OBSTETRICS

Management of late-preterm premature rupture of membranes: the PPROMEXIL-2 trial

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OBJECTIVE: The evidence for the management of near term prelabor rupture of membranes is poor. From January 2007 until September 2009, we performed the PPROM Expectant Management versus Induction of Labor (PPROMEXIL) trial. In this trial, we showed that in women with preterm prelabor rupture of membranes (PPROM), the incidence of neonatal sepsis was low, and the induction of labor (IoL) did not reduce this risk. Because the PPROMEXIL trial was underpowered and because of a lower-than-expected incidence of neonatal sepsis, we performed a second trial (PPROMEXIL-2), aiming to randomize 200 patients to improve the evidence in near-term PPROM.

STUDY DESIGN: In a nationwide multicenter study, nonlaboring women with PPROM between 34 and 37 weeks' gestational age were eligible for inclusion. Patients were randomized to IoL or expectant management (EM). The primary outcome measure was neonatal sepsis.

RESULTS: From December 2009 until January 2011, we randomized 100 women to IoL and 95 to EM. Neonatal sepsis was seen in 3 neonates (3.0%) in the IoL-group versus 4 neonates (4.1%) in the EM group (relative risk, 0.74; 95% confidence interval, 0.17–3.2). One of the sepsis cases in the IoL group resulted in neonatal death because of asphyxia. There were no significant differences in secondary outcomes.

CONCLUSION: The risk of neonatal sepsis after PPROM near term is low. Induction of labor does not reduce this risk.

Key words: induction of labor, neonatal sepsis, PPROM Expectant Management versus Induction of Labor trial, preterm prelabor rupture of membranes

Cite this article as: van der Ham DP, van der Heyden JL, Opmeer BC, et al. Management of late-preterm premature rupture of membranes: the PPROMEXIL-2 trial. Am J Obstet Gynecol 2012;207:276.e1-10.

Preterm prelabor rupture of membranes (PPROM) is associated with neonatal morbidity and mortality as well as maternal morbidity.[1-4] In

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international guidelines, no clear recommendation is given on the management of PPROM between 34 and 37 weeks.[5-7]

A recent Cochrane review on the management of PPROM prior to 37 weeks

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Received May 27, 2012; revised May 27, 2012; accepted July 17, 2012.

The authors report no conflict of interest.

The participants of the PPROMEXIL trial group, all from academic and clinical institutions in The Netherlands, are listed in the Acknowledgments.

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0002-9378/free • http://dx.doi.org/10.1016/j.ajog.2012.07.024

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demonstrated insufficient evidence for the management of PPROM in clinical practice.[1]

Given this lack of evidence to justify the induction of labor or expectant management, a randomized controlled trial was performed as the PPROMEXIL (PPROM Expectant Management versus Induction of Labor) trial.[8] In this trial, we tested the hypothesis that induction of labor (IoL) would reduce the incidence of neonatal sepsis.

In the PPROMEXIL trial, the incidence of neonatal sepsis in the expectant group was 4.1%, which is lower than the expected 7.5%, and the risk of neonatal sepsis was not decreased by induction of labor (2.6% vs 4.1%; relative risk [RR], 0.64; 95% confidence interval [CI], 0.25–1.6). In contrast, in the IoL group, the risk of neonatal hypoglycemia and hyperbilirubinemia was increased (RR, 2.2; 95% CI, 1.4–3.4, and RR, 1.5; 95% CI, 1.1–1.9, respectively). Because of this lack of power, there remained equipoise on the subject after the completion of our PPROMEXIL trial.

In view of this equipoise and in view of uncertainty of the continuation of the other large ongoing trial on the subject at that time, Preterm Prelabour Rupture of Membranes Close to Term Trial (PPROMT),[9] which was dependent on funding, we decided to set up a new trial called PPROMEXIL-2, with a similar design as our PPROMEXIL study, aiming to randomize an additional 200 women. We planned to combine the results of the PPROMEXIL trials with the results of the possible prematurely terminated PPROMT trial into an individual patient data metaanalysis, which would then reach the planned power calculation of the PPROMT trial. The decision to start PPROMEXIL-2 was made after the completion and analysis of the results of PPROMEXIL, and it should therefore be considered as an independent trial.

Materials and Methods

We performed a nationwide randomized controlled trial in The Netherlands between December 2009 until January 2011. The methods of this trial have been described earlier extensively by van der Ham et al.[8,10] The PPROMEXIL-2 trial was a randomized controlled trial that ran in 60 academic and nonacademic hospitals in The Netherlands. For the PPROMEXIL-2 trial, no changes were made in this trial protocol or in the outcome measures. This trial was registered in the ISRCTN register: ISRCTN05689407 (http://www.controlled-trials.com/ISRCTN05689407/ppromexil).

The PPROMEXIL-2 study was approved by the Medical Ethics Committee of the Maastricht University Medical Center as an amendment of the PPROMEXIL trial (MEC 05-240).

Women with a singleton or twin pregnancy were eligible for the PPROMEXIL trial when they were not in labor 24 hours after PPROM between 34 and 37 weeks of gestational age. PPROM had to be diagnosed after 26+0 weeks. Women with a monochorionic multiple pregnancy, nonreassuring cardiotocogram, meconium stained amniotic fluid, major fetal anomalies, HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome, or severe preeclampsia and signs of intrauterine infections were not eligible.

Randomization was performed in a password-protected, web-based database in a 1:1 for immediate delivery (IoL) versus expectant management (EM). If women were allocated to IoL, labor was induced within 24 hours after randomization. IoL was performed according to the Dutch national guidelines.[11] If a cesarean section was indicated (for example, in the case of a child in breech position), this was done as soon as feasible after randomization. Women allocated to EM were monitored according to a standard local protocol, until delivery started spontaneously. If a participant reached 37+0 weeks' gestational age (GA), labor was induced. Labor was induced prior to 37+0 weeks of gestation when there were clinical signs of infection or on another neonatal or maternal indication that justified induction of labor. Data were collected by research staff in a web-based, password-protected database.

The Dutch guidelines on PPROM give no clear recommendation on the use of antibiotics prior to labor. Therefore, antibiotics were administered according to local protocol. In pregnancies with PPROM prior to 34 weeks' gestation, corticosteroids were given for fetal pulmonary maturation. Administration of tocolytics was dependent on the local protocol.

Outcome measures

The primary outcome was neonatal sepsis, defined as a positive blood culture taken at birth (not *Staphylococcus epidermidis*) or within 72 hours 2 or more symptoms of infection (apnea, temperature instability, lethargy, feeding, intolerance, respiratory distress, hemodynamic instability) plus 1 of the following 3 items: (1) positive blood culture (culture-proven sepsis); (b) C-reactive protein greater than 20 (suspicion sepsis); or (3) positive surface cultures of a known virulent pathogen (suspicion of sepsis).

When the local investigator classified a case as sepsis or when criteria for sepsis were registered in the database, the case was judged by an independent panel of pediatricians (A.L.M.M., R.M.J.M.) who were not aware of the allocation of randomization. After the relevant data were presented to the panel, they adjudicated between neonatal sepsis (proven or suspected sepsis) or no sepsis.

Secondary neonatal outcome measures were respiratory distress syndrome, asphyxia, hypoglycemia, hyperbilirubinemia, total length of hospital stay and admission, and length of stay on the neonatal intensive care unit (NICU) and perinatal death.

Maternal outcome measures were antepartum hemorrhage, signs of (histological or clinical) chorioamnionitis, total length of hospital stay, and admission to the intensive care unit. Finally, we recorded mode of delivery and need for anesthesia. No changes to trial outcomes were made after the trial commenced.

Statistical analysis and metaanalysis

Within a well-organized nationwide Dutch research consortium, it seemed feasible to recruit 200 patients within approximately 1 year. These 200 patients combined with the 536 patients of the PPROMEXIL trial[8] and the estimated number of included patients at the end of 2010 for the PPROMT trial[9] would provide the power calculation as calculated by the investigators of the PPROMT trial (1812 women). Therefore,

no separate power calculation was done for this trial.

Data were analyzed on an intention-to-treat basis. The RRs, absolute risk reduction, mean difference (MD), and 95% CIs were calculated for the relevant outcome measures. $P < .05$ was considered to indicate statistical significance. Statistical analyses were performed using SPSS Statistics (version 17.0; SPSS Inc, Chicago, IL).

We further updated a recent Cochrane review[1] on the subject for sepsis (overall), culture proven neonatal sepsis, respiratory distress syndrome (RDS), and the cesarean section rate as we did after the PPROMEXIL trial[8] with the data from the PPROMEXIL trial and the current PPROMEXIL-2 trial, using Review Manager Software version 5.1.[12]

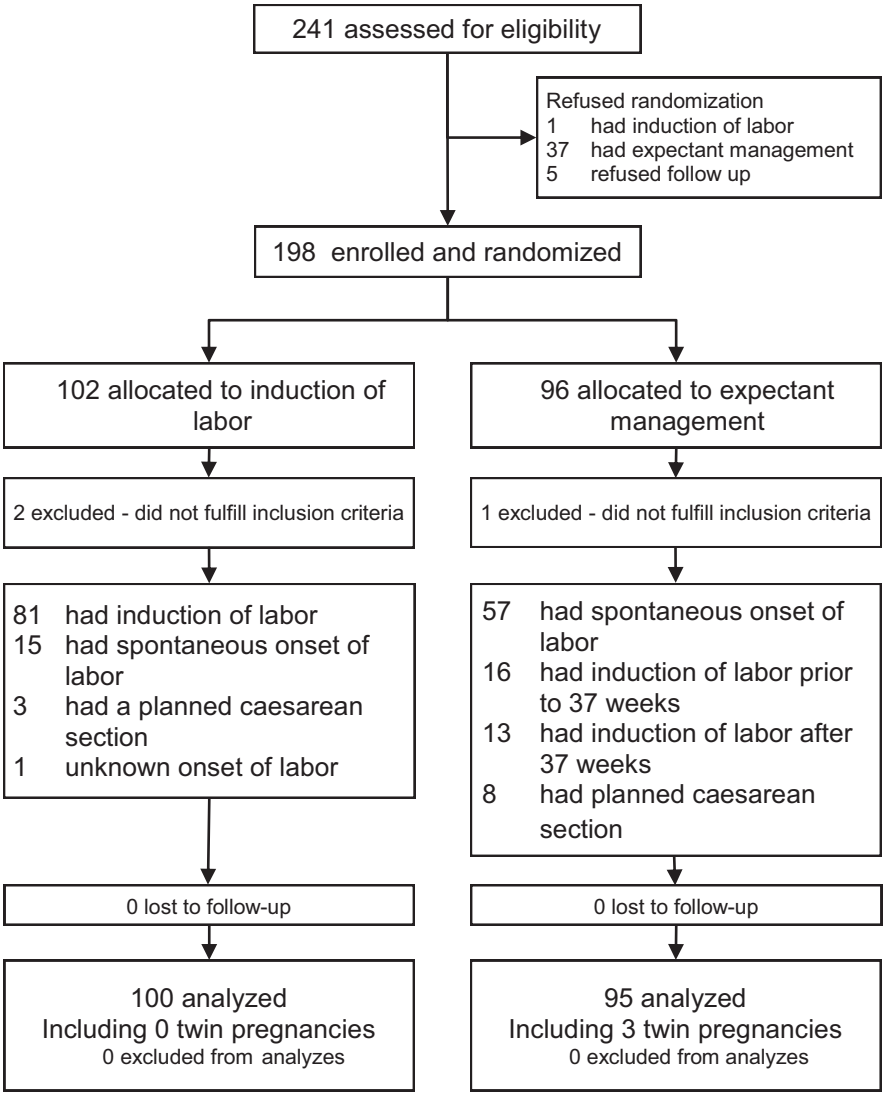
RESULTS

From December 2009 until January 2011, a total of 241 women were asked to participate in the trial, of which 198 women (82%) gave informed consent. Of these women, 3 had to be excluded because they had been randomized at a gestational age longer than 36+6 weeks. The remaining 195 women were eligible for analysis. A total of 100 women were randomized to induction of labor (IoL group) and 95 to expectant management (EM group). Figure 1 outlines the study profile.

Baseline characteristics are shown in Table 1. The median gestational age at randomization was 251 days. Thirty-three women (17%) had PPROM prior to 34 weeks' GA. Table 2 shows data on pregnancy outcome and mode of delivery. Women in the IoL group delivered on average 3.5 days earlier (95% CI, 1.8–5.2 days) than women in the EM group. Women in the EM group stayed on average 4.4 days longer in the hospital (95% CI, 2.2–6.7 days).

The mode of delivery was not statistically significant different. There were fewer cesarean sections in the IoL group (13 [13%] vs 22 [22%]; RR, 0.58; 95% CI, 0.31–1.08; $P = .081$). This difference was partly because of the higher number of planned cesarean sections in the EM group (3 vs 8), which was known at baseline and could not be due to randomization.

FIGURE 1
Trial profile



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Antibiotics during admission and during labor were administered equally. There were no differences in the rates of epidural and/or spinal analgesia.

Neonatal sepsis

Neonatal sepsis was seen in 3 neonates (3.0%) in the IoL group versus four (4.1%) in the EM group (RR, 0.74; 95% CI, 0.17–3.2) (Table 3). One neonate in the IoL group who had a proven sepsis died 48 hours postpartum because of the complications of a severe asphyxia and anemia. During labor, fetal blood sampling was performed because of a suboptimal cardiotocography. This procedure resulted in heavy blood loss, after which an emergency cesarean section was performed. An asphyctic male neonate (arterial pH 6.98 mmol/L and Apgar score 0/0) was born and was transferred to an NICU center in which multiorgan failure occurred with a Sarnat stage 3 asphyxia and positive blood cultures for group B *Streptococcus*. The child died 48 hours postpartum. This case was reported to the Medical Ethical Committee of the Maastricht University Medical Center, and it was extensively discussed by our panel of neonatologists (A.L.M.M, R.M.J.M.) as well as by an independent

TABLE 1
Baseline characteristics

Characteristics[a]	Induction of labor (n = 100)	Expectant management (n = 95)
Maternal age (range) [± SD], y	30.5 (19.4–43.6) [± 5.3]	29.4 (19.2–41.8) [± 5.0]
Nulliparous, n (range) (%)	48 (0–6) (48)	49 (0–4) (52)
Twin pregnancy, n (%)	0 (0)	3 (3.2)
Ethnic origin		
White, n (%)	78 (78)	67 (71)
Other ethnic origin, n (%)	15 (15)	18 (19)
Unknown, n (%)	7 (7.0)	10 (11)
Education		
Primary school (4-12 y), n (%)[b]	0 (0)	2 (4.0)
Secondary school (12 to 16-18 y), n (%)[b]	9 (17)	3 (6.0)
Lower professional school, n (%)[b]	5 (9.3)	6 (12)
Medium professional school, n (%)[b]	20 (37)	23 (46)
Higher professional school, n (%)[b]	19 (35)	11 (22)
University, n (%)	1 (1.9)	5 (10)
Maternal smoking, n (%)	25 (27)	25 (27)
Body mass index		
At booking (range) [± SD], kg/m^2[c]	26.2 (16.5–53.3) [± 6.6]	25.0 (15.8–46.3) [± 6.4]
At study entry (range) [± SD], kg/m^2[c]	30.1 (17.8–56.2) [± 8.1]	29.6 (20.8–46.3) [± 5.6]
Antenatal administration of corticosteroids, n (%)	20 (22)	13 (16)
Diagnostic test for rupture of membranes[d]		
Positive history, n (%)	67 (70)	71 (76)
Positive ferning, n (%)	48 (79)	34 (67)
Positive pH test, n (%)	2 (7.7)	2 (7.7)
Positive PAMG-1 test, n (%)	11 (32)	19 (50)
Decrease amniotic fluid on ultrasound, n (%)	53 (76)	52 (70)
Ruptured membranes[e]		
<34 wks, n (%)	20 (20)	13 (14)
34+0 to 34+6 wks, n (%)	11 (11)	16 (17)
35+0 to 35+6 wks, n (%)	29 (29)	28 (30)
36+0 to 36+6 wks, n (%)	40 (40)	37 (39)
Gestational age at PPROM, median [IQR], d	249 [240–254]	249 [241–253]
Gestational age at randomization, median [IQR], d	251 [242–255]	251 [243–255]
Fetal position at data entry		
Cephalic, n (%)	96 (96)	87 (92%)
Breech, n (%)	4 (4.0)	8 (8.4%)
Maternal temperature at inclusion, mean [± SD], ˚C	36.8 [± 0.44]	36.8 [± 0.44]

IQR, interquartile range; *PAMG-1,* placental alpha macroglobulin-1; *PPROM,* preterm prelabor rupture of membranes.

[a] Percentages given are related to available data per characteristic and may differ from total number of patients; [b] Percentages are given as part of known educational level; [c] Outcome characteristic with more than 5% missing data; ethnic origin: data available from 178 cases (91%); education: data available from 104 cases (53%); maternal smoking: data available from 184 cases (94%); body mass index at booking: data available from 161 cases (84%); body mass index at start study available from 84 cases (44%); antenatal administration of corticosteroids: data available from 173 cases (89%); maternal temperature at inclusion: data available from 172 cases (90%); [d] Sum of tests exceeds 100% because more than 1 test could be applied on the same patient; percentages are given as part of applied tests. Data on positive history were available from 190 of 195 cases (97%). Ferning was done in 112 cases, pH test was done in 52 cases, PAMG-1 test was done in 72 cases, and ultrasound was done in 146 cases; [e] In one woman, the term at rupture of membranes was unknown.

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gynecologist. Neonatal death was considered to be related to the severe asphyxia and anemia and not to neonatal sepsis. Induction of labor was not considered to be the cause of this severe adverse event.

Other neonatal outcomes

Table 3 shows all neonatal outcomes. Neonates born in the IoL group stayed 7.4 days in the hospital compared with 6.9 days (MD, 0.52; 95% CI, −0.5 to 2.3 days) after EM. Neonates in the IoL group were equally admitted to the NICU (7 [7.0%] cases vs 8 [8.2%] in the EM group; RR, 0.86; 95% CI, 0.32–2.3). Newborns admitted to the NICU in the IoL group stayed a shorter time than those in the EM group (mean 2.0 vs 7.0 days; MD, −5.0; 95% CI, −9.0 to −1.0).

Respiratory distress syndrome was seen in 6 newborns in the IoL group (6.0%) versus 5 in the EM group (5.1%) (RR, 1.2; 95% CI, 0.37–3.7). Hypoglycemia (8 [8.1%] vs 8 [8.2%]; RR, 0.99; 95% CI, 0.39–2.5) and hyperbilirubinemia (20 [20%] vs 21 [21%]; RR, 0.95; 95% CI, 0.55–1.6) were seen equally in both groups. For other neonatal outcome measures, there were also no significant differences between both groups.

Maternal outcomes

Table 4 shows all maternal outcomes. Clinical chorioamnionitis was not seen in the IoL group and in 4 women in the EM group (4.3%) ($P = 0.038$). The incidence of histological chorioamnionitis was 12 (18%) versus 18 (31%), respectively (RR, 0.64; 95% CI, 0.33–1.2).

Metaanalysis

In total 1428 neonates could be analyzed from 9 studies for neonatal sepsis, 1090 neonates (6 studies) for culture-proven sepsis, 1428 neonates (9 studies) for RDS, and 1417 women (9 studies) for cesarean section rate. As shown in Figure 2, the risk ratio of all outcome were not statistically different.

Comment

In this PPROMEXIL-2 trial, 195 women with PPROM between 34 and 37 weeks were included and analyzed. We found that induction of labor did not reduce the incidence of neonatal sepsis, nor did

TABLE 2
Pregnancy outcome

Outcome[a]	Induction of labor (n = 100 or 100)[b]	Expectant management (n = 95 or 98)[c]	Relative risk/mean difference (95% CI; *P* value)	Absolute risk reduction (95% CI)
Onset of labor[d]				
Spontaneously, n (%)	15 (15)	54 (57)	0.26 (0.16–0.43; < .001)	42.3% (30.0–54.5%)
Planned cesarean section, n (%)	3 (3.0)	8 (8.5)	0.36 (0.10–1.3; .100)	5.5% (−1.1% to 12.1%)
Induction, n (%)	81 (82)	32 (34)	2.40 (1.79–3.23; < .001)	−47.9% (−60.0% to −35.6%)
Gestational age at birth, mean [±SD] (median) [IQR], d	250.5 [± 6.5] (252) [244–256]	254.0 [± 5.3] (256) [251–258]	−3.5 (−5.2 to −1.8; < .001)	NA
Gestational age at birth from				
34+0 to 34+6 wks, n (%)	25 (25)	7 (7.1)	3.50 (1.59–7.72; < .001)	−17.9% (−37.7% to −8.0%)
35+0 to 35+6 wks, n (%)	21 (21)	21 (21)	0.98 (0.57–1.68; .941)	0.43% (−11.0% to 11.8%)
36+0 to 36+6 wks, n (%)	49 (50)	47 (48)	1.02 (0.77–1.36; .884)	−1.04% (−15.0% to 12.9%)
37+0 to 37+6 wks, n (%)	5 (5.0)	23 (23)	0.21 (0.08–0.54; < .001)	18.5% (9.1–27.9%)
Longer than 38 wks, n (%)	0 (0)	0 (0)	—	—
Interval between randomization and birth, mean [±SD] (median) [IQR], h	39 [± 66] (24) [12–47]	110 [± 131] (74) [33–165]	−71 (−99 to −42; < .001)	NA
Interval between rupture of membranes and birth, mean [± SD] (median) [IQR], h	133 [± 186] (63) [42–113]	193 [± 230] (123) [64–208]	−61 (−120 to −1.1; < .001)	NA
Mode of delivery				
Spontaneously vaginally, n (%)	78 (78)	68 (69)	1.12 (0.95–1.33; .169)	−8.6% (−20.8% to 3.6%)
Vaginally assisted, n (%)	9 (9.0)	8 (8.1)[e]	1.10 (0.44–2.74; .834)	−0.84% (−8.6% to 7.0%)
Cesarean section, n (%)	13 (13)	22 (22)[f]	0.58 (0.31–1.08; .081)	9.4% (−1.1% to 20.0%)
Any instrumental delivery, n (%)	22 (22)	30 (31)	0.72 (0.44–1.16; .169)	8.6% (−3.6 to 20.8%)
Antibiotics				
During admission, n (%)	36 (36%)	46 (48%)	0.74 (0.53–1.04; .079)	12.4% (−1.3% to 26.2%)
During labor, n (%)	28 (29%)	33 (36%)	0.80 (0.53–1.22; .305)	7.0% (−6.3% to 20.3%)
During admission or labor, n (%)	40 (42%)	51 (55%)	0.83 (0.62–1.11; .206)	9.5% (−5.1% to 24.1%)
Epidural and/or spinal analgesia, n (%)	25/99 (25%)	27/91 (30%)	0.85 (0.54–1.35; .495)	4.4% (−8.2 to 17.1%)
Hemorrhage, mean (range) [± SD], mL	351 (50–2000) [± 296]	505 (50–3800) [± 587]	−155 (−286 to −22; .022)	NA
Total maternal admission, mean [± SD] (median) [IQR], d	8.8 [± 5.3] (7) [5–11]	13.2 [± 9.5] (10) [7–16]	−4.4 (−6.7 to −2.2; < .001)	NA

CI, confidence interval; *EM,* expectant management; *IoL,* induction of labor; *IQR,* interquartile range; *NA,* not available.

[a] Percentages, relative risks, 95% CI, and *P* value given are related to available data per characteristic and may differ from total number of patients; [b] The number of women in the IoL group was 100, and the number of newborns in the IoL group was 100; [c] The number of women in the EM group was 95, and the number of newborns in the EM group was 98; [d] From 2 women the onset of labor was unknown; [e] Including 1 forcipal extraction; [f] Including 2 cesarean sections after vacuum extraction failed.

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it influence the rates of cesarean section and RDS. Because all cases with possible signs for neonatal sepsis were adjudicated by a panel of neonatologists, we believe that we did not miss any case of neonatal sepsis, nor did we overestimate the incidence of neonatal sepsis.

Induction of labor did reduce the risk of clinical chorioamnionitis, but we did not find a significant difference in histological chorioamnionitis. Nevertheless, incidences of chorioamnionitis were in the same magnitude as in the PPROMEXIL trial. It has been suggested in the previous studies that chorioamnionitis is related to cerebral palsy.[13-16] However, we believe that this association cannot be extrapolated to our population because these studies were reporting on very preterm infants. Because the incidence of cerebral palsy in the near term population is very low, we do not believe that this association justifies induction of labor in women with late preterm PROM.

In contrast to the PPROMEXIL trial,[8] we found no difference in the incidence of hypoglycemia and hyperbilirubinemia between both groups.

As shown in the metaanalysis based on more than 1400 neonates, expectant management seems to be a safe strategy with respect to neonatal sepsis, RDS, and cesarean section rates.

This trial has its limitations. As mentioned in the introductory text, the design of the study was approved and registered after we finished the PPROMEXIL trial and should therefore be considered as a separate trial. Because of the remaining equipoise at that moment and major funding problems of the ongoing PPROMT trial,[9] this smaller additional trial was ex-

TABLE 3
Neonatal outcome

Outcome[a]	Induction of labor (n = 100)	Expectant management (n = 98)	Relative risk/mean difference (95% CI; *P* value)	Absolute risk reduction (95% CI)
Primary outcome				
Proven neonatal sepsis, n (%)	1 (1.0)	2 (2.0)	0.49 (0.05–5.3; .549)	1.04% (−2.37% to 4.5%)
Suspected neonatal sepsis, n (%)	2 (2.0)	2 (2.0)	0.98 (0.14–6.82; .983)	0.04% (−3.9% to 4.0%)
Sepsis overall, n (%)	3 (3.0)	4 (4.1)	0.74 (0.17–3.20; .680)	1.08% (−4.1% to 6.2%)
Secondary outcome				
Apgar score, 5 min <7, n (%)	2 (2.0)	1 (1.0)	1.92 (0.18–20.8; .585)	−0.96% (−4.4% to 2.5%)
Neonatal temperature >38,0°C, n (%)[b]	3 (5.8)	2 (3.9)	1.47 (0.26–8.44; .663)	−1.85% (−10.1% to 6.4%)
pH umbilical artery <7.1 mmol/L, n (%)[b]	3 (4.1)	2 (2.7)	1.52 (0.26–8.84; .638)	−1.41% (−7.3% to 4.5%)
Birthweight, mean [±SD], g	2652 [± 393]	2718 [± 419]	−66 (−181 to 48; .256)	NA
RDS (no grade classified), n (%)	6 (6.0)	5 (5.1)	1.18 (0.37–3.73; .783)	−0.0.90% (−7.3% to 5.5%)
RDS grade I or II, n (%)	3 (3.1)	0 (0)	(*P* = .082)	−3.06% (−6.5% to 0.35%)
RDS grade III or IV, n (%)	0 (0)	0 (0)	NA	NA
Wet lung, n (%)	0 (0)	3 (3.1)	(*P* = .078)	3.06% (−0.35% to 6.5%)
Asphyxia, n (%)	1 (1.0)	0 (0)	(*P* = .319)	−1.01% (−3.0% to 0.96%)
Pneumothorax/pneumomediastinum, n (%)	0 (0)	0 (0)	NA	NA
Meconium aspiration syndrome, n (%)	1 (1.0)	0 (0)	(*P* = .321)	−1.00% (−3.0% to 0.95%)
Neonatal meningitis, n (%)	0 (0)	0 (0)	NA	NA
Late onset sepsis, n (%)	1 (1.0)	0 (0)	(*P* = .319)	−1.01% (−3.0% to 0.96%)
Hypoglycemia, n (%)	8 (8.1)	8 (8.2)	0.99 (0.39–2.53; .983)	0.08% (−7.5% to 7.7%)
Hyperbilirubinemia, n (%)	20 (20)	21 (21)	0.95 (0.55–1.64; .861)	1.02% (−10.4% to 12.4%)
Necrotizing enterocolitis, n (%)	1 (1.0)	0 (0)	(*P* = .319)	−1.01% (−3.0% to 0.96%)
HIE grade 1 or 2, n (%)	0 (0)	0 (0)	NA	NA
HIE grade 3 or 4, n (%)	1 (1.0)	0 (0)	(*P* = .319)	−1.01% (−3.0% to 0.96%)
IVH grade 1 or 2, n (%)[b]	1 (1.0)	0 (0)	(*P* = .321)	−1.01% (−3.0% to 0.96%)
IVH grade 3 or 4, n (%)[b]	0 (0)	0 (0)	NA	NA
PVL grade 1 or 2, n (%)	0 (0)	1 (1.0)	(*P* = .313)	1.03% (−0.98% to 3.0%)
PVL grade 3 or 4, n (%)	0 (0)	0 (0)	NA	NA
Convulsions, n (%)	0 (0)	0 (0)	NA	NA
Other neurological disorders, n (%)	1 (1.0)	0 (0)	(*P* = .319)	−1.01% (−3.0% to 0.96%)
Other disorders, n (%)	6 (6.1)	14 (15)	0.41 (−17 to −0.24; .044)	8.8% (0.24–17.4%)
Intrapartum death, n (%)	0 (0)	0 (0)	NA	NA
Neonatal death, n (%)	1 (1.0)[c]	0 (0)	(*P* = .321)	−1.00% (−3.0% to 0.95%)
Hospital admission, n (%)	95 (96)	95 (98)	0.98 (0.93 to 1.03; .421)	1.98% (−2.8% to 6.8%)
Length of hospital stay, mean [± SD]	7.4 [± 6.1]	6.9 [± 6.0]	0.52 (−1.2 to 2.3; .559)	NA
(median) [IQR], d	(4) [3–12]	(5) [2–9]		
NICU admission, n (%)	7 (7.0)	8 (8.2)	0.86 (0.32 to 2.3; .757)	1.16% (−6.2% to 8.5%)

CI, confidence interval; *HIE,* hypoxic ischemic encephalopathy; *IVH,* interventriculair hemorrhage; *IQR,* interquartile range; *NA,* not available; *NICU,* neonatal intensive care unit; *PVL,* periventriculair leucomalacia; *RDS,* respiratory distress syndrome.

[a] Percentages, relative risks, 95% CI, and *P* value given according to available data; [b] Outcome characteristic with more than 5% missing data; neonatal temperature data available from 103 cases (52%); pH umbilical artery <7.1 mmol/L data available from 147 (74%); [c] One neonate died because of a severe anemia after ruptured vasa previa and a proven neonatal sepsis.

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ecuted to improve the number of inclusion to perform and individual patient data metaanalysis (IPD-MA) with data of PPROMT and both PPROMEXIL trials. Recruitment of an additional 200 women within a 12 month period seemed feasible. However, near the closing of the recruitment of the patients for the PPROMEXIL-2 trial, the investigators of the PPROMT trial gained extra funding to complete their estimated inclusions (1812 women). The results as presented in the current trial should be interpreted with some caution because of the fact that no proper power calculation was done.

As in the PPROMEXIL trial[8] during which we observed lower-than-expected

TABLE 4
Maternal outcome

Outcome[a]	Induction of labor (n = 100)	Expectant management (n = 95)	Relative risk (95% CI; *P* value)	Absolute risk reduction (95% CI)
Maternal complications				
Antepartum hemorrhage, n (%)	1 (1.0)	1 (1.1)	0.95 (0.06–15.0; .971)	0.05% (−2.8% to 2.9%)
Cord prolapse, n (%)	0 (0)	0 (0)	NA	NA
Uterine rupture, n (%)	0 (0)	0 (0)	NA	NA
Clinical chorioamnionitis, n (%)	0 (0)	4 (4.3)	(*P* = .038)	4.28% (0.18–8.3%)
Infection, n (%)	1 (1.0)	2 (2.1)	0.47 (0.04–5.1; .530)	1.11% (−2.4 to 4.6%)
Sepsis, n (%)	0 (0)	0 (0)	NA	NA
Thromboembolic complications, n (%)	0 (0)	0 (0)	NA	NA
Urinary tract infections treated with antibiotics, n (%)	1 (1.0)	1 (1.1)	0.96 (0.06–15.1; .977)	0.04% (−2.8% to 2.9%)
Endometritis, n (%)	0 (0)	0 (0)	NA	NA
Pneumonia, n (%)	0 (0)	0 (0)	NA	NA
Anaphylactic shock, n (%)	0 (0)	0 (0)	NA	NA
HELLP syndrome, n (%)	0 (0)	0 (0)	NA	NA
Death, n (%)	0 (0)	0 (0)	NA	NA
Other complications, n (%)	1 (1.0)	3 (3.2)	0.32 (0.03–2.99; .289)	2.18% (−1.9% to 6.2%)
Perineum				
No laceration, n (%)	46 (47)	46 (49)	0.95 (0.71–1.28; .731)	2.47% (−12% to 17%)
First-degree laceration, n (%)	14 (14)	18 (19)	0.74 (0.39–1.40; .350)	5.01% (−5.5% to 16%)
Second-degree laceration, n (%)	9 (9.1)	8 (8.5)	1.07 (0.43–2.65; .887)	−0.58% (−8.6% to 7.4%)
Third-degree laceration, n (%)	1 (1.0)	1 (1.1)	0.95 (0.06–15.0; .971)	0.05% (−2.8% to 2.9%)
Fourth-degree laceration, n (%)	2 (2.0)	1 (1.1)	1.90 (0.18–20.6; .591)	−0.96% (−4.4% to 2.5%)
Episiotomy, n (%)	27 (27)	21 (22)	1.22 (0.74–2.00; .428)	−4.93% (−17% to 7.2%)
Delivery placenta				
Spontaneously, n (%)	78 (78)	64 (67)	1.16 (0.97–1.38; .095)	−10.6% (−23% to 1.8%)
Manual placental removal, n (%)	9 (9)	9 (9.5)	0.94 (0.39–2.27; .890)	0.57% (−7.6% to 8.8%)
During cesarean section, n (%)	13 (13)	22 (23)	0.56 (0.30–1.04; .059)	10.4% (−0.40% to 21%)
Histological chorioamnionitis, n (%)[b]	12 (18)	18 (31)	0.64 (0.33–1.23; .174)	10.4% (−4.7% to 25%)
Histological funisitis, n (%)[b]	6 (9.2)	8 (14)	0.66 (0.24–1.78; .406)	4.8% (−6.6% to 16.2%)

CI, confidence interval; *HELLP*, hemolysis, elevated liver enzymes, and low platelets; *NA*, not available.

[a] Percentages, relative risks, 95% CIs, and *P* value given are related to available data per characteristic and may differ from total number of patients; [b] Outcome characteristic with more than 5% missing data; histological chorioamnionitis data available from 124 cases (64%); histological funisitis data available from 122 cases (63%).

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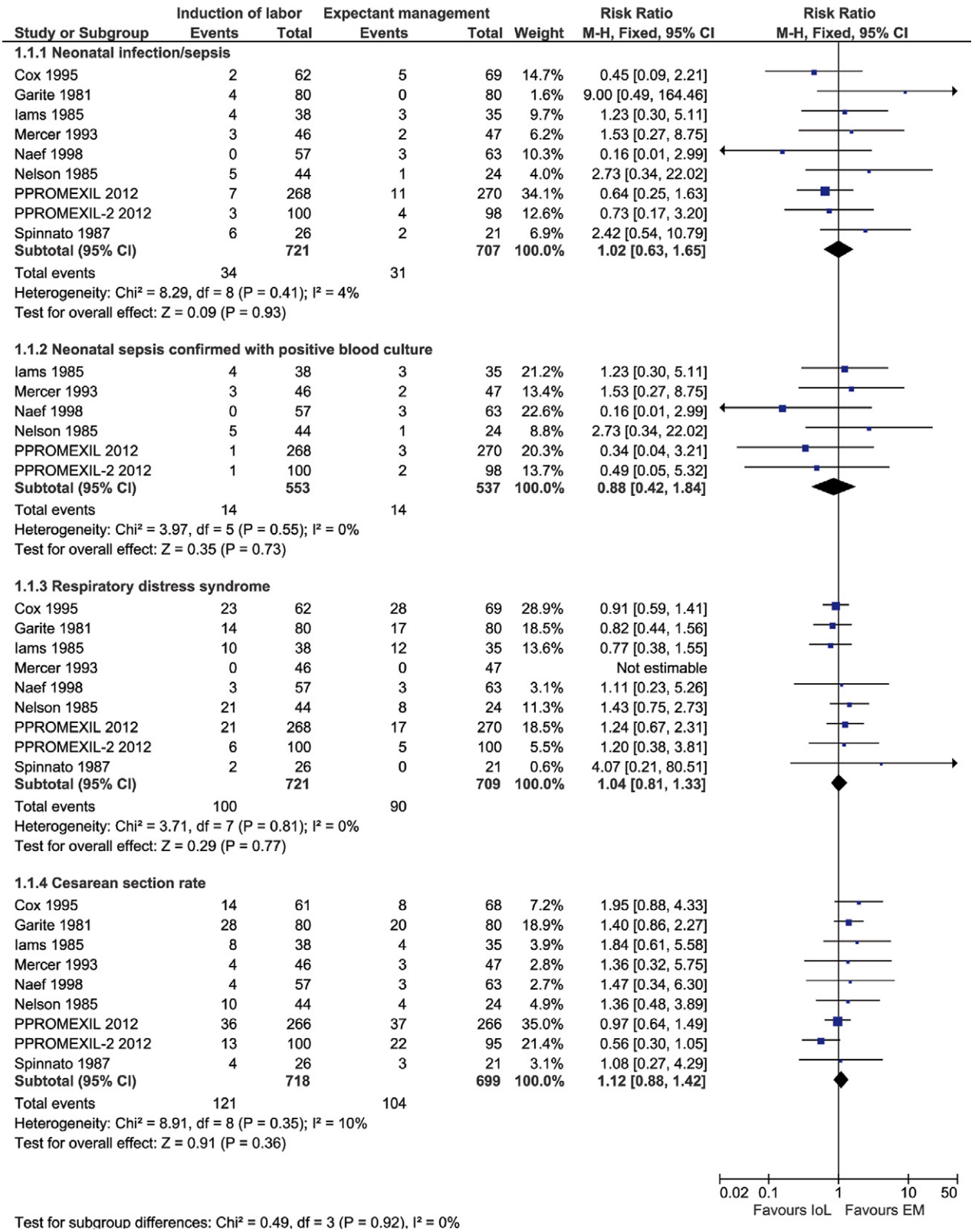
sepsis rates (2.6% in the IoL group vs 4.1% in the EM group), the incidences of sepsis in the PPROMEXIL-2 trial were low (3.0% vs 4.1%, respectively). The liberal use of antibiotic therapy before or during labor (overall 47% received antibiotics) might have contributed to a lower incidence compared with the other trials in which antibiotics were not administered prophylactically.[17-23] Improvements in the health care system over the last decades may have contributed to a reduction of the incidence of neonatal sepsis.

Expectant management prolonged gestation with 4 days, and this rather small difference, which was in line with the PPROMEXIL trial, might partly be due to the fact that the median gestational age at rupture of membranes was 35+4 weeks and the median gestational age at randomization was 35+6 weeks. The overrepresentation of women with gestational age longer than 35 weeks can be caused by the fact that women between 34 and 35 weeks of gestation more often refused to participate (mean gestational age at PPROM in the nonrandomized group was

FIGURE 2
Forest plot metaanalyses



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34+6 weeks). Furthermore, the hesitation of clinicians to induce labor before 35 weeks of gestation, which was not recommended in the Dutch guideline prior to the start of the PPROMEXIL trial,[6] may also have influenced this outcome.

If we combine the results of both PPROMEXIL trials for neonatal sepsis, we find a relative risk of 0.66 (95% CI, 0.30–1.5), and the absolute risk reduction is 1.4% (95% CI, −4.0% to 1.3%). The number needed to treat with the current combined result of the PPROMEXIL trials is 71 for 1 case of neonatal sepsis. Even if a larger trial like the current ongoing PPROMT trial[9] or a metaanalysis with independent patient data (IPD-MA) of the current PPROMEXIL trials with the PPROMT trial will find a significant difference, its clinical relevance might be debated.

In view of our recently completed PPROMEXIL and PPROMEXIL-2 studies and in view of the ongoing Australian initiated PPROMT study, one could question whether we could plan the generation of evidence more efficiently from a global perspective. Although we are in close contact with the PPROMT investigators, prospective trial registration at the moment that trials are planned would have been helpful. One could have collaborative execution of the trials under the umbrella of a prospective individual patient data metaanalysis, leaving the decision when to stop studies in such a collaborative to a Data Safety Monitoring Board overseeing all the trials. Until such scenarios have become reality, we believe that planning similar trials in different countries with a post-hoc metaanalysis of data is the best alternative.

In conclusion, this current trial expanded the amount of evidence on the management of near-term PPROM with an additional 195 women. Still, the incidence of neonatal sepsis is low after these pregnancies, and this rate is not reduced by induction of labor. Induction of labor does not increase the risk of any other adverse neonatal or maternal outcome. To this date, the PPROMEXIL trials and updated metaanalysis provide in our opinion enough evidence to prefer expectant management in women with near-term PPROM. ■

ACKNOWLEDGMENTS

We thank the research staff of our consortium (www.studies-obsgyn.nl), residents, midwives, nurses, and gynecologists of the participating centers for their help with recruitment and data collection. Maya Kruijt and Zelda van Dijk put their efforts in obtaining local ethical approval and administrative support. The PPROMEXIL collaborators are as follows: The Netherlands, F. Roumen (Atrium Medical Center, Heerlen), J. E. van de Riet (Antonius Hospital, Sneek), R. Kok (Bernhoven, Veghel/Oss), M. J. C. P. Hanssen (Bethesda Hospital, Hoogeveen), B. Dijkman (Boven IJ Hospital, Amsterdam), W. J. van Wijngaarden (Bronovo Hospital, the Hague), S. Kuppens (Catharina Hospital, Eindhoven), R. Stigter (Deventer Hospital, Deventer), N. W. E. Schuitemaker (Diakonessen Hospital, Utrecht), F. Delemarre (Elkerliek Hospital, Helmond), G. Kleiverda (Flevo Hospital, Almere), M. J. N. Weinans (Gelderse Vallei, Ede), A. J. M. Huisjes (Gelre Hospital, Apeldoorn), J. Friederich (Gemini Hospital, Den Helder), C. A. van Meir (Groene Hart Hospital, Gouda), J. W. de Leeuw (Ikazia Hospital, Rotterdam), R. J. P. Rijnders (Jeroen Bosch Hospital, Den Bosch), P. J. M. Pernet (Kennemer Gasthuis Haarlem), A. C. de Wit (Maas Hospital, Boxmeer), P. van der Salm (Meander Medical Center, Amersfoort), D. Perquin (Medical Center Leeuwarden, Leeuwarden), J. T. J. Brons (Medical Spectrum Twente, Enschede), E. van Beek (Mesos Medical Center, Oudenrijn), J. Wilpshaar (Nij Smellinghe, Drachten), E. S. A. van den Akker (OLVG, Amsterdam), H. A. Bremer (Reinier de Graaf gasthuis, Delft), K. de Boer (Rijnstate, Arnhem), J. M. Burggraaff (Scheper Hospital, Emmen), J. F. M. Molkenboer (Sint Anna Hospital, Geldrop), M. E. Kars (Sint Antonius Hospital, Nieuwegein), C. M. van Oirschot (Sint Elisabeth Hospital, Tilburg), N. van Gemund (Sint Franciscusgasthuis, Rotterdam), I. M. A. van Dooren (Sint Jansgasthuis, Weert), I. M. de Graaf (Spaarne Hospital, Hoofddorp), R. E. Bernardus (Tergooi Hospitals Blaricum/Hilversum), A. Drogtrop (TweeSteden Hospital, Tilburg), M. Buimer (Westfries Gasthuis, Hoorn), A. Koops (Wilhelmina Hospital, Assen), J. P. R. Doornbos (Zaans Medical Center, Zaandam), and A. van Ginkel (Hospital Zevenaar, Zevenaar).

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