Immediate delivery compared with expectant management after preterm pre-labour rupture of the membranes close to term (PPROMT trial): a randomised controlled trial

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Summary

Background Preterm pre-labour ruptured membranes close to term is associated with increased risk of neonatal infection, but immediate delivery is associated with risks of prematurity. The balance of risks is unclear. We aimed to establish whether immediate birth in singleton pregnancies with ruptured membranes close to term reduces neonatal infection without increasing other morbidity.

Methods The PPROMT trial was a multicentre randomised controlled trial done at 65 centres across 11 countries. Women aged over 16 years with singleton pregnancies and ruptured membranes before the onset of labour between 34 weeks and 36 weeks and 6 days weeks who had no signs of infection were included. Women were randomly assigned (1:1) by a computer-generated randomisation schedule with variable block sizes, stratified by centre, to immediate delivery or expectant management. The primary outcome was the incidence of neonatal sepsis. Secondary infant outcomes included a composite neonatal morbidity and mortality indicator (ie, sepsis, mechanical ventilation ≥24 h, stillbirth, or neonatal death); respiratory distress syndrome; any mechanical ventilation; and duration of stay in a neonatal intensive or special care unit. Secondary maternal outcomes included antepartum or intrapartum haemorrhage, intrapartum fever, postpartum treatment with antibiotics, and mode of delivery. Women and caregivers could not be masked, but those adjudicating on the primary outcome were masked to group allocation. Analyses were by intention to treat. This trial is registered with the International Clinical Trials Registry, number ISRCTN44485060.

Findings Between May 28, 2004, and June 30, 2013, 1839 women were recruited and randomly assigned: 924 to the immediate birth group and 915 to the expectant management group. One woman in the immediate birth group and three in the expectant group were excluded from the primary analyses. Neonatal sepsis occurred in 23 (2%) of 923 neonates whose mothers were assigned to immediate birth and 29 (3%) of 912 neonates of mothers assigned to expectant management (relative risk [RR] 0·8, 95% CI 0·5–1·3; p=0·37). The composite secondary outcome of neonatal morbidity and mortality occurred in 73 (8%) of 923 neonates of mothers assigned to immediate delivery and 61 (7%) of 911 neonates of mothers assigned to expectant management (RR 1·2, 95% CI 0·9–1·6; p=0·32). However, neonates born to mothers in the immediate delivery group had increased rates of respiratory distress (76 [8%] of 919 *vs* 47 [5%] of 910, RR 1·6, 95% CI 1·1–2·30; p=0·008) and any mechanical ventilation (114 [12%] of 923 *vs* 83 [9%] of 912, RR 1·4, 95% CI 1·0–1·8; p=0·02) and spent more time in intensive care (median 4·0 days [IQR 0·0–10·0] *vs* 2·0 days [0·0–7·0]; p<0·0001) compared with neonates born to mothers in the expectant management group. Compared with women assigned to the immediate delivery group, those assigned to the expectant management group had higher risks of antepartum or intrapartum haemorrhage (RR 0·6, 95% CI 0·4–0·9), intrapartum fever (0·4, 0·2–0·9), and use of postpartum antibiotics (0·8, 0·7–1·0), and longer hospital stay (p<0·0001), but a lower risk of caesarean delivery (RR 1·4, 95% CI 1·2–1·7).

Interpretation In the absence of overt signs of infection or fetal compromise, a policy of expectant management with appropriate surveillance of maternal and fetal wellbeing should be followed in pregnant women who present with ruptured membranes close to term.

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Introduction

Pre-labour rupture of the membranes (ie, rupture of the membranes before the onset of labour) occurs in 20% of all births and 40% of all preterm births.[1] At term, there is good evidence that immediate delivery is associated with a lower incidence of maternal infection and increased maternal satisfaction compared with expectant management, with no attendant risks of perinatal morbidity or mortality.[2] By contrast, the optimum management of women with preterm pre-labour rupture of membranes before 37 weeks is not clear.[3]

Practice varies substantially internationally, particularly in women who present near term (ie, beyond 34 weeks gestation).[4–6] Planned immediate delivery is both

practised[5] and recommended by the American College of Obstetricians and Gynecologists and Royal College of Obstetrics and Gynaecology on the basis of such conclusions as "at 34 0/7 weeks or greater gestation, delivery is recommended for all women with ruptured membranes",[7] and "delivery should be considered at 34 weeks of gestation".[8] These conclusions are despite the recognition that such recommendations are "based on limited and inconsistent scientific evidence".[7]

Therefore, unlike premature rupture of membranes at term, preterm premature rupture of membranes continues to pose a clinical dilemma. The risks of delay, such as placental abruption, ascending infection, intrapartum fetal distress, and cord prolapse,[9,10] need to be balanced against the attendant risk of iatrogenic prematurity from immediate delivery. At extreme preterm gestations—when the fetus has reached or is close to viability (23–30 weeks gestation)—in the absence of established infection or maternal or fetal compromise, there is unanimity that expectant management is desirable[6] because preterm fetuses born before 30 weeks have an increased risk of neonatal mortality, intraventricular haemorrhage, hyaline membrane disease, and necrotising enterocolitis. However, these risks are reduced as the gestational age extends towards term.[11] Recommendations for immediate delivery after preterm pre-labour ruptured membranes close to term need to be backed up by good clinical evidence because even mild prematurity is associated with a substantial health burden, both in the short and long term.[12]

We undertook the PPROMT trial—a pragmatic international multicentre randomised controlled trial—to establish the optimum management of birth after preterm pre-labour rupture of the membranes close to term by comparing immediate delivery with expectant management.

Methods

Study design and participants

The study took place at 65 centres in 11 countries (Australia, New Zealand, Argentina, South Africa, Brazil, UK, Norway, Egypt, Uruguay, Poland, and Romania) between May 28, 2004, and June 30, 2013 (appendix). The study protocol has been published previously.[13] All participating centres had the facilities to provide care for mothers and neonates born at 34 weeks, including the availability of respiratory support.

Eligible women were aged over 16 years with a singleton pregnancy and clinically suspected ruptured membranes between 34 weeks and 36 weeks and 6 days of gestation. Women who presented with ruptured membranes earlier in pregnancy became eligible on reaching 34 weeks of gestation. Exclusion criteria were established labour, chorioamnionitis, meconium staining, or any other contraindication to continuing the pregnancy. Group B streptococcus vaginal colonisation was not an exclusion criterion. Eligible women were identified by a local research coordinator or clinical staff and provided with the trial information sheet, and, after written informed consent, entry details were recorded on a trial entry form.

The study was approved by the institutional ethics review boards of each clinical site and the data coordinating centre (Royal North Shore Hospital, St Leonards, NSW, Australia; North Sydney Local Health District 0902-032M; Site Specific Assessment: 0904-082M). All participants gave written informed consent before enrolment.

Randomisation and masking

Women were randomly assigned (1:1) to an experimental group in which birth was planned immediately (immediate delivery group) or a control group in which participants awaited spontaneous onset of labour or birth was planned at term or if other indications arose (expectant management group). Randomisation was done via a central telephone service using a computer-generated randomisation schedule prepared by a researcher not involved in treatment allocation, with balanced, variable blocks (sizes 2, 4, and 6), stratified by centre. Masking to treatment allocation was not possible, but those adjudicating on the primary outcome of neonatal sepsis were masked to treatment allocation.

Procedures

Women in the immediate delivery group had delivery scheduled as close to randomisation as possible and preferably within 24 h. The mode of birth was identified

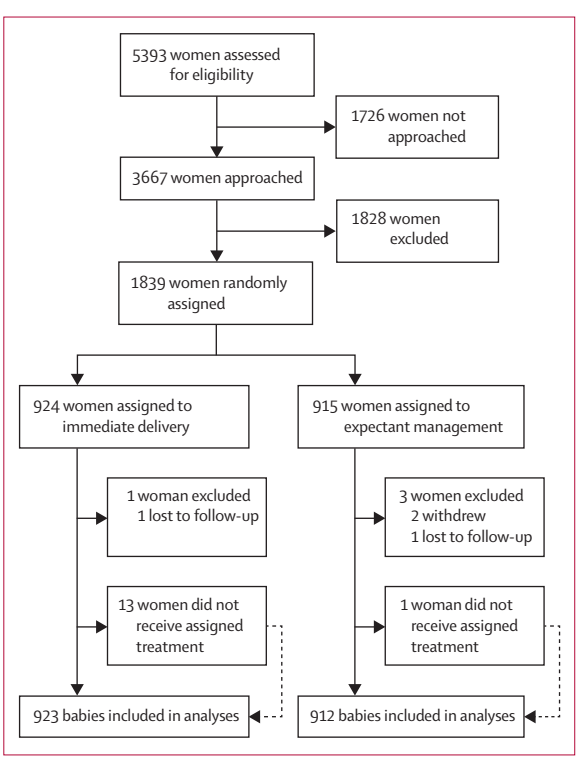

Figure 1: **Trial profile**

See Online for appendix

by usual obstetric indications. For women randomly assigned to expectant management, birth occurred after spontaneous labour, at term, or when the attending clinician felt that birth was mandated according to usual indications. Because there is no gold standard treatment with regards to inpatient or outpatient management after preterm pre-labour rupture of membranes, women were managed according to local guidelines. Throughout the recruitment period, antibiotics were deemed best practice for treatment of preterm pre-labour ruptured membranes,[14] and these were prescribed according to local protocols. Laboratory testing and other management was per usual hospital practice. Placental histology was encouraged but not uniformly requested.

	Immediate delivery (n=923)	Expectant management (n=912)
Maternal age (years)	27·9 (6·2)	28·0 (6·2)
Duration of pregnancy at rupture of membranes		
<28 weeks	13 (1%)	14 (2%)
28 weeks to 29 weeks and 6 days	14 (2%)	9 (1%)
30 weeks to 31 weeks and 6 days	21 (2%)	34 (4%)
32 weeks to 33 weeks and 6 days	161 (17%)	129 (14%)
34 weeks to 34 weeks and 6 days	212 (23%)	225 (25%)
35 weeks to 35 weeks and 6 days	279 (30%)	271 (30%)
36 weeks to 36 weeks and 6 days	223 (24%)	230 (25%)
Duration of pregnancy at randomisation		
34 weeks to 34 weeks and 6 days	363 (39%)	355 (39%)
35 weeks to 35 weeks and 6 days	278 (30%)	292 (32%)
36 weeks to 36 weeks and 6 days	282 (31%)	265 (29%)
PPROM >24 h before randomisation	328 (36%)	302 (33%)
Previous pregnancies		
0	426 (46%)	430 (47%)
1	232 (25%)	241 (26%)
≥2	265 (29%)	241 (26%)
Cephalic presentation	880 (95%)	876 (96%)
Previous caesarean delivery*	93 (10%)	85 (9%)
Previous PPROM or preterm delivery†	137 (15%)	125 (14%)
Previous stillbirth or neonatal death†	21 (2%)	24 (3%)
Pregnancy hypertension (onset ≥20 weeks)	24 (3%)	33 (4%)
Gestational diabetes	50 (5%)	48 (5%)
Antenatal urinary tract infection	99 (11%)	87 (10%)
Vaginal swab collected at randomisation‡	725 (79%)	707 (78%)
Any positive culture	186 (26%)	192 (27%)
Group B streptococcus positive	88 (12%)	83 (12%)
Antibiotics given§	795 (86%)	787 (86%)
Intravenous (with or without oral)¶	321 (35%)	286 (31%)
Oral only¶	473 (51%)	500 (55%)
Steroids given	383 (41%)	354 (39%)

Data are mean (SD), number (%), or n/N (%). Some percentages do not add up to 100 because of rounding. PPROM=preterm pre-labour rupture of membranes. *Data missing for one patient in each group. †Data missing for one patient in the expectant management group. ‡Culture resulting from vaginal swab after PPROM and at or before randomisation. §Antibiotics at randomisation or in the preceding 48 h. ¶Data for route of administration missing for one patient in the immediate delivery group and one in the expectant management group.

Table 1: **Baseline maternal and pregnancy characteristics**

In patients for whom the time of day of random assignment or preterm pre-labour rupture of membranes was missing, the hours from preterm pre-labour rupture of membranes to randomisation was imputed as the difference in days, plus 9 h, which was the median for participants without missing data. Only cultures from vaginal swabs taken between preterm pre-labour rupture of membranes and randomisation were assessed and findings of normal vaginal flora and lactobacilli were classified as negative. All other patient characteristics were reported by the participants at trial entry or collected from medical records.

Outcomes

The primary outcome was the incidence of either definite or probable neonatal sepsis established by comprehensive review of the neonatal data by a central adjudication committee masked to treatment allocation.

Definite systemic neonatal sepsis was defined as a positive culture of a known pathogen from blood or cerebrospinal fluid (CSF) for which the baby was treated with antibiotics for 5 or more days (or died before 5 days), and the presence of one or more clinical signs of infection. For organisms of low virulence or high likelihood of skin contamination of the blood culture, such as coagulase-negative *Staphylococcus*, both a positive blood culture and an abnormal full blood count or abnormal C-reactive protein were required. An abnormal full blood count consisted of abnormal white cell count lower than 5×10^9 cells per L or more than 30×10^9 cells per L, platelet count lower than 100 000 cells per mL, neutrophil count lower than $1{\cdot}5\times10^9$ cells per L or immature-to-total neutrophil count ratio greater than 0·2.[15,16] A C-reactive protein concentration higher than 95 nmol/L (10 mg/L) was regarded as abnormal.[17,18] Clinical signs of infection were respiratory distress (ie, requiring ventilation, continuous positive airway pressure, or supplemental oxygen for more than 1 h), apnoea, lethargy, abnormal level of consciousness, circulatory compromise (including hypotension, poor perfusion, need for inotropic support, or volume expansion), temperature instability (temperature <36°C or ≥38°C), or a combination thereof.

Probable neonatal sepsis was defined as the presence of clinical signs for which the baby was treated with antibiotics for 5 or more days together with one or more of an abnormal full blood count; abnormal C-reactive protein; positive Group B streptococcus antigen on bladder tap urine, blood, or CSF; elevated CSF white cell count[5] (CSF white cell count $>100\times10^6$ cells per L); growth of a known virulent pathogen (eg, Group B streptococcus, *Escherichia coli*, or Listeria) from a surface swab; or a histological diagnosis of pneumonia in an early neonatal death.

Prespecified secondary infant outcomes were a composite neonatal morbidity and mortality indicator (sepsis, mechanical ventilation ≥24 h, stillbirth, or neonatal death); respiratory distress syndrome; perinatal mortality; pneumonia; any mechanical ventilation (ie, intermittent positive pressure ventilation, continuous positive airway pressure, or high frequency ventilation) and any mechanical ventilation for at least 24 h; duration of stay in a neonatal intensive or special care unit; duration of stay in hospital; birthweight; small for gestational age (<10th percentile size); Apgar score lower than 7 at 5 min; antibiotics in the first 48 h; lumbar puncture; circulatory compromise needing arterial line, fluid bolus, or inotropic support; and receiving breast milk at discharge, either as exclusive or mixed feeding.[13,19] Neonatal outcomes were obtained from diagnoses reported by the attending clinician in the medical records and collected for 28 days or until discharge.

Secondary maternal outcomes were antepartum or intrapartum haemorrhage, antepartum or postpartum thrombosis, cord prolapse, postpartum treatment with antibiotics, intrapartum fever (pyrexia ≥38·5°C), postpartum haemorrhage (>1000 mL), mode of delivery, onset of labour, and duration of hospital stay (total days from randomisation to delivery and from delivery to discharge or transfer).[13,19] Chorioamnionitis was a trial entry exclusion criteria, but this secondary outcome is reported among the women with expectant management. Placental swabs and histological samples were also collected if available.

Statistical analysis

A sample size of 1812 (ie, 906 patients per group) was necessary to detect a reduction in neonatal sepsis of 5% in the expectant management group compared with 2·5% in the immediate delivery group, with a two-sided 5% significance level and a power of 80%. One interim analysis was done after 506 women had been recruited, before submission for further funding on Feb 25, 2010, by the independent data monitoring committee who reviewed the findings and recommended that the study continue. A difference of at least 3 SDs in an interim analysis of a major endpoint was needed to justify stopping the trial.

All analyses were by intention to treat. No participants were excluded from the primary intention-to-treat analysis for protocol violations. The primary outcome was calculated as event numbers and percentages by treatment allocation. Effect measures (relative risks [RRs]) were calculated with 95% CIs, with expectant management as the reference group. Comparison of mean birthweight was done using a *t* test. Comparisons of maternal and infant length of stay (in days) were done using non-parametric Wilcoxon Mann-Whitney tests. There was no imputation for missing outcome data. Participants with missing data were excluded from calculation of secondary outcomes, with the numbers missing reported by group.

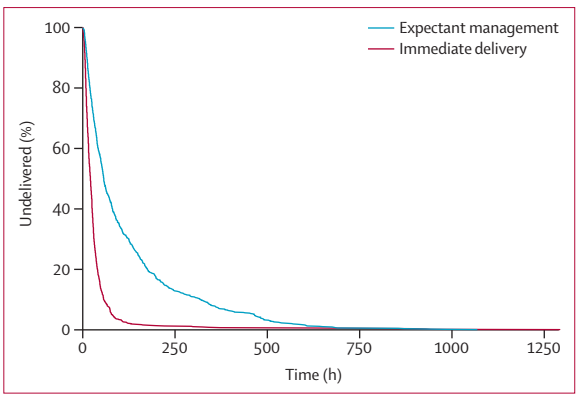

Figure 2: **Time from randomisation to delivery**

	Immediate delivery (n=923)	Expectant management (n=912)	p value
Onset of labour			
Spontaneous	180 (20%)	549 (60%)	<0·0001*
Induced	647 (70%)	310 (34%)	<0·0001
Pre-labour caesarean	96 (10%)	53 (6%)	0·0003
Cephalic presentation at birth	874 (95%)	879 (96%)	0·08
Gestational age at birth			
34 weeks	315 (34%)	161 (18%)	<0·0001†
35 weeks	273 (30%)	268 (29%)	0·93
36 weeks	306 (33%)	295 (32%)	0·71
37 weeks	23 (2%)	174 (19%)	<0·0001
38 weeks	1 (<1%)	7 (1%)	0·03
39 weeks	1 (<1%)	2 (<1%)	0·37
40 weeks	1 (<1%)	5 (1%)	0·09
41 weeks	3 (<1%)	0	0·13

Data are number (%). Some percentages do not add up to 100 because of rounding. *p value for difference in mode of delivery across treatment groups. †Wilcoxon p value for test of null hypothesis of no difference in distribution between treatment arms.

Table 2: **Labour characteristics**

Clinically meaningful criteria were specified a priori for assessment of the adequacy of the randomisation, and whether adjusted analyses were needed.[19] These were (1) a difference of more than 15% between groups in the median duration from premature rupture of membranes to randomisation; and (2) more than a 3-day difference in median gestational age at randomisation. If either criteria were met, adjusted logistic regression would be needed. No adjustment to the level of statistical significance was made for multiple comparisons.

Prespecified subgroup analyses for the primary outcome of neonatal sepsis comprised time from preterm pre-labour rupture of membranes until randomisation (<48 h, ≥48 h), gestational week of preterm pre-labour rupture of membranes (<34 weeks, ≥34 weeks), vaginal swab culture result (Group B streptococcus, other abnormal flora), and antibiotic use at randomisation.

	Immediate delivery	Expectant management	Relative risk (95% CI)	p value
Primary outcome				
Neonatal sepsis	23/923 (2%)	29/912 (3%)	0·8 (0·5–1·3)	0·37
Secondary infant outcomes				
Composite of neonatal morbidity and mortality (sepsis, ventilation ≥24 h, or death)	73/923 (8%)	61/911 (7%)	1·2 (0·9–1·6)	0·32
Perinatal or infant mortality	3/923 (<1%)	3/910 (<1%)	1·0 (0·2–4·9)	0·31
Respiratory distress syndrome	76/919 (8%)	47/910 (5%)	1·6 (1·1–2·3)	0·008
Pneumonia	3/919 (<1%)	4/910 (<1%)	0·7 (0·2–3·3)	0·27
Any mechanical ventilation (CPAP or ETT)	114/923 (12%)	83/912 (9%)	1·4 (1·0–1·8)	0·02
Mechanical ventilation for ≥24 h	56/923 (6%)	37/912 (4%)	1·5 (1·0–2·2)	0·05
Birthweight (g)	2574·7 (400·3)	2673·2 (405·5)	..	<0·0001*
SGA (<10th percentile size)	32/922 (3%)	35/906 (4%)	0·9 (0·6–1·4)	0·66
Apgar score <7 at 5 min	15/918 (2%)	18/906 (2%)	0·8 (0·4–1·6)	0·57
Antibiotics in first 48 h	422/920 (46%)	398/910 (44%)	1·0 (0·9–1·2)	0·36
Lumbar puncture	33/921 (4%)	38/911 (4%)	0·9 (0·5–1·4)	0·51
Circulatory compromise	11/921 (1%)	13/910 (1%)	0·8 (0·4–1·9)	0·66
Days in hospital	6·0 (3·0–10·0)	4·0 (3·0–8·0)	..	<0·0001†
Days in SCN or NICU	4·0 (0·0–10·0)	2·0 (0·0–7·0)	..	<0·0001†
Receiving breastmilk at discharge	695/883 (79%)	712/877 (81%)	1·0 (0·9–1·0)	0·19
Secondary maternal and pregnancy outcomes‡				
Antepartum or intrapartum haemorrhage	27/923 (3%)	46/912 (5%)	0·6 (0·4–0·9)	0·02
Cord prolapse	3/923 (<1%)	2/912 (<1%)	1·5 (0·2–8·8)	0·31
Intrapartum fever	7/923 (1%)	18/912 (2%)	0·4 (0·2–0·9)	0·02
Post-partum antibiotics	151/923 (16%)	180/912 (20%)	0·8 (0·7–1·0)	0·06
Post-partum haemorrhage	29/803 (4%)	27/782 (3%)	1·0 (0·6–1·8)	0·56
Duration of hospital stay	5·0 (3·0–7·0)	6·0 (4·0–9·0)	..	<0·0001†
Caesarean delivery	239/923 (26%)	169/912 (19%)	1·4 (1·2–1·7)	0·0001
After spontaneous labour	24/180 (13%)	54/549 (10%)	1·4 (0·9–2·1)	0·19
After labour induction	119/647 (18%)	62/310 (20%)	0·9 (0·7–1·2)	0·55
Before labour	96/923 (10%)	53/912 (6%)	1·8 (1·3–2·5)	0·0003

Data are n/N (%), mean (SD), or median (IQR). p values are from χ^2 test unless otherwise specified. CPAP=continuous positive airway pressure. ETT=endotracheal tube. NICU=neonatal intensive care unit. SGA=small for gestational age. SCN=special care nursery. *t test. †Wilcoxon p value for test of null hypothesis of no difference in distribution between groups. ‡The secondary endpoint of onset of labour is shown in table 2; there were no events reported for the secondary endpoints of antepartum or postpartum thrombosis.

Table 3: **Infant and maternal outcomes**

This trial is registered with the International Clinical Trials Registry, number ISRCTN44485060.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. JAP and CSA had full access to all the data in the study and JMM had final responsibility for the decision to submit for publication.

Results

Between May 28, 2004, and June 30, 2013, 1839 women were recruited into the PPROMT trial: 924 to the immediate delivery group and 915 to the expectant management group (figure 1). 13 women in the immediate delivery group did not receive the allocated intervention compared with one in the expectant management group. One woman was lost to follow-up in the immediate birth group and two women withdrew and one was lost to follow-up in the expectant management group. Therefore, the primary outcome was assessed for 1835 (>99%) neonates: 923 in the immediate delivery group and 912 in the expectant management group.

The baseline characteristics of the two groups were similar (table 1). The median gestational age at randomisation in each group was 247 days (IQR immediate delivery 241–252 days; expectant management 241–253 days) and the median time from ruptured membranes to randomisation was 30·4 h (IQR 10–76) in the immediate delivery group and 26·4 h (9–62; 13·4% lower) in the expectant management group, and so no adjusted analyses were done. Figure 2 shows the difference in time between randomisation and delivery for the two groups.

At the time of random assignment, 725 (79%) women assigned to immediate delivery had a swab collected and 186 (26%) isolated an abnormal organism, including

88 with Group B streptococcus. Similarly, 707 (78%) women managed expectantly had a swab collected and 192 (27%) had an abnormal organism isolated from the swab, including 83 with Group B streptococcus (table 1). At random assignment, about 40% of women in each group had received antenatal steroids and 86% had received antibiotics in the previous 48 h (table 1). Any antibiotics were prescribed before delivery for 852 (92%) women in the immediate delivery group and 844 (93%) in the expectant management group. In the expectant management group, 688 (75%) women were managed in hospital and the remainder were sent home between random assignment and delivery.

Women randomly assigned to expectant management were more likely to deliver after the spontaneous onset of labour (p<0·0001) and deliver at a later gestation (p>0·0001) than those assigned to immediate delivery (table 2). Six women randomly assigned to immediate delivery delivered after 37 weeks, including five who were found not to have premature rupture of membranes after randomisation and one who self-discharged from the enrolling hospital and gave birth later.

The primary outcome of definite or probable neonatal sepsis occurred in 23 (2%) of the 923 neonates whose mothers were assigned to immediate delivery and 29 (3%) of 912 neonates whose mothers were assigned expectant management (RR 0·8, 95% CI 0·5–1·3; table 3). There was no significant difference in the composite measure of neonatal morbidity and mortality (ie, sepsis, ventilation for at least 24 h, or perinatal death), which occurred in 73 (8%) of 923 neonates whose mothers were assigned to immediate delivery and 61 (7%) of 911 neonates whose mothers were managed expectantly (RR 1·2, 95% CI 0·9–1·6). However, neonates born after immediate delivery had significantly lower birthweight (p<0·0001), increased risk of respiratory distress (RR 1·6, 95% CI 1·1–2·3) and mechanical ventilation (1·4, 1·0–1·8), and spent more time in neonatal intensive care units or special care nurseries (p<0·0001; table 3). All other secondary infant outcomes were non-significant (table 3).

Six deaths occurred, three in each group (table 3). Among women randomly assigned to immediate delivery, the deaths were from sudden infant death syndrome (31 days of age), congenital abnormality (3 weeks of age), and fetal death at 35 weeks gestation associated with acute suppurative chorioamnionitis according to the autopsy report. Among women randomly assigned to expectant management, the deaths were from sudden infant death syndrome (5 weeks of age), a congenital abnormality (12 weeks of age), and one of unknown cause (24 h of age).

Compared with expectant management, immediate delivery was associated with a reduced likelihood of antepartum haemorrhage (27 of 923 [3%] *vs* 46 of 912 [5%]; RR 0·6, 95% CI 0·4–0·9) and intrapartum fever (seven [1%] *vs* 18 [2%]; 0·4, 0·2–0·9; table 3). 239 (26%) women assigned to immediate delivery had caesarean delivery compared with 169 (19%) of those assigned to expectant management (RR 1·4, 95% CI 1·2–1·7). 56 (6%) neonates of women in the expectant management group were delivered because of chorioamnionitis after random assignment. All other secondary maternal and pregnancy outcomes were non-significant (table 3).

Compared with expectant management, immediate delivery had no effect on sepsis, regardless of the gestational age at preterm pre-labour rupture of membranes ($p_{interaction}$=0·43), the duration of preterm pre-labour rupture of membranes ($p_{interaction}$=0·07), or the use of antibiotics at the time of preterm pre-labour rupture of membranes ($p_{interaction}$=0·64; table 4). For women assigned to immediate delivery, neonatal sepsis occurred in four of 186 (2%) neonates born to women who had a positive culture on their vaginal swab compared with nine of 192 (5%) neonates born to mothers with a positive culture and managed expectantly (RR 0·4, 95% CI 0·1–1·4; table 4). Similarly, neonatal sepsis did not differ between groups for those women with Group B streptococcus at the time of random assignment (RR 0·9, 95% CI 0·2–4·5). Of women with Group B streptococcus isolated, all of those assigned to early planned birth and 87 (99%) of 88 assigned to expectant management received intravenous antibiotics before birth.

	Immediate delivery	Expectant management	Relative risk (95% CI)	$p_{interaction}$
Duration from PPROM to randomisation				
<48 h	19/595 (3%)	18/610 (3%)	1·1 (0·6–2·0)	0·07
≥48 h	4/328 (1%)	11/302 (4%)	0·3 (0·1–1·0)	..
Gestational age at PPROM				
<34 weeks	4/209 (2%)	7/186 (4%)	0·5 (0·2–1·7)	0·43
≥34 weeks	19/714 (3%)	22/726 (3%)	0·9 (0·5–1·6)	..
Positive vaginal culture after PPROM*				
Any culture positive	4/186 (2%)	9/192 (5%)	0·5 (0·1–1·5)	0·26
Group B streptococcus	3/88 (3%)	3/83 (4%)	0·9 (0·2–4·5)	0·25
Other organism	1/98 (1%)	6/109 (6%)	0·2 (0·0–1·5)	..
Negative or no culture collected	19/737 (3%)	20/720 (3%)	0·9 (0·5–1·7)	..
Maternal antibiotics at randomisation†				
Yes	20/795 (3%)	24/787 (3%)	0·8 (0·5–1·5)	0·64
No	3/127 (2%)	5/122 (4%)	0·6 (0·1–2·4)	..

Data are number (%). PPROM=preterm pre-labour rupture of membranes. *Culture from vaginal swab after PPROM and at or before randomisation. †Antibiotics at randomisation or in preceding 48 h.

Table 4: **Prespecified subgroup analyses for neonatal sepsis**

Discussion

The findings of this trial show that for women with ruptured membranes between 34 weeks and 36 weeks and 6 days of gestation who were carrying a single fetus and who had no contraindication for expectant management, immediate delivery increased neonatal complications with

Panel: Research in context

Systematic review

For management of pregnant women who present with ruptured membranes close to term, the risks of intrauterine sepsis associated with continuation of the pregnancy need to be balanced against the risks of prematurity if birth is planned immediately. We searched the Cochrane Pregnancy and Childbirth Group's Trials Register and The Cochrane Central Register of Controlled Trials (The Cochrane Library) until Jan 29, 2015, Medline (1996 to Jan 29, 2015), and Embase (1974 to Jan 29, 2015). We also searched reference lists of trials and other review articles identified from this initial search and from our records. We identified nine studies[3,20,21] that compared immediate planned birth with expectant management in women with ruptured membranes between 34 and 37 weeks. Of these, seven were from 20–30 years ago,[3] when the practices used in the peripartum period were different and approaches to the use of antibiotics, corticosteroids for fetal lung maturation, and the ascertainment of pulmonary maturity through the use of lecithin:sphingomyelin ratio varied. Methods used in two more recent studies were representative of contemporary maternity practice.[20,21] Findings from our meta-analysis of these studies suggested that immediate birth does not reduce neonatal sepsis, but neither study was adequately powered and thus the have limited applicability.

Interpretation

The present study is, to our knowledge, the largest so far to assess immediate birth with expectant management in women with singleton pregnancies who presented with ruptured membranes close to term. Our findings show that immediate birth does not reduce neonatal sepsis, but does increase the likelihood of respiratory distress and mechanical ventilator support for the baby and caesarean section for the mother. There are some increased risks to the mother such that ongoing surveillance is needed. The results support the practice of expectant management in pregnant women with ruptured membranes close to term if there is no contraindication to extending the pregnancy.

no clinically significant decrease in neonatal sepsis. Therefore, in contrast to recent guideline recommendations,[7,8] we advocate that expectant management is preferred to immediate delivery in women with ruptured membranes close to term. Women need to be monitored because of the increased risk of antepartum haemorrhage and a greater likelihood of developing a fever.

This is, to our knowledge, the largest study to compare these two forms of accepted management (panel). Older studies that included women with premature rupture of membranes at preterm gestations did not show any reduction in neonatal sepsis or differences in neonatal morbidity with expectant management versus immediate delivery,[3] and two underpowered studies with inclusion criteria similar to the PPROMT trial, which were published whilst the present study was ongoing, reported that immediate delivery did not reduce neonatal sepsis compared with expectant management.[20,21] The investigators of these studies concluded that neither neonatal morbidity nor caesarean delivery were increased with immediate delivery compared with expectant management. The PPROMT trial is the most adequately powered study to show that immediate delivery does not reduce neonatal sepsis, but does increase the likelihood of several aspects of early neonatal morbidity, including respiratory distress syndrome, mechanical ventilation, and duration of stay in special care nurseries or neonatal intensive care units, and an increased likelihood of caesarean delivery. Conversely, expectant management resulted in a lengthier hospital stay for the mother because 688 (75%) of 912 were managed in hospital. Women managed expectantly have a greater incidence of antepartum haemorrhage and develop a fever requiring antibiotics. This is important information that care providers can discuss with women regarding best practice in this clinical situation. Furthermore, there are substantial implications for practice, and widespread adoption of expectant management after ruptured membranes close to term is likely to have substantial resource and economic benefits. We plan to assess the latter in different international settings.

The adoption of the practice of immediate delivery—advocated in recent guidelines[7,8]—is predicated on the basis of the fact that disability-free survival after early birth is high. However, there is increasing concern about the risks of adverse outcomes for late preterm neonates, with findings from studies showing an increased risk of neonatal morbidity,[22] re-admission to hospital in early childhood,[23] and academic difficulties in children at school age compared with neonates born at term.[24] These risks are thought to be associated with both gestational age and biological factors associated with the preterm birth, including preterm pre-labour rupture of membranes.[25] Immediate delivery does not seem to improve outcomes in preterm neonates and might exacerbate the risks of prematurity, especially in the absence of labour and at earlier gestational ages. Although expectant management in a potentially hostile intrauterine environment should be avoided, in a mother who is healthy, with no evidence of clinical chorioamnionitis, expectant management provides an opportunity for spontaneous labour to develop and for adaptive changes to occur in the neonate, resulting in a decreased risk of neonatal respiratory illness.[26] For some neonates, expectant management might also result in delivery at a substantially older gestational age. These factors might, in turn, result in a decrease in neonatal morbidity, decreased separation of mother and baby, improved proportion of breastfeeding mothers, and a reduction in risk of adverse childhood outcomes.

The delivery of expectant management was not prespecified in the PPROMT protocol, but was a pragmatic application of each hospital's current usual care. However, 73% of women were managed as inpatients, almost 90% received antibiotics before delivery, and about 40% were given antenatal steroids. Our findings suggest that expectant management should include careful monitoring of fever or other signs of maternal infection, symptoms of chorioamnionitis, and antepartum haemorrhage.

In addition to its size, the strengths of the PPROMT trial include the fact that it was centrally randomised, had near-complete follow-up, and was done across a range of international settings. Although the study recruited over a 10-year period, there have not been major changes in management, making the results widely generalisable. Many of the previous studies that assessed management of ruptured membranes were small and done before the widespread implementation of maternal antibiotic use to prolong latency and reduce short-term morbidity, including neonatal infection, in this population.[14,27–32] The PPROMT trial results, together with the results of the recent PPROMEXIL studies,[20,21] suggest expectant management provides benefits without incurring significant risk of harms to the neonate. However, some groups of women will need delivery after expectant management if there are signs of infection. Contrary to findings from a recent report,[33] we found that immediate delivery did not confer benefit on the women in whom Group B streptococcus was isolated from the genital tract. Such risk factors should be investigated further to identify specific indications for which immediate delivery is appropriate by undertaking an individual patient data meta-analysis of all those who participated in PPROMT and PPROMEXIL.

Contributors

JMM and CAC conceived the project. JMM and CLR wrote the first draft of the manuscript. JRB led the primary outcome adjudication committee. JAP and CSA prepared the data and did the statistical analysis. DMB collected data. All authors contributed to the design of the study and manuscript revision.

Declaration of interests

JMM, CLR, JRB, JAP, DMB, and CSA have received grants from the National Health and Medical Research Council (NHMRC). CAC has received grants from the Women's and Children's Hospital Foundation, Adelaide (SA, Australia). JGT declares no competing interests.

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