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Amnioinfusion Compared With No Intervention in Women With Second-Trimester Rupture of Membranes

A Randomized Controlled Trial

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OBJECTIVE: To assess the effectiveness of amnioinfusion in women with second-trimester preterm prelabor rupture of membranes.

METHODS: We performed a nationwide, multicenter, open-label, randomized controlled trial, the PPROM: Expectant Management versus Induction of Labor-III (PPROMEXIL-III) trial, in women with singleton pregnancies and preterm prelabor rupture of membranes at 16 0/7 to 24 0/7 weeks of gestation with oligohydramnios (single deepest pocket less than 20 mm). Participants were allocated to transabdominal amnioinfusion or no intervention in a one-to-one ratio by a web-based system. If the single deepest pocket was less than 20 mm on follow-up visits, amnioinfusion was repeated weekly until 28 0/7 weeks of gestation. The primary outcome was perinatal mortality. We needed 56 women to show a reduction in perinatal mortality from 70% to 35% (β error 0.20, two-sided α error 0.05).

RESULTS: Between June 15, 2012, and January 13, 2016, we randomized 28 women to amnioinfusion and 28 to no intervention. One woman was enrolled before the trial registration date (June 19, 2012). Perinatal mortality rates were 18 of 28 (64%) in the amnioinfusion group vs 21 of 28 (75%) in the no intervention group (relative risk 0.86, 95% CI 0.60–1.22, P=.39).

CONCLUSION: In women with second-trimester preterm prelabor rupture of membranes and oligohydramnios, we found no reduction in perinatal mortality after amnioinfusion.

CLINICAL TRIAL REGISTRATION: NTR Dutch Trial Register, NTR3492.

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When the membranes rupture at 16 0/7 to 24 0/7 weeks of gestation, known as second-trimester preterm prelabor rupture of membranes (PROM), perinatal survival is severely compromised.[1] This condition affects approximately 0.4% of pregnancies.[2]

Pregnancies complicated by second-trimester preterm PROM can result in extremely premature delivery or intrauterine infection, whereas liveborn neonates are at risk of pulmonary hypoplasia.[1,3,4] The latter is thought to be the result of impairment of fetal lung development by oligohydramnios. Affected neonates may experience life-threatening respiratory and cardiovascular problems such as pneumothorax and persistent pulmonary hypertension of the neonate.[5–7] The prevalence of pulmonary hypoplasia and associated mortality after second-trimester preterm PROM are estimated to be 20% and 70%, respectively.[1,6] Moreover, placental abruption, cord prolapse, cord compression, and structural deformities are common complications that are associated with poor neonatal outcome. Finally, if second-trimester preterm PROM is complicated by intrauterine infection, maternal health can also be compromised.[1]

It is unclear whether amnioinfusion has any beneficial effects. It has been hypothesized that by alleviating oligohydramnios, pulmonary hypoplasia could be prevented and that time to delivery may be prolonged.[8] Some observational studies have shown decreased perinatal mortality rates after amnioinfusion compared with no intervention, whereas the only randomized controlled trial (RCT) to date found no difference in perinatal mortality and neonatal morbidity.[9–13] As a result of the nature of available data, we performed this RCT to evaluate whether transabdominal amnioinfusion can reduce perinatal mortality in pregnancies complicated by second-trimester preterm PROM.

METHODS

We performed a multicenter open-label RCT, the PPROM: Expectant Management versus Induction of Labor-III (PPROMEXIL-III) trial, in six tertiary centers in the Netherlands. The study was performed within the infrastructure of the Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynecology (www.zorgevaluatienederland.nl). The trial was approved by the Medical Ethics Committee of the Academic Medical Center, Amsterdam, the Netherlands (ref. no. MEC 2011_134, August 17, 2011) with additional approval from the local boards of all participating hospitals. A data safety monitoring board was established before the study commenced. An interim analysis was planned after follow-up data had been obtained of the first 28 women who were included. In case of a significant difference in the primary outcome ($P<.05$, two-sided), the trial would have been terminated. On June 19, 2012, the PPROMEXIL-III trial was registered in the Dutch Trial Register, NTR3492. The trial protocol has been published previously.[14]

Women with viable singleton pregnancies and oligohydramnios between 16 0/7 and 24 0/7 weeks of gestation resulting from preterm PROM 3–21 days prior were eligible for inclusion. Preterm PROM was diagnosed based on a positive history of continuous vaginal fluid loss combined with the presence of fluid originating from the cervical os, confirmed by a fern or Nitrazine test, Amniocator or AmniSure. Oligohydramnios was defined as single deepest pocket less than 20 mm. We excluded women with eight or more uterine contractions per hour, suspected intrauterine infection, cervical dilatation visualized during speculum examination, or cervical length less than 25 mm on transvaginal ultrasonography. Additional exclusion criteria comprised obstetric complications necessitating termination of the pregnancy and major fetal structural anomalies compromising perinatal survival. Eligible patients were referred to participating centers and counseled about the study by a maternal–fetal medicine specialist trained in Good Clinical Practice. Written informed consent was obtained and immediately followed by randomization.

Women were randomized to amnioinfusion or no intervention in a one-to-one ratio using an online application with a computer-generated randomization sequence with a variable block size (maximum of four). Allocation was not blinded for participants, clinicians, or ultrasonographers. Pediatricians and pathologists were blinded.

Women allocated to amnioinfusion underwent the procedure less than 1 week postrandomization in an outpatient setting. Fetal growth was assessed before amnioinfusion. A 20-G needle was inserted under ultrasound guidance through the abdomen into the single deepest pocket by a senior fetal medicine specialist trained in invasive procedures. Proper placement was assured by withdrawing a small amount of amniotic fluid. Subsequently, Ringer's lactate was injected manually under continuous ultrasound monitoring. The required volume was calculated by multiplying the gestation in weeks by 10 mL. Directly after the procedure the single deepest pocket was remeasured. Problems occurring 24 hours or less after the procedure were recorded. If oligohydramnios recurred, amnioinfusion was repeated weekly until 28 0/7 weeks of gestation. Besides not being managed with amnioinfusion, the no intervention group received the same care as the amnioinfusion group.

All women received a single course of oral erythromycin starting the day of randomization (250 mg four times/d for 10 days). The first follow-up visit was scheduled after 48–72 hours. Ultrasound examination to assess fetal well-being and single deepest pocket occurred twice weekly until 28 0/7 weeks of gestation. Blood was taken every week until delivery to assess the level of C-reactive protein and leukocytes. Administration of corticosteroids to accelerate lung maturation was allowed from 23 5/7 weeks of gestation. Based on fetal presentation and the presence of maternal complaints, women were sometimes admitted to the hospital from this gestation onward. If no delivery had occurred after 2 weeks, a second course of corticosteroids was allowed when signs of preterm birth were apparent. A vaginal delivery was pursued unless there were obstetric problems necessitating a cesarean delivery.

The primary outcome was perinatal mortality, defined as fetal demise or neonatal death within 28 days postpartum. Secondary outcomes comprised cause of neonatal death; gestation at delivery; latency, defined as the time from preterm PROM to birth; indication for delivery; and cesarean delivery before or after onset of labor. Additionally, the incidences of complications were reported, including placental abruption based on clinical findings (abrupt onset of vaginal blood loss, abdominal pain, and contractions) confirmed by pathologic examination of the placenta; cord prolapse identified during digital vaginal examination; chorioamnionitis, defined as pyrexia greater than 37.5°C on two occasions more than an hour apart or a temperature greater than 38°C combined with maternal or fetal tachycardia, uterine tenderness, purulent amniotic fluid, or maternal leukocytosis (leukocytes greater than 15.000 cells/mm^3); and fetal trauma resulting from needle puncture.

Initially we aimed to report pulmonary hypoplasia based on pathologic findings during autopsy.[15,16] However, autopsy was carried out only after parents' consent, and there were only two neonatal postmortem examinations. Hence, application of this criterion was not feasible. Instead, we decided to report respiratory findings associated with pulmonary hypoplasia, which are pneumothorax confirmed by chest radiograph and pulmonary hypertension of the neonate based on echocardiography.[5–7] Furthermore, birth weight and the presence of contractures were assessed in all liveborn neonates.

We described the following endpoints in all neonates who were still alive 1 week postpartum: necrotizing enterocolitis according to Bell et al,[17] periventricular leukomalacia as classified by De Vries et al,[18] severe intraventricular hemorrhage according to Papile et al,[19] and sepsis. A positive blood culture was considered pathognomonic for sepsis. Otherwise, sepsis was suspected in case of one or more of the following symptoms: apnea, temperature instability, lethargy, feeding intolerance, respiratory distress, and hemodynamic instability combined with either C-reactive protein greater than 20 mg/L or positive surface cultures of a known pathogen. Sepsis commencing less than 72 hours postpartum was considered early onset and greater than 72 hours late onset.[20] Additionally, chronic lung disease was assessed, defined as oxygen dependency at 28 days of life.[21]

Composite neonatal morbidity was defined as the occurrence of one or more of the predefined complications within the neonatal period. Two independent neonatologists individually scored the neonatal endpoints at 6 month-corrected age of the neonate. Moreover, information was collected regarding the baseline characteristics. Data were collected by local Good Clinical Practice–trained research nurses and centrally checked using a paper case report form.

Previously, van der Heyden et al[3] reported a perinatal mortality rate of 70% in pregnancies complicated by second-trimester preterm PROM. Several observational studies estimated a 50% reduction in perinatal mortality after amnioinfusion compared with no intervention.[9–11] To show a mortality reduction from 70% to 35%, we had to randomize 56 women (β error 0.20, two-sided α error 0.05).

Data were analyzed according to the intention-to-treat principle. A Shapiro-Wilk test was applied to assess whether the distribution of continuous variables was normal. We used an independent samples *t* test or Mann-Whitney *U* test to analyze continuous variables as appropriate. The χ^2 test or Fisher exact test was applied for the comparison of dichotomous data. Results were displayed as mean and SD, median and interquartile range (IQR), or number and percentage, where appropriate.

Relative risks (RRs) and corresponding 95% CIs were calculated using a log-binomial model. We calculated hazard ratios by Cox proportional hazard analysis to compare time to delivery, which was additionally evaluated by Kaplan-Meier estimates and tested using a log-rank test, and latency. Birth weights between groups were assessed using a mean difference with corresponding 95% CI.

A post hoc analysis was performed including the following endpoints: antepartum and during labor death; postpartum death; birth weight; pneumothorax; pulmonary hypertension of the neonate; contractures; early- and late-onset sepsis; and survival with and without composite neonatal morbidity.

An additional as-treated analysis was performed for the primary outcome. $P<.05$ indicated statistical

Table 1. Baseline Characteristics of the Study Participants

Characteristic	Amnioinfusion (n=28)	No Intervention (n=28)
Age (y)	33.9±4.9	33.0±6.9
Ethnicity		
Caucasian	20 (71)	20 (71)
Other	8 (29)	8 (29)
Prepregnancy BMI (kg/m^2)	22.7 (20.3–26.1)	23.2 (21.0–24.5)
Smoker	4 (14)	3 (11)
Nulliparous	13 (46)	8 (29)
Obstetric history		
Miscarriage	10 (36)	12 (43)
Ectopic pregnancy	1 (4)	3 (11)
Abortion	3 (11)	1 (4)
Cervical insufficiency or cerclage	0 (0)	1 (4)
Preterm PROM	1 (4)	2 (7)
Preterm birth	4 (14)	4 (14)
Invasive procedure before preterm PROM		
Amniocentesis	0 (0)	1 (4)
Chorionic villus sampling	1 (4)	0 (0)
Gestation at preterm PROM (wk)	18.7±1.9	18.6±2.3
Gestation at randomization (wk)	20.4±1.9	19.9±2.5
Time between preterm PROM and randomization (wk)	1.5 (0.9–2.4)	1.0 (0.5–2.0)
Single deepest pocket at randomization (mm)	7.5 (0.0–14.8)	6.5 (0.0–13.0)
Antepartum hemorrhage	17 (61)	20 (71)
Infection parameters at randomization		
C-reactive protein (mg/L)	6.0 (4.0–18.0)	9.0 (4.4–16.0)
Leukocyte count (10^9/L)	11.3 (8.6–13.5)	12.5 (10.0–14.8)
Vaginal culture at onset of preterm PROM		
Negative	16 (57)	22 (79)
Group B streptococci	6 (21)	3 (11)
Gardnerella vaginalis	0 (0)	1 (4)
Unknown pathogen	1 (4)	0 (0)
Not performed	5 (18)	2 (7)
Male fetus	18 (64)	17 (61)

BMI, body mass index; PROM, prelabor rupture of membranes.
Data are mean±SD, n (%), or median (interquartile range).

significance. The analyses were performed using IBM SPSS Statistics 24.0.

Authors' Data Sharing Statement

Will individual participant data be available (including data dictionaries)? *Yes*
What data in particular will be shared? *All of the individual participant data collected during the trial, after deidentification*
What other documents will be available? *Study protocol, statistical analysis plan, analytic code, case report form*
When will data be available? *Immediately after publication; no end date*
With whom? *Researchers who provide a methodologically sound proposal*
For what types of analyses? *Any purpose*
By what mechanism will data be made available? *Proposals should be directed to e.pajkrt@amc.nl. To gain access, data requestors will need to sign a data access agreement. The data will be available in our databank.*

RESULTS

Between June 15, 2012, and January 13, 2016, we randomized 28 women to amnioinfusion and 28 to no intervention. One woman was enrolled before the trial registration date (June 19, 2012). The baseline characteristics were comparable between groups (Table 1).

In the amnioinfusion group, 5 of 28 (18%) women received no amnioinfusions: two women delivered before the first amnioinfusion; in one woman, the pregnancy was terminated, because of a lethal anomaly first visualized postrandomization; one woman became septic before amnioinfusion was performed; and in one woman, amnioinfusion was attempted but abandoned as a result of technical problems. In total 81 amnioinfusions were performed, with a median number of two amnioinfusions per woman (range 0–8). In both groups, 2 of

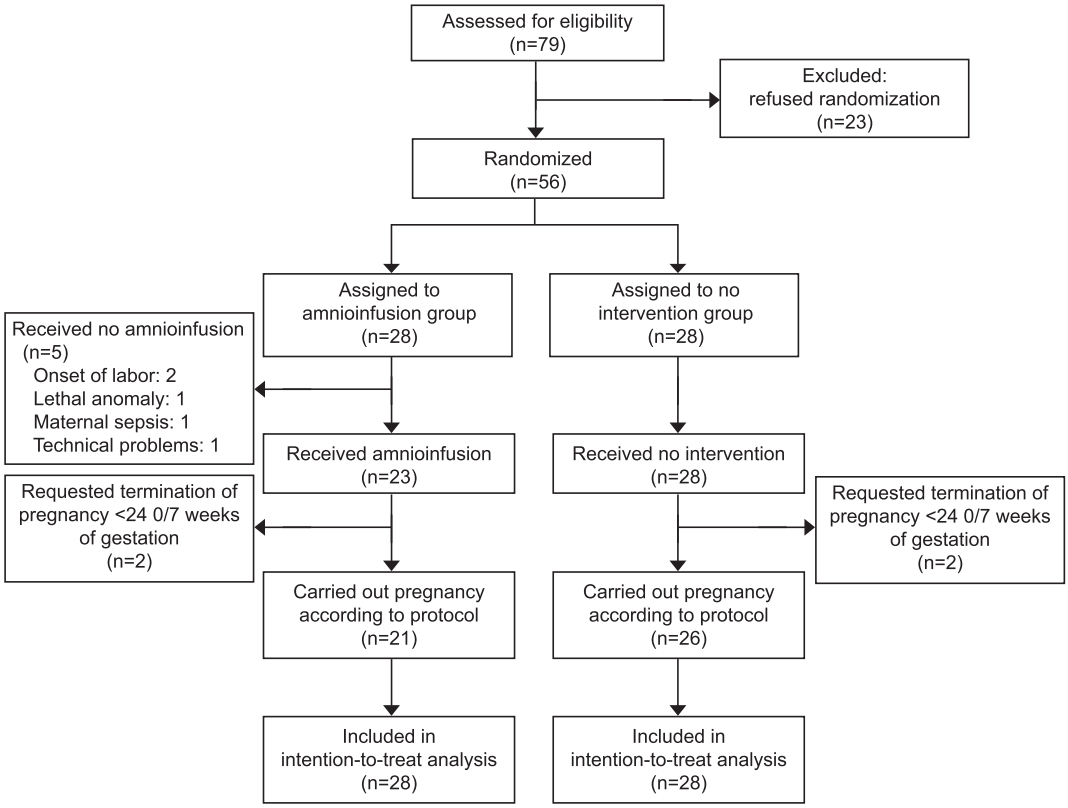

Fig. 1. Flowchart showing the derivation of the study groups. Analysis includes those who received no amnioinfusion and those who requested termination of pregnancy at less than 24 0/7 weeks of gestation.

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28 women (7%) requested to terminate the pregnancy at less than 24 0/7 weeks of gestation (Fig. 1). In 3 of 28 (11%) women in the no intervention group, the single deepest pocket spontaneously increased and remained 20 mm or greater for 48 hours or longer.

The overall perinatal mortality rate was 18 of 28 (64%) fetuses or neonates in the amnioinfusion group and 21 of 28 (75%) in the no intervention group (RR 0.86, 95% CI 0.60–1.22, *P*=.39). Post hoc analysis showed that 13 of 28 (46%) fetuses died in the amnioinfusion group vs 15 of 28 (54%) in the no intervention group (RR 0.87, 95% CI 0.51–1.47, *P*=.59), and 5 of 28 (18%) vs 6 of 28 (21%) died within the neonatal period (RR 0.83, 95% CI 0.29–2.42, *P*=.74; Appendix 1, available online at http://links.lww.com/AOG/B211).

The Kaplan-Meier analysis expressing time to delivery is displayed in Figure 2. The indications for delivery can be found in Table 2. A cesarean delivery occurred in 7 of 28 (25%) women in both arms (RR 1.00, 95% CI 0.40–2.48, *P*=1.00). Clinical chorioamnionitis was diagnosed in 9 of 28 (32%) women in both groups (RR 1.00, 95% CI 0.47–2.14, *P*=1.00). Placental abruptions were not observed nor were maternal deaths.

The neonatal endpoints are compared in Table 3. Post hoc analysis revealed that in liveborn neonates, the clinical course was complicated by a pneumothorax in 3 of 15 (20%) vs 6 of 13 (46%) neonates in the amnioinfusion and no intervention group, respectively (RR 0.43, 95% CI 0.13–1.40, *P*=.16) and by pulmonary hypertension of the neonate in 6 of 15 (40%) vs 9 of 13 (69%) (RR 0.58, 95% CI 0.28–1.19, *P*=.13). In the amnioinfusion group, 4 of 15 (27%) neonates survived without morbidity vs 2 of 13 (23%) neonates in the no intervention group (RR 1.73, 95% CI 0.38–7.98, *P*=.48) as shown by post hoc analysis (Appendix 2, available online at http://links.lww.com/AOG/B211).

As for the safety of amnioinfusion, of 81 procedures, there were four (5%) fetal and six (7%) maternal complications. One fetal demise occurred less than 30 minutes after amnioinfusion, in which the intervention was preceded by an episode of

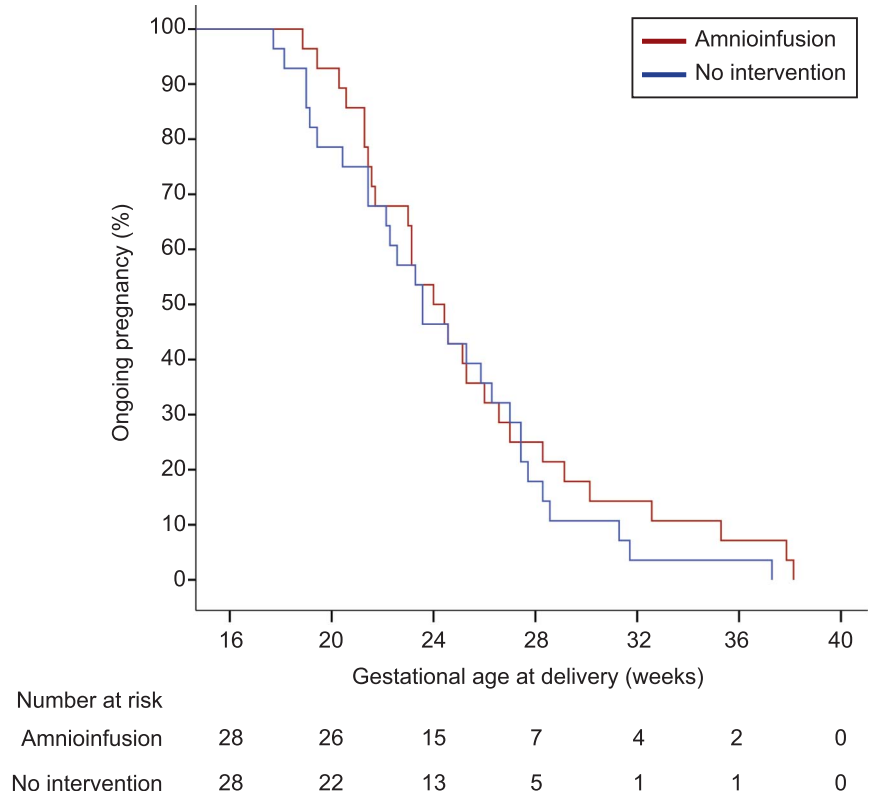

Fig. 2. Kaplan-Meier plot for time to delivery of the intention-to-treat population. Hazard ratio 0.80 (95% CI 0.47–1.37); *P*=.42.

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bradycardia. There were three reports of fetal puncture without postnatal sequelae: twice a small amount of fluid was infused intracutaneously and once intraperitoneally. Of the six minor maternal complications, a small amount of fluid was injected into the myometrium in one patient, one patient experienced continuous painless contractions leading to cessation of the procedure, one woman had severe abdominal cramps after the procedure, and vaginal bleeding postintervention occurred in three women.

In the as-treated analysis, the overall perinatal mortality rate was 11 of 21 (52%) vs 19 of 26 (73%) fetuses or neonates in the amnioinfusion and no intervention group, respectively (RR 0.72, 95% CI 0.45–1.15, *P*=.17).

DISCUSSION

This RCT found no difference in perinatal mortality in women with second-trimester preterm PROM managed with amnioinfusion compared with no intervention. Among liveborn neonates, respiratory findings associated with pulmonary hypoplasia were comparable as were additional secondary outcomes.

Several observational trials have reported a 50% reduction in perinatal mortality after amnioinfusion

Table 2. Indication for Delivery in the Intention-to-Treat Population

Indication for Delivery	Amnioinfusion (n=28)	No Intervention (n=28)	RR (95% CI)	*P*
Spontaneous onset	15 (54)	11 (39)	1.36 (0.77–2.42)	.29
Parental request at less than 24 0/7 wk of gestation	2 (7)	2 (7)	1.00 (0.15–6.61)	1.00
Lethal anomaly	1 (4)	0 (0)	—	—
Intrauterine fetal demise	1 (4)	0 (0)	—	—
Cord prolapse	5 (18)	8 (29)	0.63 (0.23–1.68)	.35
Infection	2 (7)	3 (11)	0.67 (0.12–3.69)	.64
Fetal distress	2 (7)	3 (11)	0.67 (0.12–3.69)	.64
Noncephalic position at term	0 (0)	1 (4)	—	—

RR, relative risk; —, too few cases to accurately calculate RR and *P* value.
Data are n (%) unless otherwise specified.

Table 3. Neonatal Outcome in the Intention-to-Treat Population

Outcome All Liveborn Neonates	Amnioinfusion (n=15)	No Intervention (n=13)	Mean Difference	RR (95% CI)	*P*
Birth weight (g)*	1,372±820	1,241±639	131 (−447 to 709)		.65
Pneumothorax*	3 (20)	6 (46)		0.43 (0.13–1.40)	.16
Persistent pulmonary hypertension of the neonate*	6 (40)	9 (69)		0.58 (0.28–1.19)	.13
Contractures*	1 (7)	3 (23)		0.29 (0.03–2.45)	.26
All neonates alive 1 wk postpartum	n=11	n=8			
Chronic lung disease	5 (46)	4 (50)		0.91 (0.35–2.35)	.84
Necrotizing enterocolitis	1 (9)	0 (0)		—	—
Periventricular leukomalacia > grade I	0 (0)	0 (0)		—	—
Intraventricular hemorrhage >grade II	1 (9)	0 (0)		—	—
Early-onset sepsis*†	3 (27)	3 (38)		0.73 (0.20–2.71)	.64
Late-onset sepsis*‡	3 (27)	2 (25)		1.09 (0.23–5.09)	.91

RR, relative risk; —, too few cases to accurately calculate RR and *P* value.
Data are n (%) or mean±SD.
* Data retrieved by post hoc analysis.
† Sepsis was culture proven in none of the neonates in the amnioinfusion group and in one neonate (*Escherichia coli*) in the no intervention group.
‡ Sepsis was culture-proven in one neonate (Staphylococcus aureus) in the amnioinfusion group and one neonate (coagulase-negative staphylococci) in the no intervention group.

for second-trimester preterm PROM compared with a control group.[9–11] However, the only RCT to date, the AMIPROM trial, found no difference in perinatal mortality: 19 of 28 (68%) perinatal deaths in both arms, which is in line with our findings.[13] After combining the data of the AMIPROM and PPROMEXIL-III studies in a traditional aggregate data meta-analysis, we found a comparable perinatal mortality rate for amnioinfusion and no intervention (RR 0.93, 95% CI 0.72–1.19, *P*=.54). In contrast to our findings, gestation at delivery of all liveborn neonates was higher in the AMIPROM trial and pneumothorax rates were lower. Pulmonary hypertension of the neonate was not reported. In the AMIPROM trial, women were eligible if the pregnancy was still viable 10 days after preterm PROM, in contrast to 3 days in our study, leading to a difference in gestation at randomization of approximately 1 week. Moreover, the AMIPROM protocol did not specify a maximum single deepest pocket at study entry. Several women in the amnioinfusion group thus maintained a single deepest pocket of 20 mm or greater throughout the trial and did not receive any amnioinfusions. These methodologic differences could entail a better a priori prognosis for fetomaternal outcome in the AMIPROM trial.

Strengths of our trial are its randomized design and nationwide multicenter execution. Bebbington et al[22] recently emphasized the importance of well-designed clinical trials evaluating new fetal technologies. In this field, new techniques tend to be adopted in the absence of solid evidence in the hope of improving a dismal prognosis, subjecting women and fetuses to potentially ineffective and harmful procedures. Our study contributes in making a rational choice between amnioinfusion and no intervention.

Study limitations necessitate careful interpretation of our results. First, our trial was only powered to detect a decrease in perinatal mortality from 70% to 35%. We were thus not able to detect a smaller, although potentially clinically relevant, difference. Second, pulmonary hypoplasia could not be reported, which makes comparison with other studies challenging. Lastly, long-term follow-up was not performed in our study.

These limitations notwithstanding, in our trial, amnioinfusion conferred no perinatal benefit in second-trimester preterm PROM.

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