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TABLE OF CONTENTS

ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS	4
BACKGROUND	7
OBJECTIVES	8
METHODS	8
RESULTS	12
Figure 1.	13
Figure 2.	15
DISCUSSION	17
AUTHORS' CONCLUSIONS	18
ACKNOWLEDGEMENTS	18
REFERENCES	19
CHARACTERISTICS OF STUDIES	20
DATA AND ANALYSES	22
Analysis 1.1. Comparison 1 Cervical adapter (mechanical sealing) versus standard care, Outcome 1 Neonatal sepsis.	22
Analysis 1.2. Comparison 1 Cervical adapter (mechanical sealing) versus standard care, Outcome 2 Chorioamnionitis (as defined in individual trials).	23
Analysis 2.1. Comparison 2 Immunological membrane sealant versus standard care, Outcome 1 Neonatal death (death within the first 28 days of life).	23
Analysis 2.2. Comparison 2 Immunological membrane sealant versus standard care, Outcome 2 Preterm birth less than 37 weeks' gestation.	24
Analysis 2.3. Comparison 2 Immunological membrane sealant versus standard care, Outcome 3 Neonatal sepsis.	24
Analysis 2.4. Comparison 2 Immunological membrane sealant versus standard care, Outcome 4 Respiratory distress syndrome (as defined in individual trials).	24
CONTRIBUTIONS OF AUTHORS	24
DECLARATIONS OF INTEREST	24
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	25
INDEX TERMS	25

[Intervention Review]

Sealing procedures for preterm prelabour rupture of membranes

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ABSTRACT

Background

Preterm prelabour rupture of the membranes (PPROM) complicates approximately 2% of pregnancies and can be either spontaneous or iatrogenic in nature. Complications of PPROM include prematurity, chorioamnionitis, neonatal sepsis, limb position defects, respiratory distress syndrome, pulmonary hypoplasia chronic lung disease, periventricular leukomalacia and intraventricular haemorrhage.

A number of different sealing techniques have been employed which aim to restore a physical barrier against infection and encourage the re-accumulation of amniotic fluid. Routine use of sealants is currently not recommended due to a lack of sufficient evidence to support the safety and effectiveness of such interventions.

Objectives

To assess the effects of sealing techniques following PPROM against each other, or versus standard care (including no sealant), on maternal and neonatal outcomes.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (30 May 2016) and reference lists of retrieved studies.

Selection criteria

Randomised and quasi-randomised controlled trials comparing different techniques for sealing preterm prelabour ruptured membranes. Cluster-randomised trials and trials using a cross-over design were not eligible for inclusion in this review. We planned to include abstracts when sufficient information was provided.

Data collection and analysis

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

Main results

We included two studies (involving 141 women - with data from 124 women). We considered both studies as being at high risk of bias. Meta-analysis was not possible because the included studies examined different interventions (both in comparison with standard care) and reported on few, but different, outcomes. One study compared cervical adapter (mechanical sealing), and the other study examined

an immunological membrane sealant. Neither of the included studies reported on this review's primary outcome of interest - perinatal mortality. Similarly, data were not reported for the majority of this review's secondary infant and maternal outcomes.

Cervical adapter (mechanical sealing) versus standard care (one study, data from 35 participants)

No data were reported for this review's primary outcome - **perinatal mortality**. Data were reported for few of this review's infant or maternal secondary outcomes.

There was no clear difference between the mechanical sealing group and the standard care control in relation to the incidence of **neonatal sepsis** (risk ratio (RR) 1.19, 95% confidence interval (CI) 0.28 to 5.09 (*very low-quality evidence*)) or **chorioamnionitis** (RR 1.19, 95% CI 0.28 to 5.09 (*very low-quality evidence*)).

Oral immunological membrane sealant versus standard care (one study, data from 94 participants)

No data were available for **perinatal mortality** (this review's primary outcome) or for the majority of this review's infant and maternal secondary outcomes. Compared to standard care, the immunological membrane sealant was associated with a reduction in **preterm birth less than 37 weeks** (RR 0.48, 95% CI 0.34 to 0.68 (*very low-quality evidence*)) and a reduction in **neonatal death** (RR 0.38, 95% CI 0.19 to 0.75 (*very low-quality evidence*)). However, there was no clear difference between groups in terms of **neonatal sepsis** (RR 0.64, 95% CI 0.28 to 1.46 (*very low-quality evidence*)) or **respiratory distress syndrome** (RR 0.64, 95% CI 0.28 to 1.46 (*very low-quality evidence*)).

Authors' conclusions

There is insufficient evidence to evaluate sealing procedures for PPROM. There were no data relating to this review's primary outcome (perinatal mortality) and the majority of our infant and maternal secondary outcomes were not reported in the two included studies.

There was limited evidence to suggest that an immunological membrane sealant was associated with a reduction in preterm birth at less than 37 weeks and neonatal death, but these results should be interpreted with caution as this is based on one small study, with a high risk of bias, and the intervention has not been tested in other studies.

Although midtrimester PPROM is not a rare occurrence, there are only a small amount of published data addressing the benefits and risks of sealing procedures. Most of these studies are retrospective and cohort based and could therefore not be included in our data-analysis.

This review highlights the paucity of prospective randomised trials in this area. Current evidence provides limited information both on effectiveness and safety for the interventions described. Given the paucity of high-quality data, we recommend that future research efforts focus on the conduct of randomised trials assessing the effect of promising interventions that have been only evaluated to date in cohort studies (e.g. amniopatch). Future trials should address outcomes including perinatal mortality, preterm birth, neonatal death, respiratory distress syndrome, neonatal sepsis and developmental delay. They should also evaluate maternal outcomes including sepsis, mode of delivery, length of hospital stay and emotional well-being.

PLAIN LANGUAGE SUMMARY

Treatments for improving outcomes for mother and baby when the waters have broken too early

What is the issue?

Preterm prelabour rupture of the membranes (PPROM) is when the waters break at less than 37 weeks' gestation. It occurs in one in 50 pregnancies and can happen spontaneously or after a medical procedure has been performed, for example, tests where a needle is placed in to the womb to get a sample of fluid or tissue, or after an operation has been performed on the baby inside the womb.

Why is this important?

Breaking of the waters early in pregnancy can lead to significant problems including the baby being born too soon to survive, having immature lungs, and serious infections. Preterm babies are overall more likely to be ill and to suffer from long-term disabilities, if they do survive. The survival of babies affected by PPROM is related to how early it occurs in the pregnancy and if an infection occurs. In some circumstances, the waters may reseal themselves. This is more likely to occur when no infection is present.

Several treatments to reseal the membranes have been tried, with varying success. Resealing has been attempted by:

- a) injecting clotting factors and other medicines in to the hole in the womb to create a patch over the area that is leaking;
- b) taking tablets that may stimulate the body's immune system to mend the area where the seal has broken;
- c) placing a sponge over the hole in the waters;
- d) placing a seal over the neck of the womb to stop fluid leaking out and prevent infection.

Our study is important because finding a successful treatment for PPROM may reduce the potential complications that may happen to the mother and baby such as preterm birth (being born before 37 weeks' gestation) and infections.

What did we find?

In our study we assessed the different techniques used for resealing the waters. We aimed to compare the survival of babies affected with this condition before and after birth and look at the rates of complications in both the babies and mothers. We searched for trials (30 May 2016) and found two studies that compared treatments for resealing the membranes after they had broken. These trials involved 141 women in total and compared two completely different modes of treatment.

One trial compared the use of an oral immunological membrane sealant to stimulate the body's immune system to mend the area where the seal has broken and the other trial placed a mechanical sealing device over the cervix (neck of the womb) to stop fluid leaking. Unfortunately, neither trial provided any data relating to death of the baby within the womb or in the first 28 days of life (perinatal mortality).

There was limited evidence to suggest that oral immunological membrane sealant was associated with a fewer babies being before 37 weeks' gestation and a reduction in the number of babies that died within the first 28 days. However, these results are based on *very low-quality evidence* from one small trial (with data from 94 women) that we judged to be at a high risk of bias.

There was no clear difference between the mechanical sealing device group and the control group in relation to the number of babies who contracted a serious infection (neonatal sepsis) or chorioamnionitis (a bacterial infection that causes inflammation of the membranes surrounding the baby in the womb). Although these results are based on *very low-quality evidence* from one small trial (involving 35 women) judged to be at a high risk of bias.

What does this mean?

Overall, our question remains unanswered - we do not have enough data to fully evaluate sealing procedures for PPROM.

This review demonstrates the lack of research in this area regarding the effectiveness and safety of potential treatments for PPROM. We recommend that more research is needed to look at the different techniques for sealing broken waters and that this research should focus on the effectiveness of the treatment in improving overall outcomes. The safety of the treatments to both mother and baby must be further evaluated before sealing techniques can be recommended to prevent adverse outcomes.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. SOF Cervical adapter versus standard care

'Summary of findings' table - cervical adapter versus standard care

Patient or population: preterm prelabour rupture of membranes (PPROM)

Settings: [Vaitkiene 1995](#): Tertiary perinatal referral centre

Intervention: cervical adapter (mechanical sealing)

Comparison: standard care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with standard care	Risk with Cervical adapter (mechanical sealing)				
Perinatal mortality	Study population		not estimable	(0 RCTs)	-	
	not pooled	not pooled				
Neonatal death (death within the first 28 days of life)	Study population		not estimable	(0 RCTs)	-	
	not pooled	not pooled				
Preterm birth less than 37 weeks' gestation	Study population		not estimable	(0 RCTs)	-	
	not pooled	not pooled				
Neonatal sepsis	Study population		RR 1.19 (0.28 to 5.09)	35 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{1 2}	
	158 per 1000	188 per 1000 (44 to 804)				
Respiratory distress syndrome (as defined in individual trials)	Study population		not estimable	(0 RCTs)	-	
	not pooled	not pooled				
Chorioamnionitis (as defined in individual trials)	Study population		RR 1.19 (0.28 to 5.09)	35 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{1 2}	
	158 per 1000	188 per 1000 (44 to 804)				

Postpartum endometritis/other sepsis	Study population		not estimable	(0 RCTs)	-
	not pooled	not pooled			

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

¹ The proportion of information from single study at high risk of bias is sufficient for serious concerns (-2).

² Wide confidence intervals suggests high imprecision for this outcome (-1).

Summary of findings 2. SOF Immunological sealant versus standard care

'Summary of findings' table - immunological sealant versus standard care

Patient or population: preterm prelabour rupture of membranes (PPROM)

Settings: [Dam 2011](#): Teaching hospital that provided tertiary level care

Intervention: immunological membrane sealant

Comparison: standard care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with standard care	Risk with Immunological membrane sealant				
Perinatal mortality	Study population		not estimable	(0 RCTs)	-	
	not pooled	not pooled				
Neonatal death (death within the first 28 days of life)	Study population		RR 0.38 (0.19 to 0.75)	94 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{1 2}	
	490 per 1000	186 per 1000 (93 to 368)				

Preterm birth less than 37 weeks' gestation	Study population		RR 0.48 (0.34 to 0.68)	94 (1 RCT)	⊕○○○ VERY LOW ^{1 2}
	922 per 1000	442 per 1000 (313 to 627)			
Neonatal sepsis	Study population		RR 0.64 (0.28 to 1.46)	94 (1 RCT)	⊕○○○ VERY LOW ^{1 2}
	255 per 1000	163 per 1000 (71 to 372)			
Chorioamnionitis (as defined in individual trials)	Study population		not estimable	(0 RCTs)	-
	not pooled	not pooled			
Respiratory distress syndrome (as defined in individual trials)	Study population		RR 0.64 (0.28 to 1.46)	94 (1 RCT)	⊕○○○ VERY LOW ^{1 2}
	255 per 1000	163 per 1000 (71 to 372)			
Postpartum endometritis/other sepsis	Study population		not estimable	(0 RCTs)	-
	not pooled	not pooled			

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

¹ The proportion of information from a single study at high risk of bias is sufficient to affect the interpretation of results (-2).

² Wide confidence intervals lead to increased imprecision for this outcome (-1).

BACKGROUND

Description of the condition

Preterm prelabour rupture of the membranes (PPROM) occurs when the fetal membranes rupture before 37 weeks of pregnancy and before the onset of labour. PPRM complicates approximately 2% of pregnancies and can be either spontaneous or iatrogenic (resulting from a medical or surgical procedure) in nature (RCOG 2006). Spontaneous PPRM occurs in the absence of medical intervention and is usually secondary to ascending infection. Iatrogenic PPRM occurs after medical intervention has occurred and may be secondary to invasive fetal testing such as chorionic villus sampling, amniocentesis or fetoscopy. PPRM contributes to up to 40% of preterm (before 37 weeks) births (Mercer 2003), an ever-increasing problem in modern medicine.

Complications associated with PPRM include chorioamnionitis (infection of the fetal membranes), limb position defects, and respiratory distress syndrome (RDS - a complication of lung function resulting in difficulty breathing), secondary to pulmonary hypoplasia and prematurity. Pulmonary hypoplasia (immature and small lungs from a lack of amniotic fluid) occurs in approximately 50% of cases of midtrimester PPRM diagnosed before 19 weeks' gestation (Beydoun 1986). The overall perinatal mortality for PPRM before 26 weeks when managed expectantly is 60% (Bengtson 1989).

If infection is present, the latency period between PPRM and delivery is much shorter and the neonatal mortality rate is four times higher than those without sepsis (Cotton 1984). Intrauterine infection is found in up to 36% of women with PPRM, and increases the risks of preterm delivery, neonatal sepsis, respiratory distress syndrome, chronic lung disease, periventricular leukomalacia (necrosis of brain tissue adjacent to the cerebral ventricles), intraventricular haemorrhage (bleeding in to the brain's ventricular system) and cerebral palsy (damage to motor control centres of the brain) (Yoon 2003).

Causes of spontaneous preterm prelabour membrane rupture

The fetal membranes are formed in layers (the amnion, chorion and decidua) in the second and third trimesters of pregnancy. They serve to protect the fetus from trauma and infection and also provide an environment where amniotic fluid can accumulate and allow for fetal movement. The strength of the fetal membranes is derived from the collagen in the amnion and the adherence of the layers to each other (Bryant-Greenwood 1998).

There are many potential causes for fetal membrane rupture. Chronic inflammation and infection can result in the production of inflammatory substances (hormones and cytokines) in the uterus, membranes and placenta. This can then result in uterine contractions, weakening of the membranes and ultimately PPRM (Gomez 1998). It has also been postulated that stress and strain on the membranes from uterine activity causes the membranes to become less elastic and more prone to rupture with repeated strain (Lavery 1982). Other factors that play a role in tissue degradation and immune modulation such as altered levels of hormones (including relaxin) and micro-nutrients (including vitamin C) may be important in PPRM (Qin 1997; Wideman 1964).

Iatrogenic causes of PPRM

PPROM post amniocentesis and chorionic villus sampling

Whilst the introduction of increasingly sophisticated screening tools for chromosomal abnormalities has meant that fewer pregnant women choose to have invasive testing based on maternal age, advancing technology in ultrasound screening has meant there is an ongoing need for invasive prenatal testing via chorionic villus sampling or amniocentesis (Tabor 2010). Invasive testing carries a risk of approximately 1% to 3% for subsequent amniotic fluid leakage (Tabor 2010). Subclinical leakage after amniocentesis may occur more frequently than initially thought (Devlieger 2009). PPRM following amniocentesis is usually self-limiting and resolves within days to weeks after the procedure, provided there is no locus of infection (Borgida 2000).

PPROM and fetal surgery

Improved technology and techniques in ultrasonography have resulted in increased diagnosis of fetal anomalies prior to birth, many of which are amenable to minimally invasive fetal surgery. These include congenital diaphragmatic hernia, myelomeningocele and lower urinary tract obstruction, in addition to laser ablation for the treatment for twin-to-twin transfusion syndrome. With all invasive procedures, the most common complication reported is PPRM. PPRM rates depend on the indication for the fetoscopy and the type of instruments used, with rates as high as 30% to 50% having been reported (Deprest 2006). Other variables that influence the risk of membrane rupture include the number of cannulae used, the gestational age of the fetus at the time of surgery, and the duration of the procedure (Deprest 2011). Currently, there are insufficient data to calculate the rates of spontaneous resealing of membranes after PPRM following fetal surgery.

Membrane healing

The fetal membranes are relatively avascular (without a blood supply) and demonstrate almost absent wound healing capacity in both in vitro and in vivo studies (Gratacos 2006). It has been postulated that cases of iatrogenic PPRM where re-sealing has occurred are likely due to the fetal membranes sliding over each other rather than due to cell proliferation as seen in a typical wound healing process (Behzad 1994). Cobo et al have described some documented cases of spontaneous resealing (Cobo 2007). For this reason, a latent period of between three days and two weeks is allowed prior to most sealing techniques being attempted in order to allow an opportunity for spontaneous healing to take place.

Description of the intervention

Sealing techniques

The routine use of sealants is not currently recommended for treatment of second trimester oligohydramnios (low amniotic fluid volume) caused by PPRM (RCOG 2006). This is likely to be secondary to a lack of sufficient evidence to support the safety and success of such interventions. A number of different types of sealing techniques have been employed which aim to restore a physical barrier against infection and encourage the re-accumulation of amniotic fluid. The restoration of amniotic fluid volume may prevent complications secondary to oligohydramnios such as pulmonary hypoplasia and limb reduction defects. The prevention of infection may also reduce the risk of neonatal

and maternal complications secondary to chorioamnionitis and sepsis. Ultimately, these techniques aim to prolong the duration of pregnancy and improve both maternal and neonatal outcomes.

To stimulate a true membrane wound-healing process, Deprest and colleagues have postulated that the injected matrix should contain material that triggers cell invasion (Deprest 2011). Desirable characteristics of a successful membrane sealant include: 1) stimulation of cell invasion and activation of a wound healing process, 2) an ability for delivery and activation in the presence of moisture, and 3) material that is non-toxic and does not induce a foreign body response by the woman or her fetus.

The most significant possible complication associated with sealant use is the stimulation of an inflammatory process in order to facilitate healing. This inflammatory response may then lead to secondary effects such as preterm uterine activity, and also cause membrane proliferation, which may lead to uterine synechiae (adhesions). Even if a membrane seal is initially successful, the dynamic environment of the amniotic fluid and the activity of uterine musculature will constantly challenge it.

Several different methods for sealing both iatrogenic and spontaneous ruptured membranes have been employed over the last two decades and include injection of platelets with cryoprecipitate ('amniopatch'), gelatin sponges, collagen plugs, and intracervical fibrin sealants. A variety of fibrin and maternal clot sealants have been used with some success to treat iatrogenic midtrimester PPROM. However, the application to spontaneous membrane rupture has not been sufficiently tested. Further studies are required in all fields before such strategies can be regarded as more than experimental.

Amniopatch

The first successful reported case using an amniopatch was published by Quintero in 1999 and involved the intra-amniotic injection of platelets and cryoprecipitate (Quintero 1999). While the precise mechanism of action is unclear, it has been suggested that platelet activation at the site of rupture causes adherence to areas of damage and formation of an aggregate. This plug can then be stabilised by cryoprecipitate, which initiates the healing process by providing a scaffold for amnion cells and fibroblasts to adhere.

Gelatin sponge

Other techniques that have been advocated include the use of gelatin sponges (O'Brien 2006), which appear to remain intact longer than fibrin or other blood products (Young 2000). One postulated danger to the fetus could be secondary to swallowing the sponge as it could lead to intestinal or airway obstruction, although this has not been reported in studies to date (O'Brien 2006). In vitro experiments were conducted prior to the use of a gelatin sponge on pregnant women. The in vitro studies were conducted on fetal membranes which were perforated and then occluded with the gelatin sponge. The gelatin sponge was effective in obstructing all defects < 7 mm diameter (O'Brien 2006).

Collagen plugs

Collagen plugs act as a sponge and increase in diameter after absorbing bodily fluids. As they expand, they lock the membranes against the uterine wall and create a seal.

Fibrin sealants

Fibrin sealants mimic the last step in the coagulation cascade and result in the formation of a semirigid fibrin clot that adheres to the application site and provides a barrier against the passage of fluid or air (Sciscione 2001). Fibrin sealants contain fibrinogen, Factor XIII and thrombin and various preparations with differing concentrations of constituents have been used.

Immunological supplements

Orally-administered supplements containing proteins and immunological modulators are thought to stimulate the membrane healing process (Dam 2011).

Mechanical cervical adapter

Placement of an adapter over the external cervical os is theorised to promote re-accumulation of amniotic fluid and to also provide a physical barrier or 'plug' against ascending vaginal infection (Vaitkiene 1995).

How the intervention might work

As previously described, there are many differing techniques that have been deployed in order to restore membrane integrity. All of these techniques aim at sealing the fetal membranes in order to restore amniotic fluid volume, protect against infection, and prolong the pregnancy.

Why it is important to do this review

To date, a systematic review of outcomes comparing different types of sealing procedures with each other has not been undertaken, nor has a comparison of maternal and neonatal outcomes following sealing techniques compared with expectant management alone.

OBJECTIVES

To assess the effects of sealing techniques following preterm prelabour rupture of membranes against each other, or versus standard care (including no sealant), on maternal and neonatal outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised and quasi-randomised controlled trials comparing different techniques for sealing preterm prelabour ruptured membranes. Cluster-randomised trials and trials using a cross-over design are not eligible for inclusion in this review. We planned to include abstracts when sufficient information was provided.

Types of participants

Women with known preterm prelabour rupture of membranes (PPROM) either spontaneous or as a result of an intervention during pregnancy, with a live fetus at a gestational age of less than 37 completed weeks (i.e. preterm), including women with a multiple pregnancy.

Types of interventions

The interventions and comparisons that were considered for inclusion were: one method for sealing of PPROM versus standard

care or versus active treatment or versus another method for sealing.

Types of outcome measures

Primary outcomes

- Infant - perinatal mortality (intrauterine fetal demise and neonatal death). (Intrauterine fetal demise defined as fetal death after 20 weeks' gestation and prior to delivery; neonatal death defined as death within the first 28 days of life.)

Secondary outcomes

Infant

- Intrauterine fetal demise (fetal death after 20 weeks' gestation and prior to delivery).
- Neonatal death (death within the first 28 days of life).
- Preterm birth less than 37 weeks' gestation.
- Preterm birth less than 32 weeks' gestation.
- Preterm birth less than 28 weeks' gestation.
- Gestational age at birth (weeks' gestation).
- Neonatal intensive care unit (NICU)/special care unit (SCU) admission.
- Length of stay in NICU/SCU.
- Neonatal sepsis (positive blood, urine or spinal fluid culture).
- Necrotising enterocolitis (as defined in individual trials).
- Intraventricular haemorrhage (as defined in individual trials).
- Respiratory distress syndrome (as defined in individual trials).
- Pulmonary hypoplasia (as defined in individual trials).
- Number of days requiring ventilation.
- Requirement for mechanical ventilation.
- Neurodevelopmental delay at 12 months and 24 months.

Maternal

- Chorioamnionitis (as defined in individual trials).
- Endometritis (as defined in individual trials).
- Need for antibiotics (for treatment of presumed or confirmed infection).
- Length of hospital stay (days).
- Caesarean section.
- Vaginal birth.
- Onset of labour (induction or spontaneous onset).
- Antenatal hospital admission and length of stay.
- Postpartum endometritis/other sepsis.
- Emotional well-being/anxiety/satisfaction with care.

Search methods for identification of studies

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

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting their Information Specialist (30 May 2016)

The Register is a database containing over 21,000 reports of controlled trials in the field of pregnancy and childbirth. For full search methods used to populate the Pregnancy and Childbirth

Group's Trials Register including the detailed search strategies for CENTRAL, MEDLINE, Embase and CINAHL; the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service, please follow this link to the editorial information about the [Cochrane Pregnancy and Childbirth Group](#) in *The Cochrane Library* and select the '**Specialized Register**' section from the options on the left side of the screen.

Briefly, the Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by their Information Specialist and contains trials identified from:

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

Search results are screened by two people and the full text of all relevant trial reports identified through the searching activities described above is reviewed. Based on the intervention described, each trial report is assigned a number that corresponds to a specific Pregnancy and Childbirth Group review topic (or topics), and is then added to the Register. The Information Specialist searches the Register for each review using this topic number rather than keywords. This results in a more specific search set, which has been fully accounted for in the relevant review sections ([Included studies](#); [Excluded studies](#)).

Searching other resources

We searched reference lists of published studies for any relevant trials.

We did not apply any language or date restrictions.

Data collection and analysis

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

Selection of studies

Two review authors (Rosalie Grivell and Adele Crowley) independently assessed for inclusion all the potential studies identified as a result of the search strategy. We resolved any disagreement through discussion.

Data extraction and management

We designed a form to extract data. For eligible studies, two review authors extracted the data using the agreed form. We resolved discrepancies through discussion. We entered data into Review Manager software ([RevMan 2014](#)) and checked for accuracy.

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

Assessment of risk of bias in included studies

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

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

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

We assessed the method as:

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

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

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

We assessed the methods as:

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

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

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

We assessed the methods as:

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

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

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

We assessed the 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 described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported 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 was reported, or could be supplied by the trial authors, we re-included missing data in the analyses which we undertook.

We assessed the methods as:

- low risk of bias (e.g. a cut-off level of 20% was used for completeness of data (i.e. low risk of bias => 20% missing 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 carried out with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

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

We assessed the methods as:

- low risk of bias (where it 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 could not be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

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

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

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

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

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it is likely to impact on the findings. We planned to explore the impact

of the level of bias through undertaking sensitivity analyses - see [Sensitivity analysis](#).

Assessment of the quality of the evidence using the GRADE approach

We assessed the quality of the evidence using the GRADE approach as outlined in the [GRADE handbook](#) in order to assess the quality of the body of evidence relating to the following outcomes for the two comparisons.

- Perinatal mortality
- Neonatal sepsis
- Neonatal death
- Chorioamnionitis
- Preterm birth less than 37 weeks
- Respiratory distress syndrome
- Postpartum endometritis/other sepsis

We used [GRADEpro](#) Guideline Development Tool to import data from Review Manager 5.3 ([RevMan 2014](#)) in order to create 'Summary of findings' tables. A summary of the intervention effect and a measure of quality for each of the above outcomes was produced using the GRADE approach. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

Measures of treatment effect

Dichotomous data

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

Continuous data

We did not identify any continuous outcome data. However, if we identify continuous outcome data in future updates of this review, we will use the mean difference if outcomes are measured in the same way between trials. We will use standardised mean difference to combine trials that measure the same outcome, but use different methods.

Unit of analysis issues

We did not plan to include cluster or cross-over design trials in the review.

Multiple pregnancies

In future updates, where trials include women with a twin pregnancy, we will use cluster-randomised trial methods to account for non-independence of infants from multiple pregnancies.

Multiple-armed studies

In future updates, if we include a study with multiple arms, we will combine all relevant experimental intervention groups of the study into a single group, and combine all relevant control intervention groups into a single control group ([RevMan 2014](#)).

Dealing with missing data

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

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

Assessment of heterogeneity

We were unable to carry out meta-analysis in this review. In future update, 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

In future updates, 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 carried out statistical analysis using the Review Manager software ([RevMan 2014](#)). Meta-analysis was not possible because each of our comparisons includes one study. In future updates, 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 T^2 and I^2 .

Subgroup analysis and investigation of heterogeneity

We did not combine studies in meta-analysis. In future updates, 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 so use random-effects analysis to produce it.

We plan to carry out the following subgroup analysis.

Sealing procedures for preterm prelabour rupture of membranes (Review)

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- Gestational age at ruptured membranes less than 20 weeks (19 + 6 and lower) versus gestational age greater than or equal to 20 weeks ($\geq 20 + 0$) weeks

Subgroup analysis will be restricted to this review's primary outcome.

We will assess subgroup differences by interaction tests available within RevMan (RevMan 2014). 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

In future updates of this review, we will carry out planned sensitivity analysis (where applicable) to explore the effects of trial

quality assessed by allocation concealment and other risk of bias components by omitting studies rated as high risk of bias for these components. Sensitivity analysis will be restricted to the primary outcome of this review.

RESULTS

Description of studies

Results of the search

The search of the Cochrane Pregnancy and Childbirth Group's Trials Register retrieved three reports (see: Figure 1). We included two studies (Dam 2011; Vaitkiene 1995) involving 141 women. One study has been excluded (Kubo 1991).

Figure 1. Study flow diagram.

Included studies

We included two studies ([Dam 2011](#); [Vaitkiene 1995](#)).

Design

[Dam 2011](#) conducted a "comparative prospective randomised" study.

[Vaitkiene 1995](#) conducted a prospective study comparing outcomes in two "randomly allotted" groups.

Sample sizes

[Dam 2011](#) included 46 cases in the treatment arm and 60 control patients, with a total number included in the study of 106 cases of preterm prelabour rupture of the membranes (PPROM).

[Vaitkiene 1995](#) included 35 cases of confirmed PPRM, with 16 in the treatment group and 19 controls.

Setting

[Dam 2011](#) was a study conducted in India from July 2006 to January 2007 on pregnant women attending the Obstetrics and Gynaecology Emergency Department at Eden Medical College in Kolkata. This is a large teaching hospital that provides tertiary level care.

[Vaitkiene 1995](#) was a study conducted in Lithuania at Kaunas Medical Academy in 1995. This is also a tertiary perinatal referral centre.

Participants

[Dam 2011](#) included 46 cases in the treatment arm and 60 control patients, with a total number included in the study of 106 cases of PPRM between 24 and 36 weeks' gestation. Included were singleton pregnancies, with no fetal anomaly and no evidence of infection.

[Vaitkiene 1995](#) included 35 cases of confirmed PPRM, between 22 and 37 weeks' gestation. Pregnancies were singleton, with no evidence of current infection.

Interventions and comparators

[Dam 2011](#) compared the use of oral immunological modulators versus standard care. The intervention, called 'amnioseal', was provided as an oral capsule, and is reported to be a combination of matrix metalloproteinases (MMP) inhibitors, cytokines and defensins (all molecules that modify the immune response).

[Vaitkiene 1995](#) compared the use of cervical adapters with standard care. The cervical adapter was constructed by the authors, and was a device intended to functionally close the cervix, and appears to be a cup that covers the ectocervix and a tube to which negative pressure can be applied therefore closing the tubing.

Outcomes

Neither of the included studies reported on our primary outcome, perinatal mortality.

Dam and colleagues did not report a clear primary outcome and their other outcomes are poorly reported in the two separate groups of participants ([Dam 2011](#)). They did report pregnancy continuation, oligohydramnios, neonatal mortality, septicaemia, birth asphyxia, respiratory distress syndrome, hypothermia/hypocalcaemia, jaundice and birthweight.

[Vaitkiene 1995](#) did not report a clear primary outcome. The authors reported amniotic fluid index (AFI), maternal pyelonephritis, chorioamnionitis, mastitis, and neonatal infectious morbidity (pneumonia, pyoderma, and omphalitis).

Excluded studies

One study ([Kubo 1991](#)) was excluded because it was a non-randomised study.

Risk of bias in included studies

Overall, the potential risk of bias for the included studies was high as the reports contained little methodological description. The details of the trials are given in the [Characteristics of included studies](#) table. A summary of our 'Risk of bias' judgements for the included studies is provided in [Figure 2](#).

Figure 2. '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
Dam 2011
Vaitkiene 1995

Allocation

The risk of selection bias was unclear overall for both included trials (Dam 2011; Vaitkiene 1995) as their methods of generating and concealing allocation sequence were not described in detail. They only reported that participants were "randomised" or "randomly assigned" into two treatment groups.

Blinding

With regard to blinding of participants, key study personnel and outcome assessment, we considered Dam 2011 to be at an unclear risk of performance and detection bias as blinding was not mentioned in their report. The risk of performance bias and detection bias for Vaitkiene 1995 was assessed as high risk as there was no blinding undertaken or attempted at any stage.

Incomplete outcome data

Both Dam 2011 and Vaitkiene 1995 were considered to be at high risk of attrition bias as outcome data were not available for all randomised women in both treatment groups.

In Dam 2011, the outcomes were not clearly reported in the group at 31 to 36 weeks' gestation. Also, 3/46 (6.5%) intervention and 9/60 (15%) control patients discontinued due to frank chorioamnionitis.

Similarly, in Vaitkiene 1995 there was a high risk of attrition bias. One woman out of 16 (6%) in the cervical adapter group was excluded after allocation and four out of 19 women (21%) in the no cervical adapter group went in to labour and were therefore excluded.

Selective reporting

The risk of reporting bias for both studies was unclear due to insufficient information being provided to make an assessment.

Other potential sources of bias

There were no other areas of potential bias identified in either study, therefore the risk was low.

Effects of interventions

See: [Summary of findings for the main comparison SOF Cervical adapter versus standard care](#); [Summary of findings 2 SOF Immunological sealant versus standard care](#)

Cervical adapter (mechanical sealing) versus standard care (one study, data from 35 participants)

One study (Vaitkiene 1995), involving 35 women, provided data on only two of our pre-specified outcomes, instead focusing on amniotic fluid index (AFI) and infectious complications.

Primary outcome

Perinatal mortality (intrauterine fetal demise and neonatal death) (intrauterine fetal demise defined as fetal death after 20 weeks' gestation and prior to delivery; neonatal death defined as death within the first 28 days of life)

This important outcome was not reported in Vaitkiene 1995.

Secondary outcomes

Neonatal sepsis

There was no clear difference between the mechanical sealing group and the standard care control in relation to the incidence of **neonatal sepsis** (risk ratio (RR) 1.19, 95% confidence interval (CI) 0.28 to 5.09 (*very low-quality evidence*) (Analysis 1.1)) or **chorioamnionitis** (RR 1.19, 95% CI 0.28 to 5.09 (*very low-quality evidence*) (Analysis 1.2)).

Other secondary outcomes not reported in the included studies

The majority of this review's maternal and infant secondary outcomes were not reported in the included study under this comparison. For the infant, we identified no data in relation to intrauterine fetal demise (fetal death after 20 weeks' gestation and prior to delivery); neonatal death (death within the first 28 days of life); preterm birth less than 37, 32 or 28 weeks' gestation; gestational age at birth (weeks' gestation); neonatal intensive care unit (NICU)/special care unit (SCU) admission; length of stay in NICU/SCU; necrotising enterocolitis (as defined in individual trials); intraventricular haemorrhage (as defined in individual trials); respiratory distress syndrome (as defined in individual trials); pulmonary hypoplasia (as defined in individual trials); number of days requiring ventilation; requirement for mechanical ventilation; neurodevelopmental delay at 12 months.

For the mother, the following outcomes were not reported: endometritis (as defined in individual trials); need for antibiotics (for treatment of presumed or confirmed infection); length of hospital stay (days); caesarean section; vaginal birth; onset of labour (induction or spontaneous onset); antenatal hospital admission and length of stay; postpartum endometritis/other sepsis; emotional well-being/ anxiety/satisfaction with care.

Immunological membrane sealant versus standard care (one study, data from 94 participants)

The immunological sealant trial (Dam 2011) addressed only three of this review's pre-specified outcomes.

Primary outcome

Perinatal mortality (intrauterine fetal demise and neonatal death) (Intrauterine fetal demise defined as fetal death after 20 weeks' gestation and prior to delivery; neonatal death defined as death with the first 28 days of life)

The one included study under this comparison did not report on this primary outcome.

Secondary outcomes

Compared to standard care, the immunological membrane sealant intervention as described by Dam and colleagues (Dam 2011) was associated with a reduction in **preterm birth less than 37 weeks** (RR 0.48, 95% CI 0.34 to 0.68 (*very low-quality evidence*) (Analysis 2.2)), and a reduction in **neonatal death** (RR 0.38, 95% CI 0.19 to 0.75 (*very low-quality evidence*)). However, there was no clear difference between the immunological membrane sealant group and the standard care control in relation to **neonatal sepsis** (RR 0.64, 95% CI 0.28 to 1.46 (*very low-quality evidence*) (Analysis 2.3)) or **respiratory distress syndrome** (RR 0.64, 95% CI 0.28 to 1.46 (*very low-quality evidence*) (Analysis 2.4)).

Other secondary outcomes not reported in the included studies

The majority of this review's maternal and infant secondary outcomes were not reported in the included study under this comparison. For the infant, we identified no data in relation to intrauterine fetal demise (fetal death after 20 weeks' gestation and prior to delivery); preterm birth less than 32 or 28 weeks' gestation; gestational age at birth (weeks' gestation); NICU/SCU admission; length of stay in NICU/SCU; necrotising enterocolitis (as defined in individual trials); pulmonary hypoplasia (as defined in individual trials); number of days requiring ventilation; requirement for mechanical ventilation; neurodevelopmental delay at 12 months.

For the mother, the following outcomes were not reported: chorioamnionitis (as defined in individual trials); endometritis (as defined in individual trials); need for antibiotics (for treatment of presumed or confirmed infection); length of hospital stay (days); caesarean section; vaginal birth; onset of labour (induction or spontaneous onset); antenatal hospital admission and length of stay; postpartum endometritis/other sepsis; emotional well-being/anxiety/satisfaction with care.

DISCUSSION

Summary of main results

Although midtrimester preterm prelabour rupture of the membranes (PPROM) is not a rare occurrence, there is only a small amount of published data addressing the benefits and risks of sealing procedures. Most studies to date are retrospective and cohort-based and therefore were not eligible for inclusion in this review.

This review included two studies involving 141 women. [Vaitkiene 1995](#), compared cervical adapter (mechanical sealing) versus standard care, whereas [Dam 2011](#) examined an immunological membrane sealant. Neither of the included studies reported on this review's primary outcome of interest - perinatal mortality. Similarly, data were not reported for the majority of this review's secondary infant and maternal outcomes.

Whilst data from the [Dam 2011](#) trial suggest that the immunological membrane sealant was associated with a reduction in preterm birth at 37 weeks' gestation and a reduction in neonatal death, this is based on a small sample size and the intervention has not been used in other studies. Therefore, these results should be interpreted with caution, especially since the study was assessed as being at a high risk of bias.

Overall completeness and applicability of evidence

Unfortunately, we were not able to address the primary outcome of perinatal mortality as this outcome was not reported in the included studies. Additionally, only a small fraction of this review's secondary outcomes were addressed in either study.

Overall, the available data were incomplete. The secondary outcomes measured were also not comparable between the included studies. The interventions were also different and it was not appropriate to combine data in a meta-analysis.

Quality of the evidence

The review found only two trials involving a total of 141 women. The available data were not extensive and did not address the primary outcome of perinatal mortality with sealing techniques.

On overall assessment, both included studies have been assessed as high risk of bias, with multiple domains assessed as high or unclear risk of bias (as the reports contained little methodological description).

For the mechanical intervention trial ([Vaitkiene 1995](#)), there was no mention of random sequence generation and this could not be clarified despite attempted contact with the author. Blinding of participants and personnel was also not mentioned. The risk of allocation bias was high as their methods of generating and concealing allocation sequence was not described.

The immunological intervention trial ([Dam 2011](#)) also contained little methodological descriptions with regards to random sequence generation, allocation concealment and blinding of participants. The paper did not report who measured outcomes and if any blinding was involved.

The level of the evidence for both interventions was graded very-low quality ([Summary of findings for the main comparison](#)). The outcomes were downgraded because of the design limitations, high risk of bias in the trials, and wide confidence intervals.

Potential biases in the review process

We minimised potential biases by using a thorough search strategy and by restricting study inclusion to randomised and quasi-randomised trials.

Only two studies were identified as part of this selection process.

Agreements and disagreements with other studies or reviews

A review of current evidence with regards to fetal membrane healing ([Devlieger 2009](#)) discussed the current knowledge of fetal membrane wound healing and the clinical implications. The authors reviewed in vitro and in vivo experimental interventions to seal or heal the membranes after spontaneous and iatrogenic PPRM. This review and others ([Deprest 2011](#)) highlight the varied and experimental nature of interventions for this clinical problem. Described interventions include intra-amniotic and fetoscopic platelet and cryoprecipitate instillation, and the cervical application of clotting factors or fibrin glue with or without concurrent cervical cerclage. The majority of the interventions described in the literature have not been tested in a prospective manner in clinical trials. Some interventions are described by only one or a few papers.

Commonly used experimental techniques include amniopatch, gelatin sponge, collagen plugs or fibrin sealants. There are no other prospective randomised trials with these aforementioned techniques therefore they could not be included in our review.

AUTHORS' CONCLUSIONS

Implications for practice

There were insufficient data to evaluate sealing procedures for preterm prelabour rupture of membranes. No data were available in relation to the review's primary outcome (perinatal mortality) and the review identified limited data in relation to very few of this review's maternal or infant secondary outcomes. Whilst there was limited evidence to suggest that immunological membrane sealant was associated with a reduction in preterm birth less than 37 weeks' gestation and a reduction in neonatal death – this finding should be interpreted with caution as the quality of evidence was very low due to a small sample size and high risk of bias.

Implications for research

This review highlights the paucity of prospective randomised trials in this area. Current evidence provides limited information both on effectiveness and safety for the interventions described. Given the paucity of high-quality data, we recommend that future research efforts focus on the conduct of randomised trials assessing the

effect of promising interventions that have been only evaluated to date in cohort studies (e.g. amniopatch). Future trials should address outcomes including perinatal mortality, preterm birth, neonatal death, respiratory distress syndrome, neonatal sepsis and developmental delay. They should also evaluate maternal outcomes including sepsis, mode of delivery, length of hospital stay and emotional well-being.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Dam 2011

Methods	"Comparative prospective randomised" study.	
Participants	<p>Women from 24 to 36 weeks' gestation complaining of leakage per vagina.</p> <p>Excluded if in labour, multiple pregnancy, fetal anomaly, features of chorioamnionitis, cardiac, hepatic or respiratory disorders. The study was conducted in India from July 2006 to January 2007 attending the Obstetrics and Gynaecology Emergency Department at Eden Medical College in Kolkata. This is a large teaching hospital that provides tertiary level care.</p>	
Interventions	Amnioseal capsules orally as per paper. 46 cases in the treatment arm and 60 control patients, with a total number of 106 cases of PPROM.	
Outcomes	Primary outcome not clear. Outcomes poorly defined as to affecting mother or neonate. Reports pregnancy continuation, oligohydramnios, neonatal mortality, septicaemia, birth asphyxia, respiratory distress syndrome, hypothermia/hypocalcaemia, jaundice and birthweight.	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not described. Uneven numbers randomised. No response from author after attempted to clarify.

Dam 2011 (Continued)

Allocation concealment (selection bias)	Unclear risk	See above.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding not mentioned.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See above.
Incomplete outcome data (attrition bias) All outcomes	High risk	Second group outcomes not clearly reported (31 to 36 weeks' gestation). 3/46 (6.5%) intervention and 9/60 (15%) control patients discontinued due to frank chorioamnionitis.
Selective reporting (reporting bias)	Unclear risk	There was not enough information provided to make an assessment on selective reporting bias.
Other bias	Low risk	No other areas of potential bias were identified.

Vaitkiene 1995

Methods	Randomised controlled trial.
Participants	Singleton pregnancy, 22-37 weeks' gestation, confirmed PROM, no contractions, normal CTG, no signs of chorioamnionitis. The study was conducted in Lithuania at Kaunas Medical Academy in 1995. This is also a tertiary perinatal referral centre. Included 35 cases of confirmed PPROM.
Interventions	Cervical adapter versus no cervical adapter. 35 cases of confirmed PPROM, with 16 in the treatment group and 19 controls.
Outcomes	Primary outcome not clear. Reported AFI, maternal and neonatal infectious morbidity.
Notes	Primary outcome not listed. No sample size calculation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not mentioned in methods.
Allocation concealment (selection bias)	Unclear risk	Not mentioned in methods.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Paper does not report who measured outcomes and if any blinding.

Sealing procedures for preterm prelabour rupture of membranes (Review)

Vaitkiene 1995 (Continued)

Incomplete outcome data (attrition bias) All outcomes	High risk	1 out of 16 (6%) in cervical adapter group excluded after allocation. 4 out of 19 (21%) in no cervical adapter group went in to labour and therefore excluded.
Selective reporting (reporting bias)	Unclear risk	There was not enough information provided to make an assessment on selective reporting bias.
Other bias	Low risk	No other areas of potential bias were identified.

AFI: amniotic fluid index

CTG: cardiotocograph

PPROM: preterm prelabour rupture of the membranes

PROM: preterm rupture of membranes

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Kubo 1991	Cohort comparative study, not randomised.

DATA AND ANALYSES
Comparison 1. Cervical adapter (mechanical sealing) versus standard care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Neonatal sepsis	1	35	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.28, 5.09]
2 Chorioamnionitis (as defined in individual trials)	1	35	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.28, 5.09]

Analysis 1.1. Comparison 1 Cervical adapter (mechanical sealing) versus standard care, Outcome 1 Neonatal sepsis.

Analysis 1.2. Comparison 1 Cervical adapter (mechanical sealing) versus standard care, Outcome 2 Chorioamnionitis (as defined in individual trials). **Comparison 2. Immunological membrane sealant versus standard care**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Neonatal death (death within the first 28 days of life)	1	94	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.19, 0.75]
2 Preterm birth less than 37 weeks' gestation	1	94	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.34, 0.68]
3 Neonatal sepsis	1	94	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.28, 1.46]
4 Respiratory distress syndrome (as defined in individual trials)	1	94	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.28, 1.46]

Analysis 2.1. Comparison 2 Immunological membrane sealant versus standard care, Outcome 1 Neonatal death (death within the first 28 days of life).

Analysis 2.2. Comparison 2 Immunological membrane sealant versus standard care, Outcome 2 Preterm birth less than 37 weeks' gestation.

Analysis 2.3. Comparison 2 Immunological membrane sealant versus standard care, Outcome 3 Neonatal sepsis.

Analysis 2.4. Comparison 2 Immunological membrane sealant versus standard care, Outcome 4 Respiratory distress syndrome (as defined in individual trials).

CONTRIBUTIONS OF AUTHORS

Adele Crowley is the contact person and guarantor and designed and wrote the review.

Rosalie Grivell provided general advice on the review and provided a clinical perspective.

Jodie Dodd provided general and methodological advice on the review.

DECLARATIONS OF INTEREST

Adele Crowley: none known.

Rosalie Grivell: none known..

Sealing procedures for preterm prelabour rupture of membranes (Review)

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Jodie Dodd: none known.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

When the protocol was written and published ([Crowley 2012](#)), 'Summary of findings' tables were not required, hence they have been added at the review stage.

INDEX TERMS

Medical Subject Headings (MeSH)

*Obstetric Labor, Premature; Equipment Design; Fetal Membranes, Premature Rupture [*therapy]; Immunologic Factors [*therapeutic use]; Negative-Pressure Wound Therapy [*instrumentation] [methods]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy