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[Intervention Review]

Amnioinfusion for third trimester preterm premature rupture of membranes

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ABSTRACT

Background

Preterm premature rupture of membranes (PPROM) is a leading cause of perinatal morbidity and mortality. Amnioinfusion aims to restore amniotic fluid volume by infusing a solution into the uterine cavity.

Objectives

The objective of this review was to assess the effects of amnioinfusion for PPROM on perinatal and maternal morbidity and mortality.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (2 December 2013).

Selection criteria

Randomised trials of amnioinfusion compared with no amnioinfusion in women with PPROM.

Data collection and analysis

Three review authors independently assessed trials for inclusion. Two review authors independently assessed trial quality and extracted data. Data were checked for accuracy.

Main results

We included five trials, of moderate quality, but we only analysed data from four studies (with a total of 241 participants). One trial did not contribute any data to the review.

Transcervical amnioinfusion improved fetal umbilical artery pH at delivery (mean difference 0.11; 95% confidence interval (CI) 0.08 to 0.14; one trial, 61 participants) and reduced persistent variable decelerations during labour (risk ratio (RR) 0.52; 95% CI 0.30 to 0.91; one trial, 86 participants).

Transabdominal amnioinfusion was associated with a reduction in neonatal death (RR 0.30; 95% CI 0.14 to 0.66; two trials, 94 participants), neonatal sepsis (RR 0.26; 95% CI 0.11 to 0.61; one trial, 60 participants), pulmonary hypoplasia (RR 0.22; 95% CI 0.06 to 0.88; one trial, 34 participants) and puerperal sepsis (RR 0.20; 95% CI 0.05 to 0.84; one trial, 60 participants). Women in the amnioinfusion group were also

less likely to deliver within seven days of membrane rupture (RR 0.18; 95% CI 0.05 to 0.70; one trial, 34 participants). These results should be treated with circumspection as the positive findings were mainly due to one trial with unclear allocation concealment.

Authors' conclusions

These results are encouraging but are limited by the sparse data and unclear methodological robustness, therefore further evidence is required before amnioinfusion for PPRM can be recommended for routine clinical practice.

PLAIN LANGUAGE SUMMARY

Amnioinfusion for preterm premature rupture of membranes

There is some evidence to show that restoring amniotic fluid volume with saline or a similar fluid (amnioinfusion) following preterm premature rupture of the membranes (PPROM) may be beneficial for preterm babies (by preventing infection, lung damage and death) and mothers (by preventing infection of the womb after childbirth). However, current evidence is insufficient to recommend amnioinfusion for routine use in PPRM.

Preterm premature rupture of membranes is the single most identifiable cause of preterm labour. The sac (membranes) surrounding the baby and fluid in the womb (uterus) usually breaks (ruptures) during labour. If the membranes rupture before labour and preterm (before 37 weeks) the baby has an increased risk of infection. Reduced fluid around the baby also increases the chance of the umbilical cord being compressed, which can reduce the baby's supply of nutrients and oxygen. In addition, insufficient fluid in the womb may interfere with normal lung development in very small babies and can cause fetal distress, with changes in heart rate. Extra liquid can be injected through the woman's vagina (transcervical amnioinfusion) or abdomen (transabdominal amnioinfusion) into the womb, providing more liquid to surround the baby. The review of five randomised controlled trials (with data from a total of 241 participants analysed) found some evidence to show that amnioinfusion with a saline solution may improve health outcomes and be beneficial for babies and mothers following PPRM. However, the evidence is currently insufficient to recommend its routine use because of the limited number of trials and low numbers of women in the trials.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Transabdominal amnioinfusion compared with no amnioinfusion for preterm rupture of membranes (PROM)

Patient or population: pregnant women with PROM

Settings: hospital

Intervention: transabdominal amnioinfusion

Comparison: no amnioinfusion

Out-comes	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Neonatal death	RR 0.30 (0.14 - 0.66)	94 (two studies)	⊕⊕⊕⊖ moderate	Risk of neonatal death in the amnioinfusion group was 127 per 1000 compared to 426 per 1000 in the control group.
Neonatal sepsis/infection	RR 0.26 (0.11 - 0.61)	60 (one study*)	⊕⊕⊕⊖ moderate	*Sepsis defined as micro-erythrocyte sedimentation rate > 5 mm, total leucocyte count < 5000, CRP > 6 mg/dL, platelet count < 100,000 or a positive blood culture within the first 48 hours.
Pulmonary hypoplasia	RR 0.22 (0.06 - 0.88)	34 (one study)	⊕⊕⊖⊖ low	Pulmonary hypoplasia was diagnosed according to strict clinical and radiological criteria, however, this study was small and blinding to group allocation was not described and so we downgraded this evidence from moderate to low. More evidence is needed.
Maternal puerperal sepsis	RR 0.20 (0.05 - 0.84)	60 (one study**)	⊕⊕⊕⊖ moderate	**Defined as fever > 38° C and a positive high vaginal swab culture.

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

CI: confidence interval; **CRP:** C-reactive protein; **RR:** risk ratio

BACKGROUND

Description of the condition

Preterm premature rupture of membranes (PPROM) remains the single most identifiable cause of preterm labour and a major contributor to perinatal mortality and morbidity. Oligohydramnios (reduced amniotic fluid volume) following PPRM is associated with a higher risk of chorioamnionitis, neonatal fetal infection and cord compression (Keirse 1989; Vintzileos 1985). Umbilical cord compression may cause persistent variable fetal heart rate decelerations (Gabbie 1976). Oligohydramnios is also the most important predictor of perinatal mortality in very early PPRM and adequate residual amniotic fluid plays a critical role in determining the prevalence of pulmonary hypoplasia, which is a major cause of death in these babies (Vergani 1994; Vintzileos 1985). Abnormal neurological outcomes and postural deformities in the neonate may also occur as a consequence of PPRM (Locatelli 2000).

Description of the intervention

Saline fluid or Ringers lactate/Hartmans is infused transcervically through a catheter into the uterine cavity, or transabdominally, through a narrow gauge needle. Amnioinfusion was first described as a method of preventing or relieving umbilical cord compression during labour (Miyazaki 1983). The technique has since been used prophylactically in various conditions associated with oligohydramnios, including impaired intrauterine growth and PPRM. Amnioinfusion has been shown to prolong the latency period in second trimester PPRM (Locatelli 2000; Ogunyemi 2002; Turhan 2002), improve perinatal survival (Locatelli 2006; Ogunyemi 2002) and decrease rates of pulmonary hypoplasia (Locatelli 2000). Combined with antibiotics and without, it has been used to treat and to prevent infection following premature rupture of membranes (Goodlin 1981; Monahan 1995; Ogita 1988). In a Cochrane review on amnioinfusion for suspected or potential cord compression in labour at term, amnioinfusion improved short-term measures of neonatal outcome, reduced the use of caesarean section and reduced maternal puerperal sepsis (Hofmeyr 2012). A subcutaneously implanted amniotic fluid replacement port system has been developed for long-term amnioinfusion in women with preterm premature rupture of the membranes (Tchirikov 2010).

How the intervention might work

Restoring the amniotic fluid volume cushions the fetus, thereby preventing mechanical compression of the umbilical cord and reducing fetal distress. It may prevent fetal lung hypoplasia in PPRM by preventing mechanical compression of the fetal thorax and enabling normal amniotic fluid flow into the fetal lungs (Tranquilli 2005). This effect occurs mainly in the second trimester and is considered in a separate review (Van Teeffelen 2013). Likewise, by preventing mechanical compression of the fetus, amnioinfusion may prevent postural deformities. In addition, the infused fluid may prevent intrauterine infection, possibly by the anti-bacterial effect of saline, or a diluent effect. Improvements in fetal ductus venosus and umbilical artery flow have been demonstrated following amnioinfusion for PPRM (Hsu 2009).

Why it is important to do this review

Evidence from cohort studies suggests that replenishing the amniotic fluid volume in pregnancies complicated by PPRM is beneficial to mother and child. However, amnioinfusion is an

invasive procedure and not without potential risks, thus a thorough evaluation of randomised controlled trials is required.

[*'Amnioinfusion for cord compression'* (Hofmeyr 2012), *'Prophylactic versus therapeutic amnioinfusion'* (Novikova 2012), and *'Amnioinfusion for meconium-stained liquor'* (Hofmeyr 2014), are separate reviews.]

OBJECTIVES

To assess from the best available evidence the effects of amnioinfusion for preterm premature rupture of membranes on perinatal morbidity and mortality.

METHODS

Criteria for considering studies for this review

Types of studies

Clinical trials comparing the effect of amnioinfusion for third trimester preterm premature rupture of the membranes before 37 weeks with a control group (no amnioinfusion); random allocation to treatment and control groups, with adequate allocation concealment; violations of allocated management and exclusions after allocation not sufficient to materially affect outcomes. Quasi-randomised (alternate allocation), cross-over and cluster trials were not considered eligible for inclusion.

Types of participants

Pregnant women with preterm premature rupture of membranes.

Types of interventions

Amnioinfusion compared with no amnioinfusion.

Types of outcome measures

Primary outcomes

- Indicators of fetal condition, e.g. persistent variable decelerations, Apgar scores, cord arterial pH at birth.
- Neonatal morbidity including infection, lung hypoplasia, abnormal neurological outcomes and postural deformities.
- Perinatal mortality.

Secondary outcomes

- Mode of delivery.
- Indications for delivery.
- Latency period from amnioinfusion to delivery.
- Maternal morbidity, e.g. endometritis, postpartum temperature greater than 38°C.
- Birthweight.
- Admission to neonatal intensive or high care unit.

We considered outcomes separately for transcervical and transabdominal amnioinfusion.

The methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

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 (2 December 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. monthly searches of Embase;
4. handsearches of 30 journals and the proceedings of major conferences;
5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

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

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

We did not apply any language restrictions.

Data collection and analysis

No new studies have been included for this update (2014).

For methods used in the previous version of this review, please see [Hofmeyr 2011](#).

For methods to be used in the next update, see [Appendix 1](#).

Selection of studies

T Lawrie (TL), AC Eke (ACE) and GJ Hofmeyr (GJH) independently assessed for inclusion all potential studies. No studies were identified from the updated search. Two studies previously in ongoing were excluded ([Roberts: AMIPROM](#); [Vergani 2007](#)). We resolved any disagreement through discussion. We evaluated trials under consideration for methodological quality and appropriateness for inclusion according to the prespecified selection criteria, without consideration of their results.

RESULTS

Description of studies

In total, we have included five studies; three in the transcervical amnioinfusion comparison ([Gonzalez 2001](#); [Nageotte 1985](#); [Puertas 2007](#)) and two in the transabdominal comparison ([Singla 2010](#); [Tranquilli 2005](#)). One included study contributed no data ([Gonzalez 2001](#)). See [Characteristics of included studies](#). The gestational age range for recruitment to the transcervical trials was 26 to 36+ weeks and in the transabdominal trials, 24 to 34 weeks. Transcervical amnioinfusion was performed in a total of 72 women versus 75 controls (excluding unusable data from [Gonzalez 2001](#)) and transabdominal amnioinfusion was performed in 47 women versus 47 controls; thus participant numbers for this review are small.

Risk of bias in included studies

All included studies were randomised trials. See [Figure 1](#) and [Figure 2](#) for a summary of 'Risk of bias' assessments.

Figure 1. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Gonzalez 2001	?	?	?	?	?	?	?
Nageotte 1985	?	?	?	+	?	?	?
Puertas 2007	+	+	?	+	+	+	?
Singla 2010	+	?	?	?	+	+	+
Tranquilli 2005	+	+	?	?	+	?	+

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Allocation

Randomisation was by random number table in Puertas 2007 and was computer-generated in Tranquilli 2005 and Singla 2010; the method of randomisation and group allocation was not described in Nageotte 1985 and Gonzalez 2001. Allocation concealment was described in two trials (Puertas 2007; Tranquilli 2005).

Blinding

Partial blinding was described in two trials (Nageotte 1985; Puertas 2007).

Incomplete outcome data

Incomplete outcome data were noted in the randomised clinical trial by Gonzalez et al. This is because it is an abstract only publication, hence provided insufficient detail for assessment (Gonzalez 2001). Five post-randomisation exclusions: three for non-vertex presentation and two for fetal distress were noted in the randomised trial by Nageotte et al (Nageotte 1985). Otherwise, outcome data were complete for Puertas 2007, Singla 2010 and Tranquilli 2005.

Selective reporting

In the randomised clinical trial by Tranquilli et al, the authors did not report the mode of delivery, Apgar scores or cord arterial pH for the babies delivered (Tranquilli 2005). No selective reporting was found in the Puertas 2007 and Singla 2010 trials. There was insufficient information to assess selective reporting in Gonzalez 2001 and Nageotte 1985.

Other potential sources of bias

Another source of bias was noted in the randomised clinical trial by Puertas et al, where more carriers of group B streptococcal were noted in control group (14 women versus seven women) (Puertas 2007). Even though all these women with Group B streptococcal infection received prophylactic intrapartum antibiotics, the higher incidence of Group B *Streptococcus* in the control group was a source of bias for the trial. No other biases were reported for Singla

2010 and Tranquilli 2005. There was insufficient information to assess other sources of bias in Gonzalez 2001 and Nageotte 1985.

Effects of interventions

See: [Summary of findings for the main comparison](#)

1. Transcervical amnioinfusion

Transcervical amnioinfusion improved fetal umbilical artery pH at delivery (mean difference (MD) 0.11; 95% confidence interval (CI) 0.08 to 0.14; one trial, 61 participants; [Analysis 1.6](#)) and reduced persistent variable decelerations during labour (risk ratio (RR) 0.52; 95% CI 0.30 to 0.91; one trial, 86 participants; [Analysis 1.1](#)). No significant differences in the rates of caesarean section, low Apgar scores, neonatal death or infectious morbidity were detected.

2. Transabdominal amnioinfusion

Transabdominal amnioinfusion was associated with a reduction in neonatal death (RR 0.30; 95% CI 0.14 to 0.66; two trials, 94 women; [Analysis 2.7](#)), neonatal infection/sepsis (RR 0.26; 95% CI 0.11 to 0.61; one trial, 60 participants; [Analysis 2.3](#)), and pulmonary hypoplasia (RR 0.22; 95% CI 0.06 to 0.88; one trial, 34 participants; [Analysis 2.3](#)). Women in the amnioinfusion group were also less likely to deliver within seven days of membrane rupture (RR 0.18; 95% CI 0.05 to 0.70; one trial, 34 participants; [Analysis 2.4](#)) and were less likely to experience puerperal sepsis (RR 0.20; 95% CI 0.05 to 0.84; one trial, 60 participants; [Analysis 2.9](#)). There were no significant differences between groups regarding birthweight, gestational age at delivery, admission to neonatal intensive care and neurological sequelae. Fetal distress was diagnosed less frequently in the amnioinfusion group than the control group (RR 0.27; 95% CI 0.08 to 0.88; one trial, 60 participants; [Analysis 2.1](#)), but in the absence of blinding this outcome is at risk of bias.

DISCUSSION

Summary of main results

Transabdominal amnioinfusion following preterm premature rupture of the membranes (PPROM) resulted in better neonatal outcomes (decreased sepsis, infection and death) and decreased puerperal sepsis than conventional management. The data contributing to these outcomes were mainly from one trial ([Singla 2010](#)). Transcervical amnioinfusion was associated with improved fetal heart rate patterns and umbilical cord blood pH results, but improvements in substantive clinical outcomes were not statistically significant.

Overall completeness and applicability of evidence

These results are not conclusive due to the small numbers of trials and participants. In addition, the numbers are too small to detect rare potential adverse events. The lower threshold of gestational age at which amnioinfusion may be of benefit is not known.

Quality of the evidence

The evidence is of mainly moderate quality ([Summary of findings for the main comparison](#)) and limitations can largely be attributed to the small size of studies and the lack of blinding to group allocation.

Agreements and disagreements with other studies or reviews

This evidence supports the positive findings of the non-randomised studies conducted to date.

AUTHORS' CONCLUSIONS

Implications for practice

There is currently insufficient evidence to guide clinical practice concerning the use of amnioinfusion for preterm premature rupture of the membranes.

Implications for research

Larger trials are needed to confirm and extend the findings of the trials reviewed here. Long-term follow-up of babies is desirable, especially with regard to neurological sequelae and development. Future trials and reviews may need to be stratified according to gestational age to determine whether there is a threshold for benefits and risks.

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REFERENCES

References to studies included in this review

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.

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 MMA. Transabdominal amnioinfusion in preterm premature rupture of membranes. *International Journal of Gynecology & Obstetrics* 2010;**108**:199-202.

Tranquilli 2005 {published data only}

Tranquilli AL, Giannubilo SR, Bezeccheri 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.

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.

Gowri 2004 {published data only}

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

Locatelli 2000 {published data only}

Locatelli A, Vergani P, Di Pirro G, Doria V, Biffi A, Ghidini A. Role of amnioinfusion in the management of premature rupture of membranes at < 26 weeks gestation. *American Journal of Obstetrics and Gynecology* 2000;**183**:878-82.

Mino 1999 {published data only}

Mino M, Puertas A, Carrillo M, Santiago J, Herruzo A, Miranda J. Influence of amnioinfusion on variable or prolonged

decelarations: a randomised study. *Acta Obstetrica et Gynecologica Scandinavica* 1997;**76**:95.

Mino M, Puertas A, Herruzo AJ, Miranda JA. Amnioinfusion in labor induction of term pregnancies with premature rupture of the membranes and low amniotic fluid. *International Journal of Gynecology & Obstetrics* 1998;**61**:135-40.

* Mino M, Puertas A, Miranda JA, Herruzo AJ. Amnioinfusion in term labor with low amniotic fluid due to rupture of membranes: a new indication. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 1999;**82**:29-34.

Mino M, Puertas A, Mozas J, Carrillo Badillo MP, Rodríguez Oliver A, Miranda JA. A modification of the amniotic fluid index after amnioinfusion for infants with early rupture of membranes [Modificación del índice de líquido amniótico tras amnioinfusión en gestantes con rotura prematura de membranas a término]. *Acta Ginecologica* 1997;**51**(1):11-4.

Puertas A, Mino M, Carrillo M, Mozas J, Herruzo A, Miranda J. Influence of amnioinfusion on neonatal acid-base state: a randomized study. *Acta Obstetrica et Gynecologica Scandinavica Supplement* 1997;**76**:94.

Roberts: AMIPROM {unpublished 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 17 December 2013).

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.

* Roberts D, Vause S, Martin W, Green P, Walkinshaw S, Bricker L, et al. Amnioinfusion in very early preterm premature rupture of membranes - pregnancy, neonatal and maternal outcomes in the AMIPROM randomised controlled pilot study. *Ultrasound in Obstetrics & Gynecology* 2013 Nov 21 [Epub ahead of print].

Roberts D, Vause S, Martin W, Green P, Walkinshaw S, Bricker L, et al. Pregnancy outcomes in AMIPROM: a pilot RCT on serial transabdominal amnioinfusion versus expectant management in very early preterm prelabour rupture of membranes. *BJOG: an international journal of obstetrics and gynaecology* 2013;**120**(Suppl s1):10.

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 PPROM < 25 weeks with persistent oligohydramnios (amnioinfusion initiative). *Ultrasound in Obstetrics and Gynecology* 2007;**30**:541.

Additional references

Gabbe 1976

Gabbe SG, Ettinger BB, Freeman RK, Martin CB. Umbilical cord compression associated with amniotomy: laboratory observations. *American Journal of Obstetrics and Gynecology* 1976;**126**(3):353-5.

Goodlin 1981

Goodlin RC. Intra-amniotic antibiotic infusions. *American Journal of Obstetrics and Gynecology* 1981;**139**(8):975.

Higgins 2011

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

Hofmeyr 2012

Hofmeyr GJ, Lawrie TA. Amnioinfusion for potential or suspected umbilical cord compression in labour. *Cochrane Database of Systematic Reviews* 2012, Issue 1. [DOI: [10.1002/14651858.CD000013.pub2](https://doi.org/10.1002/14651858.CD000013.pub2)]

Hofmeyr 2014

Hofmeyr GJ, Xu H, Eke AC. Amnioinfusion for meconium-stained liquor in labour. *Cochrane Database of Systematic Reviews* 2014, Issue 1. [DOI: [10.1002/14651858.CD000014.pub4](https://doi.org/10.1002/14651858.CD000014.pub4)]

Hsu 2009

Hsu TY, Hsu JJ, Fu HC, Ou CY, Tsai CC, Cheng BH, et al. The changes in Doppler indices of fetal ductus venosus and umbilical artery after amnioinfusion for women with preterm premature rupture of membranes before 26 weeks' gestation. *Taiwan Journal of Obstetrics and Gynecology* 2009;**48**(3):268-72.

Keirse 1989

Keirse MJNC, Ohlsson A, Treffers PE, Kanhai HHH. Prelabour rupture of the membranes preterm. In: Chalmers I, Enkin MW, Keirse MJNC editor(s). *Effective Care in Pregnancy and Childbirth*. Oxford: Oxford University Press, 1989:666-93.

Locatelli 2006

Locatelli A, Ghidini A, Verderio M, Andreani M, Strobelt N, Pezzullo J, et al. Predictors of perinatal survival in a cohort of pregnancies with severe oligohydramnios due to premature rupture of membranes at < 26 weeks managed with serial infusions. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2006;**128**(1-2):97-102.

Miyazaki 1983

Miyazaki FS, Taylor NA. Saline amnioinfusion for relief of prolonged variable decelerations. *American Journal of Obstetrics and Gynecology* 1983;**146**:670-8.

Monahan 1995

Monahan E, Katz VL, Cox RL. Amnioinfusion for preventing puerperal infection. A prospective study. *Journal of Reproductive Medicine* 1995;**40**(10):721-3.

Novikova 2012

Novikova N, Hofmeyr GJ, Essilfie-Appiah G. Prophylactic versus therapeutic amnioinfusion for oligohydramnios in labour. *Cochrane Database of Systematic Reviews* 2012, Issue 9. [DOI: [10.1002/14651858.CD000176.pub2](https://doi.org/10.1002/14651858.CD000176.pub2)]

Ogita 1988

Ogita S, Imanaka M, Matsumoto M, Oka T, Sugawa T. Transcervical amnioinfusion of antibiotics: a basic study for managing premature rupture of membranes. *American Journal of Obstetrics and Gynecology* 1988;**158**(1):23-7.

Ogunyemi 2002

Ogunyemi D, Thompson W. A case controlled study of serial transabdominal amnioinfusions in the management of second trimester oligohydramnios due to premature rupture of membranes. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2002;**102**(2):167-72.

RevMan 2012 [Computer program]

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

Tchirikov 2010

Tchirikov M, Steetskamp J, Hohmann M, Koelbl H. Long-term amnioinfusion through a subcutaneously implanted amniotic fluid replacement port system for treatment of PPROM in humans. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2010;**152**:30-3.

Turhan 2002

Turhan NO, Atacan N. Antepartum prophylactic transabdominal amnioinfusion in preterm pregnancies complicated by oligohydramnios. *International Journal of Gynecology & Obstetrics* 2002;**76**(1):15-21.

Van Teeffelen 2013

Van Teeffelen S, Pajkrt E, Willekes C, Van Kuijk SMJ, Mol BWJ. Transabdominal amnioinfusion for improving fetal outcomes after oligohydramnios secondary to preterm prelabour rupture of membranes before 26 weeks. *Cochrane Database of Systematic Reviews* 2013, Issue 8. [DOI: [10.1002/14651858.CD009952.pub2](https://doi.org/10.1002/14651858.CD009952.pub2)]

Vergani 1994

Vergani P, Ghidini A, Locatelli A, Cavallone M, Ciarla I, Cappellini A, et al. Risk factors of pulmonary hypoplasia in second trimester premature rupture of membranes. *American Journal of Obstetrics and Gynecology* 1994;**170**:1359-64.

Vergani 1997

Vergani P, Locatelli A, Strobelt N, Mariani S, Cavallone M, Arosio P, et al. Amnioinfusion for prevention of pulmonary hypoplasia in second-trimester rupture of membranes. *American Journal of Perinatology* 1997;**14**(6):325-9.

Vintzileos 1985

Vintzileos AM, Campbell WA, Nochimson DJ, Weinbaum PJ. Degree of oligohydramnios and pregnancy outcome in patients

with premature rupture of membranes. *Obstetrics & Gynecology* 1985;**66**(2):162-7.

References to other published versions of this review

Hofmeyr 1995

Hofmeyr GJ. Amnioinfusion for preterm prelabour rupture of membranes [revised 22 April 1993]. In: Enkin MW, Keirse MJNC, Renfrew MJ, Neilson JP, Crowther C (eds.) *Pregnancy and Childbirth Module*. In: The Cochrane Database of Systematic Reviews [database on disk and CDROM]. The Cochrane Collaboration; Issue 2, Oxford: Update Software; 1995.

Hofmeyr 1998b

Hofmeyr GJ. Amnioinfusion for preterm rupture of membranes. *Cochrane Database of Systematic Reviews* 1998, Issue 1. [DOI: [10.1002/14651858.CD000942](https://doi.org/10.1002/14651858.CD000942)]

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](https://doi.org/10.1002/14651858.CD000942.pub2)]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Gonzalez 2001

Methods	Randomised trial. Type of randomisation not specified. Abstract only.
Participants	44 pregnant women with gestational ages from 189-258 days (24 in amnioinfusion group and 20 controls).
Interventions	Amnioinfusion versus no amnioinfusion. Inclusion and exclusion criteria not specified.
Outcomes	Fetal heart rate variability, mode of delivery, cord arterial pH and perinatal morbidity.
Notes	This is an abstract only; we are not aware of any published final results. The abstract results are presented as percentages only without denominators and so could not be used in this review. Amnioinfusion reduced the percentage of caesarean sections done for fetal distress compared with the control group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Abstract only, insufficient detail provided for assessment.
Selective reporting (reporting bias)	Unclear risk	Abstract only, insufficient detail provided for assessment.

Amnioinfusion for third trimester preterm premature rupture of membranes (Review)

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Gonzalez 2001 (Continued)

Other bias	Unclear risk	Abstract only, insufficient detail provided for assessment.
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Nageotte 1985

Methods	'Assigned in a random fashion.'
Participants	<p>Inclusion criteria: spontaneous premature rupture of membranes; gestational age 26 to 35 weeks; decreased or absent amniotic fluid; vertex presentation; no gross fetal anomalies.</p> <p>Exclusion criteria: premature labour on admission; vaginal bleeding; previous caesarean section and no desire for trial of labour; antepartum fetal distress; consent refused.</p> <p>1 woman with twin pregnancy and 1 with previous caesarean section were allocated to the amnioinfusion group.</p> <p>Of 66 women allocated, 3 were excluded for a change from the vertex presentation at the time of labour, and 2 for antepartum fetal distress. Of the remainder, 29 were allocated to amnioinfusion and 32 to the control group.</p>
Interventions	<p>Labour commenced spontaneously, or induced for confirmed fetal pulmonary maturity or infection. All women had fetal scalp electrodes and uterine pressure catheters placed as early in labour as possible. Amnioinfusion with warmed saline at 10 mL per minute for 1 hour (repeated if a large volume of fluid was lost), then 3 mL per minute (total volume infused mean 1160, range 735-1650 mL); compared with no amnioinfusion.</p> <p>Caesarean section was performed for persistent late decelerations; recurrent severe variable decelerations; recurrent or uncorrectable prolonged decelerations (no mention of fetal scalp blood sampling).</p>
Outcomes	Amnionitis (2 of the following: fever 38 degrees celsius or more; leucocytosis > 15,000 per microlitre; foul-smelling amniotic fluid; uterine tenderness); intrapartum fetal heart rate tracings, evaluated in a blinded manner; endometritis (postpartum fever > 38 degrees celsius twice 4 hours apart, and uterine tenderness or foul-smelling lochia); Apgar scores; umbilical cord arterial and venous pH; neonatal morbidity and mortality.
Notes	<p>Long Beach, California, USA. March 1984 to March 1985.</p> <p>Of 66 women allocated, 5 (7.6%) were excluded, 3 for a change from the vertex presentation at the time of labour, and 2 for antepartum fetal distress.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Fetal heart rate tracings evaluated in a blinded manner.

Amnioinfusion for third trimester preterm premature rupture of membranes (Review)

Nageotte 1985 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	5 post-randomisation exclusions: 3 for non-vertex presentation and 2 for fetal distress.
Selective reporting (reporting bias)	Unclear risk	Unclear.
Other bias	Unclear risk	Unclear.

Puertas 2007

Methods	Random allocation to 2 groups using a random number table and opaque sealed envelopes.
Participants	Inclusion criteria: women with preterm premature rupture of membranes between 27 and 35 weeks of gestation; included if labour had begun spontaneously or after induction. Exclusion criteria: women with multiple gestation, presentation other than cephalic, cervical dilatation > 5 cm, cardiotocography signs compatible with non-reassuring fetal status, meconium-stained amniotic fluid, umbilical cord prolapse, uterine scarring, placenta praevia, premature detachment of the placenta, any vaginal bleeding of unknown cause, presence of oligohydramnios (amniotic fluid index < 5) prior to premature rupture of the membranes, maternal infection that could be transmitted to the fetus (human immunodeficiency virus and herpes simplex virus), fetal anomalies incompatible with life, or any known obstetric or maternal complication other than premature rupture of membranes.
Interventions	Intrapartum transcervical amnioinfusion versus a control group that had an intrauterine pressure catheter inserted but without amnioinfusion. Physiological saline at 37 degree celsius, at a rate of 600 mL/hr during the first hour. After 1 hour, amniotic fluid index was determined, and if amniotic fluid index was greater than 15, amnioinfusion was stopped. In all other women in the study group amnioinfusion continued at a rate of 180 mL/hr until the cervix was completely dilated. Fetal heart rate and uterine activity were recorded continuously throughout labour. All women who were group B streptococcus carriers received prophylactic intrapartum antibiotics.
Outcomes	Mode of delivery, PH and arterial blood concentrations, neonatal morbidity, puerperal morbidity.
Notes	More group B streptococcal carriers in control group (14 women versus 7 women).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table.
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Partial blinding. Changes in fetal heart rate analysed with the Cabaniss classification by an independent investigator.
Incomplete outcome data (attrition bias)	Low risk	Outcome data complete.

Amnioinfusion for third trimester preterm premature rupture of membranes (Review)

Puertas 2007 (Continued)

All outcomes

Selective reporting (reporting bias)	Low risk	No selective reporting.
Other bias	Unclear risk	More group B streptococcal carriers in control group (14 women versus 7 women).

Singla 2010

Methods	Randomised controlled trial conducted in Delhi, India between August 2005 and 2007.
Participants	60 women with singleton pregnancies (30 in each group) between 26 and 33 + 6 weeks' gestation with amniotic fluid index less than the 5th percentile. Excluded if evidence of chorioamnionitis, placental or fetal anomalies or active labour. Diagnosis of preterm rupture of membranes was made via the litmus paper test and confirmed using ultrasound.
Interventions	Transcervical amnioinfusion with normal saline repeated weekly if amniotic fluid index < 5 versus no amnioinfusion. All women received bed rest, antibiotics and steroids.
Outcomes	Preterm rupture of membranes to delivery interval; neonatal outcome including birthweight, intra-partum fetal distress defined as persistent tachycardia and recurrent, late or severe decelerations; early neonatal sepsis; neonatal mortality; causes of neonatal mortality; mode of delivery; postpartum sepsis.
Notes	No loss to follow-up. Baseline characteristics were similar between groups. 5 women received amnioinfusion twice, 1 woman received it 3 times.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random number table.
Allocation concealment (selection bias)	Unclear risk	Not described: "To exclude observer bias, randomisation was performedusing a computer generated random number table..." There was no mention of allocation concealment (e.g. sealed opaque envelopes).
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up.
Selective reporting (reporting bias)	Low risk	No selective reporting.
Other bias	Low risk	None other bias was noted.

Amnioinfusion for third trimester preterm premature rupture of membranes (Review)

Tranquilli 2005

Methods	Randomised controlled trial using opaque sealed envelopes and a computer random-number generator. 44 women met inclusion criteria, 4 refused to participate and 6 delivered before randomisation, leaving 34 women to be randomised.
Participants	Pregnant women included if: singleton pregnancies complicated by preterm premature rupture of membranes, gestational age between 24 and 33 weeks, evidence of preterm premature rupture of membrane within 24 hours of admission, oligohydramnios, absence of uterine contractions at the time of hospitalisation, no placental anomalies or major structural fetal anomalies and normal cardiotocography at the time of admission.
Interventions	17 women were allocated to amnioinfusion and 17 to no amnioinfusion. All women received bedrest and antibiotic prophylaxis and corticosteroid therapy. Prophylactic tocolytic treatment was administered if there were no clinical signs of chorioamnionitis or placental abruption. Women in the treatment group received weekly serial amnioinfusion if the amniotic fluid index fell below the 5th centile and/or a median pocket of amniotic fluid was < 2 cm. The mean volume infused was 250 mL N/saline (range 120-350 mL), the aim was to restore the amniotic fluid index to > 10th percentile. The amniotic fluid index was measured after the procedure and it was repeated after 24 hours and at least once weekly. If amniotic fluid index was ≤ 5 , the amnioinfusion was repeated weekly until 27 weeks of gestation. A non-stress test was performed daily. Caesarean section was done for chorioamnionitis and fetal distress (defined as persistent tachycardia with reduced variability, recurrent late or severe variable decelerations).
Outcomes	Birthweight; admission to neonatal intensive care unit; gestational age at delivery (weeks); pulmonary hypoplasia diagnosed on the basis of strict clinical and radiological criteria at 1 and 3 months after delivery; abnormal neurological outcomes. The preterm premature rupture of membrane-delivery interval was also determined.
Notes	Study conducted at the Salesi Mothers' and Children's Hospital, Ancona, Italy, from January-December 2002.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated.
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data were complete.
Selective reporting (reporting bias)	Unclear risk	Authors do not report mode of delivery, Apgar scores or cord arterial pH.

Tranquilli 2005 (Continued)

Other bias Low risk No other bias noted.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
De Santis 2003	The quality of the randomisation process was poor. Women were by chance admitted into 1 of the 2 divisions of the department of obstetrics and gynaecology. Among the 71 women who were included in the study, 37 underwent serial amnioinfusion and 34 were used as controls. Also included in the study were women who underwent preterm rupture of membrane after amniocentesis for prenatal diagnosis. 10 patients (27.0%) in the amnioinfusion group and 8 patients (23.5%) in the control group. The study is also limited by the long period in which it was performed due to the low prevalence of this disease. The control group was selected without proper randomisation therefore bias could not be excluded during the selection process.
Gowri 2004	Randomised controlled trial of amnioinfusion versus no amnioinfusion for oligohydramnios. Small numbers (9 controls versus 8 study participants), only 3 study participants who received amnioinfusion had premature rupture of membranes and these outcome data were not extractable from totals.
Locatelli 2000	<p>The study was not a randomised controlled trial. All singleton pregnancies with preterm premature rupture of membranes at < 26 weeks' gestation and lasting > 4 days between January 1991 and June 1998 were included. Consenting women with persistent (> 4 days) oligohydramnios (maximum cord-free pocket of amniotic fluid volume less or equal to 2 cm) received serial transabdominal amnioinfusions to maintain an amniotic pocket > 2 cm. The pregnancy, neonatal, and long-term neurological outcomes of the cases that spontaneously maintained a median amniotic fluid pocket > 2 cm (amnioinfusion-not-necessary group) were compared with those of women with oligohydramnios who underwent amnioinfusion but continued to have a median amniotic fluid pocket after preterm premature rupture of membranes (amniotic fluid pocket less or equal to 2 cm/persistent oligohydramnios group) and with those of women in whom oligohydramnios was alleviated by amnioinfusion for at least 48 hours (successful amnioinfusion group).</p> <p>The study also incorporated 18 cases that had been previously reported in Vergani 1997.</p>
Mino 1999	Study population were women with ruptured membranes at term, not preterm.
Roberts: AMIPROM	Excluded because even though this is a randomised controlled trial involving preterm premature rupture of membrane and amnioinfusion, the gestational ages when the preterm premature rupture of membrane occurred were in the 2nd trimester of pregnancy. There are no reported data for 3rd trimester outcomes. This was a prospective non-blinded randomised controlled trial with randomisation stratified for pregnancies where the membranes ruptured between 16 + 0 and 19 + 6 weeks' gestation and 20 + 0 and 23 + 6 weeks' gestation to minimise the risk of random imbalance in gestational age distribution between randomised groups. This study was carried out in 4 UK hospital-based Fetal Medicine Units (Liverpool Women's NHS Trust, St. Mary's Hospital Manchester, Birmingham Women's NHS Foundation Trust, Wirral University Hospitals Trust). Participants were randomly allocated to either serial weekly trans-abdominal amnioinfusions if the deepest pool of amniotic fluid was < 2 cm or expectant management until 37 weeks of pregnancy. Short-term maternal, pregnancy and neonatal and long-term outcomes for the child were studied. Long-term respiratory morbidity was assessed using validated respiratory questionnaires at 6, 12 and 18 months of age and infant lung function test at around 12 months of age. Neurodevelopment was assessed using Bayley's Scale of Infant Development II at corrected age of 2.
Vergani 2007	Excluded because even though this is a randomised controlled trial involving preterm premature rupture of membrane and amnioinfusion, the gestational ages to be considered are preterm premature rupture of membranes that occurred in the 2nd trimester of pregnancy (< 24 weeks). The study will consider singleton pregnancies, early spontaneous preterm premature rupture of mem-

Study	Reason for exclusion
	brane < 24.3 weeks, oligohydramnios (deepest vertical pocket < 2 cm) for at least 4 days and no longer than 15 days at enrolment. The study is open and will be run through a dedicated password protected website, and with a minimal number of outcome measures. Primary outcomes include survival until discharge from the neonatal intensive care unit, while secondary outcomes include latency time from preterm premature rupture of membrane 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. Statistics: 38 patients in each arm are necessary to show an increase in neonatal survival from 10% to 40%, with a power of 0.80 and alpha = 0.05. An interim analysis after recruitment of 75% of the study population will be held in order to re-calculate sample size according to the difference between the groups in latency time as the main secondary outcome.

DATA AND ANALYSES

Comparison 1. Transcervical amnioinfusion for preterm rupture of membranes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Persistent variable decelerations	1	86	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.30, 0.91]
2 Severe variable decelerations per hour in first stage	1	61	Mean Difference (IV, Fixed, 95% CI)	-1.2 [-1.83, -0.57]
3 Caesarean section	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Caesarean section overall	2	147	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.25, 1.73]
3.2 Caesarean section for fetal distress	1	86	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.12, 1.55]
4 Forceps/vacuum assisted delivery	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Overall	1	86	Risk Ratio (M-H, Fixed, 95% CI)	1.2 [0.58, 2.48]
4.2 For fetal distress	1	86	Risk Ratio (M-H, Fixed, 95% CI)	0.11 [0.01, 2.00]
5 1 minute Apgar score < 4	1	61	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.03, 2.33]
6 Umbilical arterial pH	1	61	Mean Difference (IV, Fixed, 95% CI)	0.11 [0.08, 0.14]
7 Umbilical pH ≤ 7.20	1	86	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.06, 1.11]
8 Neonatal morbidity	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Overall	1	86	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.19, 1.34]
9 Neonatal death	1	61	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.05, 5.77]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10 Maternal puerperal sepsis	2	147	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.06, 2.18]

Analysis 1.1. Comparison 1 Transcervical amnioinfusion for preterm rupture of membranes, Outcome 1 Persistent variable decelerations.

Analysis 1.2. Comparison 1 Transcervical amnioinfusion for preterm rupture of membranes, Outcome 2 Severe variable decelerations per hour in first stage.

Analysis 1.3. Comparison 1 Transcervical amnioinfusion for preterm rupture of membranes, Outcome 3 Caesarean section.

Analysis 1.4. Comparison 1 Transcervical amnioinfusion for preterm rupture of membranes, Outcome 4 Forceps/vacuum assisted delivery.

Analysis 1.5. Comparison 1 Transcervical amnioinfusion for preterm rupture of membranes, Outcome 5 1 minute Apgar score < 4.

Analysis 1.6. Comparison 1 Transcervical amnioinfusion for preterm rupture of membranes, Outcome 6 Umbilical arterial pH.

Analysis 1.7. Comparison 1 Transcervical amnioinfusion for preterm rupture of membranes, Outcome 7 Umbilical pH ≤ 7.20.

Analysis 1.8. Comparison 1 Transcervical amnioinfusion for preterm rupture of membranes, Outcome 8 Neonatal morbidity.

Analysis 1.9. Comparison 1 Transcervical amnioinfusion for preterm rupture of membranes, Outcome 9 Neonatal death.

Analysis 1.10. Comparison 1 Transcervical amnioinfusion for preterm rupture of membranes, Outcome 10 Maternal puerperal sepsis.

Comparison 2. Transabdominal amnioinfusion for preterm rupture of membranes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Fetal distress	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.27 [0.08, 0.88]
2 Gestational age at delivery (weeks)	2	94	Mean Difference (IV, Random, 95% CI)	-0.49 [-2.63, 1.65]
3 Neonatal morbidity	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Neonatal sepsis/infection	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.26 [0.11, 0.61]
3.2 Pulmonary hypoplasia	1	34	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.06, 0.88]
3.3 Abnormal neurological outcome	1	34	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.03, 2.01]
4 Delivery within 7 days	1	34	Risk Ratio (M-H, Fixed, 95% CI)	0.18 [0.05, 0.70]
5 Time to delivery (days)	1	60	Mean Difference (IV, Fixed, 95% CI)	0.57 [-2.86, 4.00]
6 Admission to neonatal intensive care unit	1	34	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.90, 1.12]
7 Neonatal death	2	94	Risk Ratio (M-H, Fixed, 95% CI)	0.3 [0.14, 0.66]
8 Birthweight (grams)	2	94	Mean Difference (IV, Random, 95% CI)	15.65 [-254.02, 285.32]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9 Maternal puerperal sepsis	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.05, 0.84]

Analysis 2.1. Comparison 2 Transabdominal amnioinfusion for preterm rupture of membranes, Outcome 1 Fetal distress.

Analysis 2.2. Comparison 2 Transabdominal amnioinfusion for preterm rupture of membranes, Outcome 2 Gestational age at delivery (weeks).

Analysis 2.3. Comparison 2 Transabdominal amnioinfusion for preterm rupture of membranes, Outcome 3 Neonatal morbidity.

Analysis 2.4. Comparison 2 Transabdominal amnioinfusion for preterm rupture of membranes, Outcome 4 Delivery within 7 days.

Analysis 2.5. Comparison 2 Transabdominal amnioinfusion for preterm rupture of membranes, Outcome 5 Time to delivery (days).

Analysis 2.6. Comparison 2 Transabdominal amnioinfusion for preterm rupture of membranes, Outcome 6 Admission to neonatal intensive care unit.

Analysis 2.7. Comparison 2 Transabdominal amnioinfusion for preterm rupture of membranes, Outcome 7 Neonatal death.

Analysis 2.8. Comparison 2 Transabdominal amnioinfusion for preterm rupture of membranes, Outcome 8 Birthweight (grams).

Analysis 2.9. Comparison 2 Transabdominal amnioinfusion for preterm rupture of membranes, Outcome 9 Maternal puerperal sepsis.

APPENDICES

Appendix 1. Methods to be used in the next update

Data collection and analysis

Selection of studies

Two review authors 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 a third author.

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 a third person. We will enter data into Review Manager software ([RevMan 2012](#)) and check 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 will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We will resolve any disagreement by discussion or by involving a third assessor.

(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);
- 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 *Cochrane 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.

Unit of analysis issues

Cluster-randomised trials

We will not consider cluster-randomised trials for inclusion.

Cross-over trials

We will not consider cross-over trials for inclusion.

Dealing with missing data

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

For all outcomes, we 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 τ^2 , I^2 and χ^2 statistics. We will regard heterogeneity as substantial if an I^2 is greater than 30% and either the τ^2 is greater than zero, or there is a low P value (< 0.10) in the χ^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. If asymmetry 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 2012](#)). 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 95% confidence intervals, and the estimates of τ^2 and I^2 .

Subgroup analysis and investigation of heterogeneity

If we identify substantial heterogeneity, we will investigate it using subgroup analyses and sensitivity 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 the following subgroup analyses.

1. Effects of transabdominal versus transcervical amnioinfusion on complications of preterm premature rupture of the fetal membranes.
2. Effects of transabdominal versus transcervical amnioinfusion at the various gestational ages in the third trimester.

The following outcomes will be used in subgroup analysis: persistent variable decelerations, Apgar scores, cord arterial pH at birth, neonatal morbidity including infection, lung hypoplasia, abnormal neurological outcomes and postural deformities, as well as perinatal mortality.

We will assess subgroup differences by interaction tests available within RevMan ([RevMan 2012](#)). 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

Sensitivity analyses will be performed for aspects of the review that might affect the results, for example, where there is risk of bias associated with the quality of some of the included trials. Sensitivity analysis will be carried out to explore the effects of fixed-effect or random-effects analyses for outcomes with statistical heterogeneity and the effects of any assumptions made.

WHAT'S NEW

Date	Event	Description
13 January 2014	New citation required but conclusions have not changed	Two studies previously in ongoing have been excluded (Roberts: AMIPROM ; Vergani 2007).
2 December 2013	New search has been performed	Search updated. No new trials identified. Title changed from "Amnioinfusion for preterm premature rupture of membranes" to "Amnioinfusion for third trimester preterm premature rupture of membranes". See Differences between protocol and review for more details.

HISTORY

Protocol first published: Issue 1, 1998

Review first published: Issue 3, 2016

Date	Event	Description
29 March 2011	New citation required but conclusions have not changed	New authors helped to prepare this update.
5 January 2011	New search has been performed	Search updated, one new trial identified (Singla 2010) and included. We have also included three trials previously awaiting classification (Gonzalez 2001 ; Puertas 2007 ; Tranquilli 2005). We have also assessed the remaining trial reports from the previous search (previously in 'awaiting classification'), resulting in four excluded studies (De Santis 2003 ; Gowri 2004 ; Locatelli 2000 ; Mino 1999) and two ongoing studies (Roberts: AMIPROMa ; Vergani 2007a).
2 July 2010	Amended	Contact details edited.
3 August 2009	Amended	Search updated. Nine reports added to Studies awaiting classification (De Santis 2003 ; Gonzalez 2001 ; Gowri 2004 ; Mino 1997a ; Mino 1999 ; Roberts 2006 ; Puertas 2007 ; Tranquilli 2005 ; Vergani 2007a).
31 October 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

GJ Hofmeyr prepared the review and maintains it. For the 2011 update, G Essilfie-Appiah assisted with the selection of studies and data extraction. T Lawrie assisted with study selection, data extraction and the text of the updated review. For the 2014 update, AC Eke assisted with the selection of studies, data extraction and the text of the updated review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- University of the Witwatersrand, South Africa.

External sources

- South African Medical research Council, South Africa.
- UNDP/UNFPA/WHO/World Bank (HRP), Switzerland.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In order to eliminate overlap between this review and a separate review ([Van Teeffelen 2013](#)), the title of this review has been changed from "*Amnioinfusion for preterm premature rupture of membranes*" to "*Amnioinfusion for third trimester preterm premature rupture of membranes*".

INDEX TERMS

Medical Subject Headings (MeSH)

*Amnion; Administration, Intravaginal; Amniotic Fluid [*physiology]; Fetal Membranes, Premature Rupture [*therapy]; Infusions, Parenteral [methods]; Injections [methods]; Isotonic Solutions [administration & dosage]; Randomized Controlled Trials as Topic; Sodium Chloride [administration & dosage]

MeSH check words

Female; Humans; Pregnancy