FACTORS ASSOCIATED WITH UNCOMPLICATED PROLONGED NEONATAL JAUNDICE IN TERM MALAY INFANTS: A CASE CONTROL STUDY

DR. NOR AMIRAH AHMAD ZAHEDI

DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE DEGREE OF MASTERS IN MEDICINE (PAEDIATRICS)

UNIVERSITI SAINS MALAYSIA

2020

TABLE OF CONTENTS

CHAPTER I:

THE PRELIMINARIES

CHAPTER II:

THE TEXT

CHAPTER III:

THE REFERENCE MATERIALS

CHAPTER I:

THE PRELIMINARIES

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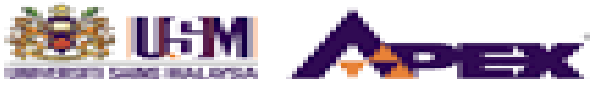

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2020

ACKNOWLEDGMENT

For the completed task, Alhamdulillah. He made it possible. To Him, am grateful and to the people, He sends over to help, thankful – my gratitude to supervisors; Associate Professor Dr. Noorizan Abd Majid(Paediatrics Gastroenterologist), Associate Professor Dr. Ariffin Nasir, Dr. Nor Rosidah Ibrahim(Neonatologist), Madam Nur Azwani, fellow lecturers, colleagues, supporting staffs, family and team of authors whom journals used as references. May this work benefit others.

LIST OF TABLES AND FIGURES

LIST OF ABBREVIATIONS AND NOMENCLATURE

AGA: Appropriate for gestational age

AUC: Area under the curve

CI: confidenceinterval

HUSM: Hospital UniversitiSains Malaysia

GDM: gestational diabetes mellitus

G6PD: Glucose 6 – Phosphate dehydrogenase

JEPeM: JawatankuasaEtikaPenyelidikan (Manusia)

LGA: Large for gestational age

OR: odds ratio

ROC: Receiver operating characteristic

SD: Standard deviation

SGA: Small for gestational age

TSH: Thyroid-stimulating hormone

ABSTRAK

Faktorberkaitanpenyakitjaundisberpanjanganbagibayimelayumatang :kajiankes-kawalan

Matlamat:Untuk menentukan faktor-faktor yang berkaitan, menyumbang kepada penyakit jaundis yang berpanjangan pada bayi Melayu matang.

Kaedah:Satu kajian kes-kawalan telah melibatkan kes -120 bayi yang berpenyakit jaundis berpanjangan dan kawalan -120 bayi yang tidak jaundis, di klinik rujukan khas hospital tertiari pada Februari 2018 sehingga September 2018. Kes dipilih daripada klinik khas jaundis berpanjangan dan kawalan adalah daripada klinik neonatal.Data dikumpulkan dari temuramah , rekod vaksinasi dan kajian semula rekod doktor. Regresi logistik univariat dan regresi logistik multivariate dilakukan menggunakan SPSS.

Keputusan:Semua bayi jaundis adalah 'unconjugated hyperbilirubinaemia' dan 44% telah sembuh jaundis dapat umur 31 hari.
Analisis univariat menghasilkan faktor ketara yang dapat dilihat pada bayi berat badan lahir SGA, ibu mengandung menghidapi diabetes mellitus gestational, kaedah kelahiran, penggunaan intrapartum oxytocin, kekurangan G6PD, hipotiroid kongenital dan jenis penyusuan.
Analisis regresi logistik berganda dengan signifikan P <0.05 dilihat pada bayi kekurangan G6PD.Hipotiroid kongenital, bayi yang dilahirkan oleh ibu gestational diabetes dan berat lahir purata (AGA) adalah faktor yang disangkal disebabkan limitasi kajian.

Kesimpulan: Kajian ini menunjukkan hubungan ketara bagi masalah kekurangan G6PD dan masalah jaundis berpanjangan bagi bayi matang

Kata kunci: jaundis neonatal berpanjangan, faktorjaundisberpanjangan

ABSTRACT

Factors associated with uncomplicated prolonged neonatal jaundice in term Malay infants: a case-control study

Aim: To determine factors associated with uncomplicated prolonged neonatal jaundice in Malay term infants.

Methods: A case-control study was conducted in 120 prolonged neonatal jaundice infants and 120 healthy control infants, in a pediatric clinic of a tertiary center between February 2018 and September 2018. Cases were selected from specialized prolonged jaundice clinic while, controls were healthy infants conveniently selected from neonatal clinic. Data was gathered from caretaker interviews, home-based vaccination records, and attending physician records. Regression analysis was performed to determine the independent associated factors of prolonged unconjugated jaundice.

Results: Hundred and twenty infants with prolonged unconjugated jaundice was analyzed in this study, of which 44.2% jaundice had resolved upon reviewed at 31 days of life. Cases and control age between 2 weeks to 8 weeks.

Univariate analysis demonstrated potentialassociations observed in maternal history of gestational diabetes mellitus, maternal intrapartum usage of oxytocin,vaginal versus caesarian delivery,SGA versus AGA birth weight babies, G6PD deficiency,congenital hypothyroidism, and exclusive breastfeeding versus mixed feeding.

G6PD deficiency was a predicted risk factor(adjusted OR 5.3 CI 1.02-28.20) for prolonged jaundice with unexpected negative association of congenital hypothyroidism(adjusted OR 0.057 95% CI 0.01-0.72), infant of maternal gestational diabetes mellitus(adjusted OR 0.31 95% CI 0.15-0.65), and SGA birth weight (adjusted OR 0.20 95% CI 0.10-0.396).

Conclusion: This study demonstrates positive relationship between G6PD deficiency and prolonged unconjugated jaundice. However, maternal history gestational diabetes mellitus, congenital hypothyroidism and SGA birth weight were protective factors for prolonged unconjugated jaundice in our population.

Keyword: prolonged neonatal jaundice, factors prolonged unconjugated jaundice

CHAPTER II

THE TEXT

SECTION A:
INTRODUCTION

INTRODUCTION

Prolonged jaundice is an uncommon condition, which affected about 2% to 15 % of infants[1]. Prolonged jaundice defined as persistent raised bilirubin> 85 umol/liter after day 14 of life in term infants[2]. Meanwhile, preterm infants have to be at the age of more than 21 days to be diagnosed as prolonged jaundice[1, 2]. This icteric feature might be observed as early as day 1 of life, which prolonged in duration or new onsets after the second weeks of life[3]. Prolonged jaundice is more prominent in term infants than premature infants[1].

The causes of prolonged jaundice are broad and might be involved multisystem. The most common cause is breast milk jaundice. However, breast milk jaundice is a benign condition, and it is a diagnosis of exclusion. Other causes to be considered include hematological disorder such as hereditary spherocytosis and G6PD deficiency, an endocrine disorder such as congenital hypothyroidism, sepsis such as urinary tract infections[4], metabolic causes such as galactosemia, aminoacidemia, and others such as neonatal hepatitis syndrome(5). As the differential diagnosis is extensive, there is a well-known challenge in managing this condition.

The crucial pathological cause to be excluded within two weeks of life is biliary atresia. The incidence of biliary atresia is varied per region as 1 in 6000 delivery in Taiwan[3] compared to 1 in 10000 delivery in South Korea[6]. Infants with biliary atresia will be presented with prolonged jaundice, tea color urine, and pale color stool. Appropriate history, physical examinations, and stool color inspection is the gold standard for screening[7]. Early detection and treatment of biliary atresia are crucial as prognosis and success rate of Kasai operation is time-dependent. The best survival prognosis was observed if surgical intervention was done within 60 days old [8].

The local protocol for the investigation of prolonged jaundice was vague. It involves multiple blood taking and urine sample collections. Unclear protocols have contributed to the high financial burden of investigations, parental anxiety, over investigations of disease[9, 10].

This observational study objective to identify the most common associated factors that contribute to prolonged jaundice. These common factors observe will help in further management and probably for the development of local guidelines.

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SECTION B:
STUDY PROTOCOL
DOCUMENT SUBMITTED FOR
ETHICAL APPROVAL

Dissertation proposal

School of Medical Science
UniversitiSains Malaysia
Prepared in partial requirement fulfillment
For the Degree of Master of Medicine (Paediatric)
2014/2018

ASSOCIATED FACTORS OF PROLONGED JAUNDICE IN INFANT: A CASE CONTROL STUDY

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PUM 0075/14

Supervisors:
Assoc.Prof. Dr. Noorizan Abd Majid
Dr Nor Rosidah Ibrahim

Dissertation Research Proposal

TITLE: ASSOCIATED FACTORS FOR PROLONGED JAUNDICE IN INFANT

1. INTRODUCTION

1.1 Background

Jaundice is a yellowish discolouration of skin and sclera by bilirubin, commonly seen newborn. Estimated about 50-60% of newborns will develop neonatal jaundice. [11].Itis usually resolved within two weeks of life spontaneously, or either with intervention.

If jaundice exceeds 14 days in term infants or 21 days in the preterm infant, it becomes prolonged jaundice. Thus further evaluations needed as it may indicate serious illness.

The list of causes of prolonged jaundice is numerous and multifactorial. If unconjugated hyperbilirubinemia, it may be related to breastfeeding, congenital hypothyroidism, urinary infections, hemolytic diseases (i.e., G6PD deficiency), Crigler Najjar, or Gilbert syndrome [12]. In comparison, conjugated hyperbilirubinemia is associated with neonatal cholestasis, metabolic causes, or neonatal hepatitis. The most critical pathology to look for is biliary atresia and other treatable cause, as Kasai orhepatoportoenterostomy success rate is time-dependent. The success rate is optimal if operations were done within the age of 31 to 45 days old.[13]

As the etiologies were extensive, prolonged jaundice needs further evaluations, and the causes need to be identified early.

1.1 JUSTIFICATION TO CONDUCT THE STUDY:

a. Provide local data of infants with prolonged jaundice.
b. Identify associated factors for prolonged jaundice; hence early intervention can be made.

1.2 LITERATURE REVIEW

TOPIC	RESEARCH RESULT	JOURNAL/ARTICLE
Prolonged jaundice, not a common condition	A prospective descriptive study of a term infant, in neonatal units – 154 infants out of 7139 live birth in an 18-month study period developed prolong jaundice.	*Investigation of prolonged jaundice, Acta Pediatric 2000*
	A prospective study of term well infants, 197 of 12 986 live births (1.5%), was referred for assessing prolonged jaundice.	*NICE recommendations for the formal assessment of babies with prolonged jaundice: too much for well infants?* *M Rodie et all* *Arch. Disease of childhood, 2010*
Type of prolonged jaundice	92% of 154 infants had unconjugated hyperbilirubinemia. One infant had a conjugated hyperbilirubinemia, giving an	*Investigation of prolonged jaundice, Acta Pediatric 2000*

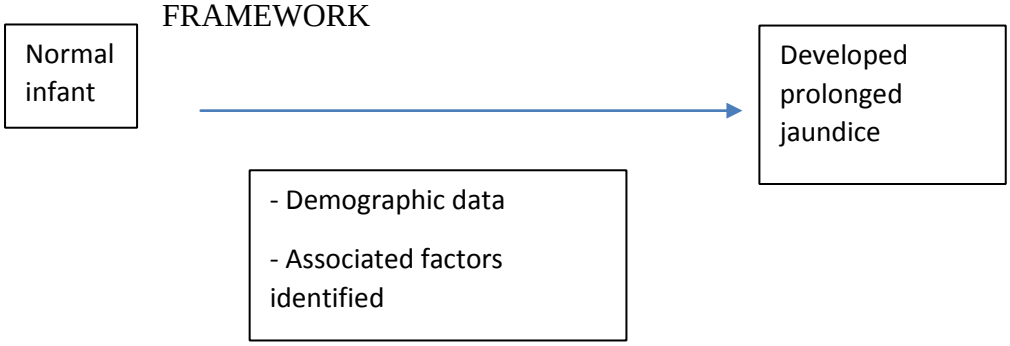
	incidence of conjugated hyperbilirubinemia of 0.14 per 1,000 live births.	
Duration of prolonged jaundice	The median duration of jaundice observed is five weeks, with 85 % of infants resolved jaundice in 6 weeks and disappeared in all unconjugated hyperbilirubinemia by the end of 8 weeks.	*Natural history and predictive risk factor of prolonged unconjugated jaundice in newborn* *M Gundur et al* *Pediatric International 2010*
Associated factors: Breastfeeding	A prospective study in Tabriz ChildrenHospital, Iran, in 6-month duration in 2009 resulted: 75 % out of 100 newborns with prolonged jaundice enrolled, was on breastfeeding.	*Underlying etiologies of prolonged icterus in neonates, M Najati, ScienceAlert 2010*
	An observational study involving 1700 samples in Michigan, the USA in 2010-2013 shows: 20-30 % of breastfed infants predominantly will have jaundice at 3-4 weeks of age.	*The natural history of prolonged jaundice in the predominantly Breastfed infant, M.* Jeffrey et all,*Pediatric 2014*
Associated factors: high cord TSH	A prospective descriptive study from July 2003 and August 2004, in northern India, 2.6 % of prolonged jaundice associated with congenital hypothyroidism	*Natural history and predictive risk factor of prolonged unconjugated jaundice in newborn* *M Gundur et al* *Pediatric International 2010*

Associated factors: G6PD deficiency	A prospective descriptive study in Northern India for 13 months from July 2003, with 71 infants involved. 24% of infants identified to have *Glucose 6-Phosphate dehydrogenase deficiency*.	*Natural history and predictive risk factor of prolonged unconjugated jaundice in newborn* *M Gundur et al* *Pediatric International 2010*
	The case series study of 69 newborns detected ten neonates with G6PD deficiency, which means that the prevalence of G6PD deficiency among Egyptian neonates with hyperbilirubinemia is 14.4% (21.2% of males).	*Glucose-6-phosphate dehydrogenase and red cell pyruvate kinase deficiency in neonatal jaundice cases in Egypt.* *PediatricHematology-Oncology. 2010*
Associated factors: Early-onset of jaundice	In 80% of prolonged unconjugated jaundice, the onset of jaundice in day 1-3 oflife had persisted until more than two weeks of age.	*Natural history and predictive risk factor of prolonged unconjugated jaundice in newborn* *M Gundur et al* *Pediatric International 2010*
Associated factors: History of prolonged jaundice in other siblings	Nearly half of the newborns in this study (n: 42 out of 77) has a history of prolonged jaundice in other siblings. It is an independent risk factor for	*Natural history and predictive risk factor of prolonged unconjugated jaundice in newborn* *M Gundur et al*

	prolonged unconjugated jaundice.	*Pediatric International 2010*
	There is a 3-fold higher risk of recurrence of jaundice in infants who had older siblings in jaundice.	*The recurrent risk for neonatal hyperbilirubinemia in siblings,* *Khoury MJ et al* *Journal Disease of childhood, 1988*
Associated factors: Antenatal history of oxytocin infusion during labour	There association the used of oxytocin in labour associated increased incidence of neonatal hyperbilirubinemia	*Oxytocin infusion in labour: the efficient of different indication & used of different diluent on neonatal bilirubin level, Oral E. et al* *Arch. Gynae.Obstetric 2003*
Associated factors: vaginal delivery versus cesarean delivery	A cross-sectional study in March 2014 at Qazvin teaching Hospital, mean of total bilirubin baby, was higher in a vaginally delivered baby than in cesarean delivered baby, with a significant p-value.	*The Relationship between Neonatal Jaundice and Maternal and Neonatal Factors* *Garosi E.* *Iranian Journal of neonatology, 2016*

2. OBJECTIVE OF STUDY:

2.1 CONCEPTUAL FRAMEWORK



2.2 RESEARCH HYPOTHESIS

2.2.1 There is an association between factors (demographic characteristics, antenatal history, delivery type, feeding, G6PD deficiency, congenital hypothyroidism, and positive family history) with prolonged jaundice.

2.3 GENERAL:

2.3.1 To study prolonged jaundice in infants, attended a paediatric clinic in HUSM.

2.4 SPECIFIC

2.4.1 To describe the demographic and clinical characteristics of prolonged jaundice infants.

2.4.2 To study associated factors contributed to prolonged jaundice.

3. METHODOLOGY

3.1 STUDY DESIGN:

The study design used is a Case-Control study

3.2 PERIOD: study will be conducted from October 2017 until March 2017 (6 months)

3.3 LOCATION: 1. Paediatric clinic Hospital USM.

2. Neonatal ward Hospital USM.

3. Health clinic i.e.Klinik Kesihatan Kubang Kerian(for control)

3.4 STUDY POPULATION:

The reference population is pediatric patients in Kelantan.

The source population is the newly diagnosed prolonged jaundice at an outpatient clinic or hospitalized in Hospital USM within the study period.

3.5 INCLUSION/ EXCLUSION CRITERIA

3.5.1 Inclusion criteria:

- Term infants
- Cases: All infants diagnosed with prolongedjaundice in the clinic or admitted in ward Hospital USM from October 2017 until March 2017
- Controls:
    - infants who are more than two weeks old to 8 weeks old under neonatal clinic follow up
    - infants who come in for monthly immunization at the nearest health clinic, up to 8 weeks old.

3.5.2 Exclusion criteria

- Prematurity
- Syndromes/ inherited causes of prolonged jaundice

3.6 SAMPLING FRAME:

All infants-age less than 4-month-old that was diagnosed with prolonged jaundice in Hospital USM

3.7 SAMPLE SIZE DETERMINATION:

Numbers of factors study: 10

: (10+1) x (5-10 cases/ control)

Sample needed: 55-110

Sample size: 110 case/ 110 control

(Hosmer&Lemeshow 2000)

3.8 SAMPLING METHODS:

Convenience sampling method applied for the study.

3.9 RESEARCH TOOL:

The patient's proforma of demographic data, detailed history, and diagnostic criteria of prolonged jaundice during the clinic visit.

Significant physical examination and laboratory investigations at the time of diagnosis will be recorded.

3.10 DATA COLLECTION:

Patients will be identified during the sampling frame from the pediatric clinic.

The patient's record was reviewed, and only those who fulfilled inclusion will be included in the study. The patient will be followed up in 8 weeks to assess jaundice progression.

All relevant data were obtained, included:

3.10.1 Baseline demographic characteristics are age, gender, birth weight, mother antenatal illness, type of delivery, feeding type, and jaundice history in siblings.

3.10.2 Baseline clinical examinations: dysmorphic features, cephalohematoma, hepatomegaly, splenomegaly, pale stool

3.10.3 Baseline investigations: glucose -6-phosphate dehydrogenase (G6PD) and cord thyroid function test.

3.10.4

3.11 DEFINITION OF OPERATIONAL TERMS

3.11.1 Prolonged jaundice: Visible jaundice persisting beyond 14 days of a term infant.

3.11.2 Hyperbilirubinaemia:if total bilirubin in infants more than 14 days old is more than 85umol/l.

3.11.3 Term: more than 37 weeks of gestation.

3.11.4 Birthweight: initial weight label based on a standardized growth chart

3.11.4.1 Small for age: less than the third centile for gestational age.

3.11.4.2 Appropriate for age: between 3rd to 95th centile for gestational age.

3.11.5 Exclusive breastfeeding: breastfeeding only.

3.11.6 Mixed feeding: a combination of feeding at least one meal of breast milk or formula feeding.

3.11.7 Gestational Diabetes Mellitus: confirm the diagnosis by a certified medical practitioner.

3.11.8 Oxytocin in labour: an infusion of oxytocin during the labour period.

3.11.9 Maternal infections: a previous maternal history of fever, with/ or suggestive biochemical evidence of infection. I.e., maternal urinary tract infection.

3.11.10 Delivery

Vaginal: spontaneous onset vaginal delivery with including assisted instrumental delivery.

Cesarean: elective and emergency cases of lower segment cesarean section delivery.

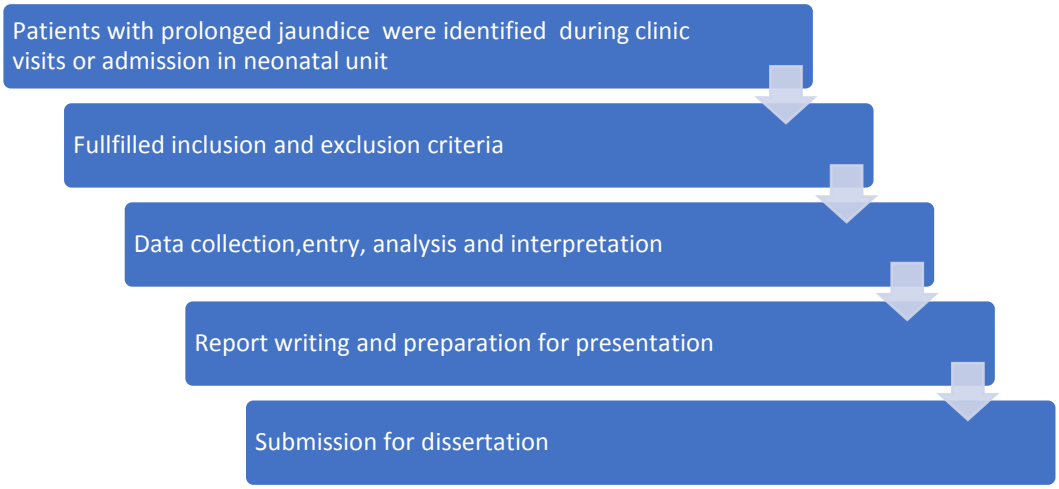
3.12 INTENDED STATISTICAL ANALYSIS

The data was processed and analyzed using IBM SPSS Statistics version 20.

The demographic and numerical data were presented by number and percentage, mean and median, according to data distribution.

Univariate and multivariate logistic regressions were used to identify factors associated with the development of prolonged jaundice.

3.13 STUDY FLOW CHART



4. EXPECTED RESULTS

4.1 DUMMY TABLES

Table 1: Demographic data infant with prolonged jaundice

Variables	Cases N: %	Controls N: %	P values
Sex # Male Female			
Age (days) + (mean: SD) Onset of jaundice Resolved jaundice			
Gestation (weeks) + (mean: SD)			
Birth weight (gram) + (mean: SD)			
Maximum total bilirubin (umol/l) + (mean: SD)			
G6PD deficiency #			
Congenital hypothyroid #			
Prolong jaundice in siblings #			
Gestational Diabetes Mellitus #			
Maternal infection #			
Delivery #			

Vaginal Caesarean			
Oxytocin in labour #			
Birth weight (gram) + (mean: SD) SGA AGA			
Feeding # Exclusive breastfeeding Mixed feeding			

chi-square + independent t-test

Table 2: Associated factors for prolonged jaundice: univariate analysis

Variables	Cases N: %	Controls N: %	Crude Odd ratio	95TH CI	P-value
Prolong jaundice in siblings					
Gestational Diabetes Mellitus					
Maternal infection					
Delivery Vaginal Caesarean					
Oxytocin in labour					
Birth weight SGA AGA					
Feeding Exclusive breastfeeding					

Mixed feeding					

Table 3: Associated factors for prolonged jaundice: multivariate logistic regression

Variables +	B	Adjusted Odd ratio	95th CI	P-value
Prolong jaundice in siblings				
G6PD deficiency				
Maternal infection				

+ Variables with $P < 0.25$ will be used for multiple logistic regression analysis

+ Preliminary model will be based on a model of fitness (ROC, Homer Lemeshaw, et al.)

5. ETHICAL ISSUE

This study will be conducted in concordance with the Declaration of Helsinki and follows the Malaysian Good Clinical Practice (GCP) Guidelines.

Ethical clearance will be obtained from the Research Ethics Committee from HUSM and KKM by National Medical Research Registry.

Vulnerable groups will be not be compromised in terms of further care and follow up. Convenient sampling will be applied.

Personal information will be safeguarded to ensure confidentiality. The risk of the safety or health of participants in the study is very minimal.

All forms are anonymous using code numbers and will be entered into SPSS software. Only research team members can access the data. Data will be presented as grouped data and will not identify the responders individually.

The researcher will keep a separate list of names, registration numbers with code numbers.

6. GANTT CHART

Project activities	2017						2018					
	J	O	S	O	N	D	J	F	M	A	M	J
Proposal Submission and Ethical application												
Data collection												
Data Analysis/Interpretation												
Presentation & Submission of Reports												
Report Writing												
Thesis submission												

7. LIMITATION OF THE STUDY:

7.1.1 The limited number of patients.

7.1.2 We have limited data collections.

7.1.3 Loss of follow up and limited study period

8. REFERENCES

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ETHICAL APPROVAL

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

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6th November 2017

Dr. Nor Amirah Ahmad Zahedi
Department of Paediatrics
School of Medical Sciences
Universiti Sains Malaysia
16150 Kubang Kerian, Kelantan.

Protocol Title : Associated Factors of Prolonged Jaundice in Infant: A Case Control Study.

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 I should be used for all communication to the JEPeM-USM related to this study. This ethical clearance is valid from **6th November 2017** until **5th November 2018.**

Study Site: Hospital Universiti Sains Malaysia and Health Clinic in Kubang Kerian, Kelantan.

The following researchers also involve in this study:

1. Assoc. Prof. Dr. Noorizan H A Majid
2. Dr. Nor Rosidah Ibrahim

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

1. Research Proposal

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

1. Patient Information Sheet and Consent Form (English version)
2. Patient Information Sheet and Consent Form (Malay version)
3. Data Collection Form (Prolonged Jaundice Checklist)

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

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) 2017: Continuing Review Application Form.** Subsequently this need to be done yearly as long as the research goes on.
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) 2017: Study Protocol Amendment Submission Form.**
3. Revisions in the informed consent form using the **JEPeM-USM FORM 3(A) 2017: Study Protocol Amendment Submission Form.**

CERTIFIED BY: National Pharmaceutical Regulatory Agency (NPRA) | Forum for Ethical Review Committees in Asia & Western Pacific Region

4. Reports of adverse events including from other study sites (national, international) using the **JEPeM-USM FORM 3(G) 2017: Adverse Events Report.**
5. Notice of early termination of the study and reasons for such using **JEPeM-USM FORM 3(E) 2017.**
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) 2017: Final Report Form.**

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

Jawatankuasa Etika Penyelidikan (Manusia), 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.

"ENSURING A SUSTAINABLE TOMORROW"