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.
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Neonatal sepsis was seen in 3 neonates 2 days earlier than in the EM group. There were no differences in other neonatal outcome. Chorioamnionitis was seen more frequently in the EM group (18% vs 31%).

The updated metaanalysis showed no difference in the risk ratio of neonatal sepsis, RDS, or cesarean section rate.

**Comment**

One hundred ninety-five women with PPROM at 34-37 weeks of gestation were included and their data analyzed. We found that the induction of labor did not reduce the incidence of neonatal sepsis or influence rates of cesarean section or 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 or overestimate the incidence of neonatal sepsis.

In contrast to the PPROMEXIL trial, we found no difference in the incidence of hypoglycemia and hyperbilirubinemia between 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 (Figure).

This trial has limitations. The study design was approved and registered after we had finished the PPROMEXIL trial. This smaller additional trial was executed to improve the number of inclusions so that we could perform a metaanalysis of individual patient data incorporating from both PPROMEXIL trials as well as an ongoing trial, which will be planned to execute as soon as the latter trial has finished inclusions. Therefore, the results, as presented in the current trial, should be interpreted with some caution because no proper power calculation was done.

Like the first PPROMEXIL trial, we observed a lower-than-expected sepsis rate. The liberal use of antibiotic therapy (47% received antibiotics) might have contributed to a lower incidence of neonatal sepsis compared with previous trials.

Expectant management prolonged gestation by 4 days. One reason for this small difference, in line with results of the PPROMEXIL trial, may be that the median gestational age at rupture of membranes was 35+4 weeks. Women with gestational age above 35 weeks were overrepresented because women at 34-35 weeks of gestation more often refused to participate (mean gestational age at PPROM in a non-randomized group 34+6 weeks). Another possible influence on this outcome was that clinicians hesitated to induce labor before 35 weeks of gestation because this timing was not recommended in the Dutch guideline before the PPROMEXIL trial began.

In conclusion, induction of labor does not increase the risk of neonatal sepsis or any other adverse neonatal or maternal outcome. To this date, the PPROMEXIL trials and the updated metaanalysis provides in our opinion enough evidence to prefer expectant management in women with near term PPROM.

**Clinical Implications**

- The incidence of neonatal sepsis in women with preterm premature rupture of membranes (PPROM) at 34-37 weeks’ gestation is low: 3.0% in women with induced labor vs 4.1% in those given expectant management.
- In women with PPROM near term, expectant management is preferred over induction of labor.

PPROMEXIL-2, no changes were made in the trial protocol or outcome measures.

Women with a singleton or twin pregnancy were eligible, not counting exclusions, if not in labor 24 hours after PPROM at 34-37 weeks of gestational age. PPROM had to be diagnosed after 26+0 weeks.

Labor was induced within 24 hours after randomization. If a cesarean section was indicated, such as for breech position, the procedure was performed as soon as feasible after randomization. Labor was induced prior to 37+0 week of gestation when there were clinical signs of infection or other neonatal or maternal indications to justify induction.

The primary outcome was neonatal sepsis, and secondary neonatal outcome measures were among others respiratory distress syndrome (RDS), hypoglycemia, hyperbilirubinemia, length of hospital or neonatal intensive care stay, perinatal death, mode of delivery, and maternal morbidity.

Because the study was started to increase the amount of evidence and combine the results in a planned individual patient data metaanalysis, no separate power calculation was done for this trial.

We further updated a recent Cochrane analysis on the management of PPROM for (proven) sepsis, RDS, and cesarean section rate.

**Results**

From December 2009 through January 2011, 241 women were asked to participate in the trial and 198 (82%) agreed. After exclusions, 195 were eligible for analysis. One hundred women were randomized to induction of labor (IoL group) and 95 to expectant management (EM group).

Women in the IoL group delivered 3.5 days earlier than in the EM group. There was no difference in mode of delivery. Neonatal sepsis was seen in 3 neonates (3.0%) in the IoL group versus 4 (4.1%) in the EM group (relative risk, 0.74; 95% confidence interval, 0.17–3.2). Neonates born after the induction of labor stayed longer in the hospital, but there was no difference in admission to the neonatal intensive care unit. There were no differences in other neonatal outcome. Chorioamnionitis was seen more frequently in the EM group (18% vs 31%).

The updated metaanalysis showed no difference in the risk ratio of neonatal sepsis, RDS, or cesarean section rate.