Research article

Antibiotics for women with prelabour rupture of membranes at term, undergoing induction of labour after 12 hours – *A randomized controlled trial*

S N M P K Gunathilaka[a], **D P G G M Prasanga**[b], **A Karunananda**[c]

Abstract

Background: Evidence for the benefits of antibiotics in prelabour rupture of membranes (PROM) at term is limited.

Aim: To evaluate the effectiveness of Cefuroxime in mothers with PROM at term undergoing induction of labour after 12 hours, in reducing feto-maternal and neonatal infections compared to a group without antibiotics.

Methods: We conducted a single centre randomized controlled trial involving 118 participants presented to professorial Obstetric unit at Teaching Hospital Peradeniya, Sri Lanka. Women with live singleton pregnancies at term (37-42 weeks of gestation) with PROM for less than 12 hours without uterine activity on admission were recruited. Participants were randomly allocated to two groups, one with antibiotic coverage (Cefuroxime) and the other without. All mothers were induced with oxytocin, if labour was not started spontaneously by 12 hours of PROM. Primary study outcomes were development of chorioamnionitis, postpartum endometritis and neonatal infection.

Results: One mother in the intervention arm (n=60) and two in the control arm (n=58) developed chorioamnionitis. There were no cases of post-partum endometritis in the intervention arm, but two were noted in the control arm. One neonate in the intervention arm and three in the control arm had sepsis. None of these three outcome measures; chorioamnionitis (OR-0.5, 95% CI 0-5.3), neonatal sepsis (OR-0.3, 95% CI 0.0-3.0) and post-partum endometritis (OR - 0.2, 95% CI 0.0-3.9) showed any significant difference between the two groups. Post-partum sepsis was not reported in both arms. Altogether, there was no statistically significant difference in maternal infection related morbidities in the intervention (n=60, 1.66%) or the control group (n=58, 6.89%) (OR-0.3, 95% CI 0.0-2.2).

Conclusions: Use of antibiotics in mothers with term PROM does not provide any significant effect on any of its outcome measures with induction of labour after 12 hours of membrane rupture, particularly in terms of maternal and neonatal infection related morbidities.

Sri Lanka Journal of Obstetrics and Gynaecology 2020; **42:** 12-20

DOI: http://doi.org/10.4038/sljog.v42i1.7927

[a] *Senior Registrar, Obstetrics and Gynaecology, Hervey Bay Hospital, Australia.*
[b] *Senior Registrar, Obstetrics and Gynaecology, WH Sunshine Hospital, Australia.*
[c] *Consultant Obstetrician and Gynaecologist, Teaching Hospital, Peradeniya, Sri Lanka.*

Correspondence: SNMPKG, e-mail: punsirikamal@yahoo.com

Received 16th April 2019.

https://orcid.org/0000-0002-3806-3969

Introduction

Prelabour rupture of membranes (PROM) is generally considered as spontaneous membrane rupture with leakage of amniotic fluid prior to onset of labour. When this occurs between 37 to 42 weeks of gestation, it is termed as "Term PROM"[1]. It is seen in 10% of all pregnancies and 84% occurs at term[2,3,4]. Judicious assessment of history, clinical findings and investigations are required for its diagnosis. Whenever the history is suggestive of membrane rupture (dribbling), its confirmation can be done by visual inspection of leaking of liquor through the "cervical os" using a sterile speculum[3,6]. Even though the reasons are not clear, ascending infections are thought to play a role in about 1/3rd of term PROM cases[2,3,4,7].

Antibacterial properties of amniotic fluid inhibit the growth of anaerobic and aerobic bacteria. But it is more prone to become infected with PROM due to migrating bacteria from vagina[8], increasing the risk of foetal, maternal and neonatal infections. These infections can be caused by organisms resident in normal vaginal flora, in addition to the well-recognized pathogens in foetal, neonatal or maternal infections such as group B *Streptococcus, Neisseria gonorrhoea* and *Listeria monocytogenes*[2].

According to some literature the incidence of chorioamnionitis in term PROM is about 6 to 10% and it increases up to 40% when membranes are ruptured for more than 24 hours[8]. Subsequent development of chorioamnionitis is enhanced by labour duration and number of vaginal examinations. Labour lasting for more than 24 hours and vaginal examinations more than 08 are strongly associated with chorioamnionitis [9,10]. Other factors which are significantly associated with chorioamnionitis are meconium stained liquor, maternal colonization with Group B *Streptococcus* (GBS), increase duration of latent period and primiparity[2].

There is no consensus over the use of prophylactic antibiotics in PROM. Therefore, some may argue that starting a prophylactic antibiotic for prevention of foetal, neonatal or maternal infections is important, while others may disagree.

Limited studies on this area have shown a reduction in maternal infectious related morbidity (chorioamnionitis and endometritis) without clear neonatal benefits[6,11]. Different antibiotics were used in these studies, such as IV Cefuroxime and Clindamycin[11] and IV Ampicillin and Gentamycin[6].

Cefuroxime is commonly used locally as a therapeutic and prophylactic antibiotic during pregnancy. It covers a wide range of organisms including those associated with intrauterine infections. It is resistant to beta lactamase enzyme by bacteria, has favourable pharmacokinetic properties and less in toxicity[12]. When given intravenously it can achieve well above its therapeutic concentrations in infant serum, cord blood and amniotic fluid in labouring women than when given orally[12,13,14,15]. Minimal inhibitory concentration is achieved when 1st dose is given within two hours prior to delivery for organisms such as GBS.

A cochrane review in 2012 showed a reduced risk of uterine infection with routine use of antibiotics in term PROM but there were no strong evidences on neonatal infections and complications[16]. The conclusions of this review were limited due to small sample sizes and low maternal infection rates in control groups. The information on adverse effects of the antibiotics on mothers or infants was insufficient too. This review emphasized the need of a randomized control trial to assess the routine use of antibiotics with a broad spectrum cover in term PROM[16]. However, the updated Cochrane review published while this study was ongoing, showed no evidence of benefit in using antibiotics for both mothers and the neonates[27].

Neither antenatal GBS screening nor rapid tests to diagnose GBS infection are available in local setup. Therefore some believe the use of a prophylactic antibiotic in term PROM is wiser in our setting with the background of limited neonatal support.

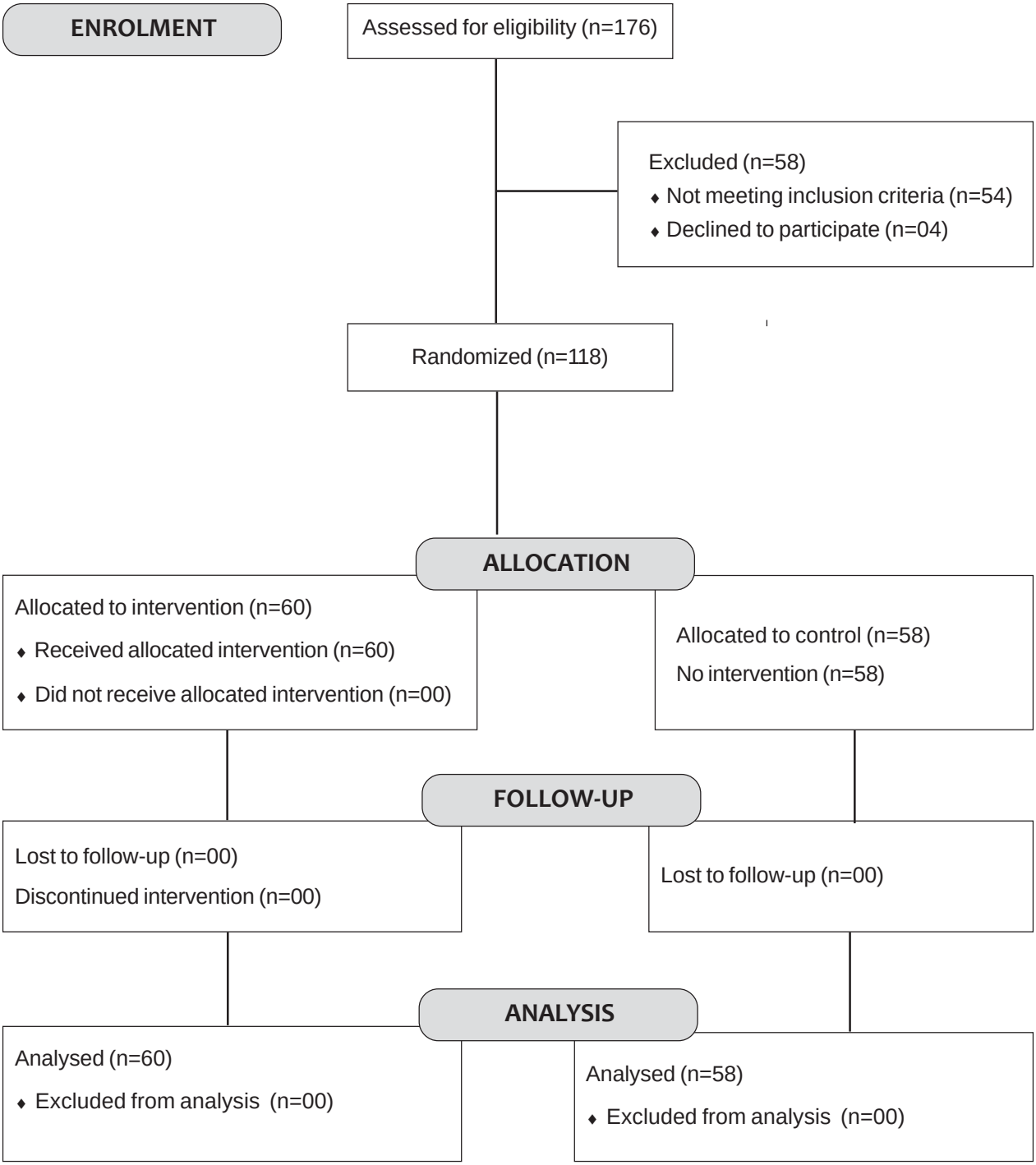
The study aims at identifying whether there are benefits of antibiotics in PROM on maternal and neonatal wellbeing are significant on prevention of chorioamnionitis, postpartum endometritis/sepsis and neonatal sepsis. Cefuroxime is used as the prophylactic antibiotic.

Materials and methods

Trial organization

This study was conducted as a single centre randomized controlled trial in accordance with CONSORT trial guidelines. It compared the outcomes of mothers with term PROM and their infants who had antibiotic, with outcomes of control group; those without antibiotic.

CONSORT Flow Diagram



Study setting, population and participant recruitment

The study was conducted in the wards 10, 11 and labour room of the professorial Obstetrics unit at Teaching Hospital, Peradeniya, Sri Lanka from July 2014 to March 2015.

Pregnant women admitted with PROM at term, who support inclusion and exclusion criteria, were recruited.

Informed, written consent was taken from eligible mothers. They were randomized to receive the antibiotic or not, using a computer generated randomization table by the admitting medical officer who was not involved in further management.

Inclusion and exclusion criteria

The inclusion criteria were gestational age more than 37 and less than 42 weeks (Confirmed by ultra sound scan (USS) at first trimester), singleton pregnancies with cephalic presentation, ruptured membranes for less than 12 hrs and absence of uterine contractions on admission.

Mothers with fetal anomalies, intra uterine deaths, placenta praevia, placental abruptions, chorioamnionitis, planned or indicated for a caesarean section (CS) on admission, allergic to cephalosporins or penicillin and contraindicated for oxytocin usage were excluded from the study.

Sample size calculation

In the study by Ovalle A[11], patients who received the prophylactic antibiotic showed 1.8% incidence of chorioamnionitis and puerperal endometritis and patients who received the placebo showed an incidence of 16%. Considering the above percentages, the sample size was calculated using standard formula[26].

Expecting a drop rate of 5%, a sample of 124 patients were planned to recruit for the study with 62 per each arm.

Trial procedures

The subjects were numbered in order of admission and categorized into two groups using computer based randomization table. Vaginal swabs were taken during speculum examination and digital vaginal examinations were avoided until onset of labor or induction. Maternal full blood count and fetal cardiotocogram were done on admission.

After initial evaluation antibiotics were administered to mothers assigned to group "A" by nursing officers in the antenatal ward. Intravenous Cefuroxime 750 mg 08 hourly for 24 hours followed by oral cefuroxime 500 mg 12 hourly for 48 hours were given while there were no antibiotics for the control group B.

Mothers who had spontaneous onset of labour within 12 hours were sent to the labour room and oxytocin was used if needed. Mothers without spontaneous onset of labour by 12 hours of rupture of membranes were induced with oxytocin; primi gravida with 5 and multi gravida with 2 units in 500 ml of normal saline, starting with 10 drops per minute and the rates were titrated according to contractions with a maximum of 05 contractions per 10 min.

Maternal body temperature (oral), pulse rate, uterine tenderness and presence of an offensive vaginal discharge were monitored four hourly. If temperature was more than 38°C, C Reactive Protein (CRP) and Full Blood Cell (FBC) count were done. Uterine tenderness was assessed on relaxed uteruses and fetal heart rate was monitored every 15 min with a hand held Doppler.

Vaginal examinations were done every 04 hourly unless frequent examinations were needed. If signs and symptoms of chorioamnionitis were detected in control group, antibiotics were started immediately. For each case, mode of delivery was decided by considering the safest option for the mother and the fetus.

In post natal ward mothers and their babies were assessed for evidences of infection, daily until 3rd day. Mothers with postpartum fevers (>38°C); even a single fever spike, were investigated with FBC, CRP and blood cultures.

Neonates with any symptoms or signs of infection, were investigated with CRP, FBC and blood cultures.

Definitions

Chorioamnionitis:

Southern Australian Perinatal Practice Guidelines[25] were used for the diagnosis.

Presence of fever (>38°C) before delivery and two of the followings,

- Maternal tachycardia >100 bpm
- Fetal tachycardia > 160 bpm
- Uterine tenderness (Assessment done routinely in all the mothers in labour)
- Offensive vaginal discharge
- Raised CRP > 40 mg/L
- Increased White Blood Cell (WBC) count > 15 × 10^9/L

Postpartum endometritis:

Fever (>38°C)[24] hours after delivery in the absence of other maternal causes, with one of the followings[6]: Uterine tenderness, WBC count >15 × 10^9/L, and CRP > 20mg/ L

Post-partum sepsis:

Fever (>38°C); even a single spike, with a positive blood culture report[6].

Neonatal sepsis:

Raised CRP (>20 mg/L), WBC <5 or >30 × 10^9/L or positive blood cultures with atleast one of the following[6]; hypo or hyperthermia, lethargy, poor feeding, tachypnoea, abdominal bloating or vomiting.

Following parameters were recorded by the medical officer in the post-natal ward who was unaware of the patient's study group.

- Time from PROM to induction of labour
- Time from PROM to delivery
- Time from induction to delivery
- Number of vaginal examinations
- Mode of delivery
- Development of chorioamnionitis
- Postpartum endometritis

Outcomes recorded in newborns were; Apgar score at 5 min, birth weight, and presence of neonatal sepsis.

Primary and secondary outcomes:

Chorioamnionitis, postpartum endometritis, postpartum sepsis and neonatal sepsis were the outcomes of the study.

Statistical analysis

All the outcome measures were analyzed by a person who was not involved in the research using the Statistical Package for the Social Sciences (SPSS) version 20. As the data were normally distributed the Chi-squared test and the student's t-test were used to compare the means and proportions. P value less than 0.05 was considered as statistically significant.

Ethical considerations

Ethical clearance for the study was obtained from the Ethical Review Committee of Faculty of Medicine, University of Peradeniya. The study was registered in Sri Lanka Clinical Trial Registry (SLCTR/2014/013).

Results

A total of 118 subjects were studied. Among them 60 were in the intervention arm (A); with antibiotics and 58 were in the control arm (B), without antibiotics.The mean age in Group A and B were 27.5 (5.0) and 29 (5.6) respectively (Table 1). Its level of significance was 0.1. Mean Body Mass Index (BMI) in Group A was 26.2 (3.3) and was 26.2 (3.4) in group B, with a level of significance of 0.9. The mean period of gestation (POG) in Group A and B were 38.8 with similar SD of 1.1. There was no statistically significant difference in age, BMI, POG and proportion of primi gravida between the two groups.

When considering the durations of PROM before admission, there was no statistically significant difference between the intervention and control groups (A -158.0 ±137.5, B -142.5 ± 117.3 p=0.512). Similarly, there was no statistically significant difference in Bishop scores of the groups on admission to the labour room (A - 7.7 ± 2.1, B - 7.6 ± 2.0, p=0.507), in the time from onset of PROM to delivery (A -539.9 ± 243.7, B - 549.7 ± 286.9, p=0.841) and the duration of labour (A -379.9±187.1, B - 385.5 ± 190.4, p=0.873) (Table 1).

There was no statistically significant difference in the number of vaginal examinations performed (A-3.8±1.5, B - 3.8±1.6, p=0.886) and the birth weight of the neonates in each group (A - 2.8 ± 0.4, B - 2.8 ± 0.4, p=0.985). Five mothers in the intervention arm (n=60) and six mothers in the control arm (n=58) had caesarean sections on obstetric indications (Table 1), with no statistically significant difference (p=0.76).

Table 1. Summary of demographic and basic clinical details

	Intervention group (n = 60)	Control group (n = 58)	Level of significance (P)
Age – Mean (SD)	27.5 (5.0)	29 (5.6)	0.124
BMI – Mean (SD)	26.2 (3.3)	26.2 (3.4)	0.999
Parity – Mean (SD)	2 (1.4)	2 (1.4)	0.680
POG – Mean (SD)	38.8 (1.1)	38.8 (1.1)	0.788
ROM prior to include into study min Mean (SD)	158 (137.5)	142.5 (117.3)	0.512
Bishop score at LR Mean (SD)	7.7 (2.1)	7.6 (2.0)	0.507
Number of VE Mean (SD)	4 (1.5)	4 (1.6)	0.886
IOL to delivery time min Mean (SD)	379.9 (187.1)	385.4 (190.4)	0.873
ROM to delivery time min Mean (SD)	539.9 (243.7)	549.7 (286.9)	0.841
Birth weight in kg Mean (SD)	2.8 (0.4)	2.8 (0.4)	0.985
Caesarean sections	5 (8.33%)	6 (10.34%)	P=0.76

BMI – Body mass index; IOL – Induction of labour; ROM – Rupture of membranes; VE – Vaginal examinations

When indications for caesarean sections were concerned majority in the intervention arm were due to fetal distress (n=2) and lack of progress (n=2) sharing 40% in each, while lack of progress was the major indication in control arm (n=3, 50%) (Table 2). One caesarean section in the intervention group and two in the control group were done due to chorioamnionitis. There were no neonates with Apgar scores of less than seven at 5 minutes in any arm.

Chorioamnionitis

There was a single case of chorioamnionitis in the intervention arm and two in the control arm (OR-0.5,95% CI 0.04-5.27). All the mothers with chorioamnionitis responded well to the treatment and were asymptomatic following delivery.

Neonatal sepsis

One neonate in the intervention arm and three in the control arm developed sepsis (OR-0.3, 95% CI 0.0-3.0). One septic neonate's mother in the control arm had chorioamnionitis before delivery. The other two mothers in the control arm and the mother of the septic neonate in the intervention arm did not have any infection related morbidity during the study period.

Postpartum endometritis and postpartum sepsis

No one developed postpartum endometritis in the intervention arm. However, two cases of post-partum endometritis were seen in the control arm on day 2 and 3. They were asymptomatic during ante-partum and intrapartum period. The difference of postpartum endometritis in the two groups was not statistically significant (OR - 0.2, 95% CI 0.01-3.88) (Table 3). None of the mothers developed post-partum sepsis.

Discussion

Current study revealed that the use of antibiotics prior to delivery in mothers with term prelabour rupture of membranes has no significant effect on reducing maternal or neonatal infection related morbidities with induction of labour after 12 hours of membrane rupture.

Occurrence of chorioamnionitis is multifactorial and hence the incidence is highly variable[6,11,17,22]. The incidence of chorioamnionitis in our study was relatively low; 1.67% in intervention arm and 3.45% in control arm; compared to studies by Carrach et al (3.2%, 4.7%)[6] and Ovalle A et al (1.8%, 16%)[11]. Further it is less than the incidences in "International Multi-centre Term PROM Study" (6.7%)[17] and in studies by Newton et al[22] (4.3%) Soper et al (10.5%, 7.9%)[23,24], which were aiming to find out the impact of PROM. Early induction and use of strict clinical criteria for diagnosis might have been the reasons for the low incidence of chorioamnionitis in our study.

Table 2. Indications for caesarean sections

Indication for caesarean section	Intervention group	Control group
Fetal distress	2 (40%)	2 (33.33%)
Lack of progress	2 (40%)	3 (50%)
Chorioamnionitis	1 (20%)	1 (16.66%)

Table 3. Postpartum complications

Complication	Intervention group (n = 60)	Control group (n = 58)	OR (95% CI)
Chorioamnionitis	01 (1.67%)	02 (3.45%)	0.47 (0.04-5.27)
Postpartum endometritis	00 (0%)	02 (3.45%)	0.19 (0.01-3.88)
Postpartum sepsis	00	00	
Maternal infection related morbidity	01 (1.66%)	04 (6.89%)	0.25 (0.03-2.22)
Neonatal sepsis	01 (1.67%)	03 (5.17%)	0.31 (0.03-3.02)
PBU admissions	02 (3.33%)	03 (5.17%)	0.63 (0.1-3.87)
Apgar < 7 at 5min	00	00	

Even though the rate of chorioamnionitis was low in intervention arm, the difference was not statistically significant (OR-0.47, 95% CI 0.04-5.27). This was keeping with the results of the study by Carrach et al[6] where intravenous Ampicillin and intramuscular Gentamycin used as the antibiotic. Similarly the intervention group had a low rate of endometritis compared to the control group and the difference was not significant which is in line with our study.

However, the study by Ovalle A. et al[11] showed a statistically significant difference in maternal infection related morbidity (Chorioamnionitis and endometritis), 1.8% versus 16% (P <0.05) in intervention and control arms respectively. Cefuroxime 750 mg intravenously every 8 h for 48 h, and clindamycin 600 mg intravenously every 6 h for 48 h, followed by orally: cefuroxime 250 mg every 12 h and clindamycin 300 mg every 6 h, up to 24 h were used as the antibiotic in their study and patients were induced with oxytocin within 24 h after admission. The late induction; 24 hours after admission might have been the cause for this difference.

When neonatal outcome is concerned, one neonate in the intervention arm (n=60) and three neonates in the control arm (n=58) had sepsis. The difference was not statistically significant (OR-0.31, 95% CI 0.03-3.02) which is similar to the findings of the study by Ovalle A. et al[11]. However there was a significant difference in neonatal sepsis in the study by Carrach et al[6].

The revised cochrane review on antibiotics for prelabour rupture of membranes at or near term was published while this study was ongoing. It showed no evidence of benefit in using antibiotics for both mothers and the neonates which is compatible with our conclusion[27].

Allergic reactions to cefuroxime were not reported in any of the cases in the intervention arm.

Conclusions

Use of antibiotics prior to delivery in term PROM has no significant effects on preventing maternal postpartum and neonatal complications; particularly in terms of infection related morbidities with early induction of labour.

Limitations

A placebo was not used for the control arm due to logistic and practical constraints, and also the study outcomes would have been further improved with a use of confirmatory test to diagnose PROM such as Amnisure.

Acknowledgements

Authors wish to thank all the mothers who took part in the study. Moreover we are grateful to Medical officers, nursing and midwifery officers of wards 10, 11 and labour ward in Teaching Hospital, Peradeniya, Sri Lanka for their valuable support in conducting this study.

References

1. Lusely DM, Philip NB. Prelabour rupture of membranes in Obstetrics and Gynaecology – An evidence based text for MRCOG. 2nd Ed, Vol 22: Edward Arnold Publishers UK.2004; 309-11.
2. Hannah ME, Seaward GR. Prelabour rupture of membranes at term: The role of induction of labour. Foetal and Maternal Medicine Review 1998; 10: 61-8.
3. Gunn GC, Mishell DRJ, Morton DG. Premature rupture of the foetal membranes. Am J Obstet Gynecology1970; 106: 469-83.
4. Grant J, Keirse MJNC. Prelabour rupture of membranes at term in effective care in pregnancy and child birth. Vol 2: Oxford University Press. 1989; 1112-7.
5. Brian M Mercer. Preterm premature rupture of membranes in Management of High Risk Pregnancy. 5th Ed, Blackwell Publishing Ltd, Oxford, UK. 2007; 345-51.
6. Carrach V, Botet F, Sentis J, et al. Administration of antibiotics to patients with rupture of membranes at term. Acta Obstet Gynaecologia Scandinavica 1998; 77: 298-302.
7. Alger LS, Pupkin MJ. Etiology of the premature rupture of the membranes. Clinical Obstetrics and Gynaecology 1986; 9: 758-70.
8. Miller JM, Pastrovek JG. The microbiology of premature rupture of membranes. Clinical Obstetrics and Gynaecology 1986; 29: 739-57.

9. Gareth Seaward, Hannah ME, et al. International multicentre Term PROM study: Evaluation of predictors of neonatal infection in infants born to patients with premature rupture of membranes at term. American Journal of Obstetrics and Gynaecology 1998 September; 179 (3): 635-9.

10. Hannah M E, Ohisson A, Farine D, et al. Induction of labour compared with expectant management for pre labour rupture of membranes at term. New England Journal of Medicine 1996; 334 (16): 1005-10.

11. Ovalle A, Martinez M, Giglio M, et al. Antibiotic treatment of patients with term premature rupture of membranes reduces the incidence of infection related complications. American Journal of Obstetrics and Gynaecology 1995; 172: 301.

12. Bousefield P, Browning AK, Mullinger BM, et al. Cefuroxime: Potential use in pregnant women at term. British Journal of Obstetrics and Gynaecology 1981; 88: 146-9.

13. Bergogne-Berezin, Pierre E, et al. Current Chemotherapy and Infectious disease – Proceedings of the 19th Inter science Conference on Antimicrobial Agents and Chemotherapy 1979; 2: 1168.

14. Craft I, Mullinger BM, et al. Current Chemotherapy and Infectious disease – Proceedings of the 19th Inter science Conference on Anti-microbial Agents and Chemotherapy 1979; 2: 1144.

15. Royal College of Obstetrics and Gynaecology. Greentop Guideline 36, 2012. available at http:// www.rcog.org.uk/womens-health/clinical guidance (Accessed 04 July 2013).

16. Chochrane database of systematic reviews. Antibiotics for prelabour rupture of membranes at or near term (review) issue 3, 2012. Available at http://www.thecochranelibrary.com (Accessed on 14 August 2013).

17. Seaward PG, Mary E Hannah, Terri L, et al. International Multicentre Term Prelabour Rupture of Membranes study: Evaluation of predictors of clinical chorioamnionitis and postpartum fever in patients with prelabour rupture of membranes at term. American Journal of Obstetrics and Gynaecology 1997; 177 (5): 1025-29.

18. Romero R, Mazor M, Morotti R, et al. Microbial invasion of the amniotic in spontaneous rupture of membranes at term. American Journal of Obstetrics and Gynaecology 1992; 166 (11): 129-33.

19. Banerjee S, Sanyal S, Banerjee U, et al. Pre labour rupture of membranes and bacteriological profile. Journal of Indian Medical Association 1997; 95 (9): 500-4.

20. Alexander JM, Mercer BM, Midovink M, Thurnau GP, et al. The impact of digital cervical examination on expectantly managed preterm rupture of membranes. American Journal of Obstetrics and Gynaecology 2000; 183: 1003-7.

21. Shuttle MF, Treflers PE, Kloosterman GJ, et al. Management of premature rupture of membranes: The risk of vaginal examination to infant. American Journal of Obstetrics and Gynaecology 1983; 146: 395-400.

22. Newton ER, Prihoda TJ, et al. Logistic regression analysis of risk factors for intra amniotic infection. Obstetrics and Gynaecology 1989; 73: 571-5.

23. Soper DE, Mayhall CG, Froggatt JW, et al. Risk factors for intra amniotic infection: A prospective study. American Journal of Obstetrics and Gynaecology 1989; 161: 562-8.

24. Soper DE, Mayhall CG, Froggatt JW, et al. Characterization and control of intra amniotic infection in an Urban Teaching Hospital. American Journal of Obstetrics and Gynaecology 1996; 175: 304-10.

25. Southern Australian Perinatal Practice Guideline. Prelabour rupture of membranes >37 wks Chapter 08, 2011. Available at http:// www.southern Australian perinatal guidelines.com (accessed 14 July 2013).

26. Stuart J Procock. Sample size calculation in clinical trials and practical approach. Jhonwiley and Sons, UK. 1983.

27. Chochrane database of systematic reviews. Antibiotics for prelabour rupture of membranes at or near term, 29 October 2014. Available at https:/ /doi.org/10.1002/14651858.CD001807.pub2 (Accessed on 16 January 2020).