Amnioinfusion in preterm premature rupture of membranes (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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Scientific summary

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Background

Fetal survival is severely compromised when the amniotic membrane ruptures between 16 and 24 weeks of pregnancy (very early preterm premature rupture of membranes). Reduced amniotic fluid volume is associated with poor lung development, whereas adequate levels lead to better perinatal outcomes. Restoring adequate amniotic fluid by means of ultrasound-guided amnioinfusion (AI) may be of benefit in improving perinatal and long-term outcomes in children of pregnancies with this condition. Current evidence is limited to mostly observational studies; therefore, the National Institute for Health and Care Excellence concluded that more information from randomised controlled trials (RCTs) is required before AI can be considered an effective therapy for very early preterm prelabour rupture of membranes (PPROM). The AI in preterm premature rupture of membranes pilot study (AMIPROM) compares outcomes in pregnancies with rupture of amniotic membranes between 16 and 24 weeks of pregnancy managed with serial weekly transabdominal AI with those managed expectantly.

Objective

The AMIPROM was conducted to assess the feasibility of recruitment, the methods for conduct and the retention through to long-term follow-up of participants with very early rupture of membranes. There was an expectation that the assessment of clinical outcomes would inform the decision about the feasibility of a larger, more definitive, clinical trial.

Methods

Trial design

A prospective RCT stratified for pregnancies in which the amniotic membrane ruptured between 16^{+0} and 19^{+6} weeks' gestation and 20^{+0} and 23^{+6} weeks' gestation was conducted.

Participants

Women with confirmed PPROM between 16^{+0} and 24^{+0} weeks' gestation were considered eligible for the study. Women with multiple pregnancies, resultant fetal abnormalities or obstetric indication for immediate delivery were excluded.

Study settings

Participants were recruited from four UK fetal medicine units – Liverpool Women's NHS Trust, St. Mary's Hospital, Manchester, Birmingham Women's NHS Foundation Trust, Wirral University Hospitals Trust.

Interventions

Participants were randomly allocated to either serial weekly transabdominal AI or expectant management (Exp) until 37 weeks of pregnancy, if the deepest pool of amniotic fluid was < 2 cm.

Outcomes

We collected all maternal, pregnancy and neonatal outcomes using predesigned data sheets. Baseline characteristics such as maternal parity, blood indices, body temperature, length of gestation at rupture of amniotic membranes, and length of gestation at randomisation were recorded. Data on AI, the deepest amniotic fluid pocket (before and after AI, in the AI arm), maternal and neonatal morbidity outcomes such

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as antenatal corticosteroid prophylaxis, use of antibiotics, abruption, antepartum haemorrhage, chorioamnionitis, gestational age at delivery, mode of delivery, onset of labour, serious maternal sepsis requiring admission to intensive therapy unit/high-dependency unit and maternal death were obtained. The neonatal outcomes recorded were gestational age at birth, birthweight, Apgar score at 5 minutes, cord blood gases, antepartum death, neonatal death, culture-positive sepsis, days on intermittent positive-pressure ventilation, continuous positive airways pressure and high-frequency oscillatory ventilation (each measured separately), pneumothorax requiring chest drain, discharge on home oxygen, O_2 requirement at day 28, O_2 requirement at week 36, necrotising enterocolitis including those who had surgery or were treated conservatively), treated seizures, treated retinopathy, intraventricular haemorrhage grade (0–3), periventricular leukomalacia, any shunting procedures and fixed orthopaedic deformities. Long-term respiratory morbidity was assessed using validated respiratory questionnaire scores at 6, 12 and 18 months of age and infant lung function test *z*-value at around 12 months of age. Neurodevelopment was assessed using Bayley's Scale of Infant Development II at the corrected age of 2 years.

Randomisation and blinding

The randomisation sequence was generated in blocks of four. Telephone randomisation was used and, owing to the nature of the intervention, neither the participants nor the investigators were blinded to the allocation. Analysis was based on intention to treat (ITT).

Statistical methods

Statistical analysis was performed by the Clinical Trials Research Centre, University of Liverpool. The short-term outcomes statistical analysis plan (SAP) was written prior to completion of recruitment. The Data Monitoring Committee (DMC) agreed to unblinding of the short-term data to the trial team with the caveat that any trial publication should include both short-term and long-term outcome results. This was done once all the short-term outcome data had been analysed using the ITT principle and presented to the DMC. The DMC also requested that a per-protocol analysis be done on the short-term outcome data, defined as mothers who had AI or attended at least one hospital visit (Exp arm). The long-term outcomes SAP incorporated details of the per-protocol analysis the DMC had requested.

Sensitivity analyses were performed to explore the effects of missing data on the long-term outcomes. These considered the neonatal deaths and imputed on a worst-case scenario basis. Where other imputations were considered, these are described alongside the analyses.

Results

Of the 77 eligible women, 58 were randomised to the study (11 declined study, seven miscarried and one decided too late to be included). There was a postrandomisation exclusion in each arm owing to termination of pregnancy for fetal abnormality, leaving 28 women randomised to serial AI and 28 to Exp. Participants were recruited between 2002 and 2009, with annual recruitment rates varying between 2 and 14. Recruitment to the study improved significantly after National Institute for Health Research (NIHR) funding was received in 2007. The median number of AI required was three.

There was no apparent difference in baseline characteristics, maternal morbidity outcomes or pregnancy outcomes. There was no significant difference in neonatal and fetal death combined [19/28 vs. 19/28; relative risk (RR) 1.0; 95% confidence interval (CI) 0.70 to 1.43]. There was no difference in serious neonatal morbidity. Nine children in the AI arm and eight children in the Exp arm survived to be assessed for long-term outcomes. Five children scored < –2.00 in one or more lung function tests (three children from the AI arm and two from the Exp arm) and three children had respiratory questionnaire scores suggestive of asthma.

Three children in each arm had Bayley's scores < 70 in either mental or Psychomotor Development Index (PDI). Of these children, one in each arm also had abnormal lung function tests. The overall chance of surviving without long-term respiratory or neurodevelopmental disability is 7.1%; 4/28 (14%) in the AI arm and 0/28 in the Exp arm (0%) (RR 9.0; 95% CI 0.51 to 159.70).

Conclusions

This study is, to our knowledge, the first to collect data on long-term outcomes in randomised children born after very early PPROM in a randomised trial of serial antenatal AI. The study was not designed to show a difference between the arms and the number of survivors is too small to draw any conclusions about long-term outcomes. It does, however, signal that a larger definitive study to evaluate whether AI has a cost-effective and acceptable role in improving healthy survival in these pregnancies is indicated. The pilot findings do not suggest that clinicians should alter the current practice of expectantly managing rupture of amniotic membranes between 16^{+0} and 24^{+0} weeks of pregnancy.

The research implications centre around determining whether there is a clinically important difference in healthy survival in amnioinfused babies compared with those managed expectantly. We have demonstrated that an adequately funded multicentre randomised trial, with long-term infant follow-up as the primary outcome, is feasible. A larger definitive study with full health economic analysis and patient perspective assessment is required to show whether AI can improve the healthy survivor rate.

Trial registration

The trial is registered as ISRCTN 8192589.

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