Using vaginal Group B *Streptococcus* colonisation in women with preterm premature rupture of membranes to guide the decision for immediate delivery: a secondary analysis of the PPROMEXIL trials

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Objective To investigate whether vaginal Group B *Streptococcus* (GBS) colonisation or other baseline characteristics of women with preterm premature rupture of membranes (PPROM) can help in identifying subgroups of women who would benefit from immediate delivery.

Design Secondary analysis of the PPROMEXIL trials.

Setting Sixty hospitals in the Netherlands.

Population Women with PPROM between 34 and 37 weeks of gestation.

Methods Random assignment of 723 women to immediate delivery or expectant management.

Main outcome measures Early onset neonatal sepsis.

Results Vaginal GBS colonisation status was the only marker which was significantly associated with the benefit of immediate delivery (*P* for interaction: 0.04). GBS colonisation was observed in 14% of women. The risk of early onset neonatal sepsis in GBS-positive women was high (15.2%) when they were managed expectantly but this risk was reduced to

1.8% with immediate delivery. The early onset neonatal sepsis risk was much lower in neonates of GBS-negative women: 2.6% after expectant management and 2.9% with immediate delivery. We estimated that by inducing labour only in GBS-positive women, there would be a 10.4% increase in term delivery rate, while keeping neonatal sepsis and caesarean delivery rates comparable to a strategy of labour induction for all.

Conclusions Our *post hoc* findings suggest that women with PROM between 34 and 37 weeks might benefit from immediate delivery if they have GBS vaginal colonisation, while in GBS-negative women labour induction could be delayed until 37 weeks.

Keywords Early onset neonatal sepsis, group B *streptococcus*, preterm premature rupture of membranes, treatment selection marker, vaginal culture.

Linked article This article is commented on by Gilbert R, p. 1273 in this issue. To view this mini commentary visit http://dx.doi.org/10.1111/1471-0528.12940.

Introduction

Preterm premature rupture of membranes (PPROM) refers to rupture of the membranes before the onset of labour in women with a pregnancy <37 weeks of gestation. It complicates 1–3% of all pregnancies and is responsible for approximately 30% of preterm births.[1–5] The management of PPROM is a controversial topic in maternal fetal medicine[6] and there is no consensus on the optimal timing of delivery of women with PPROM between 34^{+0} and 37^{+0} weeks.

Recently our group reported two PPROMEXIL trials in which PPROM patients between 34 and 37 weeks of gestation were randomly allocated to either immediate delivery by labour induction or expectant management. Immediate delivery was found to result in a trivially lower, non-significant neonatal sepsis rate: 2.6 versus 4.1%. The two strategies were also comparable in terms of rates of respiratory distress syndrome and caesarean delivery rates.[7,8] A meta-analysis on more than 1400 participants of PPROM-EXIL and seven other trials[3,9–14] supported this finding: immediate delivery results in no significant benefit or harm compared to expectant management (pooled relative risk [RR] 1.02; 95% confidence interval [CI] 0.63–1.65).[8]

A matter of concern is whether this finding is generalisable to all women with PPROM after 34 weeks. Bacterial infection causing neonatal sepsis is most commonly due to the Group B *Streptococcus* (GBS).[15] The primary source of GBS infection is vertical transmission of maternal genitourinary or gastrointestinal GBS colonisation, which generally occurs after rupture of membranes or onset of labour.[16–18] The time between rupture of membranes and delivery is a known risk factor for increased risk of neonatal GBS sepsis[19] and women who undergo expectant management strategy have a longer time to delivery compared with women in whom labour is induced immediately. Therefore, we hypothesised that fetuses of women with GBS colonisation might be at a higher risk of neonatal sepsis if they undergo expectant management and they may benefit more from undergoing immediate delivery.

To examine this hypothesis we performed a *post hoc* analysis of pooled data from the PPROMEXIL I and II trials. We compared the benefits and harms of immediate delivery versus expectant management between women who had vaginal GBS colonisation and those without GBS colonisation. We also evaluated other potential markers that could be informative for selection of patients for immediate delivery.

Methods

Study design and patients

The PPROMEXIL I trial (ISRCTN29313500)[7] and PPROMEXIL II trial (ISRCTN05689407)[8] were multicentre open-label randomised controlled trials, in which all eight academic and 52 non-academic hospitals in the Netherlands participated. The background, methods, baseline characteristics of the randomised patients, and results have previously been reported elsewhere.[7,8,20]

In brief, the two trials included 723 women (Figure S1) with a singleton or twin pregnancy between 34 and 37 weeks of gestation who were not in labour 24 hours after PPROM. Participants were randomly allocated to either immediate delivery or expectant management. Baseline characteristics of the women in the study groups are summarised in Table S1 and the observed outcomes are presented in Table 1.

In the immediate delivery group, labour was induced within 48 hours after randomisation. In women who had an absolute contraindication to vaginal delivery, a primary caesarean delivery was performed. In the expectant management group, women were monitored based on the local protocol until the onset of spontaneous delivery. In the majority of the participating centres, women had an inpatient management. Under strict conditions a minority of centres allowed outpatient management.

Maternal monitoring consisted of daily temperature measurement, twice weekly blood sampling for leucocyte count and C-reactive protein measurement. When a patient in the expectant management group reached 37^{+0} weeks of gestational age, labour was induced. Prior to 37^{+0} weeks, labour was induced if there were clinical signs of infection or if another fetal or maternal indication occurred that warranted induction of labour.[7]

A vaginal swab was collected either at study entry or at admission to the hospital and was used for bacterial culture. If antibiotic prophylaxis was started, this was only done after vaginal culture collection. The swab for culture was taken from the posterior fornix of the vagina. Due to the fact that the PPROMEXIL trials were large pragmatic trials, with 60 participating hospitals across The Netherlands, with limited funding, there was no uniform guideline on how to handle specimens after collection. In the participating centres, samples were cultured on either colistin-oxolinic acid blood agar (COB), blood agar with sheep blood agar (BA + 5% SB) or tryptone soya broth with X and V factor (TSB + XV) in order to identify GBS.

The national guidelines of the Dutch Society for Obstetrics and Gynaecology did not indicate whether or not to start antibiotics in women with PPROM prior to 37 weeks.[21] Thus, antepartum and intrapartum administration of antibiotics was given according to local protocols. If antibiotics were given antepartum, this was empirical in the vast majority while awaiting culture results and were started on admission. If antibiotics were not started on admission, they were dependent on culture results. In case of a positive GBS culture the national guideline recommends starting

Table 1. Pregnancy, neonatal and maternal outcomes in the participants of the PPROMEXIL trials

Outcomes	Expectant management (n = 359)	Immediate delivery (n = 364)	P–value
Pregnancy outcomes			
Gestational age at birth (weeks), median (IQR)	36^{+4} (35^{+6} to 37^{+0})	36^{+0} (35^{+1} to 36^{+4})	<0.001
Interval between randomization and birth (hours), median (IQR)	68 (28–154)	25 (13–38)	<0.001
Interval between rupture of membranes and birth (hours), median (IQR)	113 (65–234)	62 (46–103)	<0.001
Delivery by caesarean section	54 (15)	47 (13)	0.409
Neonatal outcomes			
Early onset sepsis, n (%)	15 (4)	10 (3)	0.292
Late onset sepsis, n (%)	1 (0)	0 (0)	0.322
Respiratory distress syndrome, n (%)	20 (6)	26 (7)	0.354
Birth weight (g), median (IQR)	2730 (2469–2985)	2615 (2365–2900)	0.017
Maternal outcomes			
Clinical chorioamnionitis, n (%)	19 (5)	6 (2)	0.007
Sepsis, n (%)	1 (0)	0 (0)	0.314
Endometritis, n (%)	4 (1)	2 (0·5)	0.404
Histological chorioamnionitis, n (%)	80 (22)	55 (15)	0.006

IQR, interquartile range.

antibiotic treatment and inducing labour.[18] During labour without known culture results, antibiotics were started if there were signs or symptoms of an infection.[17]

The primary outcome of the trials was early onset neonatal sepsis, defined as a positive blood culture taken at birth (not *Staphylococcus epidermidis*) or, within 72 hours, two or more symptoms of infection (apnoea, temperature instability, lethargy, feeding intolerance, respiratory distress, haemodynamic instability) plus one of the following three items: (i) positive blood culture, (ii) C-reactive protein >20 mmol/l, or (iii) positive surface cultures of a known virulent pathogen.

Secondary neonatal outcome measures were respiratory distress syndrome (RDS; according to the Organ dysfunction criteria with radiographic confirmation)[20], late onset neonatal sepsis, hypoglycaemia, hyperbilirubinaemia, total length of hospital stay, and admission to the neonatal intensive care unit (NICU). Secondary maternal outcome measures were clinical chorioamnionitis, endometritis and sepsis.[20] Finally, we recorded mode of delivery.

Statistical analysis

The primary aim of our analyses was to evaluate whether and to what extent vaginal GBS colonisation was associated with a differential benefit from immediate delivery. We modelled this association using a logistic regression model with neonatal sepsis as the outcome of interest, and GBS culture, treatment (immediate delivery versus expectant management) and interaction between GBS and treatment as independent variables. In a separate model we also investigated the presence of interaction between GBS and time from randomisation to delivery on the risk of neonatal sepsis. Using the same modelling strategy, we then explored the interaction between treatment and other potential treatment selection markers: gestational age at PPROM, time from PPROM to study entry, positive vaginal culture for specimens other than GBS, maternal age, and parity. We assumed that any reduction in neonatal sepsis risk as a result of labour induction would justify inducing labour. Therefore, markers that showed a significant interaction with treatment in the logistic regression model (P-value < 0.1) would have the potential to be useful for treatment selection.

We then explored the effect of immediate delivery in GBS colonised (GBS-positive) and non-colonised women (GBS-negative) on other outcomes, including rates of term delivery (>37 weeks), clinical chorioamnionitis, respiratory distress syndrome and caesarean delivery.

We evaluated a GBS-based treatment selection rule and estimated the expected amount of population-level gain and harm from the proposed strategy compared with the two other strategies: expectant management strategy for all women or inducing labour in all women. For each estimation of the GBS-based strategy outcomes, we used the observed outcome rates separately in GBS-positive and GBS-negative women after expectant management and after induction of labour. We then multiplied the proportion of women who were GBS-positive by the outcome rate in the

GBS-positive women who received the recommended treatment in our study groups and summed it up with the proportion of GBS-negative women multiplied by the outcome rate in that group with the recommended treatment. To estimate the 95% confidence interval of the estimated outcomes, we used non-parametric bootstrapping ($n = 1000$).

All analyses of this paper were exploratory and performed based on the intention-to-treat principle. We used R for Windows (Version 2.15.2; R Foundation for Statistical Computing, Vienna, Austria).

Results

The baseline characteristics of the PPROMEXIL participants are summarised in Table S1 and the main results of the trials in Table 1. Overall, the PPROMEXIL trials showed that immediate delivery did not significantly reduce the risk of neonatal sepsis compared with expectant management. Immediate delivery lowered the risk of clinical chorioamnionitis but did not affect the caesarean delivery rate or the risk of RDS in neonates.

Among the participating women, 103 (14%) had vaginal GBS colonisation. As presented in Table 2 and Figure 1, the risk of neonatal sepsis in these 103 women who had GBS colonisation was high when women were managed expectantly (7/46, 15.2%) but the risk was significantly lower (1/57, 1.8%) in the immediate delivery group (odds ratio (OR) 0.10; 95% CI: 0.01–0.84). This corresponds to a number needed to treat (NNT) of 7.5. Conversely, the neonatal sepsis risk was much lower in neonates of women without GBS colonisation, both with expectant management (2.6%) and after immediate delivery (2.9%; OR: 1.2; 95% CI: 0.4–3.0). The difference between the effect of immediate delivery in GBS-positive versus GBS-negative women was found to be statistically significant (P for interaction: 0.040). Likewise, as illustrated in Figure 2, in the GBS colonised women, longer time to delivery was associated with a higher risk of neonatal sepsis, whereas there was no such association in the GBS-negative women (P for interaction: 0.095).

The risk of other neonatal or maternal infectious complications, such as clinical chorioamnionitis and histological chorioamnionitis, was also higher in women with GBS colonisation (Table 2); in both GBS-positive and GBS-negative women these risks were lower after immediate delivery.

The results of our investigations of other potential treatment selection markers are presented in Table S2. None of the studied markers – gestational age at PPROM, time from PPROM to study entry, maternal age, parity, or positive vaginal culture other than GBS – could modify the effect of labour induction on risk of neonatal sepsis; all P-values of interaction were above 0.1.

Table 3 presents the distribution of antibiotic prophylaxis and the occurrence of neonatal sepsis in strata of GBS colonisation and the trial treatments. In total, 77% of women with GBS colonisation and 36% of women without GBS colonisation had received antibiotic prophylaxis during admission and/or delivery. In GBS-positive women who had undergone expectant management the risk of neonatal sepsis was high, even with antibiotic prophylaxis during admission and delivery (13%), whereas with immediate delivery, the risk was 6% without any antibiotic treatment. We observed no neonatal sepsis among 39 GBS-positive women who had immediate delivery combined with any antibiotic prophylaxis before or during delivery. In GBS-negative women, the risk of neonatal infection was 2.7%; in these women, there was no pattern of risk reduction by immediate delivery or any strategy of antibiotic prophylaxis. However, given the small numbers and heterogenic treatment protocols, investigating the effect of antibiotic prophylaxis is not within the scope of this paper.

Discussion

Main findings

The analyses reported here show that immediate delivery may be a very effective strategy to reduce early onset neonatal sepsis rate in PPROM women who have vaginal GBS colonisation, with an 86% relative risk reduction and a number needed to treat of 7.5. We acknowledge that this was a secondary analysis of two randomised trials, not pre-specified as such in the trial protocols, so our findings should be validated before they are applied in clinical practice.

Strengths and limitations

A strength of this analysis is that it is based on randomised trial data where women had been randomly allocated to expectant management strategy or immediate labour induction. None of the baseline maternal and fetal risk factors affected the choice of treatment. When investigating markers, we did not choose empirical categories, but studied continuous variables.

For some patients, vaginal swabs were obtained during admission and not at study entry. Yet, considering the fact that admissions occurred in almost all cases within 1 week, we do not expect vaginal GBS colonisation to change within a week. The use of antibiotics differed between groups but as antibiotics were more often given to GBS-positive women, this is unlikely to affect our conclusion.

In this study we obtained only a vaginal swab, which may lead to an underestimation of the proportion of women who were GBS carriers. Therefore, our interpretation of the results is based on vaginal GBS colonisation only. Whether women with anal colonisation would also

Table 2. Relationship between vaginal GBS colonisation and the occurrence of fetal and maternal outcomes in each trial arm

Outcomes	GBS Colonisation (n = 103)			No GBS Colonisation (n = 619)		
	Expectant management (n = 46)	Immediate delivery (n = 57)	Odds ratio (95% CI)	Expectant management (n = 313)	Immediate delivery (n = 306)	Odds ratio (95% CI)
Primary outcome						
Early onset neonatal sepsis*, n (%)	7 (15.2)	1 (1.8)	0.10 (0.01–0.84)	8 (2.6)	9 (2.9)	1.16 (0.44–3.03)
Secondary neonatal outcomes						
Term delivery, n (%)	13 (28.3)	4 (7.0)	0.19 (0.06–0.64)	96 (30.7)	17 (5.6)	0.13 (0.08–0.23)
Respiratory distress syndrome, n (%)	2 (4.8)	5 (9.6)	2.13 (0.39–11.57)	18 (5.9)	21 (7.2)	1.23 (0.64–2.36)
Hypoglycaemia, n (%)	8 (19.0)	12 (23.1)	1.28 (0.47–3.48)	22 (7.3)	43 (15.0)	2.24 (1.30–3.84)
Hyperbilirubinemia, n (%)	19 (45.2)	21 (40.4)	0.82 (0.36–1.87)	67 (22.0)	87 (30.4)	1.55 (1.07–2.24)
Length of hospital stay, mean ± SD, median (IQR)	6.6 ± 5.3, 6 (2.0–8.0)	8.1 ± 6.1, 7 (3.0–11.0)	1.5** (−0.79 – 3.89)	6.1 ± 7.6, 4 (2.9–9.0)	7.3 ± 6.9, 5 (2.0–11.0)	1.2** (0.03 – 2.37)
NICU admission, n (%)	5 (10.9)	6 (10.5)	0.97 (0.28–3.39)	17 (5.4)	23 (7.5)	1.42 (0.74–2.70)
Secondary maternal outcomes						
Clinical chorioamnionitis, n (%)	5 (10.9)	3 (5.4)	0.46 (0.11–2.06)	14 (4.5)	3 (1.0)	0.21 (0.06–0.74)
Histological chorioamnionitis, n (%)	16 (53.3)	11 (25.6)	0.30 (0.11–0.81)	64 (28.4)	44 (19.9)	0.63 (0.40–0.97)
Caesarean delivery, n (%)	7 (15.2)	11 (19.3)	1.33(0.47–3.77)	47 (15.0)	36 (11.8)	0.76 (0.47–1.20)

*P-value for interaction = 0.04; The interaction P-value tests whether the two odds ratios (OR) are significantly different.
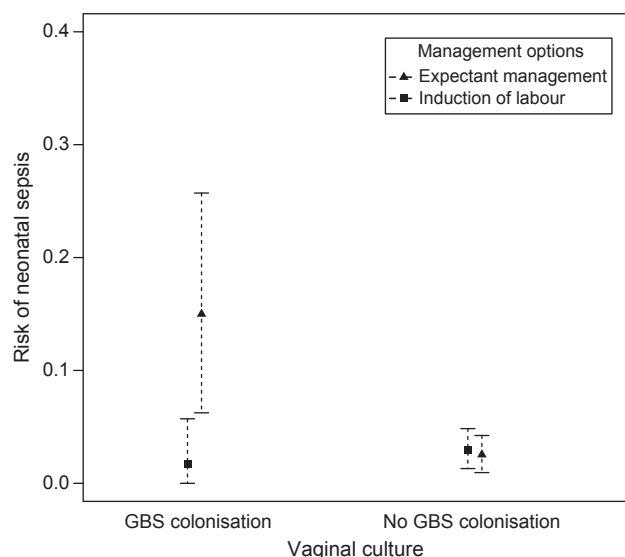**Mean difference with 95% CI.

Figure 1. The association between vaginal GBS colonisation and the risk of early onset neonatal sepsis after expectant management and induction of labour. The dashed lines show the 95% confidence interval around the risk estimates.
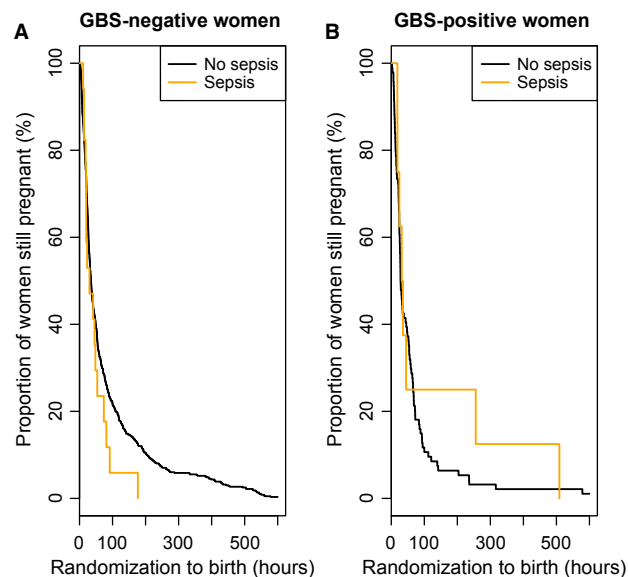

Figure 2. Kaplan–Meier curves of gestational age at delivery and early onset neonatal sepsis in GBS-negative and GBS-positive women.

benefit from immediate delivery could not be investigated in our study. Future studies may need to clarify whether a vaginal–anal swab performs better than a vaginal swab alone in terms of treatment selection.

Moreover, the original PPROMEXIL trials and our analyses were not powered to detect any possible differences in the risk of rare outcomes such as maternal sepsis.

Interpretation

Considering that the result of GBS culture is available within 18–72 hours, the GBS-based strategy proposed here may introduce some delay in inducing labour for women who turn out to be GBS-positive. However, in our trials women were entered into the study at least 24 hours after the rupture of membranes, which is roughly equivalent to the delay which results from GBS culture. Therefore, we think that selecting patients based on a GBS culture may still be a reasonable strategy. However, a PCR assay is available for the detection of GBS, which gives an immediate result with a promising sensitivity of 98.5%, at a specificity of 99.6%, a positive predictive value of 97.8%, and a negative predictive value of 99.7%.[22] This rapid test could be a preferable method and maximise the benefits of inducing labour for the GBS-positive women.

If the preliminary findings of this analysis are confirmed, we propose a GBS-based treatment selection strategy in near term PPROM women. In this strategy, all women are first evaluated for vaginal GBS colonisation at the time of presentation after PPROM and receive empirical antibiotic treatment for GBS while awaiting the evaluation result. If GBS status turns out positive, they undergo immediate delivery. Women with a negative GBS status may be managed expectantly, with a delay of induction of labour until 37 weeks.

Expected impact of a GBS-based treatment strategy

We estimate that by applying the proposed GBS-based treatment strategy in a population of women with a similar GBS colonisation rate of about 15%, the neonatal sepsis rate would potentially be 2.4% (95% CI 1–4). This is approximately 2% lower than with a strategy of managing all women expectantly (Figure 3A). As, in a GBS-based strategy, immediate delivery is performed only in women who have GBS colonisation, the term delivery (>37 weeks) rate would be about 12%, which is slightly less than if all women were managed expectantly (15%), but significantly higher than if they had undergone immediate delivery (1.9%) (Figure 3B). Correspondingly, compared with a strategy of inducing labour for all, the GBS-based strategy could result in about a 1% reduction in RDS rate (from 7.8 to 6.5; Figure 3C), a 7.1% reduction in neonatal hypoglycaemia rate (from 16.4 to 9.5; Figure 3D), a 7.5% reduction in neonatal hyperbilirubinaemia rate (from 32.0 to 24.5; Figure 3E) and a 1.9% reduction in NICU admission rate (from 7.9 to 6.0; Figure 3F). Our analysis also showed that the average length of hospital stay could be reduced by a day, from 7.4 to 6.4 days.

We observed that immediate delivery reduced the risk of clinical chorioamnionitis in both GBS-positive and GBS-negative women (Figure 3G). Therefore, a strategy of immediate delivery in only GBS-positive woman would

Table 3. The distribution of antibiotic prophylaxis and the occurrence of early onset neonatal sepsis in strata of GBS colonisation and the trial treatments

Vaginal culture	Group	Antibiotic prophylaxis		Total (%)	Early onset neonatal sepsis	
		During admission*	During delivery**		n	Rate (%)
GBS$^+$	EM	−	−	5 (11)	1	20
		−	+	5 (11)	1	20
		+	−	5 (11)	1	20
		+	+	30 (67)	4	13
	IoL	−	−	17 (30)	1	6
		−	+	4 (7)	0	0
		+	−	5 (9)	0	0
		+	+	30 (54)	0	0
GBS$^-$	EM	−	−	192 (63)	5	3
		−	+	19 (6)	1	5
		+	−	45 (15)	0	0
		+	+	49 (16)	2	4
	IoL	−	−	192 (63)	4	2
		−	+	22 (7)	2	9
		+	−	33 (11)	1	3
		+	+	56 (18)	2	3

*Augmentin 625 mg orally every 6 hours (or 1200 mg intravenously every 8 hours); penicillin 2 500 000 IE every 4 hours, erythromycin 250 mg every 6 hours, amoxicillin 500 mg (orally) or 1000 mg (intravenously) every 8 hours.

**Amoxicillin 500 mg (orally) or 1000 mg (intravenously) every 8 hours, penicillin 2 500 000 IE every 4 hours and erythromycin 250 mg every 6 hours.

result in a 4.6% risk of clinical chorioamnionitis, which would be comparable to a strategy of expectant management for all (5.3%) but would be significantly higher than a strategy of inducing labour for all (1.9%). The caesarean delivery rate could also be slightly higher in the GBS-based strategy than in the two other strategies (Figure 3E).

Chorioamnionitis is a risk factor for postpartum endometritis and adverse neonatal outcomes. If the proposed strategy results in higher chorioamnionitis rates than an induction for all strategy, it might also be associated with an increase in the risk of postpartum endometritis and adverse neonatal outcomes. Nevertheless, the observed rate of endometritis in the trial participants was very low in both trial arms, 1% in women managed expectantly and 0.5% in women in whom labour was induced (Table 2), suggesting that the risk of this complication could be limited.

Our proposed GBS-based strategy includes a combination of immediate delivery and antibiotic prophylaxis. However, we could not estimate the effect of antibiotic prophylaxis in this study. As a consequence, all the presented estimates of the impact of the GBS-based strategy were calculated without this component and may be biased.

Moreover, the rate of RDS is about twice as high in babies delivered immediately with GBS colonisation compared with expectant management. This might be reduced without increasing infection rates by using intravenous penicillin prophylaxis for 5–7 days before delivery. This alternative strategy should also be evaluated in further studies.

Guidelines concerning this clinical dilemma in near term PROM women are not straightforward. The ACOG guideline recommends induction of labour if PPROM occurs at or beyond 34 weeks of gestation.[23] The British RCOG guideline states that delivery should be considered from 34 weeks of gestation onwards.[7] The Dutch NVOG guideline advises expectant management until 35 gestational weeks (if there are no maternal or fetal indications for immediate delivery), induction of labour should be discussed with the woman from 35 weeks onwards, and it is strongly recommended beyond 37 weeks of gestation.[7]

Our proposed decision rule is based on an exploratory analysis; validation of these findings in another independent trial would add to the credibility of the findings. To our knowledge, the PPROMT trial is a randomised trial of immediate delivery versus expectant management in 1800 women with PPROM close to term in Australia which is currently recruiting patients.[24] An attractive option would be to analyse this trial when it is available in the same way, to see whether our findings can be replicated. Otherwise, a new relatively small randomised trial could be planned in women with GBS colonisation to validate the superiority of
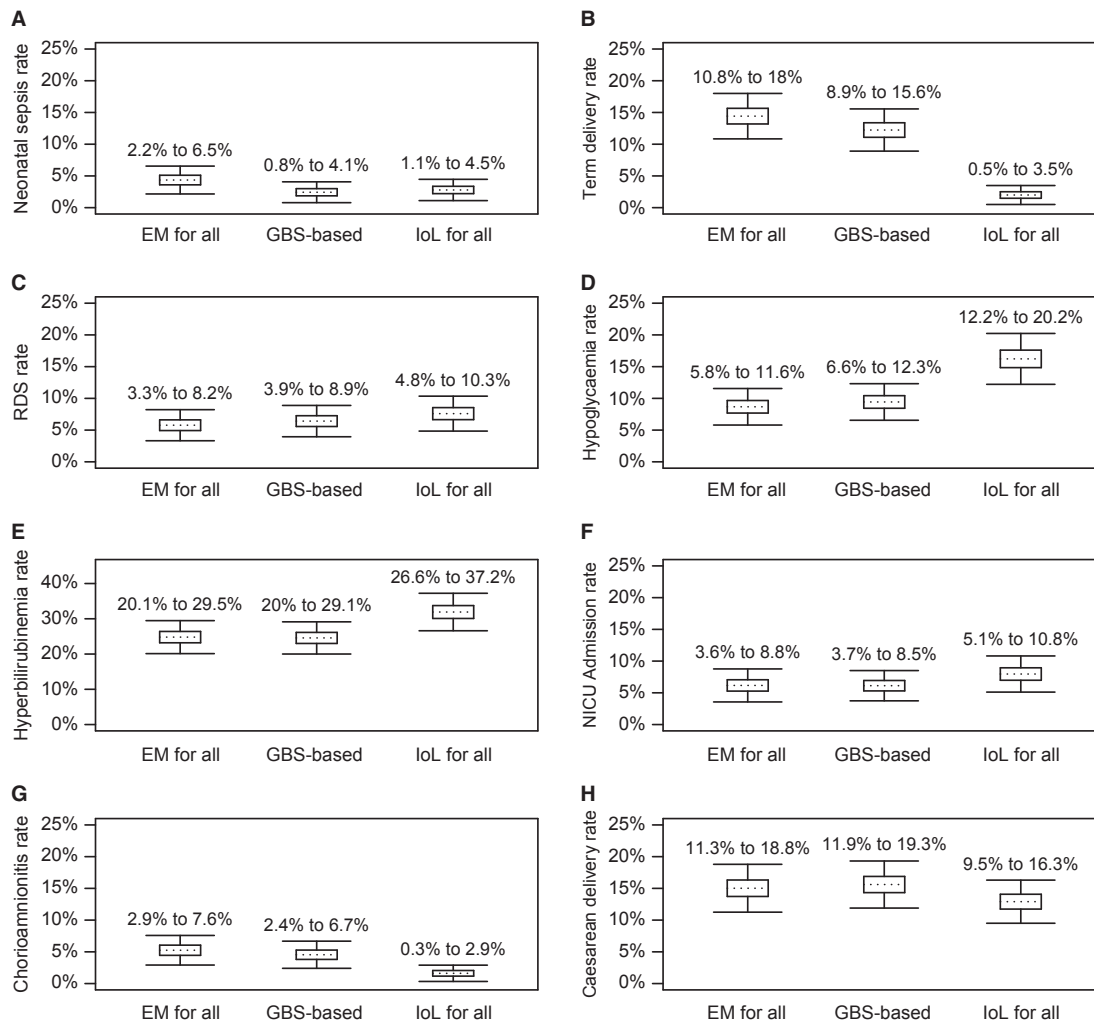
Figure 3. Impact of a GBS-based labour induction strategy compared with the strategy of induction of labour (IoL) in all or expectant management (EM) in all on the rate of (A) early onset neonatal sepsis, (B) term delivery, (C) respiratory distress syndrome (RDS), (D) hypoglycaemia, (E) hyperbilirubinaemia, (F) NICU admission, (G) clinical chorioamnionitis, and (H) caesarean delivery rate. Boxes depict quartiles of the risk and the lines extending vertically from the boxes indicate 95% confidence intervals, which are also presented above each plot.

immediate delivery against expectant management. Evaluation of the cost-effectiveness of the proposed decision rule is also another important step.

Conclusion

If our preliminary findings are confirmed, we suggest a GBS-based immediate delivery strategy in women with PPROM between 34 and 37 weeks, in which women are tested for GBS colonisation status and receive empirical antibiotic treatment for GBS while awaiting culture results and, if positive, undergo immediate delivery, irrespective of other factors. Women with a negative GBS status can be managed expectantly, with a delay of induction of labour until 37 weeks. Based on the observed outcomes in the PPROMEXIL trials, we estimated that this simple

GBS-based strategy could result in an early onset neonatal sepsis rate comparable to that with a strategy of inducing labour in all women, while avoiding 86% of immediate delivery in low risk patients, Consequently, this would prevent 10% of avoidable preterm deliveries, resulting in lower RDS, hypoglycaemia and hyperbilirubinaemia rates, and a shorter neonatal hospital stay.

Disclosure of interests
We declare that we have no conflicts of interest.

Contribution to authorship
Conceived and designed the study: PT, BWJM, CW. Collected the data: DPvdH, SMCV, MTMF, CJMdG, JJD, MAO, CW, KWMB, MP, MW, BMA, JMS, BNB, ALMM, BWJM. Analysed the data: PT, MHZ, DPvdH, PMB,

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Baseline characteristics of the participants of PPROMEXIL trials.

Table S2. The relationship between other potential treatment selection factors and early onset neonatal sepsis in each trial arm.

Figure S1. Trial profile. ∎

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