Amnioinfusion versus Usual Care in Women with Prelabor Rupture of Membranes in Midtrimester: A Systematic Review and Meta-Analysis of Short- and Long-Term Outcomes

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Keywords
Amnioinfusion · Prelabor rupture of membranes · Midtrimester prelabor rupture of membranes · Pulmonary hypoplasia

Abstract
Introduction: Midtrimester prelabor rupture of membranes (PROM) between 16 and 24 weeks of gestational age is a major obstetric complication with high rates of perinatal morbidity and mortality. Amnioinfusion has been proposed in women with midtrimester PROM to target oligohydramnios and subsequently enhance pulmonary development and perinatal outcomes.

Material and Methods: The purpose of this study was to perform a systematic review and meta-analysis including all randomized clinical trials investigating amnioinfusion versus no intervention in women with PROM between 16\textsuperscript{th} and 24\textsuperscript{th} weeks of gestational age. Databases Central, Embase, Medline, ClinicalTrials.gov and references of identified articles were searched from inception of database to December 2021. The primary outcome was perinatal mortality. Secondary outcomes included neonatal, maternal, and long-term developmental outcomes as defined in the core outcome set for preterm birth studies. Summary measures were reported as pooled relative risk (RR) or mean difference with corresponding 95% confidence interval (CI).

Results: Two studies (112 patients, 56 in the amnioinfusion group and 56 in the no intervention group) were included in this review. Pooled perinatal mortality was 66.1% (37/56) in the amnioinfusion group compared with 71.4% (40/56) in no intervention group (RR 0.92, 95% CI: 0.72–1.19). Other neonatal and maternal core outcomes were similar in both groups, although due to the relatively small number of events and wide CIs, there is a possibility that amnioinfusion can be associated with clinically important benefits and harms. Long-term healthy survival was seen in 35.7% (10/28) of children assessed for follow-up and treated with amnioinfusion versus 28.6% (8/28) after no intervention (RR 1.30, 95% CI: 0.47–3.60, “best case scenario”).

Conclusions: Based on these findings, the benefits of amnioinfusion for midtrimester PROM <24 weeks of gestational age are unproven, and the potential harms remain undetermined.
Introduction

Midtrimester prelabor rupture of membranes (PROM between 16\(^{0}\) and 24\(^{0}\) weeks of gestational age) complicates 0.4–0.7% of all pregnancies. After midtrimester PROM, an immature or extreme premature delivery can follow. Ongoing pregnancies are challenged by oligohydramnios (amniotic fluid single deepest pool <2 cm) and intrauterine infections, with subsequently maternal, fetal, or neonatal complications. Live-born neonates are at risk of pulmonary hypoplasia as a result of underdevelopment of the alveolar system due to (prolonged) PROM [1–3]. One of the proposed interventions for this pregnancy complication is serial transabdominal amniinfusion. Amnioinfusion could restore residual amniotic fluids and therefore might positively contribute to pulmonary development and reduce the rate of pulmonary hypoplasia and other pulmonary morbidities [4]. Furthermore, it may prevent compression of the umbilical cord, prevent skeletal deformities, and increase time to delivery [4]. Recently, two randomized controlled trials (RCTs) investigated the effectiveness of amnioinfusion compared to no intervention in pregnancies complicated by PROM in the midtrimester period [5, 6]. No differences were seen in perinatal mortality, and other neonatal, or maternal outcomes. These trials additionally assessed long-term neurodevelopmental outcomes and respiratory function as part of study follow-up [6, 7]. They showed that amnioinfusion compared to no intervention did not improve long-term outcomes up to 5 years of corrected age. However, both trials concluded that they were underpowered to evaluate a smaller, yet clinically relevant, difference in outcomes after amnioinfusion compared to no intervention, and larger trials are needed. The aim of this study was to perform a systematic review and meta-analyses to evaluate perinatal mortality and other neonatal, maternal, and long-term outcomes in all RCTs investigating amnioinfusion versus no intervention in women with PROM <24 weeks of gestational age.

Methods

Study Selection

The reporting of this systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [8]. The review was registered with the PROSPERO International Prospective Register of Systematic Reviews (#CRD42018107802). An electronic search was performed, assisted by a medical librarian, in Central, Embase, and Medline from inception to November 2020 to identify published RCTs eligible for inclusion. To identify ongoing studies, clinical trial registries were searched. Searches contained the following keywords: preterm prelabor rupture of membranes, midtrimester rupture of membranes, second-trimester rupture of membranes, amnioinfusion, and randomized clinical trial (online suppl. Table 1; see www.karger.com/doi/10.1159/000526020 for all online suppl. material). No restrictions for language, date of publication, or geographic location were applied. Two review authors (A.d.R. and S.B.) independently assessed all potentially eligible studies. Any disagreements were resolved by discussion with a third author (E.P.). Additionally, to identify additional publications, bibliographies of eligible studies and identified review articles were searched.

Eligibility Criteria

RCTs were included if they randomized women with confirmed midtrimester PROM (i.e., between 16\(^{0}\) and 23\(^{0}\) weeks) to transabdominal amnioinfusion (i.e., intervention group) or no intervention or care as usual (i.e., control group). Amnioinfusion was defined as serial transabdominal infusion of fluid. In the control group, no intervention was defined as expectant management or care as usual, including the option to administer antibiotics, tocolysis, or steroids as defined per local protocol. To reduce the possibility of bias, quasi-random study designs were excluded. Trials including women with signs of intrauterine infection at onset of midtrimester or premature PROM, pregnancy complications (e.g., such as hypertension, preeclampsia, or HELLP syndrome), an obstetric indication for immediate delivery (signs of fetal distress, abortion, cord prolapse, or advanced labor), or evidence of a major, confirmed fetal abnormality were excluded.

Risk of Bias and Quality Assessment

The risk of bias in included RCTs was assessed using the Cochrane Collaboration’s tool for assessing risk of bias (Fig. 2; online suppl. Table 3) [9]. Review authors’ judgments were categorized as “low risk,” “high risk,” or “unclear risk” of bias. Risk of bias assessment was done by two different reviewers (A.d.R. and S.B.). All conflicts were resolved through discussion or consultation with a third author (E.P.).

Outcomes

The prespecified primary outcome was perinatal mortality (defined as stillbirth, intrapartum death, or neonatal death within 28 days postpartum). Neonatal and maternal outcomes were prespecified and consistent with the core outcome set for preterm birth studies [10]. Additional neonatal and maternal outcomes included time of latency (time from PROM to birth), being a “short-term healthy survivor” (as defined by trials), placental abruption, antepartum hemorrhage, reason for delivery, mode of delivery, and umbilical cord prolapse. Definitions of outcomes were as reported by trial. Furthermore, long-term outcomes were assessed, including long-term respiratory and neurodevelopmental outcome, and being an overall “long-term healthy survivor” (as defined by trials: long-term development with no respiratory problems and no neurodevelopmental delay).

Statistical Analysis

Data extraction was completed by two independent investigators (A.d.R. and L.v.d.W.). Each investigator independently extracted data from each study and analyzed data using RStudio (RStudio Team(2020). RStudio: integrated Development for R. RStudio, PBC, Boston). Dichotomous data were entered in a 2 × 2 table to calculate pooled risk ratios (RRs); for continuous data,
mean differences with corresponding 95% confidence intervals (CIs) were calculated and reported. Meta-analysis was performed using a fixed-effect model, considering the low number of included studies and assuming that included studies have a comparable treatment effect (effect of amnioinfusion on perinatal outcomes). Heterogeneity was measured using $I^2$ (Higgins $I^2$). If substantial statistical heterogeneity was detected (defined as >80%), data were not combined in meta-analysis but reported separately. Potential publication bias was planned to be assessed with Begg’s and Egger’s tests. Reporting bias (publication bias) was planned to be investigated if there were >10 studies in the meta-analysis. A p value <0.05 was considered statistically significant.

**GRADE Assessment**

The quality of evidence was assessed using the GRADE approach for following outcomes: perinatal mortality and the overall chance of being a long-term “healthy survivor.” The GRADEpro Guideline Development Tool was used to create a Summary of Findings table. The quality of evidence could be graded from “high quality” to “moderate quality” or “low or very low quality” depending on assessment of the trials’ risks of bias, the indirectness of evidence, heterogeneity or inconsistency, imprecision of pooled effect estimates, and potential publication bias.

**Results**

**Study Characteristics**

Figure 1 shows the flow diagram (Preferred Reporting Items for Systematic Reviews and Meta-Analyses template). The literature search identified 84 unique articles, of which three titles met the inclusion criteria (shown in Fig. 1). One study was excluded because the trial was never executed [11], leaving two studies eligible for inclusion in this systematic review and meta-analysis (online suppl. Table 1 shows search strategy; online suppl. Table 2 shows characteristics of excluded studies).

**Characteristics of Included Trials**

Included trials randomized patients between 16+0 and 23+6 weeks of gestational age and were carried out in The Netherlands and the UK between 2002 and 2016 [5, 6]. Details of included trials are listed in Table 1 (study flow diagram is shown in online suppl. material. Fig. 8). The PPROMEXIL-III (Preterm Prelabor Rupture of Mem-
Table 1. Characteristics of the multicenter randomized trials comparing amnioinfusion to no intervention

| Study: Van Kempen 2019 | Study: Roberts 2014 |
|------------------------|----------------------|
| PPROMEXIL-III          | AMIPROM              |

| Registration number   | NTR3492              | ISRCTN 8192589 |
|-----------------------|-----------------------|----------------|
| Type of study         | RCT                   | RCT            |
| Sample size           | 56 (28 vs. 28)        | 58 (28 vs. 28)*|
| Countries of          | The Netherlands, between 2012 and 2016* | The UK, between 2002 and 2009* |
| recruitment           |                       |                |
| Participants          | Singleton pregnancies with PROM between 16–24 weeks of gestation with oligohydramnios (single deepest pocket <20 mm) | Singleton pregnancies with PROM between 16–24 weeks gestation |
| Intervention          | Serial transabdominal amnioinfusion | Serial transabdominal amnioinfusion |
| Comparator            | No intervention: expectant management until ≥37 weeks of gestational age unless there was an obstetric indication for earlier delivery or delivery by caesarean section | No intervention: expectant management until ≥37 weeks of gestational age unless there was an obstetric indication for earlier delivery or delivery by caesarean section |
| Inclusion criteria    | PROM at 16–23 weeks of gestational age and oligohydramnios (single deepest pocket <20 mm); present for ≥3 and <21 days | PROM at 16–23 weeks of gestational age, present for ≥10 days* |
| Exclusion criteria    | Multiple pregnancy, signs of uterine contractions (eight contractions/hour), evidence of intrauterine infection (temperature >38°C with fetal tachycardia or uterine tenderness or purulent amniotic fluid), women with cervical incompetence (cervical dilatation visualized during speculum examination or a cervical length of <25 mm on transvaginal ultrasound), and high risk pregnancy | Multiple pregnancy, advanced labor (>5 cm cervical dilation), evidence of serious maternal infection, high-risk pregnancy |
| Clinical management   | Both groups received a single course of oral erythromycin (250 mg 4 times per day for 10 days); administration of antenatal corticosteroids could be considered from 23–35 weeks. If no delivery had occurred after 2 weeks, a second course of corticosteroids was allowed when signs of preterm birth were apparent, according to local protocol. Hospital admission for rest was recommended after 24 weeks of gestation, but not mandatory | Both groups received a single course of oral erythromycin (250 mg 4 times per day for 10 days); administration of antenatal corticosteroids at 26–28 weeks (as a matter of routine prophylaxis). Earlier antenatal corticosteroids (between 23 and 25 weeks) were given at clinicians’ discretion. Hospital admission for rest was recommended between 26 and 30 weeks of gestation but was not mandatory |
| Timing of randomization | After ≥3 and <21 days PROM and oligohydramnios | After ≥10 days PROM |
| Timing of procedure   | As soon as possible after randomization, and not later than 1 week after randomization | As soon as possible after randomization |
| Methods of procedure  | Manual injection of Ringer’s lactate under continuous ultrasound monitoring. Volume injected was calculated by multiplying the gestational age in weeks by 10 mL. Participants were seen twice weekly, and amnioinfusion was repeated weekly if the single deepest pocket of amniotic fluid was measured at <20 mm. This procedure was repeated until 28 weeks of gestation | Manual injection of Hartmann’s solution or normal saline under continuous ultrasound monitoring. Volume injected was calculated by multiplying the gestational age in weeks by 10 mL. Participants were seen weekly, and amnioinfusion was repeated if the single deepest pocket of amniotic fluid was measured at <20 mm. This procedure was repeated until 34 weeks of gestation |
| Primary outcome       | Perinatal mortality, defined as intrauterine death, intrapartum death, or neonatal death in the first 28 days of life | Perinatal mortality defined as death before, and up to 28 days after birth |
| Long-term follow-up   | Study: de Ruigh 2020, a long-term follow-up of the PPROMEXIL-III trial. Assessment of neurodevelopmental outcome at 2–5 years of corrected age using the Bayley Scales of Infant and Toddler Development, third edition (BSID-III) or the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III), as appropriate. Other questionnaires for assessment of behavior (Child Behaviour Checklist), sensory processing (Infant/Toddler Sensory Profile), and health outcomes. Outcome: “healthy survivor,” defined as: surviving without long-term respiratory problems or neurodevelopmental delay | Study: Roberts 2014, AMIPROM. Assessment of neurodevelopmental outcome at 2 years of corrected age using the Bayley Scales of Infant Development, second edition (BSID-II). Assessment of respiratory problems at 6, 12, and 18 months using a validated respiratory questionnaire and a whole body plethysmography. Outcome: “healthy survivor,” defined as: surviving without long-term respiratory problems or neurodevelopmental delay |

* Indicates an obstetric indication to terminate pregnancy. ** Indicates the presence of a lethal anomaly.
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branes Expectant management or Amnioinfusion) randomized women with midtrimester PROM, between three and 21 days after diagnoses, and oligohydramnios (single deepest pocket <20 mm). The AMIPROM trial (Amnioinfusion in Preterm Premature Rupture of Membranes) randomized women with midtrimester PROM, at least 10 days after the diagnoses of PROM and regardless of amniotic fluid level. In both studies, patients received a single course of antibiotics at hospital admission. Administration of antenatal corticosteroids was considered according to local protocol. Administration of tocolysis was not required for amnioinfusion. After evaluating short-term outcomes, both trials also assessed long-term neurodevelopment and respiratory outcomes in survivors. The PPROMEXIL-III trial assessed neurodevelopment between 2 and 5 years of age with the Bayley third edition (Bayley-III) or Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III) and respiratory problems using respiratory and general health questionnaires. The AMIPROM trial assessed development at 2 years of corrected gestational age using the Bayley Scales of Infant Development, second edition (Bayley-II) and respiratory function using validated respiratory questionnaires and whole body plethysmography at the age of 18 months. In online suppl. material Table 4, baseline characteristics of participants in included trials are shown. Mean gestational age at PROM was 19.0 weeks in the amnioinfusion group versus 18.9 in the no intervention group; PROM at randomization was 20.9 weeks versus 20.5 weeks, respectively. A positive vaginal culture for group B *Streptococcus* was seen in 12.5% of women randomized to amnioinfusion and in 8% randomized to expectant management. Nearly 90% of women in both treatment groups received antenatal maternal antibiotics (90.9% vs. 89.3%) and in almost 40%, antenatal corticosteroids were administrated (40% in the amnioinfusion group vs. 41.1% in the no intervention group).

**Risk of Bias of Included Studies**

Figure 2 and online suppl. material, Table 3 shows the risk of bias. None of the studies were double blinded; thus, all studies were judged to be at high risk of performance bias as assessed by the Cochrane Collaboration’s tool. Publication bias was not assessed since less than 10 publications with the primary outcome were included.

**Primary Outcome**

No differences between groups were seen in the prespecified outcome perinatal mortality: 37/56 (66.1%) pregnancies in amnioinfusion group versus 40/56 (71.4%) pregnancies in no intervention group, RR 0.92, 95% CI: 0.72–1.19 (Table 2; Fig. 3), intention-to-treat analysis).
Table 2. Amnioinfusion versus no intervention, meta-analysis, and summary of primary and secondary outcomes

| Trial | Amnioinfusion | No intervention | I², % | RR or MD (95% CI) |
|-------|---------------|-----------------|-------|------------------|
| **Primary outcome** | | | | |
| Perinatal mortality (stillbirth, intrapartum death, or neonatal death within 28 days postpartum) | | | | |
| PPROMEXIL-III 2019 (n = 56) | 18/28 (64.3%) | 21/28 (75.0%) | 0 | 0.92 (0.72; 1.19) |
| AMIPROM 2014 (n = 56) | 19/28 (67.9%) | 19/28 (67.9%) | | |
| Total (n = 112) | 37/56 (66.1%) | 40/56 (71.4%) | | |
| **Secondary neonatal outcomes** | | | | |
| Fetal death | PPROMEXIL-III 2019 | 13/28 (46.4%) | 15/28 (53.6%) | 34 | 0.69 (0.44; 1.10) |
| AMIPROM 2014 | 5/28 (17.9%) | 11/28 (39.3%) | | |
| Total | 18/56 (32.1%) | 26/56 (46.4%) | | |
| Neonatal death (death postpartum and within 28 days after birth) | PPROMEXIL-III 2019 | 5/28 (18%) | 6/28 (21%) | 24 | 1.36 (0.76; 2.41) |
| AMIPROM 2014 | 14/28 (50%) | 8/28 (28.6%) | | |
| Total | 19/56 (33.9%) | 14/56 (25.0%) | | |
| Gestational age at birth of all pregnancies (weeks) | PPROMEXIL-III 2019 | 24.3 [21.4–28.0] | 23.6 [20.7–27.4] | – | – |
| AMIPROM 2014 | NR | NR | | |
| Total | – | – | | |
| Gestational age at birth of all live-born neonates (weeks) (mean (SD) or [IQR]) | PPROMEXIL-III 2019 | 28.9 (4.9) [25.1–32.6] | 28.4 (3.6) [26.1–30.0] | 19 | –0.37 [-1.96; 1.21] |
| AMIPROM 2014 | 28.5 (4.4) [19.4–37.6] | 29.4 (3.3) [24.9–38.1] | | |
| Total | 28.9 (4.9) [25.1–32.6] | 29.4 (3.3) [24.9–38.1] | | |
| Time of latency (time from PROM to birth) (days) | PPROMEXIL-III 2019 | 44.0 [19.3–57.8] | 24.5 [16.0–68.8] | – | – |
| AMIPROM 2014 | NR | NR | | |
| Total | – | – | | |
| Birthweight (kilograms) | PPROMEXIL-III 2019 | 1.37 (0.82) | 1.24 (0.64) | 29 | –0.13 [-0.46; 0.19] |
| AMIPROM 2014 | 1.18 (0.62) | 1.46 (0.67) | | |
| Total | – | – | | |
| Culture proven neonatal sepsis | PPROMEXIL-III 2019 | 1/11 (9%) | 2/8 (25%) | 0 | 0.50 (0.21; 1.20) |
| AMIPROM 2014 | 5/23 (21.7%) | 7/17 (41.2%) | | |
| Total | 6/34 (17.6%) | 9/25 (36.0%) | | |
| Chronic lung disease or oxygen at day 28 | PPROMEXIL-III 2019 | 5/11 (45.5%) | 4/8 (50.0%) | 0 | 0.94 (0.44; 2.05) |
| AMIPROM 2014 | 3/9 (33.3%) | 3/9 (33.3%) | | |
| Total | 8/20 (40.0%) | 7/17 (41.2%) | | |
| Pneumothorax | PPROMEXIL-III 2019 | 3/15 (20%) | 6/13 (46.2%) | 0 | 0.54 (0.22; 1.34) |
| AMIPROM 2014 | 3/23 (13%) | 3/17 (17.7%) | | |
| Total | 6/38 (15.8%) | 9/30 (30.0%) | | |
| Persistent pulmonary hypertension of the neonate | PPROMEXIL-III 2019 | 6/15 (40%) | 9/13 (69.2%) | – | – |
| AMIPROM 2014 | NR | NR | | |
| Total | – | – | | |
| Pulmonary hypoplasia | PPROMEXIL-III 2019 | – | – | – | – |
| AMIPROM 2014 | – | – | | |
| Total | – | – | | |
| Necrotizing enterocolitis | PPROMEXIL-III 2019 | 11/11 (9.1%) | 0/8 (0%) | 0 | 2.08 (0.25; 17.25) |
| AMIPROM 2014 | 2/7 (28.6%) | 1/17 (5.9%) | | |
| Total | 3/34 (8.8%) | 1/25 (4.0%) | | |
| Periventricular leukomalacia | PPROMEXIL-III 2019 | 0/11 (0%) | 0/8 (0%) | – | – |
| AMIPROM 2014 | 0/23 (0%) | 1/17 (5.9%) | | |
| Total | 0/34 (0%) | 1/25 (4.0%) | | |
| Intraventricular hemorrhage (°grade II) | PPROMEXIL-III 2019 | 1/11 (9.1%) | 0/8 (0%) | 0 | 1.53 (0.19; 12.43) |
| AMIPROM 2014 | 1/27 (3.7%) | 1/28 (3.6%) | | |
| Total | 2/38 (5.3%) | 1/36 (2.8%) | | |
| Postural orthopedic deformities | PPROMEXIL-III 2019 | 1/15 (7%) | 3/13 (23%) | 0 | 0.32 (0.07; 1.55) |
| AMIPROM 2014 | 1/23 (4.3%) | 2/17 (11.8%) | | |
| Total | 2/38 (5.3%) | 5/40 (8.0%) | | |
| “Short-term healthy survivor” | PPROMEXIL-III 2019 | 4/15 (26.6%) | 2/13 (15.4%) | 0 | 1.69 (0.62; 4.62) |
| AMIPROM 2014 | 5/28 (17.9%) | 3/28 (10.7%) | | |
| Total | 9/43 (20.9%) | 5/41 (12.2%) | | |
When analyzing the outcome perinatal mortality per protocol, perinatal mortality rates were seen in 28/43 (55.8%) pregnancies in the amnioinfusion group as compared to 35/51 (68.6%) pregnancies in the no intervention group (RR 0.85, CI: 0.36–1.99). In both treatment groups, the majority of fetus died before 24 weeks of GA (44/112 [39.3%] of pregnancies). The most common causes were stillbirth, spontaneous immature delivery, and cord prolapse. Mortality after 24 weeks of GA was mostly caused by cord prolapse, extreme prematurity, and pulmonary hypoplasia. No differences were seen in fetal death or neonatal death in women treated with amnioinfusion or no intervention (Table 2; online suppl Fig. 1, 2).
Secondary Outcomes

In the PPROMEXIL-III trial, GA at birth of the live-born neonates occurred at a median of 27.0 weeks in the amnioinfusion group and at 27.4 weeks in the expectant management group. In the AMIPROM trial, women delivered at a mean of 28.5 weeks and 29.8 weeks, respectively. Regarding any prespecified secondary neonatal outcome, no differences were seen between both treatment groups (Table 2). Pulmonary hypoplasia was diagnosed in the AMIPROM trial in 5/14 (35.7%) cases of neonatal death in the amnioinfusion group versus 2/8 (20.0%) cases in the no intervention group (online suppl. material Fig. 3) [12]. Pneumothorax was observed in 6/38 (15.8%) live-born neonates in the amnioinfusion group versus 9/30 (30.0%) live-born neonates in the no intervention group (RR: 0.54, 95% CI: 0.22–1.34, Table 2; online suppl. Fig. 4). Persistent pulmonary hypertension of the neonate was measured in the PPROMEXIL-III trial, showing PPHN in 40% of live-born neonates following amnioinfusion and in 69.2% of live-born neonates following no intervention [5]. The outcome “short-term healthy survivor” occurred slightly more often in the amnioinfusion group, although no difference was seen between both groups (20.9% of children vs. 12.2% children, RR: 1.69, 95% CI: 0.62–4.62) (Table 2; online suppl. Fig. 5). For maternal outcomes, no differences were seen between both treatment groups. Substantial statistical heterogeneity was measured between studies for onset of labor and vaginal mode of delivery. The high level of heterogeneity observed for mode of delivery may be due to the low number of cesarean sections performed in the PPROMEXIL-III trial (vaginal delivery: n = 42/56 [75%] pregnancies, cesarean section: n = 14/56 [25%] pregnancies) as compared to the AMIPROM trial (vaginal delivery: n = 34/56 [60.7%] pregnancies, cesarean section: n = 22/56 [39.3%] pregnancies). The low number of cesarean sections in the PPROMEXIL-III may be explained by the fact that all deliveries <24 weeks of GA were vaginal deliveries in that trial. There was a comparable rate of chorioamnionitis between the amnioinfusion group and no intervention (23.6% of mothers vs. 28.6% of mothers, RR: 0.82, 95% CI: 0.44–1.54, Table 2; online suppl. material Fig. 6). In both groups, one case of maternal sepsis was seen, and no maternal deaths occurred (Table 2). As for the safety of the intervention, the PPROMEXIL-III trial reports six minor maternal complications after the procedure of amnioinfusion (6 complications in 81 procedures [7%], complications reported were pain during or after the procedures, vaginal bleeding postintervention, and a small amount of fluid injected into the myometrium).

Long-Term Child Outcomes

In both the PPROMEXIL-III and AMIPROM trial, 17/56 (30.4%) neonates survived after discharge from hospital. In 27 children, neurodevelopment and/or respiratory function was assessed (PPROMEXIL-III trial n = 14/17 [82.4%] survivors, amnioinfusion, n = 10/10 [100%] survivors vs. no intervention, n = 4/7 [57.1%] survivors; AMIPROM trial n = 13/17 survivors [76.5%], amnioinfusion, n = 8/9 [88.9%] survivors vs. no intervention, n = 5/8 [62.5%] survivors, online suppl. Fig. 8). A mild (−1 SD) delay was seen in 4 out of 18 (22.2%) children in the amnioinfusion group versus 3 out of 9 (33.3%) children in the no intervention group (percentage of all assessed surviving children with a mild delay: 3/18 [16.6%] vs. 3/9 [33.3%], RR: 0.62, 95% CI: 0.20–1.97, Table 3; online suppl. Table 5). A further
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Table 3. Long-term secondary outcomes: long-term respiratory and neurodevelopmental outcome

| Trial                        | Amnioinfusion | No intervention | I², % | RR (95% CI) |
|------------------------------|---------------|-----------------|-------|-------------|
| Survivors                    |               |                 |       |             |
| Follow-up PPROMEXIL-III 2020| 10/28 (41.7%) | 7/28 (35.7%)    | 36.8  | 1.00 [0.64; 1.57] |
| AMIPROM 2014                 | 9/28 (32.1%)  | 8/28 (28.6%)    |       |             |
| Total                        | 19/56 (38.6%) | 15/56 (29.8%)   |       |             |

Respiratory problems

| Follow-up PPROMEXIL-III 2020| 1/10 (10.0%)* | 0/4 (0%)         |       |             |
| AMIPROM 2014                |               |                 |       |             |
| Total                        |               |                 |       |             |

Visits to hospital clinics for respiratory problems

| Follow-up PPROMEXIL-III 2020| 1/10 (10.0%)* | 1/4 (25.0%)*    |       |             |
| AMIPROM 2014                |               |                 |       |             |
| Total                        |               |                 |       |             |

Antiasthmatic medication

| Follow-up PPROMEXIL-III 2020| 2/10 (20.0%)| 1/4 (25.0%)*    |       |             |
| AMIPROM 2014                |               |                 |       |             |
| Total                        |               |                 |       |             |

Neurodevelopmental delay

| Follow-up PPROMEXIL-III 2020| 2/10 (20.0%)| 2/4 (50.0%)*    |       |             |
| AMIPROM 2014                |               |                 |       |             |
| Total                        |               |                 |       |             |

Mild (−1 SD)*

| Follow-up PPROMEXIL-III 2020| 1/10 (10.0%)* | 0/4 (0%)         |       |             |
| AMIPROM 2014                |               |                 |       |             |
| Total                        |               |                 |       |             |

Severe (−2 SD)**

| Follow-up PPROMEXIL-III 2020| 1/10 (10.0%)| 0/4 (0%)         |       |             |
| AMIPROM 2014                |               |                 |       |             |
| Total                        |               |                 |       |             |

Long-term healthy survivor – worst case scenario

| Follow-up PPROMEXIL-III 2020| 5/28 (17.9%) | 2/28 (7.1%)     |       |             |
| AMIPROM 2014                |               |                 |       |             |
| Total                        |               |                 |       |             |

Long-term healthy survivor – best case scenario

| Follow-up PPROMEXIL-III 2020| 5/28 (17.9%) | 5/28 (17.1%)    |       |             |
| AMIPROM 2014                |               |                 |       |             |
| Total                        |               |                 |       |             |

Aggregate data for not reported outcomes were not collected. Only published data were included. Outcomes are complete-case analysis for which no data are missing, as a result of there being no validated methods available to handle missing data. Study data are presented as number in the amnioinfusion group versus number in the expectant management group with percentages, as mean (SD), or median [IQR] unless stated otherwise. SD, standard deviation; IQR, interquartile range; RR, risk ratio. * Respiratory questionnaires of the Follow-up PPROMEXIL-III study were obtained at 2 years of corrected age and of AMIPROM at 18 months of corrected age. + Respiratory symptoms include at least once a week respiratory symptoms interfering with daily activities (i.e., not able to attend school or not able to play) in the past 4 weeks. In the respiratory questionnaire of the AMIPROM trial, the median (IQR) daytime symptoms score was 6.5 (2–17) versus 6 (4–21). †Total of all children assessed for long-term follow-up examinations. Percentages represent number of children/number of children assessed for follow-up. § Defined as visits to a pediatric pulmonologist from birth until current age. ¶ Respiratory questionnaires of three children were not returned and were thus excluded from analysis. ‖ Defined as attendance to hospital clinics for chest problems. # Antiasthmatic medication taken at least one time/week from birth until current age. $Medicines taken as treatment for chest symptoms for up to 1 week at any one time. All medicines were inhalers for asthma. ¶¶ Neurodevelopmental delay in the Follow-up PPROMEXIL-III study was assessed by BSID-III with outcomes in two subscales (CCS and MCS) at corrected age <42 months and by the WPPSI-III with outcomes in three subscales (PIQ, VIQ, FSIQ) at corrected age of >42 months. Mean score of 100 with SD of 15 points for both tests. Neurodevelopmental delay in the AMIPROM trial was assessed by BSID-II with outcomes in two subscales (MDI and PDI) at corrected age of 2 years. Mean score of 100 with SD of 15 points.
breakdown of percentages of long-term neurodevelopmental delay is shown in the online supplementary material, Table 5. Long-term respiratory problems assessed by parental questionnaires showed no differences between treatment groups (Table 3; online suppl. Table 5). Both the follow-up PPROMEXIL-III and AMIPROM trial reported on the outcome: long-term survival without neurodevelopmental delay or respiratory problems (defined as “long-term healthy survivor”). In total, ten children treated with amnioinfusion could be classified as healthy survivor compared to eight children in the no intervention group showing a pooled RR of 1.30 (95% CI: 0.47–3.60) (reported best case scenario, defined as “all children lost to follow-up were healthy,” Table 3; online suppl. Table 5 and Fig. 7, 8).

GRADE Assessment
GRADE decisions for the prespecified primary and secondary outcome: perinatal mortality, short-term healthy survivor, and long-term healthy survivor are shown in the Summary of Findings table (online suppl. material, Table 6). Forest plots for all GRADE outcomes comprise Figure 3 and online supplementary material Figure 5. According to the GRADE methodology, both outcomes were graded as moderate quality (defined as, “further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate”).

Discussion

Main Findings
This systematic review and meta-analysis showed no difference in perinatal mortality in women treated with amnioinfusion as compared to expectant management for midtrimester PROM. No differences between both treatment arms for any other core neonatal or maternal outcomes were detected. This review also investigated the long-term effects of amnioinfusion or no intervention on neurodevelopmental outcome and respiratory function in survivors at the age of 18 months to 5 years old. Also, no differences were shown between treatment groups for long-term outcomes. However, looking at the overall pooled estimates for all perinatal, neonatal, and maternal outcomes, the measures of effect seem to be slightly in favor of amnioinfusion. Further research is necessary to investigate the effectiveness of this treatment.

Quality of Evidence
The quality of evidence was graded using the GRADE tool and was classified as moderate due to the limited number of RCTs and small sample sizes. Furthermore, included individual trials had no noticeable risk of bias, apart from lack of blinding which was due to the nature of the intervention.

Strength and Limitations
One of the strengths of this systematic review is that it provides a comprehensive overview of available RCTs with a strict definition for very early (midtrimester) PROM (between 16 and 24 weeks of gestation). Furthermore, the two well-conducted RCTs in this meta-analysis showed minor protocol differences and comparable inclusion and exclusion criteria, making it possible to aggregate data with low levels of heterogeneity. Even though solely including RCTs is one of the main strengths, it might also be a limitation. When only including RCTs for evaluating the effectiveness of an intervention, an accurate estimate for the population included in the trial will be reported but will not always yield relevant information about the effects in a particular target population [13]. A second limitation to this meta-analysis is the small number of included RCTs and, consequently, the small total sample size. As previously published by our study group, further research and a much larger sample size (“a sample of 1,352 women per arm is needed to detect a decrease of 5% in perinatal mortality [from 71% to 66%], with an alpha of 0.05 and a power of 80%”) are required to effectively assess the effect of amnioinfusion in this population [7].

Comparison with Existing Literature
Previously, one other review included RCTs evaluating amnioinfusion versus no intervention in midtrimester PROM. This Cochrane review performed in 2013 included two ongoing trials at the time, the AMIPROM trial and an RCT by Locatelli et al. [5, 6, 11, 14]. The study by Locatelli et al. [11] has never been executed (online suppl. Table 2). In 2012, Porat et al. [15] performed a systematic review and meta-analysis, including both comparative observational cohort studies and RCTs in which serial transabdominal amnioinfusion was compared with conventional treatment (or no intervention). They concluded that amnioinfusion for early PROM reduced perinatal mortality in observational studies and showed a trend toward reduced mortality in RCTs. However, they included studies with PROM up to 33+6 weeks of gestational age. None of the studies included women up to maximum 24 weeks of gestational age, and three studies included women with PROM between 25 and 34 weeks of gestational age [16–18]. Results were not stratified for these differences in gestational age. When including preg-
nancies with PROM >24 weeks of gestation, it is thought that these pregnancies would show better outcomes as the critical time for lung development (the preglendular or canalicular period) is mostly between 16+0 and 24+0 weeks of gestation. Lack of adequate volumes of amniotic fluid in that time period will lead to sustained breathing movements, interruption of lung development and thus under-development of the alveolar system, pulmonary hypoplasia and its (often fatal) consequences.

**Comparability and Differences between Included Studies**

Our review reflects the results of the two individual trials included in this review (i.e., PPROMEXIL-III and AMIPROM trial), as both trials concluded that no reduction was found in perinatal mortality or other secondary outcomes. However, the included trials have some minor protocol differences. First of all, levels of amniotic fluid prior to randomization differed. The PPROMEXIL-III only included women with oligohydramnios, while the AMIPROM specified no maximum amniotic fluid level (i.e., pool depth of <2 cm) for inclusion. Therefore, the AMIPROM potentially included more women with favorable outcome, since a higher level of amniotic fluid is correlated with better perinatal outcomes [19, 20]. Furthermore, both studies required a deepest pool level of <2 cm for the procedure of amnioinfusion; thus, in the AMIPROM study, four women randomized to this intervention never received treatment because they maintained a deepest pool of amniotic fluid >2 cm throughout the duration of their participation. In the PPROMEXIL-III trial, five women in the amnioinfusion group did not receive the treatment they were allocated to due to other reasons: onset of labor, detection of lethal anomaly after the 20-week anomalies scan, maternal sepsis, or technical problems during the procedure. When comparing the primary outcome in a per protocol analysis in this review, comparable perinatal mortality rates for both treatment arms were seen. In addition, the PPROMEXIL-III included women with an ongoing pregnancy 3 days after midtrimester PROM, while the AMIPROM included women 10 days after PROM. It has been observed that most patients with an (active) infection after PROM will deliver within 72 h, and at least half of the patients with mid trimester PROM deliver immature within the first 7 days after rupture of membranes [21]. Inclusion in the AMIPROM trial after this time period of 7 days could lead to a better a priori prognosis of these women. Another difference is the diagnosis of pulmonary hypoplasia between studies. Pulmonary hypoplasia is a crucial outcome measure for evaluating the effect of amnioinfusion. In the AMIPROM trial, lethal pulmonary hypoplasia was based on autopsy data. This differed from the PPROMEXIL-III trial, in which pulmonary hypoplasia was diagnosed based on respiratory symptoms (pneumothorax, PPHN) associated with pulmonary hypoplasia, therefore also including neonates that survived. The clinical definition of pulmonary hypoplasia is inconsistent [22]. A uniform diagnosis is needed.

The intervention of amnioinfusion is an invasive procedure. The two RCTs in this review showed some fetal complications: one fetal demise occurred 30 min after amnioinfusion and mild fetal trauma was reported in three cases. These three fetuses were punctured by the amnioinfusion needle, but no trauma with postnatal complications occurred. In both RCTs, PPROMEXIL and AMIPROM, the procedure did not seem to be associated with any severe maternal complications. Still, the presence of oligohydramnios complicates the procedures of amnioinfusion more than routine diagnostic amniocentesis and thus should only be performed by experienced fetal medicine specialists.

**Conclusion**

At present, the benefits of amnioinfusion for mid trimester PROM are unclear, and the potential harms remain unknown. No differences in perinatal mortality rates are shown in women treated with amnioinfusion as compared to no intervention for mid trimester PROM. However, it must be noticed that patient numbers in this meta-analysis are small; therefore results and conclusions should be interpreted with care. Results of this review justify the need for additional research and especially adequately powered RCTs to demonstrate a smaller but clinically relevant effect, before this therapy can be considered for routine clinical use. Performing an international, multicenter study may be the only way to achieve this large sample size.

**Statement of Ethics**

An ethics statement is not applicable because this study is based exclusively on published literature.

**Conflict of Interest Statement**

Ben Willem Mol reports consultancy for ObsEva, Merck, and Guerbet. Ben Willem Mol is supported by an NHMRC Practitioner Fellowship (GNT1082548). The other authors declare no competing interests.
Funding Sources

No financial support was received for this study

Author Contributions

Annemijn A. de Ruigh, Noor E. Simons, Larissa I. van der Windt, and Sofie H. Breuking participated in protocol development, literature search, data collection, data analysis, interpretation, and writing. Annemijn A. de Ruigh, Noor E. Simons, Larissa I. van der Windt Sofie H. Breuking, Janneke van’t Hooft, Augustinus S. van Teeffelen, Zarko Alfirevic, Devender Roberts, Ben Willem Mol, and Eva Pajkrt participated in protocol development, data analysis, and interpretation. Annemijn A. de Ruigh, Noor E. Simons, Larissa I. van der Windt Sofie H. Breuking, Janneke van’t Hooft, Augustinus S. van Teeffelen, Zarko Alfirevic, Devender Roberts, Ben Willem Mol, and Eva Pajkrt were given the opportunity to comment on the draft manuscript; they were sent the paper as prepared for submission and saw and approved the final version.

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Data Availability Statement

All data generated or analyzed during this study are included in this article and its supplementary material files. Further inquiries can be directed to the corresponding author.