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

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2010, Issue 1

http://www.thecochranelibrary.com

TABLE OF CONTENTS

[Intervention Review]

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

Caroline A Crowther[1], Zarko Alfirevic[2], Shanshan Han[1], Ross R Haslam[3]

[1]ARCH: Australian Research Centre for Health of Women and Babies, Discipline of Obstetrics and Gynaecology, The University of Adelaide, Adelaide, Australia. [2]School of Reproductive and Developmental Medicine, Division of Perinatal and Reproductive Medicine, The University of Liverpool, Liverpool, UK. [3]Department of Perinatal Medicine, The University of Adelaide, Adelaide, Australia

Contact address: Caroline A Crowther, ARCH: Australian Research Centre for Health of Women and Babies, Discipline of Obstetrics and Gynaecology, The University of Adelaide, Women's and Children's Hospital, 72 King William Road, Adelaide, South Australia, 5006, Australia. 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 1, 2010.
Review content assessed as up-to-date: 9 November 2009.

Citation: 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. Art. No.: CD000019. DOI: 10.1002/14651858.CD000019.pub2.

ABSTRACT

Background

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

Objectives

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

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (July 2009), the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2009, Issue 2), MEDLINE (1965 to July 2009), EMBASE (1988 to July 2009) and reference lists. 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. The main outcomes considered were fetal and infant mortality, infant morbidity, childhood development and maternal morbidity.

Data collection and analysis

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

Main results

Over 4600 women were recruited into the 13 included trials. The five trials had a low risk of bias in the five risk of bias domains. Overall, prenatal TRH, in addition to corticosteroids, did not reduce the risk of neonatal respiratory disease or chronic oxygen dependence, and did not improve any of the 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 monitored were more likely to occur in women receiving TRH. In the infants, prenatal TRH increased the risk of needing ventilation (risk ratio (RR) 1.16, 95% confidence interval (CI) 1.03 to 1.29, three trials, 1969 infants), having a low Apgar score at five minutes (RR 1.48, 95% CI 1.14 to 1.92, three trials, 1969 infants) and, for the two trials providing data, was associated with poorer outcomes at childhood follow up.

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 very preterm birth do 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 steroids on the lungs of babies born too early, and may increase harm. Babies born very early are at risk of breathing difficulties (respiratory distress syndrome). TRH increases thyroid hormones in the baby and it has been thought that adding TRH to steroids for women giving birth early may increase the benefit on steroids on the baby's lungs. However, this review of 13 trials, involving over 4600 women, shows that TRH, given with steroids to women at risk of early birth, does not further reduce the breathing difficulties for the babies; and adverse effects were more common for both baby and mother.

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 (AIHW 2006). Preterm babies who survive the early weeks of life are at risk of long-term neurological disability (Saigal 2008). 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 2007; 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 and thyroid hormones levels 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 in 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 assesses the effectiveness and safety, using the best available evidence, of prenatal TRH given in addition to corticosteroids to women at risk of preterm birth.

OBJECTIVES

To assess the effects of thyrotropin-releasing hormone 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 trials with reported data that compare outcomes in women and babies exposed to prenatal thyrotropin-releasing hormone and corticosteroids with outcomes in controls receiving corticosteroids alone, with or without placebo. The trials used some form of random allocation and reported data on one or more of the prestated outcomes.

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. Predefined subgroups were planned to examine separately the primary outcomes for infants based on the reasons the women were considered at risk of preterm birth, and the number of infants *in utero* (singleton, twins or higher order multiple pregnancy).

Types of interventions

Thyrotropin-releasing hormone (TRH), any dosage, administered to the women intravenously and corticosteroids compared with corticosteroids with either placebo or no placebo. Predefined subgroups were to examine separately the primary outcomes for infants based on the dose of TRH given and the gestational age TRH treatment was given.

Types of outcome measures

Prespecified clinical measures of outcome related to fetal and neonatal mortality, neonatal morbidity, childhood development and maternal morbidity (*see* table of 'Comparisons and data').

Primary outcomes

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

1. Death prior to hospital discharge;
2. need for oxygen therapy at 28 days, or death;
3. need for oxygen therapy greater than or equal to 28 days;
4. need for oxygen therapy;
5. respiratory distress syndrome (RDS);
6. severe RDS (variously defined by authors);
7. use of respiratory support (mechanical ventilation or continuous positive airway pressure, or both).

Secondary outcomes

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

For the infant

1. Admission to neonatal intensive care unit;
2. periventricular haemorrhage;
3. periventricular haemorrhage grade 3/4;
4. periventricular leucomalacia;
5. air leak syndrome;
6. pulmonary haemorrhage;
7. necrotising enterocolitis;
8. patent ductus arteriosus;
9. low Apgar score at five minutes;
10. gestational age at birth;
11. use of surfactant;
12. neurodevelopmental abnormality at follow up;
13. visual impairment at follow up;
14. hearing impairment at follow up;
15. motor delay at follow up;
16. motor impairment at follow up;
17. fine motor delay at follow up;
18. sensory impairment at follow up;
19. language development delay at follow up;
20. social delay at follow up;
21. Bayley Mental Development Index;

22. Bayley Psychomotor Developmental Index.

The Bayley Scales of infant development yield a mental and motor development index, based on norms of a mean of 100 and a standard deviation of 16. The mental scale measures shape discrimination, attention, fine motor dexterity, imitation, comprehension of directions, naming and problem solving. The motor scale measures sitting, standing, walking, grasping, walking up and down steps, and other gross motor skills (Swaiman 1999).

For the mother

1. Nausea;
2. vomiting;
3. light headedness;
4. urgency of micturition;
5. facial flushing;
6. systolic blood pressure rise during treatment (greater than 25 mmHg);
7. diastolic blood pressure rise during treatment (greater than 15 mmHg).

While we sought all the above outcomes from the included trials, only those with data appear in the analysis tables. Outcomes were included in the analysis if reasonable measures were taken to minimise observer bias and data were available for analysis according to original treatment allocation.

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 (12 July 2009).

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

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

Details of the search strategies for CENTRAL and MEDLINE, 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.

In addition, 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). *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

Selection of studies

Two of the three review authors (CA Crowther, Z Alfirevic, SS Han) 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 person.

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 person. Data was entered into Review Manager software (RevMan 2008) 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 of the three review authors (CA Crowther, Z Alfirevic, SS Han) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). Any disagreement was resolved by discussion or by involving a third assessor.

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

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

We assessed the methods as:

- adequate (e.g. random number table; computer random number generator; tossing a coin, minimisation);
- inadequate (odd or even date of birth; hospital or clinic record number); or
- unclear.

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

We described for each included study the method used to conceal the allocation sequence in sufficient detail and determine whether intervention allocation could have been foreseen in advance of, or during, recruitment.
We assessed the methods as:
- adequate (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- inadequate (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth;
- unclear.

(3) Blinding (checking for possible performance bias)

We described for each included study all the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We also provided any information relating to whether the intended blinding was effective. Where blinding is not possible we assessed whether the lack of blinding was likely to have introduced bias.
We assessed the methods as:
- adequate, inadequate or unclear for participants;
- adequate, inadequate or unclear for personnel;
- adequate, inadequate or unclear for outcome assessors;

where adequate is when there was blinding or where we assess that the outcome or the outcome measurement is not likely to have been influenced by lack of blinding.

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

We described for each included study the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported, the numbers (compared with the total randomised participants), reasons for attrition/exclusion where reported, and any re-inclusions in analyses which we undertake.
We assessed the methods as:
- adequate (e.g. where there were no missing data or where reasons for missing data are balanced across groups);
- inadequate (e.g. where missing data are likely to be related to outcomes or are not balanced across groups);
- unclear (e.g. where there is insufficient reporting of attrition or exclusions to permit a judgement to be made).

(5) Selective reporting bias

We described for each included study how the possibility of selective outcome reporting bias was examined by us and what we found.
We assessed the methods as:
- adequate (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
- inadequate (where not all the study's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear.

(6) Other sources of bias

We described for each included study any important concerns we have about other possible sources of bias. For example, was there a potential source of bias related to the specific study design? Was the trial stopped early due to some data-dependent process? Was there extreme baseline imbalance? Has the study been claimed to be fraudulent?
We assessed whether each study was free of other problems that could put it at risk of bias:
- yes;
- no;
- unclear.

(7) Overall risk of bias

We made explicit judgements about risk of bias for important outcomes both within and across studies. With reference to (1) to (6) above we assessed the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. We explored the impact of the level of bias through undertaking sensitivity analyses, *see* Sensitivity analysis.

Measures of treatment effect

We carried out statistical analysis using the Review Manager software (RevMan 2008). We used fixed-effect meta-analysis for combining data in the absence of significant heterogeneity if trials are sufficiently similar.

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 if outcomes are measured in the same way between trials. We used the standardised mean difference to combine trials that measure the same outcome, but use different methods. If there is evidence of skewness, this was reported.

Unit of analysis issues

Cluster-randomised trials

We included cluster-randomised trials in the analyses along with individually randomised trials. Their sample sizes was adjusted using the methods described in Gates 2005 using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), or from another source. If ICCs from other sources were used, this was reported and sensitivity analyses conducted to investigate the effect of variation in the ICC. If we identified both cluster-randomised trials and individually randomised trials, we planned to synthesise the relevant information. We considered 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 acknowledged heterogeneity in the randomisation unit and performed a separate meta-analysis. Therefore, the meta-analysis was performed in two parts as well.

Dealing with missing data

For included studies levels of attrition were noted. The impact of including studies with high levels of missing data in the overall assessment of treatment effect was explored by using sensitivity analysis.

Where data were not reported for some outcomes or groups we attempted to contact the study authors for further information.

Assessment of heterogeneity

We applied tests of heterogeneity between trials, if appropriate, using the I^2 statistic. If we identified high levels of heterogeneity among the trials (exceeding 50%), we explored it by prespecified subgroup analysis and performed sensitivity analysis. A random-effects meta-analysis was used as an overall summary if this is considered appropriate.

Assessment of reporting biases

Where we suspect reporting bias (*see* 'Selective reporting bias' above) we attempted to contact study authors asking them to provide missing outcome data Where this is not possible, and the missing data were thought to introduce serious bias, the impact of including such studies in the overall assessment of results was explored by a sensitivity analysis.

Where we suspect publication bias (e.g. where only statistically significant results are reported) this was explored using funnel plots. We will involve the project statistician in the interpretation of such analysis.

Intention-to-treat analysis

We analysed data on all participants with available data in the group to which they are allocated, regardless of whether or not they received the allocated intervention. If in the original reports participants are not analysed in the group to which they were randomised, and there is sufficient information in the trial report, we attempted to restore them to their allocated group.

Incomplete outcome data (attrition and exclusions)

See Assessment of risk of bias in included studies and Assessment of reporting biases sections.

Selective outcome reporting bias

Already addressed in Assessment of risk of bias in included studies and Assessment of reporting biases sections above.

Data synthesis

We synthesised data separately for studies with a low risk of bias and those with a high risk of bias to explore the impact of possible bias on review findings.

When appropriate we synthesised data from studies where results were expressed as dichotomous and continuous data. We involved the project statistician before attempting to synthesise different measures of treatment effect.

Subgroup analysis and investigation of heterogeneity

We conducted planned subgroup analyses classifying whole trials by interaction tests as described by Deeks 2001.

We planned secondary 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 thyrotropin-releasing hormone (TRH) treatment was given, the dose of TRH given, and 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:
(i) birth less than 24 hours after first dose;
(ii) birth between 24 hours and 10 days, inclusive, after first dose;
(iii) birth more than 10 days after first dose.
Initial analyses were limited to the prespecified outcomes and sensitivity and secondary analyses to the prespecified primary outcomes.

Sensitivity analysis

We carried out sensitivity analysis to explore the effect of trial quality for important outcomes in the review. Where there is risk of bias associated with a particular aspect of study quality (e.g. inadequate allocation concealment) this was explored by sensitivity analysis.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.
See Characteristics of included studies table.
Twenty-two trials of prenatal thyrotropin-releasing hormone (TRH) were identified, of which 13 met our inclusion criteria. Of the other nine trials, seven were excluded as no clinically meaningful data were reported in a format suitable for inclusion (Crowther 1995a; Devlieger 1997; Dola 1997; Roti 1990; Torres 1994; Torres 1995; Voto 1998). One trial was excluded following confirmation from the trialist that no women were enrolled due to the infeasibility of having a placebo controlled group (Yoder 1997). One other trial is reported as planned (Pearlman 1997). Over 4600 women were recruited into the 13 trials that met the prespecified criteria for inclusion in this review (Abuhamad 1999; ACTOBAT 1995; Ballard 1992a; Ballard 1998; Campos 1993; Carlan 1991; Ceriani 1992; Chile 1998; Europe 1999; Jikihara 1990; Kim 2000; Knight 1994; Morales 1989).
Gestational age at trial entry varied between 24 to 33 completed weeks; 24 to 31 completed weeks (ACTOBAT 1995; Ballard 1992a; Campos 1993), 24 to less than 30 weeks (Ballard 1998), 24 to less than 33 weeks (Chile 1998; Knight 1994), 24 to less than 34 weeks (Carlan 1991); 24 to 34 weeks (Abuhamad 1999); less than 32 weeks (Europe 1999); less than 34 weeks (Morales 1989); 23 to 29 completed weeks (Jikihara 1990); 26 to 31 weeks (Ceriani 1992) and 26 to 34 weeks (Kim 2000).
All trials used antenatal corticosteroids, an inclusion criterion. The TRH regimens varied. Ballard 1992a; Ballard 1998; Campos 1993; Chile 1998; Europe 1999 and Jikihara 1990 used 400 μg every eight hours up to a maximum of four doses; Carlan 1991; Kim 2000 and Morales 1989 used a similar regimen, but up to a maximum of six doses; Abuhamad 1999 used 500 μg every eight hours up to a maximum of four doses, repeated weekly for a maximum of four weeks or until delivery; Knight 1994 used 400 μg 12 hourly up to a maximum of four doses; 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 times only.

Risk of bias in included studies

See 'Risk of bias' tables.

Sequence generation

Six of the 13 included trials used adequate methods for sequence generation. Three trials (ACTOBAT 1995; Chile 1998; Europe 1999) used central telephone randomisation, and three trials (Ballard 1992a; Ballard 1998; Knight 1994) used pharmacy allocation.
Sequence generation was unclear for the remaining seven trials (Abuhamad 1999; Campos 1993; Carlan 1991; Ceriani 1992; Jikihara 1990; Kim 2000; Morales 1989).

Allocation concealment

Seven of the 13 trials (Abuhamad 1999; ACTOBAT 1995; Ballard 1992a; Ballard 1998; Chile 1998; Europe 1999; Knight 1994) demonstrated an adequate method for allocation concealment.
Four trials (Abuhamad 1999; Ballard 1992a; Ballard 1998; Knight 1994) used a central allocation by using random list in pharmacy.
Three trials (ACTOBAT 1995; Chile 1998; Europe 1999) used central telephone randomisation service.
Allocation concealment was unclear in the remaining six trials (Campos 1993; Carlan 1991; Ceriani 1992; Jikihara 1990; Kim 2000; Morales 1989).

Blinding

Nine of the 13 included trials (Abuhamad 1999; ACTOBAT 1995; Ballard 1992a; Ballard 1998; Ceriani 1992; Chile 1998; Europe 1999; Knight 1994; Morales 1989) were blinded throughout the study.
In ACTOBAT 1995, assessment of neonatal outcomes was blinded, placebo was used except for the first 198 recruits.
Three trials (Ballard 1992a; Ballard 1998; Ceriani 1992), were described as "blinded trial" and a placebo was used.
In Chile 1998, Europe 1999 and Knight 1994, all patients, investigators, clinicians and pregnancy outcome assessors were blinded, placebo was used in all three trials.
In Morales 1989, neonate outcome recorders and neonatal respiratory distress assessors were blinded.

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

Addressing incomplete outcome data

Losses to follow up in five trials (Abuhamad 1999; ACTOBAT 1995; Ballard 1998; Europe 1999; Knight 1994) was less than 3%. In Chile 1998, losses to follow up were 21/370 (5.7%); 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 1992a; 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 groups of 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 1992a; Campos 1993 and Morales 1989.

Selective reporting

There was no obvious risk of selective reporting in nine of the 13 trials (Abuhamad 1999; ACTOBAT 1995; Ballard 1998; Carlan 1991; Chile 1998; Europe 1999; Jikihara 1990; Kim 2000; Knight 1994).

The remaining four trials (Ballard 1992a; Campos 1993; Ceriani 1992; Morales 1989) only present 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 1992a (343/446; 77% infants excluded), and probably from 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 1992a report 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 glucocorticosteroids, or both). Campos 1993 reported data on fully treated infants (received all doses of TRH or glucocorticosteroids, or both) who were born within 48 hours of the last hormonal dose.

Neurological outcomes at childhood follow up were reported for only two trials (ACTOBAT 1995; 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 date were available for all infants. A subset of 39 of 52 (75%) children recruited at a single centre to 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.

Effects of interventions

Thirteen trials involving over 4600 women were included. All trials used a combination of TRH and antenatal corticosteroids in the experimental group and corticosteroids alone in the control group.

Comparison of TRH with steroids versus steroids alone

(1) 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 either for death prior to hospital discharge alone (risk ratio (RR) 1.05, 95% confidence interval (CI) 0.86 to 1.27, six trials, 3694 infants) or combining death with need for oxygen at 28 days as a single measure of adverse outcome. No differences were seen in chronic oxygen dependence (need for oxygen at 28 days), need for oxygen therapy, the risk of respiratory distress syndrome (RDS) (RR 1.07, 95% CI 0.98 to 1.16, nine trials, 3833 infants) or severe RDS (RR 0.85, 95% CI 0.69 to 1.04, three trials, 2119 infants). Significant heterogeneity was found for the risk of RDS (I^2 = 47.9%) and severe RDS (I^2 = 73.1%). The need for respiratory support was increased in the TRH treated group (RR 1.16, 95% CI 1.03 to 1.29, three trials, 1969 infants).

Secondary outcomes

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) or on need for admission to the neonatal intensive care unit were discernible. Similarly no effects were seen on the risk of periventricular haemorrhage, severe periventricular haemorrhage, air leak syndrome, necrotising enterocolitis, patent ductus arteriosus, pulmonary haemorrhage or use of surfactant. A low Apgar score at five minutes was more common in TRH treated infants (RR 1.48, 95% CI 1.14 to 1.92, three trials, 1969 infants). Significant heterogeneity was seen for air leak syndrome (I^2 = 55.3%) and pulmonary haemorrhage (I^2 = 56.2%).

The outcome of children at 12 months of age was available for two trials (ACTOBAT 1995; Europe 1999) and showed an increased

risk in the TRH treated group of motor delay (RR 1.31, 95% CI 1.09 to 1.56, one trial, 972 infants), motor impairment (RR 1.51, 95% CI 1.01 to 2.24, one trial, 972 infants), sensory impairment (RR 1.97, 95% CI 1.10 to 3.53, one trial, 1004 infants), and social delay (RR 1.25, 95% CI 1.03 to 1.51, one trial, 966 infants) but not of neurological abnormality overall (RR 4.75, 95% CI 0.61 to 37.01, one trial, 39 infants). At 24 months the mean Bayley Mental Developmental Index (MDI) was lower (worse) in the TRH exposed children (MD -15.70, 95% CI -30.86 to -0.54, one trial, 39 infants).

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), vomiting (RR 2.35, 95% CI 1.35 to 4.09, one trial, 1011 women), light headedness (RR 1.73, 95% CI 1.36 to 2.22, one trial, 1011 women), urgency of micturition (RR 2.39, 95% CI 1.75 to 3.27, one trial, 1011 women), and facial flushing (RR 2.67, 95% CI 2.26 to 3.16, three trials, 2523 women). 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) and maternal diastolic blood pressure (greater than 15 mmHg) (RR 1.62, 95% CI 1.24 to 2.12, one trial, 1011 women) in women given prenatal TRH.

(2) Trials with low risk of bias analysed by intention to treat

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

No beneficial effects of prenatal TRH were seen for any of the infant outcomes (death, death or need for oxygen at 28 days, chronic oxygen dependence, need for oxygen therapy, the risk of RDS or severe RDS. Significant heterogeneity was found for the risk of RDS and severe RDS. The use of respiratory support remained increased in the TRH treated group (RR 1.16, 95% CI 1.03 to 1.29, three trials, 1969 infants).

(3) Subgroup analyses based on the timing of delivery

(3.1) Birth less than 24 hours after first dose

Six trials contributed data (ACTOBAT 1995; Ballard 1992a; Ballard 1998; Chile 1998; Europe 1999; Knight 1994). Babies who were born less than 24 hours after trial entry made up 13% of the total population studied. No beneficial effects of prenatal TRH were seen for any of the outcomes (death prior to hospital discharge, death or need for oxygen at 28 days, chronic oxygen dependence, need for oxygen therapy, the risk of RDS, severe RDS, or use of respiratory support).

(3.2) Birth between 24 hours and 10 days, inclusive, after first dose

Six trials contributed data (ACTOBAT 1995; Ballard 1992a; Ballard 1998; Chile 1998; Europe 1999; Knight 1994). Babies born between 24 hours and 10 days from trial entry accounted for 38% of the total trial population. Significant heterogeneity was found for the risk of RDS (I^2 = 45.9%). No beneficial effects were discernible for death prior to hospital discharge, need for oxygen therapy or death at 28 days, chronic oxygen dependence, need for oxygen therapy, RDS, or the use of respiratory support, although severe RDS was less common in the TRH treated group using the data available from the three earlier trials (RR 0.65, 95% CI 0.49 to 0.85, three trials, 874 infants).

(3.3) Birth more than 10 days after first dose

Five trials contributed data (ACTOBAT 1995; Ballard 1998; Chile 1998; Europe 1999; Knight 1994). The greatest proportion of babies, 49%, were born more than 10 days after trial entry. Need for oxygen therapy or death at 28 days (RR 1.35, 95% CI 1.02 to 1.78, five trials, 1685 infants), and RDS (RR 1.33, 95% CI 1.05 to 1.68, four trials, 1515 infants), were more common in the TRH treated infants. No effect from prenatal TRH was discernible on death prior to hospital discharge, need for oxygen therapy at 28 days, need for oxygen therapy, use of respiratory support or severe RDS. Significant heterogeneity (I^2 = 49.2%) was seen for death prior to discharge.

(4) Intention-to-treat analysis based on the TRH dose

(4.1) 400 μg treatment dosage

Six trials contributed data (Ballard 1998; Carlan 1991; Chile 1998; Europe 1999; Jikihara 1990; Knight 1994). No beneficial effects of prenatal TRH were seen for any of the infant outcomes (death prior to hospital discharge, death or need for oxygen at 28 days, chronic oxygen dependence, need for oxygen therapy, the risk of RDS, severe RDS, or use of respiratory support. Significant heterogeneity was found for the risk of RDS (I^2 = 59.1%) and severe RDS (I^2 = 86.4%).

(4.2) 200 μg treatment dosage

One trial contributed data (ACTOBAT 1995). An increased use of respiratory support (RR 1.15, 95% CI 1.01 to 1.31, one trial, 1369 infants) and a trend towards an increased risk of RDS (RR 1.17, 95% CI 1.00 to 1.36, one trial, 1369 infants) were seen in the TRH treated infants. There was no clear effect of prenatal TRH on death prior to hospital discharge, need for oxygen therapy or death at 28 days, need for oxygen therapy at 28 days, need for oxygen therapy or severe RDS.

(5) Analysis restricted to mothers and babies receiving 'optimal treatment'

This 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, nine trials contributed data (ACTOBAT 1995; Ballard 1998; Campos 1993; Ceriani 1992; Chile 1998; Europe 1999; Jikihara 1990; Knight 1994; Morales 1989). 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. This represented 23% of all babies recruited to the study. Ceriani 1992 reported data for infants fully treated (received all doses of TRH or glucocorticosteroids, or both) and born within 10 days of entry. Campos 1993 reported the data on fully treated (received all doses of TRH or glucocorticosteroids, or both) who were born within 48 hours of the last hormonal dose. In addition, the data from ACTOBAT 1995; Ballard 1998; Chile 1998; Europe 1999; Jikihara 1990 and Knight 1994 included in this analysis, related to infants born between 24 hours to 10 days after entry into the trial.

No beneficial effects of prenatal TRH were seen for death prior to hospital discharge, death or need for oxygen at 28 days, chronic oxygen dependence, need for oxygen therapy, RDS, or the use of respiratory support. Significant heterogeneity was found for the risk of RDS (I^2 = 53.6%) and severe RDS (I^2 = 61.2%). No reduced risk of RDS was seen (RR 0.91, 95% CI 0.82 to 1.02, eight trials, 1535 infants). Severe RDS was less common in the TRH treated infants (RR 0.63, 95% 0.49 to 0.86, two trials, 694 infants).

DISCUSSION

This review does not show that prenatal administration of thyrotropin-releasing hormone (TRH), in addition to corticosteroids, prior to very preterm birth reduces the risk of respiratory disease in infants born preterm, or reduces the other infant morbidity or mortality. Indeed the data show the treatment has adverse effects for women and their infants. All side-effects monitored were more likely to occur in women receiving TRH, although their clinical significance and the consumers' feelings about them have not been assessed. For the infants, prenatal TRH increased the risk of infants needing respiratory support, and in the two trials with data, was associated with adverse neurodevelopmental outcome at follow up.

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 1992a; Morales 1989). However, a significant proportion of babies in all the studies (49%) were born more than 10 days after trial entry. The data in this review show that these babies, if exposed to prenatal TRH, were more likely to need oxygen therapy or have died at 28 days and were more likely to develop respiratory distress syndrome (RDS) compared with babies born more than 10 days after trial entry in the control group. This highlights the importance of 'intention-to-treat' 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 (Liggins 1972). Infants exposed to TRH in this timed subgroup, or a similar 'optimal' timing variously defined by the authors, showed a reduced risk of severe RDS. Currently 'intention-to-treat' data for severe RDS are only available for the three earlier trials for this timed subgroup (ACTOBAT 1995; Ballard 1992a; Knight 1994) so the information on severe RDS from the more recent trials will be important to include if they become available.

AUTHORS' CONCLUSIONS

Implications for practice

On the basis of the currently available evidence prenatal thyrotropin-releasing hormone, in addition to corticosteroids, given to women at risk of very preterm birth does not reduce the severity of neonatal lung disease, increases the chances of the infant needing respiratory support and has maternal side-effects.

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 long-term morbidity.

Further information on long-term follow up of all babies included in the trials, to confirm or refute the adverse effects of prenatal thyrotropin-releasing hormone (TRH) on childhood outcome, is awaited.

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 any women due to the infeasibility of having a placebo controlled group (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, Prof JE Hiller, Dr H Jikihara, Dr DB Knight and Professor FR Moya. We also thank Philippa Middleton for assisting the update of this review.

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 & 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 af 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 1992a *{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 J, Cernades C, 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.

Europe 1999 ***{unpublished data only}***

* Alfirevic 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.

Alfirevic 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 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.

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 & Gynecology* 1989;**73**:111–6.

References to studies excluded from this review

Crowther 1995a ***{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?. XIII World Congress of Gynecology and Obstetrics (FIGO); 1991; Singapore. Singapore, 1991: 31.

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.

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-isoimmunized fetuses: a randomized clinical trial. *Prenatal and Neonatal Medicine* 1998;**3**:447–51.

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

AIHW 2006
Australian Institute of Health and Welfare. *Australia's Health 2006. AIHW cat. no. AUS73*. Canberra: AIHW, 2006.

Ballard 1992b
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 2007
Crowther CA, Harding JE. Repeat doses of prenatal corticosteroids for women at risk of preterm birth for preventing neonatal respiratory disease. *Cochrane Database of Systematic Reviews* 2007, Issue 3. [DOI: 10.1002/14651858.CD003935.pub2]

Deeks 2001
Deeks JJ, Altman DG, Bradburn MJ. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: Egger M, Davey Smith G, Altman DG editor(s). *Systematic reviews in health care: meta-analysis in context*. London: BMJ Books, 2001.

Gates 2005
Gates S. Methodological Guidelines. In: The Editorial Team. Pregnancy and Childbirth Group. About the Cochrane Collaboration (Collaborative Review Groups (CRGs)) 2005, Issue 2.

Higgins 2008
Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1 [updated September 2008]. The Cochrane Collaboration, 2008. Available from www.cochrane-handbook.org.

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

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.

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 Instiitute of Health and Welfare, National Perinatal Statistics Unit, 2001.

RevMan 2008
The Cochrane Collaboration. Review Manager (RevMan). 5.0. Copenhagen, The Nordic Cochrane Centre: The Cochrane Collaboration, 2008.

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]

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.

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]

Swaiman 1999

Swaiman KF, Ashwal S. *Pediatric neurology: principles and practice*. 3rd Edition. St. Louis, MI: Mosby, 1999:557.

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 1995b

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.

Crowther 2004

Crowther CA, Alfirevic Z, 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]

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	Method of treatment allocation: random list in pharmacy. No stratification stated. Placebo used. No sample size calculation given. Intention-to-treat analysis. No losses to follow up. Source of funding: not stated.
Participants	Location: 1 centre in Norfolk, East Virginia, USA. 103 women with a singleton pregnancy with PPROM at 24-34 weeks' gestation. (55 in the TRH group vs 48 in the placebo group). Gestational age range: 24-34 weeks. Not eligible if preterm labour, chorioamnionitis or multiple pregnancy
Interventions	500 mcg of TRH or placebo x 4 every 8 hours (total 2000 mcg). Treatment was completed weekly for a maximum of 4 weeks or until delivery. Betamethasone 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	Use of surfactant not stated.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Random number list in pharmacy was used. Patients were allocated to study groups by using sealed envelopes
Allocation concealment?	Yes	Central allocation by using a random list in pharmacy.
Blinding? All outcomes	Yes	Placebo used; TRH and placebo packs were prepared by pharmacy; patients and treating physicians were blinded
Incomplete outcome data addressed? All outcomes	Yes	No losses to follow up. No data excluded.
Free of selective reporting?	Unclear	Insufficent information to make the judgement.
Free of other bias?	Unclear	Insufficent information to make the judgement.

ACTOBAT 1995

Methods	Method of treatment allocation: centrally by telephone. Stratification by centre and gestational age. Placebo used. Sample size calculation. Intention-to-treat analyses. Losses to follow up at hospital discharge 3/1234 (< 1%), one in TRH group and 2 in placebo group. Losses to follow up at 1 year 145/1234 (11%). Source of funding: National Health and Medical Research Council, Australia; Queen Victoria Hospital Foundation; Channel 7 Children's Research Foundation; SIDS Foundation SA
Participants	Location: 18 centres in Australia from 1990-1993. 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 - < 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 mcg of TRH or placebo in 50 ml saline over 20 minutes x 4 every 12 hours (total 800 mcg). Only one course of TRH was given. Betamethasone to all women
Outcomes	Primary outcome: frequency and severity of respiratory distress syndrome; 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 outcome: 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	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

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Randomisation: central telephone randomisation service.
Allocation concealment?	Yes	Central randomisation.
Blinding? All outcomes	Yes	Quote:"assessment of neonatal outcomes was masked throughout the study period" Placebo used expect the first 198 recruits (16%).
Incomplete outcome data addressed? All outcomes	Yes	1 women and her baby in TRH group and 2 in the control group were lost to follow

ACTOBAT 1995 (*Continued*)

		up
Free of selective reporting?	Yes	All prespecified outcomes reported; analyses were based on intention to treat
Free of other bias?	Yes	No obvious risk of other bias.

Ballard 1992a

Methods	Method of treatment allocation: table of random numbers in each pharmacy. Stratification by centre. Placebo used. Sample size calculation. 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%). 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
Participants	Location: 4 centres in the USA between 1986-1989. 850 women with threatened preterm delivery (404 in the TRH group and 446 in the placebo group). Gestational age range: < 32 weeks. Not eligible if evidence of lung maturity
Interventions	400 mcg of TRH or placebo in 50 ml saline as a 20 minute infusion x 4 every 8 hours (total 1600 mcg). Only one course of TRH was given. Betamethasone to all women
Outcomes	Apgar scores; resuscitation measures; respiratory morbidity (respiratory distress, chronic lung disease); other complications of prematurity (patent ductus arteriosus, necrotising enterocolitis, intraventricular haemorrhage, retinopathy of prematurity)
Notes	Surfactant not given to any baby in the trial.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Quote: "treatment groups were assigned centrally (Yale) with a table of random numbers"
Allocation concealment?	Yes	Central allocation by using a random number table.
Blinding? All outcomes	Yes	Described as a "blinded" trial, placebo used.

Ballard 1992a (*Continued*)

Incomplete outcome data addressed? All outcomes	No	Not an intention-to-treat analysis. Losses to follow up to hospital discharge was 103/404 (23%)
Free of selective reporting?	No	Analysis restricted to fully treated infants (at least 3 doses) who delivered 1-10 days from entry
Free of other bias?	Yes	No obvious risk of other bias.

Ballard 1998

Methods	Method of treatment allocation: pharmacies at the participating centres. Stratification by centre. Placebo used. Sample size calculation. Intention-to-treat analyses. Losses to follow up at hospital discharge 15/996 (1.5%) women. 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
Participants	Location: 13 North American centres between 1992-1996. 981 women in active labour with gestational age range 24 - < 30 weeks, delivering 1134 liveborn 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 mcg of TRH or placebo in 50 ml saline as a 20 minute infusion x 4 every 8 hours (total 1600 mcg). Only 1 course of TRH was given. Betamethasone 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 outcome: 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	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

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Randomisation: randomisation schedule was only kept in pharmacies at the participating centres

Ballard 1998 (*Continued*)

Allocation concealment?	Yes	Central allocation: pharmacy-controlled randomisation.
Blinding? All outcomes	Yes	Described as "double-blinded trial"; placebo used.
Incomplete outcome data addressed? All outcomes	Yes	Analyses were based on intention to treat; losses to follow up at hospital discharge 15/996 (1.5%) women
Free of selective reporting?	Yes	All prespecified outcomes reported.
Free of other bias?	Yes	No other obvious risk of bias.

Campos 1993

Methods	Method of treatment allocation: sealed envelopes. Placebo used. Not an intention-to-treat analysis. Analysis restricted to 135 infants who received all doses of TRH and/or glucocorticoid and who delivered within 48 hours of the last hormonal dose
Participants	Location: Chile. Women at risk of preterm birth with a gestational age between 24-32 weeks (number of women not stated; 135 infants)
Interventions	400 mcg of TRH x 4 every 8 hours (total 1600 mcg) or no TRH (not clear if placebo). Betamethasone to all women
Outcomes	Mortality and respiratory morbidity.
Notes	Use of surfactant unclear.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Described as "prospectively randomised trial"; no other information available
Allocation concealment?	Unclear	Insufficent information to make the judgement.
Blinding? All outcomes	Unclear	Placebo used; no further information was available.
Incomplete outcome data addressed? All outcomes	No	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

Campos 1993 (*Continued*)

Free of selective reporting?	No	Analysis restricted to 135 infants who received all doses and who delivered within 48 hours of the last hormonal dose
Free of other bias?	Yes	Insufficent information to make the judgement.

Carlan 1991

Methods	Method of treatment allocation: unclear, reported as 'prospectively randomised'. No placebo used. Sample size calculation not given. Excluded 5 patients who 'sealed' and 2 with evidence of pulmonary maturity. Losses to follow up at hospital discharge 7/44 (15.9%). Funding source not stated.
Participants	Location: Tampa, Florida. 44 women with preterm prelabour rupture of the membranes between 24-34 weeks' gestation
Interventions	3 study groups. Group 1 (n = 13) given 400 mcg of TRH intravenously x 6 every 8 hours (total 2400 mcg) 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	Respiratory distress syndrome; duration of ventilation; length of stay in neonatal intensive care
Notes	Use of surfactant not stated.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Within this abstract, reported as 'prospectively randomised'; no information was available on randomisation methods
Allocation concealment?	Unclear	No details were given on allocation concealment.
Blinding? All outcomes	Unclear	No placebo used; no other information given on blinding.
Incomplete outcome data addressed? All outcomes	No	Losses to follow up at hospital discharge 7/44 (15.9%) (excluded 5 patients who 'sealed' and 2 with evidence of pulmonary

Carlan 1991 (*Continued*)

		maturity). Analysis was based on 37 patients
Free of selective reporting?	Unclear	Insufficent information to make the judgement.
Free of other bias?	Unclear	Insufficent information to make the judgement.

Ceriani 1992

Methods	Method of treatment allocation: unclear. Placebo used. Sample size calculation not given. Probably an intention-to-treat analysis. Analysis restricted to 57 premature infants from 52 mothers born within 10 days of TRH treatment (26 babies in the TRH group and 31 babies in the placebo group). Losses to follow up unclear. Source of funding not stated.
Participants	Location: Buenos Aires, Argentina. 52 women at a gestational age between 26 - < 31 weeks who delivered 57 infants within 10 days of treatment. No exclusion criteria reported
Interventions	200 mcg of TRH or placebo x 2 every 12 hours (total 400 mcg). Betamethasone to all women
Outcomes	Respiratory distress syndrome; need for and duration of oxygen; duration of ventilation; bronchopulmonary dysplasia
Notes	Use of surfactant not reported. Final report not available.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Within the abstract, described as "randomised trial"; no information was available on randomisation methods
Allocation concealment?	Unclear	No information was available on allocation concealment.
Blinding? All outcomes	Yes	Described as "double blind"; placebo used.
Incomplete outcome data addressed? All outcomes	Unclear	No details was given on loss to follow up; probably an intention-to-treat analysis
Free of selective reporting?	Unclear	Insufficent information to make the judgement.

Free of other bias?	Unclear	Insufficent information to make the judgement.

Chile 1998

Methods	Method of treatment allocation: computerised randomisation program. Stratification by centre. Placebo used. Sample size calculation. Intention-to-treat analyses. Losses to follow up at hospital discharge 21/370 (5.7%). Source of funding: Fondo Nacional de Ciencia Tecnologia grant no. 193-0854
Participants	Location: 7 maternity centres in Chile between 1993-1996. 370 women with a singleton gestation between 24 - < 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
Interventions	400 mcg of TRH or placebo in 50 ml saline as a 30 minute infusion x 4 every 8 hours (total 1600 mcg). Only 1 course of TRH was given. Betamethasone to all women
Outcomes	Primary outcomes: respiratory distress syndrome; need for oxygen therapy at 28 days; neonatal mortality. Secondary outcomes: need for and duration of mechanical ventilation; air leaks; intracranial haemorrhage; patent ductus arteriosus; pulmonary haemorrhage; necrotising enterocolitis; infectious complications
Notes	Surfactant was given after birth to all infants weighing < 1 kg and to other infants if signs of respiratory distress were present

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Randomisation: computerised randomisation program.
Allocation concealment?	Yes	Quote: 'use of a computerised randomisation program including stratification by centre'
Blinding? All outcomes	Yes	Quote: 'the content of these vials remained blinded for all patients, investigators, and clinicians until the trial was finalized'; placebo used
Incomplete outcome data addressed? All outcomes	Yes	Intention-to-treat analyses. Losses to follow up at hospital discharge 21/370 (5.7%; 8

Chile 1998 (*Continued*)

		in the TRH group and 13 in the placebo group, due to either delivered elsewhere or lost to follow up)
Free of selective reporting?	Yes	No obvious risk of selective reporting.
Free of other bias?	Yes	No obvious risk of other bias.

Europe 1999

Methods	Method of treatment allocation: central telephone randomisation service. Minimisation by centre, gestational age, labour and membrane status and whether the pregnancy was multiple. Placebo used. Sample size calculation. Intention-to-treat analyses. Losses to follow up at hospital discharge 1/225 (< 1%). Source of funding: Medical Research Council, UK; The European Union and UCB Pharm. The drugs were supplied by UCB Pharm
Participants	Location: 31 centres in Europe between 1996-1997. 225 women where the risk of preterm delivery was sufficient to prescribe prenatal corticosteroids, at a gestational age between 25-30 weeks for the Thyroneth trial and < 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 mcg 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 mcg). 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 respiratory distress syndrome or died within 72 hours of birth. Secondary outcomes: need to stop the infusion because of side effects; major neonatal morbidity
Notes	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

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Randomisation: a central telephone randomisation service.
Allocation concealment?	Yes	Central randomisation service used.

Europe 1999 (*Continued*)

Blinding? All outcomes	Yes	The caregivers, the women, pregnancy outcome assessors were all blinded (placebo used)
Incomplete outcome data addressed? All outcomes	Yes	Losses to follow up at hospital discharge 1/225 (< 1%); intention-to-treat analyses
Free of selective reporting?	Yes	No obvious risk of selective reporting.
Free of other bias?	Yes	Trial was stopped early due to new information becoming available from two other trials shortly after the start of recruitment to the trial

Jikihara 1990

Methods	Method of treatment allocation: unclear. Reports states 'randomly assigned'. Placebo not used. Sample size calculation not stated. Probably an intention-to-treat analysis. Losses to follow up at hospital discharge not stated. Source of funding not stated.
Participants	Location: single centre study from Osaka, Japan between 1988-1990. 80 women with threatened preterm labour with or without ruptured membranes between 23 to < 30 weeks' gestation, (63 infants in the TRH group and 61 in the control group). Exclusion criteria not stated
Interventions	400 mcg of TRH iv x 4 every 8 hours (total 1600 mcg) compared with no treatment. Betamethasone 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	Surfactant used for some babies. Final report not available.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Within this abstract, described as "randomly assigned"; no other details given
Allocation concealment?	Unclear	Insufficent information to make the judgement.
Blinding? All outcomes	Unclear	Placebo not used; no other information was available.

Jikihara 1990 (*Continued*)

Incomplete outcome data addressed? All outcomes	Unclear	Probably an intention-to-treat analysis. Losses to follow up at hospital discharge not stated
Free of selective reporting?	Unclear	Insufficent information to make the judgement.
Free of other bias?	Unclear	Insufficent information to make the judgement.

Kim 2000

Methods	Method of treatment allocation: 'were randomised'. No stratification stated. No use of placebo stated. Probably an intention-to-treat analysis. No sample size calculation given. No losses to follow up stated
Participants	Location: single centre study from Seoul, Korea. 61 women with preterm labour at 26-34 weeks' gestation (30 in the TRH and dexamethasone group vs 31 in the dexamethasone alone group
Interventions	400 mcg 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: respiratory distress syndrome. Other outcomes: changes of surfactant synthesis; and various neonatal outcomes
Notes	Use of surfactant not stated.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Within this abstract, described as "participants were randomised into a study group or a control group". No details was given on randomisation methods
Allocation concealment?	Unclear	No information was given on allocation concealment.
Blinding? All outcomes	Unclear	No details on blinding; placebo not used.
Incomplete outcome data addressed? All outcomes	Unclear	No information given on losses to follow up.

Kim 2000 (*Continued*)

Free of selective reporting?	Unclear	Insufficent information to make the judgement.
Free of other bias?	Unclear	Insufficent information to make the judgement.

Knight 1994

Methods	Method of treatment allocation: women were randomised from random number tables in blocks of 100 to receive either TRH or placebo. Drugs prepared by hospital pharmacist in sets of identical, serially numbered vials. Blinding of investigators, patients and clinicians. Placebo used. Sample size calculation. Intention-to-treat analyses. Losses to follow up at hospital discharge 9/418 (2.2%) babies. Source of funding: not stated.
Participants	Location: single centre study from Auckland, New Zealand between 1985-1990. 378 women at risk of preterm delivery sufficient to use prenatal corticosteroids between 24-33 weeks' gestation (183 in the TRH group vs 195 in the placebo group). These women delivered 418 infants (405 liveborn)
Interventions	400 mcg of TRH or placebo as iv bolus (1 minute) x 4 every 12 hours (total 1600 mcg) . Betamethasone to all women
Outcomes	Primary outcomes: respiratory distress syndrome; chronic lung disease. Secondary outcomes: death; other complications of prematurity (intraventricular haemorrhage, patent ductus arteriosus, necrotising enterocolitis, retinopathy of prematurity) . Maternal side-effects
Notes	Surfactant was not available.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	By using random number tables.
Allocation concealment?	Yes	Drugs prepared by hospital pharmacist in sets of identical, serially numbered vials
Blinding? All outcomes	Yes	Investigators, patients and clinicians were blinded. Placebo used
Incomplete outcome data addressed? All outcomes	Yes	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)

Knight 1994 (*Continued*)

Free of selective reporting?	Yes	No obvious risk of selective reporting.
Free of other bias?	Yes	No obvious risk of other bias.

Morales 1989

Methods	Method of treatment allocation: unclear. Report states 'randomised into 2 groups by means of sealed envelopes blocked for gestational age'. Placebo not used. Sample size calculation not given. Not an intention-to-treat analysis. 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. Post randomisation exclusions of pregnancies complicated by lethal anomalies or L/S ratios of 2 or more. Source of funding: not stated.
Participants	Location: single centre study from Tampa, Florida, USA between 1986-1987. 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 mcg of TRH iv x 6 every 8 hours (total 2400 mcg) compared with no treatment. Betamethasone 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	Surfactant not available for use.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Quote: "'randomised into two groups by means of sealed envelopes blocked for gestational age"
Allocation concealment?	Unclear	No detail was given on allocation concealment.
Blinding? All outcomes	Yes	The perinatal research nurse who record 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 addressed? All outcomes	No	Not an intention-to-treat analysis. Infant outcomes restricted to 100 infants (50 in the TRH group and 50 in the control

Morales 1989 (*Continued*)

		group) delivered by 1 week from the start of therapy
Free of selective reporting?	No	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
Free of other bias?	Yes	No other obvious risk of bias.

IM: intramuscular
iv: intravenous
L/S: lecithin/sphyngomyelin
mcg: micrograms
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
Crowther 1995a	The aim of the trial was to assess the effects of 200 mcg and 400 mcg of maternally administered TRH or saline control on cord and neonatal blood levels of TSH, and thyroid hormone levels in 26 infants. No clinically meaningful data available in a format suitable for inclusion
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. No clinically meaningful data available in a format suitable for inclusion
Dola 1997	No clinically meaningful data available in a format suitable for inclusion. 1 placebo group did not receive corticosteroids.
Roti 1990	Trial comparing thyroid hormone and prolactin levels in neonatal blood following TRH administration. No clinically meaningful data available in a format suitable for inclusion
Torres 1994	Comparison of neonatal T4 levels in 112 infants either exposed to 400 mcg TRH doses x 6 or not. Unclear if a randomised trial. No clinical data available in a format suitable for inclusion
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 mcg, 200 mcg, 400 mcg of TRH or saline placebo. No clinically meaningful data available in a format suitable for inclusion

(*Continued*)

Voto 1998	The aim of the trial was to compare TSH, thyroid hormone and prolactin levels on fetal blood in 35 women who had received 400 mcg doses of TRH or placebo. No clinically meaningful data available in a format suitable for inclusion
Yoder 1997	Trial stopped without enrolling any women due to the infeasibility of having a placebo controlled group

mcg: microgram
TRH: thyrotropin-releasing hormone
TSH: thyroid stimulating hormone

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

Pearlman 1997

Trial name or title	Trial to compare steroids vs steroids + TRH to mothers at 23-28 weeks with PROM
Methods	
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

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 Need for oxygen therapy or death at 28 days	6	3694	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.95, 1.18]
3 Need for oxygen therapy >= 28 days	5	2511	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.85, 1.19]
4 Need for oxygen therapy	4	2387	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.97, 1.13]
5 Respiratory distress syndrome	9	3833	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.98, 1.16]
6 Severe respiratory distress syndrome	3	2119	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.69, 1.04]
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]
9 Periventricular haemorrhage	6	3645	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.93, 1.26]
10 Severe periventricular 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, Fixed, 95% CI)	1.09 [0.83, 1.45]
12 Pulmonary haemorrhage	3	1969	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.36, 1.52]
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, Fixed, 95% CI)	1.01 [0.86, 1.19]
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 Maternal nausea	3	2370	Risk Ratio (M-H, Fixed, 95% CI)	3.92 [3.13, 4.92]
18 Maternal vomiting	1	1011	Risk Ratio (M-H, Fixed, 95% CI)	2.35 [1.35, 4.09]
19 Maternal light headedness	1	1011	Risk Ratio (M-H, Fixed, 95% CI)	1.73 [1.36, 2.22]
20 Urgency of micturition	1	1011	Risk Ratio (M-H, Fixed, 95% CI)	2.39 [1.75, 3.27]
21 Maternal facial flushing	3	2523	Risk Ratio (M-H, Fixed, 95% CI)	2.67 [2.26, 3.16]
22 Maternal systolic blood pressure rise >= 25 mmHg	1	1011	Risk Ratio (M-H, Fixed, 95% CI)	1.80 [1.05, 3.06]
23 Maternal diastolic blood pressure rise >= 15 mmHg	1	1011	Risk Ratio (M-H, Fixed, 95% CI)	1.62 [1.24, 2.12]
24 Gestational age at birth	2	1563	Mean Difference (IV, Fixed, 95% CI)	-0.43 [-0.86, 0.01]
25 Any neurodevelopmental abnormality at follow up	1	39	Risk Ratio (M-H, Fixed, 95% CI)	4.75 [0.61, 37.01]
26 Motor delay at follow up	1	971	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [1.09, 1.56]
27 Motor impairment at follow up	1	972	Risk Ratio (M-H, Fixed, 95% CI)	1.51 [1.01, 2.24]
28 Fine motor delay at follow up	1	926	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.91, 1.32]
29 Sensory impairment at follow up	1	1004	Risk Ratio (M-H, Fixed, 95% CI)	1.97 [1.10, 3.53]
30 Language delay at follow up	1	1004	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.93, 1.54]
31 Social delay at follow up	1	966	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [1.03, 1.51]
32 Bayley Mental Developmental Index	1	39	Mean Difference (IV, Fixed, 95% CI)	-15.70 [-30.86, -0.54]

33 Bayley Psychomotor Developmental Index	1	39	Mean Difference (IV, Fixed, 95% CI)	-5.0 [-13.90, 3.90]

Comparison 2. 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]
2 Need for oxygen therapy or death at 28 days	5	3570	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.94, 1.17]
3 Need for oxygen therapy >= 28 days	4	2387	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.84, 1.18]
4 Need for oxygen therapy	4	2387	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.97, 1.13]
5 Respiratory distress syndrome	5	3521	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.98, 1.17]
6 Severe respiratory distress syndrome	3	2119	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.69, 1.04]
7 Use of respiratory support	3	1969	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [1.03, 1.29]

Comparison 3. TRH + steroids versus steroids alone (birth < 24 hours after first dose)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death prior to hospital discharge	4	245	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.49, 1.53]
2 Need for oxygen therapy or death at 28 days	5	457	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.74, 1.08]
3 Need for oxygen therapy >= 28 days	5	306	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.54, 1.13]
4 Need for oxygen therapy	1	155	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.85, 1.07]
5 Respiratory distress syndrome	5	495	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.87, 1.10]
6 Severe respiratory distress syndrome	3	270	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.57, 1.30]
7 Use of respiratory support	1	155	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.82, 1.19]

Comparison 4. TRH + steroids versus steroids alone (birth >= 24 hours to <= 10 days after first dose)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death prior to hospital discharge	5	1164	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.69, 1.22]
2 Need for oxygen therapy or death at 28 days	5	1317	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.84, 1.09]
3 Need for oxygen therapy >= 28 days	5	1152	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.77, 1.12]
4 Need for oxygen therapy	2	577	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.92, 1.08]
5 Respiratory distress syndrome	6	1485	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.86, 1.06]
6 Severe respiratory distress syndrome	3	874	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.49, 0.85]
7 Use of respiratory support	2	577	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.93, 1.17]

Comparison 5. TRH + steroids versus steroids alone (birth > 10 days after first dose)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death prior to hospital discharge	4	1129	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.78, 2.29]
2 Need for oxygen therapy or death at 28 days	5	1685	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [1.02, 1.78]
3 Need for oxygen therapy >= 28 days	4	1116	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.81, 2.10]
4 Need for oxygen therapy	1	708	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.88, 1.42]
5 Respiratory distress syndrome	4	1555	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [1.05, 1.69]
6 Severe respiratory distress syndrome	2	887	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.62, 1.82]
7 Use of respiratory support	1	708	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [0.94, 1.91]

Comparison 6. TRH (400 mcg treatment dosage) + 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	5	2297	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.77, 1.23]
2 Need for oxygen therapy or death at 28 days	5	2297	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.92, 1.19]
3 Need for oxygen therapy >= 28 days	4	1142	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.73, 1.23]
4 Need for oxygen therapy	3	1018	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.93, 1.18]
5 Respiratory distress syndrome	6	2300	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.79, 1.23]
6 Severe respiratory distress syndrome	2	750	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.60, 1.13]

7 Use of respiratory support	2	600	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.95, 1.46]

Comparison 7. TRH (200 mcg treatment dose) + 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	1	1397	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.87, 1.75]
2 Need for oxygen therapy or death at 28 days	1	1397	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.91, 1.30]
3 Need for oxygen therapy >= 28 days	1	1369	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.84, 1.30]
4 Need for oxygen therapy	1	1369	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.95, 1.16]
5 Respiratory distress syndrome	1	1369	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [1.00, 1.36]
6 Severe respiratory distress syndrome	1	1369	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.66, 1.14]
7 Use of respiratory support	1	1369	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [1.01, 1.31]

Comparison 8. 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	7	1150	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.68, 1.19]
2 Need for oxygen therapy or death at 28 days	5	1317	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.84, 1.09]
3 Need for oxygen therapy >= 28 days	5	981	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.79, 1.17]
4 Need for oxygen therapy	1	506	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.91, 1.09]
5 Respiratory distress syndrome	8	1535	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.82, 1.02]
6 Severe respiratory distress syndrome	2	694	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.49, 0.86]
7 Use of respiratory support	1	506	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.94, 1.22]

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

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

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

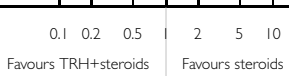
Outcome: 1 Death prior to hospital discharge

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	64/699	52/698		29.5 %	1.23 [0.87, 1.75]
Ballard 1998	54/563	52/571		29.2 %	1.05 [0.73, 1.51]
Chile 1998	28/180	24/166		14.1 %	1.08 [0.65, 1.78]
Europe 1999	8/136	17/139		9.5 %	0.48 [0.21, 1.08]
Jikihara 1990	10/63	6/61		3.5 %	1.61 [0.62, 4.17]
Knight 1994	21/201	26/217		14.2 %	0.87 [0.51, 1.50]
Total (95% CI)	**1842**	**1852**		**100.0 %**	**1.05 [0.86, 1.27]**

Total events: 185 (TRH+steroids), 177 (Steroids)

Heterogeneity: $Chi^2 = 5.63$, df = 5 (P = 0.34); $I^2 = 11\%$

Test for overall effect: Z = 0.46 (P = 0.64)



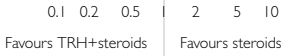
Analysis 1.2. Comparison 1 TRH + steroids versus steroids alone (intention to treat), Outcome 2 Need for oxygen therapy or death at 28 days.

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

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

Outcome: 2 Need for oxygen therapy or death at 28 days

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	185/699	170/698		35.2 %	1.09 [0.91, 1.30]
Ballard 1998	178/563	159/571		32.6 %	1.14 [0.95, 1.36]
Chile 1998	40/180	33/166		7.1 %	1.12 [0.74, 1.68]
Europe 1999	34/136	43/139		8.8 %	0.81 [0.55, 1.18]
Jikihara 1990	26/63	19/61		4.0 %	1.32 [0.82, 2.13]
Knight 1994	49/201	62/217		12.3 %	0.85 [0.62, 1.18]
Total (95% CI)	**1842**	**1852**		**100.0 %**	**1.06 [0.95, 1.18]**
Total events: 512 (TRH+steroids), 486 (Steroids)					
Heterogeneity: Chi^2 = 5.22, df = 5 (P = 0.39); I^2 =4%					
Test for overall effect: Z = 1.10 (P = 0.27)					



Analysis 1.3. Comparison 1 TRH + steroids versus steroids alone (intention to treat), Outcome 3 Need for oxygen therapy >= 28 days.

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

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

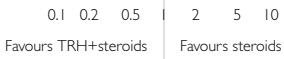
Outcome: 3 Need for oxygen therapy >= 28 days

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	135/684	129/685		57.4 %	1.05 [0.84, 1.30]
Chile 1998	14/172	10/160		4.6 %	1.30 [0.60, 2.85]
Europe 1999	29/136	30/132		13.6 %	0.94 [0.60, 1.47]
Jikihara 1990	18/63	15/61		6.8 %	1.16 [0.65, 2.09]
Knight 1994	30/201	41/217		17.6 %	0.79 [0.51, 1.21]
Total (95% CI)	**1256**	**1255**		**100.0 %**	**1.01 [0.85, 1.19]**

Total events: 226 (TRH+steroids), 225 (Steroids)

Heterogeneity: Chi^2 = 2.09, df = 4 (P = 0.72); I^2 =0.0%

Test for overall effect: Z = 0.09 (P = 0.93)



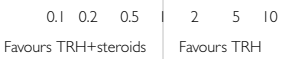
Analysis 1.4. Comparison 1 TRH + steroids versus steroids alone (intention to treat), Outcome 4 Need for oxygen therapy.

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

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

Outcome: 4 Need for oxygen therapy

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	371/684	354/685		58.0 %	1.05 [0.95, 1.16]
Chile 1998	91/172	75/160		12.7 %	1.13 [0.91, 1.40]
Europe 1999	75/136	65/132		10.8 %	1.12 [0.89, 1.41]
Knight 1994	102/201	117/217		18.4 %	0.94 [0.78, 1.13]
Total (95% CI)	**1193**	**1194**		**100.0 %**	**1.05 [0.97, 1.13]**
Total events: 639 (TRH+steroids), 611 (Steroids)					
Heterogeneity: Chi^2 = 2.09, df = 3 (P = 0.55); I^2 =0.0%					
Test for overall effect: Z = 1.18 (P = 0.24)					



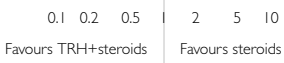
Analysis 1.5. Comparison 1 TRH + steroids versus steroids alone (intention to treat), Outcome 5 Respiratory distress syndrome.

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

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

Outcome: 5 Respiratory distress syndrome

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
Abuhamad 1999	23/55	18/48		2.9 %	1.12 [0.69, 1.80]
ACTOBAT 1995	242/684	208/685		31.2 %	1.17 [1.00, 1.36]
Ballard 1998	265/563	257/571		38.3 %	1.05 [0.92, 1.19]
Carlan 1991	5/13	1/11		0.2 %	4.23 [0.58, 30.99]
Chile 1998	41/172	29/160		4.5 %	1.32 [0.86, 2.01]
Europe 1999	59/136	49/132		7.5 %	1.17 [0.87, 1.57]
Jikihara 1990	19/63	27/61		4.1 %	0.68 [0.43, 1.09]
Kim 2000	13/30	9/31		1.3 %	1.49 [0.75, 2.96]
Knight 1994	45/201	69/217		10.0 %	0.70 [0.51, 0.97]
Total (95% CI)	**1917**	**1916**		**100.0 %**	**1.07 [0.98, 1.16]**
Total events: 712 (TRH+steroids), 667 (Steroids)					
Heterogeneity: Chi^2 = 15.35, df = 8 (P = 0.05); I^2 =48%					
Test for overall effect: Z = 1.55 (P = 0.12)					



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

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

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

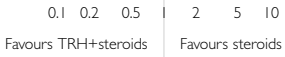
Outcome: 6 Severe respiratory distress syndrome

Study or subgroup	TRH+steorids n/N	Steroids n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
ACTOBAT 1995	85/684	98/685		57.8 %	0.87 [0.66, 1.14]
Chile 1998	30/172	19/160		11.6 %	1.47 [0.86, 2.50]
Knight 1994	29/201	54/217		30.6 %	0.58 [0.39, 0.87]
Total (95% CI)	**1057**	**1062**		**100.0 %**	**0.85 [0.69, 1.04]**

Total events: 144 (TRH+steorids), 171 (Steroids)

Heterogeneity: Chi^2 = 7.44, df = 2 (P = 0.02); I^2 =73%

Test for overall effect: Z = 1.55 (P = 0.12)



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

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

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

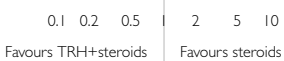
Outcome: 7 Use of respiratory support

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	292/684	255/685		72.2 %	1.15 [1.01, 1.31]
Chile 1998	58/172	43/160		12.6 %	1.25 [0.90, 1.75]
Europe 1999	61/136	53/132		15.2 %	1.12 [0.84, 1.48]
Total (95% CI)	**992**	**977**		**100.0 %**	**1.16 [1.03, 1.29]**

Total events: 411 (TRH+steroids), 351 (Steroids)

Heterogeneity: Chi^2 = 0.31, df = 2 (P = 0.86); I^2 =0.0%

Test for overall effect: Z = 2.55 (P = 0.011)



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

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

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

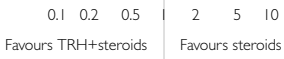
Outcome: 8 Admission to neonatal intensive care unit

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	472/684	450/685		80.7 %	1.05 [0.98, 1.13]
Europe 1999	109/136	106/132		19.3 %	1.00 [0.89, 1.12]
Total (95% CI)	**820**	**817**		**100.0 %**	**1.04 [0.98, 1.11]**

Total events: 581 (TRH+steroids), 556 (Steroids)

Heterogeneity: $Chi^2 = 0.53$, df = 1 (P = 0.47); $I^2 = 0.0\%$

Test for overall effect: Z = 1.21 (P = 0.23)



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

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

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

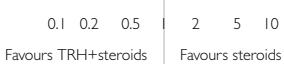
Outcome: 9 Periventricular haemorrhage

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	93/684	86/685		32.9 %	1.08 [0.82, 1.42]
Ballard 1998	124/563	117/571		44.5 %	1.07 [0.86, 1.35]
Chile 1998	19/172	17/160		6.7 %	1.04 [0.56, 1.93]
Europe 1999	11/136	9/132		3.5 %	1.19 [0.51, 2.77]
Jikihara 1990	7/63	10/61		3.9 %	0.68 [0.28, 1.67]
Knight 1994	28/201	23/217		8.5 %	1.31 [0.78, 2.20]
Total (95% CI)	**1819**	**1826**		**100.0 %**	**1.08 [0.93, 1.26]**

Total events: 282 (TRH+steroids), 262 (Steroids)

Heterogeneity: $Chi^2 = 1.65$, df = 5 (P = 0.90); $I^2 = 0.0\%$

Test for overall effect: Z = 1.03 (P = 0.30)



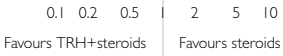
Analysis 1.10. Comparison 1 TRH + steroids versus steroids alone (intention to treat), Outcome 10 Severe periventricular haemorrhage.

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

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

Outcome: 10 Severe periventricular haemorrhage

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	13/684	16/685		25.0 %	0.81 [0.39, 1.68]
Ballard 1998	38/563	32/571		49.8 %	1.20 [0.76, 1.90]
Europe 1999	11/136	9/132		14.3 %	1.19 [0.51, 2.77]
Jikihara 1990	5/63	4/61		6.4 %	1.21 [0.34, 4.30]
Knight 1994	5/201	3/217		4.5 %	1.80 [0.44, 7.43]
Total (95% CI)	**1647**	**1666**		**100.0 %**	**1.13 [0.82, 1.57]**
Total events: 72 (TRH+steroids), 64 (Steroids)					
Heterogeneity: Chi^2 = 1.30, df = 4 (P = 0.86); I^2 =0.0%					
Test for overall effect: Z = 0.74 (P = 0.46)					



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

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

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

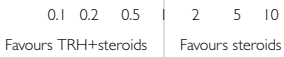
Outcome: 11 Air leak syndrome

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	41/684	44/685		49.4 %	0.93 [0.62, 1.41]
Ballard 1998	32/563	30/571		33.4 %	1.08 [0.67, 1.76]
Chile 1998	18/172	5/160		5.8 %	3.35 [1.27, 8.81]
Europe 1999	7/136	10/132		11.4 %	0.68 [0.27, 1.73]
Total (95% CI)	**1555**	**1548**		**100.0 %**	**1.09 [0.83, 1.45]**

Total events: 98 (TRH+steroids), 89 (Steroids)

Heterogeneity: Chi² = 6.71, df = 3 (P = 0.08); I² =55%

Test for overall effect: Z = 0.63 (P = 0.53)



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

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

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

Outcome: 12 Pulmonary haemorrhage

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	3/684	11/685		64.0 %	0.27 [0.08, 0.97]
Chile 1998	7/172	4/160		24.1 %	1.63 [0.49, 5.46]
Europe 1999	3/136	2/132		11.8 %	1.46 [0.25, 8.57]
Total (95% CI)	**992**	**977**		**100.0 %**	**0.74 [0.36, 1.52]**

Total events: 13 (TRH+steroids), 17 (Steroids)

Heterogeneity: Chi² = 4.55, df = 2 (P = 0.10); I² =56%

Test for overall effect: Z = 0.82 (P = 0.41)

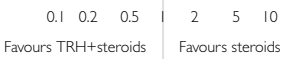
Analysis 1.13. Comparison 1 TRH + steroids versus steroids alone (intention to treat), Outcome 13 Necrotising enterocolitis.

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

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

Outcome: 13 Necrotising enterocolitis

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	26/684	29/685		47.3 %	0.90 [0.53, 1.51]
Ballard 1998	19/563	18/571		29.2 %	1.07 [0.57, 2.02]
Chile 1998	6/172	11/160		18.6 %	0.51 [0.19, 1.34]
Europe 1999	5/136	3/132		5.0 %	1.62 [0.39, 6.63]
Total (95% CI)	**1555**	**1548**		**100.0 %**	**0.91 [0.64, 1.30]**
Total events: 56 (TRH+steroids), 61 (Steroids)					
Heterogeneity: Chi^2 = 2.28, df = 3 (P = 0.52); I^2 =0.0%					
Test for overall effect: Z = 0.51 (P = 0.61)					



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

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

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

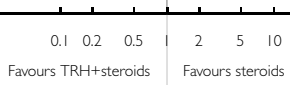
Outcome: 14 Patent ductus arteriosus

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	75/684	68/685		27.4 %	1.10 [0.81, 1.51]
Ballard 1998	100/563	102/571		40.8 %	0.99 [0.77, 1.28]
Chile 1998	28/172	21/160		8.8 %	1.24 [0.74, 2.09]
Europe 1999	21/136	13/132		5.3 %	1.57 [0.82, 3.00]
Jikihara 1990	15/63	16/61		6.5 %	0.91 [0.49, 1.67]
Knight 1994	12/201	29/217		11.2 %	0.45 [0.23, 0.85]
Total (95% CI)	**1819**	**1826**		**100.0 %**	**1.01 [0.86, 1.19]**

Total events: 251 (TRH+steroids), 249 (Steroids)

Heterogeneity: Chi^2 = 8.96, df = 5 (P = 0.11); I^2 =44%

Test for overall effect: Z = 0.11 (P = 0.91)



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

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

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

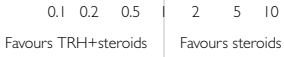
Outcome: 15 Low Apgar score at 5 minutes

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	103/684	66/685		79.0 %	1.56 [1.17, 2.09]
Chile 1998	18/172	14/160		17.4 %	1.20 [0.62, 2.32]
Europe 1999	3/136	3/132		3.6 %	0.97 [0.20, 4.72]
Total (95% CI)	**992**	**977**		**100.0 %**	**1.48 [1.14, 1.92]**

Total events: 124 (TRH+steroids), 83 (Steroids)

Heterogeneity: Chi^2 = 0.80, df = 2 (P = 0.67); I^2 =0.0%

Test for overall effect: Z = 2.92 (P = 0.0035)



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

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

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

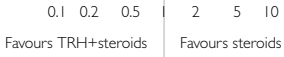
Outcome: 16 Use of surfactant

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	81/684	69/685		20.3 %	1.18 [0.87, 1.59]
Ballard 1998	217/563	202/571		58.9 %	1.09 [0.94, 1.27]
Chile 1998	41/172	36/160		11.0 %	1.06 [0.72, 1.57]
Europe 1999	37/136	33/132		9.8 %	1.09 [0.73, 1.63]
Total (95% CI)	**1555**	**1548**		**100.0 %**	**1.10 [0.98, 1.25]**

Total events: 376 (TRH+steroids), 340 (Steroids)

Heterogeneity: Chi^2 = 0.24, df = 3 (P = 0.97); I^2 =0.0%

Test for overall effect: Z = 1.56 (P = 0.12)



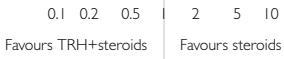
Analysis 1.17. Comparison 1 TRH + steroids versus steroids alone (intention to treat), Outcome 17 Maternal nausea.

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

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

Outcome: 17 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		86.6 %	3.69 [2.91, 4.70]
Ballard 1998	53/486	10/495		12.8 %	5.40 [2.78, 10.49]
Knight 1994	2/183	0/195		0.6 %	5.33 [0.26, 110.20]
Total (95% CI)	**1175**	**1195**		**100.0 %**	**3.92 [3.13, 4.92]**
Total events: 303 (TRH+steroids), 77 (Steroids)					
Heterogeneity: Chi^2 = 1.17, df = 2 (P = 0.56); I^2 =0.0%					
Test for overall effect: Z = 11.85 (P < 0.00001)					



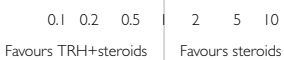
Analysis 1.18. Comparison 1 TRH + steroids versus steroids alone (intention to treat), Outcome 18 Maternal vomiting.

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

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

Outcome: 18 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		100.0 %	2.35 [1.35, 4.09]
Total (95% CI)	**506**	**505**		**100.0 %**	**2.35 [1.35, 4.09]**
Total events: 40 (TRH+steroids), 17 (Steroids)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.02 (P = 0.0025)					



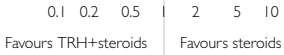
Analysis 1.19. Comparison 1 TRH + steroids versus steroids alone (intention to treat), Outcome 19 Maternal light headedness.

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

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

Outcome: 19 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		100.0 %	1.73 [1.36, 2.22]
Total (95% CI)	**506**	**505**		**100.0 %**	**1.73 [1.36, 2.22]**
Total events: 139 (TRH+steroids), 80 (Steroids)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.39 (P = 0.000011)					



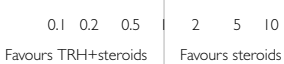
Analysis 1.20. Comparison 1 TRH + steroids versus steroids alone (intention to treat), Outcome 20 Urgency of micturition.

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

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

Outcome: 20 Urgency of micturition

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	115/506	48/505		100.0 %	2.39 [1.75, 3.27]
Total (95% CI)	**506**	**505**		**100.0 %**	**2.39 [1.75, 3.27]**
Total events: 115 (TRH+steroids), 48 (Steroids)					
Heterogeneity: not applicable					
Test for overall effect: Z = 5.45 (P < 0.00001)					



Analysis 1.21. Comparison 1 TRH + steroids versus steroids alone (intention to treat), Outcome 21 Maternal facial flushing.

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

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

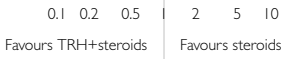
Outcome: 21 Maternal facial flushing

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	233/506	86/505		57.7 %	2.70 [2.18, 3.35]
Ballard 1998	163/563	63/571		41.9 %	2.62 [2.01, 3.43]
Knight 1994	1/183	0/195		0.3 %	3.20 [0.13, 77.95]
Total (95% CI)	**1252**	**1271**		**100.0 %**	**2.67 [2.26, 3.16]**

Total events: 397 (TRH+steroids), 149 (Steroids)

Heterogeneity: Chi^2 = 0.04, df = 2 (P = 0.98); I^2 =0.0%

Test for overall effect: Z = 11.53 (P < 0.00001)



Analysis 1.22. Comparison 1 TRH + steroids versus steroids alone (intention to treat), Outcome 22 Maternal systolic blood pressure rise >= 25 mmHg.

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

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

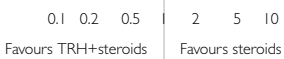
Outcome: 22 Maternal systolic blood pressure rise >= 25 mmHg

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	36/506	20/505		100.0 %	1.80 [1.05, 3.06]
Total (95% CI)	**506**	**505**		**100.0 %**	**1.80 [1.05, 3.06]**

Total events: 36 (TRH+steroids), 20 (Steroids)

Heterogeneity: not applicable

Test for overall effect: Z = 2.16 (P = 0.031)



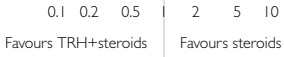
Analysis 1.23. Comparison 1 TRH + steroids versus steroids alone (intention to treat), Outcome 23 Maternal diastolic blood pressure rise >= 15 mmHg.

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

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

Outcome: 23 Maternal diastolic blood pressure rise >= 15 mmHg

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	115/506	71/505		100.0 %	1.62 [1.24, 2.12]
Total (95% CI)	**506**	**505**		**100.0 %**	**1.62 [1.24, 2.12]**
Total events: 115 (TRH+steroids), 71 (Steroids)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.50 (P = 0.00046)					



Analysis 1.24. Comparison 1 TRH + steroids versus steroids alone (intention to treat), Outcome 24 Gestational age at birth.

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

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

Outcome: 24 Gestational age at birth

Study or subgroup	TRH+steroids N	Mean(SD)	Steroids N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
ACTOBAT 1995	615	32.14 (4.63)	616	32.63 (4.84)		67.0 %	-0.49 [-1.02, 0.04]
Chile 1998	172	31.6 (3.4)	160	31.9 (3.6)		33.0 %	-0.30 [-1.05, 0.45]
Total (95% CI)	**787**		**776**			**100.0 %**	**-0.43 [-0.86, 0.01]**
Heterogeneity: Chi^2 = 0.16, df = 1 (P = 0.69); I^2 =0.0%							
Test for overall effect: Z = 1.93 (P = 0.053)							
Test for subgroup differences: Not applicable							

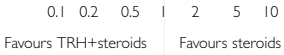
Analysis 1.25. Comparison 1 TRH + steroids versus steroids alone (intention to treat), Outcome 25 Any neurodevelopmental abnormality at follow up.

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

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

Outcome: 25 Any neurodevelopmental abnormality 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
Europe 1999	5/20	1/19		100.0 %	4.75 [0.61, 37.01]
Total (95% CI)	**20**	**19**		**100.0 %**	**4.75 [0.61, 37.01]**
Total events: 5 (TRH+steroids), 1 (Steroids)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.49 (P = 0.14)					



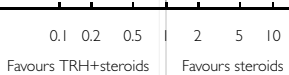
Analysis 1.26. Comparison 1 TRH + steroids versus steroids alone (intention to treat), Outcome 26 Motor delay at follow up.

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

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

Outcome: 26 Motor delay 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
ACTOBAT 1995	195/503	139/468		100.0 %	1.31 [1.09, 1.56]
Total (95% CI)	**503**	**468**		**100.0 %**	**1.31 [1.09, 1.56]**
Total events: 195 (TRH+steroids), 139 (Steroids)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.94 (P = 0.0033)					



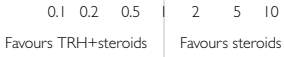
Analysis 1.27. Comparison 1 TRH + steroids versus steroids alone (intention to treat), Outcome 27 Motor impairment at follow up.

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

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

Outcome: 27 Motor impairment 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
ACTOBAT 1995	56/494	36/478		100.0 %	1.51 [1.01, 2.24]
Total (95% CI)	**494**	**478**		**100.0 %**	**1.51 [1.01, 2.24]**
Total events: 56 (TRH+steroids), 36 (Steroids)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.01 (P = 0.045)					



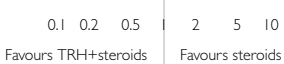
Analysis 1.28. Comparison 1 TRH + steroids versus steroids alone (intention to treat), Outcome 28 Fine motor delay at follow up.

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

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

Outcome: 28 Fine motor delay 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
ACTOBAT 1995	159/473	139/453		100.0 %	1.10 [0.91, 1.32]
Total (95% CI)	**473**	**453**		**100.0 %**	**1.10 [0.91, 1.32]**
Total events: 159 (TRH+steroids), 139 (Steroids)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.95 (P = 0.34)					



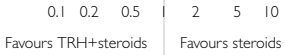
Analysis 1.29. Comparison 1 TRH + steroids versus steroids alone (intention to treat), Outcome 29 Sensory impairment at follow up.

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

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

Outcome: 29 Sensory impairment 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
ACTOBAT 1995	33/514	16/490		100.0 %	1.97 [1.10, 3.53]
Total (95% CI)	**514**	**490**		**100.0 %**	**1.97 [1.10, 3.53]**
Total events: 33 (TRH+steroids), 16 (Steroids)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.27 (P = 0.023)					



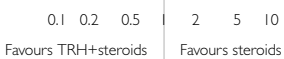
Analysis 1.30. Comparison 1 TRH + steroids versus steroids alone (intention to treat), Outcome 30 Language delay at follow up.

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

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

Outcome: 30 Language delay 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
ACTOBAT 1995	110/512	88/492		100.0 %	1.20 [0.93, 1.54]
Total (95% CI)	**512**	**492**		**100.0 %**	**1.20 [0.93, 1.54]**
Total events: 110 (TRH+steroids), 88 (Steroids)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.43 (P = 0.15)					



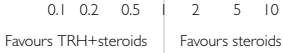
Analysis 1.31. Comparison 1 TRH + steroids versus steroids alone (intention to treat), Outcome 31 Social delay at follow up.

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

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

Outcome: 31 Social delay 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
ACTOBAT 1995	165/487	130/479		100.0 %	1.25 [1.03, 1.51]
Total (95% CI)	**487**	**479**		**100.0 %**	**1.25 [1.03, 1.51]**
Total events: 165 (TRH+steroids), 130 (Steroids)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.26 (P = 0.024)					



Analysis 1.32. Comparison 1 TRH + steroids versus steroids alone (intention to treat), Outcome 32 Bayley Mental Developmental Index.

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

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

Outcome: 32 Bayley Mental Developmental Index

Study or subgroup	TRH+steroids N	Mean(SD)	Steroids N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Europe 1999	18	90.8 (26.9)	21	106.5 (20.3)		100.0 %	-15.70 [-30.86, -0.54]
Total (95% CI)	**18**		**21**			**100.0 %**	**-15.70 [-30.86, -0.54]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.03 (P = 0.042)							
Test for subgroup differences: Not applicable							

Analysis 1.33. Comparison 1 TRH + steroids versus steroids alone (intention to treat), Outcome 33 Bayley Psychomotor Developmental Index.

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

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

Outcome: 33 Bayley Psychomotor Developmental Index

Study or subgroup	TRH+steroids N	Mean(SD)	Steroids N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Europe 1999	18	94.1 (15.8)	21	99.1 (11.9)		100.0 %	-5.00 [-13.90, 3.90]
Total (95% CI)	**18**		**21**			**100.0 %**	**-5.00 [-13.90, 3.90]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.10 (P = 0.27)

Test for subgroup differences: Not applicable

Analysis 2.1. Comparison 2 TRH + steroids versus steroids alone (high-quality trials), Outcome 1 Death prior to hospital discharge.

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

Comparison: 2 TRH + steroids versus steroids alone (high-quality trials)

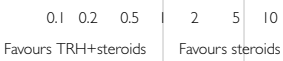
Outcome: 1 Death prior to hospital discharge

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	64/699	52/698		30.5 %	1.23 [0.87, 1.75]
Ballard 1998	54/563	52/571		30.3 %	1.05 [0.73, 1.51]
Chile 1998	28/180	24/166		14.6 %	1.08 [0.65, 1.78]
Europe 1999	8/136	17/139		9.9 %	0.48 [0.21, 1.08]
Knight 1994	21/201	26/217		14.7 %	0.87 [0.51, 1.50]
Total (95% CI)	**1779**	**1791**		**100.0 %**	**1.03 [0.84, 1.25]**

Total events: 175 (TRH+steroids), 171 (Steroids)

Heterogeneity: Chi^2 = 4.81, df = 4 (P = 0.31); I^2 =17%

Test for overall effect: Z = 0.26 (P = 0.79)



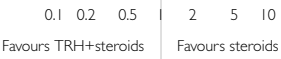
Analysis 2.2. Comparison 2 TRH + steroids versus steroids alone (high-quality trials), Outcome 2 Need for oxygen therapy or death at 28 days.

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

Comparison: 2 TRH + steroids versus steroids alone (high-quality trials)

Outcome: 2 Need for oxygen therapy or death at 28 days

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	185/699	170/698		36.6 %	1.09 [0.91, 1.30]
Ballard 1998	178/563	159/571		34.0 %	1.14 [0.95, 1.36]
Chile 1998	40/180	33/166		7.4 %	1.12 [0.74, 1.68]
Europe 1999	34/136	43/139		9.2 %	0.81 [0.55, 1.18]
Knight 1994	49/201	62/217		12.8 %	0.85 [0.62, 1.18]
Total (95% CI)	**1779**	**1791**		**100.0 %**	**1.05 [0.94, 1.17]**
Total events: 486 (TRH+steroids), 467 (Steroids)					
Heterogeneity: Chi^2 = 4.36, df = 4 (P = 0.36); I^2 =8%					
Test for overall effect: Z = 0.88 (P = 0.38)					



Analysis 2.3. Comparison 2 TRH + steroids versus steroids alone (high-quality trials), Outcome 3 Need for oxygen therapy >= 28 days.

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

Comparison: 2 TRH + steroids versus steroids alone (high-quality trials)

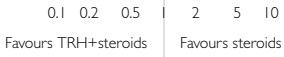
Outcome: 3 Need for oxygen therapy >= 28 days

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	135/684	129/685		61.6 %	1.05 [0.84, 1.30]
Chile 1998	14/172	10/160		5.0 %	1.30 [0.60, 2.85]
Europe 1999	29/136	30/132		14.6 %	0.94 [0.60, 1.47]
Knight 1994	30/201	41/217		18.9 %	0.79 [0.51, 1.21]
Total (95% CI)	**1193**	**1194**		**100.0 %**	**1.00 [0.84, 1.18]**

Total events: 208 (TRH+steroids), 210 (Steroids)

Heterogeneity: Chi^2 = 1.85, df = 3 (P = 0.60); I^2 =0.0%

Test for overall effect: Z = 0.05 (P = 0.96)



Analysis 2.4. Comparison 2 TRH + steroids versus steroids alone (high-quality trials), Outcome 4 Need for oxygen therapy.

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

Comparison: 2 TRH + steroids versus steroids alone (high-quality trials)

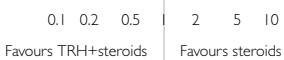
Outcome: 4 Need for oxygen therapy

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	371/684	354/685		58.0 %	1.05 [0.95, 1.16]
Chile 1998	91/172	75/160		12.7 %	1.13 [0.91, 1.40]
Europe 1999	75/136	65/132		10.8 %	1.12 [0.89, 1.41]
Knight 1994	102/201	117/217		18.4 %	0.94 [0.78, 1.13]
Total (95% CI)	**1193**	**1194**		**100.0 %**	**1.05 [0.97, 1.13]**

Total events: 639 (TRH+steroids), 611 (Steroids)

Heterogeneity: Chi^2 = 2.09, df = 3 (P = 0.55); I^2 =0.0%

Test for overall effect: Z = 1.18 (P = 0.24)



Analysis 2.5. Comparison 2 TRH + steroids versus steroids alone (high-quality trials), Outcome 5 Respiratory distress syndrome.

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

Comparison: 2 TRH + steroids versus steroids alone (high-quality trials)

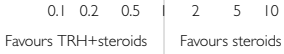
Outcome: 5 Respiratory distress syndrome

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	242/684	208/685		34.1 %	1.17 [1.00, 1.36]
Ballard 1998	265/563	257/571		41.9 %	1.05 [0.92, 1.19]
Chile 1998	41/172	29/160		4.9 %	1.32 [0.86, 2.01]
Europe 1999	59/136	49/132		8.2 %	1.17 [0.87, 1.57]
Knight 1994	45/201	69/217		10.9 %	0.70 [0.51, 0.97]
Total (95% CI)	**1756**	**1765**		**100.0 %**	**1.07 [0.98, 1.17]**

Total events: 652 (TRH+steroids), 612 (Steroids)

Heterogeneity: Chi^2 = 9.04, df = 4 (P = 0.06); I^2 =56%

Test for overall effect: Z = 1.57 (P = 0.12)



Analysis 2.6. Comparison 2 TRH + steroids versus steroids alone (high-quality trials), Outcome 6 Severe respiratory distress syndrome.

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

Comparison: 2 TRH + steroids versus steroids alone (high-quality trials)

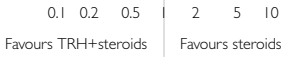
Outcome: 6 Severe respiratory distress syndrome

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	85/684	98/685		57.8 %	0.87 [0.66, 1.14]
Chile 1998	30/172	19/160		11.6 %	1.47 [0.86, 2.50]
Knight 1994	29/201	54/217		30.6 %	0.58 [0.39, 0.87]
Total (95% CI)	**1057**	**1062**		**100.0 %**	**0.85 [0.69, 1.04]**

Total events: 144 (TRH+steroids), 171 (Steroids)

Heterogeneity: Chi^2 = 7.44, df = 2 (P = 0.02); I^2 =73%

Test for overall effect: Z = 1.55 (P = 0.12)



Analysis 2.7. Comparison 2 TRH + steroids versus steroids alone (high-quality trials), Outcome 7 Use of respiratory support.

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

Comparison: 2 TRH + steroids versus steroids alone (high-quality trials)

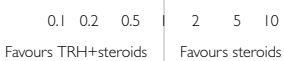
Outcome: 7 Use of respiratory support

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	292/684	255/685		72.2 %	1.15 [1.01, 1.31]
Chile 1998	58/172	43/160		12.6 %	1.25 [0.90, 1.75]
Europe 1999	61/136	53/132		15.2 %	1.12 [0.84, 1.48]
Total (95% CI)	**992**	**977**		**100.0 %**	**1.16 [1.03, 1.29]**

Total events: 411 (TRH+steroids), 351 (Steroids)

Heterogeneity: Chi^2 = 0.31, df = 2 (P = 0.86); I^2 =0.0%

Test for overall effect: Z = 2.55 (P = 0.011)



Analysis 3.1. Comparison 3 TRH + steroids versus steroids alone (birth < 24 hours after first dose), Outcome 1 Death prior to hospital discharge.

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

Comparison: 3 TRH + steroids versus steroids alone (birth < 24 hours after first dose)

Outcome: 1 Death prior to hospital discharge

Study or subgroup	TRH+steroids n/N	Steroids n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
ACTOBAT 1995	11/76	13/82		0.91 [0.44, 1.91]
Chile 1998	0/7	0/6		0.0 [0.0, 0.0]
Europe 1999	1/13	3/10		0.26 [0.03, 2.11]
Knight 1994	6/26	5/25		1.15 [0.40, 3.30]
Total (95% CI)	**122**	**123**		**0.87 [0.49, 1.53]**

Total events: 18 (TRH+steroids), 21 (Steroids)

Heterogeneity: Chi^2 = 1.59, df = 2 (P = 0.45); I^2 =0.0%

Test for overall effect: Z = 0.50 (P = 0.62)

Analysis 3.2. Comparison 3 TRH + steroids versus steroids alone (birth < 24 hours after first dose), Outcome 2 Need for oxygen therapy or death at 28 days.

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

Comparison: 3 TRH + steroids versus steroids alone (birth < 24 hours after first dose)

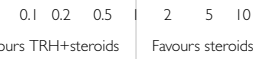
Outcome: 2 Need for oxygen therapy or death at 28 days

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	28/76	39/82		32.0 %	0.77 [0.53, 1.12]
Ballard 1998	60/108	60/104		52.1 %	0.96 [0.76, 1.22]
Chile 1998	2/7	0/6		0.5 %	4.38 [0.25, 76.54]
Europe 1999	7/13	7/10		6.7 %	0.77 [0.40, 1.47]
Knight 1994	9/26	10/25		8.7 %	0.87 [0.42, 1.77]
Total (95% CI)	**230**	**227**		**100.0 %**	**0.90 [0.74, 1.08]**

Total events: 106 (TRH+steroids), 116 (Steroids)

Heterogeneity: $Chi^2 = 2.35$, df = 4 (P = 0.67); $I^2 = 0.0\%$

Test for overall effect: Z = 1.15 (P = 0.25)



Analysis 3.3. Comparison 3 TRH + steroids versus steroids alone (birth < 24 hours after first dose), Outcome 3 Need for oxygen therapy >= 28 days.

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

Comparison: 3 TRH + steroids versus steroids alone (birth < 24 hours after first dose)

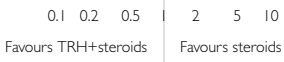
Outcome: 3 Need for oxygen therapy >= 28 days

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	19/76	31/79		63.4 %	0.64 [0.40, 1.03]
Ballard 1992a	7/29	7/35		13.2 %	1.21 [0.48, 3.04]
Chile 1998	2/7	0/6		1.1 %	4.38 [0.25, 76.54]
Europe 1999	6/13	4/10		9.4 %	1.15 [0.44, 3.01]
Knight 1994	3/26	6/25		12.8 %	0.48 [0.13, 1.72]
Total (95% CI)	**151**	**155**		**100.0 %**	**0.78 [0.54, 1.13]**

Total events: 37 (TRH+steroids), 48 (Steroids)

Heterogeneity: $Chi^2 = 4.14$, df = 4 (P = 0.39); $I^2 = 3\%$

Test for overall effect: Z = 1.32 (P = 0.19)



Analysis 3.4. Comparison 3 TRH + steroids versus steroids alone (birth < 24 hours after first dose), Outcome 4 Need for oxygen therapy.

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

Comparison: 3 TRH + steroids versus steroids alone (birth < 24 hours after first dose)

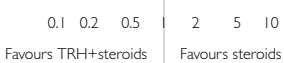
Outcome: 4 Need for oxygen therapy

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	65/76	71/79		100.0 %	0.95 [0.85, 1.07]
Total (95% CI)	**76**	**79**		**100.0 %**	**0.95 [0.85, 1.07]**

Total events: 65 (TRH+steroids), 71 (Steroids)

Heterogeneity: not applicable

Test for overall effect: Z = 0.82 (P = 0.41)



Analysis 3.5. Comparison 3 TRH + steroids versus steroids alone (birth < 24 hours after first dose), Outcome 5 Respiratory distress syndrome.

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

Comparison: 3 TRH + steroids versus steroids alone (birth < 24 hours after first dose)

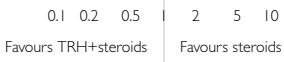
Outcome: 5 Respiratory distress syndrome

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	54/76	56/79		32.2 %	1.00 [0.82, 1.23]
Ballard 1992a	15/29	17/35		9.0 %	1.06 [0.65, 1.74]
Ballard 1998	81/108	83/104		49.7 %	0.94 [0.81, 1.09]
Chile 1998	2/7	2/6		1.3 %	0.86 [0.17, 4.37]
Knight 1994	14/26	13/25		7.8 %	1.04 [0.62, 1.74]
Total (95% CI)	**246**	**249**		**100.0 %**	**0.98 [0.87, 1.10]**

Total events: 166 (TRH+steroids), 171 (Steroids)

Heterogeneity: $Chi^2 = 0.53$, df = 4 (P = 0.97); $I^2 = 0.0\%$

Test for overall effect: Z = 0.38 (P = 0.70)



Analysis 3.6. Comparison 3 TRH + steroids versus steroids alone (birth < 24 hours after first dose), Outcome 6 Severe respiratory distress syndrome.

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

Comparison: 3 TRH + steroids versus steroids alone (birth < 24 hours after first dose)

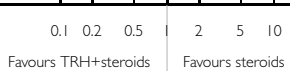
Outcome: 6 Severe respiratory distress syndrome

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	18/76	23/79		63.6 %	0.81 [0.48, 1.38]
Ballard 1992a	3/29	3/35		7.7 %	1.21 [0.26, 5.53]
Knight 1994	9/26	10/25		28.7 %	0.87 [0.42, 1.77]
Total (95% CI)	**131**	**139**		**100.0 %**	**0.86 [0.57, 1.30]**

Total events: 30 (TRH+steroids), 36 (Steroids)

Heterogeneity: $Chi^2 = 0.23$, df = 2 (P = 0.89); $I^2 = 0.0\%$

Test for overall effect: Z = 0.73 (P = 0.47)



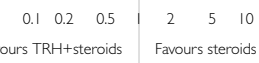
Analysis 3.7. Comparison 3 TRH + steroids versus steroids alone (birth < 24 hours after first dose), Outcome 7 Use of respiratory support.

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

Comparison: 3 TRH + steroids versus steroids alone (birth < 24 hours after first dose)

Outcome: 7 Use of respiratory support

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	56/76	59/79		100.0 %	0.99 [0.82, 1.19]
Total (95% CI)	**76**	**79**		**100.0 %**	**0.99 [0.82, 1.19]**
Total events: 56 (TRH+steroids), 59 (Steroids)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.14 (P = 0.89)					



Analysis 4.1. Comparison 4 TRH + steroids versus steroids alone (birth >= 24 hours to <= 10 days after first dose), Outcome 1 Death prior to hospital discharge.

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

Comparison: 4 TRH + steroids versus steroids alone (birth >= 24 hours to <= 10 days after first dose)

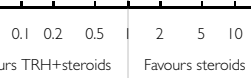
Outcome: 1 Death prior to hospital discharge

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	37/274	28/244		34.7 %	1.18 [0.74, 1.86]
Ballard 1992a	7/91	9/89		10.7 %	0.76 [0.30, 1.95]
Chile 1998	23/109	17/98		21.0 %	1.22 [0.69, 2.14]
Europe 1999	6/36	10/35		11.9 %	0.58 [0.24, 1.43]
Knight 1994	8/87	20/101		21.7 %	0.46 [0.22, 1.00]
Total (95% CI)	**597**	**567**		**100.0 %**	**0.92 [0.69, 1.22]**

Total events: 81 (TRH+steroids), 84 (Steroids)

Heterogeneity: Chi^2 = 6.23, df = 4 (P = 0.18); I^2 =36%

Test for overall effect: Z = 0.61 (P = 0.54)



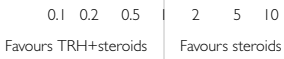
Analysis 4.2. Comparison 4 TRH + steroids versus steroids alone (birth >= 24 hours to <= 10 days after first dose), Outcome 2 Need for oxygen therapy or death at 28 days.

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

Comparison: 4 TRH + steroids versus steroids alone (birth >= 24 hours to <= 10 days after first dose)

Outcome: 2 Need for oxygen therapy or death at 28 days

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	117/274	104/244		40.3 %	1.00 [0.82, 1.22]
Ballard 1998	72/169	67/164		24.9 %	1.04 [0.81, 1.34]
Chile 1998	32/109	24/98		9.3 %	1.20 [0.76, 1.89]
Europe 1999	17/36	26/35		9.7 %	0.64 [0.43, 0.95]
Knight 1994	31/87	47/101		15.9 %	0.77 [0.54, 1.09]
Total (95% CI)	**675**	**642**		**100.0 %**	**0.96 [0.84, 1.09]**
Total events: 269 (TRH+steroids), 268 (Steroids)					
Heterogeneity: Chi^2 = 7.23, df = 4 (P = 0.12); I^2 =45%					
Test for overall effect: Z = 0.66 (P = 0.51)					



Analysis 4.3. Comparison 4 TRH + steroids versus steroids alone (birth >= 24 hours to <= 10 days after first dose), Outcome 3 Need for oxygen therapy >= 28 days.

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

Comparison: 4 TRH + steroids versus steroids alone (birth >= 24 hours to <= 10 days after first dose)

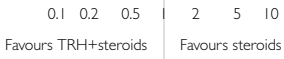
Outcome: 3 Need for oxygen therapy >= 28 days

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	90/266	82/240		54.3 %	0.99 [0.78, 1.26]
Ballard 1992a	12/91	17/89		10.8 %	0.69 [0.35, 1.36]
Chile 1998	11/109	7/98		4.6 %	1.41 [0.57, 3.50]
Europe 1999	14/36	19/35		12.1 %	0.72 [0.43, 1.19]
Knight 1994	24/87	31/101		18.1 %	0.90 [0.57, 1.41]
Total (95% CI)	**589**	**563**		**100.0 %**	**0.93 [0.77, 1.12]**

Total events: 151 (TRH+steroids), 156 (Steroids)

Heterogeneity: $Chi^2 = 2.84$, df = 4 (P = 0.59); $I^2 = 0.0\%$

Test for overall effect: Z = 0.79 (P = 0.43)



Analysis 4.4. Comparison 4 TRH + steroids versus steroids alone (birth >= 24 hours to <= 10 days after first dose), Outcome 4 Need for oxygen therapy.

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

Comparison: 4 TRH + steroids versus steroids alone (birth >= 24 hours to <= 10 days after first dose)

Outcome: 4 Need for oxygen therapy

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	209/266	190/240		86.0 %	0.99 [0.91, 1.09]
Europe 1999	33/36	32/35		14.0 %	1.00 [0.87, 1.15]
Total (95% CI)	**302**	**275**		**100.0 %**	**0.99 [0.92, 1.08]**

Total events: 242 (TRH+steroids), 222 (Steroids)

Heterogeneity: $Chi^2 = 0.02$, df = 1 (P = 0.90); $I^2 = 0.0\%$

Test for overall effect: Z = 0.15 (P = 0.88)

Analysis 4.5. Comparison 4 TRH + steroids versus steroids alone (birth >= 24 hours to <= 10 days after first dose), Outcome 5 Respiratory distress syndrome.

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

Comparison: 4 TRH + steroids versus steroids alone (birth >= 24 hours to <= 10 days after first dose)

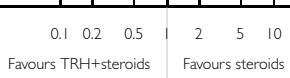
Outcome: 5 Respiratory distress syndrome

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	132/266	116/240		33.4 %	1.03 [0.86, 1.23]
Ballard 1992a	32/91	35/89		9.7 %	0.89 [0.61, 1.31]
Ballard 1998	111/169	112/164		31.2 %	0.96 [0.83, 1.12]
Chile 1998	33/109	21/98		6.1 %	1.41 [0.88, 2.27]
Europe 1999	25/36	26/35		7.2 %	0.93 [0.70, 1.25]
Knight 1994	25/87	49/101		12.4 %	0.59 [0.40, 0.87]
Total (95% CI)	**758**	**727**		**100.0 %**	**0.96 [0.86, 1.06]**

Total events: 358 (TRH+steroids), 359 (Steroids)

Heterogeneity: Chi^2 = 9.24, df = 5 (P = 0.10); I^2 =46%

Test for overall effect: Z = 0.86 (P = 0.39)



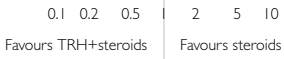
Analysis 4.6. Comparison 4 TRH + steroids versus steroids alone (birth >= 24 hours to <= 10 days after first dose), Outcome 6 Severe respiratory distress syndrome.

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

Comparison: 4 TRH + steroids versus steroids alone (birth >= 24 hours to <= 10 days after first dose)

Outcome: 6 Severe respiratory distress syndrome

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	46/266	54/240		53.6 %	0.77 [0.54, 1.09]
Ballard 1992a	8/91	12/89		11.5 %	0.65 [0.28, 1.52]
Knight 1994	16/87	40/101		34.9 %	0.46 [0.28, 0.77]
Total (95% CI)	**444**	**430**		**100.0 %**	**0.65 [0.49, 0.85]**
Total events: 70 (TRH+steroids), 106 (Steroids)					
Heterogeneity: Chi^2 = 2.58, df = 2 (P = 0.28); I^2 =22%					
Test for overall effect: Z = 3.12 (P = 0.0018)					



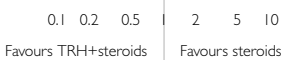
Analysis 4.7. Comparison 4 TRH + steroids versus steroids alone (birth >= 24 hours to <= 10 days after first dose), Outcome 7 Use of respiratory support.

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

Comparison: 4 TRH + steroids versus steroids alone (birth >= 24 hours to <= 10 days after first dose)

Outcome: 7 Use of respiratory support

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	177/266	149/240		84.2 %	1.07 [0.94, 1.22]
Europe 1999	27/36	29/35		15.8 %	0.91 [0.71, 1.15]
Total (95% CI)	**302**	**275**		**100.0 %**	**1.05 [0.93, 1.17]**
Total events: 204 (TRH+steroids), 178 (Steroids)					
Heterogeneity: Chi^2 = 1.51, df = 1 (P = 0.22); I^2 =34%					
Test for overall effect: Z = 0.75 (P = 0.46)					



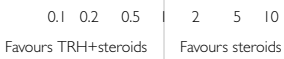
Analysis 5.1. Comparison 5 TRH + steroids versus steroids alone (birth > 10 days after first dose), Outcome 1 Death prior to hospital discharge.

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

Comparison: 5 TRH + steroids versus steroids alone (birth > 10 days after first dose)

Outcome: 1 Death prior to hospital discharge

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	16/349	11/372		48.7 %	1.55 [0.73, 3.29]
Chile 1998	5/56	7/56		32.0 %	0.71 [0.24, 2.12]
Europe 1999	0/54	3/63		14.8 %	0.17 [0.01, 3.15]
Knight 1994	7/88	1/91		4.5 %	7.24 [0.91, 57.64]
Total (95% CI)	**547**	**582**		**100.0 %**	**1.33 [0.78, 2.29]**
Total events: 28 (TRH+steroids), 22 (Steroids)					
Heterogeneity: Chi^2 = 5.90, df = 3 (P = 0.12); I^2 =49%					
Test for overall effect: Z = 1.04 (P = 0.30)					



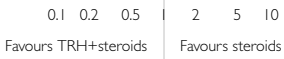
Analysis 5.2. Comparison 5 TRH + steroids versus steroids alone (birth > 10 days after first dose), Outcome 2 Need for oxygen therapy or death at 28 days.

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

Comparison: 5 TRH + steroids versus steroids alone (birth > 10 days after first dose)

Outcome: 2 Need for oxygen therapy or death at 28 days

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	40/349	27/372		34.6 %	1.58 [0.99, 2.52]
Ballard 1998	39/270	28/286		36.0 %	1.48 [0.94, 2.33]
Chile 1998	6/56	10/56		13.2 %	0.60 [0.23, 1.54]
Europe 1999	5/54	8/63		9.8 %	0.73 [0.25, 2.10]
Knight 1994	9/88	5/91		6.5 %	1.86 [0.65, 5.34]
Total (95% CI)	**817**	**868**		**100.0 %**	**1.35 [1.02, 1.78]**
Total events: 99 (TRH+steroids), 78 (Steroids)					
Heterogeneity: Chi^2 = 5.09, df = 4 (P = 0.28); I^2 =21%					
Test for overall effect: Z = 2.08 (P = 0.037)					



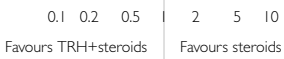
Analysis 5.3. Comparison 5 TRH + steroids versus steroids alone (birth > 10 days after first dose), Outcome 3 Need for oxygen therapy >= 28 days.

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

Comparison: 5 TRH + steroids versus steroids alone (birth > 10 days after first dose)

Outcome: 3 Need for oxygen therapy >= 28 days

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	26/342	16/366		55.3 %	1.74 [0.95, 3.18]
Chile 1998	1/56	3/56		10.7 %	0.33 [0.04, 3.11]
Europe 1999	5/54	6/63		19.8 %	0.97 [0.31, 3.01]
Knight 1994	3/88	4/91		14.1 %	0.78 [0.18, 3.37]
Total (95% CI)	**540**	**576**		**100.0 %**	**1.30 [0.81, 2.10]**
Total events: 35 (TRH+steroids), 29 (Steroids)					
Heterogeneity: Chi^2 = 3.05, df = 3 (P = 0.38); I^2 =1%					
Test for overall effect: Z = 1.08 (P = 0.28)					



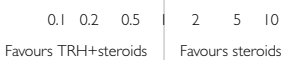
Analysis 5.4. Comparison 5 TRH + steroids versus steroids alone (birth > 10 days after first dose), Outcome 4 Need for oxygen therapy.

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

Comparison: 5 TRH + steroids versus steroids alone (birth > 10 days after first dose)

Outcome: 4 Need for oxygen therapy

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	97/342	93/366		100.0 %	1.12 [0.88, 1.42]
Total (95% CI)	**342**	**366**		**100.0 %**	**1.12 [0.88, 1.42]**
Total events: 97 (TRH+steroids), 93 (Steroids)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.89 (P = 0.38)					

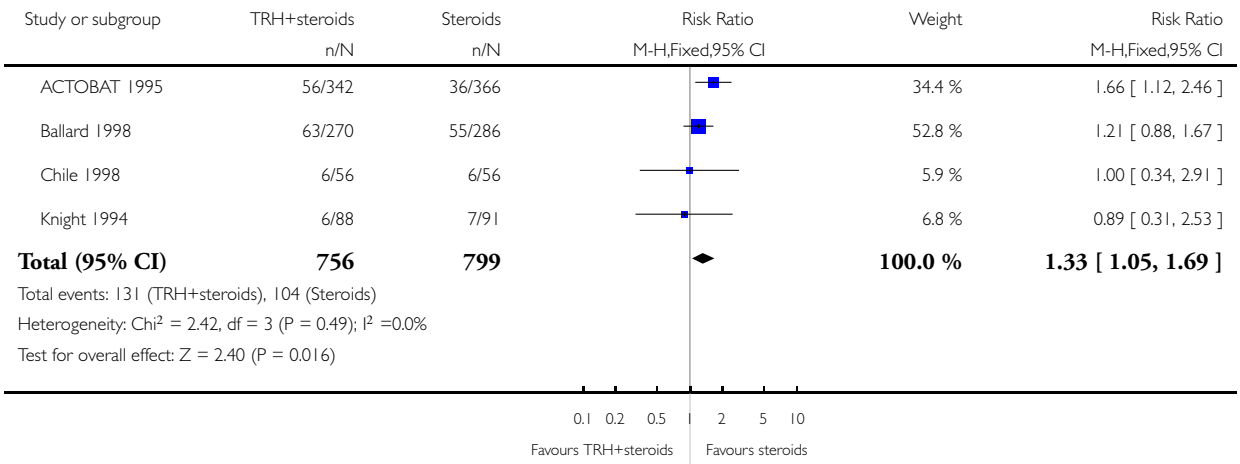


Analysis 5.5. Comparison 5 TRH + steroids versus steroids alone (birth > 10 days after first dose), Outcome 5 Respiratory distress syndrome.

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

Comparison: 5 TRH + steroids versus steroids alone (birth > 10 days after first dose)

Outcome: 5 Respiratory distress syndrome

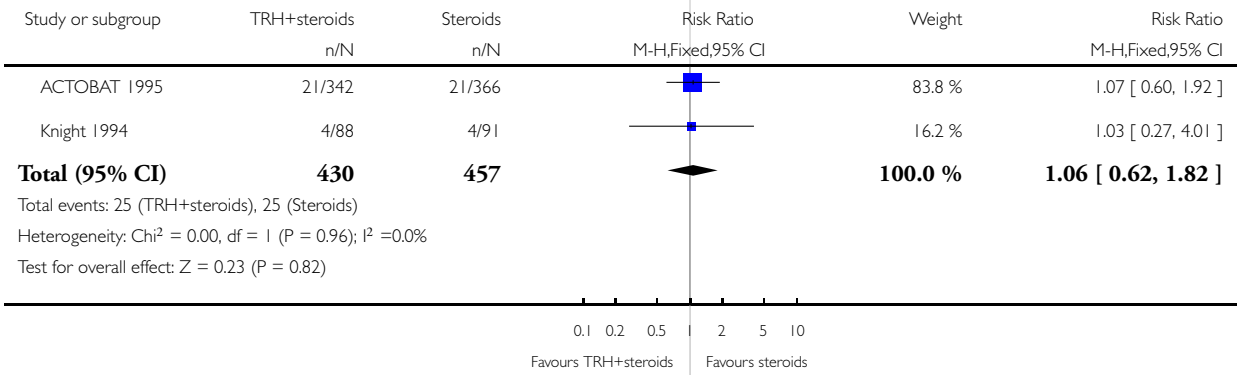


Analysis 5.6. Comparison 5 TRH + steroids versus steroids alone (birth > 10 days after first dose), Outcome 6 Severe respiratory distress syndrome.

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

Comparison: 5 TRH + steroids versus steroids alone (birth > 10 days after first dose)

Outcome: 6 Severe respiratory distress syndrome



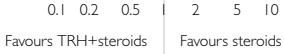
Analysis 5.7. Comparison 5 TRH + steroids versus steroids alone (birth > 10 days after first dose), Outcome 7 Use of respiratory support.

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

Comparison: 5 TRH + steroids versus steroids alone (birth > 10 days after first dose)

Outcome: 7 Use of respiratory support

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	59/342	47/366		100.0 %	1.34 [0.94, 1.91]
Total (95% CI)	**342**	**366**		**100.0 %**	**1.34 [0.94, 1.91]**
Total events: 59 (TRH+steroids), 47 (Steroids)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.64 (P = 0.10)					



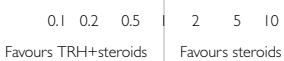
Analysis 6.1. Comparison 6 TRH (400 mcg treatment dosage) + steroids versus steroids alone (intention to treat), Outcome 1 Death prior to hospital discharge.

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

Comparison: 6 TRH (400 mcg treatment dosage) + steroids versus steroids alone (intention to treat)

Outcome: 1 Death prior to hospital discharge

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
Ballard 1998	54/563	52/571		41.5 %	1.05 [0.73, 1.51]
Chile 1998	28/180	24/166		20.1 %	1.08 [0.65, 1.78]
Europe 1999	8/136	17/139		13.5 %	0.48 [0.21, 1.08]
Jikihara 1990	10/63	6/61		4.9 %	1.61 [0.62, 4.17]
Knight 1994	21/201	26/217		20.1 %	0.87 [0.51, 1.50]
Total (95% CI)	**1143**	**1154**		**100.0 %**	**0.97 [0.77, 1.23]**
Total events: 121 (TRH+steroids), 125 (Steroids)					
Heterogeneity: Chi^2 = 4.52, df = 4 (P = 0.34); I^2 =12%					
Test for overall effect: Z = 0.24 (P = 0.81)					



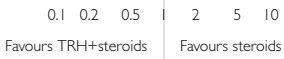
Analysis 6.2. Comparison 6 TRH (400 mcg treatment dosage) + steroids versus steroids alone (intention to treat), Outcome 2 Need for oxygen therapy or death at 28 days.

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

Comparison: 6 TRH (400 mcg treatment dosage) + steroids versus steroids alone (intention to treat)

Outcome: 2 Need for oxygen therapy or death at 28 days

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
Ballard 1998	178/563	159/571		50.3 %	1.14 [0.95, 1.36]
Chile 1998	40/180	33/166		10.9 %	1.12 [0.74, 1.68]
Europe 1999	34/136	43/139		13.6 %	0.81 [0.55, 1.18]
Jikihara 1990	26/63	19/61		6.2 %	1.32 [0.82, 2.13]
Knight 1994	49/201	62/217		19.0 %	0.85 [0.62, 1.18]
Total (95% CI)	**1143**	**1154**		**100.0 %**	**1.05 [0.92, 1.19]**
Total events: 327 (TRH+steroids), 316 (Steroids)					
Heterogeneity: Chi^2 = 5.14, df = 4 (P = 0.27); I^2 =22%					
Test for overall effect: Z = 0.69 (P = 0.49)					



Analysis 6.3. Comparison 6 TRH (400 mcg treatment dosage) + steroids versus steroids alone (intention to treat), Outcome 3 Need for oxygen therapy >= 28 days.

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

Comparison: 6 TRH (400 mcg treatment dosage) + steroids versus steroids alone (intention to treat)

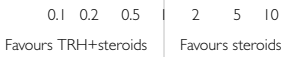
Outcome: 3 Need for oxygen therapy >= 28 days

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
Chile 1998	14/172	10/160		10.9 %	1.30 [0.60, 2.85]
Europe 1999	29/136	30/132		31.9 %	0.94 [0.60, 1.47]
Jikihara 1990	18/63	15/61		16.0 %	1.16 [0.65, 2.09]
Knight 1994	30/201	41/217		41.3 %	0.79 [0.51, 1.21]
Total (95% CI)	**572**	**570**		**100.0 %**	**0.95 [0.73, 1.23]**

Total events: 91 (TRH+steroids), 96 (Steroids)

Heterogeneity: Chi^2 = 1.78, df = 3 (P = 0.62); I^2 =0.0%

Test for overall effect: Z = 0.37 (P = 0.71)



Analysis 6.4. Comparison 6 TRH (400 mcg treatment dosage) + steroids versus steroids alone (intention to treat), Outcome 4 Need for oxygen therapy.

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

Comparison: 6 TRH (400 mcg treatment dosage) + steroids versus steroids alone (intention to treat)

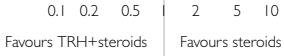
Outcome: 4 Need for oxygen therapy

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
Chile 1998	91/172	75/160		30.3 %	1.13 [0.91, 1.40]
Europe 1999	75/136	65/132		25.7 %	1.12 [0.89, 1.41]
Knight 1994	102/201	117/217		43.9 %	0.94 [0.78, 1.13]
Total (95% CI)	**509**	**509**		**100.0 %**	**1.04 [0.93, 1.18]**

Total events: 268 (TRH+steroids), 257 (Steroids)

Heterogeneity: Chi^2 = 2.08, df = 2 (P = 0.35); I^2 =4%

Test for overall effect: Z = 0.71 (P = 0.48)



Analysis 6.5. Comparison 6 TRH (400 mcg treatment dosage) + steroids versus steroids alone (intention to treat), Outcome 5 Respiratory distress syndrome.

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

Comparison: 6 TRH (400 mcg treatment dosage) + steroids versus steroids alone (intention to treat)

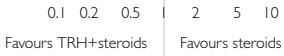
Outcome: 5 Respiratory distress syndrome

Study or subgroup	TRH+steroids n/N	Steroids n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Ballard 1998	265/563	257/571		30.1 %	1.05 [0.92, 1.19]
Carlan 1991	5/13	1/11		1.2 %	4.23 [0.58, 30.99]
Chile 1998	41/172	29/160		14.9 %	1.32 [0.86, 2.01]
Europe 1999	59/136	49/132		21.0 %	1.17 [0.87, 1.57]
Jikihara 1990	19/63	27/61		13.3 %	0.68 [0.43, 1.09]
Knight 1994	45/201	69/217		19.5 %	0.70 [0.51, 0.97]
Total (95% CI)	**1148**	**1152**		**100.0 %**	**0.99 [0.79, 1.23]**

Total events: 434 (TRH+steroids), 432 (Steroids)

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 12.21$, df = 5 (P = 0.03); $I^2 = 59\%$

Test for overall effect: Z = 0.13 (P = 0.89)



Analysis 6.6. Comparison 6 TRH (400 mcg treatment dosage) + steroids versus steroids alone (intention to treat), Outcome 6 Severe respiratory distress syndrome.

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

Comparison: 6 TRH (400 mcg treatment dosage) + steroids versus steroids alone (intention to treat)

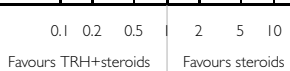
Outcome: 6 Severe respiratory distress syndrome

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
Chile 1998	30/172	19/160		27.5 %	1.47 [0.86, 2.50]
Knight 1994	29/201	54/217		72.5 %	0.58 [0.39, 0.87]
Total (95% CI)	**373**	**377**		**100.0 %**	**0.82 [0.60, 1.13]**

Total events: 59 (TRH+steroids), 73 (Steroids)

Heterogeneity: $Chi^2 = 7.37$, df = 1 (P = 0.01); $I^2 = 86\%$

Test for overall effect: Z = 1.20 (P = 0.23)



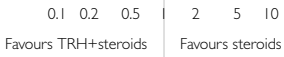
Analysis 6.7. Comparison 6 TRH (400 mcg treatment dosage) + steroids versus steroids alone (intention to treat), Outcome 7 Use of respiratory support.

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

Comparison: 6 TRH (400 mcg treatment dosage) + steroids versus steroids alone (intention to treat)

Outcome: 7 Use of respiratory support

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
Chile 1998	58/172	43/160		45.3 %	1.25 [0.90, 1.75]
Europe 1999	61/136	53/132		54.7 %	1.12 [0.84, 1.48]
Total (95% CI)	**308**	**292**		**100.0 %**	**1.18 [0.95, 1.46]**
Total events: 119 (TRH+steroids), 96 (Steroids)					
Heterogeneity: Chi^2 = 0.28, df = 1 (P = 0.60); I^2 =0.0%					
Test for overall effect: Z = 1.51 (P = 0.13)					



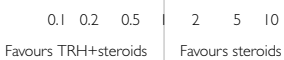
Analysis 7.1. Comparison 7 TRH (200 mcg treatment dose) + steroids versus steroids alone (intention to treat), Outcome 1 Death prior to hospital discharge.

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

Comparison: 7 TRH (200 mcg treatment dose) + steroids versus steroids alone (intention to treat)

Outcome: 1 Death prior to hospital discharge

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	64/699	52/698		100.0 %	1.23 [0.87, 1.75]
Total (95% CI)	**699**	**698**		**100.0 %**	**1.23 [0.87, 1.75]**
Total events: 64 (TRH+steroids), 52 (Steroids)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.15 (P = 0.25)					



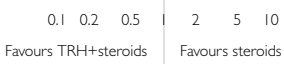
Analysis 7.2. Comparison 7 TRH (200 mcg treatment dose) + steroids versus steroids alone (intention to treat), Outcome 2 Need for oxygen therapy or death at 28 days.

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

Comparison: 7 TRH (200 mcg treatment dose) + steroids versus steroids alone (intention to treat)

Outcome: 2 Need for oxygen therapy or death at 28 days

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	185/699	170/698		100.0 %	1.09 [0.91, 1.30]
Total (95% CI)	**699**	**698**		**100.0 %**	**1.09 [0.91, 1.30]**
Total events: 185 (TRH+steroids), 170 (Steroids)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.91 (P = 0.37)					



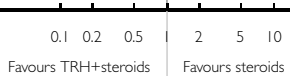
Analysis 7.3. Comparison 7 TRH (200 mcg treatment dose) + steroids versus steroids alone (intention to treat), Outcome 3 Need for oxygen therapy >= 28 days.

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

Comparison: 7 TRH (200 mcg treatment dose) + steroids versus steroids alone (intention to treat)

Outcome: 3 Need for oxygen therapy >= 28 days

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	135/684	129/685		100.0 %	1.05 [0.84, 1.30]
Total (95% CI)	**684**	**685**		**100.0 %**	**1.05 [0.84, 1.30]**
Total events: 135 (TRH+steroids), 129 (Steroids)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.42 (P = 0.67)					



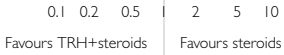
Analysis 7.4. Comparison 7 TRH (200 mcg treatment dose) + steroids versus steroids alone (intention to treat), Outcome 4 Need for oxygen therapy.

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

Comparison: 7 TRH (200 mcg treatment dose) + steroids versus steroids alone (intention to treat)

Outcome: 4 Need for oxygen therapy

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	371/684	354/685		100.0 %	1.05 [0.95, 1.16]
Total (95% CI)	**684**	**685**		**100.0 %**	**1.05 [0.95, 1.16]**
Total events: 371 (TRH+steroids), 354 (Steroids)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.95 (P = 0.34)					



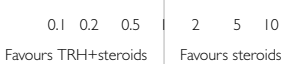
Analysis 7.5. Comparison 7 TRH (200 mcg treatment dose) + steroids versus steroids alone (intention to treat), Outcome 5 Respiratory distress syndrome.

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

Comparison: 7 TRH (200 mcg treatment dose) + steroids versus steroids alone (intention to treat)

Outcome: 5 Respiratory distress syndrome

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	242/684	208/685		100.0 %	1.17 [1.00, 1.36]
Total (95% CI)	**684**	**685**		**100.0 %**	**1.17 [1.00, 1.36]**
Total events: 242 (TRH+steroids), 208 (Steroids)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.97 (P = 0.049)					



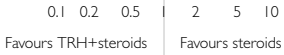
Analysis 7.6. Comparison 7 TRH (200 mcg treatment dose) + steroids versus steroids alone (intention to treat), Outcome 6 Severe respiratory distress syndrome.

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

Comparison: 7 TRH (200 mcg treatment dose) + steroids versus steroids alone (intention to treat)

Outcome: 6 Severe respiratory distress syndrome

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	85/684	98/685		100.0 %	0.87 [0.66, 1.14]
Total (95% CI)	**684**	**685**		**100.0 %**	**0.87 [0.66, 1.14]**
Total events: 85 (TRH+steroids), 98 (Steroids)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.02 (P = 0.31)					



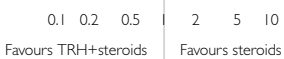
Analysis 7.7. Comparison 7 TRH (200 mcg treatment dose) + steroids versus steroids alone (intention to treat), Outcome 7 Use of respiratory support.

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

Comparison: 7 TRH (200 mcg treatment dose) + steroids versus steroids alone (intention to treat)

Outcome: 7 Use of respiratory support

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	292/684	255/685		100.0 %	1.15 [1.01, 1.31]
Total (95% CI)	**684**	**685**		**100.0 %**	**1.15 [1.01, 1.31]**
Total events: 292 (TRH+steroids), 255 (Steroids)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.06 (P = 0.040)					



Analysis 8.1. Comparison 8 TRH + steroids versus steroids alone (optimally treated variously defined), Outcome 1 Death prior to hospital discharge.

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

Comparison: 8 TRH + steroids versus steroids alone (optimally treated variously defined)

Outcome: 1 Death prior to hospital discharge

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	37/274	28/244		34.2 %	1.18 [0.74, 1.86]
Ceriani 1992	3/26	5/31		5.3 %	0.72 [0.19, 2.71]
Chile 1998	23/109	17/98		20.7 %	1.22 [0.69, 2.14]
Europe 1999	6/36	10/35		11.7 %	0.58 [0.24, 1.43]
Jikihara 1990	0/5	3/4		4.4 %	0.12 [0.01, 1.80]
Knight 1994	8/87	20/101		21.4 %	0.46 [0.22, 1.00]
Morales 1989	3/50	2/50		2.3 %	1.50 [0.26, 8.60]
Total (95% CI)	**587**	**563**		**100.0 %**	**0.90 [0.68, 1.19]**

Total events: 80 (TRH+steroids), 85 (Steroids)

Heterogeneity: $Chi^2 = 8.72$, df = 6 (P = 0.19); $I^2 = 31\%$

Test for overall effect: Z = 0.73 (P = 0.46)

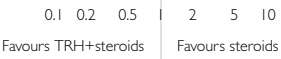
Analysis 8.2. Comparison 8 TRH + steroids versus steroids alone (optimally treated variously defined), Outcome 2 Need for oxygen therapy or death at 28 days.

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

Comparison: 8 TRH + steroids versus steroids alone (optimally treated variously defined)

Outcome: 2 Need for oxygen therapy or death at 28 days

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	117/274	104/244		40.3 %	1.00 [0.82, 1.22]
Ballard 1998	72/169	67/164		24.9 %	1.04 [0.81, 1.34]
Chile 1998	32/109	24/98		9.3 %	1.20 [0.76, 1.89]
Europe 1999	17/36	26/35		9.7 %	0.64 [0.43, 0.95]
Knight 1994	31/87	47/101		15.9 %	0.77 [0.54, 1.09]
Total (95% CI)	**675**	**642**		**100.0 %**	**0.96 [0.84, 1.09]**
Total events: 269 (TRH+steroids), 268 (Steroids)					
Heterogeneity: Chi^2 = 7.23, df = 4 (P = 0.12); I^2 =45%					
Test for overall effect: Z = 0.66 (P = 0.51)					



Analysis 8.3. Comparison 8 TRH + steroids versus steroids alone (optimally treated variously defined), Outcome 3 Need for oxygen therapy >= 28 days.

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

Comparison: 8 TRH + steroids versus steroids alone (optimally treated variously defined)

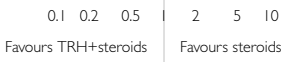
Outcome: 3 Need for oxygen therapy >= 28 days

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	90/266	82/240		60.4 %	0.99 [0.78, 1.26]
Chile 1998	11/109	7/98		5.2 %	1.41 [0.57, 3.50]
Europe 1999	14/36	19/35		13.5 %	0.72 [0.43, 1.19]
Jikihara 1990	2/5	1/4		0.8 %	1.60 [0.21, 11.92]
Knight 1994	24/87	31/101		20.1 %	0.90 [0.57, 1.41]
Total (95% CI)	**503**	**478**		**100.0 %**	**0.96 [0.79, 1.17]**

Total events: 141 (TRH+steroids), 140 (Steroids)

Heterogeneity: Chi^2 = 2.36, df = 4 (P = 0.67); I^2 =0.0%

Test for overall effect: Z = 0.40 (P = 0.69)



Analysis 8.4. Comparison 8 TRH + steroids versus steroids alone (optimally treated variously defined), Outcome 4 Need for oxygen therapy.

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

Comparison: 8 TRH + steroids versus steroids alone (optimally treated variously defined)

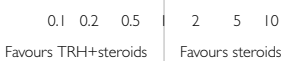
Outcome: 4 Need for oxygen therapy

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	209/266	190/240		100.0 %	0.99 [0.91, 1.09]
Total (95% CI)	**266**	**240**		**100.0 %**	**0.99 [0.91, 1.09]**

Total events: 209 (TRH+steroids), 190 (Steroids)

Heterogeneity: not applicable

Test for overall effect: Z = 0.16 (P = 0.87)



Analysis 8.5. Comparison 8 TRH + steroids versus steroids alone (optimally treated variously defined), Outcome 5 Respiratory distress syndrome.

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

Comparison: 8 TRH + steroids versus steroids alone (optimally treated variously defined)

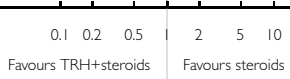
Outcome: 5 Respiratory distress syndrome

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	132/266	116/240		34.0 %	1.03 [0.86, 1.23]
Ballard 1998	111/169	112/164		31.7 %	0.96 [0.83, 1.12]
Campos 1993	13/66	25/69		6.8 %	0.54 [0.30, 0.97]
Ceriani 1992	6/26	9/31		2.3 %	0.79 [0.33, 1.94]
Chile 1998	33/109	21/98		6.2 %	1.41 [0.88, 2.27]
Jikihara 1990	1/5	1/4		0.3 %	0.80 [0.07, 9.18]
Knight 1994	25/87	49/101		12.6 %	0.59 [0.40, 0.87]
Morales 1989	14/50	22/50		6.1 %	0.64 [0.37, 1.10]
Total (95% CI)	**778**	**757**		**100.0 %**	**0.91 [0.82, 1.02]**

Total events: 335 (TRH+steroids), 355 (Steroids)

Heterogeneity: Chi^2 = 15.07, df = 7 (P = 0.04); I^2 =54%

Test for overall effect: Z = 1.68 (P = 0.093)



Analysis 8.6. Comparison 8 TRH + steroids versus steroids alone (optimally treated variously defined), Outcome 6 Severe respiratory distress syndrome.

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

Comparison: 8 TRH + steroids versus steroids alone (optimally treated variously defined)

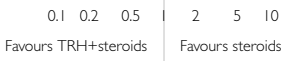
Outcome: 6 Severe respiratory distress syndrome

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	46/266	54/240		60.5 %	0.77 [0.54, 1.09]
Knight 1994	16/87	40/101		39.5 %	0.46 [0.28, 0.77]
Total (95% CI)	**353**	**341**		**100.0 %**	**0.65 [0.49, 0.86]**

Total events: 62 (TRH+steroids), 94 (Steroids)

Heterogeneity: Chi^2 = 2.58, df = 1 (P = 0.11); I^2 =61%

Test for overall effect: Z = 2.96 (P = 0.0031)



Analysis 8.7. Comparison 8 TRH + steroids versus steroids alone (optimally treated variously defined), Outcome 7 Use of respiratory support.

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

Comparison: 8 TRH + steroids versus steroids alone (optimally treated variously defined)

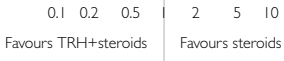
Outcome: 7 Use of respiratory support

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	177/266	149/240		100.0 %	1.07 [0.94, 1.22]
Total (95% CI)	**266**	**240**		**100.0 %**	**1.07 [0.94, 1.22]**

Total events: 177 (TRH+steroids), 149 (Steroids)

Heterogeneity: not applicable

Test for overall effect: Z = 1.04 (P = 0.30)



APPENDICES

Appendix 1. Search strategy for additional author searching

Authors 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

Last assessed as up-to-date: 9 November 2009.

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 (Ballard 1992b). Risk of bias tables updated. Authors of two studies previously reported as ongoing were contacted (Pearlman 1997; Yoder 1997).

HISTORY

Protocol first published: Issue 2, 1995

Review first published: Issue 2, 1995

Date	Event	Description
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

CA Crowther and Z Alfirevic contributed to the development of the protocol. CA Crowther and Z Alfirevic identified and selected trials for inclusion, performed the data extraction and data entry for the previous review. All review authors contributed to the final version of this updated review. For this update, SS Han and CA Crowther assessed identified studies for eligibility and SS Han prepared the initial draft of the risk of bias tables and the new format text of the review.

DECLARATIONS OF INTEREST

Prof CA Crowther and A/Prof RR Haslam were two of the chief investigators for the Australian Collaborative Trial of thyrotropin-releasing hormone (ACTOBAT 1995) and Prof Z Alfirevic one of the principal investigators for the European TRH trial (Europe 1999).

SOURCES OF SUPPORT

Internal sources

- 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

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Female; Humans; Pregnancy