Table 1. Characteristics of included studies

1. Randomized studies

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|  | **De Santis et al., 2003 [34]** | **AMIPROM trial, 2014 [17]** | **PROMEXIL-III trial, 2019 [19]** |
| Methods | Quasi-Randomized-controlled study | Open-labelled randomized-controlled trial | Open-labelled randomized-controlled trial |
| Participants | 37 women in the amnioinfusion group and 34 women in the conventional treatment group | 28 patients in each group | 28 patients in each group |
| Inclusion criteria | * PPROM<26 weeks of gestational age * Singleton pregnancy * Severe (AFI<30 mm) and persistent (≥7 days) oligohydramnios | * Singleton pregnancy * PPROM between 16 weeks’ gestation and 24 weeks’ gestation | * Singleton pregnancies * Oligohydramnios between 16 0/7 and 24 0/7 weeks of gestation resulting from preterm PROM 3–21 days prior |
| Exclusion criteria | * Active labor (<3 cm of cervical dilatation, <2 uterine contractions in 10 min) * Clinical chorioamnionitis | * Multiple pregnancies * Resultant fetal abnormalities * Obstetric indication for immediate delivery (i.e. fetal bradycardia, abruption, cord prolapse, advanced labour > 5 cm) | * Eight or more uterine contractions per hour * Suspected intrauterine infection * Cervical dilatation visualized during speculum examination * Cervical length less than 25 mm on transvaginal US * Obstetric complications necessitating termination of the pregnancy * Major fetal structural anomalies compromising perinatal survival |
| Diagnosis of PPROM | History, sterile speculum examination, vaginal pH > 5, measurement of AFI by US | Presence of amniotic fluid in the posterior fornix on speculum examination with severe oligohydramnios on ultrasound examination | Oligohydramnios with a positive history of continuous vaginal fluid loss combined with the presence of fluid originating from the cervical os, confirmed with positive fern or nitrazine test or positive Amniocator or AmniSure |
| Interventions | **All of participants:**   * Hospital bed rest * Antibiotic prophylaxis (mezlocillin, 2g IV twice daily for at least 7 days) or the treatment was arranged according to the result of cultures, tocolytic treatment for uterine contractions (isoxsuprine IV or oral) * Corticosteroid (betamethasone) after 25 weeks * Fetal evaluations: cardiotocography after 26 weeks and modified BPP every 3 days | * **All of participants:** * Hospital admission for bed rest between 26+0- and 30+0-weeks’ gestation but was not mandatory. * Antibiotic (oral erythromycin) for 10 days after diagnosis of PPROM. * Prophylactic corticosteroids at 26+0 weeks’ gestation, earlier antenatal corticosteroids (between 23+0- 25+6 weeks’ gestation) were given at the clinician’s discretion | **All of participants:**   * Hospital admission was based on fetal presentation and the presence of maternal complaints * Antibiotic (oral erythromycin 250 mg four times/day) starting at the day of randomization for 10 days * First follow-up visit was done after 2-3 days then, twice weekly US to assess fetal well-being and single deepest pocket until 28 0/7 weeks of gestation * Weekly measurement of CRP and leukocytes until delivery * First dose of corticosteroids administration was allowed from 23 5/7 weeks of gestation, if no delivery had occurred after 2 weeks, a 2nd dose was allowed when there were signs of preterm birth |
| **AI group exclusively:**  Weekly saline infusion, at least 7 days after PPROM, was performed in a sufficient amount to increase AFI to 10 cm, antibiotics and tocolysis at the time of AI | **AI group exclusively:**  Weekly administration of saline/Hartmann’s solution (10 ml per week of gestation) was performed only if the deepest pool of amniotic fluid < 2 cm at US | **AI group exclusively:**  Administration of Ringer’s lactate (multiplying the gestation in weeks by 10 mL), if oligohydramnios recurred, weekly AI was performed until 28-week gestation |
| Notes | Pregnant women (n=18) who underwent PPROM after amniocentesis for prenatal diagnosis were included in the study. Among those, 10 women (27.0%) were in the AI and 8 women (23.5%) were in the conventional treatment group | Between 2002 and 2006, a small number of randomized women in the AI arm never developed a deepest pool of amniotic fluid < 2 cm and, therefore, never required AI; recruiters were advised that from then on, they should randomize only at the visit in which the deepest pool measured < 2 cm between 16+0 and 24+0 weeks’ gestation |  |

B. Observational trials

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|  | **Vergani et al., 1997 [9]** | **Ogunyemi and Thompson 2002 [7]** | **De Carolis et al., 2004 [16]** | **Locatelli et al., 2008 [10]** | **Melekoglu and Celik, 2022** |
| Methods | Observational | Observational | Observational | Observational | Observational |
| Participants | 18 patients in intervention group and 16 patients in historic cohort group who did not undergo the procedure | 12 patients in each group | 45 women in the amnioinfusion group and 44 women in the standard treatment group | 29 women in the TAI group and 15 women in the standard treatment group | 27 women in the TAI group and 36 women in the standard treatment group |
| Inclusion criteria | * PROM at ≤25 completed weeks' gestation * No labor * Persistent oligohydramnios persistent for >4 days | * Gestational age <26 weeks * AFI <5 cm * Normal fetal anatomical scan * Absence of gross infection * Stable mother, and fetus | * PPROM<26 weeks of gestational age * Singleton * Severe oligohydramnios (AFI<3 mm) * Without signs of labor or infections | * Singleton * PPROM <25 weeks lasting >4 days * Confirmed oligohydramnios defined as deepest pocket of amniotic fluid≤ 2 cm and lasting ≥4 days * Placental slides available for histopathological examination | * Singleton * PPROM between 18-24 gestational age * Confirmed oligohydramnios * Without signs of labor or infections |
| Exclusion criteria | * Amniotic fluid leakage following second-trimester amniocentesis * Clinical chorioamnionitis, presence of uterine contractions >4 /hours * Structural fetal abnormalities * Maternal immunological diseases e.g., acquired immunodeficiency syndrome * Multiple gestations | * Presence of active labor at the time of presentation and clinical chorioamnionitis | * Multiple pregnancies * Fetal malformation * Obstetric complications * Maternal medical problems * Lack of consent | * Patients who did not develop severe oligohydramnios | * Multiple pregnancies * Fetal malformation * Obstetric complications * Maternal medical problems * Lack of consent |
| Diagnosis of PPROM | Observation of vaginal amniotic fluid pooling and positive nitrazine test on sterile speculum examination | Observation of vaginal pooling, positive Nitrazine test or ferning on speculum evaluation | History, sterile speculum examination, vaginal pH > 5, measurement of AFI by US | Presence of pooled amniotic fluid on a sterile speculum examination with persistence of oligohydramnios in the serial ultrasonographic observations | sterile speculum examination, vaginal pH > 5, measurement of AFI by US and Amniosure test in the suspected cases |
| Interventions | **All of participants:**   * Hospital bed rest during the first week, then home bed rest until 25 weeks, after which all patients had hospital bed rest until delivery * Tocolytic treatment (IV ritodrine) was administered after 25 weeks * Corticosteroids (betamethasone 12 mg intramuscularly repeated after 24 hr) * 1-week course of prophylactic antibiotic therapy (Sulbactam-Ampicillin) 3 g intravenously every 8 hours, if cervical or vaginal culture results were positive for potentially pathogenic bacteria, targeted antibiotic treatment was given * Twice weekly US measurement of amniotic fluid volume, twice weekly assessment of biophysical profile after 25 weeks | **All of participants:**   * Initial bedrest in hospital * Corticosteroid therapy at least once after 24 weeks of gestation * Tocolytic treatment (magnesium sulfate and terbutaline) * Prophylactic intravenous antibiotics * Delivery: clinical chorioamnionitis, established labor, fetal distress, placental abruption or fetal distress | **All of participants:**   * Antibiotic prophylaxis * Tocolytic treatment if necessary * Evaluation of risk of infection: body temperature measurement every 8 h; cervicovaginal cultures, weekly CRP, fibrinogen and erythrocyte sedimendation every 3 days * Fetal evaluations: Daily cardiotocography after 26 weeks and ultrasound every 3 days. | **All of participants:**   * Initial hospital bed rest for 7 days, re-admission after 25 weeks' gestation until delivery * Antibiotic prophylaxis (sulbactam–ampicillin 3 g every 8 h or amoxicillin–clavulanic acid 2 g every 8 h i.v.) for 7 days * Vaginal cultures were obtained every 2 weeks; if positive, targeted treatment was given * Corticosteroid (bethamethasone 12 mg repeated 24 hours later) was administered after 25 weeks' gestation * Tocolytic treatment in the presence of preterm labor (intravenous ritodrine) * Amniotic fluid volume was assessed weekly on the outpatients, and every other day from submission until delivery * Fetal status evaluations: Monitorization of fetal heart rate daily, and performance of biophysical profile twice a week | **All of participants:**   * Hospital bed rest until delivery * Corticosteroids (betamethasone 12 mg intramuscularly repeated after 24 hr) after 24 weeks of gestation * Weekly leucocyte count, CRP and procalcitonin were obtained * Prophylactic intravenous antibiotics * Weekly US measurement of amniotic fluid volume,assessment of biophysical profile and Doppler * Magnesium sulphate administration if delivery was anticipated between 24 and 32 weeks of gestation |
| **AI group exclusively:**  1-2 times weekly to aim to restore AFI >5 cm | **AI group exclusively:**  Prior to the procedure, IV magnesium sulfate 4 g loading dose followed by 1 g/h was initiated and discontinued 12 h post-procedure if preterm labor did not ensue. Fetal monitoring was obtained for at least 30 min. Weekly AI with warm 0.9% normal saline with ampicillin 1 g/L until 27 weeks’ gestation if AFI ≤ 5cm | **AI group exclusively:**  Slow drip of preheated saline infusion (20-30 min) until the AFI (>100 mm) or was suspended in the presence of vaginal loss of fluid and/or blood, or if contractions occurred. Antibiotics (mezlocilline 2g 2 i.v) and tocolysis (isoxsuprine, i.v.) was given at the time of AI. | **AI group exclusively:**  AI with normal saline solution to aim at restoring a normal amount of amniotic fluid (10 ml per week of gestational age), if oligohydramnios (mean deepest pocket of fluid < 2 cm) recurred and persistent for > 4 days, AI was repeated | **AI group exclusively:**  Weekly AI with normal saline solution with the targeted deepest vertical pocket >2 cm during  the amnioinfusion |
| Notes | One patient in TAI group had cerclage |  |  |  |  |

NA: not applicable; AFI: amniotic fluid index; PPROM: preterm premature rupture of membranes; USG:ultrasonography; AI:amnioinfusion; IV:intravenous; BPP=biophysical profile; BPD:bronchopulmonary dysplasia; WBC:white blood cell; CRP:C-reactive protein; IVH:intraventricular hemorrhage; UTI: urinary tract infections; RDS:respiratory distress syndrome; NEC:necrotizing enterocolitis; PVL=periventricular leukomalacia; HVS: high vaginal swap