AMIPROM:
A randomised controlled trial of amnioinfusion versus expectant management in very early preterm premature rupture of membranes – a pilot study

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AMIPROM: A pilot study

AMNIOINFUSION IN PRETERM PREMATURE RUPTURE OF MEMBRANES

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BACKGROUND

Premature rupture of membranes (PROM) is one of the major causes of perinatal mortality and morbidity because it is the cause of preterm delivery in 30% of cases.[1,2] Fetal survival is even more compromised when the membranes rupture early in the second trimester (very early PROM).

The management of cases with very early PROM has changed over the years. Traditionally, termination of pregnancy was offered for these women because of the presumed risk of maternal sepsis and very poor fetal outcome. Expectant management has, however, been shown to be relatively safe for mothers over the past few years and results in the survival of a small proportion of infants. It is the current mainstay of management in very early PROM.

Underdevelopment of fetal lungs (pulmonary hypoplasia), a complication of prolonged PROM is a major cause of death in these babies. The other major cause of death or damage is premature birth. The perinatal mortality rate in very early PROM can be as high as 54% [3] and the incidence incidence of pulmonary hypoplasia ranges from 5% to 13%.[3] Recent papers have suggested that oligohydramnios is the most important predictor of perinatal mortality in very early PROM and that adequate residual amniotic fluid plays a critical role in determining the prevalence of pulmonary hypoplasia.[4,5] As a result of this, amnioinfusion is being used to restore the amniotic fluid volume in pregnancies complicated by very early PROM and this has been shown to significantly improve the perinatal outcome.[6] Locatelli et al found, that women with persistent oligohydramnios after amnioinfusion had a significantly shorter interval to delivery, lower neonatal survival(20%),higher rates of pulmonary hypoplasia (62%),and abnormal neurological outcomes(60%) than women in whom amnioinfusion was successful (all $p<0.01$).[7] There is, however, not enough evidence available from randomised controlled trials comparing expectant management of very early PROM with amnioinfusion. These studies are limited by the absence of data for outcomes in pregnancies with very early PROM not treated by amnioinfusion. Moreover, amnioinfusion is an invasive intervention, and although anecdotally these studies suggest that it carries minimal risk to the mother and fetus[7], this needs to be assessed by prospective studies. More information is required from randomised controlled trials before amnioinfusion can be considered routine therapy for such pregnancies.

STUDY DESIGN

A randomised controlled trial

AIM

- To compare the neonatal, maternal and pregnancy outcomes in very early PROM managed expectantly with those managed with serial amnioinfusions.

PRIMARY OUTCOME

This is a pilot study, therefore all outcomes will be reported including:

-fetal and neonatal death,

-neonatal morbidity,

-long term respiratory morbidity (assessed by questionnaire on respiratory symptoms at 6, 12 and 18 months corrected age and lung function tests)

-long term developmental outcomes (assessed by cerebral palsy, developmental delay at 2 years age, corrected for prematurity, using Bayley's score)

-maternal morbidity

-maternal death

-pregnancy outcomes

DEFINITIONS

- **Very early PROM:** Spontaneous rupture of membranes after 16 weeks gestation and prior to 24 weeks gestation
- **Respiratory morbidity:** requiring supplemental oxygen at day 28 post delivery.
- **Pulmonary hypoplasia:** In survivors, this will be assessed by means of formal infant lung function tests at 12 months age, corrected for prematurity (*ref: Beardsmore et al, 1994, 1996)*
- **Chorioamnionitis:** temperature $\geq 37.5^{O}C$ and/or foul smelling amniotic fluid/ tender irritable uterus/ WCC $\geq$20,000/ CRP$\geq$35 or histological evidence of chorioamnionitis. UTI needs to be excluded.
- **Maternal death:** any maternal death
- **Neonatal sepsis:** culture positive infection
- **Long term respiratory morbidity:** questionnaire assessed respiratory symptoms (*ref: Shaw et al, 2001*) at 6, 12 and 18 months age, corrected for prematurity.
- **Long term neurological problems:** cerebral palsy, developmental delay at 2 years age, corrected for prematurity. (Griffith's/Bayley's score)
- **Oligohydramnios on ultrasound scan:** Amniotic fluid index

≤ 5cms or single deepest pocket < 2cms (*ref Magann et al, AmJOG 182(6):1581-8,2000)*

SAMPLE SIZE

An initial sample size was calculated for this study based on an audit performed at The Liverpool Women's Hospital. The audit revealed a composite adverse outcome of 75% in pregnancies with very early PROM: deaths 65% and 10% respiratory morbidity in the survivors (25% of survivors).

To reduce the composite outcome by half, the trial would need 31 cases and 31 controls. (80% power). A reduction in composite outcome by 50% has been chosen because the nature of the intervention is such (i.e invasive and repeated) that only a large difference would justify its introduction into routine practice.

In the above-mentioned audit, 48 patients were studied over a 3.5-year period (~14 per annum). If we assume that 75% of women whose pregnancies are affected by very early PROM agree to take part in the study, it would take 6 years to recruit the necessary cases to complete the study. To reduce the time for recruitment, it is proposed that a multicentre trial be undertaken.

It is proposed that there will be five hospitals taking part in the study. If each hospital recruits five patients a year, recruitment will take less than three years.

Multicentre Research Ethics Committee approval was obtained in February 2002.

The trial is now an HTA funded pilot study. The sample size will therefore be the number recruited at the end of the specified recruitment period. The funders suggested that smaller differences in substantive outcomes (rather than composite) are of interest and that a much larger 'definitive' study should be considered to determine effectiveness (or lack of it) with much greater precision. The sample size calculations are therefore only indicative and will be treated as such by the Data Monitoring Committee

ELIGIBILITY CRITERIA

- All women with very early PROM who are booked at recruiting centre.
- All women with very early PROM booked at other hospitals in the region but who are referred for assessment or delivery to the recruiting centre.

ENTRY CRITERIA

- Singleton pregnancy
- Rupture of membranes between 16 weeks gestation and 24 weeks gestation
- Rupture of membranes confirmed by presence of amniotic fluid in the posterior fornix on speculum examination and/or severe oligohydramnios on ultrasound examination

EXCLUSION CRITERIA

- Obstetric indication for immediate delivery (i.e. fetal bradycardia, abruption, cord prolapse, advanced labour > 5cm)
- Multiple pregnancy
- Fetal abnormality

SCIENTIFIC RATIONALE FOR STUDY

Rationale for amnioinfusion:

Oligohydramnios is associated with a shorter interval from preterm premature rupture of membranes to delivery and this therefore has a significant effect on perinatal mortality.[8] Oligohydramnios is also the single most important independent predictor of pulmonary hypoplasia.[4] Pulmonary hypoplasia carries a significant risk of perinatal mortality and therefore oligohydramnios appears to be a causative factor in both outcomes. It is also said to be associated with a higher risk of chorioamnionitis and neonatal infection. [5]

Adequate amniotic fluid volume on the other hand, is associated with better outcomes in pregnancies affected by very early PROM. Locatelli et al, found that pregnancies with a median residual amniotic fluid pocket persistently less than 2cms were at highest risk of poor perinatal and long term neurological. Pregnancies with a pocket greater than 2cms, after amnioinfusion or spontaneously, had significantly better perinatal outcome (73-92%) and lower pulmonary hypoplasia rates.[7] Other authors corroborate this finding. [9,10] Amnioinfusion has also been found to be a useful tool for prophylactic therapy of pulmonary hypoplasia and neonatal respiratory distress syndrome in selected cases of oligohydramnios associated with intrauterine growth retardation.[11]

To date, there have only been observational comparative studies into amnioinfusion in very early preterm premature rupture of membranes. One randomised controlled trial has been performed, but this trial only included women who ruptured their membranes after 24 weeks of pregnancy and the numbers included in the study were small (17 in each arm). This is not the group that the proposed research will be examining as the risks for adverse perinatal outcome are much higher when the membranes rupture between 16-24 weeks of pregnancy.

A comparative study, by Vergani et al, 2004, compared women with successful amnioinfusion and those with persistent oligihydramnios after amnioinfusion at less than 26 weeks. They found a 50% improvement in pulmonary hypoplasia, neonatal survival and abnormal neurological outcome in survivors. This study suffers from lack of data in women who did not have amnioinfusion, which is the default management in most units. This group first published results of their observational data in 2001. Our methodology is based on theirs.

The results from these studies would suggest that the restoration of amniotic fluid after amnioinfusion results in a much better outcome than if oligohydramnios persists. Serial amnioinfusion is recommended, even in those pregnancies where fluid is not retained at first amnioinfusion, because it can be retained at subsequent procedures.

Two other comparative studies (De Carolis 2004, Ogunyemi 2002) in women with premature rupture of membranes before 27 weeks of pregnancy, failed to show any significant difference in pulmonary hypoplasia rates or neonatal mortality when amnioinfusion was compared to expectant management. The case selection in these trials is not random and therefore it is difficult to use the information from these trials in routine practice. A further, very small UK trial of 19 women by Tan et al, 2003, suffers from a large attrition rate secondary to termination of pregnancy.
NICE guidance after review of existing literature suggests that 'current evidence on the safety and efficacy of therapeutic amnioinfusion does not appear adequate for it to be used without special arrangements for consent and for audit and research. Clinicians are encouraged to enter patients into well designed randomised controlled trials comparing therapeutic amnioinfusion with no intervention'. NICE may review the procedure upon publication of further evidence. This trial will aim to provide that evidence.

Rationale for infant lung function tests:

Pulmonary hypoplasia is extremely difficult to diagnose antenatally or for that matter, postnatally. Ultrasound indicators of pulmonary hypoplasia such as, thoracic circumference, thoracic/abdominal circumference ratio and fetal lung length have been described, but the correlation with outcome is not consistently good. This information will however, be collected for this study. Pathological criteria such as lung/body ratio less than 0.08 or abnormally low alveolar counts adjusted for gestational age are used.[7] In this study, pathological criteria will not be used because death before discharge is a primary outcome. We are interested in the prevalence of pulmonary hypoplasia in the survivors and some formal test for assessing this is necessary. Although radiological criteria such as small, well-aerated lung fields with elevated diaphragms and a bell-shaped chest can be used, these are subjective assessments. Beardsmore et al, have studied respiratory function in infants following repair of oesophageal atresia and in children with cystic fibrosis from infancy to school age.[12,13] They use infant respiratory function tests, which can be adjusted for the clinical condition being studied.[14] These tests provide an objective measurement of infant lung function and are therefore currently the best method of assessing long term respiratory function. Less serious respiratory morbidity will be assessed by means of a validated questionnaire described in the methods.

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RANDOMISATION

Liverpool Clinical Trials Unit, Royal Liverpool and Broadgreen University Hospitals drew up the telephone randomisation list. Telephone randomisation will be used. Randomisation is stratified by gestational age.

DATA MONITORING

In view of the small number of cases to be studied in order to half the primary outcome, an interim analysis will not be performed.

A Trial Steering Committee (TSC) based on MRC recommendation for conduct of clinical trials has been set up. A Data Monitoring Committee (DMC) has been set up. The DMC will be independent of the applicants and of the TSC, while reporting to the TSC and, via the TSC, to the HTA programme. No overseas members are proposed.

RESEARCH GOVERNANCE

The trial is sponsored by The Liverpool Women's Hospital NHS Foundation Trust R&D Dept. The trial protocol is published on the North West Clinical Trials network website. www.rwctognetwork.org.uk

The trial has been adopted by the UKCRN.

Each trial centre will report the following serious untoward adverse events to the Steering Committee and the sponsor:

- Fetal injury caused by the procedure
- Fetal death caused by the procedure
- Maternal sepsis requiring HDU/ITU admission
- Maternal death

SAEs will be reported using the standard SAE/AE report form.

STATISTICAL ANALYSIS

Dichotomous data will be analysed as relative risks with 95% confidence intervals. Logistic regression will be used to correct for confounding factors such as gestational age at rupture of membranes and at delivery. Continuous data will be analysed as weighted mean difference with 95% confidence intervals. Statistical analysis and trial support had been requested from MCRN Clinical Trials Unit, Institute of Child Health, Royal Liverpool Children's Hospital, Liverpool, L12 2AP.

TRIAL PROCEDURES

On admission: Speculum examination and HVS
Check temperature
FBC and CRP
Inform AMIPROM team
Good documentation of clinical findings (tender uterus, any foul smelling discharge)

First fetal-medicine consultation:

- Ultrasound confirmation of clinical findings
- Discussion re: prognosis of very early PROM
- Discussion regarding study and routine management
- Detailed information leaflet is given
- Treat with oral Erythromycin for 10 days
- Review 5-10 days later

Second fetal medicine consultation:

If woman decides against taking part in the study, default management will be conservative management. An initial amnioinfusion may need to be performed to confirm normal fetal anatomy

If patient agrees to take part in the study

- Obtain informed consent
- Fill maternal demographics form
- Fill randomisation form
- Telephone randomisation to either amnioinfusion arm or conservative management using separate randomisation sheet.
- In-patient or out-patient management following procedure according to discretion of attending physician
- Weekly FBC and CRP checks
- Watch for any signs of chorioamnionitis

INTERVENTIONS

Expectant management group

FIRST VISIT

- Following randomisation to expectant management, check HVS results and antibiotics have been given if culture positive
- Ultrasound examination to exclude fetal anomaly
- Measure amniotic fluid (deepest pocket)
- Fill data sheet 1: expectant management arm

SUBSEQUENT VISITS

- Weekly follow up visits at recruiting/referring hospital
- Fill data sheet 2.

Amnioinfusion group

FIRST VISIT

- Following randomisation to amnioinfusion, check HVS results and antibiotics have been given if culture positive
- Ultrasound examination to exclude fetal anomaly
- Measure amniotic fluid (deepest pocket)
- If deepest pocket ≥ 2cms, no amnioinfusion
- If deepest pocket < 2cms, perform amnioinfusion (10mls/week of gestation age, Hartmanns/Saline, see method for amnioinfusion – Appendix 1.)
- Ultrasound assessment of fetus following amnioinfusion to assess fetal heart, further anatomy and amniotic fluid
- Fill data sheet 1.

SUBSEQUENT VISITS

- 1st subsequent visit for all cases should be 3-4 days later
- No amnioinfusion if pocket is ≥2 cm
- Repeat amnioinfusion if pocket < 2 cm
- Serial weekly amnioinfusions are carried on if amniotic fluid pocket is < 2 cm until 34 weeks gestation
- Fill data sheet 2.

STEROID ADMINISTRATION

- Single course of betamethasone 12mg, 12 hours apart (24 hours apart if given as outpatient) at 25-26 weeks gestation
- Further doses of steroids can be given at the discretion of the attending physician

DELIVERY

- Induction of labour at 37 weeks gestation unless there is an obstetric indication for earlier delivery or delivery by Caesarean section (elective or emergency).
- Fill data sheet no. 3. Complete and return data sheet no. 3 to principal investigator when woman discharged from hospital or in the event of transfer to ITU/another hospital.
- See appendix 2 for neonatal data sheets.

Appendix 1.

METHOD FOR AMNIOINFUSION

Equipment required

Sterile abdominal tap pack as usually used in each recruiting unit for sterile invasive procedures

5ml syringe	1
20 gauge needle for injection	1
1% Lignocaine	5mls
20 gauge needle with trocar (outer sleeve 20 gauge)	1
Three way tap	1
50 ml syringe with screw top	1
Connection tubing for infusion	1
Hartmann's solution	500mls

Procedure

The procedure will be performed under lignocaine local anaesthesia, according to the protocol for sterile invasive procedure in each recruiting unit.

Prior to commencing the procedure, attach the three-way tap to the tubing of infusion and attach the tubing to the bag of 500mls Hartmann's solution. Run the Hartmann's through avoiding air bubbles. The 50 ml syringe can be attached to the side port of the three-way tap leaving one port free to be attached to the needle once it is inserted.

Use a size 18Ch needle with trocar for the procedure. Once the needle has been introduced and is found to be clear of fetal parts and umbilical cord, attach the third port of the three-way tap to the needle. A test dose of 10 mls Hartmann's can be introduced under ultrasound visualisation.

Once sure that satisfactory amnioinfusion can be performed, draw up 50mls of Hartmann's at a time and introduce into uterine cavity under ultrasound control to a maximum of 10mls/week gestational age[7]. The Hartmann's solution should be at room temperature.

Withdraw the needle under ultrasound control once the correct amount of fluid has been inserted. Complete ultrasound examination and measurements required for the study.

Appendix 2.

NEONATAL FOLLOW UP

- Fill immediate delivery data in data sheet 4 at delivery and attach form to the baby's case sheet.

- If admitted to neonatal intensive care unit, fill remaining parts of data sheet 4.

- Complete and return data sheet 4 to principal investigator when the baby is discharged or in the event of neonatal death.

- The investigators will fill in data sheet 5 once long term follow up has been undertaken.

- Long term assessment of neurological outcome: An appointment will be sent to all surviving children at postnatal age 2 to attend for a Griffith's/Bayley's assessment of development

- Long term follow up for respiratory problems:

    - Questionnaires will be sent out to parents of surviving babies at 6, 12 and 18 months postnatal age.
    - Formal respiratory function tests on surviving infants will be performed. Parents will be provided with information sheets about the infant lung function tests when their child approaches one year of age. As some time will have elapsed and the tests necessitate a visit to Leicester, separate information sheets and consent forms have been provided for this part of the study.

- Long term follow up for those babies with postural deformities: Orthopaedic surgeons will be contacted for information on surviving babies referred for surgery.

DATA SHEET 1: amnioinfusion arm

Maternal demographics : Name

Age

Unit No

Addressograph label

Parity .....

HVS .....

WCC .....

CRP .....

Temperature .....

Tender irritable uterus .....

Foul smelling discharge .....

Gestation at PPROM …… weeks

Gestation at 1st amnioinfusion …… weeks

Fluid instilled	Pocket before amnioinfusion	Pocket after amnioinfusion

Thoracic circumference ……..

Abdominal circumference ……..

Lung length ……..

DATA SHEET 1: expectant management arm

Maternal demographics : Name

Age

Unit No

Mother's GP

Addressograph label

Parity .....

HVS .....

WCC .....

CRP .....

Temperature .....

Tender irritable uterus .....

Foul smelling discharge .....

Gestation at PPROM …… weeks

Gestation at 1st visit …… weeks

Amniotic fluid pocket at 1st visit ……..

Thoracic circumference at 1st visit ……..

Abdominal circumference at 1st visit ……..

Lung length at 1st visit ……..

Addressograph label

DATA SHEET 2.

Subsequent Visits (scan examinations)

Visit No.	Gestation	Amnioinfusion (Y/N)	Fluid instilled	Pocket before	Pocket after	Thoracic circumference	Lung length	Abdominal circumference

DATA SHEET 3: maternal outcome

Mother's addressograph label

Maternal

Gestational age at delivery	…… weeks
Onset of labour	spontaneous/ induced
Mode of Delivery	Normal/ Instrumental/ Emergency LSCS/Elective LSCS
No. of doses of steroids	.....
Dates of steroid administration	.....
Abruptio placenta	yes/no
Antepartum haemorrhage	yes/no
Chorioamnionitis	yes/no
Required antibioitics antenatally?	yes/no
If yes, name antibiotic and duration of treatment	.....
Required antibiotics postnatally?	yes/no
If yes, name antibiotic and duration of treatment	.....
Serious maternal sepsis requiring ITU/HDU admission	yes/no

If yes, state number of days in ITU/HDU .....

Maternal death yes/no

If yes, state cause of death .....

(see reverse of sheet for results of maternal investigations)

Maternal investigations

Date	Gestation	Haemoglobin g/dl	White cell count $x10^9$/ml	Platelet count	HVS	Tender uterus	CRP	Temperature

DATA SHEET 4: neonatal outcomes

Mother's addressograph label

Baby's name .....

Baby's date of birth .....

Gender Male Female

Address ……

……

……

Gestational age at delivery ..... weeks

Birth weight ..... kgs

Apgar at 1 minute…….. Apgar at 5 minutes…….

Cord Ph …….. Base excess …….....

Lactate ……..

Booking hospital ……

Delivery hospital ……

Reason for delivery ……

Antenatal steroids (date) …….....

Antepartum death ……..

Neonatal death ……..

Date of death ……..

Culture positive sepsis ……..

Date and site 1 ……..

Date and site 2 ……..

Date and site 3 ……..

Date and site 4 ……..

Date and site 5 ……..

Date and site 6 ……..

Days IPPV ……..

Days CPAP ……..

Days HFOV ……..

Pneumothorax (chest drain) ……..

Home 0_2 ……..

0_2 at day 28 ……..

0_2 at week 36 ……..

NEC (operated) ……..

NEC (treated as such) ……..

Treated seizures ……..

Treated retinopathy ……..

IVH grade (0 – 3) ……..

PVL ……..

Shunt ……..

Orthopaedic deformities (fixed) Fixed Postural

Describe site and type of deformity

.....

.....

Referred to orthopaedic surgeons? Y N

If yes, surgery required? Y N

Describe site and type of surgery

.....

.....

Discharge date ……..

Discharge destination ……..

Discharge address ……..

……..

……..

……..

……..

……..

Data Sheet 4: Oxygen requirement

(maximum daily $Fi0_2$ required for > 1 hour)

Day 1	.....	**Day 15**	.....
Day 2	.....	**Day 16**	.....
Day 3	.....	**Day 17**	.....
Day 4	.....	**Day 18**	.....
Day 5	.....	**Day 19**	.....
Day 6	.....	**Day 20**	.....
Day 7	.....	**Day 21**	.....
Day 8	.....	**Day 22**	.....
Day 9	.....	**Day 23**	.....
Day 10	.....	**Day 24**	.....
Day 11	.....	**Day 25**	.....
Day 12	.....	**Day 26**	.....
Day 13	.....	**Day 27**	.....
Day 14	.....	**Day 28**	.....

DATA SHEET 5: long term neonatal outcomes

Respiratory questionnaire @ 6 months age, corrected for prematurity
Performed Y N If no, reason why……

……..

Respiratory questionnaire @ 12 months age, corrected for prematurity
Performed Y N If no, reason why……

……..

Respiratory questionnaire @ 18 months age, corrected for prematurity
Performed Y N If no, reason why……

……..

Infant lung function tests
Performed Y N If no, reason why……

……..

Griffiths/Bayley's assessment
Performed Y N If no, reason why……

……..

Orthopaedic follow up results
Performed Y N If no, reason why……

……..

TO INVESTIGATORS:
Please **staple** completed results of the tests above to this sheet

The Consort E-Flowchart