

RCT
Potential PURL Review Form
PURL Jam Version
Version #11 October 29, 2009

PURLs Surveillance System
Family Physicians Inquiries Network

SECTION 1: Identifying Information for Nominated Potential PURL
[to be completed by PURLs Project Manager]

- 1. Citation** Morris JM, Roberts CL, Bowen JR, Patterson JA, Bond DM, Algert CS, Thornton JG, Crowther CA; PPRMT Collaboration. Immediate delivery compared with expectant management after preterm pre-labour rupture of the membranes close to term (PPROMT trial): a randomised controlled trial. Lancet. 2016 Jan 30;387(10017):444-52.
- 2. Hypertext link to PDF of full article** <http://www.ncbi.nlm.nih.gov/pubmed/?term=26564381>
- 3. First date published study available to readers** 01/30/16
- 4. PubMed ID** 26564381
- 5. Nominated By** Jim Stevermer Other:
- 6. Institutional Affiliation of Nominator** University of Missouri Other:
- 7. Date Nominated** 03/15/16
- 8. Identified Through** InfoPOEMs Other:
- 9. PURLS Editor Reviewing Nominated Potential PURL** Kate Rowland Other:
- 10. Nomination Decision Date** 04/04/16
- 11. Potential PURL Review Form (PPRF) Type** RCT
- 12. Other comments, materials or discussion**
- 13. Assigned Potential PURL Reviewer**
- 14. Reviewer Affiliation** University of Chicago Other:
- 15. Date Review Due** 06/02/16
- 16. Abstract** 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.

FUNDING:

Australian National Health and Medical Research Council, the Women's and Children's Hospital Foundation, and The University of Sydney.

17. Pending 06/02/2016
PURL Review
Date

SECTION 2: Critical Appraisal of Validity

[to be completed by the Potential PURL Reviewer]

[to be revised by the Pending PURL Reviewer if needed]

- | | |
|--|--|
| <p>1. Number of patients starting each arm of the study?</p> | 1839 total-924 women to immediate delivery and 915 women to expectant management final analysis was 910 women and 923 babies for immediate delivery and 911 women and 912 babies in expectant management . |
| <p>2. Main characteristics of study patients (inclusions, exclusions, demographics, settings, etc.)?</p> | Inclusion, singleton-pregnant women >16 years old, at gestational age between 34 weeks and 36 weeks 6 days, clinically suspected ROM. Exclusion : if in established labor, chorioamnionitis, meconium staining or other contraindication to continuing pregnancy. Settings are 65 centers in 11 countries (AUstralia, New Zealand, Argentina, South Africa Brazil, UK, Norway, Egypt, Uruguay, Poland, Romania) between May 28, 2004-June 30, 2013.(Identified by a local research coordinator, data coordinated in Australia site.) |
| <p>3. Intervention(s) being investigated?</p> | whether immediate birth (vs expectant management) shows better outcomes, of several types |

4. Comparison treatment(s), placebo, or nothing? comparison is expectant management
5. Length of follow up? Note specified end points e.g. death, cure, etc. until hospital discharge for mother and neonate following delivery up to 28 days maximum.
6. What outcome measures are used? List all that assess effectiveness. Primary outcome = neonatal sepsis, either definite or probable, as reviewed by a central adjudication committee
secondary outcome for neonate= composite neonatal M&M(sepsis, mechanical ventilation >/=24 hours, stillbirth, neonatal death
secondary outcomes for mother=antepartum/intrapartum hemorrhage, antepartum/intrapartum thrombosis, cord prolapse, postpartum treatment w antibiotics, intrapartum fever, postpartum hemorrhage (>1L), mode of delivery, onset of labor, and duration of hospital stay or to transfer, chorioamnionitis was excluded but reported for expectant management trial women.
7. What is the effect of the intervention(s)? Include absolute risk, relative risk, NNT, CI, p-values, etc. absolute-immediate delivery group showed 23/923 or 2% neonatal sepsis vs 29/912 (3%) expectant management with a relative risk 0.8 (95% CI 0.5-1.3, p value 0.37)
8. What are the adverse effects of intervention compared with no intervention? immediate birth resulted in increased rates of respiratory distress and any mechanical ventilation and more days in ICU.
positive effects of immediate birth were lower risk of ante/intrapartum hemorrhage, intrapartum fever, use of postpartum antibiotics, and shorter hospital stay.
9. Study addresses an appropriate and clearly focused question - **select one**
 Well covered
 Adequately addressed
 Poorly addressed
 Not applicable
- Comments: since this is 'pragmatic' across multiple centers, some of the definitions might show some local variation, but not completely discussed.
10. Random allocation to comparison groups
 Well covered
 Adequately addressed
 Poorly addressed
 Not applicable
 Comments: done by central telephone service using computer generated randomization schedule with balanced variable blocks of sizes 2,4,and 6) stratified by center.
11. Concealed allocation to comparison groups
 Well covered
 Adequately addressed
 Poorly addressed
 Not applicable
 Comments: those reviewing for the primary outcomes from charts were blinded to the group allocation.
12. Subjects and investigators kept "blind" to comparison group allocation
 Well covered
 Adequately addressed
 Poorly addressed
 Not applicable
 Comments:
12. Comparison groups are similar at the start of the trial
 Well covered
 Adequately addressed
 Poorly addressed
 Not applicable

Comments: randomized , stratified by center

14. Were there any differences between the groups/arms of the study other than the intervention under investigation? If yes, please indicate whether the differences are a potential source of bias.

- Well covered
 Adequately addressed
 Poorly addressed
 Not applicable

Comments: none see paragraph 2 and 3 under results

15. Were all relevant outcomes measured in a standardized, valid, and reliable way?

- Well covered
 Adequately addressed
 Poorly addressed
 Not applicable

Comments: some variation in local treatment patterns, eg in swab collection, management in or out of hospital, for instance, and choice of antibiotics, lab testing types , placental histology assessment .

16. Are patient oriented outcomes included? If yes, what are they?

Yes, neonatal sepsis is primary and is patient oriented,. secondary outcomes also patient oriented, especially mode of delivery, neonatal morbidity and mortality.

17. What percent dropped out, and were lost to follow up? Could this bias the results? How?

4 excluded = 2 withdrew, 2 lost to FU, also 14 did not receive assigned treatment.

18. Was there an intention-to-treat analysis? If not, could this bias the results? How?

yes, intention to treat analysis done

19. If a multi-site study, are results comparable for all sites?

not described!!

20. Is the funding for the trial a potential source of bias? If yes, what measures were taken to insure scientific integrity?

no potential bias perceived-Australian NHMRC, womens and childrens hospital foundation and U of Sydney

21. To which patients might the findings apply? Include patients in the study and other patients to whom the findings may be generalized.

women with PPROM from 34-36w6d gestation

22. In what care settings might the findings apply, or not apply?

hospital settings, birthing centers

23. To which clinicians or policy makers might the findings be relevant?

clinicians-family med, obgyne physicians and nurse midwives

SECTION 3: Review of Secondary Literature
[to be completed by the Potential PURL Reviewer]
[to be revised by the Pending PURL Reviewer as needed]

Citation Instructions

For UpTo Date citations, use style modified from http://www.uptodate.com/home/help/faq/using_UTD/index.html#cite & AMA style. Always use Basow DS as editor & current year as publication year.

EXAMPLE: Auth I. Title of article. {insert author name if given, & search terms or title.} In: Basow DS, ed. UpToDate [database online]. Waltham, Mass: UpToDate; 2009. Available at: <http://www.uptodate.com>. {Insert dated modified if given.} Accessed February 12, 2009. {whatever date PPRF reviewer did their search.}

For DynaMed, use the following style:

Depression: treatment {insert search terms or title}. In: DynaMed [database online]. Available at: <http://www.DynamicMedical.com>. Last updated February 4, 2009. {Insert dated modified if given.} Accessed June 5, 2009. {search date}

1. DynaMed excerpts

updates "immediate delivery and expectant management associated with similar rates of neonatal sepsis and infant morbidity and mortality, but immediate birth may increase risk of infant respiratory distress and lower birth weight, while expectant management may increase risk for maternal hemorrhage in suspected PPRM at 34-36 weeks gestation (Lancet 2016 Jan 30) view update

2. DynaMed citation/access date

Title. Preterm PRemature rupture of membranes(PPROM) Author. Chisholm In: DynaMed [database online]. Available at: www.DynamicMedical.com Last updated: May 23, 2016. Accessed June 6, 2016

3. Bottom line recommendation or summary of evidence from DynaMed (1-2 sentences)

Controversial area. The final viewpoint summarizes this subject article, also. Preterm premature rupture of membranes (PPROM)

4. UpToDate excerpts

excerpt 1

INTRODUCTION — Premature rupture of membranes (PROM) refers to membrane rupture before the onset of uterine contractions (also known as prelabor rupture of membranes); preterm PROM (PPROM) refers to PROM before 37/7ths weeks of gestation.

The management of PPRM is among the most controversial issues in perinatal medicine. Points of contention include:

- Expectant management versus intervention
 - Use of tocolytics
 - Duration of administration of antibiotic prophylaxis
 - Timing of administration of antenatal corticosteroids
 - Methods of testing for maternal/fetal infection
 - Timing of delivery
- Preterm premature (prelabor) rupture of membranes

excerpt 2:

Expedient delivery of women with PPRM is clinically appropriate if intrauterine infection, abruptio placentae, nonreassuring fetal testing, or a high risk of cord prolapse is present or suspected. In each of these conditions, fetal well-being can deteriorate with expectant management, and there are no therapeutic interventions available other than delivery. (See "Placental abruption: Clinical features and diagnosis" and "Intraamniotic infection (chorioamnionitis)" and "Umbilical cord prolapse".)

In the absence of these complications, we do not intervene to effect delivery prior to 34 weeks. Our simplified algorithm for management of women with PPRM at 26 to 36 weeks is shown in the algorithm (algorithm 1). As noted, most patients who are initially managed expectantly will be delivered at 34 weeks of gestation; in some, delivery will be delayed until 36 weeks of gestation. A detailed analysis of the nuances of management is beyond the scope of this topic review; however, several aspects of

management will be discussed.

The optimal time for intervention varies among institutions and depends on the balance between morbidity related to prematurity and morbidity related to complications of PPRM. The American College of Obstetricians and Gynecologists (ACOG) suggests delivery for all patients ≥ 34 weeks of gestation [50]. (See 'Timing of delivery for expectantly managed pregnancies' below.)

Meta-analyses of randomized trials, and subsequent randomized trials, have not provided conclusive evidence favoring induction or expectant management of PPRM between 28 and 37 weeks [51-55]. The complexity of management decisions was illustrated by the Preterm Prelabour Rupture of the Membranes close to Term (PPROMT) trial [51]. This multicenter, international randomized trial (65 centers in 11 countries) was focused specifically on patients who developed PPRM between 34 and 36 6/7ths weeks of gestation and were randomly assigned to immediate delivery (n = 924) or expectant management (n = 915). The trial found that rates of neonatal sepsis (primary outcome) were 2 to 3 percent and did not differ significantly between the two groups. Infants in the immediate delivery group were more likely to develop respiratory distress syndrome (8 versus 5 percent, relative risk [RR] 1.6, 95% CI 1.1-2.3), require mechanical ventilation (12 versus 9 percent, RR 1.4, 95% CI 1.0-1.8), and spend more time in the neonatal intensive care unit (six versus four days) than infants delivered to mothers in the expectant management group. There was no difference between groups in the composite neonatal outcome of sepsis, ventilation for ≥ 24 hours, or death. However, mothers assigned to expectant management were more likely to develop antepartum or intrapartum bleeding (5 versus 3 percent), develop intrapartum fever (2 versus 1 percent), and require use of therapeutic antibiotics (20 versus 16 percent). They also had a longer hospital stay (six versus five days) and a lower frequency of cesarean delivery (19 versus 26 percent). This trial had several limitations that preclude extrapolating these findings to contemporary populations in the United States. For example, the trial was conducted over 10 years, during which obstetric and neonatal management has likely changed. In addition, the study was conducted at many different facilities with different levels of resources and different management strategies. Some patients were managed as outpatients, which is not done in the United States; there were no clear criteria for determining the timing of delivery in the expectantly managed group; there were significant variations in protocols for laboratory testing and administration of prophylactic antibiotics, and there were inconsistencies in the use of corticosteroids

5. UpToDate citation/access date

Always use Basow DS as editor & current year as publication year.

Title. Preterm premature (prelabor) rupture of membranes Author. Duff, Patrick In: UpToDate [database online]. Available at: <http://www.uptodate.com>. Last updated: May 31, 2016. Accessed

6. Bottom line recommendation or summary of evidence from UpToDate (1-2 sentences)

Inconsistent recommendation and does reference the article under review. Defaults to ACOG recommendation.

7. PEPID PCP excerpts www.pepidonline.com username: fpinauthor pw: pepidpcp

not done

8. PEPID citation/access data

Author. Title. In: PEPID [database online]. Available at: <http://www.pepidonline.com>. Last updated: . Accessed

9. PEPID content updating

1. Do you recommend that PEPID get updated on this topic?

Yes, there is important evidence or recommendations that are missing

No, this topic is current, accurate and up to date.

If yes, which PEPID Topic, Title(s):

2. Is there an EBM Inquiry (HelpDesk Answers and Clinical Inquiries) as indicated by the EB icon (EB) that should be updated on the basis of the review?

Yes, there is important evidence or recommendations that are missing

No, this topic is current, accurate and up to date.

If yes, which Evidence Based Inquiry(HelpDesk Answer or Clinical Inquiry), Title(s):
I found only 2011 emedicine reference from 2011 so not something relevant for this review

<https://mospace.umsystem.edu/xmlui/bitstream/handle/10355/14739/PrematureRuptureMembranes.pdf?sequence=1&isAllowed=y>

10. Other excerpts (USPSTF; other guidelines; etc.)

a-Cochrane (no specific reference for this PPRM for 34-37 weeks found)

b-Medscape (good for general overview, but no specific PPRM for 34-37 weeks found.)

c-ACOG bulletin

"More recently, two randomized controlled trials evaluated delivery versus expectant management between 34 weeks and 37 weeks of gestation and included a total of 736 women (50, 51). Combining data from the two studies, induction of labor did not produce a statistically significant reduction in the rate of neonatal sepsis (2.7% at 34 weeks versus 4.1% at 37 weeks of gestation, relative risk [RR], 0.66; 95% confidence interval [CI], 0.3–1.5). However, induction of labor did significantly reduce the risk of chorioamnionitis (1.6% at 34 weeks versus 5.3% at 37 weeks of gestation, RR, 0.31; 95% CI, 0.1–0.8), although there were no other significant differences between the two groups. These studies did not have sufficient power to show a statistically significant reduction in the rate of neonatal sepsis because the overall rate of sepsis was lower than anticipated. These findings are consistent with other smaller, similarly designed trials (52, 53) and those conducted in women at term (13, 42).

"Despite these data, the optimal gestational age for delivery remains controversial. Recently there has been a focus on the short-term (54) and long-term (55) risks associated with late preterm birth. However, the relevance of this to the management of women with ruptured membranes is unclear because neonates born from pregnancies complicated by preterm PROM have a higher rate of adverse outcomes compared with controls."

11. Citations for other excerpts

ACOG practice bulletin Jan2016. Premature Rupture of Membranes, Practice Bulletin Summary 160 , January 2016.

"At 34 0/7 weeks or greater gestation, delivery is recommended for all women with ruptured membranes. " (Level B)

12. Bottom line recommendation or summary of evidence from Other Sources (1-2 sentences)

Resources report this current review, but still show that they prefer to default to delivery at this gestation of 34 0/7-36 6/7 so far, often citing the ACOG bulletin update on this issue.

SECTION 4: Conclusions

**[to be completed by the Potential PURL Reviewer]
[to be revised by the Pending PURL Reviewer as needed]**

1. Validity: How well does the study minimize sources of internal bias and maximize internal validity?

Give one number on a scale of 1 to 7
(1=extremely well; 4=neutral; 7=extremely poorly)
1 2 3 4 5 6 7

2. If 4.1 was coded as 4, 5, 6, or 7, please describe the potential bias and how it could affect the study results. Specifically, what is the likely direction in which potential sources of internal bias might affect the results?

since multicenter, may be hard to be sure about internal bias

3. Relevance: Are the results of this study generalizable to and relevant to the health care needs of patients cared for by "full scope" family physicians?

Give one number on a scale of 1 to 7
(1=extremely well; 4=neutral; 7=extremely poorly)
1 2 3 4 5 6 7

4. If 4.3 was coded as 4, 5, 6, or 7, please provide an

explanation.

5. Practice changing

potential: If the findings of the study are both valid and relevant, does the practice that would be based on these findings represent a change from current practice?

6. If 4.5 was coded as 1, 2, 3, or 4, please describe the potential new practice recommendation. Please be specific about what should be done, the target patient population and the expected benefit.

7. Applicability to a Family

Medical Care Setting:

Is the change in practice recommendation something that could be done in a medical care setting by a family physician (office, hospital, nursing home, etc), such as a prescribing a medication, vitamin or herbal remedy; performing or ordering a diagnostic test; performing or referring for a procedure; advising, educating or counseling a patient; or creating a system for implementing an intervention?

8. If you coded 4.7 as a 4, 5, 6 or 7, please explain.

9. Immediacy of

Implementation: Are there major barriers to immediate implementation? Would the cost or the potential for reimbursement prohibit implementation in most family medicine practices? Are there regulatory issues that prohibit implementation? Is the service, device, drug or other essentials available on the market?

10. If you coded 4.9 as 4, 5, 6, or 7, please explain why.

11. Clinical meaningful outcomes or patient oriented outcomes

oriented outcomes: Are the outcomes measured in the study clinically meaningful or patient oriented?

Give one number on a scale of 1 to 7

(1=definitely a change from current practice; 4=uncertain; 7=definitely not a change from current practice)

1 2 3 4 5 6 7

need input from my Delivering colleagues

Give one number on a scale of 1 to 7

(1=definitely could be done in a medical care setting; 4=uncertain; 7=definitely could not be done in a medical care setting)

1 2 3 4 5 6 7

Give one number on a scale of 1 to 7

(1=definitely could be immediately applied; 4=uncertain; 7=definitely could not be immediately applied)

1 2 3 4 5 6 7

some hospital policy and protocols might need to be changed in some settings.

Give one number on a scale of 1 to 7

(1=definitely clinically meaningful or patient oriented; 4=uncertain; 7=definitely not clinically meaningful or patient oriented)

1 2 3 4 5 6 7

12. If you coded 4.11 as a 4, 5, 6, or 7 please explain why.

13. In your opinion, is this a Pending PURL?

Criteria for a Pending PURL:

- Valid: Strong internal scientific validity; the findings appears to be true.
- Relevant: Relevant to the practice of family medicine
- Practice changing: There is a specific identifiable new practice recommendation that is applicable to what family physicians do in medical care settings and seems different than current practice.
- Applicability in medical setting:
- Immediacy of implementation

14. Comments on your response in 4.13

Give one number on a scale of 1 to 7

(1=definitely a Pending PURL; 4=uncertain; 7=definitely not a Pending PURL)

1 2 3 4 5 6 7

need input on practice changing aspect