05, 95% confidence interval (CI) 0.86 to 1.27, six trials, 3694 infants), neonatal respiratory distress syndrome (average RR 1.05, 95% CI 0.91 to 1.22, nine trials, 3833 infants), or chronic lung disease (RR 1.01, 95% CI 0.85 to 1.19, five trials, 2511 infants), and did not improve any of the secondary fetal, neonatal or childhood outcomes assessed by intention-to-treat analyses.

Indeed, the data showed prenatal TRH to have adverse effects for women and their infants. All side effects reported (nausea, vomiting, light headedness, urgency of micturition, facial flushing) were significantly more likely to occur in women receiving TRH. In the infants, prenatal TRH increased the risk of needing respiratory support (RR 1.16, 95% CI 1.03 to 1.29, three trials, 1969 infants), and of having a low Apgar score at five minutes (RR 1.48, 95% CI 1.14 to 1.92, three trials, 1969 infants). Only three trials provided data on childhood follow-up, and while one trial suggested poorer outcomes for infants who were exposed to prenatal TRH, the other two trials, that assessed infants using an established developmental instrument, showed no clear differences between groups in follow-up outcomes.

Sensitivity analyses by trial quality, or subgroups with differing times from entry to birth, or different dose regimens of TRH, did not change these findings.

Authors' conclusions

Prenatal TRH in addition to corticosteroids, given to women at risk of preterm birth, does not improve infant outcomes and can cause maternal side effects.

PLAIN LANGUAGE SUMMARY

Thyrotropin-releasing hormone added to corticosteroids for women at risk of preterm birth for preventing neonatal respiratory disease

Thyrotropin-releasing hormone (TRH) given with corticosteroids does not improve the benefit of corticosteroids on the lungs of babies born too early, and may increase harm.

Babies born preterm (before 37 weeks of pregnancy) are at risk of breathing difficulties (such as respiratory distress syndrome). TRH increases thyroid hormones in the baby and it has been thought that adding TRH to corticosteroids for women giving birth early may increase the benefit of corticosteroids on the baby's lungs.

This review included 15 trials, of a moderate risk of bias, that involved over 4600 women and their babies. In this review, TRH, given with corticosteroids to women at risk of early birth, was not shown to further reduce the breathing difficulties for the babies. Babies born to mothers who had received TRH with corticosteroids, were more likely to require support for breathing than babies born to mothers who received only corticosteroids. Women receiving TRH were more likely to experience adverse side effects, such as nausea, vomiting and flushing than women who only received corticosteroids.

Therefore, based on the current available evidence, TRH is not recommended to be given to women at risk of preterm birth for preventing neonatal respiratory disease.

BACKGROUND

Preterm birth remains the leading cause of early neonatal death and infant mortality, often from respiratory distress syndrome as a consequence of immature lung development (Nassar 2001). Between 5% and 9% of pregnant women will give birth before 37 weeks' gestation, with higher rates in developing countries (Li 2012). Preterm babies who survive the early weeks of life are at risk of long-term neurological disability (Moore 2012; Saigal 2008; Serenius 2013). Parents are understandably worried and distressed when their baby is born preterm. Strategies to reduce the risk of preterm birth and, in particular, neonatal respiratory disease receive considerable attention (Crowther 2011; Roberts 2006; Stevens 2007).

The first report of a trial of prenatal thyrotropin-releasing hormone (TRH) given with antenatal corticosteroids to women threatening to give birth preterm with the aim of enhancing lung development was presented, in abstract form, by Liggins and his co-workers in 1988 (Liggins 1988). The rationale for the use of TRH was based on previous research by Liggins' group (Schellenberg 1988). In an elegant series of experiments in preterm lambs they showed both an increase in lung fluid phospholipids and an increase in lung distensibility when thyroid hormones were used in combination with corticosteroids. TRH and glucocorticoids showed similar synergism (Liggins 1988).

Thyroid hormones (T3 and T4) given antenatally to the mother do not readily reach the fetal circulation due to metabolism by the placenta and membranes. However, TRH given to the mother elevates thyroid stimulating hormone (TSH) and thyroid hormones concentrations in the fetus (Roti 1981). The exact action of TRH on the fetal lung is not known and it is possible that any action may be mediated via non-hormonal pathways.

In adults, intravenous TRH administration is associated with side effects, which are often transient, of nausea, vomiting, light headedness, facial flushing, metallic taste, and a rise in blood pressure (Jackson 1982).

Since the initial abstract reported by Liggins 1988, the use of prenatal TRH as an intervention strategy to reduce the risk of neonatal lung disease and its sequelae has been evaluated in several randomised trials.

This review updates a previously published Cochrane review on TRH added to corticosteroids for women at risk of preterm birth for preventing neonatal respiratory disease (Crowther 2004). The previous version of this review was able to include 13 trials, and concluded that prenatal TRH in addition to corticosteroids does not improve infants outcomes, and can be associated with maternal side effects.

This review assesses the current available evidence regarding the effectiveness and safety of prenatal TRH given in addition to corticosteroids to women at risk of preterm birth.

OBJECTIVES

To assess the effects of TRH administered in addition to corticosteroids to women at risk of preterm birth on fetal and infant mortality and morbidity, and on maternal side effects.

METHODS

Criteria for considering studies for this review

Types of studies

All published, unpublished and ongoing randomised controlled trials and quasi-randomised controlled trials with reported data that compare outcomes in women and babies exposed to prenatal thyrotropin-releasing hormone (TRH) and corticosteroids with outcomes in controls receiving corticosteroids alone, with or without placebo. We planned to include cluster-randomised trials, and exclude cross-over trials. We planned to include studies published as abstracts only.

Types of participants

Women at sufficiently high risk of preterm birth to warrant administration of prenatal corticosteroids to promote fetal lung maturity. High-risk groups were those women showing signs of threatening to give birth preterm, or needing early delivery because of maternal or fetal complications.

Types of interventions

TRH (any dosage) administered to the women intravenously and corticosteroids, compared with corticosteroids with either placebo or no placebo.

Types of outcome measures

Pre-specified clinical measures of outcome related to fetal and neonatal mortality, neonatal morbidity, childhood development and maternal morbidity.

Primary outcomes

Primary outcomes were chosen to be most representative of the clinically important measures of effectiveness and safety for the infants.

1. Death prior to hospital discharge;
2. chronic lung disease (variously defined by authors);
3. respiratory distress syndrome (RDS).

Secondary outcomes

Secondary outcomes included other measures of effectiveness, complications and health services use.

For the infant

1. Chronic lung disease (variously defined by authors) or death;
2. need for oxygen therapy;
3. severe RDS (variously defined by authors);
4. use of respiratory support (mechanical ventilation or continuous positive airway pressure, or both);
5. admission to neonatal intensive care unit;
6. intraventricular haemorrhage;
7. intraventricular haemorrhage grade three or four;
8. periventricular leucomalacia;
9. air leak syndrome;
10. pulmonary haemorrhage;
11. necrotising enterocolitis;
12. patent ductus arteriosus;

13. low Apgar score at five minutes;
14. gestational age at birth;
15. use of surfactant;
16. neurodevelopmental abnormality at follow-up (variously defined by authors);
17. visual impairment at follow-up (variously defined by authors);
18. hearing impairment at follow-up (variously defined by authors);
19. motor delay at follow-up (variously defined by authors);
20. motor impairment at follow-up (variously defined by authors);
21. fine motor delay at follow-up (variously defined by authors);
22. sensory impairment at follow-up (variously defined by authors);
23. language development delay at follow-up (variously defined by authors);
24. social delay at follow-up (variously defined by authors);
25. Bayley Mental Development Index (variously defined by authors);
26. Bayley Psychomotor Developmental Index (variously defined by authors).

For the mother

1. Nausea;
2. vomiting;
3. light headedness;
4. urgency of micturition;
5. facial flushing;
6. systolic blood pressure rise during treatment (variously defined by authors);
7. diastolic blood pressure rise during treatment (variously defined by authors).

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (30 June 2013).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

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

Details of the search strategies for CENTRAL, MEDLINE and Embase, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the [Cochrane Pregnancy and Childbirth Group](#).

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-

ordinator searches the register for each review using the topic list rather than keywords.

[For details of additional searching carried out in the previous version of the review ([Crowther 2004](#)), please see: [Appendix 1](#).]

Searching other resources

We searched reference lists of trials and other review articles and contacted researchers. We contacted authors of [Pearlman 1997](#) and [Yoder 1997](#) for further information.

We did not apply any language restrictions.

Data collection and analysis

The following methods were used for this update.

Please see [Crowther 2004](#) for methods used in the previous version of this review.

Selection of studies

Two review authors independently assessed for inclusion all the potential studies we identified as a result of the search strategy. We resolved any disagreement through discussion, or if required we consulted a third review author.

Data extraction and management

We designed a form to extract data. At least two review authors extracted the data using the agreed form. We resolved discrepancies through discussion, or if required we consulted a third review author. Data were entered into Review Manager software ([RevMan 2012](#)) and checked for accuracy.

When information regarding any of the above was unclear, we attempted to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We resolved any disagreement by discussion or by involving a third assessor.

(1) Sequence generation (checking for possible selection bias)

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

We assessed the method as:

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

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

We described for each included study the method used to conceal the allocation sequence and determine whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as:

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

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

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

We assessed the methods as:

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

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

We described for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the trial authors, we re-included missing data in the analyses which we undertook.

We assessed methods as:

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

(5) Selective reporting bias

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found.

We assessed the methods as:

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

(6) Other sources of bias

We described for each included study any important concerns we had about other possible sources of bias.

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

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Cochrane Handbook* (Higgins 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it was likely to impact on the findings. We planned to explore the impact of the level of bias through undertaking sensitivity analyses - see [Sensitivity analysis](#).

Measures of treatment effect

Dichotomous data

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

Continuous data

For continuous data, we used the mean difference when outcomes were measured in the same way between trials. If necessary, we would have used the standardised mean difference to combine trials that measured the same outcome, but used different methods.

Unit of analysis issues

Cluster-randomised trials

We did not identify any cluster-randomised trials for inclusion. In future updates of this review, if we identify cluster-randomised trials, we plan to include them in the analyses along with individually-randomised trials. We will adjust their sample sizes using the methods described in the *Cochrane Handbook* using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population (Higgins 2011). If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect

of intervention and the choice of randomisation unit is considered to be unlikely.

We also plan to acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

Cross-over trials

We considered cross-over trials as inappropriate for inclusion in this review.

Dealing with missing data

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

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

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the τ^2 , I^2 and χ^2 statistics. We regarded heterogeneity as substantial if an I^2 was greater than 30% and either a τ^2 was greater than zero, or there was a low P value (less than 0.10) in the χ^2 test for heterogeneity.

Assessment of reporting biases

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

Data synthesis

We carried out statistical analysis using Review Manager software (RevMan 2012). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar. Where there was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or where substantial statistical heterogeneity was detected, we used random-effects meta-analysis to produce an overall summary if an average treatment effect across trials was considered clinically meaningful. The random-effects summary has been treated as the average range of possible treatment effects and we have discussed the clinical implications of treatment effects differing between trials. If the average treatment effect was not clinically meaningful, we would not have combined trials.

Where we used random-effects analyses, we have presented the results as the average treatment effect with its 95% confidence interval, and the estimates of τ^2 and I^2 .

Subgroup analysis and investigation of heterogeneity

Where we identified substantial heterogeneity, we investigated it using subgroup analyses and sensitivity analyses. We considered whether an overall summary was meaningful, and if it was, we used random-effects analysis.

We planned subgroup analyses to examine separately the primary outcomes for infants based on:

- the reasons the women were considered at risk of preterm birth;
- the number of infants *in utero* (singleton, twins or higher order multiple pregnancy);
- the gestational age TRH treatment was given;
- the dose of TRH given;
- the outcome for optimally treated infants, which was variously defined by the authors.

These analyses were only possible for the dose of TRH given, and the outcome for optimally treated infants.

The greatest beneficial effect of antenatal corticosteroids was observed in the group of infants delivered 24 hours or more and 10 days or less after start of therapy (Liggins 1972). An expectation that this may be the case for the combination of prenatal TRH and corticosteroids prompted the secondary timed analysis as follows:

1. birth less than 24 hours after first dose;
2. birth between 24 hours and 10 days, inclusive, after first dose;
3. birth more than 10 days after first dose.

Initial analyses were limited to the pre-specified outcomes and sensitivity and secondary analyses to the pre-specified primary outcomes, and the secondary outcomes:

- chronic lung disease (variously defined by authors) or death;
- need for oxygen therapy;
- severe RDS (variously defined by authors);
- use of respiratory support (mechanical ventilation or continuous positive airway pressure, or both).

We assessed subgroup differences by interaction tests available within RevMan (RevMan 2012). We have reported the results of subgroup analyses quoting the χ^2 statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

We carried out a sensitivity analysis to explore the effects of trial quality assessed by sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting, by omitting studies rated as 'unclear risk of bias' or 'high risk of bias' for these components. The sensitivity analysis has been restricted to those pre-specified outcomes listed above.

RESULTS

Description of studies

See [Characteristics of included studies](#), [Characteristics of excluded studies](#), and [Characteristics of ongoing studies](#).

Results of the search

The updated search of the Pregnancy and Childbirth Group's Specialist Register identified four reports that have been added as additional references under previously included trials ([Chile 1998](#); [Kim 2000](#); [Knight 1994](#)). We have included two additional trials in this update that were previously excluded, due to not reporting any relevant outcome data ([Crowther 1995](#); [Voto 1998](#)).

Therefore, of the 22 studies that were identified, 15 met our inclusion criteria ([Abuhamad 1999](#); [ACTOBAT 1995](#); [Ballard 1992b](#); [Ballard 1998](#); [Campos 1993](#); [Carlan 1991](#); [Ceriani 1992](#); [Chile 1998](#); [Crowther 1995](#); [Europe 1999](#); [Jikihara 1990](#); [Kim 2000](#); [Knight 1994](#); [Morales 1989](#); [Voto 1998](#)).

We excluded six trials ([Devlieger 1997](#); [Dola 1997](#); [Roti 1990](#); [Torres 1994](#); [Torres 1995](#); [Yoder 1997](#)), and one study is classified as ongoing (reported as 'planned') ([Pearlman 1997](#)).

Included studies

Over 4600 women were recruited into the 15 trials that met the pre-specified criteria for inclusion in this review ([Abuhamad 1999](#); [ACTOBAT 1995](#); [Ballard 1992b](#); [Ballard 1998](#); [Campos 1993](#); [Carlan 1991](#); [Ceriani 1992](#); [Chile 1998](#); [Crowther 1995](#); [Europe 1999](#); [Jikihara 1990](#); [Kim 2000](#); [Knight 1994](#); [Morales 1989](#); [Voto 1998](#)).

Gestational age at trial entry varied between 24 to 33 completed weeks: 24 to 31 completed weeks in [ACTOBAT 1995](#), [Ballard 1992b](#) and [Campos 1993](#); 24 to less than 30 weeks in [Ballard 1998](#); 24 to less than 33 weeks in [Chile 1998](#) and [Knight 1994](#); 24 to less than 34 weeks in [Carlan 1991](#) and [Crowther 1995](#); 24 to 34 weeks in [Abuhamad 1999](#); less than 32 weeks in [Europe 1999](#); less than 34 weeks in [Morales 1989](#); 23 to 29 completed weeks in [Jikihara 1990](#); 26 to 31 weeks in [Ceriani 1992](#); and 26 to 34 weeks in [Kim 2000](#).

All trials used the administration of antenatal corticosteroids as an inclusion criterion. The thyrotropin-releasing hormone (TRH) regimens varied as follows.

- [Ceriani 1992](#) used 200 µg TRH, 12-hourly, given twice and [ACTOBAT 1995](#) used 200 µg TRH, 12-hourly, given up to a maximum of four doses.
- [Ballard 1992b](#), [Ballard 1998](#), [Campos 1993](#), [Chile 1998](#), [Europe 1999](#) and [Jikihara 1990](#) used 400 µg TRH every eight hours up to a maximum of four doses.
- [Voto 1998](#) used 400 µg TRH every six hours for four doses.
- [Knight 1994](#) used 400 µg TRH every 12 hours for a maximum of four doses.
- [Carlan 1991](#), [Kim 2000](#) and [Morales 1989](#) used 400 µg TRH every eight hours for up to six doses.
- [Abuhamad 1999](#) used 500 µg TRH every eight hours up to a maximum of four doses, repeated weekly for a maximum of four weeks or until delivery.
- In [Crowther 1995](#), two treatment groups received either 200 µg TRH or 400 µg TRH over 30 minutes.

For further details see: [Characteristics of included studies](#).

Excluded studies

We excluded six trials ([Devlieger 1997](#); [Dola 1997](#); [Roti 1990](#); [Torres 1994](#); [Torres 1995](#); [Yoder 1997](#)) for a variety of reasons. In four trials it was unclear as to whether all women (including those in the control group) received corticosteroids ([Devlieger 1997](#); [Dola 1997](#); [Roti 1990](#); [Torres 1995](#)); in one trial a cross-over design was used ([Devlieger 1997](#)); for one trial it was unclear as to whether it was randomised ([Torres 1994](#)); and one trial stopped without enrolling any women ([Yoder 1997](#)).

For further details see: [Characteristics of excluded studies](#).

Risk of bias in included studies

See [Characteristics of included studies](#), [Figure 1](#) and [Figure 2](#) for further information on the risk of bias in the included studies. Overall, the risk of bias in the 15 included trials was judged to be moderate.

Figure 1. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

Allocation

Six of the 15 included trials used adequate methods for sequence generation. Four trials ([ACTOBAT 1995](#); [Chile 1998](#); [Europe 1999](#); [Voto 1998](#)) used central telephone randomisation, and two trials ([Ballard 1992b](#); [Knight 1994](#)) used random number tables. Sequence generation was unclear for the remaining trials ([Abuhamad 1999](#); [Ballard 1998](#); [Campos 1993](#); [Carlan 1991](#); [Ceriani 1992](#); [Crowther 1995](#); [Jikihara 1990](#); [Kim 2000](#); [Morales 1989](#)).

Eight of the 15 trials ([Abuhamad 1999](#); [ACTOBAT 1995](#); [Ballard 1992b](#); [Ballard 1998](#); [Chile 1998](#); [Europe 1999](#); [Knight 1994](#); [Voto 1998](#)) reported an adequate method for concealing allocation. Four trials ([Abuhamad 1999](#); [Ballard 1992b](#); [Ballard 1998](#); [Knight 1994](#)) used a central allocation (pharmacy-controlled), and three trials

([ACTOBAT 1995](#); [Chile 1998](#); [Europe 1999](#)) used central telephone randomisation service. [Voto 1998](#) used sequentially numbered drug containers of identical appearance. Allocation concealment was unclear in the remaining seven trials ([Campos 1993](#); [Carlan 1991](#); [Ceriani 1992](#); [Crowther 1995](#); [Jikihara 1990](#); [Kim 2000](#); [Morales 1989](#)).

Blinding

Seven of the 15 included trials ([ACTOBAT 1995](#); [Ballard 1992b](#); [Ballard 1998](#); [Chile 1998](#); [Europe 1999](#); [Knight 1994](#); [Voto 1998](#)) were blinded throughout the study. In [ACTOBAT 1995](#), assessment of neonatal outcomes was blinded, and a placebo was used except for with the first 198 women recruited. In the other six studies, all women, investigators, clinicians and pregnancy outcome assessors

were blinded, and a placebo was used (Ballard 1992b; Ballard 1998; Chile 1998; Europe 1999; Knight 1994; Voto 1998).

In Abuhamad 1999, while a placebo was used and women and personnel were blinded, the blinding of outcome assessors was not detailed. Similarly, in Ceriani 1992, while a placebo was used, and the trial was described as "double-blind", no detail regarding blinding of outcome assessors was provided. In Morales 1989, neonate outcome recorders and neonatal respiratory distress assessors were blinded, however a placebo was not used (and thus women and other study personnel were not blinded).

Blinding was unclear in six trials (Campos 1993; Carlan 1991; Crowther 1995; Jikihara 1990; Kim 2000) due to limited information available.

Incomplete outcome data

Losses to follow-up in six trials (Abuhamad 1999; ACTOBAT 1995; Ballard 1998; Crowther 1995; Europe 1999; Knight 1994) were less than 3%. In Chile 1998, losses to follow-up were 21/370 (5.7%) for the main trial; however for the follow-up, losses were over 50%. In Voto 1998 data were missing for 4/35 (11.4%) of women; and in Carlan 1991, losses to follow-up were 7/44 (15.9%). No information was available on losses to follow-up in two trials (Jikihara 1990; Kim 2000).

In Ballard 1992b; Campos 1993; Carlan 1991 and Morales 1989, outcome data were only available for a subgroup of participants expected to benefit most from the exposure to prenatal TRH.

An intention-to-treat analysis (with data analysed from all women randomised) was reported as being used in six trials (Abuhamad 1999; ACTOBAT 1995; Ballard 1998; Chile 1998; Europe 1999; Knight 1994), was probably used in three others (Carlan 1991; Jikihara 1990; Kim 2000) and was not used in Ballard 1992b; Campos 1993 and Morales 1989.

Selective reporting

There was no obvious risk of selective reporting in five of the 15 trials (ACTOBAT 1995; Ballard 1998; Chile 1998; Europe 1999; Knight 1994). In six trials there was insufficient information to make a clear judgement (Abuhamad 1999; Carlan 1991; Ceriani 1992; Crowther 1995; Jikihara 1990; Kim 2000; Voto 1998).

Four trials (Ballard 1992b; Campos 1993; Ceriani 1992; Morales 1989) only presented outcomes for a subgroup of participants expected to benefit most from the exposure to prenatal TRH. This led to significant numbers of women who were randomised, being excluded from analysis in Morales 1989 (148/248; 60% excluded); Ballard 1992b (343/446; 77% infants excluded); probably Ceriani 1992 (percentage not reported); and Campos 1993 (percentage not reported). Morales 1989 gave outcome data for infants delivered within one week from the start of therapy. Ballard 1992b reported data for neonates born after full treatment, weighing less than 1500 g at birth and delivering less than 10 days after TRH treatment. Ceriani 1992 reported data for infants born within 10 days of entry who were fully treated (received all doses of TRH or corticosteroids, or both). Campos 1993 reported data on fully treated infants (received all doses of TRH or corticosteroids, or both) who were born within 48 hours of the last hormonal dose.

Neurological outcomes at childhood follow-up were reported for three trials (ACTOBAT 1995; Chile 1998; Europe 1999). ACTOBAT 1995 assessed neurological outcomes with a questionnaire completed by parents when their infants were 12 months of age. Some data were available for 1022 (81%) of the 1262 infants discharged home alive, but not all outcome data were available for all infants. A subset of 39 of 52 (75%) children recruited at a single centre in Europe 1999 (16% of the infants recruited to the trial overall and alive at end of data collection) were assessed at 12 months and 24 months using the Bayley Scales of Infant Development and by a paediatrician. Similarly, at 18 months, 66 (49%) of the 134 infants enrolled during a 12-month period (July 1997 to December 1998) of the Chile 1998 study were assessed using the Bayley Scales of Infant Development (2nd edition) by a neonatologist or neonatal fellow.

Other potential sources of bias

Ten of the 15 trials were judged to be at a low risk of other potential bias, with no other obvious sources of bias identified (ACTOBAT 1995; Ballard 1992b; Ballard 1998; Campos 1993; Chile 1998; Crowther 1995; Europe 1999; Knight 1994; Morales 1989; Voto 1998). For the other five trials, the risk of other potential bias was judged to be unclear, with insufficient information available to make a confident judgement (Abuhamad 1999; Carlan 1991; Ceriani 1992; Jikihara 1990; Kim 2000).

Effects of interventions

Fifteen trials involving over 4600 women were included, although only 13 trials contributed data to the meta-analyses. All trials used a combination of TRH and antenatal corticosteroids in the intervention group and corticosteroids alone (with or without a placebo) in the control group.

Comparison of TRH with corticosteroids versus corticosteroids alone

All eligible trials analysed by intention-to-treat

Nine trials involving 3833 women contributed data (Abuhamad 1999; ACTOBAT 1995; Ballard 1998; Carlan 1991; Chile 1998; Europe 1999; Jikihara 1990; Kim 2000; Knight 1994).

Primary outcomes

No beneficial effects of prenatal TRH were seen for the primary outcomes: death prior to hospital discharge (risk ratio (RR) 1.05, 95% confidence interval (CI) 0.86 to 1.27, six trials, 3694 infants) (Analysis 1.1), chronic lung disease (RR 1.01, 95% CI 0.85 to 1.19, five trials, 2511 infants) (Analysis 1.2) or respiratory distress syndrome (RDS) (average RR 1.05, 95% CI 0.91 to 1.22, nine trials, 3833 infants) (Analysis 1.3). Moderate statistical heterogeneity was found for the outcome RDS ($\text{Tau}^2 = 0.02$; $I^2 = 48\%$), and thus a random-effects model was used.

Secondary outcomes

For the infant

No effects of prenatal TRH were shown on the composite outcome of death or chronic lung disease (RR 1.06, 95% CI 0.95 to 1.18, six trials, 3694 infants) (Analysis 1.4), on the need for oxygen therapy (RR 1.05, 95% CI 0.97 to 1.13, four trials, 2387 infants) (Analysis 1.5), or on the outcome severe RDS (average RR 0.88, 95% CI 0.57 to 1.36, three trials, 2119 infants; $\text{Tau}^2 = 0.11$; $I^2 = 73\%$) (Analysis 1.6). The

need for respiratory support was significantly increased in the TRH treated group (RR 1.16, 95% CI 1.03 to 1.29, three trials, 1969 infants) ([Analysis 1.7](#)).

No effects of prenatal TRH on gestational age at birth (mean difference (MD) -0.43 weeks, 95% CI -0.86 to 0.01, two trials, 1563 infants) ([Analysis 1.17](#)) or on need for admission to the neonatal intensive care unit (RR 1.04, 95% CI 0.98 to 1.11, two trials, 1637 infants) ([Analysis 1.8](#)) were discernible. Similarly, no effects were seen on the risk of intraventricular haemorrhage (RR 1.08, 95% CI 0.93 to 1.26, six trials, 3645 infants) ([Analysis 1.9](#)), severe intraventricular haemorrhage (RR 1.13, 95% CI 0.82 to 1.57, five trials, 3313 infants) ([Analysis 1.10](#)), air leak syndrome (average RR 1.14, 95% CI 0.71 to 1.83, four trials, 3103 infants) ([Analysis 1.11](#)), pulmonary haemorrhage (RR 0.83, 95% CI 0.25 to 2.80, three trials 1969 infants) ([Analysis 1.12](#)), necrotising enterocolitis (RR 0.91, 95% CI 0.64 to 1.30, four trials, 3103 infants) ([Analysis 1.13](#)), patent ductus arteriosus (average RR 1.00, 95% CI 0.79 to 1.28, six trials, 3645 infants) ([Analysis 1.14](#)), or use of surfactant (RR 1.10, 95% CI 0.98 to 1.25, four trials, 3103 infants) ([Analysis 1.16](#)). A low Apgar score at five minutes was significantly more common in TRH treated infants (RR 1.48, 95% CI 1.14 to 1.92, three trials, 1969 infants) ([Analysis 1.15](#)). Moderate statistical heterogeneity was seen for the outcomes air leak syndrome ($\text{Tau}^2 = 0.12$; $I^2 = 55\%$), pulmonary haemorrhage ($\text{Tau}^2 = 0.64$; $I^2 = 56\%$) and patent ductus arteriosus ($\text{Tau}^2 = 0.04$; $I^2 = 44\%$), and thus for each outcome, a random-effects model was used.

For the child

Outcomes for children at 12 months of age or later were available from three trials ([ACTOBAT 1995](#); [Chile 1998](#); [Europe 1999](#)). As the three trials followed up infants at different ages (i.e. 18 versus 24 months) and used different methods of assessment, it was difficult to pool these data in meta-analyses.

In the [ACTOBAT 1995](#) trial, an increased risk in the TRH treated group was shown for motor delay (RR 1.31, 95% CI 1.09 to 1.56, 971 infants) ([Analysis 1.18](#)), motor impairment (RR 1.51, 95% CI 1.01 to 2.24, 972 infants) ([Analysis 1.19](#)), sensory impairment (RR 1.97, 95% CI 1.10 to 3.53, 1004 infants) ([Analysis 1.21](#)), and social delay (RR 1.25, 95% CI 1.03 to 1.51, 966 infants) ([Analysis 1.23](#)); but not for fine motor delay (RR 1.10, 95% CI 0.91 to 1.32, 926 infants) ([Analysis 1.20](#)), or language delay (RR 1.20, 95% CI 0.93 to 1.54, 1004 infants) ([Analysis 1.22](#)).

While the [Europe 1999](#) trial did not find any difference in neurological abnormality overall between the two groups (RR 4.75, 95% CI 0.61 to 37.01, 39 infants) ([Analysis 1.24](#)), at 24 months, the mean Bayley Mental Developmental Index (MDI) was significantly lower (worse) in the TRH exposed children (MD -15.70, 95% CI -30.86 to -0.54, 39 infants). However, in the [Chile 1998](#) trial, at 18 months, no significant difference between groups was shown in the Bayley MDI (MD 0.00, 95% CI -8.36 to 8.36, 60 infants); and when the data from the two trials were pooled, no difference was shown overall (MD -6.52, 95% CI -21.69 to 8.64; $\text{Tau}^2 = 84.25$; $I^2 = 68\%$) ([Analysis 1.25](#)). The Bayley Psychomotor Developmental Index (PDI) was not shown to be significantly different between groups at follow-up in either the [Europe 1999](#) trial or the [Chile 1998](#) trial (pooled MD -2.73, 95% CI -8.58 to 3.12, 99 infants) ([Analysis 1.26](#)). The [Chile 1998](#) trial (assessing 60 infants) also found no significant differences on follow-up between the TRH and corticosteroids and corticosteroids only group for the mean Bayley Behavioural Rating Scale (BRS) (MD

9.00, 95% CI -4.88 to 22.88) ([Analysis 1.27](#)), the mean Language Developmental Age (LDA) (MD 2.00, 95% CI -0.36 to 4.36) ([Analysis 1.28](#)), or for the mean Cognitive Developmental Age (CDA) (MD 1.70, 95% CI -0.64 to 4.04) ([Analysis 1.29](#)). No ophthalmologic or hearing abnormalities were reported at follow-up for the 60 infants assessed in [Chile 1998](#) ([Analysis 1.31](#)), and only one serious neurological abnormality at follow-up was reported in each group ([Analysis 1.30](#)); an infant from the TRH and corticosteroids group was reported to have congenital ventriculomegaly, and one infant in the corticosteroids only group was reported to have hypotonia of congenital origin.

For the mother

Maternal side effects were more frequent in the TRH treated women; nausea (RR 3.92, 95% CI 3.13 to 4.92, three trials, 2370 women) ([Analysis 1.32](#)), vomiting (RR 2.35, 95% CI 1.35 to 4.09, one trial, 1011 women) ([Analysis 1.33](#)), light headedness (RR 1.73, 95% CI 1.36 to 2.22, one trial, 1011 women) ([Analysis 1.34](#)), urgency of micturition (RR 2.39, 95% CI 1.75 to 3.27, one trial, 1011 women) ([Analysis 1.35](#)), and facial flushing (RR 2.67, 95% CI 2.26 to 3.16, three trials, 2523 women) ([Analysis 1.36](#)). In the [Crowther 1995](#) trial, side effects of nausea, urgency of micturition, or facial flushing occurred in four (of eight) women receiving 200 µg TRH and six (of nine) receiving 400 µg; it was not detailed if any of the nine control women experienced side effects. There was a significant rise in maternal systolic blood pressure (greater than 25 mmHg) (RR 1.80, 95% CI 1.05 to 3.06, one trial, 1011 women) ([Analysis 1.37](#)) and maternal diastolic blood pressure (greater than 15 mmHg) (RR 1.62, 95% CI 1.24 to 2.12, 1011 women) ([Analysis 1.38](#)) in women given prenatal TRH in the [ACTOBAT 1995](#) trial.

Subgroup analysis based on dose of TRH

Subgroup analyses were performed based on the dose regimen of TRH used (considering dose subgroups 200 µg (x four every 12 hours) versus 400 µg (x four every eight to 12 hours) versus 400 µg (x six every eight hours) versus 500 µg (x four every eight hours)).

The subgroup analyses revealed no subgroup differences for the outcomes death prior to hospital discharge for the infant ($\text{Chi}^2 = 1.19$, $P = 0.28$, $I^2 = 15.8\%$) ([Analysis 2.1](#)); chronic lung disease (variously defined) ($\text{Chi}^2 = 0.31$, $P = 0.58$, $I^2 = 0\%$) ([Analysis 2.2](#)); RDS ($\text{Chi}^2 = 3.46$, $P = 0.33$, $I^2 = 13.2\%$) ([Analysis 2.3](#)); chronic lung disease or death ($\text{Chi}^2 = 0.11$, $P = 0.74$, $I^2 = 0\%$) ([Analysis 2.4](#)); the need for oxygen therapy ($\text{Chi}^2 = 0.00$, $P = 0.95$, $I^2 = 0\%$) ([Analysis 2.5](#)); severe RDS ($\text{Chi}^2 = 0.01$, $P = 0.93$, $I^2 = 0\%$) ([Analysis 2.6](#)); or the use of respiratory support ($\text{Chi}^2 = 0.05$, $P = 0.83$, $I^2 = 0\%$) ([Analysis 2.7](#)) indicating no differential effects for these primary and other pre-specified infant outcomes according to the dose regimen administered.

Subgroup analysis based on timing of birth

We also performed subgroup analyses based on the timing of birth, with six trials contributing data ([ACTOBAT 1995](#); [Ballard 1992b](#); [Ballard 1998](#); [Chile 1998](#); [Europe 1999](#); [Knight 1994](#)). Babies born less than 24 hours after trial entry made up 13% of the total population, and babies born between 24 hours and 10 days from trial entry accounted for 38% of the total population; while babies born more than 10 days after trial entry accounted for the majority of the population (49%).

Considering the timing of birth, the subgroup analyses did not reveal any significant subgroup differences for the outcomes death prior to hospital discharge for the infant ($\text{Chi}^2 = 0.45$, $P = 0.80$, $I^2 = 0\%$) (Analysis 3.1); chronic lung disease (variously defined) ($\text{Chi}^2 = 2.76$, $P = 0.25$, $I^2 = 27.6\%$) (Analysis 3.2); chronic lung disease or death ($\text{Chi}^2 = 3.70$, $P = 0.16$, $I^2 = 45.9\%$) (Analysis 3.4); the need for oxygen therapy ($\text{Chi}^2 = 1.37$, $P = 0.50$, $I^2 = 0\%$) (Analysis 3.5); severe RDS ($\text{Chi}^2 = 3.13$, $P = 0.21$, $I^2 = 36.1\%$) (Analysis 3.6); or the use of respiratory support ($\text{Chi}^2 = 2.40$, $P = 0.30$, $I^2 = 16.6\%$) (Analysis 3.7) indicating no differential effects for these infant outcomes according to timing of birth after trial entry.

Considering the outcome RDS, the subgroup interaction test indicated a significant difference ($\text{Chi}^2 = 6.39$, $P = 0.04$, $I^2 = 68.7\%$) (Analysis 3.3), suggesting a possible differential treatment effect based on timing of delivery in favour of corticosteroids alone (as compared with TRH and corticosteroids) for babies born more than 10 days after trial entry (RR 1.33, 95% CI 1.05 to 1.68). This difference was not seen in either of the other two timing of birth subgroups, or in the main analysis.

Analysis restricted to mothers and babies receiving 'optimal treatment'

A secondary analysis was performed in order to allow the additional inclusion of data from three trials (Campos 1993; Ceriani 1992; Morales 1989) in which results were reported only for a subgroup of participants regarded as optimally treated by the respective trialists. Overall, 10 trials contributed data (ACTOBAT 1995; Ballard 1992b; Ballard 1998; Campos 1993; Ceriani 1992; Chile 1998; Europe 1999; Jikihara 1990; Knight 1994; Morales 1989) to the 'optimal treatment' subgroup. Optimal treatment was described variously by different authors. Morales 1989 presented outcome data for infants delivered within one week of the start of therapy, which represented only 40% of the total number of babies in the study. Ceriani 1992 reported data for infants fully treated (received all doses of TRH or corticosteroids, or both) and born within 10 days of entry. Campos 1993 reported the data on fully treated infants (received all doses of TRH or corticosteroids, or both) who were born within 48 hours of the last hormonal dose. The included data from ACTOBAT 1995; Ballard 1992b; Ballard 1998; Chile 1998; Europe 1999; Jikihara 1990 and Knight 1994 relate to infants born between 24 hours to 10 days after entry into the trial.

No beneficial effects of prenatal TRH were seen between groups for death prior to hospital discharge (RR 0.88, 95% CI 0.67 to 1.14, nine trials, 1465 infants) (Analysis 4.1), chronic lung disease (RR 0.87, 95% CI 0.72 to 1.04, eight trials, 1318 infants) (Analysis 4.2), RDS (average RR 0.89, 95% CI 0.77 to 1.03, 10 trials, 1786 infants; $\text{Tau}^2 = 0.02$; $I^2 = 40\%$) (Analysis 4.3), chronic lung disease or death (RR 0.96, 95% CI 0.84 to 1.09; five trials, 1317 infants) (Analysis 4.4), the need for oxygen therapy (RR 0.99, 95% CI 0.91 to 1.09; one trial, 506 infants) (Analysis 4.5), or for the use of respiratory support (RR 1.07, 95% CI 0.94 to 1.22; one trial, 506 infants) (Analysis 4.7) for the optimally treated subgroup of infants. A statistically significant reduction in severe RDS was however observed for the infants exposed to TRH as compared corticosteroids alone when considering only optimally treated infants (RR 0.65, 95% CI 0.49 to 0.86; two trials, 694 infants) (Analysis 4.6).

When we performed subgroup interaction tests comparing all treated infants versus only those considered 'optimally treated', no significant subgroup differences were observed between the two

groups for the outcomes: death ($\text{Chi}^2 = 1.12$, $P = 0.29$, $I^2 = 11.0\%$) (Analysis 4.1), chronic lung disease ($\text{Chi}^2 = 1.40$, $P = 0.24$, $I^2 = 28.6\%$) (Analysis 4.2), RDS ($\text{Chi}^2 = 2.47$, $P = 0.12$, $I^2 = 59.5\%$) (Analysis 4.3), chronic lung disease or death ($\text{Chi}^2 = 1.45$, $P = 0.23$, $I^2 = 31.0\%$) (Analysis 4.4), the need for oxygen therapy ($\text{Chi}^2 = 0.79$, $P = 0.37$, $I^2 = 0\%$) (Analysis 4.5), severe RDS ($\text{Chi}^2 = 2.26$, $P = 0.13$, $I^2 = 55.7\%$) (Analysis 4.6), or for the use of respiratory support ($\text{Chi}^2 = 0.74$, $P = 0.39$, $I^2 = 0\%$) (Analysis 4.7) indicating no clear differential effects based on optimal treatment for these primary and pre-specified infant outcomes.

Sensitivity analysis by quality rating

Five trials (ACTOBAT 1995; Ballard 1998; Chile 1998; Europe 1999; Knight 1994), considered at a low risk of bias in the domains of sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting, were included in a sensitivity analysis.

No beneficial effects of prenatal TRH were seen for any of the primary infant outcomes of death (RR 1.03, 95% CI 0.84 to 1.25, five trials, 3570 infants) (Analysis 5.1), chronic lung disease (RR 1.00, 95% CI 0.84 to 1.18, four trials, 2387 infants) (Analysis 5.2), and RDS (RR 1.06, 95% CI 0.91 to 1.24, five trials, 3521 infants) (Analysis 5.3), nor for any of the other pre-specified infant outcomes, including chronic lung disease or death (RR 1.05, 95% CI 0.94 to 1.17, five trials, 3570 infants) (Analysis 5.4), the need for oxygen therapy (RR 1.05, 95% CI 0.97 to 1.13, four trials, 2387 infants) (Analysis 5.5), and severe RDS (average RR 0.88, 95% CI 0.57 to 1.36, three trials, 2119 infants; $\text{Tau}^2 = 0.11$; $I^2 = 73\%$) (Analysis 5.6), as in the main analysis.

The significant increase in the use of respiratory support for infants exposed to TRH as compared with corticosteroids alone persisted in the sensitivity analysis (with data from the same three trials included: ACTOBAT 1995; Chile 1998; Europe 1999) (RR 1.16, 95% CI 1.03 to 1.29, three trials, 1969 infants) (Analysis 5.7).

DISCUSSION

This review does not show that prenatal administration of thyrotropin-releasing hormone (TRH), in addition to corticosteroids, prior to preterm birth reduces the risk of respiratory disease in infants born preterm, or reduces other infant morbidity or mortality. Indeed the data show that this treatment may have adverse effects for women and their infants. All maternal side effects reported in the included trials (nausea, vomiting, light headedness, urgency of micturition, facial flushing) were more likely to occur in women receiving TRH, although their clinical significance and women's perceptions of their importance have not been assessed. For the infants, prenatal TRH increased the risk of infants needing respiratory support, and of having a low Apgar score at five minutes.

In one of the three trials with follow-up data, prenatal TRH was associated with adverse neurodevelopmental outcomes in childhood (such as motor and social delay, and motor and sensory impairment) (ACTOBAT 1995). However, the other two trials that assessed neurodevelopmental outcomes at follow-up using an established developmental instrument (Bayley Infant Scales) (Chile 1998; Europe 1999), did not show any significant differences between groups on follow-up, apart from a significantly lower (worse) Mental Developmental Index for infants exposed to

prenatal TRH at 24-month follow-up in one trial ([Europe 1999](#)), which was not confirmed in the second trial ([Chile 1998](#)).

The first two full trial reports published showed promising therapeutic effects of prenatal TRH, but reported neonatal outcome data only in minority subgroups of babies entered into the trials ([Ballard 1992b](#); [Morales 1989](#)). However, a significant proportion of babies in all of the studies (49%) were born more than 10 days after trial entry. The data in this review show that these babies (born more than 10 days after trial entry), if exposed to prenatal TRH in addition to corticosteroids, were more likely to develop respiratory distress syndrome (RDS) compared with babies in the control group, who received only corticosteroids. This highlights the importance of 'intention-to-treat' analyses, and subgroup analyses in this review, since many of the studies excluded categories of babies. Even where data were available for all women who were randomised, results from subgroup analyses (e.g. by timing of treatment) are less reliable than overall analyses. However, it is important to show the data by subgroups since timing of treatment appears to be an important consideration.

The expectation was that the greatest beneficial effect of prenatal TRH would be seen in infants born between 24 hours and 10 days of trial entry as shown with antenatal corticosteroids alone ([Liggins 1972](#)). Infants exposed to TRH in this timed subgroup, and a similar 'optimal' timing subgroup, did show a reduced risk of severe RDS; however, subgroup interaction tests were not significant, and therefore no firm conclusion could be made regarding this particular group of infants. Intention-to-treat data for severe RDS were only available from three earlier trials for this timed subgroup (birth more than 24 hours and less than 10 days after first dose) ([ACTOBAT 1995](#); [Ballard 1992b](#); [Knight 1994](#)) and thus it would be important to include any further data on severe RDS from the more recent trials if they became available.

AUTHORS' CONCLUSIONS

Implications for practice

Based on the current available evidence, TRH should not be given to pregnant women at risk of preterm birth in an attempt to prevent neonatal respiratory disease.

This review found that prenatal TRH in addition to corticosteroids given to women at risk of preterm birth does not reduce the risk or severity of neonatal lung disease, may increase the chances of the infant needing respiratory support, and is associated with adverse side effects for the mother.

Implications for research

In the light of the evidence reviewed, no further randomised controlled trials are warranted.

Given the trend to adverse neonatal findings in babies who were born 10 days or more after trial entry, trials should aim to provide outcome and follow-up data on all babies recruited. Those trials that reported data on only minority subgroups of babies should consider retrieving outcome data on the other babies, in particular on mortality and longer-term morbidity.

Adverse maternal side effects of therapy were significant for women receiving prenatal TRH. The duration of the adverse effects, their clinical significance and the consumers' feelings about these have not been assessed.

Five of the trials included in this review have only been reported in abstract form ([Abuhamad 1999](#); [Carlan 1991](#); [Ceriani 1992](#); [Jikihara 1990](#); [Kim 2000](#)). One trial using 400 µg TRH treatment dosage was planned in the USA in 1997 and stopped without enrolling ([Yoder 1997](#)). Another trial of TRH administration after prelabour rupture of membranes preterm was reported as planned in 1997 ([Pearlman 1997](#)).

ACKNOWLEDGEMENTS

Professor Adrian Grant compiled the first version of this review published in 1989. We are very grateful to the people who responded to our requests for further information including Professor Yoder and Professor Abuhamad and to the investigators of all the trials who provided additional unpublished information, particularly Professor RA Ballard, Professor M Bracken, Professor JE Hiller, Dr H Jikihara, Dr DB Knight and Professor FR Moya.

We thank Emily Bain and Philippa Middleton from the Australian Research Centre for Health of Women and Babies at The University of Adelaide for assisting with this update of the review.

As part of the pre-publication editorial process, this review has been commented on by three peers (an editor and two referees who are external to the editorial team) and the Group's Statistical Adviser.

The National Institute for Health Research (NIHR) is the largest single funder of the Cochrane Pregnancy and Childbirth Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NIHR, NHS or the Department of Health.

REFERENCES

References to studies included in this review

Abuhamad 1999 {published data only}

Abuhamad A, Green G, Heyl P, de Veciana M. The combined use of corticosteroids and thyrotropin releasing hormone in pregnancies with preterm rupture of membranes: a randomised double blind controlled trial. *American Journal of Obstetrics and Gynecology* 1999;**180**(1 Pt 2):S96.

ACTOBAT 1995 {published and unpublished data}

Crowther C, Hiller J, Haslam R, Robinson J, the ACTOBAT Study Group. Australian Collaborative Trial of Betamethasone and TRH for the prevention of neonatal respiratory disease (ACTOBAT). *International Journal of Gynecology and Obstetrics* 1994;**46**:59.

Crowther CA, Hiller JE, Haslam RR, Robinson JS, the ACTOBAT Study Group. Australian collaborative trial of antenatal thyrotropin-releasing hormone: Adverse effects at 12-month follow-up. *Pediatrics* 1997;**99**:311-7.

Hiller JE, Crowther CA, Haslam RR, Robinson JS, the ACTOBAT Study Group. Australian collaborative trial of antenatal thyrotropin-releasing hormone (ACTOBAT): 12 month follow-up. 4th Annual Congress of the Perinatal Society of Australia & New Zealand; 1998 March 30-April 4; Alice Springs, Australia. Alice Springs, 1998:77.

* The ACTOBAT Study Group. Australian collaborative trial of betamethasone and thyrotropin releasing hormone (ACTOBAT) for the prevention of neonatal respiratory disease. *Lancet* 1995;**345**:877-82.

Ballard 1992b {published and unpublished data}

Ballard PL, Ballard RA, Creasy RK, Padbury J, Polk DH, Bracken M, et al. Plasma thyroid hormones and prolactin in premature infants and their mothers after treatment with thyrotropin-releasing hormone. *Pediatric Research* 1992;**32**(6):673-8.

Ballard RA, Ballard PL, Creasy R, Gross I, Main D, Padbury JF, et al. Prenatal treatment with thyrotropin releasing hormone plus corticosteroid: absence of maternal, fetal or neonatal side effects. *Clinical Research* 1990;**38**:192A.

Ballard RA, Ballard PL, Creasy R, Gross I, Main D, Padbury JF, et al. Prenatal treatment with thyrotropin releasing hormone plus corticosteroid: absence of maternal, fetal or neonatal side effects. *Pediatric Research* 1991;**29**:202A.

Ballard RA, Ballard PL, Creasy R, Gross I, Padbury JF, TRH Study Group. Thyrotropin releasing hormone plus corticosteroids decreases chronic lung disease in very low birth weight infants. *Pediatric Research* 1991;**29**(4):1828A.

* Ballard RA, Ballard PL, Creasy R, Padbury J, Polk DH, Bracken M, et al. Respiratory disease in very-low birthweight infants after prenatal thyrotropin-releasing hormone and glucocorticoid. *Lancet* 1992;**339**:510-5.

Ballard 1998 {published data only}

Ballard PL, Ballard RA, Ning Y, Cnann A, Boardman C, Pinto-Martin J, et al. Plasma thyroid hormones in premature infants: effect of gestational age and antenatal thyrotropin-releasing hormone treatment. *Pediatric Research* 1998;**44**:642-9.

Ballard RA, Ballard PL, Boardman C, Cnaan A, Davis DJ, Hart MC, et al. Antenatal thyrotropin releasing hormone (TRH) for the prevention of chronic lung disease (CLD) in the preterm infant. *Pediatric Research* 1997;**41**:246A.

* Ballard RA, Ballard PL, Cnaan A, Pinto-Martin J, Davis DJ, Padbury JF, et al. Antenatal thyrotropin-releasing hormone to prevention lung disease in preterm infants. *New England Journal of Medicine* 1998;**338**:493-8.

Campos 1993 {published data only}

Campos G, Herrman F, Dorner M. Combined hormonal therapy for the prevention of respiratory distress syndrome and its consequences. *Seminars in Perinatology* 1993;**17**(4):267-74.

Carlan 1991 {published data only}

Carlan SJ, Parsons M, O'Brien WF, Krammer J. Pharmacologic pulmonary maturation in preterm premature rupture of membranes. *American Journal of Obstetrics and Gynecology* 1991;**164**:371.

Ceriani 1992 {published data only}

Althabe F, Fustihara C, Althabe O, Cernades JMC. Controlled trial of prenatal betamethasone plus TRH vs betamethasone plus placebo for prevention of RDS in preterm infants. *Pediatric Research* 1991;**29**:200A.

* Ceriani Cernadas J, Fustihara C, Althabe F, Althabe O. Controlled trial of prenatal betamethasone (B) plus TRH for prevention of respiratory distress syndrome (RDS) in preterm infants. *Pediatric Research* 1992;**32**:738.

Chile 1998 {published data only}

* Collaborative Santiago Surfactant Group. Collaborative trial of prenatal thyrotropin-releasing hormone and corticosteroids for prevention of respiratory distress syndrome. *American Journal of Obstetrics and Gynecology* 1998;**178**:33-9.

Maturana A, Torres J, Salinas R, Moya F, for the Collaborative Group. Controlled trial of prenatal thyrotropin-releasing hormone (TRH) and betamethasone (B) for prevention of respiratory distress syndrome (RDS). *Pediatric Research* 1997;**41**:163A.

Reyes G, Gonzalez AR, Gomez G, Blasini I, Rivera CE. Comparative study of the effectiveness of thyroxine and steroids on reduction of neonatal morbidity: outcome at 20 months follow-up. *Puerto Rico Health Sciences Journal* 2004;**23**(1):9-12.

Santiago R, Romaguera J. Steroids vs steroids and thyroxine to accelerate fetal maturation of patients in arrested preterm labor. *Puerto Rico Health Sciences Journal* 1999;**18**:156.

Crowther 1995 {published data only}

* Crowther C, Haslam R, Hiller J, McGee T, Ryall R, Robinson J. Thyrotropin-releasing hormone: Does two hundred micrograms provide effective stimulation to the preterm fetal pituitary gland compared with four hundred micrograms?. *American Journal of Obstetrics and Gynecology* 1995;**173**:719-23.

Crowther CA, Haslam RR, Hiller JE, McGee T, Robinson JS. Thyrotrophin releasing hormone (TRH) and lung maturation: does 200mcg TRH provide effective stimulation to the preterm fetal pituitary gland compared with 400mcg TRH?. *International Journal of Gynecology and Obstetrics* 1991;**36** Suppl:32.

Europe 1999 {unpublished data only}

* Alfievic Z, Boer K, Brocklehurst P, Buimer M, Elbourne D, Kok J, et al. Two trials of antenatal thyrotrophin-releasing hormone for fetal maturation: stopping before the due date. *British Journal of Obstetrics and Gynaecology* 1999;**106**:898-906.

Alfievic Z, Elbourne D, Brocklehurst P, Truesdale A, Neilson J. Randomised controlled trial of antenatal administration of thyrotropin releasing hormone (TRH) to women at risk of premature delivery. *Prenatal and Neonatal Medicine* 1996;**1**(1):10.

Briet JM, van Sonderen L, Buimer M, Boer K, Kok JH. Neurodevelopmental outcome of children treated with antenatal thyrotropin-releasing hormone. *Pediatrics* 2002;**110**(2 Pt 1):249-53.

Brocklehurst P. Antenatal thyrotropin-releasing hormone for fetal maturity: two concurrent randomised controlled trials (The Antenatal TRH Trial and the Thyroneth Trial). *British Journal of Obstetrics and Gynaecology* 1998;**105**:81.

Jikihara 1990 {published and unpublished data}

Jikihara H, Sawada Y, Imai S, Morishige K, Taniguchi T, Nohara A, et al. Maternal administration of thyrotropin-releasing hormone for prevention of neonatal respiratory distress syndrome. Proceedings of 6th Congress of the Federation of the Asia-Oceania Perinatal Societies; 1990 Oct 22-26; Perth, Western Australia. 1990:87.

Kim 2000 {published data only}

Kim EA, Park SJ, Yoon HS, Kim KS, Won HS, Lee IS, et al. Antenatal thyrotropin-releasing hormone to prevent respiratory distress syndrome in Korean preterm. *Pediatric Academic Societies Annual Meeting*; 2000 May 12-16; Boston, MA, USA. 2000.

Kim EA, Park SJ, Yoon HS, Kim KS, Won HS, Lee IS, et al. Antenatal thyrotropin-releasing hormone to prevent respiratory distress syndrome in Korean preterm. *Pediatric Research* 2000;**47**:407A.

Knight 1994 {published and unpublished data}

Knight DB, Liggins GC, Wealthall SR. A randomised controlled trial of the effect of thyrotropin-releasing hormone with betamethasone in mothers likely to deliver prematurely on neonatal outcome. Proceedings of the Australian Perinatal Society; 1992; Queensland, Australia. 1992:A9.

* Knight DB, Liggins GC, Wealthall SR. A randomized, controlled trial of antepartum thyrotropin-releasing hormone and betamethasone in the prevention of respiratory disease in preterm infants. *American Journal of Obstetrics and Gynecology* 1994;**171**:11-6.

Knight DB, Wealthall SR, Liggins GC, Howie RN. A randomised double blind controlled trial of antepartum TRH with betamethasone in the prevention of neonatal respiratory disease. *New Zealand Medical Journal* 1989;**102**:195.

Liggins GC, Knight DB, Wealthall SR, Howie RN. A randomized double-blind trial of antepartum TRH and steroids in the prevention of neonatal respiratory disease. *Clinical reproductive medicine - the Liggins years*; 1988 July 29-30; Auckland, New Zealand. 1988.

Morales 1989 {published data only}

Morales WJ, O'Brien WF, Angel JL, Knuppel RA, Sawai S. Fetal lung maturation: the combined use of corticosteroids and thyrotropin-releasing hormone. *Obstetrics and Gynecology* 1989;**73**:111-6.

Voto 1998 {published data only}

Voto L, Lede R, Scaglia H, Zylberstein C, Zapasterio J, Orti J, et al. Effects of maternal administration of betamethasone, with and without TRH, on serum PRL, TSH and iodothyronine levels in Rh-immunized fetuses: a randomized clinical trial. *Prenatal and Neonatal Medicine* 1998;**3**:447-51.

References to studies excluded from this review

Devlieger 1997 {published data only}

* Devlieger R, Vanderlinden S, de Zegher F, Van Assche FA, Spitz B. Effect of antenatal thyrotropin-releasing hormone on uterine contractility, blood pressure, and maternal heart rate. *American Journal of Obstetrics and Gynecology* 1997;**177**(2):431-3.

Spitz B, Devlieger R, Van Assche FA. Antenatal TRH-treatment: effects on uterine contractions, blood pressure and maternal heart rate. 10th World Congress of the International Society for the Study of Hypertension in Pregnancy; 1996 August 4-8; Seattle, Washington, USA. 1996:191.

Dola 1997 {published data only}

* Dola C, Nageotte P, Rumney P, Towers C, Asrat T, Freeman R, et al. The effects of antenatal treatment with betamethasone and thyrotropin-releasing hormone (TRH) in patients with preterm premature rupture of the membrane (PPROM). *American Journal of Obstetrics and Gynecology* 1997;**176**:549.

Jackson D, Nageotte M, Towers C, Asrat T, Freeman R, Gardner K, et al. Thyroid-releasing hormone (TRH) versus betamethasone or placebo in preterm premature ruptured membranes: a prospective randomised study. *American Journal of Obstetrics and Gynecology* 1991;**170**:383.

Roti 1990 {published data only}

Roti E, Gardini E, Minelli R, Bianconi L, Alboni A, Braverman LE. Thyrotropin releasing hormone does not stimulate prolactin

release in the preterm human fetus. *Acta Endocrinologica* 1990;**122**(4):462-6.

Torres 1994 {published data only}

Torres BA, Stromquist CI, Moya FR, DeClue T. Prenatal administration of thyrotropin-releasing hormone and postnatal thyroxine values. *Lancet* 1994;**343**:730.

Torres 1995 {published data only}

Torres J, Foradori A, Salinas R, Poblete JP, Maturana A, Roman A, et al. Dose related response of the fetal pituitary-thyroid axis to maternal administration of thyrotropin-releasing hormone (TRH). *Pediatric Research* 1995;**2**:241A.

Yoder 1997 {published data only}

Yoder BA. Trial to compare antenatal steroids alone, TRH alone, steroids + TRH and placebo in infants <32 weeks' gestation. Personal communication 1997.

References to ongoing studies

Pearlman 1997 {unpublished data only}

Pearlman SA. Trial to compare steroids vs steroids + TRH to mothers at 23-28 weeks with PROM. Personal communication March 6 1997.

Additional references

Ballard 1992a

Ballard PL, Ballard RA, Creasy RK, Padbury J, Polk DH, Bracken M, et al. Plasma thyroid hormones and prolactin in premature infants and their mothers after treatment with thyrotropin-releasing hormone. *Pediatric Research* 1992;**32**(6):673-8.

Crowther 2011

Crowther CA, McKinlay CJD, Middleton P, Harding JE. Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes. *Cochrane Database of Systematic Reviews* 2011, Issue 6. [DOI: [10.1002/14651858.CD003935.pub3](https://doi.org/10.1002/14651858.CD003935.pub3)]

Higgins 2011

Higgins JPT, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Jackson 1982

Jackson I. Thyrotropin-releasing hormone. *New England Journal of Medicine* 1982;**306**:145-50.

Li 2012

Li Z, Zeki R, Hilder L, Sullivan EA. Australia's Mothers and Babies 2010. Perinatal statistics series no. 27. Cat. no. PER 57. Canberra: AIHW National Perinatal Epidemiology and Statistics Unit, 2012.

Liggins 1972

Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. *Pediatrics* 1972;**50**:515-25.

Liggins 1988

Liggins GC, Schellenberg JC, Manzai M, Kitterman JA, Lee CC. Synergisms of cortisol and thyrotropin releasing hormone in lung maturation in fetal sheep. *Journal of Applied Physiology* 1988;**65**:1880-4.

Moore 2012

Moore T, Hennessy EM, Myles J, Johnson SJ, Draper ES, Costeloe KL, et al. Neurological and developmental outcome in extremely preterm children born in England in 1995 and 2006: the EPICure studies. *British Medical Journal* 2012;**345**:e7961.

Nassar 2001

Nassar N, Sullivan EA. Australia's Mothers and Babies 1999. Vol. AIHW Cat. No. PER 19 (Perinatal Statistics Series no. 11). Sydney: Australian Institute of Health and Welfare, National Perinatal Statistics Unit, 2001.

RevMan 2012 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012.

Roberts 2006

Roberts D, Dalziel S. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database of Systematic Reviews* 2006, Issue 3. [DOI: [10.1002/14651858.CD004454.pub2](https://doi.org/10.1002/14651858.CD004454.pub2)]

Roti 1981

Roti E, Gnudi A, Braverman L, Robuschi G, Emanuele R, Bandini P, et al. Human cord blood concentrations of thyrotropin, thyroglobulin and iodothyronines after maternal administration of thyrotropin releasing hormone. *Journal of Clinical Endocrinology and Metabolism* 1981;**53**:813-7.

Saigal 2008

Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. *Lancet* 2008;**371**(9608):261-9.

Schellenberg 1988

Schellenberg JC, Liggins GC, Manzai M, Kitterman JA, Lee C. Synergistic hormonal effects on lung maturation in fetal sheep. *Journal of Applied Physiology* 1988;**65**:94-100.

Serenius 2013

Serenius F, Källén K, Blennow M, Ewald U, Fellman V, Holmström G, et al. Neurodevelopmental outcome in extremely preterm infants at 2.5 years after active perinatal care in Sweden. *JAMA* 2013;**309**(17):1810-20.

Stevens 2007

Stevens TP, Blennow M, Myers EH, Soll R. Early surfactant administration with brief ventilation vs. selective surfactant

and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome. *Cochrane Database of Systematic Reviews* 2007, Issue 4. [DOI: [10.1002/14651858.CD003063.pub3](https://doi.org/10.1002/14651858.CD003063.pub3)]

References to other published versions of this review

Crowther 1991

Crowther CA Grant AM. Antenatal thyrotropin-releasing hormone prior to preterm delivery. In: Chalmers I (ed) Oxford Database of Perinatal Trials. Version 1.2. Disc Issue 6 1991.

Crowther 1995

Crowther CA, Alfirevic Z. Antenatal thyrotropin-releasing hormone (TRH) prior to preterm delivery [revised 28 April 1994]. In: Enkin MW, Keirse MJNC, Renfrew MJ, Neilson JP, Crowther C (eds.) Pregnancy and Childbirth Module. In: The Cochrane Pregnancy and Childbirth Database [database on disk and CDROM]. The Cochrane Collaboration; Issue 2, Oxford: Update Software; 1995.

Crowther 1997

Crowther CA, Alfirevic Z, Haslam RR. Antenatal thyrotropin-releasing hormone (TRH) prior to preterm delivery. In: Neilson JP, Crowther CA, Hodnett ED, Hofmeyr GJ, Keirse MJNC (eds.)

Pregnancy and Childbirth Module of The Cochrane Database of Systematic Reviews, [updated 03 June 1997]. Available in The Cochrane Library [database on disk and CDROM]. The Cochrane Collaboration; Issue 3. Oxford: Update Software; 1997. Updated quarterly.

Crowther 1999

Crowther CA, Alfirevic Z, Haslam RR. Prenatal thyrotropin-releasing hormone for preterm birth. *Cochrane Database of Systematic Reviews* 1999, Issue 3. [DOI: [10.1002/14651858.CD000019](https://doi.org/10.1002/14651858.CD000019)]

Crowther 2004

Crowther CA, Alfirevic Z, Han S, Haslam RR. Thyrotropin-releasing hormone added to corticosteroids for women at risk of preterm birth for preventing neonatal respiratory disease. *Cochrane Database of Systematic Reviews* 2004, Issue 2. [DOI: [10.1002/14651858.CD000019.pub2](https://doi.org/10.1002/14651858.CD000019.pub2)]

Grant 1989

Grant AM. Antenatal TRH for prevention of neonatal respiratory disease. In: Chalmers I (ed) Oxford Database of Perinatal Trials. Version 1.00. Disc Issue 1 1989.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Abuhamad 1999

Methods	Randomised controlled trial.
Participants	Setting: 1 centre in Norfolk, East Virginia, USA. 103 women with a singleton pregnancy with PPROM at 24 to 34 weeks' gestation (55 in the TRH group vs 48 in the placebo group). Gestational age range: 24 to 34 weeks. Exclusions: preterm labour, chorioamnionitis or multiple pregnancy.
Interventions	500 µg of TRH or placebo x 4 every 8 hours (total 2000 µg). Treatment was completed weekly for a maximum of 4 weeks or until delivery. Betamethasone was given to all women (12 mg IM every 24 hours for 2 doses).
Outcomes	Primary outcome: length of stay in neonatal intensive care unit. Secondary outcomes: length of ventilation; RDS; bronchopulmonary dysplasia.
Notes	No sample size calculation given. Source of funding: not stated. Use of surfactant not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote from abstract "103 pregnancies were blindly randomized [random # list]".

Abuhamad 1999 (Continued)

Allocation concealment (selection bias)	Low risk	Central allocation by using a random list in pharmacy. Patients were allocated to study groups by using sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo used; TRH and placebo packs were prepared by pharmacy; patients and treating physicians were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors not detailed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up. No data excluded. Intention-to-treat analysis performed.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to make a judgement.
Other bias	Unclear risk	Insufficient information to make a judgement.

ACTOBAT 1995

Methods	Randomised controlled trial.
Participants	Setting: 18 centres in Australia from 1990 to 1993. 1234 women with a singleton or twin pregnancy at sufficient risk of preterm birth to warrant prenatal corticosteroid treatment (616 in the TRH group vs 618 in the placebo group). Gestational age range: 24 to less than 32 weeks. Not eligible if heart disease in the mother or the fetus, maternal hypertension, maternal hyperthyroidism, intrauterine growth restriction with cardiotocographic abnormalities, high likelihood of imminent delivery (< 6 hours), chorioamnionitis, or evidence of lung maturity.
Interventions	200 µg of TRH or placebo in 50 mL saline over 20 minutes x 4 every 12 hours (total 800 µg). Only 1 course of TRH was given. Betamethasone was given to all women.
Outcomes	Primary outcomes: frequency and severity of RDS; need for and duration of oxygen therapy; need for and duration of ventilatory support; chronic lung disease (defined as need for oxygen at 28 days of life); need for oxygen therapy or death at 28 days and duration of stay on the neonatal unit. Secondary outcomes: stillbirths and neonatal deaths; gestational age at delivery; birthweight; air leak syndrome; patent ductus arteriosus; pulmonary haemorrhage; intraventricular haemorrhage; maternal events after randomisation; childhood outcomes.
Notes	Sample size calculation. Source of funding: National Health and Medical Research Council, Australia; Queen Victoria Hospital Foundation; Channel 7 Children's Research Foundation; SIDS Foundation SA. Placebo not available for the first 220 women enrolled. Surfactant became available during the time course of the trial and was given as needed for respiratory distress. Surfactant was given to 81 (12%) babies in the TRH group and 69 (10%) babies in the placebo group.

Risk of bias

Bias	Authors' judgement	Support for judgement
------	--------------------	-----------------------

ACTOBAT 1995 (Continued)

Random sequence generation (selection bias)	Low risk	Computer random number generator; stratification by centre and gestational age.
Allocation concealment (selection bias)	Low risk	Central telephone randomisation service.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo used except for the first 198 recruits (16%).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "assessment of neonatal outcomes was masked throughout the study period".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up at hospital discharge 3/1234 (< 1%), 1 in TRH group and 2 in placebo group. Losses to follow-up at 1 year 145/1234 (11%). Analyses were based on intention-to-treat.
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported.
Other bias	Low risk	No obvious risk of other bias.

Ballard 1992b

Methods	Randomised controlled trial.
Participants	Setting: 4 centres in the USA between 1986 to 1989. 850 women with threatened preterm delivery (404 in the TRH group and 446 in the placebo group). Gestational age range: less than 32 weeks. Not eligible if evidence of lung maturity.
Interventions	400 µg of TRH or placebo in 50 mL saline as a 20-minute infusion x 4 every 8 hours (total 1600 µg). Only 1 course of TRH was given. Betamethasone was given to all women.
Outcomes	Apgar scores; resuscitation measures; respiratory morbidity (RDS, chronic lung disease); other complications of prematurity (patent ductus arteriosus, necrotising enterocolitis, intraventricular haemorrhage, retinopathy of prematurity).
Notes	Sample size calculation. Source of funding: March of Dimes - National Foundation; Mount Zion General Research Support; National Heart, Lung, and Blood Institute; Perinatal Associates Inc.; Yale Children's Clinical Research Center; Harbor-UCLA project. Abbott Laboratories provided the TRH. Surfactant not given to any baby in the trial.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "treatment groups were assigned centrally (Yale) with a table of random numbers". Stratification by centre.

Ballard 1992b (Continued)

Allocation concealment (selection bias)	Low risk	Central allocation by pharmacy.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as a "blinded" trial with a placebo used.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All analyses and assays were performed in a blinded manner."
Incomplete outcome data (attrition bias) All outcomes	High risk	Not an intention-to-treat analysis. Analysis restricted to fully treated infants (at least 3 doses) who delivered 1-10 days from entry (114 infants delivered to 99 women in the TRH group and 117 babies delivered to 105 women in the placebo group). Losses to follow-up to hospital discharge 103/404 (23%).
Selective reporting (reporting bias)	High risk	Analysis restricted to fully treated infants (at least 3 doses) who delivered 1-10 days from entry.
Other bias	Low risk	No obvious risk of other bias.

Ballard 1998

Methods	Randomised controlled trial.
Participants	Setting: 13 North American centres between 1992 to 1996. 981 women in active labour with gestational age range 24 to less than 30 weeks, delivering 1134 live-born infants. Data available for 1101 infants only for timing outcomes, since infusion times were missing in 33 cases. Not eligible if bleeding, infection, hypertension, fetus with hydrops, life-threatening fetal anomaly, or 1 dead fetus in a multiple pregnancy.
Interventions	400 µg of TRH or placebo in 50 mL saline as a 20 minute infusion x 4 every 8 hours (total 1600 µg). Only 1 course of TRH was given. Betamethasone was given to all women.
Outcomes	Primary outcomes: infant death on or before 28th day after delivery or chronic lung disease (need for oxygen therapy for 21 of the first 28 days of life, including day 28). Secondary outcomes: chronic lung disease or death at 36 weeks postmenstrual age or less; complications of prematurity (patent ductus arteriosus, necrotising enterocolitis, intraventricular haemorrhage, retinopathy of prematurity).
Notes	Sample size calculation. Source of funding: National Institutes of Health, USA, Perinatal Associates Inc., Hospital for Sick Children, Toronto, Children's Hospital of Eastern Ontario Research Institution. Ferring and Abbott Laboratories provided the TRH. Infants weighing 800 g or less were treated at birth with surfactant. Infants weighing more than 800 g were treated with surfactant as needed for respiratory distress.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The randomisation schedule was only kept in pharmacies at the participating centres. Stratification by centre. Unclear how the schedule was generated.

Ballard 1998 (Continued)

Allocation concealment (selection bias)	Low risk	Central allocation: pharmacy-controlled randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as "double-blinded trial"; placebo used.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All analyses and assays were performed in a blinded fashion."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analyses were based on intention-to-treat; losses to follow-up at hospital discharge 15/996 (1.5%) women.
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported.
Other bias	Low risk	No other obvious risk of bias.

Campos 1993

Methods	Randomised controlled trial.
Participants	Setting: Chile. Women at risk of preterm birth with a gestational age between 24 to 32 weeks (number of women not stated; 135 infants).
Interventions	400 µg of TRH x 4 every 8 hours (total 1600 µg) or no TRH (not clear if placebo). Betamethasone to all women.
Outcomes	Mortality and respiratory morbidity.
Notes	Use of surfactant unclear.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as "prospectively randomised trial"; no other information available.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make the judgement, "sealed envelopes" were used.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Placebo used; no further information was available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	As above.

Campos 1993 (Continued)

Incomplete outcome data (attrition bias) All outcomes	High risk	Not based on an intention-to-treat analysis. Analysis restricted to 135 infants who received all doses and who delivered within 48 hours of the last hormonal dose.
Selective reporting (reporting bias)	High risk	Analysis restricted to 135 infants who received all doses and who delivered within 48 hours of the last hormonal dose.
Other bias	Low risk	Insufficient information to make the judgement.

Carlan 1991

Methods	Randomised controlled trial.
Participants	Setting: Tampa, Florida. 44 women with preterm prelabour rupture of the membranes between 24 to 34 weeks' gestation.
Interventions	3 study groups. Group 1 (n = 13) given 400 µg of TRH intravenously x 6 every 8 hours (total 2400 µg) and betamethasone, Group 2 (n = 11) given only betamethasone and Group 3 (n = 13) given nothing for pulmonary maturity. [This last group was not analysed in the review, as study inclusion criteria specified that all women must have received corticosteroids.] Treatment was repeated weekly until delivery or 34 weeks' gestation.
Outcomes	RDS; duration of ventilation; length of stay in neonatal intensive care.
Notes	Sample size calculation not given. Funding source not stated. Use of surfactant not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Within this abstract, reported as "prospectively randomised"; no information was available on randomisation methods.
Allocation concealment (selection bias)	Unclear risk	No details were given on allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No placebo used; no other information given on blinding.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	As above.
Incomplete outcome data (attrition bias) All outcomes	High risk	Losses to follow-up at hospital discharge 7/44 (15.9%) (excluded 5 patients who "sealed" and 2 with evidence of pulmonary maturity). Analysis was based on 37 patients.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to make the judgement.

Carlan 1991 (Continued)

Other bias	Unclear risk	Insufficient information to make the judgement.
------------	--------------	---

Ceriani 1992

Methods	Randomised controlled trial.
Participants	Setting: Buenos Aires, Argentina. 52 women at a gestational age between 26 to less than 31 weeks who delivered 57 infants within 10 days of treatment. No exclusion criteria reported.
Interventions	200 µg of TRH or placebo x 2 every 12 hours (total 400 µg). Betamethasone was given to all women.
Outcomes	RDS; need for and duration of oxygen; duration of ventilation; bronchopulmonary dysplasia.
Notes	Sample size calculation not given. Source of funding not stated. Use of surfactant not reported. Final report not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Within the abstract, described as "randomised trial"; no information was available on randomisation methods.
Allocation concealment (selection bias)	Unclear risk	No information was available on allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as "double blind"; placebo used.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blind outcome assessment not detailed (trial described as "double blind" only).
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details was given on loss to follow-up (unclear); probably an intention-to-treat analysis. Analysis of 57 premature infants from 52 mothers treated for 10 days prior to labour (26 babies in the TRH group and 31 babies in the placebo group).
Selective reporting (reporting bias)	Unclear risk	Insufficient information to make the judgement.
Other bias	Unclear risk	Insufficient information to make the judgement.

Chile 1998

Methods	Randomised controlled trial.
---------	------------------------------

Chile 1998 (Continued)

Participants	<p>Setting: 7 maternity centres in Chile between 1993 to 1996.</p> <p>370 women with a singleton gestation between 24 to less than 33 weeks' gestation at risk of preterm delivery were eligible. Not eligible if insulin-dependent diabetes, prenatal diagnosis of a major fetal anomaly, Rhesus isoimmunisation, eclampsia, significant heart disease, chorioamnionitis, imminent delivery or contraindications to the use of corticosteroids or TRH.</p>
Interventions	400 µg of TRH or placebo in 50 mL saline as a 30-minute infusion x 4 every 8 hours (total 1600 µg). Only 1 course of TRH was given. Betamethasone was given to all women.
Outcomes	<p>Primary outcomes: RDS; need for oxygen therapy at 28 days; neonatal mortality.</p> <p>Secondary outcomes: need for and duration of mechanical ventilation; air leaks; intracranial haemorrhage; patent ductus arteriosus; pulmonary haemorrhage; necrotising enterocolitis; infectious complications. For the follow-up study: developmental scores using the Bayley Infant Scales II (MDI: Mental Developmental Index; PDI: Psychomotor Developmental Index; BRS: Behavioural Rating Scale; LDA: Language Developmental Age; CDA: Cognitive Developmental Age); ophthalmological and hearing abnormalities; serious neurological abnormalities.</p>
Notes	<p>Sample size calculation.</p> <p>Source of funding: Fondo Nacional de Ciencia Tecnologia grant no. 193-0854.</p> <p>Surfactant was given after birth to all infants weighing < 1 kg and to other infants if signs of respiratory distress were present.</p> <p>For the follow-up: of the 134 infants born during the study period, 66 came for follow-up (including 4 pairs of twins). Only twin 1 was included in the analysis. Therefore, 60 infants who reached 18 months during the period July 1997 to December 1998 were contacted and invited for medical and neurodevelopmental follow-up evaluations.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation: computerised randomisation program. Stratification by centre.
Allocation concealment (selection bias)	Low risk	Quote: "use of a computerised randomisation program including stratification by centre".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: 'the content of these vials remained blinded for all patients, investigators, and clinicians until the trial was finalized'; placebo used.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above; members of the group of investigators collected data. Follow-up was conducted by a neonatologist/neonatal fellow who was blind to group allocation.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Intention-to-treat analyses. Losses to follow-up at hospital discharge 21/370 (5.7%; 8 in the TRH group and 13 in the placebo group, due to either delivered elsewhere or lost to follow-up). For the follow-up 49% of infants were recruited (those turning 1 between July 1997 and December 1998).
Selective reporting (reporting bias)	Low risk	No obvious risk of selective reporting.
Other bias	Low risk	No obvious risk of other bias.

Crowther 1995

Methods	Randomised controlled trial.
Participants	Setting: Australia. 26 women (8 in the 200 µg TRH group, 9 in the 400 µg TRH group, 9 in the control group) expected to deliver within 1 to 4 hours with a gestational age between 24 weeks and 33+6 weeks, who had received at least 1 dose of betamethasone at least 12 hours before entry. Women were excluded who had contraindications to TRH treatment.
Interventions	3 treatment groups: 200 µg TRH or 400 µg TRH intravenously mixed with 50 mL of 0.9% sodium chloride in water infused over 30 minutes, compared with control (no detail of a placebo).
Outcomes	Maternal pulse rates, systolic and diastolic blood pressures (10 minutes and end of infusion), maternal side effects of treatment, cord blood: TSH, T4, T3, PRL (and 2-hour, 24-hour, 48-hour neonatal blood).
Notes	The sample size was determined by the number of women recruited during the 6 months of the study. Funding: Women's and Children's Hospital Foundation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote "women were randomly assigned to one of the three treatment groups...by opening the next in a series of study envelopes".
Allocation concealment (selection bias)	Unclear risk	As above.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No placebo; blinding not detailed.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	As above.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses/exclusions.
Selective reporting (reporting bias)	Unclear risk	Outcomes not all clearly pre-specified, and with no access to a trial protocol it is difficult to assess selective reporting. Some incomplete reporting "The neonatal outcome was similar between the three treatment groups".
Other bias	Low risk	No other obvious sources of bias identified.

Europe 1999

Methods	Randomised controlled trial.
Participants	Setting: 31 centres in Europe between 1996 to 1997.

Europe 1999 (Continued)

225 women where the risk of preterm delivery was sufficient to prescribe prenatal corticosteroids, at a gestational age between 25 to 30 weeks for the Thyroneth trial and less than 32 weeks for the Antenatal TRH trial. Not eligible if uncontrolled hypertension, persistent cardiac arrhythmia, intrauterine growth restriction with cardiotocographic abnormality, severe maternal disease such as cardiac disease, current thyroid disease, prolactinoma, intrauterine infection and insulin-dependent diabetes.

Interventions	400 µg of TRH or placebo in 50 mL saline as a 20-minute infusion (Thyroneth trial) and a 30-minute infusion (Antenatal TRH trial) x 4 every 8 hours (total 1600 µg). Only 1 course of TRH was given. Betamethasone to all women.
Outcomes	Primary outcomes: death or oxygen dependency at 28 days after birth. For the Thyroneth trial the proportion of infants who developed RDS or died within 72 hours of birth. Secondary outcomes: need to stop the infusion because of side effects; major neonatal morbidity.
Notes	<p>Sample size calculation.</p> <p>Source of funding: Medical Research Council, UK; The European Union and UCB Pharm. The drugs were supplied by UCB Pharm.</p> <p>Surfactant was used for babies in the Thyroneth trial if respiratory distress present. In the Antenatal TRH trial many centres used prophylactic surfactant for all preterm babies.</p> <p>Trial was stopped early due to new information becoming available from two other trials shortly after the start of recruitment to the trial.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation: a central telephone randomisation service.
Allocation concealment (selection bias)	Low risk	Central randomisation service used.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The caregivers, the women, pregnancy outcome assessors were all blinded (placebo used).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up at hospital discharge 1/225 (< 1%); intention-to-treat analyses.
Selective reporting (reporting bias)	Low risk	No obvious risk of selective reporting.
Other bias	Low risk	No other obvious risk of bias.

Jikihara 1990

Methods	Randomised controlled trial.
---------	------------------------------

Thyrotropin-releasing hormone added to corticosteroids for women at risk of preterm birth for preventing neonatal respiratory disease (Review)

24

Jikihara 1990 (Continued)

Participants	<p>Setting: single-centre study from Osaka, Japan between 1988 to 1990.</p> <p>80 women with threatened preterm labour with or without ruptured membranes between 23 to less than 30 weeks' gestation, (63 infants in the TRH group and 61 in the control group). Exclusion criteria not stated.</p>
Interventions	400 µg of TRH iv x 4 every 8 hours (total 1600 µg) compared with no treatment. Betamethasone was given to all women.
Outcomes	Respiratory morbidity; need for ventilation; need for oxygen at 28 days; death; intraventricular haemorrhage; patent ductus arteriosus; maternal side effects of treatment.
Notes	<p>Sample size calculation not stated.</p> <p>Source of funding not stated.</p> <p>Surfactant used for some babies. Final report not available.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Within this abstract, described as "randomly assigned"; no other details given.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to make the judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Placebo not used; no other information was available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	As above.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Probably an intention-to-treat analysis. Losses to follow-up at hospital discharge not stated.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to make the judgement.
Other bias	Unclear risk	Insufficient information to make the judgement.

Kim 2000

Methods	Randomised controlled trial.
Participants	<p>Setting: single-centre study from Seoul, Korea.</p> <p>61 women with preterm labour at 26 to 34 weeks' gestation (30 in the TRH and dexamethasone group vs 31 in the dexamethasone alone group).</p>

Kim 2000 (Continued)

Interventions	400 µg of TRH every 8 hours intravenously (maximum 6 doses) along with 6 mg dexamethasone at 12 hour intervals intravenously (maximum 4 doses) or control group receiving same regimen of dexamethasone.
Outcomes	Primary outcomes: RDS. Other outcomes: changes of surfactant synthesis; and various neonatal outcomes.
Notes	No sample size calculation given. Use of surfactant not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Within this abstract, described as "participants were randomised into a study group or a control group". No details was given on randomisation methods. No stratification stated.
Allocation concealment (selection bias)	Unclear risk	No information was given on allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details on blinding; placebo not used.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	As above.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information given on losses to follow-up. Probably an intention-to-treat analysis.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to make the judgement.
Other bias	Unclear risk	Insufficient information to make the judgement.

Knight 1994

Methods	Randomised controlled trial.
Participants	Settong; single-centre study from Auckland, New Zealand between 1985 to 1990. 378 women at risk of preterm delivery sufficient to use prenatal corticosteroids between 24 to 33 weeks' gestation (183 in the TRH group vs 195 in the placebo group). These women delivered 418 infants (405 liveborn).
Interventions	400 µg of TRH or placebo as iv bolus (1 minute) x 4 every 12 hours (total 1600 µg). Betamethasone was given to all women.
Outcomes	Primary outcomes: RDS; chronic lung disease. Secondary outcomes: death; other complications of prematurity (intraventricular haemorrhage, patent ductus arteriosus, necrotising enterocolitis, retinopathy of prematurity). Maternal side effects.

Knight 1994 (Continued)

Notes	Sample size calculation.
	Source of funding: not stated.
	Surfactant was not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Women were randomised from random number tables in blocks of 100 to receive either TRH or placebo.
Allocation concealment (selection bias)	Low risk	Drugs prepared by hospital pharmacist in sets of identical, serially numbered vials.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Investigators, patients and clinicians were blinded. Placebo used.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above. The identify of the vials was not known until all data collection was complete.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analyses. Losses to follow-up at hospital discharge 9/418 babies (2.2%, with 4 from the TRH group and 5 from the placebo group).
Selective reporting (reporting bias)	Low risk	No obvious risk of selective reporting.
Other bias	Low risk	No obvious risk of other bias.

Morales 1989

Methods	Randomised controlled trial.
Participants	Setting: single-centre study from Tampa, Florida, USA between 1986 to 1987. 248 women (119 in the TRH group vs 129 in the control group) at risk of preterm delivery at less than 34 weeks. No exclusion criteria stated.
Interventions	400 µg of TRH iv x 6 every 8 hours (total 2400 µg) compared with no treatment. Betamethasone was given to all women.
Outcomes	Respiratory morbidity; intraventricular haemorrhage; fetal lung maturity on L/S ratio after 1 week of therapy; cord blood thyroid function tests.
Notes	Sample size calculation not given. Source of funding: not stated. Surfactant not available for use.

Morales 1989 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "'randomised into two groups by means of sealed envelopes blocked for gestational age'".
Allocation concealment (selection bias)	Unclear risk	No detail was given on allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Placebo not used (therefore unclear for women and personnel).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The perinatal research nurse who recorded the clinical course of the neonate during its stay in the intensive care unit was blinded. 2 investigators who graded the neonatal respiratory distress were blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Not an intention-to-treat analysis. Post randomisation exclusions of pregnancies complicated by lethal anomalies or L/S ratios of 2 or more. Losses to follow-up at hospital discharge 148/248 (59.7%). Infant outcomes restricted to 100 infants (50 in the TRH group and 50 in the control group) delivered by 1 week from the start of therapy.
Selective reporting (reporting bias)	High risk	No separate information reported about neonates morbidity for those delivered after 1 week of therapy. Post randomisation exclusions of pregnancies complicated by lethal anomalies or L/S ratios of 2 or more.
Other bias	Low risk	No other obvious risk of bias.

Voto 1998

Methods	Randomised controlled trial.
Participants	<p>Setting: Juan A Fernandez Hospital, University of Buenos Aires from October 1994 to July 1995.</p> <p>35 women (18 in the TRH group and 17 in the placebo group) with singleton pregnancies affected with fetal haemolytic disease due to Rh-isoimmunisation, with an indication for their first cordocentesis and induction of fetal lung maturation.</p> <p>No exclusion criteria were stated.</p>
Interventions	400 µg of TRH iv x 4 every 6 hours compared with a normal saline placebo (administered with the same treatment regimen). All women received 2 doses of betamethasone (12 mg intramuscularly 24 hours apart), the first administered at entry.
Outcomes	Fetal and maternal serum prolactin, TSH and iodothyronine concentrations.
Notes	Sample size calculation not given.

Risk of bias

Bias	Authors' judgement	Support for judgement
------	--------------------	-----------------------

Voto 1998 (Continued)

Random sequence generation (selection bias)	Low risk	A computer-generated randomised sequence was used, with a block design with permuting blocks of 4.
Allocation concealment (selection bias)	Low risk	Packs were prepared and numbered by an independent statistician. Once an entry form was completed, a consecutive number corresponding to a sealed treatment pack was assigned.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The trial was described as "double-blind" with the use of a matching placebo.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Cordocentesis was not successful in 3 cases in the TRH group and 1 in the placebo group, and therefore data were analysed for 15/18 women in the TRH group and 16/17 women in the placebo group.
Selective reporting (reporting bias)	Unclear risk	No clinical outcome data reported.
Other bias	Low risk	No other obvious risk of bias.

IM: intramuscular

iv: intravenous

L/S: lecithin/sphingomyelin

PPROM: preterm, prelabour rupture of the membranes

RDS: respiratory distress syndrome

TRH: thyrotropin-releasing hormone

vs: versus

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Devlieger 1997	The aim of the trial was to evaluate the effects of TRH on uterine contractility, blood pressure and maternal heart rate. 30 women were recruited. It is unclear as to whether all women received corticosteroids, and the trial has a cross-over design.
Dola 1997	The placebo group did not appear to have received corticosteroids.
Roti 1990	Trial comparing thyroid hormone and prolactin levels in neonatal blood following TRH administration. It is unclear as to whether all women included in the trial received corticosteroids.
Torres 1994	Comparison of neonatal T4 levels in 112 infants either exposed to 400 µg TRH doses x 6 or not. It is unclear if this was a randomised trial.
Torres 1995	The aim of the trial was to compare TSH and thyroid hormone levels in the cord blood of 21 infants whose mothers had received either 100 µg, 200 µg, 400 µg of TRH or saline placebo. It is unclear whether all women received corticosteroids.
Yoder 1997	Trial stopped without enrolling any women due to the infeasibility of having a placebo controlled group.

TRH: thyrotropin-releasing hormone

TSH: thyroid stimulating hormone

vs: versus

Characteristics of ongoing studies *[ordered by study ID]*

Pearlman 1997

Trial name or title	Trial to compare corticosteroids vs corticosteroids + TRH to mothers at 23 to 28 weeks with PROM.
Methods	No information.
Participants	No information.
Interventions	No information.
Outcomes	No information.
Starting date	No information.
Contact information	No information.
Notes	Personal communication.

PROM: prelabour rupture of the membranes

TRH: thyrotropin-releasing hormone

vs: versus

DATA AND ANALYSES

Comparison 1. TRH + steroids versus steroids alone (intention-to-treat)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death prior to hospital discharge	6	3694	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.86, 1.27]
2 Chronic lung disease	5	2511	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.85, 1.19]
3 Respiratory distress syndrome	9	3833	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.91, 1.22]
4 Chronic lung disease or death	6	3694	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.95, 1.18]
5 Need for oxygen therapy	4	2387	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.97, 1.13]
6 Severe respiratory distress syndrome	3	2119	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.57, 1.36]
7 Use of respiratory support	3	1969	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [1.03, 1.29]
8 Admission to neonatal intensive care unit	2	1637	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.98, 1.11]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9 Intraventricular haemorrhage	6	3645	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.93, 1.26]
10 Severe intraventricular haemorrhage	5	3313	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.82, 1.57]
11 Air leak syndrome	4	3103	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.71, 1.83]
12 Pulmonary haemorrhage	3	1969	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.25, 2.80]
13 Necrotising enterocolitis	4	3103	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.64, 1.30]
14 Patent ductus arteriosus	6	3645	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.79, 1.28]
15 Low Apgar score at 5 minutes	3	1969	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [1.14, 1.92]
16 Use of surfactant	4	3103	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.98, 1.25]
17 Gestational age at birth	2	1563	Mean Difference (IV, Fixed, 95% CI)	-0.43 [-0.86, 0.01]
18 Motor delay at follow-up	1	971	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [1.09, 1.56]
19 Motor impairment at follow-up	1	972	Risk Ratio (M-H, Fixed, 95% CI)	1.51 [1.01, 2.24]
20 Fine motor delay at follow-up	1	926	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.91, 1.32]
21 Sensory impairment at follow-up	1	1004	Risk Ratio (M-H, Fixed, 95% CI)	1.97 [1.10, 3.53]
22 Language delay at follow-up	1	1004	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.93, 1.54]
23 Social delay at follow-up	1	966	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [1.03, 1.51]
24 Any neurodevelopmental abnormality at follow-up	1	39	Risk Ratio (M-H, Fixed, 95% CI)	4.75 [0.61, 37.01]
25 Bayley Mental Developmental Index	2	99	Mean Difference (IV, Random, 95% CI)	-6.52 [-21.69, 8.64]
25.1 24 months	1	39	Mean Difference (IV, Random, 95% CI)	-15.70 [-30.86, -0.54]
25.2 18 months	1	60	Mean Difference (IV, Random, 95% CI)	0.0 [-8.36, 8.36]
26 Bayley Psychomotor Developmental Index	2	99	Mean Difference (IV, Fixed, 95% CI)	-2.73 [-8.58, 3.12]
26.1 24 months	1	39	Mean Difference (IV, Fixed, 95% CI)	-5.0 [-13.90, 3.90]
26.2 18 months	1	60	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-8.77, 6.77]
27 Bayley Behavioural Rating Scales (18 months)	1	60	Mean Difference (IV, Fixed, 95% CI)	9.0 [-4.88, 22.88]
28 Bayley Language Developmental Age (18 months)	1	60	Mean Difference (IV, Fixed, 95% CI)	2.0 [-0.36, 4.36]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
29 Bayley Cognitive Developmental Age (18 months)	1	60	Mean Difference (IV, Fixed, 95% CI)	1.70 [-0.64, 4.04]
30 Serious neurological abnormality at follow-up	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.06, 13.35]
31 Ophthalmological or hearing abnormalities at follow-up	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
32 Maternal nausea	3	2370	Risk Ratio (M-H, Fixed, 95% CI)	3.92 [3.13, 4.92]
33 Maternal vomiting	1	1011	Risk Ratio (M-H, Fixed, 95% CI)	2.35 [1.35, 4.09]
34 Maternal light headedness	1	1011	Risk Ratio (M-H, Fixed, 95% CI)	1.73 [1.36, 2.22]
35 Urgency of micturition	1	1011	Risk Ratio (M-H, Fixed, 95% CI)	2.39 [1.75, 3.27]
36 Maternal facial flushing	3	2523	Risk Ratio (M-H, Fixed, 95% CI)	2.67 [2.26, 3.16]
37 Maternal systolic blood pressure rise $\geq$ 25 mmHg	1	1011	Risk Ratio (M-H, Fixed, 95% CI)	1.80 [1.05, 3.06]
38 Maternal diastolic blood pressure rise $\geq$ 15 mmHg	1	1011	Risk Ratio (M-H, Fixed, 95% CI)	1.62 [1.24, 2.12]

Analysis 1.1. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 1 Death prior to hospital discharge.

Analysis 1.2. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 2 Chronic lung disease.

Analysis 1.3. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 3 Respiratory distress syndrome.

Analysis 1.4. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 4 Chronic lung disease or death.

Analysis 1.5. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 5 Need for oxygen therapy.

Analysis 1.6. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 6 Severe respiratory distress syndrome.

Analysis 1.7. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 7 Use of respiratory support.

Analysis 1.8. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 8 Admission to neonatal intensive care unit.

Analysis 1.9. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 9 Intraventricular haemorrhage.

Analysis 1.10. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 10 Severe intraventricular haemorrhage.

Analysis 1.11. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 11 Air leak syndrome.

Analysis 1.12. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 12 Pulmonary haemorrhage.

Analysis 1.13. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 13 Necrotising enterocolitis.

Analysis 1.14. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 14 Patent ductus arteriosus.

Analysis 1.15. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 15 Low Apgar score at 5 minutes.

Analysis 1.16. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 16 Use of surfactant.

Analysis 1.17. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 17 Gestational age at birth.

Analysis 1.18. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 18 Motor delay at follow-up.

Analysis 1.19. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 19 Motor impairment at follow-up.

Analysis 1.20. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 20 Fine motor delay at follow-up.

Analysis 1.21. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 21 Sensory impairment at follow-up.

Analysis 1.22. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 22 Language delay at follow-up.

Analysis 1.23. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 23 Social delay at follow-up.

Analysis 1.24. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 24 Any neurodevelopmental abnormality at follow-up.

Analysis 1.25. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 25 Bayley Mental Developmental Index.

Analysis 1.26. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 26 Bayley Psychomotor Developmental Index.

Analysis 1.27. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 27 Bayley Behavioural Rating Scales (18 months).

Analysis 1.28. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 28 Bayley Language Developmental Age (18 months).

Analysis 1.29. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 29 Bayley Cognitive Developmental Age (18 months).

Analysis 1.30. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 30 Serious neurological abnormality at follow-up.

Analysis 1.31. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 31 Ophthalmological or hearing abnormalities at follow-up.

Study or subgroup	TRH+steroids n/N	Steroids n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for overall effect: Not applicable					
			Favours TRH+steroids 0.01 0.1 1 10 100 Favours steroids		

Analysis 1.32. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 32 Maternal nausea.

Study or subgroup	TRH+steroids n/N	Steroids n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
ACTOBAT 1995	248/506	67/505		86.58%	3.69[2.91,4.7]
Ballard 1998	53/486	10/495		12.79%	5.4[2.78,10.49]
Knight 1994	2/183	0/195		0.63%	5.33[0.26,110.2]
Total (95% CI)	1175	1195		100%	3.92[3.13,4.92]
Total events: 303 (TRH+steroids), 77 (Steroids)					
Heterogeneity: Tau ² =0; Chi ² =1.17, df=2(P=0.56); I ² =0%					
Test for overall effect: Z=11.85(P<0.0001)					
			Favours TRH+steroids 0.1 0.2 0.5 1 2 5 10 Favours steroids		

Analysis 1.33. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 33 Maternal vomiting.

Study or subgroup	TRH+steroids n/N	Steroids n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
ACTOBAT 1995	40/506	17/505		100%	2.35[1.35,4.09]
Total (95% CI)	506	505		100%	2.35[1.35,4.09]
Total events: 40 (TRH+steroids), 17 (Steroids)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.02(P=0)					
			Favours TRH+steroids 0.1 0.2 0.5 1 2 5 10 Favours steroids		

Analysis 1.34. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 34 Maternal light headedness.

Study or subgroup	TRH+steroids n/N	Steroids n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
ACTOBAT 1995	139/506	80/505		100%	1.73[1.36,2.22]
Total (95% CI)	506	505		100%	1.73[1.36,2.22]
Total events: 139 (TRH+steroids), 80 (Steroids)					
Heterogeneity: Not applicable					
Test for overall effect: Z=4.39(P<0.0001)					
			Favours TRH+steroids 0.1 0.2 0.5 1 2 5 10 Favours steroids		

Analysis 1.35. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 35 Urgency of micturition.

Analysis 1.36. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 36 Maternal facial flushing.

Analysis 1.37. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 37 Maternal systolic blood pressure rise >= 25 mmHg.

Analysis 1.38. Comparison 1 TRH + steroids versus steroids alone (intention-to-treat), Outcome 38 Maternal diastolic blood pressure rise >= 15 mmHg.

Comparison 2. TRH + steroids versus steroids alone (dose of TRH subgroups)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death prior to hospital discharge	6	3694	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.86, 1.27]
1.1 200 µg (x 4 every 12 hours)	1	1397	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.87, 1.75]
1.2 400 µg (x 4 every 8-12 hours)	5	2297	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.77, 1.23]
2 Chronic lung disease	5	2511	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.85, 1.19]
2.1 200 µg (x 4 every 12 hours)	1	1369	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.84, 1.30]
2.2 400 µg (x 4 every 8-12 hours)	4	1142	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.73, 1.23]
3 Respiratory distress syndrome	9	3833	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.91, 1.22]
3.1 200 µg (x 4 every 12 hours)	1	1369	Risk Ratio (M-H, Random, 95% CI)	1.17 [1.00, 1.36]
3.2 400 µg (x 4 every 8-12 hours)	5	2276	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.78, 1.20]
3.3 400 µg (x 6 every 8 hours)	2	85	Risk Ratio (M-H, Random, 95% CI)	1.67 [0.87, 3.19]
3.4 500 µg (x 4 every 8 hours)	1	103	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.69, 1.80]
4 Chronic lung disease or death	6	3694	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.95, 1.18]
4.1 200 µg (x 4 every 12 hours)	1	1397	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.91, 1.30]
4.2 400 µg (x 4 every 8-12 hours)	5	2297	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.92, 1.19]
5 Need for oxygen therapy	4	2387	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.97, 1.13]
5.1 200 µg (x 4 every 12 hours)	1	1369	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.95, 1.16]
5.2 400 µg (x 4 every 8-12 hours)	3	1018	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.93, 1.18]
6 Severe respiratory distress syndrome	3	2119	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.57, 1.36]
6.1 200 µg (x 4 every 12 hours)	1	1369	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.66, 1.14]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.2 400 µg (x 4 every 8-12 hours)	2	750	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.37, 2.26]
7 Use of respiratory support	3	1969	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [1.03, 1.29]
7.1 200 µg (x 4 every 12 hours)	1	1369	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [1.01, 1.31]
7.2 400 µg (x 4 every 8-12 hours)	2	600	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.95, 1.46]

Analysis 2.1. Comparison 2 TRH + steroids versus steroids alone (dose of TRH subgroups), Outcome 1 Death prior to hospital discharge.

Analysis 2.2. Comparison 2 TRH + steroids versus steroids alone (dose of TRH subgroups), Outcome 2 Chronic lung disease.

Analysis 2.3. Comparison 2 TRH + steroids versus steroids alone (dose of TRH subgroups), Outcome 3 Respiratory distress syndrome.

Analysis 2.4. Comparison 2 TRH + steroids versus steroids alone (dose of TRH subgroups), Outcome 4 Chronic lung disease or death.

Analysis 2.5. Comparison 2 TRH + steroids versus steroids alone (dose of TRH subgroups), Outcome 5 Need for oxygen therapy.

Analysis 2.6. Comparison 2 TRH + steroids versus steroids alone (dose of TRH subgroups), Outcome 6 Severe respiratory distress syndrome.

Analysis 2.7. Comparison 2 TRH + steroids versus steroids alone (dose of TRH subgroups), Outcome 7 Use of respiratory support.

Comparison 3. TRH + steroids versus steroids alone (timing of delivery subgroups)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death prior to hospital discharge	5	2538	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.70, 1.26]
1.1 Birth < 24 hours after first dose	4	245	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.50, 1.59]
1.2 Birth ≥ 24 hours to ≤ 10 days after first dose	5	1164	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.59, 1.27]
1.3 Birth > 10 days after first dose	4	1129	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.47, 3.34]
2 Chronic lung disease	5	2574	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.81, 1.10]
2.1 Birth < 24 hours after first dose	5	306	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.54, 1.13]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 Birth $\geq$ 24 hours to $\leq$ 10 days after first dose	5	1152	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.77, 1.12]
2.3 Birth > 10 days after first dose	4	1116	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.81, 2.10]
3 Respiratory distress syndrome	6	3535	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.91, 1.10]
3.1 Birth < 24 hours after first dose	5	495	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.87, 1.08]
3.2 Birth $\geq$ 24 hours to $\leq$ 10 days after first dose	6	1485	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.81, 1.10]
3.3 Birth > 10 days after first dose	4	1555	Risk Ratio (M-H, Random, 95% CI)	1.33 [1.05, 1.68]
4 Chronic lung disease or death	5	3459	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.84, 1.11]
4.1 Birth < 24 hours after first dose	5	457	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.75, 1.08]
4.2 Birth $\geq$ 24 hours to $\leq$ 10 days after first dose	5	1317	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.77, 1.11]
4.3 Birth > 10 days after first dose	5	1685	Risk Ratio (M-H, Random, 95% CI)	1.30 [0.92, 1.83]
5 Need for oxygen therapy	2	1440	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.94, 1.10]
5.1 Birth < 24 hours after first dose	1	155	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.85, 1.07]
5.2 Birth $\geq$ 24 hours to $\leq$ 10 days after first dose	2	577	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.92, 1.08]
5.3 Birth > 10 days after first dose	1	708	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.88, 1.42]
6 Severe respiratory distress syndrome	3	2031	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.61, 0.93]
6.1 Birth < 24 hours after first dose	3	270	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.57, 1.30]
6.2 Birth $\geq$ 24 hours to $\leq$ 10 days after first dose	3	874	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.49, 0.85]
6.3 Birth > 10 days after first dose	2	887	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.62, 1.82]
7 Use of respiratory support	2	1440	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.92, 1.17]
7.1 Birth < 24 hours after first dose	1	155	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.82, 1.19]
7.2 Birth $\geq$ 24 hours to $\leq$ 10 days after first dose	2	577	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.87, 1.19]
7.3 Birth > 10 days after first dose	1	708	Risk Ratio (M-H, Random, 95% CI)	1.34 [0.94, 1.91]

Analysis 3.1. Comparison 3 TRH + steroids versus steroids alone (timing of delivery subgroups), Outcome 1 Death prior to hospital discharge.

Analysis 3.2. Comparison 3 TRH + steroids versus steroids alone (timing of delivery subgroups), Outcome 2 Chronic lung disease.

Analysis 3.3. Comparison 3 TRH + steroids versus steroids alone (timing of delivery subgroups), Outcome 3 Respiratory distress syndrome.

Analysis 3.4. Comparison 3 TRH + steroids versus steroids alone (timing of delivery subgroups), Outcome 4 Chronic lung disease or death.

Analysis 3.5. Comparison 3 TRH + steroids versus steroids alone (timing of delivery subgroups), Outcome 5 Need for oxygen therapy.

Analysis 3.6. Comparison 3 TRH + steroids versus steroids alone (timing of delivery subgroups), Outcome 6 Severe respiratory distress syndrome.

**Analysis 3.7. Comparison 3 TRH + steroids versus steroids alone
(timing of delivery subgroups), Outcome 7 Use of respiratory support.** **Comparison 4. TRH + steroids versus steroids alone (optimally treated variously defined)**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death prior to hospital discharge	10		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Optimally treated infants	9	1465	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.67, 1.14]
1.2 All treated infants	6	3694	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.86, 1.27]
2 Chronic lung disease	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Optimally treated infants	8	1318	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.72, 1.04]
2.2 All treated infants	5	2511	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.85, 1.19]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Respiratory distress syndrome	13		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Optimally treated infants	10	1786	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.77, 1.03]
3.2 All treated infants	9	3833	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.91, 1.22]
4 Chronic lung disease or death	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Optimally treated infants	5	1317	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.84, 1.09]
4.2 All treated infants	6	3694	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.95, 1.18]
5 Need for oxygen therapy	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Optimally treated infants	1	506	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.91, 1.09]
5.2 All treated infants	4	2387	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.97, 1.13]
6 Severe respiratory distress syndrome	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Optimally treated infants	2	694	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.49, 0.86]
6.2 All treated infants	3	2119	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.69, 1.04]
7 Use of respiratory support	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Optimally treated infants	1	506	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.94, 1.22]
7.2 All treated infants	3	1969	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [1.03, 1.29]

Analysis 4.1. Comparison 4 TRH + steroids versus steroids alone (optimally treated variously defined), Outcome 1 Death prior to hospital discharge.

Analysis 4.2. Comparison 4 TRH + steroids versus steroids alone (optimally treated variously defined), Outcome 2 Chronic lung disease.

Analysis 4.3. Comparison 4 TRH + steroids versus steroids alone (optimally treated variously defined), Outcome 3 Respiratory distress syndrome. **Analysis 4.4. Comparison 4 TRH + steroids versus steroids alone (optimally treated variously defined), Outcome 4 Chronic lung disease or death.**

Analysis 4.5. Comparison 4 TRH + steroids versus steroids alone (optimally treated variously defined), Outcome 5 Need for oxygen therapy.

Analysis 4.6. Comparison 4 TRH + steroids versus steroids alone (optimally treated variously defined), Outcome 6 Severe respiratory distress syndrome.

Analysis 4.7. Comparison 4 TRH + steroids versus steroids alone (optimally treated variously defined), Outcome 7 Use of respiratory support.

Comparison 5. TRH + steroids versus steroids alone (high-quality trials)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death prior to hospital discharge	5	3570	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.84, 1.25]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Chronic lung disease	4	2387	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.84, 1.18]
3 Respiratory distress syndrome	5	3521	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.91, 1.24]
4 Chronic lung disease or death	5	3570	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.94, 1.17]
5 Need for oxygen therapy	4	2387	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.97, 1.13]
6 Severe respiratory distress syndrome	3	2119	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.57, 1.36]
7 Use of respiratory support	3	1969	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [1.03, 1.29]

Analysis 5.1. Comparison 5 TRH + steroids versus steroids alone (high-quality trials), Outcome 1 Death prior to hospital discharge.

Analysis 5.2. Comparison 5 TRH + steroids versus steroids alone (high-quality trials), Outcome 2 Chronic lung disease.

Analysis 5.3. Comparison 5 TRH + steroids versus steroids alone (high-quality trials), Outcome 3 Respiratory distress syndrome.

Analysis 5.4. Comparison 5 TRH + steroids versus steroids alone (high-quality trials), Outcome 4 Chronic lung disease or death.

Analysis 5.5. Comparison 5 TRH + steroids versus steroids alone (high-quality trials), Outcome 5 Need for oxygen therapy.

Analysis 5.6. Comparison 5 TRH + steroids versus steroids alone (high-quality trials), Outcome 6 Severe respiratory distress syndrome.

Analysis 5.7. Comparison 5 TRH + steroids versus steroids alone (high-quality trials), Outcome 7 Use of respiratory support.

APPENDICES

Appendix 1. Search strategy for additional author searching

For the previous version of the review (Crowther 2004), we searched the Cochrane Central Register of Controlled Trials (*The Cochrane Library*, 2009, Issue 2), MEDLINE (1965 to 13 July 2009) and EMBASE (1988 to 13 July 2009) using the terms 'thyrotropin-releasing hormone' or 'TRH'.

WHAT'S NEW

Date	Event	Description
17 July 2013	New citation required but conclusions have not changed	New search for eligible studies; four reports identified, no new studies included. Follow-up data for one trial incorporated (Chile 1998). Two previously excluded trials (excluded based on no relevant outcome data) have been included (Crowther 1995; Voto 1998). Methods updated.

Date	Event	Description
17 July 2013	New search has been performed	Review updated.

HISTORY

Protocol first published: Issue 2, 1995

Review first published: Issue 2, 1995

Date	Event	Description
12 July 2009	New search has been performed	New search for eligible studies; no new studies identified. One new report of a previously published trial added (for Ballard 1992a). 'Risk of bias' tables updated. Authors of two studies previously reported as ongoing were contacted (Pearlman 1997 ; Yoder 1997).
10 November 2008	Amended	Contact details updated.
30 October 2008	Amended	Converted to new review format.
5 February 2004	New citation required but conclusions have not changed	Two more trials have been included and three excluded, in this update. The review has been edited in response to editorial comments. However, the conclusions remain largely unchanged.
31 July 2003	New search has been performed	New studies found and included or excluded.

CONTRIBUTIONS OF AUTHORS

For this update, CA Crowther assessed identified studies for eligibility and prepared the new format text of the review, with assistance from SS Han. All review authors contributed to the final version of this updated review.

DECLARATIONS OF INTEREST

CA Crowther and RR Haslam were two of the chief investigators for the Australian Collaborative Trial of thyrotropin-releasing hormone ([ACTOBAT 1995](#)) and the [Crowther 1995](#) trial; and Z Alfirevic was one of the principal investigators for the European TRH trial ([Europe 1999](#)). Therefore, all tasks relating to these studies (assessment of eligibility for inclusion, assessment of risk of bias, and data extraction) were carried out by other members of the review team who were not directly involved in the trials.

SOURCES OF SUPPORT

Internal sources

- ARCH, Robinson Institute, Discipline of Obstetrics and Gynaecology, The University of Adelaide, Australia.
- Division of Perinatal and Reproductive Medicine, The University of Liverpool, UK.
- Department of Perinatal Medicine, Women's and Children's Hospital, Adelaide, Australia.

External sources

- National Health and Medical Research Council, Australia.
- Department of Health and Ageing, Australia.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In this update, we have reduced the number of primary infants outcomes to three (death prior to hospital discharge, chronic lung disease (variously defined by authors), and respiratory distress syndrome), and the other outcomes have been moved to 'secondary outcomes'.

We have clarified that in relation to follow-up outcomes, the definitions are 'variously defined by authors'. We have changed the wording for the outcome 'need for oxygen therapy at 28 days' to 'chronic lung disease (variously defined by authors)' to be more inclusive.

We have updated the review methods.

INDEX TERMS

Medical Subject Headings (MeSH)

*Obstetric Labor, Premature; Drug Therapy, Combination [methods]; Glucocorticoids [*therapeutic use]; Infant, Premature; Randomized Controlled Trials as Topic; Respiratory Distress Syndrome, Newborn [*prevention & control]; Thyrotropin-Releasing Hormone [adverse effects] [*therapeutic use]

MeSH check words

Female; Humans; Infant, Newborn; Pregnancy