

**NEONATAL SEPSIS IN TERM NEONATES BORN TO MOTHERS WITH
PROLONGED RUPTURE OF MEMBRANE IN HOSPITAL UNIVERSITI SAINS
MALAYSIA**

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**DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE
REQUIREMENTS FOR THE DEGREE OF MASTER OF MEDICINE
(PAEDIATRICS)**



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We must be willing to get rid of the life we have planned, so as to have the life that is waiting for us – Joseph Campbell

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LIST OF ABBREVIATION AND NOMENCLATURE

PROM	Prolonged rupture of membranes
CRP	C-Reactive Protein
TWC	Total white count
PLT	Platelets
Hospital USM	Hospital Universiti Sains Malaysia
SVD	Spontaneous vaginal delivery
LSCS	Lower section caesarean section
VAD	Vacuum-assisted delivery
GBS	Group B Streptococcus
UTI	Urinary tract infection

NEONATAL SEPSIS IN TERM NEONATES BORN TO MOTHERS WITH PROLONGED RUPTURE OF MEMBRANES IN HOSPITAL UNIVERSITI SAINS MALAYSIA

ABSTRACT

Background: Prolonged rupture of membrane (PROM) is the most common problem in obstetrics complaints which consists of approximately 8-10% in all pregnancy and 60% occur at term. The aim of this study was to determine the proportion of neonatal sepsis among term neonates (≥ 37 weeks gestation) born to mother with PROM and its associated factors.

Methods: This prospective study was performed at a tertiary center, from July 2021 to January 2022. All neonates born to mothers with PROM at 37 weeks gestation and above were included in this study. Factors studied were maternal urinary tract infection, maternal chorioamnionitis, maternal high vaginal swab cultures, methods of delivery, intrapartum antibiotics, and neonatal gender. Simple and multiple logistic regression was performed to identify the associated factors and predictors for neonatal sepsis

Results: There were 5934 infants born during this study period. About 136 term neonates fulfilled the inclusion criteria and were evaluated. The incidence rate of PROM is 2.2%. Meanwhile, the proportion of neonatal clinical sepsis is 50% among term neonates with maternal PROM. Multivariate analysis showed no significant predictor for neonatal sepsis.

Conclusion: Clinical sepsis is a relevant complication of PROM. There is no significant factor maternal risk factor following PROM for neonatal sepsis. However, early detection of signs and symptoms of neonatal sepsis is important to reduce the risk of mortality as well as morbidity.

Keyword: Prolonged rupture of membranes (PROM), term neonates, sepsis

ABSTRAK

Pengenalan: Prolonged rupture of membranes (PROM) atau dikenali sebagai pecah air ketuban sebelum bersalin merupakan masalah yang paling sering ditemukan dalam aduan obstetrik. Lebih kurang 8-10%, pesakit datang dengan simptom pecah air ketuban sebelum bersalin dan dari jumlah tersebut kira-kira 60% simptom ini terjadi pada kehamilan cukup bulan. Tujuan kajian ini dijalankan adalah untuk menentukan kadar insiden pecah air ketuban sebelum bersalin, serta mengenal pasti faktor risiko lain terhadap ibu dan komplikasi terhadap bayi daripada ibu yang datang dengan symptom pecah air ketuban sebelum bersalin.

Kaedah: Ini adalah kajian prospektif yang telah dijalankan di Hospital Sains Malaysia, Kubang Kerian, Kelantan, bermula dari Julai 2021 sehingga Januari 2022. Bayi yang lahir daripada ibu yang mengalami pecah air ketuban sebelum kelahiran pada kehamilan lebih daripada 37 minggu termasuk dalam kajian ini. Selain itu juga, factor risiko wanita hamil lain seperti jangkitan kuman air kencing, jangkitan kuman, jenis kelahiran, penggunaan antibiotic semasa proses kelahiran dinilai. Statistik dibuat untuk mengenal pasti faktor risiko wanita hamil terhadap jangkitan kuman kepada bayi.

Keputusan: 5934 orang bayi lahir sepanjang tempoh kajian ini dijalankan. 136 orang bayi yang memenuhi inklusi kriteria. Kadar insiden PROM adalah 2.2% sementara 50% adalah kadar jangkitan kuman dikalangan bayi sepanjang tempoh kajian ini dijalankan. Walau bagaimanapun, analisis multivariat menunjukkan bahawa tiada faktor-faktor yang ketara di antara ibu hamil terhadap kadar jangkitan kuman di kalangan bayi.

Kesimpulan: Jangkitan kuman merupakan salah satu komplikasi utama daripada ibu hamil yang mengalami pecah air ketuban. Walau bagaimana pon daripada hasil kajian ini tidak menunjukkan faktor ketara antara ibu hamil dengan kadar jangkitan kuman tetapi kita mestilah mengenal pasti tanda-tanda awal jangkitan kuman untuk mengurangkan risiko kematian dan jugak komplikasi lain dikalangan bayi baru lahir.

Kata Kunci: Prolonged rupture of membranes (PROM), neonate, sepsis

CHAPTER II:

THE TEXT

Section A:

Introduction

INTRODUCTION

Prolonged rupture of membranes (PROM) is defined as the rupture of amniotic membranes 12–18 hours or more prior to delivery of the baby and is a common cause of hospital admission and antibiotic use. ⁽¹⁾ The incidence of PROM worldwide is varying, ranging from 5-10% as recorded by the World Health Organization. ^(1,24)

The etiology of PROM seems to be multifactorial. Several predisposing factors like black race, low socioeconomic level and smoking, history of PROM in previous pregnancy, vaginal bleeding, multifetal pregnancy and polyhydramnios may play role in PROM. ⁽³⁾ Although prenatal care has been developed, but severe complications related to PROM is still occurring among mothers and foetus ⁽⁵⁾

As been reported by many studies, the most common and serious complication of PROM is neonatal sepsis. ⁽¹⁾ When PROM occurs, the rate of neonatal infections will increase relatively by ten folds. ⁽²⁾ In 2020, WHO reported that 24% of neonatal deaths are caused by severe neonatal infection. ⁽²⁴⁾

The association between neonatal sepsis and the duration of membrane rupture was first reported in 1963 in a study which showed a higher rate of newborn with either clinical or proven sepsis to mothers with ruptured membranes of more than 6 hours. ⁽¹⁾

At present, there are limited studies on PROM in relation to neonatal sepsis in Southeast Asian countries including Malaysia. Most of the studies focus on mothers with a gestational age of 34 and above.

We decided to perform this study to determine the proportion of neonatal sepsis among term neonates (≥ 37 weeks gestation) born to mother with PROM and its associated factor

SECTION B:
STUDY PROTOCOL

2.2.1 Documents submitted for ethical approval

Research title:

NEONATAL SEPSIS IN TERM NEONATES BORN TO MOTHER WITH PROLONGED RUPTURE OF MEMBRANES IN HOSPITAL UNIVERSITI SAINS MALAYSIA

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1. INTRODUCTION**1.1 BACKGROUND**

Prolonged rupture of membranes (PROM) is defined as the rupture of amniotic membranes 12–18 hours or more prior to delivery of the baby and is a common cause of hospital admission and antibiotic use¹. The incidence of PROM worldwide is variable, ranging from 8-10% as recorded by the World Health Organization. PROM complicates approximately 8%–10% of all pregnancies, and 60% of PROM occurs at term. When it occurs, the rate of neonatal infection will increase relatively ten folds².

The etiology of PROM seems to be multifactorial. Several predisposing factors like black race, low socioeconomic level, smoking habit, history of PROM in a previous pregnancy, vaginal bleeding, multifetal pregnancy, and polyhydramnios may play role in PROM⁴. Although prenatal care has been improved, severe complications related to PROM are still occurring among mothers and fetuses⁵.

The association between neonatal sepsis and the duration of membrane rupture was first reported in 1963 in a study that showed a higher rate of newborns with either clinical or proven sepsis to mothers with ruptured membranes of more than 6 hours⁶. The most significant maternal risk of term PROM is intrauterine infection, the risks of which increase with the duration of membrane rupture⁷.

In 2005, the WHO reported that 37% of child mortality occurs below 5 years of age, and neonatal sepsis accounted for 29% of deaths within that age group. Results of an epidemiological study done by the WHO and UNICEF in 2010 found that there were 7.6 million cases of under-five mortality, of which 64% (4.879 million) occurred due to infection and the remaining 40.3% (3.072 million) occurred in neonates⁷.

1.2 JUSTIFICATION TO CONDUCT THE STUDY

Problem statement/rationale:

- In the absence of early specific and sensitive diagnostic tools for neonatal sepsis, management of infants born to mothers with PROM proves to be a dilemma, especially for asymptomatic term neonates at birth
- This diagnostic challenge might justify the practice of admitting all neonates born to mothers with PROM and administering empirical broad-spectrum antibiotics.
- This is where the problem lies, as many of these asymptomatic neonates do not have sepsis, and yet take empirical antibiotics for an extended period.
- This practice drastically increases the load on neonatal units and exposes the neonates to hospital-acquired infections and medication side effects
- This study also reviews the outcome of neonates to mothers with PROM and identify significant risk factors that indicate the need for antibiotic administration.

1.2 LITERATURE REVIEW

Manae Al-Lawana et al conducted a study regarding Prolonged Rupture of Membranes, Neonatal Outcomes, and Management Guidelines and was published in 2019. This study was conducted in Jordan University Hospital NICU. The main objective is to evaluate the clinical outcomes of newborns exposed to PROM and their incidence of early onset of sepsis (EOS). All admitted neonates born to mothers with PROM between January 2011 and December 2015 were included. They were identified from the hospital database. Their medical charts were reviewed for demographic and clinical data. Laboratory investigations including blood culture results were also documented. Only neonates who were 34 weeks' gestational age were included in the analysis. Regarding blood investigations, a full blood count is usually done within the first 12 hours in all infants. However, the practice regarding C-Reactive Protein (CRP) is variable. While it was checked for most infants at 48 hours to guide response to treatment, initial CRP at 6 - 12 hours of age was not performed for all of them. A total of 176 were neonates included. All mothers had unknown group B streptococcus (GBS) status. Out of them, 74.4% were asymptomatic. Nine infants (5%) had positive culture, and 23 infants (13%) had culture negative

Hassan Boskabadi, Gholamali Maamouri, and Shahin Mafineja conducted a study regarding Neonatal Complication Related to Prolonged Rupture of Membranes and was published in 2010. They recruited 150 infants in Ghaem hospital, Mashhad, Iran from March 2008 to April 2010. Twelve (7.7%) infants had definitive infections (meningitis, sepsis, pneumonia), 101(67%) infants were premature and 88(58.6%) infants had mothers with a history of antibiotic intake. Maternal risk factors were reported in the following order: previous PROM (10%), addiction (8%), high urinary tract infection (5/3%), diabetes (4.7%), placenta abruption (4.7%), preeclampsia (3/3%) and cerclage (2%). Neonatal complications related to PROM were prematurity (67.3%), respiratory distress syndrome (22.6%), asphyxia (8.6%), meningitis (5.2%), sepsis (4%), pneumonia (1.3%) and death (4.6%). History of antibiotic administration to mothers with PROM was negative in four babies with sepsis and one with meningitis.

Another study regarding Risk Factors for Neonatal Sepsis in Pregnant Women with Premature Rupture of the Membrane was conducted by Dwiana Octiyanta and William Timotious Wahono from the Department of Obstetrics and Gynecology, Faculty of Medicine, Indonesia University, Indonesia. This study was published in 2018. A total of 405 pregnant women with PROM were included in this study. There were 21 cases (5.2%)

of neonatal sepsis. The analysis showed the risk factor of neonatal sepsis was higher in pregnant women with PROM more than 18 hours before hospital admission (OR 3.08), PROM more than 15 hours (OR 7.32), PROM more than 48hours (OR 5.77)

Another study conducted by Khaled A. Abdel Baseer, Mostafa Mohamed, and Eman A. Abd-Elmawgood regarding Risk Factors of Respiratory Diseases Among Neonates in the Neonatal Intensive Care Unit of Qena University Hospital, Egypt, published in 2020. This study was conducted in the neonatal intensive care unit of Qena University Hospital, Egypt from July 2017 to July 2018. A total of 312 neonates were admitted to the neonatal intensive care unit, out of them 145 suffered respiratory diseases giving a prevalence of (46.5%), and (55.9%) were males. The mean neonatal age at admission was 4.33 ± 7.19 days and the mean gestational age was 34.49 ± 3.31 weeks. The most commonly detected respiratory diseases were respiratory distress syndrome (RDS; 49.6%), transient tachypnoea of the newborn (TTN; 22%), neonatal pneumonia (17.2%), and meconium aspiration syndrome (MAS; 6.21%). Premature rupture of membrane (PROM), maternal diabetes, and fetal prematurity had the highest risk factors for respiratory disease occurrence in neonates. The neonatal mortality rate was 26.2%, mainly due to hyaline membrane disease and pneumonia.

According to Tomoyuki Shimokaze, Kazuhiro Akaba, Michio Banzai, Kaori Kihara, Emi Saito, and Hiroshi Kanasugi from the Departments of Pediatrics, Saiseikai Yamagata Hospital, Japan regarding Premature rupture of membranes and neonatal respiratory morbidity at 32–41 weeks' gestation: A retrospective single-centre cohort study. This study was published in 2015. They recruited 4,629 consecutive singleton infants. Respiratory morbidity was limited to respiratory distress syndrome and transient tachypnoea of the newborn, both of which are related to prematurity. Delivery modes were divided into four groups based on the existence of PROM and labour onset, and the respiratory morbidity was examined according to the number of weeks of gestational age. Multivariate analysis including PROM and delivery mode was conducted to examine the association of respiratory morbidity. Respiratory morbidity or a positive pressure requirement delivered after PROM and intact amniochorionic membranes accompanied by labour were similar at all weeks. Around 37 weeks, the absence of labour onset was associated with a risk of respiratory morbidity or positive pressure requirement. Significant respiratory risk was not associated with the incidence of PROM (adjusted odds ratio [aOR]: 0.98, (0.52–1.83)), the interval from rupture to delivery (aOR: 1.00 (0.99–1.01)), clinical chorioamnionitis, induction management, pregnancy-related complications, or neonatal sex. Delivery by

cesarean section and early gestational age presented a significant risk for respiratory morbidity.

2 RESEARCH QUESTIONS

- 2.1 What is the duration of prolonged rupture of the membrane as a predicting factor for sepsis and mortality?
- 2.2 What is the relation between PROM and with GBS status of the mother?
- 2.3 Does the administration of intrapartum antibiotics reduce the risk of neonatal sepsis?

3 OBJECTIVE THE OF STUDY

- 3.1 GENERAL: To determine the incidence rate of PROM and evaluate the maternal risk factors and outcome of term neonate related to PROM
- 3.2 SPECIFIC OBJECTIVE
 - 3.2.1 To determine the proportion rate of clinical neonatal sepsis in terms of infants born to maternal PROM > 18 hours?
 - 3.2.2 To describe the association between intrapartum antibiotics in mother PROM with neonatal sepsis/clinical sepsis?
 - 3.2.3 To describe risk factors in mothers (e.g. positive GBS) with PROM associated with neonatal sepsis/clinical sepsis?

4 METHODOLOGY

4.1 STUDY DESIGN

The study design used is a Prospective Study

4.2 STUDY PERIOD

Study will be conducted from 1st July 2021 until 30th January 2022

4.3 STUDY LOCATION

4.3.1 Hospital USM, Health Campus, Kubang Kerian, Kelantan.

4.4 REFERENCE POPULATION

Term neonates who were born to mother with prolonged rupture of membranes more than 18 hours

4.5 SOURCE POPULATION

Term neonates who were born to mother with prolonged rupture of membranes more than 18 hours in Hospital USM

5. STUDY PARTICIPANTS

5.1 INCLUSION CRITERIA

5.1.1 Term neonates who were born to mothers with PROM more than 18 hours

5.2 EXCLUSION CRITERIA

5.2.1 Congenital anomaly

5.2.2 Family history of primary immunodeficiency

5.2.3 Baby admitted for a non-infectious cause such as asphyxia, meconium aspiration syndrome (MAS), hypoxic ischaemic encephalopathy (HIE)

6. SAMPLING FRAME

No sampling method was applied. All eligible samples will be recruited

6.1 SAMPLE SIZE CALCULATION

- Sample size is calculated for objective 1 using the proportion formula

$$n = \frac{1.96^2 \times P(1 - P)}{\Delta^2}$$

- P=prevalence neonatal sepsis (%) based on study by Hassan Boskabadi et al. Iran 2011(Neonatal complication related with prolonged rupture of membranes)
- Based on sample size calculation, precision $\pm$ with 95% confidence interval, sample required is 112
- Adding 20% missing data, n =136
- Sample size for objective 2 using PS Power and sample size

The screenshot shows a software interface for sample size calculation. On the left, under the heading 'Input', there are five input fields arranged in two columns. The first column contains α (0.05) and *power* (0.8). The second column contains p_0 (0.24), p_1 (0.4), and m (1). On the right side of the interface, there are two buttons: 'Calculate' and 'Graphs'.

- P0 =prevalence (%) asymptomatic infant of mother with PROM who received adequate antibiotic prior to delivery
- P1= prevalence (%) symptomatic infant of mother with PROM who received adequate antibiotic prior to delivery

Description
We are planning a study of independent cases and controls with 1 control(s) per case. Prior data indicate that the failure rate among controls is 0.24. If the true failure rate for experimental subjects is 0.4, we will need to study 132 experimental subjects and 132 control subjects to be able to reject the null hypothesis that the failure rates for experimental and control subjects are equal with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05. We will use an uncorrected chi-squared statistic to evaluate this null hypothesis.

7. RESEARCH TOOL

Patient's proforma consisting of demographic data, maternal history of pregnancy and delivery including age, smoking habit, gestation, urinary tract infection within the pregnancy, duration of PROM, antibiotic intake and duration of antibiotic before delivery, delivery problems, presentation of chorioamnionitis symptoms, route of delivery and mothers. Neonates history such as birth weight, gender, Apgar score, lab investigation (septic workup: FBC/DC, CRP at birth and 12 hours life, blood culture), symptomatic or not, medication, and length of hospital stay were recorded.

8. DATA COLLECTION:

- 8.1.1 Patient will be identified as a mother who has a history of prolonged rupture of membranes from labour room HUSM from 1st July 2021 until 30th January 2022
- 8.1.2 Mother's records were reviewed, and the neonates were examined and only those who fulfilled inclusion criteria will be included in the study
- 8.1.3 All relevant data were obtained, including:
 - maternal history of pregnancy and delivery including age, smoking habit, gestation, urinary tract infection, duration of PROM, antibiotic intake and duration of antibiotic before delivery, delivery problems, presentation of chorioamnionitis's symptoms, and also the mode of delivery.
 - Neonates history such as birth weight, gender, Apgar score, lab investigation (septic workup: FBC/DC, CRP at birth, blood culture), symptoms, medication, and length of hospital stays.
 - Repeated sample for FBC/DC and CRP after 12 hours of life

- In the asymptomatic neonate, if both results are revealed normal, hence the baby will be discharged home. If the second result is abnormal, the baby will be admitted to NICU and antibiotics will be started as a routine practice in our unit.

9. DEFINITION OF OPERATIONAL TERMS

9.1.1 Prolonged rupture of membranes

Rupture of membranes 18 hours or more prior to the delivery.

Canavan TP, Simhan HN, Caritis S. *An evidence-based approach to the evaluation and treatment of premature rupture of membranes: Part I. Obstet Gynecol Surv.* 2004;**59(9)**:669-677

9.1.2 Neonatal sepsis

Neonatal sepsis refers to an infection involving the bloodstream in neonates or infants less than 28 days olds

Meenakshi Singh; Cory P. Gray.,2019: Neonatal Sepsis

9.1.3 Leucocytosis

Leucocytosis is defined as TWC more than 30,000/mm³

Pesce MA. Reference ranges for laboratory tests and procedures. In: Kliegman RM, Behrman RE, Jenson HB, Stanton BF, editors. *Nelson Textbook of Pediatrics*. Philadelphia: Saunders; 2008

9.1.4 Maternal antibiotic

Maternal antibiotics defined as antibiotic prophylaxis will be administered to the mother if a prolonged rupture of membranes is more than 12 hours.

William E Scorza, MD, Management of prelabour rupture of the fetal membranes at term: UpToDate

9.1.5 Adequate antibiotic

Adequate when performed with a recommended antibiotic at least four hours prior to delivery.

Aida et al, 2016: Appropriateness of Intrapartum Antibiotic Prophylaxis to Prevent Neonatal Group B Streptococcus Disease

9.1.6 Maternal Chorioamnionitis

Chorioamnionitis or intraamniotic infection is an acute inflammation of the membranes and chorion of the placenta, typically due to ascending polymicrobial bacterial infection in the setting of membrane rupture. Clinical presentation is fever, uterine fundal tenderness, maternal tachycardia ($>100/\text{min}$), fetal tachycardia ($>160/\text{min}$), and purulent or foul amniotic fluid

Alan T.N. Tita and William W Andrew, 2010: Diagnosis and Management of Clinical Chorioamnionitis

9.1.7 Term newborn

The term is defined as more than 37 completed weeks of gestation at the time of birth.

<https://manual.jointcommission.org/releases/TJC2017B2/index.html>

9.1.8 Clinical Neonatal Sepsis

Presence of at least one or more signs and symptoms of sepsis with one or more abnormal laboratory parameters. Signs of neonatal sepsis include hypoglycaemia, feeding intolerance, respiratory distress, and less active.

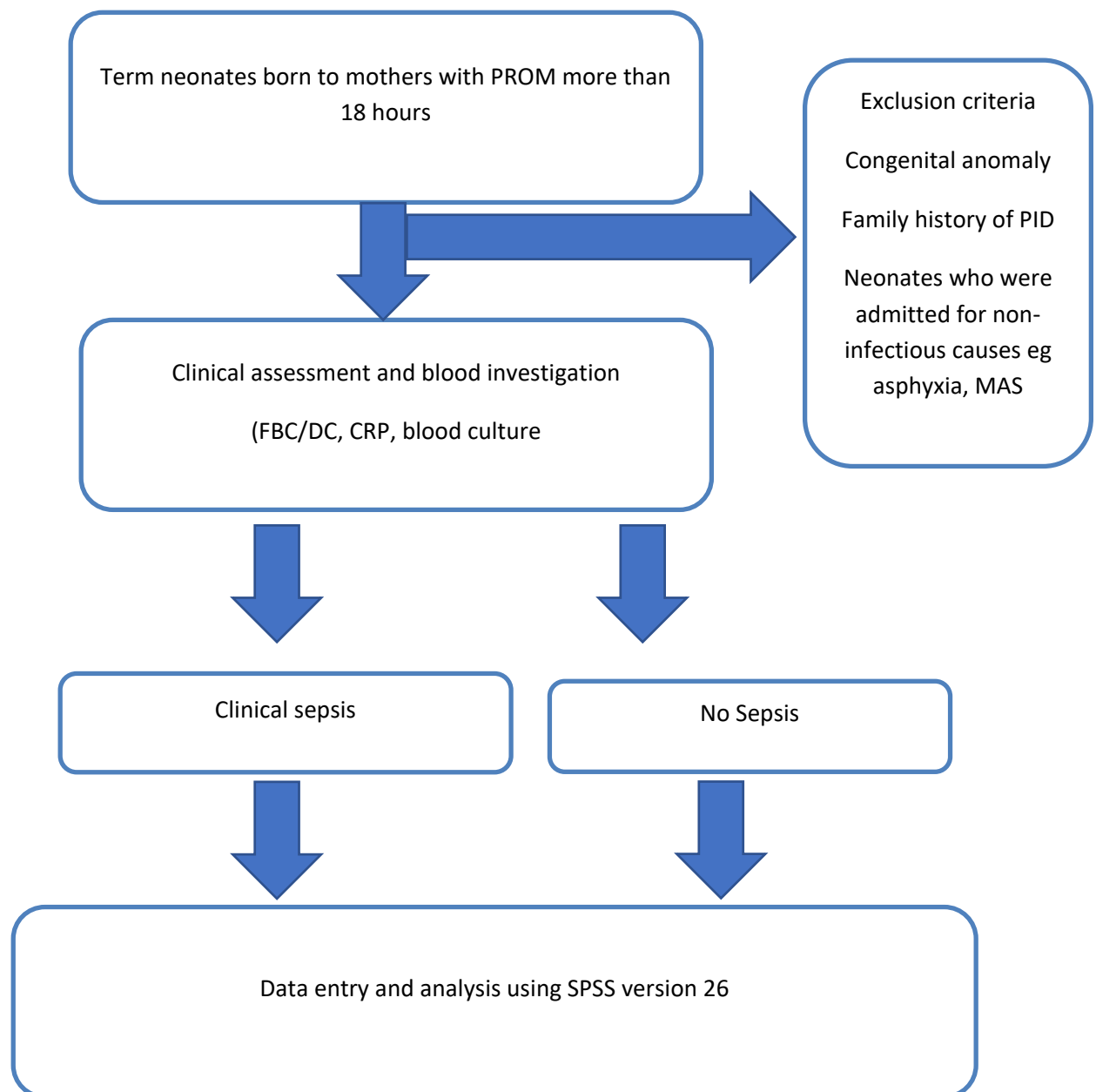
9.1.9 Congenital anomalies

Congenital anomalies encompass a wide array of structural and functional abnormalities that can occur in isolation or in a group of defects such as neural tube defects, orofacial clefts, omphalocele, gastroschisis, trisomy 13, 18, and 21, congenital heart defects, oesophageal atresia, congenital diaphragmatic hernia.

10. INTENDED STATISTICAL ANALYSIS

- Data will be entered and analyzed using SPSS version 26, and P-values less than 0.05 were reported as statistically significant
- Descriptive statistics will be used to summarize the socio-demographic characteristics of participants.
- Multiple logistic regression will be used for dependent variables.
- For dependent variable is intrapartum antibiotic, duration of PROM, maternal chorioamnionitis, maternal high vaginal swab culture, and maternal urinary tract infection.
- Expected outcome: positive blood culture, positive CRP, leucocytosis/leukopenia, thrombocytosis, or thrombocytopenia

11. STUDY FLOW CHART



12. EXPECTED RESULTS

DUMMY TABLES

1. Table 1: Demographic Details

Characters	Distribution
Gestation age	
Birth weight (kg)	
Gender Male Female	
Mode of delivery	
Apgar Score	

2. Table 2: Infection risk factor in Term Admitted due to PROM

Characteristic	Symptomatic	Asymptomatic
Duration of PROM ➤ 18 H – 24H ➤ > 24 H		
Maternal UTI		
GBS status		
Maternal chorioamnionitis		
Maternal fever during labour		
Adequate intrapartum antibiotic		

3. Table 3: Clinical Characteristics and Outcomes of Term Neonates Admitted due to PROM

Characteristic	Symptomatic (%)	Asymptomatic (%)	OR	P value
Status at birth				
TWC				
Leucocytosis				
Leucopenia				
Thrombocytopenia				
CRP positive				
Blood culture positive				
Mortality				

4. Table 4: Comparison between symptomatic and asymptomatic neonates

Characteristics	Symptomatic (%)	Asymptomatic (%)
Gender		
Mode of delivery		
Apgar Score		
SGA		
Maternal Chorioamnionitis		
Maternal received antibiotic		
Abnormal TWC		
Positive CRP		
Positive blood culture		
GBS status		
Length of hospital stays		

5. Table 5: Logistic regression analysis of variable affecting the outcome of neonatal sepsis

Variables		Odd ratio	CI 95%		P value
			Min	Max	
Sex	Male				
	Female				
Risk factors for neonatal sepsis	Duration of PROM Maternal UTI Maternal HVS C&S Maternal chorioamnionitis Intrapartum antibiotic				
Clinical characteristics of neonatal sepsis	Leucocytosis Leucopenia Thrombocytopenia Positive CRP Blood culture				
Management	Antibiotic Mechanical ventilation LOS				

13. ETHICAL ISSUE

- Personal information will be safeguarded to ensure confidentiality.
- All forms are anonymous using code numbers and will be entered into the SPSS software. Only research team members can access the data. Data will be presented as grouped data and will not identify the responders individually. A separate list of names and, registration numbers with code numbers will be kept by the researcher.
- Parents will be informed of their participation in this study and the aim of this study. Parents also will be informed that researchers are part of the managing team. Consent will be obtained. If parents choose to be in this group of study, they will be reassured that their baby will get optimal care.

14. VULNERABILITY

- In Our current practice in NICU, a neonate who was born to a mother with PROM more than 18 hours will be referred to a medical officer. If the patient is asymptomatic, the mother received adequate antibiotic intrapartum, FBC/DC, CRP, and a blood culture will be taken. If FBC/DC result is revealed normal then the baby will be discharged to the mother, but if abnormal FBC such as leucocytosis or leukopenia, thrombocytosis, or thrombocytopenia, neonates will be admitted to our NICU and started on an antibiotic. However, in symptomatic neonates, they will be admitted to our NICU after birth, septic workup (FBC/DC, blood culture, CRP) and urine GBS will be taken, and started empirical antibiotics.
- In this study, neonates will be managed as the current practice for all symptomatic and asymptomatic neonates. However, in an asymptomatic baby, a septic workup will be repeated after 12 hours of life.
- In asymptomatic neonates, if both results are normal, they will be discharged. However, the if second sample results show an abnormality such as leucocytosis, leukopenia, thrombocytosis, thrombocytopenia, or positive CRP, they will be admitted to our NICU for the administration of empirical antibiotics.

15. GANTT CHART

Project activities	2020		2020	2021	2021
	Feb- May	Jun- Novemb er	Dec	Jan	Feb
Proposal Submission and Ethical application					
Data collection					
Data Analysis/Interpretation					
Report Writing					
Thesis submission					

16. REFERENCES

1. Manar Al-lawama, Ala AlZaatreha, Rawan Elrajabi, Sultan Abdelhamid, Eman BadranaManae: *Prolonged Rupture of Membranes, Neonatal Outcomes and Management Guidelines. J Clin Med Res.* 2019;**11(5)**:360-366
2. AL-Qa QK, AL- Awayshed F. *Neonatal outcome and prenatal antibiotic treatment in premature rupture of membranes. Pak J Med Sci.* 2005;**21(4)**:441-4.
3. Joshi NS, Gupta A, Allan JM, Cohen RS, Aby JL, Kim JL, Benitz WE, Frymoyer A. *Management of Chorioamnionitis-Exposed Infants in the Newborn Nursery Using a Clinical Examination-Based Approach. Hosp Pediatr.* 2019 Apr;**9(4)**:227-233. doi: 10.1542/hpeds.2018-0201. Epub 2019 Mar 4. PMID: 30833294.
4. Boskabadi H, Maamouri G, Mafinejad S. *Neonatal complications related with prolonged rupture of membranes. Macedonian Journal of Medical Sciences.* 2011; **4**:93-98
5. Ayenew Engida Yismaw, Tirngo Yihunie Abebil, Mulunesh Abuhay Biweta and Bilen Mekonnen Araya, *Proportion of neonatal sepsis and determinant factors among neonates admitted in University of Gondar comprehensive specialized hospital neonatal Intensive care unit Northwest Ethiopia, BMC Res Notes* (2019) **12**:542
6. Joshi NS, Gupta A, Allan JM, Cohen RS, Aby JL, Weldon B, Kim JL, Benitz WE, Frymoyer A. *Clinical Monitoring of Well-Appearing Infants Born to Mothers with Chorioamnionitis. Pediatrics.* 2018 Apr;**141(4)**: e20172056. doi: 10.1542/peds.2017-2056. PMID: 29599112.
7. Dwiana Ocviyanti and William Timotius Wahono, *Risk Factor for Neonatal Sepsis in Pregnant Women with Premature Rupture of the Membrane Hindawi Journal of Pregnancy* Volume 2018, Article ID 4823404, 6 pages
8. Diana Olita'a,Roland Barnabas, Gamini Vali Boma, Wendy Pameh, John Vince, Trevor Duke *Simplified management Protocol for term neonates after prolonged rupture of membranes in setting with high rates of neonatal sepsis and mortality: a quality improved study, BMJ,* 2019;**104**:115–120

9. Pesce MA. Reference ranges for laboratory tests and procedures. In: Kliegman RM, Behrman RE, Jenson HB, Stanton BF, editors. *Nelson Textbook of Pediatrics*. Philadelphia: Saunders; 2008
10. Bianco A, Larosa E, Pileggi C, Pavia M, *The Collaborative Working Group (2016)* *Appropriateness of Intrapartum Antibiotic Prophylaxis to Prevent Neonatal Group B Streptococcus Disease*. PLoS ONE **11(11)**: e0166179. <https://doi.org/10.1371/journal.pone.0166179>
11. Tanya M. Medina MD, D Ashley Hill MD, *Preterm Premature Rupture of Membranes: Diagnosis and Management*, *American Family Physician*, Volume 73, **Number 4**, February 15, 2006

2.2.1 Ethical approval letter



**Jawatankuasa Etika
Penyelidikan Manusia USM (JEPeM)**

Human Research Ethics Committee USM (HREC)

**Universiti Sains Malaysia
Kampus Kelantan**

16150 Kubang Kerian, Kelantan, Malaysia.

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29th September 2020

Dr. Rosmaniza Ibrahim
Department of Paediatrics
School of Medical Sciences
Universiti Sains Malaysia
16150 Kubang Kerian, Kelantan.

JEPeM Code : USM/JEPeM/20060306

Protocol Title : The Outcome of Neonatal Sepsis in Term Newborn with Prolonged Rupture of Membranes in Hospital Universiti Sains Malaysia.

Dear Dr.,

We wish to inform you that your study protocol has been reviewed and is hereby granted approval for implementation by the Jawatankuasa Etika Penyelidikan Manusia Universiti Sains Malaysia (JEPeM-USM). Your study has been assigned study protocol code **USM/JEPeM/20060306**, which should be used for all communications to JEPeM-USM in relation to this study. This ethical approval is valid from **29th September 2020 until 28th September 2021**.

Study Site: Hospital Universiti Sains Malaysia.

The following researchers are also involved in this study:

1. Dr. Nor Rosidah Ibrahim
2. Assoc. Prof. Dr. Ariffin Nasir

The following documents have been approved for use in the study.

1. Research Proposal

In addition to the abovementioned documents, the following technical documents were included in the review on which this approval was based:

1. Parental Information Sheet and Consent Form (English version)
2. Parental Information Sheet and Consent Form (Malay version)
3. Data Collection Form

The list of JEPeM-USM members present during the full board meeting reviewing your protocol is attached.

While the study is in progress, we request you to submit to us the following documents:

1. Application for renewal of ethical approval 60 days before the expiration date of this approval through submission of **JEPeM-USM FORM 3(B) 2019: Continuing Review Application Form**.
2. Any changes in the protocol, especially those that may adversely affect the safety of the participants during the conduct of the trial including changes in personnel, must be submitted or reported using **JEPeM-USM FORM 3(A) 2019: Study Protocol Amendment Submission Form**.
3. Revisions in the informed consent form using the **JEPeM-USM FORM 3(A) 2019: Study Protocol Amendment Submission Form**.
4. Reports of adverse events including from other study sites (national, international) using the **JEPeM-USM FORM 3(G) 2019: Adverse Events Report**.

5. Notice of early termination of the study and reasons for such using JEPeM-USM FORM 3(E) 2019.
6. Any event which may have ethical significance.
7. Any information which is needed by the JEPeM-USM to do ongoing review.
8. Notice of time of completion of the study using JEPeM-USM FORM 3(C) 2019: Final Report Form.

Please note that forms may be downloaded from the JEPeM-USM website: www.jepem.kk.usm.my

JEPeM-USM is in compliance with the Declaration of Helsinki, International Conference on Harmonization (ICH) Guidelines, Good Clinical Practice (GCP) Standards, Council for International Organizations of Medical Sciences (CIOMS) Guidelines, World Health Organization (WHO) Standards and Operational Guidance for Ethics Review of Health-Related Research and Surveying and Evaluating Ethical Review Practices, EC/IRB Standard Operating Procedures (SOPs), and Local Regulations and Standards in Ethical Review.

Thank you.

Sincerely,



PROF. DR. HANS AMIN VAN ROSTENBERGHE

Chairperson

Jawatankuasa Etika Penyelidikan (Manusia) JEPeM
Universiti Sains Malaysia



**Jawatankuasa Etika
Penyelidikan Manusia USM (JEPeM)**
Human Research Ethics Committee-USM (HREC)

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24th August 2021

Dr. Rosmaniza Ibrahim
Department of Paediatrics
School of Medical Sciences
Universiti Sains Malaysia
16150, Kubang Kerian, Kelantan.

JEPeM USM Code: USM/JEPeM/20060306

Study Protocol Title: The Outcome of Neonatal Sepsis in Term Newborn with Prolonged Rupture of Membranes in Hospital Universiti Sains Malaysia.

Dear Dr.,

We wish to inform you that Jawatankuasa Etika Penyelidikan Manusia, Universiti Sains Malaysia (JEPeM-USM) acknowledged receipt your application for continuing review dated 27th July 2021.

Upon review of JEPeM-USM Form 3(B) 2019: Continuing Review Application Form, the committee **AGREED** for the **EXTENSION OF APPROVAL (commencing on 29th September 2021 to 28th September 2022)**. The report is included in the protocol file.

Thank you for your continuing compliance with the requirements of the JEPeM-USM.

"PRIHATIN RAKYAT: DARURAT MEMERANGI COVID-19"

"WAWASAN KEMAKMURAN BERSAMA 2030"

"BERKHIDMAT UNTUK NEGARA"

Sincerely,

ASSOC. PROF. DR. AZLAN HUSIN
Chairperson
Jawatankuasa Etika Penyelidikan (Manusia), JEPeM
Universiti Sains Malaysia

c.c Secretary
Jawatankuasa Etika Penyelidikan (Manusia), JEPeM
Universiti Sains Malaysia

2.3 Section C:

Manuscript ready for submission

ABSTRACT

Background: Prolonged rupture of membrane (PROM) is the most common problem in obstetrics complaints which consists of approximately 8-10% in all pregnancy and 60% occur at term. The aim of this study was to determine the proportion of neonatal sepsis among term neonates (≥ 37 weeks gestation) born to mother with PROM and its associated factors.

Methods: This prospective study was performed at tertiary centre, from July 2021 to January 2022. All neonates born to mother with PROM at 37 weeks gestation and above were included in this study. Factors studied were maternal urinary tract infection, maternal chorioamnionitis, maternal high vaginal swab cultures, methods of delivery, intrapartum antibiotics, and neonatal gender. Simple and multiple logistic regression was performed to identify the associated factors and predictors for neonatal sepsis

Results: There were 5934 infants born during this study period. About 136 term neonates fulfilled the inclusion criteria were evaluated. The incidence rate of PROM is 2.2%. Meanwhile, the proportion of neonatal clinical sepsis is 50% among term neonates with maternal PROM. Multivariate analysis showed no significant predictor for neonatal sepsis.

Conclusion: Clinical sepsis is a relevant complication of PROM. There is no significant factor maternal risk factor following PROM for neonatal sepsis. However, early detection of signs and symptoms of neonatal sepsis is important to reduce the risk of mortality as well as morbidity.

Keyword: Prolonged rupture of membranes (PROM), term neonates, sepsis

INTRODUCTION

Prolonged rupture of membranes (PROM) is defined as the rupture of amniotic membranes 12–18 hours or more prior to delivery of the baby and is a common cause of hospital admission and antibiotic use (1). The incidence of PROM worldwide is varying, ranging from 5-10% as recorded by the World Health Organization (1,2).

The aetiology of PROM seems to be multifactorial. Several factors such as black race, low socioeconomic level, smoking, history of PROM in previous pregnancy, vaginal bleeding, twin pregnancy and polyhydramnios may play role in PROM (3,4). Although prenatal care has been developed, but severe complications related to PROM is still occurring among mothers and neonates (5).

As been reported by many studies, the most common and serious complication of PROM is neonatal sepsis (1,3,4). When PROM occurs, the rate of neonatal infections will increase relatively by ten folds (3). In 2020, WHO reported that 24% of neonatal deaths are caused by severe neonatal infection (2).

The association between neonatal sepsis and the duration of membrane rupture was first reported in 1963 in a study which showed a higher rate of neonates with either clinical or proven sepsis to mothers with ruptured membranes of more than 6 hours (1).

At present, there are limited studies on PROM in term neonate's relation to neonatal sepsis in Southeast Asian countries including Malaysia. Most of the studies focus on mothers with gestational age of 34 and above.

We decided to perform this study to determine the proportion of neonatal sepsis among term neonates (≥ 37 weeks gestation) born to mother with PROM and its associated factors.