Immediate delivery compared with expectant management after preterm pre-labour rupture of the membranes close to term

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Abstract

Background

Pre-labor rupture of the membranes prior to but close to term is associated with an increased risk of neonatal infection, but labor induction is associated with risks of prematurity. The balance of risks is unclear.

Aims

To test the hypothesis that a policy of inducing labor reduces neonatal infection without increasing other morbidity.

Methods

A multicenter randomized controlled trial. Participants were women with ruptured membranes prior to the onset of labor between 34+0 and 36+6 weeks, and no clinical signs of infection. The experimental group had labor induced immediately. Participants in the control group awaited the spontaneous onset of labor. The primary outcome was definite or probably neonatal infection.

Main results. The induction policy did not reduce neonatal infection. 23/923 (2.5%) intervention and 29/912 (3.2%) expectant; RR 0.8 (95% CI 0.5 – 1.3). Rates of perinatal death (3 immediate v 3 expectant), ventilation more than 24 hours 56 (6.1%) v 37 (4.1%) or infection were combined into a predefined composite neonatal morbidity outcome 73 (7.9%) immediate v 61 (6.7%) expectant RR 1.2 (0.9-1.6). However babies born to the immediate delivery group had increased rates of respiratory distress (76 (8.3%) v 47 95.2%) RR 1.6 (1.1 – 2.30 and any mechanical ventilation 114 (12.4%) v 83 (9.1%), RR 1.4 (1.0-1.8) and spent more time in newborn intensive or special care median 4 v 2 days P = 0.001.

Conclusion: In the absence of overt signs of infection or fetal compromise an expectant policy with regard to labor induction should be followed.

Prelabor rupture of the membranes (rupture of the membranes prior to the onset of labor) occurs in 20% of all births and 40% of all preterm births. 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.[1] In contrast the optimal management of women with **preterm** prelabor rupture of membranes (PPROM) prior to 37 weeks, is not clear.[2]

There is substantial practice variation internationally particularly in women who present near term, beyond 34 weeks gestation.[3-5] Planned immediate delivery is both practiced[4] and recommended based upon conclusions that "compared with expectant management, induction of labor is associated with shorter latency to delivery and lower risk for maternal infection without excess risk for cesarean delivery".[6] This is despite recognition by professional bodies such as the American and British Colleges of Obstetricians and Gynecologists that such recommendations are "based on limited and inconsistent scientific evidence.[7,8]

Unlike PROM at term, pre-term PROM, therefore, continues to pose a clinical dilemma. The risks from delay such as placental abruption, ascending infection, intrapartum fetal distress and cord prolapse[9,10] need to be balanced against the risks of iatrogenic prematurity from immediate delivery. At extreme preterm gestations (less than 30 weeks), in the absence of established infection or maternal or fetal compromise, there is unanimity that expectant management is desirable[5] because the risk of neonatal mortality, intraventricular hemorrhage, hyaline membrane disease and necrotizing enterocolitis. However, tThese risksare reduced as the gestational age extends towards term.[11] Recommendations for immediate delivery following preterm ruptured membranes close to term require grounding in good clinical evidence as even mild prematurity is associated with a significant health burden both in the short and long term.[12] We undertook an international multicentre randomized controlled trial to establish the optimal management of birth following preterm premature rupture of the membranes close to term (PPROMT): comparing immediate delivery with expectant management, the PPROMT Trial (ISRCTN44485060)

Methods

Recruitment

Eligible women were aged over 16 with a singleton pregnancy and clinically suspected ruptured membranes between 34^0 weeks and 36^6 weeks gestation. Women who presented with ruptured membranes earlier in pregnancy became eligible if they reached 34 weeks gestation. Exclusion criteria were established labor, chorioamnionitis, meconium staining, or any other contraindication to continuing the pregnancy. Group B streptococcus (GBS) vaginal colonization was not an exclusion criterion. The study took place in 65 centers in 11 countries (Australia, New Zealand, Argentina, South Africa, Brazil, UK, Norway, Egypt, Uruguay, Poland, Romania) between May 2004 and June 2013. All participating centers had the facilities for mothers and babies born at 34 weeks, including respiratory support. The study was approved by the institutional ethics review boards of each clinical site. All participants gave written informed consent before enrollment.

Protocol[13]

Eligible women were identified by a local research coordinator or clinical staff, provided the trial information sheet, and after written informed consent entry details were recorded on a trial entry form and they were randomized via a central telephone service using a computer generated randomization schedule in a 1:1 ration in balanced blocks of variable size, stratified by center. An automated process collected basic patient identifying information and, after confirmation that entry into the study was sought, a study number and the treatment allocation was provided.

Participants were randomly assigned to immediate delivery or expectant management. The former group had delivery scheduled as close to randomization as possible and preferably within 24 hours. The mode of birth was determined by usual obstetric indications. For women randomized to expectant management, birth occurred after spontaneous labor, at term or when the attending clinician felt that birth was mandated according according to the usual indications. For much of the recruitment period antibiotics were considered best practice in the presence of preterm prelabor ruptured membranes[14] and these were prescribed according to local protocols. Placental histology was encouraged but not uniformly requested.

Study outcomes

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

Definite systemic neonatal infection (definite sepsis) was defined a positive culture of a known pathogen from blood or cerebrospinal fluid (CSF), the baby treated with antibiotics for 5 or more days (or died before 5 days), and the presence of clinical signs of infection. For organisms of low virulence and/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 (CRP) were required. An abnormal full blood count (FBC) included abnormal white cell count [WCC] $<5 \times 10^9$ /L or $>30 \times 10^9$ /L, platelet count <100,000, neutrophil count $<1.5 \times 10^9$ /L or raised immature to total neutrophil ratio (I:T ratio >0.2).[15,16] A CRP >10mg/L was considered abnormal.[17,18]

Clinical signs of infection included respiratory distress (requiring ventilation, continuous positive airway pressure or supplemental oxygen for more than one hour), apnea, lethargy, abnormal level of consciousness, circulatory compromise (including hypotension, poor perfusion, need for inotropic support or volume expansion) and/or temperature instability (temperature $<36^oC$ or $\geq 38^oC$).

Probable neonatal infection was defined as the presence of clinical signs where the baby was treated with antibiotics for 5 or more days together with one or more of: an abnormal FBC; abnormal CRP; positive GBS antigen on bladder tap urine, blood or CSF; elevated CSF white cell count [5] (CSF WCC>100×10^6/L); growth of a known virulent pathogen (eg GBS, E.coli, Listeria) from surface swab; or a histologic diagnosis of pneumonia in an early neonatal death.

Pre-specified secondary neonatal outcomes[13,19] included composite neonatal morbidity (sepsis, mechanical ventilation >24 hours, stillbirth or neonatal death), respiratory distress, perinatal mortality, pneumonia, mechanical ventilation (intermittent positive pressure ventilation, continuous positive airway pressure or high frequency ventilation) for greater than 24 hours, duration of stay in a neonatal intensive or special care unit, duration of stay in hospital, birth weight, Apgar score ≤7 at 5 minutes,

antibiotics in the first 48 hours, lumbar puncture, circulatory compromise requiring arterial line, fluid bolus or inotropic support, and receiving breast milk at discharge (exclusive or mixed feeding). 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 included antepartum or intrapartum hemorrhage, antepartum or postpartum thrombosis, cord prolapse, postpartum treatment with antibiotics, intrapartum fever (pyrexia ≥38.5C), postpartum hemorrhage (>1000 ml), mode of delivery, onset of labor and duration of hospitalization (total days from randomization to delivery, and from delivery to discharge or transfer).
Chorioamnionitis was a trial entry exclusion criteria but this outcome is reported among the women with expectant management. Placental swabs and histology were also collected if available.
As far as I can see you've not reported the following maternal secondary outcomes from trial registration.
2.3. Post-partum fever
2.8. Assisted vaginal delivery
2.9. Maternal satisfaction
2.10. Views of care
time to fully establish breast feeding
2.13. Maternal emotional wellbeing
2.14. Anxiety and depression

Other measures:
Where time of day of randomization or PPROM were missing, the hours from PPROM to randomization was imputed as the difference in days, plus 9 hours (the median for non-missing participants). Only cultures from vaginal swabs taken between PPROM and randomization 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.

Statistical Analysis

A sample size of 1812 (906 patients per arm) was necessary to detect a reduction in neonatal sepsis of 5% in the expectantly managed arm compared with 2.5% in the immediate delivery arm with a two-sided 5% significance level and a power of 80%. One interim analysis was performed in February 2010 by the independent data monitoring committee, prior to submission for further funding, who reviewed the findings (506 women had been recruited) and recommended that the study continue. A difference of at least three standard deviations in 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 due to protocol violations. The primary outcome was calculated as event numbers and percentages, by treatment allocation. Effect measures (relative risk [RR]) were calculated with a 95% confidence interval (95% CI), using expectant management as the reference group. Comparison of mean birthweight was performed using a t-test. Comparisons of maternal and infant length of stay (days) were performed 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.

Predefined criteria for whether adjusted analyses were required[19] were a relative difference of >15% between arms in the median duration from PROM to randomization; and/or a >3 day difference in median gestational age at randomization. If either had been met, adjusted logistic regression would have been performed. No adjustment to the level of statistical significance was made for multiple comparisons.
Pre-specified subgroup analyses for the primary outcome of neonatal sepsis included time from PPROM until randomization (<48 hours, ≥48 hours); gestational week of PPROM (<34 weeks, ≥34 weeks); vaginal swab culture result (GBS, other abnormal flora); and antibiotic administration at randomization.

Results

between May 2004 and June 2013 a total of 1839 women were recruited into the study. Figure 1 demonstrates the flow of participants through the study. Thirteen women in

the immediate delivery arm did not receive the allocated intervention compared with only one protocol violation in the expectant management arm. The primary outcome was assessed for 1835 (99.8%) of those women randomized (immediate delivery 923; expectant management 912).

The baseline characteristics of the two arms were similar (Table 1). The median gestational age at randomization in each arm was 247 days and the median time in hours from ruptured membranes to randomization was 30.4 hours in the immediate delivery arm and 26.4 hours (13.4% lower) in the expectantly managed arm so no adjusted analyses were performed. Figure 2 shows the difference in time between randomization and delivery for the two arms of the trial.

At the time of randomization, approximately 40% of women in each arm had received antenatal steroids and 86% received antibiotics (Table 1). Any antibiotics prior to delivery were prescribed for 852 (92.3%) women in the immediate delivery arm and 844 (92.5%) in the expectant management arm. In the expectant management arm 688 (73.2%) women were managed in hospital and the remainder were sent home between randomization and delivery.

Women randomized to expectant management were more likely to deliver following the spontaneous onset of labor, have a cephalic presentation at birth and deliver at a later gestation than those allocated to immediate delivery (Table 2). Six women randomized to "immediate delivery" delivered after 36 weeks including 5 who were found not to have PROM after randomization and 1 who self-discharged from the enrolling hospital and birthed later.

The primary outcome of definite or probable neonatal sepsis occurred in 23 (2.5%) of the 923 neonates whose mothers were assigned to immediate delivery and 29 (3.2%) of the 912 neonates whose mothers were assigned expectant management (RR 0.8; 95% CI, 0.5 to 1.3) (Table 3). There was no significant difference in the composite measure of mortality and neonatal morbidity including sepsis, ventilation >24 hours and perinatal death, occurring in 73 (7.9%) of those allocated immediate delivery and 61 (6.7%) of those managed expectantly. However, those babies born following immediate delivery

had significantly lower birthweights, increased risk of respiratory distress and mechanical ventilation, and spent more time in newborn intensive care or special care nursery (Table 4).

There were six perinatal deaths, three in each arm of the trial. Among women randomized to immediate delivery the deaths were from: sudden infant death syndrome (SIDS) (4 weeks of age); congenital abnormality (3 weeks of age); and fetal death at 35 weeks gestation associated with acute suppurative chorioamnionitis based on the autopsy report.. Among women randomized to expectant management the deaths were from: SIDS (5 weeks of age); a congenital abnormality (12 weeks of age); and one of unknown cause (at 24 hours of age).

Expectant management was associated with a greater likelihood of antepartum hemorrhage (2.9% vs 5%) and intrapartum fever (0.8% vs 2.1%) (Table 3). Cesarean delivery occurred in 239 (25.9%) women allocated to immediate delivery compared with 169 (18.5%) of those women allocated to expectant care (RR 1.4; 95% CI, 1.2 to 1.7). Fifty six (6.1%) women in the expectant management arm were delivered because of choriamnionitis subsequent to randomization.

Neonatal sepsis was not significantly associated with immediate delivery or expectant management in any of the strata of the prespecified subgroup analyses (Table 4). Immediate delivery had no influence on sepsis regardless of the gestational age at PPROM, the duration of PPROM or the administration of antibiotics at the time of PPROM. Of women managed expectantly 191 (?%) women had an abnormal organism isolated from the swab including 78 with GBS. In those allocated to immediate delivery 190 (?%) women had a swab collected that isolated an abnormal organism, including 83 with GBS. For women allocated to immediate delivery neonatal sepsis occurred in 2.1% of neonates born to women who had a positive culture on their vaginal swab compared with 4.7% in those born to mothers with a positive culture and managed expectantly (RR 0.4; 95% CI, 0.1 to 1.4).

Discussion

This trial demonstrates that for women with ruptured membranes between 34^0 and 36^6

weeks gestation carrying a single fetus and no contraindication for expectant management, immediate delivery increased neonatal complications with no clinically significant decrease in neonatal sepsis. Therefore in contrast to recent guideline recommendations,[6,8] we advocate that expectant management is preferred to immediate delivery in women with ruptured membranes close to term.

This is the largest study to compare these two forms of currently accepted management. Older studies that included women with PROM at preterm gestations were unable to demonstrate any reduction in neonatal sepsis or differences in neonatal morbidity[2] and two underpowered studies with inclusion criteria similar to the PPROMT Trial published while the present studty was ongoing also reported that immediate delivery did not reduce neonatal sepsis. [20] [21] They concluded that there was no increase in neonatal morbidity or cesarean delivery. The PPROMT Trial is the most adequately powered study to demonstrate that immediate delivery does not reduce neonatal sepsis but does increase the likelihood of several aspects of early neonatal morbidity including respiratory distress, mechanical ventilation and duration of stay in newborn intensive care. This has significant implications for practice and widespread adoption of expectant management following ruptured membranes close to term is likely to have significant resource and economic benefits.

The adoption of the practice of immediate delivery, advocated in recent guidelines is predicated on the fact that disability free survival rates following birth are very high. However, there is increasing concern about the risks of adverse outcome for late preterm neonates, with studies identifying an increased risk of neonatal morbidity [22], rehospitalisation in early childhood [23] and academic difficulties in children at school age [24]. These risks are thought to be associated with both gestational age and biological factors associated with the preterm birth, including PPROM [25], however, immediate delivery does not appear to improve outcomes in preterm neonates and may exacerbate the risks of prematurity because of birth in the absence of labor and earlier gestational age. Although expectant management in a potentially hostile intrauterine environment should be avoided, in a mother who remains well, with no evidence of clinical chorioamnionitis, expectant management provides an opportunity for spontaneous labor to develop and for adaptive changes to occur in the neonate resulting in decreased

risk of neonatal respiratory illness [26]. For some neonates, expectant management may also result in delivery at a substantially older gestational age. These factors may in turn result in a decrease in neonatal morbidity, decreased separation of mother and baby, improved breast feeding rates and a reduction in risk of adverse childhood outcomes.

In circumstances such as PPROM, where the risks and benefits of immediate delivery compared with expectant management have been unclear, policy makers have called on clinicians to develop evidence-based data to assess risk/benefit ratios for diagnosis specific indications for delivery at late-preterm gestations [22]

The PPROMT trial is sufficiently large to provide evidence of the risks and benefits associated with immediate delivery following PPROM. Risks identified with immediate delivery include an increase in respiratory distress requiring ventilator support for the baby, an increase in duration of admission to a neonatal intensive care or special care nursery and an increased likelihood of cesarean for the mother. On the other hand expectant management does not appear to significantly increase the likelihood of neonatal sepsis, but resulted in a lengthier hospital stay for the mother as most were managed as inpatients. This is important information that care providers can discuss with women regarding best practice in this clinical situation.

Although expectant management was provided according to each hospital's current usual care, 75% of women were managed as inpatients and over 90% received antibiotics prior to delivery. Our findings suggest that expectant management should include careful monitoring for/heightened surveillance of fever, symptoms of chorioamnionitis and antepartum hemorrhage.

In addition to its size, the strengths of the PPROMT trial include the fact that it reflects contemporary maternity practice, was centrally randomized, had near complete follow up and was conducted across a range of international settings making the results widely generalizable. Many previous studies evaluating the management of ruptured membranes were small and performed prior to the widespread implementation of

maternal antibiotic administration to prolong latency and reduce short term morbidity, including neonatal infection.[14,27-32] The PPROMT Trial results, together with the results of the recent PPROMEXIL studies,[20,21] suggest there are benefits from expectant management without incurring significant risk of harms. It may be possible that there are groups of women who benefit from immediate delivery. Contrary to a recent report,[33] our findings were that immediate delivery did not confer benefit on the women in whom Group B Streptococcus was isolated from the genital tract. There are opportunities to explore such risk factors further to identify specific indications for which immediate delivery is appropriate by performing an individual patient data meta-analysis of all those who participated in PPROMT and PPROMEXIL.

Conclusion

Contrary to the advice of many current guidelines, the PPROMT Trial found that expectant management does not increase the risk of neonatal sepsis but reduces neonatal morbidity in neonates of women who present with ruptured membranes close to term and that this should be advocated as best practice internationally.

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Figure 1: Randomization and follow-up of study participants

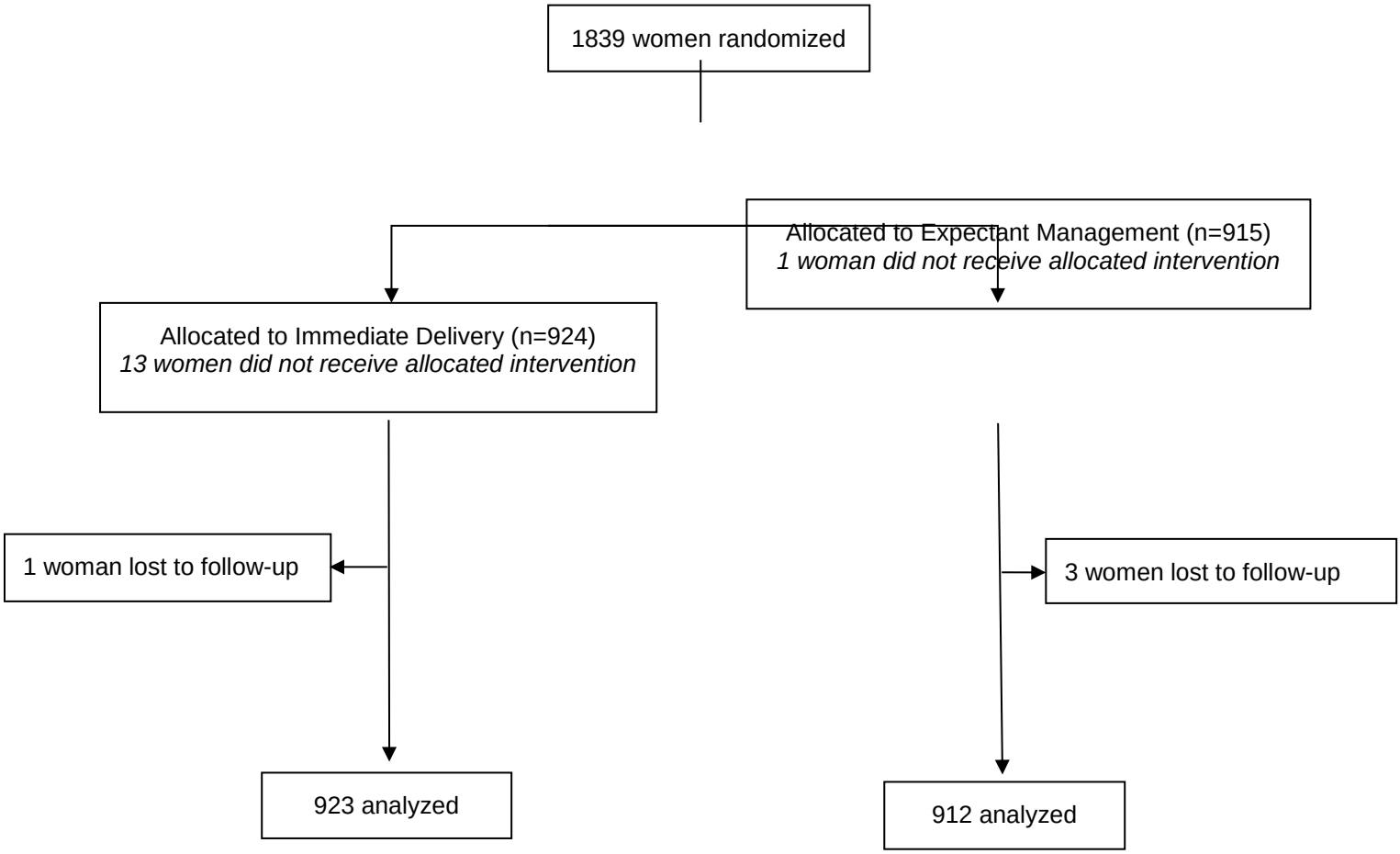

Figure 2: Time from randomization until birth, by treatment assignment

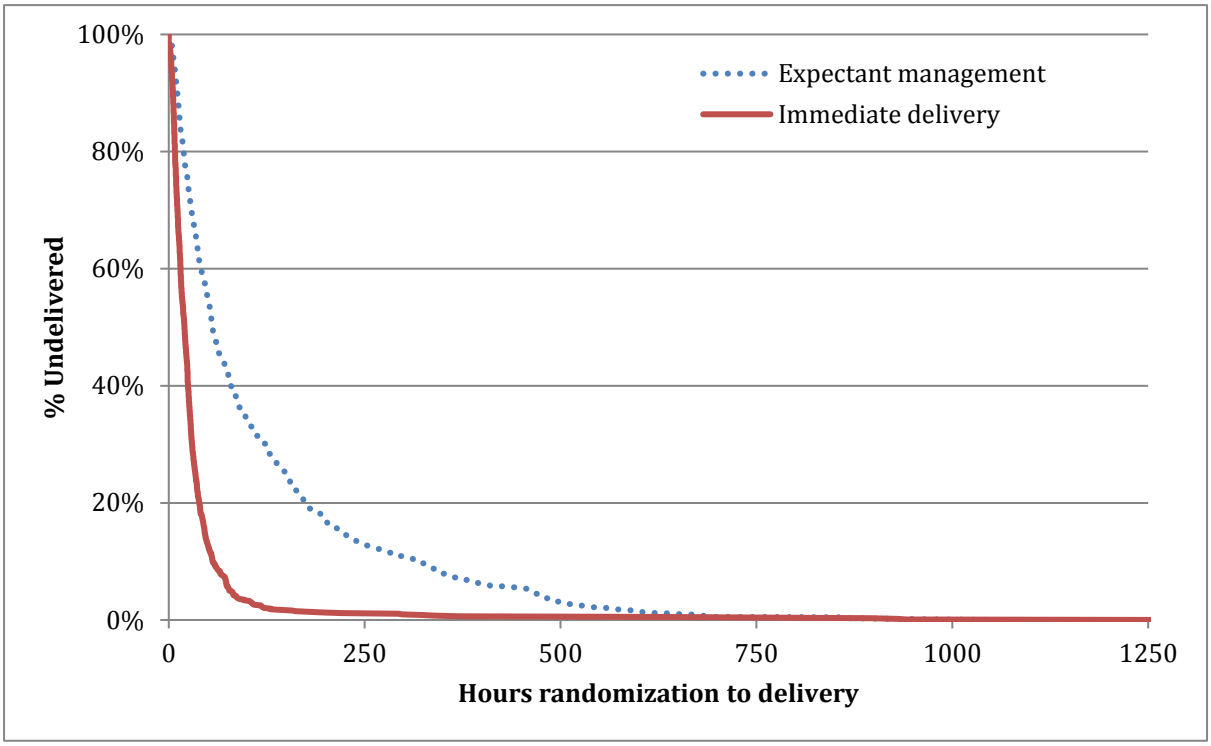

Table 1 Maternal and pregnancy factors at or before time of randomization, by treatment assignment

	Immediate delivery N=923 n (%)	Expectant management N=912 n (%)
Rupture of membranes		
<28⁰ weeks	13 (1.4)	14 (1.5)
28⁰ to 29⁶ weeks	14 (1.5)	9 (1.0)
30⁰ to 31⁶ weeks	21 (2.3)	34 (3.7)
32⁰ to 33⁶ weeks	161 (17.4)	129 (14.1)
34⁰ to 34⁶ weeks	212 (23.0)	225 (24.7)
35⁰ to 35⁶ weeks	279 (30.2)	271 (29.7)
36⁰ to 36⁶ weeks	223 (24.2)	230 (25.2)
Randomised		
34⁰ to 34⁶ weeks	363 (39.3)	355 (38.9)
35⁰ to 35⁶ weeks	278 (30.1)	292 (32.0)
36⁰ to 36⁶ weeks	282 (30.6)	265 (29.1)
PPROM ≥ 48 hours before randomization	328 (35.5)	302 (33.1)
Maternal age (years) (mean, std.dev.)	27.9 (6.2)	28.0 (6.2)
Previous pregnancies		
0	426 (46.2)	430 (47.1)
1	232 (25.1)	241 (26.4)
≥ 2	265 (28.7)	241 (26.4)
Cephalic presentation	880 (95.3)	876 (96.1)
Previous cesarean delivery	93 (10.1)	85 (9.3)
Previous PPROM or preterm delivery	137 (14.8)	125 (13.7)
Previous stillbirth or neonatal death	21 (2.3)	24 (2.6)
Pregnancy hypertension (onset ≥ 20 weeks)	24 (2.6)	33 (3.6)
Gestational diabetes	50 (5.4)	48 (5.3)
Antenatal urinary tract infection	99 (10.7)	87 (9.5)
Antibiotics given*		
intravenous (+/- oral)	321 (34.8)	286 (31.4)
oral only	473 (51.2)	500 (54.8)
Steroids given	383 (41.5)	354 (38.8)
Positive culture from a vaginal swab†		
any positive culture	190 (20.6)	191 (20.9)
Group B streptococcus positive	83 (9.0)	78 (8.6)

* antibiotics at randomization or in preceding 48 hours

† culture resulting from vaginal swab after PPROM and at or before randomization

Missing data (#immediate delivery, # expectant management): Previous CS (1,1); Previous PPROM (0,1); Previous stillbirth (0,1); Antibiotics (2,4); Positive culture (223,230)

Table 2 Labor characteristics, by treatment assignment

Labor characteristic	Immediate delivery N=920 n (%)	Expectant management N=915 n (%)	P value
Onset of labor			
Spontaneous	180 (19.5)	549 (60.2)	<0.0001*
Induced	647 (70.1)	310 (34.0)	
Pre-labor cesarean	96 (10.4)	53 (5.8)	
Cephalic presentation at birth	49 (5.3)	33 (3.6)	<0.0001†
Gestational age at birth	315 (34.1)	161 (17.7)	
34 weeks	273 (29.6)	268 (29.4)	
35 weeks	306 (33.2)	295 (32.3)	
36 weeks	23 (2.5)	174 (19.1)	
37 weeks	1 (0.1)	7 (0.8)	
38 weeks	1 (0.1)	2 (0.2)	
39 weeks	1 (0.1)	5 (0.5)	
40 weeks	3 (0.3)	0 (0.0)	
41 weeks	180 (19.5)	549 (60.2)	<0.0001*

* 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 3 Infant and maternal outcomes by treatment assignment

Infant outcome	Immediate delivery n (%)	Expectant management n (%)	Relative risk RR (95% CI)
Neonatal sepsis	23/ 923 (2.5)	29/ 912 (3.2)	0.8 (0.5, 1.3)
Secondary infant outcomes			
Composite of neonatal morbidity (sepsis, ventilation ≥24 hours or death)	73/ 923 (7.9)	61/ 911 (6.7)	1.2 (0.9, 1.6)
Perinatal death	3/ 923 (0.3)	3/ 910 (0.3)	1.0 (0.2, 4.9)
Respiratory distress syndrome	76/ 919 (8.3)	47/ 910 (5.2)	1.6 (1.1, 2.3)
Pneumonia	3/ 919 (0.3)	4/ 910 (0.4)	0.7 (0.2, 3.3)
Any mechanical ventilation (CPAP or ETT)	114/ 923 (12.4)	83/ 912 (9.1)	1.4 (1.0, 1.8)
mechanical ventilation for ≥ 24 hours	56/ 923 (6.1)	37/ 912 (4.1)	1.5 (1.0, 2.2)
Mean birthweight in grams (SD)	2574.7 (400.3)	2673.2 (405.5)	<.0001
SGA <10th percentile size	32/ 922 (3.5)	35/ 906 (3.9)	0.9 (0.6, 1.4)
Apgar score <7 at 5 minutes	15/ 918 (1.6)	18/ 906 (2.0)	0.8 (0.4, 1.6)
Antibiotics in first 48 hours	422/ 920 (45.9)	398/ 910 (43.7)	1.0 (0.9, 1.2)
Lumbar puncture	33/ 921 (3.6)	38/ 911 (4.2)	0.9 (0.5, 1.4)
Circulatory compromise	11/ 921 (1.2)	13/ 910 (1.4)	0.8 (0.4, 1.9)
Infant days in hospital*	6.0 (3.0, 10.0)	4.0 (3.0, 8.0)	<.0001
Days in SCN/NICU†*	4.0 (0.0, 10.0)	2.0 (0.0, 7.0)	<.0001
Receiving breast milk at discharge	695/ 883 (78.7)	712/ 877 (81.2)	1.0 (0.9, 1.0)
Secondary maternal and pregnancy outcomes			
Antepartum hemorrhage	27/ 923 (2.9)	46/ 912 (5.0)	0.6 (0.4, 0.9)
Cord prolapse	3/ 923 (0.3)	2/ 912 (0.2)	1.5 (0.2, 8.8)
Intrapartum fever	7/ 923 (0.8)	18/ 912 (2.0)	0.4 (0.2, 0.9)
Postpartum antibiotics	151/ 923 (16.4)	180/ 912 (19.7)	0.8 (0.7, 1.0)
Postpartum hemorrhage (PPH)	29/ 803 (3.6)	27/ 782 (3.5)	1.0 (0.6, 1.8)
Maternal duration of hospitalization*	5.0 (3.0, 7.0)	6.0 (4.0, 9.0)	<.0001
Cesarean delivery (CD)	239/ 923 (25.9)	169/ 912 (18.5)	1.4 (1.2, 1.7)
CD following spontaneous labor	24/ 180 (13.3)	54/ 549 (9.8)	1.4 (0.9, 2.1)
CD following labor induction	119/ 647 (18.4)	62/ 310 (20.0)	0.9 (0.7, 1.2)
Pre-labor cesarean delivery	96/ 923 (10.4)	53/ 912 (5.8)	1.8 (1.3, 2.5)
Missing but pre-specified secondary outcomes			
2.3. Post-partum fever			
2.8. Assisted vaginal delivery			
2.9. Maternal satisfaction			
2.10. Views of care			
time to fully establish breast feeding			
2.13. Maternal emotional wellbeing			

2.14. Anxiety and depression

CPAP continuous positive pressure ventilation; ETT endotracheal tube; SD standard deviation; SGA small for gestational age; SCN special care nursery; NICU neonatal intensive care

* median and interquartile range reported for duration of admission, Wilcoxon P value for test of null hypothesis of no difference in distribution between treatment arms
† days in a Special Care Nursery and/or Neonatal Intensive Care Unit

Missing data (#immediate delivery, # expectant management): composite (0,1); perinatal death (0,2); RDS (4,2); Pneumonia (4,2); birthweight (0,2); SGA (1,6), Apgar (5,6); antibiotics (3,2); lumbar puncture (2,1); Circulatory compromise (2,2) infant days in hospital (2,3); days in SCN/NICU (1,2); Breast milk at discharge (40,35); PPH (120,130); maternal duration of hospitalization (2,2)

Table 4: Pre-specified subgroup analyses for neonatal sepsis by treatment assignment

Infant outcome	Immediate delivery Sepsis n/N (%)	Expectant management Sepsis n/N (%)	Neonatal sepsis RR (95% CI)
Duration from PPROM to randomization			
< 48 hours	19/ 595 (3.2)	18/ 610 (3.0)	1.1 (0.6, 2.0)
≥ 48 hours	4/ 328 (1.2)	11/ 302 (3.6)	0.3 (0.1, 1.0)
Gestation of PPROM			
before 34 weeks	4/ 209 (1.9)	7/ 186 (3.8)	0.5 (0.2, 1.7)
≥ 34 weeks	19/ 714 (2.7)	22/ 726 (3.0)	0.9 (0.5, 1.6)
Vaginal culture after PPROM*			
GBS	3/ 83 (3.6)	3/ 78 (3.8)	0.9 (0.2, 4.5)
other organism	1/ 107 (0.9)	6/ 113 (5.3)	0.2 (0.0, 1.4)
negative or no culture collected	19/ 733 (2.6)	20/ 721 (2.8)	0.9 (0.5, 1.7)
Vaginal culture after PPROM*			
Any culture positive	4/ 190 (2.1)	9/ 191 (4.7)	0.4 (0.1, 1.4)
Negative or no culture collected	19/ 733 (2.6)	20/ 721 (2.8)	0.9 (0.5, 1.7)
Maternal antibiotics at randomization†			
Yes	20/ 795 (2.5)	24/ 787 (3.0)	0.8 (0.5, 1.5)
No	3/ 127 (2.4)	5/ 122 (4.1)	0.6 (0.1, 2.4)

* culture from vaginal swab after PPROM and at or before randomization

† antibiotics at randomization or in preceding 48 hours

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