Review

Immediate Delivery Compared With Expectant Management in Late Preterm Prelabor Rupture of Membranes

An Individual Participant Data Meta-analysis

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OBJECTIVE: To compare the effects of immediate delivery an expectant management among women whose pregnancies were complicated by preterm prelabor rupture of membranes (PROM) in the late preterm period (from 34 0/7 weeks until 36 6/7 weeks of gestation).

DATA SOURCES: PubMed, Scopus, ClinicalTrials.gov, EMBASE, and the Cochrane Central Register of Controlled Trials were searched from inception until December 2016.

METHODS OF STUDY SELECTION: We included all randomized controlled trials with individual participant data reporting on late preterm PROM with randomization to immediate delivery or expectant management. The primary outcome was a composite of adverse neonatal outcomes: probable or definitive neonatal sepsis, necrotizing enterocolitis, respiratory distress syndrome, stillbirth, or neonatal death.

TABULATION, INTEGRATION AND RESULTS: Of eight eligible trials (total n=3,203 mothers), three (2,563 mothers, 2,572 neonates) had individual participant data available. The composite adverse neonatal outcome occurred in 9.6% of neonates in the immediate delivery group and 8.3% in the expectant management group (relative risk [RR] 1.20, 95% CI 0.94–1.55). Neonatal sepsis rates were 2.6% and 3.5%, respectively (RR 0.74, 95% CI 0.47–1.15). Neonates in the immediate delivery group were more likely to be diagnosed with respiratory distress syndrome (RR 1.47, 95% CI 1.10–1.97), and to be admitted to the neonatal intensive care unit or special care nursery (RR 1.17, 95% CI 1.11–1.23) and had longer admissions. Mothers randomized to immediate delivery were less likely to have an antepartum hemorrhage (RR 0.57, 95%

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Each author has indicated that he or she has met the journal's requirements for authorship.

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Dr. van der Ham was first author on both of the PPROMEXIL trials. Dr. Morris was the first author of the PPROMT study. Dr. Mol has been a consultant for ObsEva, Merck, and Guerbet. The other authors did not report any potential conflicts of interest.

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CI 0.34–0.95) or chorioamnionitis (RR 0.21, 95% CI 0.13–0.35), but more likely to undergo cesarean delivery (RR 1.26, 95% CI 1.08–1.47).

CONCLUSION: In women with late preterm PROM, immediate delivery and expectant management resulted in comparable rates of the composite of adverse neonatal outcomes. Effects on individual secondary maternal and neonatal outcomes were mixed.

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Preterm prelabor rupture of membranes (PROM) is defined as rupture of membranes before 37 weeks of gestation. It occurs in 3% of all pregnancies and complicates 40% of all preterm births.[1,2] After preterm PROM, there is a risk of ascending infection to the mother and fetus as well as risks associated with prematurity for the neonate after a planned or spontaneous birth.[3,4] It is widely accepted that, for women who experience preterm PROM at term, immediate delivery decreases the risk of maternal infection.[5] In contrast, the timing of birth with preterm PROM in the late preterm period (ie, between 34 0/7 and 36 6/7 weeks of gestation) varies by regional practice.

There is no international consensus with respect to timing of birth after late preterm PROM. The American College of Obstetricians and Gynecologists' guidelines advocate expectant management for women without evidence of infection in the preterm period, between 23 and 34 weeks of gestation, and suggest delivery at 34 weeks of gestation if labor has not ensued.[6] The Royal College of Obstetricians and Gynecologists guidelines and the Dutch Society of Obstetrics and Gynecology suggest that at 34 or 35 weeks of gestation, either planned delivery or awaiting labor could be considered in a shared care decision model.[7,8]

Several recent randomized controlled trials (RCTs) have been conducted to compare immediate delivery compared with expectant management in women with late preterm PROM. A recent Cochrane review compared immediate delivery with expectant management between 24 and 37 weeks of gestation and showed that expectant management before 37 weeks of gestation was associated with improved outcomes for both mothers and neonates.[9]

Our goal was to establish the optimal management of women whose pregnancies were complicated by preterm PROM in the late preterm period by utilizing individual participant data meta-analysis because this methodology allows better classification of subgroups for participant and intervention-level characteristics.[10,11]

SOURCES

This individual participant data meta-analysis followed the Preferred Reporting Item for Systematic Reviews and Meta-analyses individual participant data reporting statement.[12] Before data collection, the review was registered with the PROSPERO International Prospective Register of Systematic Reviews (CRD #42016032972). An a priori designed research protocol defined methods.[12–14] The protocol was approved by the ethics committee at the participating institutions and the central data center before the commencement of the project.

Two authors (J.Q.-N. and A.A.d.R.), with aid of a clinical medical librarian, performed an electronic search in PubMed, Scopus, ClinicalTrials.gov, EMBASE, and the Cochrane Central Register of Controlled Trials from inception until December 18, 2016. We used the following search strategy: (preterm prelabor rupture of membranes OR preterm prelabor rupture of membranes OR PPROM OR preterm premature rupture of membranes OR preterm rupture of membranes OR expectant management OR watchful waiting) AND ([obstet* OR labor OR labor OR pregnan* OR caesarean section OR delivery OR gestation OR trimester] OR [neonatal AND sepsis] OR Chorioamnionitis) AND ([clinical AND trial] OR clinical trial OR random*). No restrictions for language or geographic location were applied. A reference list of trials and reviews identified by the search was screened. The risk of bias of included studies was assessed using the Cochrane Handbook.[15]

STUDY SELECTION

We included RCTs reporting on women with confirmed preterm PROM in the late preterm period (ie, between 34 0/7 and 36 6/7 weeks of gestation) who were randomized to either immediate delivery (intervention group) compared with expectant management (control group). When trials included a wider gestational age than our criteria, we attempted to obtain the gestational age-specific data by contacting researchers directly. All investigators were contacted, and trials unable to provide individual participant data were excluded from the primary analysis (Appendix 2, available online at http://links.lww.com/AOG/B57, for a list of excluded trials). Trials including women with alternative indications for induction (eg, intrauterine growth restriction, diabetes, gestational hypertension or preeclampsia, severe oligohydramnios) before preterm PROM were also

excluded. Only trials with adequate allocation concealment were eligible for inclusion. The two review authors (J.Q.-N. and A.A.d.R.) independently assessed all potentially eligible studies. Any disagreements were resolved by discussion.

Studies included in the individual participant data meta-analysis provided deidentified individual participant data. These data were recoded if necessary and checked with respect to range, internal consistency, missing or extreme values, errors, and consistency with previously published reports. Trial details were crosschecked against published reports, trial protocols, and data collection sheets. Inconsistencies or missing data were discussed with trialists, discrepancies were resolved, and corrections were made if necessary. Each trial was analyzed individually, and the resulting analyses and trial data were sent to the trialists for verification before analysis.

The prespecified primary outcome was a composite of adverse neonatal outcomes: probable or definitive neonatal sepsis, necrotizing enterocolitis, respiratory distress syndrome (RDS), stillbirth, or neonatal death (within 28 days after birth). Each component of the composite was defined by the individual trial. Prespecified secondary neonatal outcomes included each of the components of the composite, birth weight, low umbilical cord arterial pH (less than 7.10), Apgar score less than 7 at 5 minutes, treatment with antibiotics, ventilation requirements (continuous positive airway pressure, high-frequency oscillatory ventilation, or endotracheal tube) for any amount of time, hyperbilirubinemia, admission to and length of stay in the neonatal intensive care unit (NICU) or special care nursery, length of stay in the hospital, and neonatal death at 48 hours, at 28 days, or at any time reported by the trial.

Prespecified secondary maternal outcomes included antepartum hemorrhage (greater than 1,000 mL), endometritis, deep vein thrombosis or thromboembolic event (diagnosed in the antenatal or postpartum period), length of stay in the hospital after delivery, and maternal death. Modes of delivery were defined as spontaneous vaginal delivery (vertex), vaginal breech delivery, operative vaginal delivery, scheduled cesarean delivery, or unscheduled cesarean delivery (ie, performed in labor). Other delivery outcomes included umbilical cord prolapse, clinical chorioamnionitis, meconium-stained fluids, and postpartum hemorrhage (greater than 1,000 mL) (see Appendix 3, available online at http://links.lww.com/AOG/B57, for variation of definitions between trials).

We performed prespecified subgroup analyses for group B streptococci (GBS) positivity, preterm PROM occurring less than 34 0/7 weeks and greater than 34 0/7 weeks of gestation, preterm PROM by gestational age, receiving antibiotics for preterm PROM latency, steroids for fetal maturation, tocolysis, and any positive vaginal culture (including GBS and other pathogens not consistent with normal flora). A post hoc analysis was performed examining latency period, separated into greater than 7 days, 7–14 days, and less than 14 days from preterm PROM to delivery. Subgroup analyses were conducted for the primary outcome as well as the components of the neonatal composite.

A prespecified analysis plan was agreed on by all authors. Analyses were conducted using an intention-to-treat approach. For the primary and each of the secondary outcomes, a one-step linear modeling approach was used. The treatment effect and other covariates as applicable were treated as fixed effects. Statistical heterogeneity between studies was investigated by fitting a trial-by-treatment interaction term to the one-step fixed-effect model. Immediate delivery was considered the experimental arm. A relative risk (RR) above 1 therefore indicated an increase in risk of that outcome for the immediate delivery group. For binary outcomes, RR with two-sided P values and 95% CIs was calculated using log-binomial regression models. For continuous outcomes, linear regression models were used and results were presented as mean differences with two-sided P values and 95% CI. For count outcomes, robust Poisson regression models were used to estimate risk increase and calculate two-sided P values. Generalized estimating equations were used to take into account correlations between outcomes resulting from multiple births. All analyses were adjusted for gestational age at randomization and trial. For binary outcomes, the fixed-effect binomial regression models did not converge when adjusting for gestational age at randomization as a continuous variable. Gestational age was thus included in the model as a dichotomized variable (above or below median of 35.48 weeks of gestation). We conducted sensitivity analyses calculating mixed-effect models including gestational ages as a continuous variable for the primary outcome and its components. The results were robust to whether gestational age at randomization was controlled for as a dichotomous or a continuous variable. No adjustments were made for multiple comparisons. For neonatal outcomes including the primary outcome, the unit of analysis was the individual neonate; for maternal

outcomes, the unit of analysis was the pregnancy. For nonconverging models with the neonate as the unit of analysis, the analysis was repeated using only the first-born in the cases of multiple births. For each predefined subgroup, separate treatment effects were calculated. Differences in treatment effects across subgroups were investigated by fitting subgroup-by-treatment interactions and calculating two-sided *P* values. Prespecified sensitivity analyses were performed excluding twins and including trials that included late preterm PROM for which individual participant data were not available to assess the robustness of the results. The main analysis was completed in SAS 9.4. Data cleaning and descriptive analyses were conducted using SPSS 22.

RESULTS

Eight trials were eligible for inclusion (total n=3,203 mothers); five did not have individual participant data available for analysis and were thus excluded (total n=640 excluded) (Fig. 1) (Koroveshi GQR, Koroveshi E, Kuli G, Kodra N, Nurce A, Kodra N. Incidence of sepsis in late preterm babies born from pregnancies complicated with premature preterm rupture of membranes [abstract no. 622]. J Perinatal Med 2013;41[suppl 1].).[16–22] Each of the three included trials concluded that immediate delivery did not improve neonatal outcomes and advocated for expectant management. Two included studies, PPROM: Expectant Management versus Induction of Labor (PPROMEXIL) and PPROM: Expectant Management versus Induction of Labor-2 Trial (PPROMEXIL-2), were conducted in the Netherlands using an identical protocol and included women with a singleton or twin pregnancy. One included study, the Preterm Pre-labour Rupture of Membranes close to Term Trial (PPROMT), was a multinational trial including women with a singleton pregnancy (Table 1).[18,21,22] In the PPROMEXIL and PPROMEXIL-2 studies, women could be included if they did not experience labor within 24 hours of preterm PROM; in the PPROMT study, women were included if labor did not ensue within 4 hours. All women were randomized at or after 34 0/7 weeks of gestation. Administration of antibiotics, corticosteroids, and tocolysis were according to local hospital protocol. Vaginal and GBS cultures were collected according to hospital protocol. Included trials had a low risk of bias (Appendices 4 and 5, available online at http://links.lww.com/AOG/B57).

There was a total of 2,563 mothers (2,572 neonates) randomized with 1,289 mothers (1,291 neonates) allocated to the immediate delivery group and 1,274 mothers (1,281 neonates) to the expectant management group (Table 2). Median gestational age at preterm PROM and randomization was comparable between groups. Group B streptococci culture was positive in 13% in the immediate delivery group compared with 11% in the expectant management group. The majority of women received latency antibiotics (immediate delivery 76%, expectant management 78%), but the rate of antibiotic administration varied by trial (92% in PPROMT, 35% in PPROMEXIL, 41% in PPROMEXIL-2). A smaller proportion of mothers received antenatal steroids or tocolysis (Appendix 6, available online at http://links.lww.com/AOG/B57).

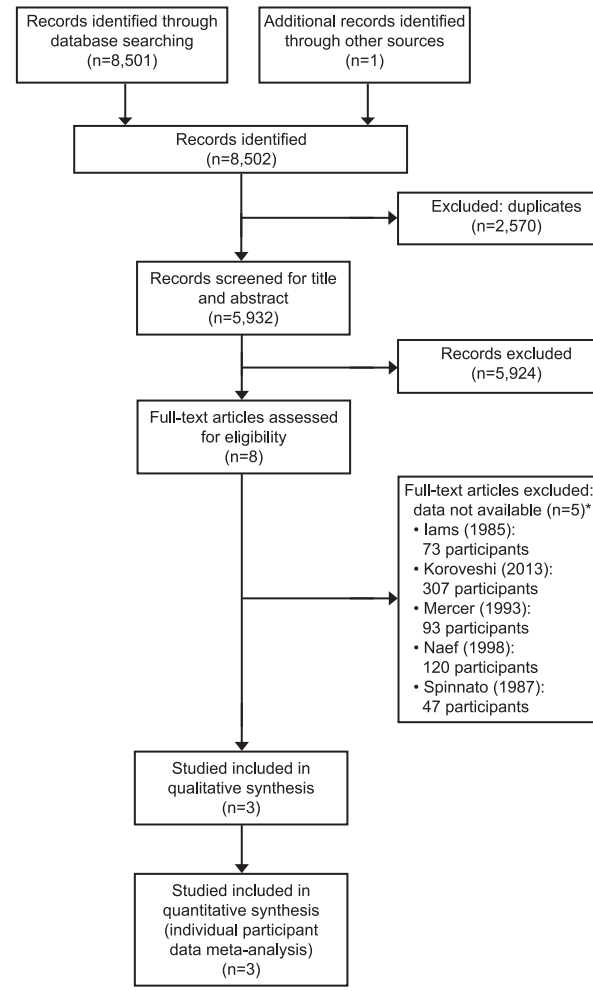

Fig. 1. Identification and selection of studies. Authors of eight studies were contacted for availability of data for individual patient data meta-analysis. *Five authors no longer had individual participant data available.

Quist-Nelson. Management of Late Preterm PROM. Obstet Gynecol 2018.

Table 1. Characteristics of the Randomized Trials Included in the Preterm Premature Rupture of Membranes Meta-analysis Collaboration

Characteristic	Study Acronym		
	PPROMEXIL	PPROMEXIL-2	PPROMT
Registration no.	ISRCTN29313500	ISRCTN05689407	ISRCTN44485060
Sample size	536 (266 vs 266)	195 (95 vs 100)	1,835 (912 vs 923)
Country of recruitment	Netherlands	Netherlands	Multicounty*
Participants	Singleton or twin pregnancies with PPROM at 34 0/7–36 6/7 wk of gestation†	Singleton or twin pregnancies with PPROM 34 0/7–36 6/7 wk of gestation†	Singleton pregnancy with PPROM 34 0/7–36 6/7 wk of gestation‡
Intervention	Immediate delivery (induction or cesarean)	Immediate delivery (induction or cesarean)	Immediate delivery (induction or cesarean)
Comparator	Expectant management, until labor, chorioamnionitis, nonreassuring fetal status, or term (37 0/7 wk of gestation or greater)	Expectant management, until labor, chorioamnionitis, nonreassuring fetal status, or term (37 0/7 wk of gestation or greater)	Expectant management until labor, term (37 0/7 wk of gestation or greater) or other indications arose
Inclusion criteria	PPROM at 34 0/7–36 6/7 wk of gestation, PPROM greater than 24 h	PPROM at 34 0/7–36 6/7 wk of gestation, PPROM greater than 24 h	Singleton pregnancy, rupture of membranes confirmed
Exclusion criteria	Nonreassuring FHT, meconium-stained fluids, evidence of intrauterine infection, high-risk pregnancy§	Nonreassuring FHT, meconium-stained fluids, evidence of intrauterine infection, high-risk pregnancy§	PTL, chorioamnionitis, meconium-stained amniotic fluid‖
Clinical management	Antibiotics, corticosteroids, tocolysis according to local protocol	Antibiotics, corticosteroids, tocolysis according to local protocol	Antibiotics, corticosteroids, tocolysis according to local protocol
Randomization timing	After greater than 24 h PPROM	After greater than 24 h PPROM	After greater than 4 h PPROM
Primary outcome	Neonatal sepsis All cases of neonatal sepsis were extensively reviewed by a board of pediatricians unaware of the allocation of randomization **Definitive**: positive blood culture taken at birth or within 72 h after birth (taken at NICU or ward); if the culture was considered to be a contaminant, neonates were not classified as definitive sepsis	Neonatal sepsis All cases of neonatal sepsis were extensively reviewed by a board of pediatricians unaware of the allocation of randomization **Definitive**: positive blood culture taken at birth or within 72 h after birth (taken at NICU or ward); if the culture was considered to be a contaminant, neonates were not classified as definitive sepsis	Neonatal sepsis All cases of neonatal sepsis were extensively reviewed by a board of pediatricians **Definitive**: positive blood culture of a known pathogen from blood or CSF for which the neonate was treated with antibiotics for 5 d or greater (or died before 5 d) and the presence of 1 or more clinical signs of infection; if organism was of low virulence or high likelihood of skin contamination of the blood culture, the neonate had to also have abnormal CBC (WBC less than 5×10^9 cells/L or greater than 30 cells/L, platelet count less than 100,000 cells/mL, neutrophil count less than 1.5×10^9 cells per L or I/T ratio greater than 0.2), or CRP (greater than 95 nmol/L)

(*continued*)

Table 1. Characteristics of the Randomized Trials Included in the Preterm Premature Rupture of Membranes Meta-analysis Collaboration (*continued*)

Characteristic	Study Acronym		
	PPROMEXIL	PPROMEXIL-2	PPROMT
	Probable: two or more symptoms of infection within 72 h after birth; signs of infection included: apnea, temperature instability, lethargy, feeding intolerance, respiratory distress, hemodynamic instability, plus one of the following: CRP greater than 20 mmol/L or a positive surface cultures of a known virulent pathogen	**Probable**: two or more symptoms of infection within 72 h after birth; signs of infection included: apnea, temperature instability, lethargy, feeding intolerance, respiratory distress, hemodynamic instability, plus one of the following: CRP greater than 20 mmol/L or a positive surface cultures of a known virulent pathogen	**Probable:** clinical signs for which the neonate was treated with antibiotics for 5 d or greater plus one or more of the following: abnormal CBC (criteria as in definite neonatal sepsis); abnormal CRP; positive GBS antigen on bladder tap urine, blood, or CSF; elevated CSF white cell count; growth of a known virulent pathogen from a surface swab; or a histologic diagnosis of pneumonia in an early neonatal death[‡]

PPROMEXIL, PPROM: Expectant Management versus Induction of Labor; PPROMT, Preterm Pre-labour Rupture of Membranes close to Term Trial; PPROM, preterm prelabor rupture of membranes; FHT, fetal heart tracing; PTL, preterm labor; NICU, neonatal intensive care unit; CSF, cerebrospinal fluid; CBC, complete blood count; WBC, white blood cell count; I/T, immature to total neutrophil; CRP, C-reactive protein; GBS, group B streptococci.

* Conducted in 11 countries, including Australia, New Zealand, Argentina, South Africa, Brazil, United Kindgdom, Norway, Egypt, Uruguay, Poland, and Romania.

† Women diagnosed with PPROM after 26 0/7 wk of gestation and who did not deliver by 34 0/7 wk of gestation were also eligible for randomization at 34 0/7 wk of gestation.

‡ Women diagnosed with PPROM at any gestational age and who did not deliver by 34 0/7 wk of gestation were also eligible for randomization at 34 0/7 wk of gestation.

§ Including major fetal anomalies, hemolysis elevated liver enzymes low platelets (HELLP) syndrome, severe preeclampsia, monochorionic multiple pregnancy.

‖ Including hypertensive disorders, diabetes mellitus, active herpes simplex virus, placenta previa, fetal anomalies.

For the primary outcome, there was no statistically significant difference between the immediate delivery and expectant management groups (Fig. 2). The composite of adverse neonatal outcomes occurred in 9.6% of the participants in the immediate delivery group compared with 8.3% in the expectant management group (RR 1.20, 95% CI 0.94–1.55, P=.15) (Table 3). There was no statistically significant difference in neonatal sepsis between both groups (2.6% vs 3.5%, RR 0.74, 95% CI 0.47–1.15, P=.18), but neonates randomized to immediate delivery were significantly more likely to be diagnosed with RDS (8.0% vs 5.4%, RR 1.47, 95% CI 1.10–1.97) and hyperbilirubinemia (50.9% vs 43.0%, RR 1.18, 95% CI 1.09–1.28). The rate of stillbirth or neonatal death was low and similar between the two groups (0.4% vs 0.3%, but too few cases to calculate RR and CI). Neonates born to mothers in the immediate delivery group were significantly more likely to be admitted to the NICU or special care nursery (69% vs 59%, RR 1.17, 95% CI 1.11–1.23) and had longer NICU or special care nursery admissions (4.0 vs 3.0 days, 26% increase, 95% CI 15–37%) and longer hospital stays (6.0 vs 4.0, 23% increase, 95% CI 15–31%). Women randomized to immediate delivery were significantly less likely to have antepartum hemorrhage (1.7% vs 3.0%, RR 0.57, 95% CI 0.34–0.95, P=.029), more likely to have scheduled cesarean delivery (8.2% vs 5.6%, RR 1.63, 95% CI 1.21–2.21, P<.001) as well as overall cesarean rates delivery (22% vs 18%, RR 1.26, 95% CI 1.08–1.47). Women randomized to immediate delivery were less likely to be diagnosed with chorioamnionitis (1.3% vs 6.4%, RR 0.21, 95% CI 0.13–0.35). There were no maternal deaths.

The subgroup analyses for positive vaginal culture, GBS positivity, antepartum tocolysis, corticosteroid administration, administration of maternal latency antibiotics, or preterm PROM before or after 34 0/7 weeks of gestation all showed no difference in treatment effect for the composite of adverse neonatal outcomes or any component of the primary outcome (Appendix 7, available online at http://links.lww.com/AOG/B57). In the subgroup analysis for women with a positive vaginal culture at randomization, immediate delivery decreased the risk of neonatal sepsis (2.3% vs 6.5%, RR 0.35, 95% CI 0.14–0.86,

Table 2. Baseline Characteristics

Baseline Characteristics	PPROMEXIL (n=537/531)*	PPROMEXIL-2 (n=200/197)*	PPROMT (n=1,835)*	PPROMM Collaboration (n=2,572/2,563)*	
				Immediate Delivery (n=1,291/1,289)*	Expectant Management (n=1,281/1,274)*
Maternal					
Maternal age (y)	29.7±5.3	30.0±5.2	27.9±6.1	28.5±5.9	28.4±6.0
Primigravida (1st pregnancy)	303 (56)	100 (50)	711 (39)	551 (43)	557 (44)
Twin pregnancies	6 (1.1)	3 (1.5)	0 (0.0)	2 (0.2)	7 (0.5)
Maternal smoking	144 (27)	55 (28)	508 (28)	362 (29)	341 (27)
Previous cesarean delivery	33 (6.1)	12 (6.0)	178 (9.7)	118 (9.1)	105 (8.2)
Pregnancy					
Gestational age at PPROM	35.2±1.4, 35.6 (34.7–36.1)	35.0±1.8, 35.6 (34.4–36.3)	34.7±1.9, 35.1 (34.0–35.8)	34.8±1.8, 35.3 (34.1–36.0)	34.8±1.8, 35.3 (34.3–36.0)
Gestational age at randomization (wk)	35.7±0.9, 35.9 (35.1–36.5)	35.7 (1.0), 35.9 (34.8–36.5)	34.3 (0.9), 35.3 (34.4–36.1)	35.4 (0.9), 35.4 (34.5–36.3)	35.4 (0.9), 35.5 (34.6–36.2)
Time from PPROM to randomization	3.7±5.3, 1.8 (1.5–2.7)	4.7±8.2, 1.8 (1.5–3.4)	3.9±10.0, 1.0 (0.0–3.0)	4.0±8.9, 1.6 (1.0–3.0)	4.0±9.2, 1.6 (1.0–2.9)
Cephalic presentation at the time of randomization†	495 (92)	183 (92)	1,652 (90)	1,175 (91)	1,155 (90)
GBS-positive at PPROM or randomization‡	83 (15)§	22 (11)§	200 (11)	164 (13)§	140 (11)§
Vaginal culture positive at PPROM or randomization (other than GBS)‡	24 (4.5)§	9 (4.5)§	226 (12.3)	121 (9.4)§	138 (11)§
Any vaginal culture positive at PPROM or randomization (GBS included)‡	107 (20)§	31 (16)§	383 (21)	259 (10)§	262 (10)§
Male neonate†	289 (54)	102 (51)	1,000 (55)	715 (56)	676 (53)

PPROMM Collaboration, Preterm Premature Rupture of Membranes Meta-analysis Collaboration; PPROMEXIL, PPROM: Expectant Management versus Induction of Labor; PPROMT, Preterm Pre-labour Rupture of Membranes close to Term Trial; PPROM, preterm prelabor rupture of membranes; IQR, interquartile range; GBS, group B streptococci.

Data are mean±SD, n (%), or median (interquartile range).

* Number of trial participants is presented as neonates/mothers or neonates.

† Data calculated by number of neonates; all other data points calculated by number of mothers.

‡ Vaginal culture other than GBS includes: bacterial vaginosis, *Candida albicans, Candida glabrata, Candida tropicalis,* chlamydia, coagulase-negative staphylococcus, *Enterococcus* species, *Escherichia coli, Haemophilus influenzae, Staphylococcus aureus, Staphylococcus agalactiae,* trichomoniasis, *Ureaplasma urealyticum.*

§ Outcome characteristic with greater than 5% missing data.

P=.02), whereas there was no such association for women with a negative vaginal culture at randomization (*P* value for interaction=.04) (Appendix 8, available online at http://links.lww.com/AOG/B57). The subgroup analysis for GBS positivity showed no difference for the primary outcome or neonatal sepsis (Appendix 7, http://links.lww.com/AOG/B57). A post hoc subgroup analysis examining the period of latency showed no significant difference in the primary outcome or neonatal sepsis for those who experienced prolonged preterm PROM.

A sensitivity analysis excluding multiple gestations did not change the primary outcome or its components (Appendix 9, available online at http://links.lww.com/AOG/B57). Similarly, when all studies that only enrolled women in the late preterm period were examined in a traditional aggregate data meta-analysis, no difference in outcomes was found between treatment groups for neonatal sepsis, RDS, or cesarean delivery (Appendix 10, available online at http://links.lww.com/AOG/B57) compared with the results of the individual participant data meta-analysis.

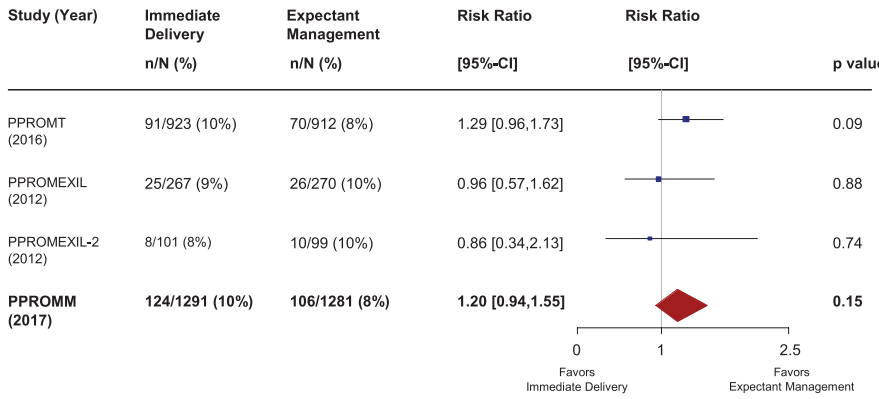

Fig. 2. Immediate delivery vs expectant management for the primary outcome: a composite of adverse neonatal outcomes. Preterm Premature Rupture of Membranes Meta-analysis (PPROMM) indicates studies included in this individual participant data meta-analysis. PPROMT, Preterm Prelabour Rupture of Membranes close to Term Trial; PPROMEXIL, PPROM Expectant Management versus Induction of Labor Trial; PPROMEXIL-2, PPROM Expectant Management versus Induction of Labor-2 Trial.

Quist-Nelson. Management of Late Preterm PROM. Obstet Gynecol 2018.

DISCUSSION

The results of this individual participant data meta-analysis show no significant difference between immediate delivery and expectant management for women with late preterm PROM for our primary outcome, a composite of adverse neonatal outcome that includes probable or definitive neonatal sepsis, necrotizing enterocolitis, RDS, stillbirth, or neonatal death. Assessment of other perinatal outcomes showed that the risk of RDS, hyperbilirubinemia, and NICU or special care nursery admission increased with immediate delivery, as expected when neonates are delivered at an earlier gestational age. Women randomized to immediate delivery were less likely to be diagnosed with chorioamnionitis or experience antepartum hemorrhage, but more likely to have a cesarean delivery.

We did not identify a statistically significant difference in neonatal sepsis between treatment groups. This is notable because neonatal sepsis was the primary outcome in each trial, yet even with a larger study population like our study, the incidence of neonatal sepsis is low and not appreciably different between groups. However, immediate delivery did reduce the risk of neonatal sepsis in the subgroup of patients with a positive vaginal culture at the time of randomization. Notably, the data for any positive vaginal cultures include 14 different pathogens (Table 2; Appendix 8 [http://links.lww.com/AOG/B57]) and had more than 5% missing data. Among the other subgroup analyses conducted (latency antibiotics, corticosteroids, GBS, tocolysis, and timing from preterm PROM), no statistically significant treatment effect on the primary outcome or its components was seen. However, many of the subgroup analyses were based on small numbers, because the incidence of women receiving corticosteroids, tocolysis, or experiencing preterm PROM before 32 0/7 weeks of gestation was low. Latency antibiotic uptake varied by hospital protocol, and specific treatment regimens were not available for this analysis.

Study strengths include utilizing an individual participant data meta-analysis, because this methodology has been shown to be more robust in enabling examination of treatment effects within clinically relevant subgroups.[10,11] To our knowledge, this is the only individual participant data meta-analysis on this topic. Limitations include the exclusion of five RCTs for which individual participant data were not available (n=640) (Koroveshi et al, J Perinatal Med 2013;41[suppl 1]).[16,17,19,20] Three of the five excluded studies covered a broader gestational age range, and it is unclear how many study participants would have qualified for our analysis limited to the late preterm period.[16,17,20] We performed a sensitivity analysis for sepsis, cesarean delivery, and RDS with the addition of the two studies that included only women in the late preterm period (472 additional women) and found no difference between treatment groups for any of the studied outcomes compared with the results of the individual participant data meta-analysis (Appendix 10, http://links.lww.com/AOG/B57) (Koroveshi et al, J Perinatal Med 2013;41[suppl 1]).[19] Notably, the three included trials were at low risk of bias compared with other studies included in the secondary analysis (Appendices 4 and 5, http://links.lww.com/AOG/B57).[18,21,22] Our study is also limited by the definition of neonatal sepsis, which varied by individual trials (Table 1). Neonatal sepsis was the primary outcome in all included RCTs. Its diagnosis has concerning clinical implications, but there is not a standardized definition.[23,24] Another notable difference between the included trials is that PPROMEXIL and PPROMEXIL-2 did not randomize women until

Table 3. Primary and Secondary Outcomes

Outcome	Immediate Delivery (n=1,291/1,289)*	Expectant Management (n=1,281/1,274)*	Adjusted RR†/Mean Difference (95% CI)	*P*	Hetero-geneity *P*
Primary outcome					
Composite of adverse neonatal outcome‡§	124/1,291 (9.6)	106/1,281 (8.3)	1.20 (0.94 to 1.55)	.15	.67
Components of neonatal composite					
Neonatal sepsis§	33/1,291 (2.6)	45/1,281 (3.5)	0.74 (0.47 to 1.15)	.18	.93
NEC§	1/1,291 (0.1)	0/1,281 (0.0)	—	—	—
RDS§	103/1,291 (8.0)	69/1,281 (5.4)	1.47 (1.10 to 1.97)	**.009**	.65
Stillbirth§	2/1,291 (0.2)	0/1,281 (0.0)	—	—	—
Neonatal death§ (within 28 d after birth)	2/1,291 (0.2)	1/1,281 (0.1)	—	—	—
Secondary neonatal outcomes					
Neonatal sepsis§	33/1,291 (2.6)	45/1,281 (3.5)	0.74 (0.47 to 1.15)	.18	.93
Definitive sepsis§	4/1,291 (0.3)	7/1,281 (0.5)	0.54 (0.16 to 1.82)	.31	.85
Probable sepsis§	29/1,291 (2.2)	38/1,281 (3.0)	0.75 (0.46 to 1.21)	.23	.81
NEC§	1/1,291 (0.1)	0/1,281 (0.0)	—	—	—
RDS§	103/1,291 (8.0)	69/1,281 (5.4)	1.47 (1.10 to 1.97)	**.009**	.65
Stillbirth§	2/1,291 (0.2)	0/1,281 (0.0)	—	—	—
Neonatal death§					
Within 48 h after birth	1/1,291 (0.1)	1/1,281 (0.1)	—	—	—
Within 28 d after birth	2/1,291 (0.2)	1/1,281 (0.1)	—	—	—
Any reported after birth	3/1,291 (0.4)	3/1,281 (0.3)	—	—	—
Apgar score less than 7 at 5 min§	19/1,283 (1.5)	20/1,271 (1.6)	0.93 (0.50 to 1.74)	.83	.64
Low umbilical cord arterial pH (less than 7.10 mmol/L)§‖	16/674 (2.4)	12/661 (1.8)	1.40 (0.66 to 3.00)	.38	.88
Birth weight (g)§	2,598±409.6, 2,560 (2,310–2,860)	2,687.8±409.0, 2,670 (2,410–2,950)	−90.4 (−120.0 to −60.8)	<**.0001**	.80
Hyperbilirubinemia§	655/1,288 (50.9)	549/1,277 (43.0)	1.18 (1.09 to 1.28)	<**.0001**	.04
Any mechanical ventilation (CPAP or ETT)§	123/1,291 (9.5)	97/1,281 (7.6)	1.26 (0.98 to 1.62)	.069	.02
Antibiotic administration (any after admission)§	519/1,291 (51)	498/1,281 (49)	1.05 (0.96 to 1.15)	.25	.20
Admission to NICU or SCN§	885/1,290 (69)	752/1,281 (59)	1.17 (1.11 to 1.23)	<**.0001**	.48
LOS in NICU or SCN (d)§	6.1±6.9, 4.0 (0.0–10.0)	4.9±6.6, 3.0 (0.0–8.0)	#	<**.001**	.47
LOS in hospital (d)§	7.5±6.7, 6.0 (3.0–10.0)	6.1±5.7, 4.0 (2.0–8.0)	**	<**.0001**	.39
Secondary maternal outcomes					
Antepartum hemorrhage	22/1,289 (1.7)	38/1,274 (3.0)	0.57 (0.34 to 0.95)	**.029**	.33
Endometritis	3/1,289 (0.2)	8/1,274 (0.6)	0.38 (0.10 to 1.42)	.13	.88
Thromboembolic complications¶	0/1,289 (0.0)	4/1,274 (0.3)	—	—	—
LOS in hospital (d)	3.45±2.7, 3.0 (2.0–4.0)	3.39+2.7, 3.0 (2.0–4.0)	††	.51	.71
Maternal death	0/1,289 (0.0)	0/1,274 (0.0)	—	—	—

(*continued*)

Table 3. Primary and Secondary Outcomes (*continued*)

Outcome	Immediate Delivery (n=1,291/1,289)*	Expectant Management (n=1,281/1,274)*	Adjusted RR†/Mean Difference (95% CI)	*P*	Hetero-geneity *P*
Secondary delivery outcomes					
Mode of delivery§					
Vaginal delivery	891/1,291 (69)	923/1,281 (72)	0.96 (0.92 to 1.01)	.15	.031
Vaginal breech	18/1,291 (1.4)	19/1,281 (1.5)	0.88 (0.47 to 1.65)	.69	.82
Operative vaginal delivery	92/1,291 (7.1)	109/1,281 (8.5)	0.83 (0.64 to 1.09)	.18	.71
Cesarean delivery, scheduled	107/1,291 (8.2)	68/1,213 (5.6)	1.63 (1.21 to 2.21)	**.001**	.26
Cesarean delivery, labor	181/1,291 (14)	158/1,281 (12)	1.14 (0.94 to 1.40)	.19	.21
Cesarean delivery, total	288/1,291 (22)	226/1,281 (18)	RR 1.26 (1.08 to 1.47)	**.0032**	.0143
Meconium-stained§ fluids	28/1,289 (2.2)	40/1,274 (3.1)	0.69 (0.43 to 1.11)	.12	.32
Umbilical cord prolapse	4/1,289 (0.3)	2/1,274 (0.2)	—	—	—
Clinical chorioamnionitis	17/1,289 (1.3)	82/1,274 (6.4)	0.21 (0.13 to 0.35)	**<.0001**	.14
Postpartum hemorrhage	53/1,291 (4.1)	57/1,274 (4.4)	0.94 (0.65 to 1.35)	.72	.46

RR, relative risk; NEC, necrotizing enterocolitis; —statistical model does not converge, too few cases to calculate RR; RDS, respiratory distress syndrome; IQR, interquartile range; CPAP, continuous positive airway pressure; ETT, endotracheal tube; NICU, neonatal intensive care unit; SCN, special care nursery; LOS, length of stay.

Data are n/N (%), mean±SD, or median (interquartile range) unless otherwise specified.

Bold indicates significant values.

For the purposes of the analysis, immediate delivery was considered the experimental arm. An RR above 1 therefore indicates an increase in risk of that outcome for the immediate delivery group. All analyses are conducted with immediate delivery as the intervention group.

* Number of trial participants is presented as neonates/mothers or neonates.

† Adjusted for trial and gestational age at randomization.

‡ Neonatal composite includes: probable or definitive neonatal sepsis, necrotizing entercolitis, respiratory distress syndrome, stillbirth, or neonatal death. Each component of the composite was defined by the individual trial definition.

§ Data calculated by number of neonates; all other data points calculated by number of mothers.

‖ Outcome characteristic with more than 5% missing data. Likely data are missing as a result of umbilical atrial pH measurement not tested at the time of delivery.

¶ Deep vein thrombosis or thromboembolism.

Poisson regression used. Neonates in the intervention group (immediate delivery) are predicted to have a 26% (95% CI 15–37%) longer stay in the SCN or NICU vs the control group (expectant management).

** Poisson regression used. Neonates in the intervention group (immediate delivery) are predicted to have a 23% (95% CI 15–31%) longer stay in the hospital vs the control group (expectant management).

†† Poisson regression used. Maternal LOS in the hospital is not significantly different across treatment groups. The average days of stay at the hospital can be multiplied by 1.02 for the immediate delivery group.

they had been greater than 24 hours without evidence of labor; in the PPROMT study, women were randomized after 4 hours of preterm PROM without evidence of labor. There were 241 women in PPROMT who were randomized to expectant management but delivered within 24 hours of randomization and thus would not have qualified for the PPROMEXIL trials.

Our subgroup analyses showed an increased risk of sepsis for neonates born to women randomized to expectant management who had a positive vaginal culture. Like with any subgroup analysis results, these should be seen as exploratory as a result of concerns of multiple testing and should be investigated in future studies.[25] This subgroup of positive vaginal culture included GBS, yet GBS positivity alone did not increase the risk of the primary outcome or neonatal sepsis (Appendix 7, http://links.lww.com/AOG/B57). This is in contrast to the findings previously published, demonstrating a protective effect of immediate delivery for women who are GBS-positive.[26]

There is limited evidence regarding long-term outcomes of expectant management or immediate delivery after late preterm PROM. There are data that raise concerns of long-term neurologic outcomes after preterm PROM, even in the absence of infection.[27] In contrast, there is also evidence that children born in the late preterm period have higher risks of morbidity and academic difficulties as compared with children born at term.[28,29] More research is needed to examine

the longitudinal outcomes specifically related to preterm PROM in the late preterm.

In conclusion, in women with late preterm PROM, immediate delivery and expectant management resulted in comparable rates of the composite of adverse neonatal outcomes. Effects on individual secondary maternal and neonatal outcomes were mixed. In women with late preterm PROM, expectant management is an acceptable alternative to immediate delivery given the current balance of benefits and harms for mothers and their neonates.

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