Appendix 1. Contributors

Contributors to the PPROMEXIL and PPROMEXIL-2 trials: Sylvia M. C. Vijgen, Jan G. Nijhuis, Johannes J. van Beek, Brent C. Opmeer, Antonius L. M. Mulder, Rob Moonen, Mariët Groenewout, Mariëlle G. van Pampus, Gerald D. Mantel, Kitty W. M. Bloemenkamp, Wim J. van Wijngaarden, Marko Sikkema, Monique C. Haak, Paula J. M. Pernet, Martina Porath, Jan F. M. Molkenboer, Simone Kuppens, Anneke Kwee, Michael E. Kars, Mallory Woiski, Martin J. N. Weinans, Hajo I. J. Wildschut, Bettina M. C. Akerboom, Jantien L. van der Heyden, Maureen T.M. Franssen, Christianne J.M. de Groot, J. (Hans) J. Duvekot, Bettina M.C. Akerboom, Aren J. van Loon, Jan W. de Leeuw

Contributors of PPROMT trial: Christine L Roberts, Jennifer R Bowen, Diana M Bond, Charles S Algert, Jim G Thornton, Caroline A Crowther

Quist-Nelson J, de Ruigh AA, Seidler AL, van der Ham DP, Willekes C, Berghella V, et al. Immediate delivery compared with expectant management in late preterm prelabor rupture of membranes: a meta-analysis. Obstet Gynecol 2018; 131.
The authors provided this information as a supplement to their article.

Appendix 2. Characteristics of Excluded Studies (Ordered by First Author)

Study	Reason for exclusion
Iams 1985	RCT. Study included 73 women with PPROM from 28-34 weeks' gestation of which 38 women were randomized to early delivery, 35 to expectant management. The trialist were unable to provide individual participant data and unable to extract a subgroup of women between 34+0 and 36+6 weeks' gestational age.
Koroveshi 2013	RCT. Study included 307 women with PPROM from 34-37 weeks' gestational age of which 157 women were randomized to planned early delivery and 150 to expectant management. No peer-reviewed data was available. Abstract only. Trialist intended to participate in this study, however we were not able to obtain relevant individual patient data.
Mercer 1993	RCT. Study included 93 women with confirmed PPROM between 32+0 and 36+6 weeks' gestational age of which 46 were randomized to induction of labor and 47 to expectant management. Unable to extract a subgroup of women between 34+0 and 36+6 weeks' gestational age.
Naef 1998	RCT. Study included 120 women with PPROM between 34+0 and 36+6 weeks' gestational age of which 57 were randomized to early delivery and 63 to expectant management. The trialist were unable to provide individual participant data.
Spinnato 1987	RCT. Study included 47 women with PPROM from 25-36 weeks' gestational age of which 26 were randomized to early delivery and 21 to expectant management. The trialist were unable to provide individual participant data and unable to extract a subgroup of women between 34+0 and 36+6 weeks' gestational age.

PPROM, preterm premature rupture of membranes; RCT, randomized controlled trial.

Appendix 3. Trial Definition of Each of the Components of the Primary Outcome

Component of primary outcome	PPROMEXIL and PPROMEXIL-2* Trial definition	PPROMT Trial definition	PPROMM
Definite neonatal sepsis	Definitive sepsis was classified as a positive blood culture taken at birth or within 72 hours after birth (taken at NICU or ward). If the culture was considered to be a contaminant babies were not classified as definitive sepsis. All cases of neonatal sepsis were extensively reviewed by a board of pediatricians unaware of the allocation of randomization.	Positive blood culture of a known pathogen from blood or CSF for which the baby was treated with antibiotics for ≥5 days (or died before 5 days) 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, then infant had to also have abnormal CBC (WBC<5x109 cell/L or >30 cells/L, platelet count <100 000 cells/mL, neutrophil count < 1.5×10^9 cells per L or I/T ratio > 0.2), or CRP (>95nmol/L)	Trialist defined.
Probable neonatal sepsis	Two or more symptoms of infection within 72 hours after birth. Signs of infection included: apnea, temperature instability, lethargy, feeding intolerance, respiratory distress, hemodynamic instability, plus one of the following: CRP >20 mmol/L or a positive surface cultures of a known virulent pathogen.	Clinical signs for which the baby was treated with antibiotics for ≥5 days 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 WBC; growth of a known virulent pathogen from a surface swab; or a histological diagnosis of pneumonia in an early neonatal death‡	Trialist defined.
NEC	Necrotizing enterocolitis according to modified Classification by Bell[31].	At least four of the symptoms listed below, plus a profile consistent with definite NEC plus the baby warranted treatment that included nil by mouth, and antibiotics. NEC symptoms must include at least one systemic sign (apnoea, bradycardia, temperature instability, or lethargy) and one intestinal sign (residuals more than 25% of previous feed on two consecutive occasions, abdominal distension, bilious vomiting, or faecal blood) and may also include dilated bowel. A profile consistent with definite NEC includes at least one of the following: abdominal wall cellulitis and palpable abdominal mass, or pneumatosis intestinalis, or portal vein gas, or a persistent dilated loop on serial X-rays, or a surgical or post mortem diagnosis.	Trialist defined.
Respiratory distress syndrome	Organ dysfunction criteria $PaCO_2/FiO_2$ < 300 in absence of cyanotic heart disease or pre-existing lung disease Or $PaCO_2$ > 65 torr or 20mmHg over baseline $PaCO_2$ Or Proven need or > 50% FIO2 to maintain saturation > 92%) Or Clinical symptoms such as expiratory grunting, tachypnea, retractions, nose flaring, or requiring the need of > 21 % oxygen to maintain a saturation of > 86%.	Increasing respiratory distress or oxygen requirements, or need for ventilator support for the first 6 hours of life with a CXR showing generalised reticulo-granular pattern +/- air bronchogram.	Trialist defined.

* Both trials used identical trial protocol.

Abbreviations: NICU, neonatal intensive care unit; CSF, cerebral spinal fluid; CBC, complete blood count; WBC, white blood count; L, liter; I/T, immature to total neutrophil count; CRP, C reactive protein; GBS, group B streptococcus; NEC, necrotizing enterocolitis; $PaCO_2$,partial pressure of carbon dioxide; FiO_2, fraction of inspired oxygen; CXR, chest X-ray

Appendix 4. Risk of Bias Tables of All Eligible Studies

Koroveshi 2013

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation process has not been described. Method of randomization not described. They do state: "Patients were randomized"
Allocation concealment (selection bias)	Unclear risk	Method used to conceal the allocation sequence has not been described.
Blinding of participants and personnel (performance bias)	Unclear risk	Blinding is not possible. However the risk of bias was unclear as there were no specific assessment criteria for outcomes described. Unclear whether lack of binding could have affected outcomes or treatment decisions.
Blinding of outcome assessment (detection bias)	Unclear risk	Not clear. Not described in the abstract. The assessment of neonatal and maternal outcomes was not described.
Incomplete outcome data (attrition bias)	Unclear risk	Not clear. The abstract does not describe the completeness of the outcome data for each main outcome. The numbers in each group (intervention group and control group) are comparable with the total number of randomized participants (150+157 = 307 participants), so there seem to be no attrition or exclusion.
Selective reporting (reporting bias)	High risk	No previously published study protocol, no published manuscript available on the study results. Only 3 outcomes reported, the abstract fails to include results for a key outcome that would be expected to have been reported for such a study, such as neonatal death, chorioamnionitis.
Other bias	Unclear risk	No peer-reviewed paper published. Therefore the overall risk of bias is unclear.

Morris 2016

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was done via a central telephone service using a computer-generated randomization schedule in a 1:1 ratio balanced blocks of variable size, stratified by centre.
Allocation concealment (selection bias)	Low risk	A central telephone service was used for randomization allocation.
Blinding of participants and personnel (performance bias)	Low risk	Blinding is not possible. Furthermore, the outcome is not likely to be influenced by lack of blinding. However, because there were specific outcome criteria pre-specified the risk of bias is low.
Blinding of outcome assessment (detection bias)	Low risk	For most outcomes no blinding of the outcome assessment, however it is not likely that the outcome is influenced by lack of blinding. For neonatal sepsis a board of paediatricians assessed all cases unaware of the allocation of randomization.
Incomplete outcome data (attrition bias)	Low risk	Reporting on exclusion of patients for randomization. Reported on missing outcome data by group. All analysis were performed by intention-to-treat, no participants were excluded from the analysis.
Selective reporting (reporting bias)	Low risk	A study protocol is available and all pre-specified outcomes of interest have been reported in the published manuscript.
Other bias	Low risk	The study appears to be free of other sources of bias.

Naef 1998

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Eligible and consenting gravid women were randomly assigned to either expectant management (observation) or active treatment (oxytocin) group by use of blinded computer-generated random number cards in opaque sealed envelopes.
Allocation concealment (selection bias)	Unclear risk	Opaque sealed envelopes were used. Not stated if the envelopes were sequentially numbered.

Blinding of participants and personnel (performance bias)	Low risk	Blinding is not possible. Furthermore, the outcome is not likely to be influenced by lack of blinding. However, because there were specific outcome criteria pre-specified the risk of bias is low.
Blinding of outcome assessment (detection bias)	Unclear risk	For neonatal outcomes, neonatologists were not blinded for the allocation of randomization. It was not specified if there was any blinding for maternal outcomes.
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	No previously published study protocol. However, it is clear that the published report includes all expected outcomes.
Other bias	Low risk	The study appears to be free of other sources of bias.

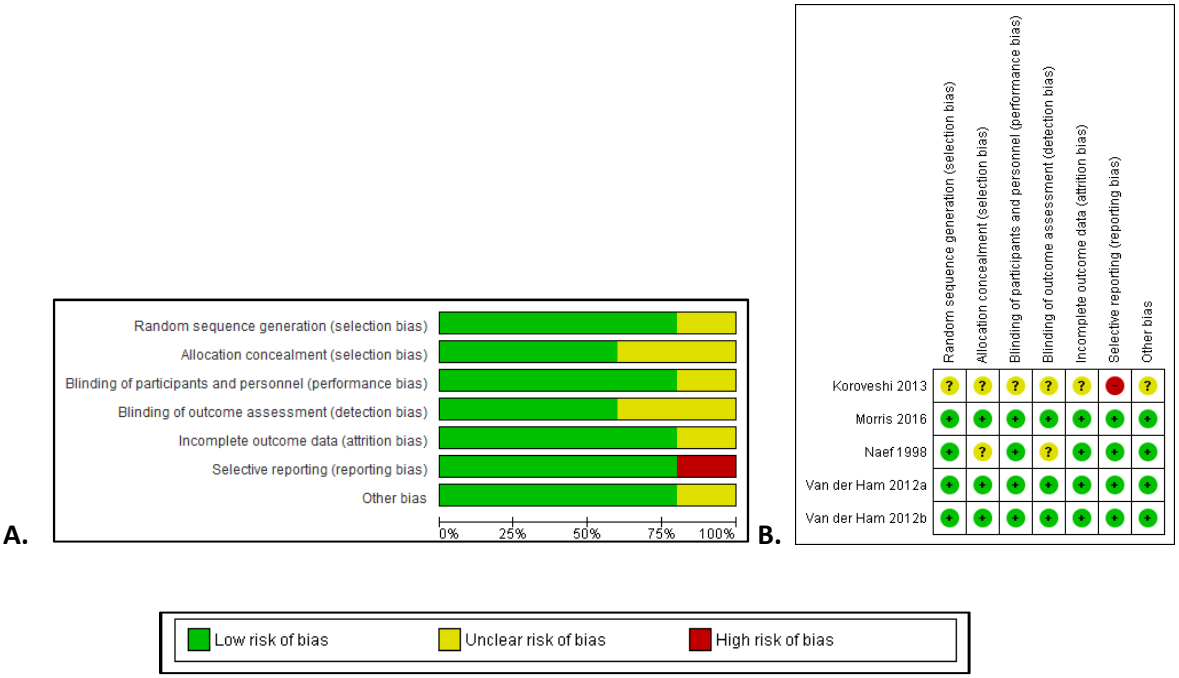
Van der Ham 2012a

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization was performed using a web-based application. Randomization sequence explained.
Allocation concealment (selection bias)	Low risk	A web-based allocation was used.
Blinding of participants and personnel (performance bias)	Low risk	Blinding is not possible. Furthermore, the outcome is not likely to be influenced by lack of blinding. However, because there were specific outcome criteria pre-specified the risk of bias is low.
Blinding of outcome assessment (detection bias)	Low risk	For most outcomes no blinding of the outcome assessment, however it is not likely that the outcome is influenced by lack of blinding. For neonatal sepsis a board of paediatricians assessed all cases unaware of the allocation of randomization.
Incomplete outcome data (attrition bias)	Low risk	Imputation of missing data has not been described. Reported on missing outcome data by group.
Selective reporting (reporting bias)	Low risk	A study protocol is available and all pre-specified outcomes of interest have been reported in the published manuscript.
Other bias	Low risk	The study appears to be free of other sources of bias.

Van der Ham 2012b

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was performed using a web-based application. Randomization sequence explained.
Allocation concealment (selection bias)	Low risk	A web-based allocation was used.
Blinding of participants and personnel (performance bias)	Low risk	Blinding is not possible. Furthermore, the outcome is not likely to be influenced by lack of blinding. However, because there were specific outcome criteria pre-specified the risk of bias is low.
Blinding of outcome assessment (detection bias)	Low risk	For most outcomes no blinding of the outcome assessment, however it is not likely that the outcome is influenced by lack of blinding. For neonatal sepsis a board of paediatricians assessed all cases unaware of the allocation of randomization.
Incomplete outcome data (attrition bias)	Low risk	Imputation of missing data has not been described. Reported on missing outcome data by group.
Selective reporting (reporting bias)	Low risk	A study protocol is available and all pre-specified outcomes of interest have been reported in the published manuscript.
Other bias	Low risk	The study appears to be free of other sources of bias.

Appendix 5. A. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all studies eligible for inclusion. B. Risk of bias summary: judgments of risk of bias for each study eligible for inclusion.



Appendix 6. Interventions

Interventions	PPROMEXIL (n=537/531)*	PPROMEXIL-2 (n=200/197)*	PPROMT (n=1835)*	PPROMM Collaboration (n=2572/2563)*		Risk Ratio/Mean difference (95% CI)	*p* value	Hetero-geneity *p* value
				Immediate delivery (n=1291/1289)*	Expectant management (n=1281/1274)*			
Tocolysis given	23 (4.3%)	6 (5.6%)	100 (5.4%)	61 (4.9%)	68 (5.5%)	0.89 (0.64-1.25)	0.51	0.83
Antenatal steroid administered	76 (14%)	34 (17%)	737 (40%)	440 (34%)	406 (32%)	1.07 (0.97-1.17)	0.16	0.59
Maternal latency antibiotics administered	184 (35%)	80 (41%)	1696 (92%)	980 (76%)	980 (78%)	0.99 (0.96-1.01)	0.28	0.38
Gestational age at birth (weeks) (mean±SD, median [IQR])	36.1 ±0.9, 36.3 [35.4-36.9]	36.1 ±0.9, 36.3 [35.6-36.7]	35.7±1.0, 35.7 [34.9-36.6]	35.6±1.0, 35.6 [34.7-36.4]	36.1 ±1.0, 36.1 [35.4-36.9]	-0.49 (-0.54 to -0.44)	**<0.0001**	0.97
Time from PPROM to delivery (days) (mean±SD, median [IQR])	6.4 ±8.4, 3.0 [2.0-6.0]	7.5 ±10.4, 4.0 [2.0-8.0]	6.8 ±11.8, 2.9 [1.4-6.4]	5.2 ±9.7, 2.3 [1.3-4.5]	8.3 ±12.1, 4.1 [2.0-9.0]	‡	**<0.0001**	**<0.0001**†

Spontaneous labor	199 (37%)	71 (36%)	729 (40%)	233/1289 (18%)	768/1273 (60%)	0.30 (0.27-0.34)	**<0.0001**	0.14
Induction	314 (59%)	113 (59%)	957 (52%)	950/1287 (74%)	434/1271 (34%)	2.19 (2.02-2.38)	**<0.0001**	0.12

Data are presented as total number in trial or mean ±SD or median [IQR]. For all calculations the denominator was mothers.

Significant values are bolded.

* Number of trial participants are presented as (neonates/mothers) or (neonates).

† Heterogeneity due to different trial protocols, in PPROMT the time between PPROM and randomization was set to be 4 hours, in PROMEXIL the time from PPROM to randomization was 24 hours.

‡ Exp(-0.48)= 0.62 (women randomized to immediate delivery can expect 38% shorter duration between PPROMM and delivery)

Upper CI = Exp(-0.51) = 0.60 (40 % shorter), lower CI = exp(-0.45) = 0.64 (36% shorter)

Abbreviations: CI, confidence interval; SD, standard deviation; IQR, interquartile range; PPROM, preterm prelabor rupture of membranes.

Appendix 7. Subgroup Analysis Immediate Delivery Versus Expectant Management for Women With a Vaginal Culture Positive for GBS at the Time of PPROM or Randomization for Primary Outcome

Primary outcome: composite of adverse neonatal outcomes		**Immediate delivery**	**Expectant management**	**Adjusted Relative Risk* (90% CI)**		
Subgroup	**Trial**	**n/N (%)**	**n/N (%)**	**Adjusted RR**	***p* Value**	**Interaction *P* Value**
GBS positive	PPROMT	7/83 (8.4%)	6/78 (7.7%)	1.09 (0.39-3.08)	0.87	**0.10**
	PPROMEXIL	4/48 (8.3%)	8/35 (23%)	0.37 (0.12-1.14)	0.09	
	PPROMEXIL-2	2/10 (20%)	3/12 (25%)	0.68 (0.18-2.63)	0.46	
	PPROMM	**13/141 (9.2%)**	**17/125 (14%)**	**0.66 (0.33-1.30)**	**0.23**	
GBS negative	PPROMT	84/840 (10%)	64/834 (7.7%)	1.31 (0.96-1.78)	0.09	
	PPROMEXIL	21/219 (9.6%)	18/235 (7.7%)	1.23 (0.67-2.24)	0.50	
	PPROMEXIL-2	6/91 (6.5%)	7/87 (8.0%)	0.88 (0.30-2.60)	0.82	
	PPROMM	**111/1150 (9.7%)**	**89/1156 (7.5%)**	**1.30 (0.99-1.71)**	**0.06**	

Data are presented as n/N (%). Totals for each subgroup are bolded.

* Adjusted for trial and gestational age at randomization

Abbreviations: CI, confidence interval; GBS, Group B Streptococcus.

Subgroup analysis immediate delivery versus expectant management for women with a vaginal culture positive for GBS at the time of PPROM or randomization for outcome of neonatal sepsis.

Outcome: neonatal sepsis		**Immediate delivery**	**Expectant management**	**Adjusted Relative Risk* (90% CI)**		
Subgroup	**Trial**	**n/N (%)**	**n/N (%)**	**Adjusted RR**	***p* Value**	**Interaction *P* Value**
GBS positive	PPROMT	3/83 (3.6%)	3/78 (3.8%)	0.94 (0.20-4.54)	0.94	**0.14**
	PPROMEXIL	0/48 (0.0%)	6/35 (17%)	-	-	
	PPROMEXIL-2	1/10 (10%)	1/12 (8.3%)	0.88 (0.067-11.54)	0.92	
	PPROMM	**4/141 (2.8%)**	**10/125 (8.0 %)**	**0.34 (0.11-1.04)**	**0.04**	
GBS negative	PPROMT	20/840 (2.4%)	26/834 (3.1%)	0.76 (0.43-1.35)	0.35	
	PPROMEXIL	7/219 (3.2%)	5/235 (2.1%)	1.50 (0.48-4.64)	0.48	
	PPROMEXIL-2	2/91 (2.2%)	4/87 (4.6%)	0.61 (0.10-3.51)	0.58	

	PPROMM	**29/1150 (2.5%)**	**35/1156 (3.0%)**	**0.85 (0.52-1.39)**	**0.53**	

Data are presented as n/N (%). Totals for each subgroup are bolded.

CI, confidence interval; GBS, Group B Streptococcus

* Adjusted for trial and gestational age at randomization

Abbreviations: CI, confidence interval; GBS, Group B Streptococcus.

Appendix 8. Subgroup Analysis Immediate Delivery Versus Expectant Management for Women With Positive Vaginal Culture at the Time of PPROM or Randomization; Outcome: Neonatal Sepsis.

Outcome: neonatal sepsis		**Immediate delivery**	**Expectant management**	**Adjusted Relative Risk[*] (90% CI)**		
Subgroup	**Trial**	**n/N (%)**	**n/N (%)**	**Adjusted RR**	***p* Value**	**Interaction *P* Value**
Any vaginal culture positive[†]	PPROMT	4/190 (2.1%)	9/193 (4.7%)	0.45 (0.14-1.44)	0.17	**0.04**
	PPROMEXIL	1/55 (1.8%)	7/52 (14%)	0.14 (0.0173-1.06)	0.02	
	PPROMEXIL-2	1/14 (7.1%)	1/17 (5.9%)	-	-	
	Total	**6/259 (2.3%)**	**17/262 (6.5%)**	**0.35 (0.14-0.86)**	**0.02**	
Any vaginal culture negative	PPROMT	19/733 (2.6%)	20/719 (4.7%)	0.93 (0.50-1.73)	0.82	
	PPROMEXIL	6/212 (2.8%)	4/218 (1.8%)	1.53 (0.42-5.34)	0.50	
	PPROMEXIL-2	2/85 (2.3%)	4/82 (4.9%)	0.60 (0.10-3.46)	0.57	
	Total	**27/1032 (2.6%)**	**28/1019 (2.7%)**	**0.98 (0.58-1.67)**	**0.95**	

Outcome: neonatal sepsis		Immediate delivery	Expectant management	Adjusted Relative Risk* (90% CI)		
Subgroup	**Trial**	**n/N (%)**	**n/N (%)**	**Adjusted RR**	***p* Value**	**Interaction *P* Value**

Data are presented as n/N (%). Totals for subgroups are bolded.

* Adjusted for trial and gestational age at randomization

† Vaginal culture includes: Bacterial Vaginosis, Candida albicans, Candida glabrata, Candida Tropicalis, Chlamydia, Coagulase negative staphylococcus, Enterococcus, Escherichia coli, Group B streptococcus, Hemophilus influenza, Staphylococcus aureus, Staphylococcus agalactiae, Trichomoniasis, Ureaplasma urealyticum **Abbreviations**: CI, confidence interval.

Appendix 9. Primary Outcomes PPROMM When Excluding Twin Pregnancies

	Immediate delivery (n=1287)*	**Expectant management (n=1267)***	**Adjusted RR† /Mean difference (95% CI)**	***p* value**	**Heterogeneity p-value**
Primary outcome					
Composite of adverse neonatal outcome‡	124/1287 (10.4%)	103/1267 (8.1%)	1.18 (0.92-1.51)	0.19	0.56
Components of neonatal composite					
Neonatal sepsis	33/1287 (2.6%)	43/1267 (3.4%)	0.75 (0.48-1.17)	0.21	0.89
NEC	1/1287 (0.1%)	0/1266 (0.0%)	-	-	-
RDS	103/1287 (8.0%)	68/1267 (5.4%)	1.48 (1.12-1.99)	**0.008**	0.72
Stillbirth	2/1287 (0.2%)	0/1267 (0.0%)	-	-	-
Neonatal death (within 28 days after birth)	2/1287 (0.2%)	1/1267 (0.1%)	-	-	-

Data are presented as n/N (%). Statistically significant values are bolded. All analyses are conducted with immediate delivery as the intervention group. Data calculated by number of infants.

* Number of trial participants are presented as neonates, twins are excluded for these analysis.

†Adjusted for trial and gestational age at randomization.

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

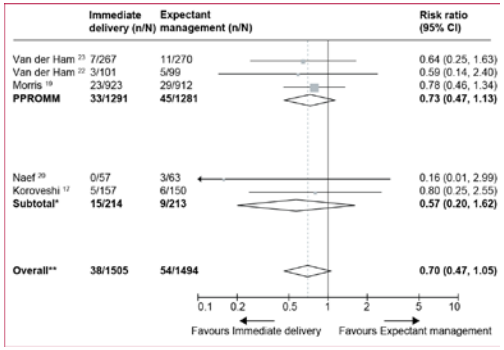
- Statistical model does not converge, too few cases to calculate RR

Abbreviations: RR, relative risk; NEC, necrotizing enterocolitis; RDS, respiratory distress syndrome.

Quist-Nelson J, de Ruigh AA, Seidler AL, van der Ham DP, Willekes C, Berghella V, et al. Immediate delivery compared with expectant management in late preterm prelabor rupture of membranes: a meta-analysis. Obstet Gynecol 2018; 131.
The authors provided this information as a supplement to their article.

Appendix 10. Sensitivity analyses. A. Neonatal sepsis including Preterm Pre-labour Rupture of Membranes close to Term Trial (PPROMT), PPROM Expectant Management versus Induction of Labor (PPROMEXIL), PPROM Expectant Management versus Induction of Labor-2 (PPROMEXIL-2), Koroveshi et al, and Naef et al. PPROMM (Preterm Premature Rupture of Membranes Meta-analysis) indicates studies included in this individual participant data meta-analysis. Comparison: Immediate delivery compared with expectant management for late preterm period, for outcome of neonatal sepsis. Trials included in individual participant data meta-analysis (IPDMA), excluded from IPDMA, and all trials combined using published data. B. Respiratory distress syndrome (RDS) including PPROMT, PPROMEXIL, PPROMEXIL-2, Koroveshi et al, and Naef et al. PPROMM indicates studies included in this individual participant data meta-analysis. Comparison: Immediate delivery compared with expectant management, outcome: RDS. Trials included in IPDMA, excluded from IPDMA, and all trials combined using published data. C. Cesarean delivery including PPROMT, PPROMEXIL, PPROMEXIL-2, Koroveshi et al, and Naef et al. PPROMM indicates studies included in this individual participant data meta-analysis. Comparison: Immediate delivery compared with expectant management, outcome: cesarean delivery. Trials included in IPDMA, excluded from IPDMA, and all trials combined using published data. *Subtotal represents the studies that could not provide individual participant data, but covered the same late preterm gestational ages. **Overall represents all five eligible studies randomizing expectant management compared with immediate delivery in the late preterm period.

A.



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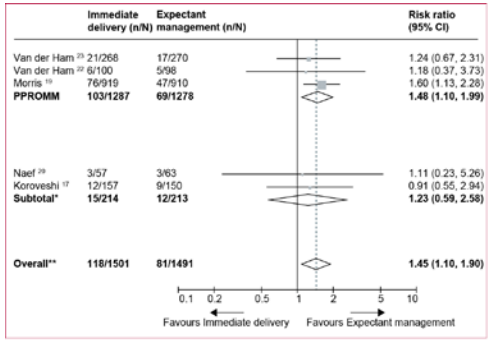

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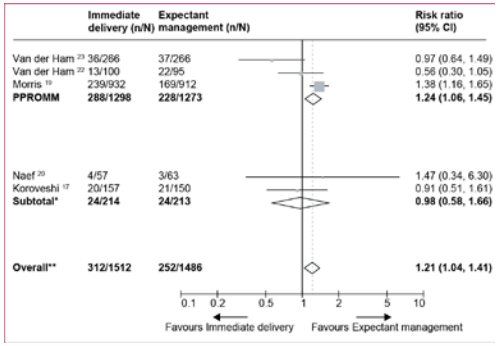

Quist-Nelson J, de Ruigh AA, Seidler AL, van der Ham DP, Willekes C, Berghella V, et al. Immediate delivery compared with expectant management in late preterm prelabor rupture of membranes: a meta-analysis. Obstet Gynecol 2018; 131.
The authors provided this information as a supplement to their article.