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Transabdominal amnioinfusion for improving fetal outcomes after oligohydramnios secondary to preterm prelabour rupture of membranes before 26 weeks (Review)

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Transabdominal amnioinfusion for improving fetal outcomes after oligohydramnios secondary to preterm prelabour rupture of membranes before 26 weeks

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ABSTRACT

Background

Preterm prelabour rupture of membranes (PPROM) before 26 weeks can delay lung development and can cause pulmonary hypoplasia, as a result of oligohydramnios. Restoring the amniotic fluid volume by transabdominal amnioinfusion might prevent abnormal lung development and might have a protective effect for neurological complications, fetal deformities and neonatal sepsis.

Objectives

To assess the effectiveness of transabdominal amnioinfusion in improving perinatal outcome in women with oligohydramnios secondary to rupture of fetal membranes before 26 weeks.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (30 April 2013).

Selection criteria

All randomised controlled trials comparing transabdominal amnioinfusion with no transabdominal amnioinfusion. Cluster- or quasi-randomised trials were not eligible for inclusion. In cases where only an abstract was available, we attempted to find the full articles.

Data collection and analysis

Two review authors assessed trials for inclusion. No eligible trials were identified.

Main results

There are no included studies.

Authors' conclusions

There is currently no evidence to evaluate the use of transabdominal amnioinfusion in women with oligohydramnios secondary to rupture of fetal membranes before 26 weeks for improving perinatal outcome. Further research examining the effects of this intervention is needed. Two randomised controlled trials are ongoing but final data have not yet been published.

PLAIN LANGUAGE SUMMARY

Transabdominal amnioinfusion for improving fetal outcomes after oligohydramnios secondary to preterm prelabour rupture of membranes before 26 weeks

Babies born after preterm prelabour rupture of membranes (PPROM) between 16 and 26 weeks of pregnancy are prone to underdevelopment of the lungs. When the membranes containing the fluid that surrounds the baby (amniotic fluid) rupture, a shortage of this fluid can occur, a condition that is called oligohydramnios. Oligohydramnios is thought to interfere with normal lung development so that it is delayed, resulting in a condition that is called pulmonary hypoplasia.

Pulmonary hypoplasia can present as severe breathing problems or as milder and even transient breathing problems. It can be accompanied by bleeding in the lung and can also result in chronic breathing problems due to scarring of lung tissue. There may also be neurological complications, fetal deformities and neonatal sepsis with oligohydramnios.

Replacement of fluid via a needle passed through the abdominal wall in the uterine cavity and into a pocket of amniotic fluid, (transabdominal amnioinfusion) under ultrasound guidance has been proposed to improve pregnancy outcome. Most clinical experience suggests that amnioinfusion is safe for both the mother and the baby, however, we did not identify any randomised trials of transabdominal amnioinfusion following PPRM before 26 weeks for inclusion in this review. Currently, there is no evidence to evaluate the use of transabdominal amnioinfusion in women with oligohydramnios following rupture of fetal membranes before 26 weeks for improving birth outcomes.

BACKGROUND

Description of the condition

It is thought that the formation of lung tissue is dependent on an adequate amount of amniotic fluid, especially during the interval between 16 and 26 weeks (the midtrimester). A reduced amount of amniotic fluid (oligohydramnios) after preterm prelabour rupture of membranes (PPROM) in this interval might cause pulmonary hypoplasia ([van Teeffelen 2010a](#)). Oligohydramnios is commonly defined as a single deepest pocket of amniotic fluid of less than 2 cm or an amniotic fluid index of less than 5 cm as measured by ultrasound.

Pulmonary hypoplasia is a term used to describe pulmonary underdevelopment. It is characterised by an inadequate formation of the respiratory tree resulting in a reduced amount of functional lung tissue, with reduced capacity for gas exchange.

Pulmonary hypoplasia poses a serious threat to the neonate and is associated with high mortality and morbidity rates. It can present

as severe breathing problems resulting in early neonatal death or, as milder and even transient breathing problems. It may be accompanied by bleeding in the lungs. It can also result in chronic breathing problems due to scarring of lung tissue ([Sherer 1990](#)). Perinatal mortality approximates 70% in most series (55% to 100%) ([Laudy 2000](#)).

An internationally recognised definition of pulmonary hypoplasia does not exist, rather a diagnosis is made by eliminating other possible causes of symptoms. Congenital pneumonia, infant respiratory distress syndrome and pulmonary hypoplasia sometimes occur simultaneously, and have overlapping symptoms. Post mortem diagnosis is not uniform throughout the literature, however, post mortem criteria are more objective than those for infants who survive.

Apart from PPRM, numerous other conditions are associated with pulmonary hypoplasia. These include renal and urinary tract abnormalities leading to decreased amniotic fluid, decreased amniotic fluid unrelated to disorders of the urinary system, diaphragmatic hernia, fetal oedema, skeletal and muscular pathologies, central nervous system abnormalities, and other conditions causing

compression of the fetal thorax (Lauria 1995).

Description of the intervention

Transabdominal amnioinfusion has been attempted for diagnostic and therapeutic purposes in women with second trimester oligohydramnios (Gramellini 2003). The aim of the procedure is to restore the amount of amniotic fluid, by infusing fluid through a needle passed through the abdominal wall into the womb. After sterile preparation of the abdomen, a pocket of amniotic fluid is identified by ultrasound guidance, after which a needle is advanced into this pocket. After insuring proper placement by withdrawing a small amount of fluid, the desired volume of fluid is infused, by manual push or infusion pump. The procedure can be repeated if oligohydramnios recurs or persists (it is then called serial amnioinfusion).

How the intervention might work

The mechanism by which oligohydramnios impairs lung development is not fully understood. Several mechanisms have been proposed (mechanical effects, effects on fetal breathing movements, effects on the transcription of growth factors, and effects of inflammation and infection (Williams 2012). Restitution of amniotic fluid volume in cases of artificially induced oligohydramnios in experimental animals has prevented pulmonary hypoplasia (Nakayama 1983; Sherer 1990).

Persistent oligohydramnios appears to be a poor prognostic sign in terms of pulmonary hypoplasia or other morbidity as described in a review by Laudy and Wladimiroff (Laudy 2000). Restoring the amniotic fluid volume might prevent abnormal lung growth and development. Furthermore, it has been hypothesised that amnioinfusion might also have a protective effect for other neurological complications and fetal deformities (Gramellini 2003). Dilution, and the antibacterial effect of the infused fluid might have a protective effect for neonatal sepsis (Singla 2010). There is no consensus on the definition of successful amnioinfusion. Leakage of the infused fluid has been described. In two observational studies, in only 24% to 30% of cases was infused fluid retained 48 hours after the intervention (Tan 2003; Vergani 2004).

Why it is important to do this review

In another Cochrane review Hofmeyr et al reviewed amnioinfusion for PPRM before 37 weeks with the aim to assess the effects of amnioinfusion for PPRM on perinatal and maternal morbidity and mortality (Hofmeyr 2011). Hofmeyr's review reports on transabdominal as well as transcervical amnioinfusion. It was concluded that transcervical amnioinfusion reduced variable decelerations during labour and improved fetal umbilical artery pH at

delivery. Transabdominal amnioinfusion was associated with a reduction in neonatal death, neonatal sepsis, pulmonary hypoplasia and puerperal sepsis. Furthermore, the interval between PPRM and birth seemed to be longer in the amnioinfused group. It was stressed that the results should be interpreted with caution, since the positive findings were mainly due to one trial with unclear allocation concealment.

The present review, in contrast, specifically considers women with rupture of membranes before 26 weeks and subsequent oligohydramnios who are treated with transabdominal amnioinfusion.

PPROM before 26 weeks with oligohydramnios is a distinct condition within PPRM in general, with a distinct pathophysiology leading to abnormal lung development and a very poor prognosis. To date, no effective management has been recognised, although several therapies have been investigated. Some of these therapies aim to normalise the amniotic fluid volume, either by preventing further leakage of amniotic fluid (occlusion by fibrin, platelets, cryoprecipitate), or to add fluid to the amniotic cavity by transabdominal amnioinfusion.

Antepartum amnioinfusion for the management of oligohydramnios is a difficult procedure. Technical difficulty lies in the fact that the needle has to be inserted in a pocket of amniotic fluid where, in severe oligohydramnios, such a pocket may be difficult to identify.

Some researchers have claimed that the procedure, if successful, has been shown to decrease the risk of pulmonary hypoplasia and significantly improves perinatal outcome (Chin 2009).

Recently Porat et al (Porat 2012) reviewed transabdominal amnioinfusion for PPRM with associated oligohydramnios. Just as in Hofmeyr's review, studies on PPRM before 37 weeks were included. Porat 2012 meta-analysed available randomised controlled trials (RCTs) as well as observational studies. Two RCTs and one quasi-randomised RCT were included in the review as well as four observational studies. The two RCTs were carried out on women with PPRM between 24 and 34 completed weeks; the two RCTs were also included in the review by Hofmeyr (Hofmeyr 2011). The quasi-randomised study included only women with PPRM before 26 weeks of gestation (De Santis 2003). Of the four observational studies, two were on very early PPRM. Porat et al concluded that serial transabdominal amnioinfusion might improve early PPRM associated morbidity and mortality, however, a large randomised trial is needed.

A meta-analysis of all randomised controlled trials on women with PPRM before 26 weeks and associated oligohydramnios could indicate if serial transabdominal amnioinfusion is a safe and effective intervention for this specific obstetric problem.

OBJECTIVES

To assess the effectiveness of transabdominal amnioinfusion in improving perinatal outcome in women with oligohydramnios

secondary to rupture of fetal membranes before 26 weeks.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials. Cluster- or quasi-randomised trials were not eligible for inclusion. In cases where only an abstract was available, we attempted to find the full articles.

Types of participants

Women with a pregnancy complicated by premature prelabour rupture of membranes (PPROM) before 26 weeks and subsequent oligohydramnios.

Types of interventions

Transabdominal amnioinfusion versus standard management.

Types of outcome measures

Primary outcomes

- Perinatal mortality, defined as intrauterine death, intrapartum death or neonatal death in the first 28 days of life.

Secondary outcomes

- Pulmonary hypoplasia as defined by the individual trials.
- Retention of infused fluid as defined by a single deepest pocket of amniotic fluid of more than 2 cm or an amniotic fluid index of more than five, for at least 48 hours.
- Gestational age at birth.
- Latency (interval between PPRM and birth).
- Neonatal mortality, defined as neonatal death in the first 28 days of life.
- Stillbirth (intrauterine death).

Neonatal morbidity

- Sepsis as defined by the individual trials.
- Respiratory distress syndrome as defined by the individual trials.
- Necrotising enterocolitis as defined by the individual trials.
- Chronic lung disease as defined by the individual trials.

- Periventricular leucomalacia as defined by the individual trials.
- Severe intraventricular haemorrhage as defined by the individual trials.
- Postural deformities as defined by the individual trials.

Adverse events

- Placental abruption.
- Cord prolapse.
- Chorioamnionitis as defined by the individual trials.
- Fetal trauma due to puncture.
- Premature labour and birth.
- Maternal sepsis as defined by the individual trials.
- Maternal death.

Search methods for identification of studies

Electronic searches

We contacted the Trials Search Co-ordinator to search the Cochrane Pregnancy and Childbirth Group's Trials Register (30 April 2013).

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

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

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

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

We did not apply any language restrictions.

Data collection and analysis

Selection of studies

Two review authors (Stijn Van Teeffelen and Eva Pajkrt) independently assessed for inclusion all the potential studies that were identified as a result of the search strategy. We resolved any disagreement through discussion or, if required, we consulted Ben Willem Mol (BWM).

There are no included studies. Data collection and analysis methods to be used in future updates of this review are provided in [Appendix 1](#).

RESULTS

Description of studies

Results of the search

The search of the Cochrane Pregnancy and Childbirth Group's Trials Register retrieved 11 reports. There are no included studies. We excluded nine studies ([De Santis 2003](#); [Gonzalez 2001](#); [Gowri 2004](#); [Leake 1983](#); [Nageotte 1985](#); [Puertas 2007](#); [Singla 2010](#); [Tranquilli 2005](#); [Vergani 2007](#)) and two studies are ongoing ([Locatelli 2008](#); [Roberts 2006](#)).

Included studies

There are no included studies.

Excluded studies

We excluded nine studies from the review because they did not meet our study eligibility criteria (see [Characteristics of excluded studies](#)).

[De Santis 2003](#) used a quasi-randomisation process in which women with PPROM before 26 weeks were allocated to amnioinfusion or expectant management, participants were admitted by chance into one of two departments, amnioinfusion was given in only one of these departments.

[Gowri 2004](#) studied a group of 17 participants of which only three had premature rupture of membranes, data on their outcomes could not be extracted. [Leake 1983](#) studied 35 participants with preterm labour and or ruptured membranes who received ritodrine or a placebo to study its effect on neonatal glucose homeostasis. [Singla 2010](#) and [Tranquilli 2005](#) were excluded since the inclusion criteria did not fit the criteria for this review (they studied participants with PPROM after 24 weeks) and [Puertas 2007](#) and [Nageotte 1985](#) studied intrapartum amnioinfusion in women with PPROM between 26 and 35 weeks. We excluded [Gonzalez 2001](#) since we could not find the final data published (preliminary results). The [Vergani 2007](#) report is a study proposal.

Risk of bias in included studies

There are no included studies.

Effects of interventions

There are no included studies.

DISCUSSION

No randomised controlled trials of transabdominal amnioinfusion to improve perinatal outcome in women with oligohydramnios secondary to rupture of fetal membranes before 26 weeks were identified for inclusion in this review. Two randomised controlled trials have started ([Locatelli 2008](#); [Roberts 2006](#)) but final data have not yet been published.

At this point, transabdominal amnioinfusion cannot be recommended for women with oligohydramnios secondary to rupture of fetal membranes before 26 weeks. Women requesting a trial of therapy should be informed of the lack of any well-designed studies assessing effectiveness, and the risk of adverse events.

AUTHORS' CONCLUSIONS

Implications for practice

There is currently no evidence to evaluate the use of transabdominal amnioinfusion for improving perinatal outcome in women with oligohydramnios secondary to rupture of fetal membranes before 26 weeks.

Implications for research

Randomised controlled studies to determine the effectiveness of transabdominal amnioinfusion in women with oligohydramnios secondary to rupture of fetal membranes before 26 weeks are needed.

ACKNOWLEDGEMENTS

As part of the pre-publication editorial process, this review has been commented on by five peers (an editor and four referees who are external to the editorial team), a member of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.

The National Institute for Health Research (NIHR) is the largest single funder of the Cochrane Pregnancy and Childbirth Group. The views and opinions expressed therein are those of the authors

and do not necessarily reflect those of the NIHR, NHS or the Department of Health.

REFERENCES

References to studies excluded from this review

De Santis 2003 {published data only}

De Santis M, Scavo M, Noia G, Masini L, Piersigilli F, Romagnoli C, et al. Transabdominal amnioinfusion treatment of severe oligohydramnios in preterm premature rupture of membranes at less than 26 gestational weeks. *Fetal Diagnosis and Therapy* 2003;**18**(6):412–7.

Gonzalez 2001 {published data only}

Gonzalez R, Malde J, Carrillo MP, Sancho-Minano J, Garrote A, Munoz A, et al. The use of amnioinfusion in preterm deliveries. Preliminary results [abstract]. *Journal of Perinatal Medicine* 2001;**29** Suppl 1(Pt 2):629.

Gowri 2004 {published data only}

Gowri R, Soundararaghavan S. Evaluation of transabdominal amnioinfusion in the antepartum management of oligohydramnios complicating preterm pregnancies. *Journal of Obstetrics and Gynecology of India* 2004;**54**(5):460–3.

Leake 1983 {published data only}

Leake RD, Hobel CJ, Okada DM, Ross MG, Williams PR. Neonatal metabolic effects of oral ritodrine hydrochloride administration. *Pediatric Pharmacology* 1983;**3**:101–6.

Nageotte 1985 {published data only}

Nageotte MP, Freeman RK, Garite TJ, Dorchester W. Prophylactic intrapartum amnioinfusion in patients with preterm premature rupture of membranes. *American Journal of Obstetrics and Gynecology* 1985;**153**:557–62.

Puertas 2007 {published data only}

Puertas A, Tirado P, Perez I, Lopez MS, Montoya F, Canizares JM, et al. Transcervical intrapartum amnioinfusion for preterm premature rupture of the membranes. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2007;**131**(1):40–4.

Singla 2010 {published data only}

Singla A, Yadav P, Vaid NB, Suneja A, Faridi MM. Transabdominal amnioinfusion in preterm premature rupture of membranes. *International Journal of Gynecology & Obstetrics* 2010;**108**(3):199–202.

Tranquilli 2005 {published data only}

Tranquilli AL, Giannubilo SR, Bezzeccheri V, Scagnoli C. Transabdominal amnioinfusion in preterm premature rupture of membranes: a randomised controlled trial. *BJOG: an international journal of obstetrics and gynaecology* 2005;**112**(6):759–63.

Vergani 2007 {published data only}

Vergani P, Deprest J, Strobelt N, Locatelli A. Proposal for open randomized trial comparing perinatal outcome following expectant management versus amnioinfusion in PPRM < 25 weeks with persistent oligohydramnios

(amnioinfusion initiative) [abstract]. *Ultrasound in Obstetrics and Gynecology* 2007;**30**:541.

References to ongoing studies

Locatelli 2008 {published data only}

Locatelli A. Open randomized trial comparing perinatal outcome following expectant management versus amnioinfusion in PPRM <25 wks with persistent oligohydramnios. <http://clinicaltrials.gov/ct2/show/record/NCT00787163> (accessed 6 July 2012) 2008.

Roberts 2006 {published data only}

Roberts D, Alfirevic Z, Bricker L, Beardsmore C, Paturi P, Taylor S, et al. Amnioinfusion in preterm premature rupture of membranes (AMIPROM study). Current Controlled Trials (www.controlled-trials.com/) (accessed 23 March 2009).
Roberts D, Beardsmore C, Shaw B, Martin W, Vause S, Bricker L, et al. AMIPROM: a pilot RCT on serial transabdominal amnioinfusion versus expectant management in very early PROM. *Ultrasound in Obstetrics & Gynecology* 2012;**40**(Suppl 1):80.

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Chin 2009

Chin TW, Natarajan G, Abdulhamid I. Pediatric pulmonary hypoplasia treatment and management. <http://emedicine.medscape.com/article/1005696-treatment> (accessed 2012) 2009.

Egger 1997

Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**(7109):629–34.

Gramellini 2003

Gramellini D, Fieni S, Kaihura C, Piantelli G, Verrotti C. Antepartum amnioinfusion: a review. *Journal of Maternal-Fetal & Neonatal Medicine* 2003;**14**(5):291–6.

Hadi 1994

Hadi HA, Hodson CA, Strickland D. Premature rupture of the membranes between 20 and 25 weeks' gestation: role of amniotic fluid volume in perinatal outcome. *American Journal of Obstetrics and Gynecology* 1994;**170**(4):1139–44.

Harbord 2006

Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Statistics in Medicine* 2006;**25**(20):3443–57.

Higgins 2011

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March 2011]. The Cochrane Collaboration, 2011.
Available from www.cochrane-handbook.org.

Hofmeyr 2011

Hofmeyr GJ, Essilfie-Appiah G, Lawrie TA. Amnioinfusion for preterm premature rupture of membranes. *Cochrane Database of Systematic Reviews* 2011, Issue 12. DOI: 10.1002/14651858.CD000942.pub2

Laudy 2000

Laudy JA, Wladimiroff JW. The fetal lung. 2: Pulmonary hypoplasia. *Ultrasound in Obstetrics & Gynecology* 2000;**16**(5):482–94.

Lauria 1995

Lauria MR, Gonik B, Romero R. Pulmonary hypoplasia: pathogenesis, diagnosis, and antenatal prediction. *Obstetrics & Gynecology* 1995;**86**(3):466–75.

Nakayama 1983

Nakayama DK, Glick PL, Harrison MR, Villa RL, Noall R. Experimental pulmonary hypoplasia due to oligohydramnios and its reversal by relieving thoracic compression. *Journal of Pediatric Surgery* 1983;**18**(4):347–53.

Porat 2012

Porat S, Amsalem H, Shah PS, Murphy KE. Transabdominal amnioinfusion for preterm premature rupture of membranes: a systematic review and metaanalysis of randomized and observational studies. *American Journal of Obstetrics and Gynecology* 2012;**207**(5):393.e1–11. [PUBMED: 22999157]

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Sherer 1990

Sherer DM, Davis JM, Woods JR Jr. Pulmonary hypoplasia: a review. *Obstetrical & Gynecological Survey* 1990;**45**(11):792–803.

Tan 2003

Tan LK, Kumar S, Jolly M, Gleeson C, Johnson P, Fisk NM. Test amnioinfusion to determine suitability for serial therapeutic amnioinfusion in midtrimester premature rupture of membranes. *Fetal Diagnosis and Therapy* 2003;**18**(3):183–9. DOI: 10.1159/000069375

van Teeffelen 2010a

van Teeffelen AS, van der Ham DP, Oei SG, Porath MM, Willekes C, Mol BW. The accuracy of clinical parameters in the prediction of perinatal pulmonary hypoplasia secondary to midtrimester prelabour rupture of fetal membranes: a meta-analysis. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 2010;**148**(1):3–12. [PUBMED: 19892458]

Vergani 2004

Vergani P, Locatelli A, Verderio M, Assi F. Premature rupture of the membranes at <26 weeks' gestation: role of amnioinfusion in the management of oligohydramnios. *Acta Bio-Medica de L'Ateneo Parmense* 2004;**75**(Suppl 1):62–6.

Williams 2012

Williams O, Hutchings G, Hubinont C, Debauche C, Greenough A. Pulmonary effects of prolonged oligohydramnios following mid-trimester rupture of the membranes--antenatal and postnatal management. *Neonatology* 2012;**101**(2):83–90. [PUBMED: 21934333]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
De Santis 2003	Quasi-randomised study. Participants were admitted by chance into 1 of 2 departments and study treatment was given in only 1 of these departments
Gonzalez 2001	Preliminary results presented on 5th World Congress of Perinatal Medicine - Barcelona, Spain, 23-27 September, 2001, final data are not published to our knowledge
Gowri 2004	The criteria in this trial do not match the criteria for this review. In the trial 3 out of 17 study participants did match the criteria, however, data on their outcomes could not be extracted
Leake 1983	Participants and intervention do not match the criteria for this review
Nageotte 1985	The participants included in this review are women with PPRM between 26 and 35 weeks, intervention is done intrapartum rather than antepartum; this does not fit the criteria for this review
Puertas 2007	Intervention and women do not fit the criteria for this review (intervention: transcervical intrapartum amnioinfusion rather than transabdominal amnioinfusion. Participants were women with PPRM between 27 and 35 weeks)
Singla 2010	The participants included in this review are women with PPRM between 26 and 33 + 6 weeks; this does not fit the criteria for this review
Tranquilli 2005	The participants included in this review are women with PPRM between 24 and 33 weeks; this does not fit the criteria for this review
Vergani 2007	This is a proposal for a randomised controlled trial. Final results of this trial have not been published to our knowledge, starting date is not stated. Author is co-author of the ongoing study (Locatelli 2008).

PPROM: preterm prelabour rupture of membranes

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

[Locatelli 2008](#)

Trial name or title	Amnioinfusion Initiative: open randomized trial comparing perinatal outcome following expectant management versus amnioinfusion in PPRM < 25 wks with persistent oligohydramnios
Methods	Open, multicentre randomised trial. Sample size not stated.

Locatelli 2008 (Continued)

Participants	Inclusion criteria: single pregnancy, early spontaneous PPROM < 24.3 weeks, oligohydramnios (deepest vertical pocket < 2 cm) for at least 4 days and no longer than 15 days at enrolment
Interventions	Serial amnioinfusions.
Outcomes	Primary outcome: survival till discharge from the neonatal intensive care unit. Secondary outcomes: latency time from PPROM to delivery, gestational age at birth, indication for delivery, number of days of ventilatory support, serious neurologic morbidity, neonatal sepsis prevalence, need for oxygen at 36 weeks post-conception
Starting date	September 2008.
Contact information	Anna Locatelli, MD Tel: +39 039 233 4720 anna.locatelli@unimib.it
Notes	Final data have not been published to our knowledge.

Roberts 2006

Trial name or title	Amnioinfusion in preterm premature rupture of membranes (AMIPROM study)
Methods	Randomised controlled trial.
Participants	15 women with pregnancies with very early PROM in each arm.
Interventions	Serial amnioinfusions.
Outcomes	The study will compare the neonatal, maternal and pregnancy outcomes
Starting date	01/10/2007.
Contact information	Dr Devender Roberts Fetal Centre Liverpool Women's Hospital Crown Street Liverpool United Kingdom L8 7SS +44 (0)151 708 9988
Notes	Final data have not been published to our knowledge.

PPROM: preterm prelabour rupture of membranes

APPENDICES

Appendix I. Data collection and analysis methods to be used in future updates of this review

Data collection and analysis

Selection of studies

Two review authors (Stijn Van Teeffelen (SvT) and Eva Pajkrt (EP)) will independently assess for inclusion all the potential studies we identify as a result of the search strategy. We will resolve any disagreement through discussion or, if required, we will consult Ben Willem Mol (BWM).

Data extraction and management

We will design a form to extract data. For eligible studies, at least two review authors will extract the data using the agreed form. We will resolve discrepancies through discussion or, if required, we will consult BWM. Data will be entered into Review Manager software (RevMan 2011) and checked for accuracy.

When information regarding any of the above is unclear, we will attempt to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors (SvT and EP) will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions (Handbook)* (Higgins 2011). Any disagreement will be resolved by discussion or by involving a third assessor (BWM).

(1) Random sequence generation (checking for possible selection bias)

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

We will assess the method as:

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

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

We will describe for each included study the method used to conceal allocation to interventions prior to assignment and will assess whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We will assess the methods as:

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

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

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

We will assess the methods as:

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

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

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

We will assess methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

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

We will assess methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation). We will categorise studies with more than 10% missing data as inadequate;
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

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

We will assess the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; 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 risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We will describe for each included study any important concerns we have about other possible sources of bias.

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

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

(7) Overall risk of bias

We will make explicit judgements about whether studies are at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2011). With reference to (1) to (6) above, we will assess the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. We will explore the impact of the level of bias through undertaking sensitivity analyses - see Sensitivity analysis.

Measures of treatment effect

Dichotomous data

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

Continuous data

For continuous data, we will use the mean difference if outcomes are measured in the same way between trials. We will use the standardised mean difference to combine trials that measure the same outcome, but use different methods.

Dealing with missing data

If details on the study design, participants or methods are missing, or details of outcomes measures (e.g. summary statistics) are incompletely presented in a paper, we will contact the trial authors. If they do not respond in a reasonable time (i.e. six weeks), we will use the available information. On the study level, we will note levels of attrition. For all outcomes, we will carry out analyses, as far as possible, on an intention-to-treat basis, i.e. we will attempt to include all participants randomised to each group in the analyses, and all participants will be analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial will be the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

We will assess statistical heterogeneity in each meta-analysis using the T^2 , I^2 and Chi^2 statistics. We will regard heterogeneity as substantial if the I^2 is greater than 30% and either the T^2 is greater than zero, or there is a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

If there are 10 or more studies in the meta-analysis, we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually, and use formal tests for funnel plot asymmetry. For continuous outcomes we will use the test proposed by [Egger 1997](#), and for dichotomous outcomes we will use the test proposed by [Harbord 2006](#). If asymmetry is detected in any of these tests or is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We will carry out statistical analysis using the Review Manager software ([RevMan 2011](#)). We will use fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are estimating the same underlying treatment effect: i.e. where trials are examining the same intervention, and the trials' populations and methods are judged sufficiently similar. If there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity is detected, we will use random-effects meta-analysis to produce an overall summary if an average treatment effect across trials is considered clinically meaningful. The random-effects summary will be treated as the average range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful, we will not combine trials.

If we use random-effects analyses, the results will be presented as the average treatment effect with its 95% confidence interval, and the estimates of T^2 and I^2 .

Subgroup analysis and investigation of heterogeneity

If we identify substantial heterogeneity, we will investigate it using subgroup analyses. We will consider whether an overall summary is meaningful, and if it is, use random-effects analysis to produce it.

We plan to carry out two subgroup analysis for the primary outcome. In the first subgroup analysis we will assess the differences between the participants from the intervention group who retain amniotic fluid ('successful amnioinfusion') versus the standard care group, and the differences between the participants from the intervention group who do not retain amniotic fluid ('unsuccessful' amnioinfusion) versus the standard care group. The reason for this subgroup analysis is to test if even without retainment of amniotic fluid, amnioinfusion is beneficial (by means of dilution and flushing of contaminated material in the womb) compared with standard care. Successful amnioinfusion as defined by study specific criteria for diagnosing oligohydramnios (timing of measurement, cut-off value used for ultrasound assessment of amount of fluid).

In the literature, the incidence of spontaneous re-accumulation of amniotic fluid after PPRM has been reported as 25% ([Hadi 1994](#)). The incidence of retainment of transabdominally amnioinfused fluid after PPRM has been reported by two authors. Tan et al. found

in 27 amnioinfused women retainment of fluid after 48 hours in only four cases (24%), whereas this was 30% in 36 women in a study by Vergani et al (Tan 2003; Vergani 2004). Hypothetically, the retainment of amnioinfused fluid could be partly caused by nothing more than spontaneous re-accumulation. This could be due to spontaneous resealing of the membrane defect, which occurs anyway in some women, with or without amnioinfusion. In that case benefit from amnioinfusion would be small or even absent.

Therefore, in the second subgroup analysis we will compare the groups with retainment of amniotic fluid in the treatment group, versus the group with spontaneous re-accumulation in the standard care group, and the group which does not retain amniotic fluid with the group in the standard care group that shows no signs of spontaneous re-accumulation. This is possible if frequent ultrasound monitoring of amniotic fluid volume is done in both groups. This subgroup analysis will only be performed if enough data are available from the randomised trials.

We will assess subgroup differences by interaction tests available within RevMan (RevMan 2011). We will report the results of subgroup analyses quoting the χ^2 statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

If applicable, we will conduct sensitivity analyses to determine the impact on the overall study outcome by (1) excluding studies at high risk of bias, (allocation and sequence generation) and (2) excluding studies that describe a loss to follow-up of over 25%.

CONTRIBUTIONS OF AUTHORS

Stijn van Teeffelen: designing and co-ordinating the review. Data collection for the review. Screening retrieved papers against the eligibility criteria. Writing the review.

Ben Willem J Mol: conceiving and providing general advice on the review. Screening retrieved papers against eligibility criteria. Providing a methodological perspective on the review.

Eva Pakr: providing general advice on the review. Screening retrieved papers against the eligibility criteria. Providing a clinical perspective on the review.

Christine Willekes: providing general advice on the review. Providing a clinical perspective on the review.

Sander van Kuijk: providing a methodological perspective on the review.

DECLARATIONS OF INTEREST

None known.

INDEX TERMS

Medical Subject Headings (MeSH)

*Amnion; *Fetal Membranes, Premature Rupture; *Obstetric Labor, Premature; Abnormalities, Multiple [prevention & control]; Fluid Therapy; Gestational Age; Infusions, Parenteral [*methods]; Lung [abnormalities]; Lung Diseases [prevention & control]; Oligohydramnios [etiology; *therapy]

MeSH check words

Female; Humans; Pregnancy