COMPARISON BETWEEN TWO DIFFERENT ANTIBIOTIC REGIMES

(2 GRAMS STAT THEN 1 GRAM 4 HOURLY AMPICILLIN VERSUS 1 GRAM STAT THEN 500 MG 6 HOURLY OF AMPICILLIN)

AS ANTIBIOTIC PROPHYLAXIS OF MATERNAL AND NEONATAL SEPSIS IN PROM ≥ 18 HOURS

PROSPECTIVE RANDOMISED CONTROLLED TRIAL IN HOSPITAL SULTAN ISMAIL, JOHOR BAHRU, JOHOR

BY

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ABSTRACT

COMPARISON BETWEEN TWO DIFFERENT ANTIBIOTIC REGIMES (2 GRAMS STAT THEN 1 GRAM 4 HOURLY AMPICILLIN VERSUS 1 GRAM STAT THEN 500 MG 6 HOURLY OF AMPICILLIN) AS ANTIBIOTIC PROPHYLAXIS OF MATERNAL AND NEONATAL SEPSIS IN PROM ≥ 18 HOURS, PROSPECTIVE RANDOMISED CONTROLLED TRIAL IN HOSPITAL SULTAN ISMAIL, JOHOR BAHRU, JOHOR

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Introduction: Pre-labour rupture of membranes is a common clinical problem with the predominant risk to the fetus is ascending infection. The risks to the mother are of uterine infection, via either chorioamnionitis and postpartum endometritis. Ampicillin group antibiotic is currently used as prophylaxis. Across the region, many antibiotic regime and dosage is recommended. Several studies showed conflicting outcome in search for optimal dosage.

Objective: The aim of this study is to evaluate maternal and fetal outcome of two different regimes of Ampicillin dosage for antibiotic prophylaxis.

Patient and Methods: A total of 292 patients were recruited in this study. Patients with term uneventful antenatal whom demonstrated PROM more than 18 hours were randomized into two different Ampicillin dosage regimes; a) 2 grams stat and 1 gram 4 hourly, b) 1 gram stat and 500 mg 6 hourly. Maternal outcome in term of duration of PROM, prostin insertion, level of WCC, temperature of 38^0C, dosage of antibiotic given prior to delivery, numbers of vaginal examinations, maternal chorioamnionitis and incident of postpartum endometritis were recorded. Fetal outcome measured include Apgar score at 1 minute, Apgar score at 5 minutes, NICU admission, early onset of neonatal sepsis and perinatal mortality. Both group were compared and t-test performed with significant level of $p<0.05$ is used.

Results: A number of 146 patients in each armed fulfilled the inclusion criteria. There were no cases of postpartum endometritis and perinatal mortality recorded.

Majority of patients delivered vaginally (88% in 2 gram groups, 99% in 1 gram group) followed by LSCS (23.35 in 2 grams group, 19.2% in 1 gram group). There were three cases of chorioamnionitis in 2 grams group (2.1%) and two cases (1.4%) in 1 gram group. Apgar score at 1 minute showed significant difference between two group with a number of nine cases (6.2%) less than 7 in 2 grams group and six cases (4.2%) in 1 gram group ($p=0.049$). There were 5 babies diagnosed as early onset of neonatal sepsis in 2 grams group (3.4%) and 3 babies in 1 gram group (2.1%). However, there were no significant different between two group Ampicillin regimes in relation to duration of PROM, prostin insertion, level of WCC, temperature of 38^0C, dosage of antibiotic given prior to delivery, numbers of vaginal examinations, Apgar score at 5 minutes, NICU admission and early onset of neonatal sepsis.

Conclusion: Data from this study showed that there is no significant difference between the different dosage used as antibiotic prophylaxis for PROM patients with respect to maternal and fetal outcome (short and medium term outcome).

Dato Dr Ghazali bin Ismail: Supervisor

Associate Profesor Dr Pazudin bin Ismail: Co-Supervisor

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TABLE OF CONTENTS

CONTENTS	PAGE
ACKNOWLEDGEMENT	i
TABLE OF CONTENTS	ii
LIST OF TABLES	v
ABBREVIATIONS	vii
ABSTRACT Malay version English version	 xi ix
3.0 INTRODUCTION 1.1 State of Johor 1.2 Hospital Sultan Ismail, Johor Bahru 1.3 Obstetrics and Gynecology Department 1.4 Study Introduction	 1 2 2 6
2.0 LITERATURE REVIEW	8
3.0 OBJECTIVE OF THE STUDY	11
4.0 DEFINATION OF CLINICAL VARIABLE AND OUTCOMES	14

5.0 BACKGROUND OF THE STUDY	18
6.0 METHODOLOGY	20
6.1 Study setting	20
6.2 Study design	20
6.3 Study population	20
6.4 Sample size calculation	20
6.5 Inclusion / Exclusion criteria	22
6.6 Study period	23
6.7 Sampling methods/ Data collection	23
6.8 Flow chart of the study	27
6.9 Statistical analysis	28
6.10 Ethical approval	28
6.11 Ethical issue	28
7.0 RESULTS	29
8.0 DISCUSSION	53
9.0 CONCLUSION	64
10.0 LIMITATION	67
11.0 REFERENCES	68
12.0 APPENDICES	
12.1 Borang Maklumat Kajian	80
12.2 Borang keizinan pesakit	86
12.3 Patient Information Sheet	95

12.4 Ethical Approval	98

LIST OF TABLES

		PAGE
Table 7.1.1	Comparison between two antibiotic regimes with maternal race	29
Table 7.1.2	Comparison between two antibiotic regimes with age	30
Table 7.1.3	Comparison between two antibiotic regimes with parity	31
Table 7.1.4	Comparison between two antibiotic regimes with gestation	32
Table 7.1.5	Comparison between two antibiotic regimes with mode of delivery	33
Table 7.2.1	Comparison between two antibiotic regimes with clinical chorioamnionitis	34
Table 7.2.2	Comparison between two antibiotic regimes with postpartum endometritis	35
Table 7.2.3	Comparison between two antibiotic regimes with allergic reaction	35
Table 7.3.1	Comparison between two antibiotic regimes with Apgar score at 1 minute	36
Table 7.3.2	Comparison between two antibiotic regimes with Apgar score at 5 minutes	37

Table 7.3.3	Comparison between two antibiotic regimes with NICU admission	38
Table 7.3.4	Reason for NICU admission	38
Table 7.3.5	Comparison between two antibiotic regimes with diagnosis of early onset of neonatal infection	39
Table 7.3.6	Comparison between two antibiotic regimes with perinatal mortality	40
Table 7.4.1	Comparison between two antibiotic regimes and chorioamnionitis and early onset of neonatal sepsis in term of duration of PROM	41
Table 7.4.2	Comparison between two antibiotic regimes and chorioamnionitis and early onset of neonatal sepsis in term of prostin insertion	43
Table 7.4.3	Comparison between two antibiotic regimes and chorioamnionitis and early onset of neonatal sepsis in term of level of white cell count	45
Table 7.4.4	Comparison between two antibiotic regimes and chorioamnionitis and early onset of neonatal sepsis in term of temperature of 38^0C	47

Table 7.4.5	Comparison between two antibiotic regimes and chorioamnionitis and early onset of neonatal sepsis in term of number of vaginal examination	49
Table 7.4.6	Comparison between two antibiotic regimes and chorioamnionitis and early onset of neonatal sepsis in term of dosage of antibiotic prior to delivery	51

ABBREVIATIONS

BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
CRP	C Reactive Protein
CTG	Cardiotogograph
EOS	Early onset of neonatal sepsis
GBS	Group B *Streptococcus*
G6PD	Glucose-6-phosphate dehydrogenase deficiency
HO	House Officer
LSCS	Lower Segment Caesarean Section
MRN	Medical Record Number
MRSA	Methicillin- Resistant *Staphylococcus aureus*
NICU	Neonatal Intensive Care Units
ORACLE	Overview of the Role of Antibiotics in Curtailing Labor and Early Delivery
PPROM	Premature Prelabour Rupture Of Membrane

SVD	Spontaneous Vaginal Delivery
TTN	Transient Tachypnea of Newborn
VE	Vaginal Examination

ABSTRAK

Pengenalan:

Pecah air ketuban sebelum proses kelahiran merupakan masalah klinikal yang biasa berlaku di mana, risiko khusus terdapat bayi adalah jangkitan kuman. Risiko terhadap ibu adalah jangkitan kuman terhadap rahim samada korioamnionitis dan ‘endometritis’ selepas bersalin. Pada masa ini, antibiotik kumpulan Ampicillin digunakan untuk tujuan pencegahan. Sepanjang peredaran zaman, pelbagai regim dan dos antibiotik digunakan. Beberapa kajian menunjukan percanggahan pendapat dan kesan dalam pencarian dos yang optimum.

Objektif:

Kajian ini ingin melihat dan mengkaji kesan dua regim dos administrasi Ampicillin yang berbeza terhadap ibu dan bayi sebagai antibiotic pencegahan.

Kaedah:

Sejumlah 292 pesakit telah direkrutkan dalam kajian ini. Pesakit yang cukup bulan dengan kandungan yang normal tetapi mengalami PROM lebih daripada 18 jam dibahagi kepda dua kumpulan dos Ampicillin; a) 2 gram serta merta dan 1 gram setiap 4 jam, b) 1 gram serta merta dan 500 miligram setiap 6 jam. Kesan terhadap ibu dalam durasi pecah air

ketuban, kemasukan prostin, tahap sel darah putih, demam dengan suhu 380c, dos antibiotik digunakan sebelum kelahiran, bilangan pemeriksaan vagina, korioamnionitis serta ‘endometritis’ selepas bersalin diambil kira. Kesan terhadap bayi pula, kajian ini mengambil kira skor Apgar pada 1 minit, skor Apgar pada 5 minit, kemasukan ke wad NICU, bayi yang dijangkiti kuman dan bayi yang meninggal dunia. Kedua-dua kumpulan dibandingkan dan ujian-t telah digunakan dengan paras signifikan $p<0.05$ telah digunakan.

Keputusan:

Sejumlah 146 pesakit telah mematuhi syarat-syarat kelayakan dalam setiap kumpulan. Tiada kes endometritis dan kematian bayi dilaporkan. Kebanyakan pesakit melahirkan secara semulajadi (88% dalam kumpulan 2 gram, 99% dalam kumpulan 1 gram) diikuti dengan kelahiran secara pembedahan *Caesarean* (23.3% dalam kumpulan 2 gram, 19.2% dalam kumpulan 1 gram). Terdapat tiga kes korioamnionitis pada kumpulan 2 gram (2.1%) dan dua kes korioamnionitis dalam kumpulan 1 gram (1.4%). Skor Apgar pada 1 minit (kurang daripada skor 7) menunjukkan perbezaan yang signifikan antara dua kumpulan dengan jumlah sembilan kes (6.2%) dalam kumpulan 2 gram dan enam kes (4.2%) dalam kumpulan 1 gram ($p=0.049$). Terdapat 5 bayi disahkan dijangkiti kuman dalam kumpulan 2 gram (3.4%) dan 3 bayi dalam kumpulan 1 gram (2.1%). Walaubagaimanapun, tidak terdapat perbezaan yang signifikan antara dua kumpulan ini bagi durasi pecah air ketuban, kemasukan prostin, tahap sel darah putih, demam dengan suhu 38^0C, dos antibiotik digunakan sebelum kelahiran, bilangan pemeriksaan vagina, skor Apgar pada 5 minit, kemasukan ke dalam wad NICU, masa tinggal di hospital dan bayi yang dijangkiti kuman.

Kesimpulan:

Dari data yang diperolehi pada kajian ini menunjukkan tidak terdapat perbezaan yang signifikan di antara perbezaan dos antibiotik yang digunakan sebagai pencegahan antibiotik bagi pesakit PROM terhadap kesannya pada ibu dan bayi (dalam jangka masa yang pendek dan sederhana).

Kata kunci: PROM, GBS, antibiotik pencegahan

ABSTRACT

Introduction:

Pre-labour rupture of membranes is a common clinical problem with the predominant risk to the fetus is ascending infection. The risks to the mother are of uterine infection, via either chorioamnionitis and postpartum endometritis. Ampicillin group antibiotic is currently used as prophylaxis. Across the region, many antibiotic regime and dosage is recommended. Several studies showed conflicting outcome in search for optimal dosage.

Objective:

The aim of this study is to evaluate maternal and fetal outcome of two different regimes of Ampicillin dosage for antibiotic prophylaxis.

Methods:

A total of 292 patients were recruited in this study. Patients with term uneventful antenatal whom demonstrated PROM more than 18 hours were randomized into two different Ampicillin dosage regimes; a) 2 grams stat and 1 gram 4 hourly, b) 1 gram stat and 500 mg 6 hourly. Maternal outcome in term of duration of PROM, prostin insertion, level of WCC, temperature of 38^0C, dosage of antibiotic given prior to delivery, numbers of vaginal examinations, maternal chorioamnionitis and incident of postpartum endometritis were recorded. Fetal outcome measured include Apgar score at 1 minute, Apgar score at 5 minutes, NICU admission, early onset of neonatal sepsis and perinatal mortality. Both group were compared and t-test performed with significant level of $p<0.05$ is used.

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A number of 146 patients in each armed fulfilled the inclusion criteria. There were no cases of postpartum endometritis and perinatal mortality recorded.

Majority of patients delivered vaginally (88% in 2 gram groups, 99% in 1 gram group) followed by LSCS (23.35 in 2 grams group, 19.2% in 1 gram group). There were three cases of chorioamnionitis in 2 grams group (2.1%) and two cases (1.4%) in 1 gram group. Apgar score at 1 minute showed significant difference between two group with a number of nine cases (6.2%) less than 7 in 2 grams group and six cases (4.2%) in 1 gram group (p=0.049). There were 5 babies diagnosed as early onset of neonatal sepsis in 2 grams group (3.4%) and 3 babies in 1 gram group (2.1%). However, there were no significant different between two group Ampicillin regimes in relation to duration of PROM, prostin insertion, level of WCC, temperature of 38^0C, dosage of antibiotic given prior to delivery, numbers of vaginal examinations, Apgar score at 5 minutes, NICU admission and early onset of neonatal sepsis.

Conclusion:

Data from this study showed that there is no significant difference between the different dosage used as antibiotic prophylaxis for PROM patients with respect to maternal and fetal outcome (short and medium term outcome).

Keywords: PROM, GBS, antibiotic prophylaxis

1.0 INTRODUCTION

1.1 The State of Johor

Johor is located in the southern most part of Peninsular Malaysia, is the second largest state in West Malaysia with a total land area of 19,210 km^2 (7,420 sq mi), and a population of 3,233,434 as of 2010. The state's ethnic composition consists of Malay 58.9%, Chinese 33.6%, Indian 7.1%, and other ethnic groups 0.4%. Johor is surrounded by Pahang to the north, Malacca and Negeri Sembilan to the northwest, and the Straits of Johor to the south which separates Johor and the Republic of Singapore. The state also shares a maritime border with the Riau Archipelago from the east and Riau mainland on the west by the South China Sea and the Strait of Malacca respectively, both of Indonesian territories. The State of Johor is divided into the 8 districts of Johor Bahru, Muar, Batu Pahat, Pontian, Mersing, Kota Tinggi, Segamat and Kluang.

To the Siamese, Johor is “Gangganu” or “Treasured Stones”. It was also once known as the “End of the Land” or Ujong Tanah as it occupies the tail portion of mainland Asia. Its present name, Johor, is derived from an Arabic word ‘Jauhar’ which means ‘Precious Jewel”. Johor is also known by its Arabic honorific, *Darul Ta'zim*, or "Abode of Dignity", and as Johore in English.

1.2 Hospital Sultan Ismail, Johor Bahru

Hospital Sultan Ismail (HSI) is a tertiary specialist hospital equipped with THIS (Total Hospital Information System) which is a fully computerized system. Construction of the hospital is in line with government's objective of making Malaysia a developed nation through Vision 2020 and Malaysia Ministry Vision. To achieve the above goals, the hospital is designed and equipped with sophisticated world class facilities. It is a government tertiary referral hospital, located on 50 acres of prime land in Johor Bahru with 22 wards, 704 beds and 18 operating theatres.

The hospital is named in honour of Sultan Ismail of Johor. In July 2004, part of the hospital was opened but it closed down two months later due to the presence of fungal infection detected in hospital. It was reopened in February 2006.

1.3 Obstetrics and Gynecology Department

The department of Obstetrics and Gynaecology was first established in 2006, making it one of the earliest departments in HSI is staffed with two consultant specialists, five specialists, four registrars, eight medical officers and minimum fifteen house officers. Dato Dr Ghazali bin Ismail has been instrumental in the smooth running of this department which further helped by experienced specialists.

The total number of deliveries is increasing from 5249 in year 2007 to 10139 in year 2010, with an average of 800-1000 deliveries per month. Similarly, the number of patient's visit also increase tremendously from 2740 in year 2006 to 17070 in year 2010.

This department has 1 labour suite equipped with 17 beds, 1 pregnancy assessment centre (PAC) which equipped with 6 beds, 1 maternity theatre, 4 wards with 112 beds and 1 specialist clinic.

Total delivery in 2011 was 11300. Majority born via spontaneous vaginal delivery about 8996 (79.6%) deliveries, followed by LSCS about 1511 (13.3%) deliveries, 527 (4.6%) of vacuum assisted deliveries and 102 (0.9%) for forceps deliveries. Breech delivery account about 73 (0.6%) deliveries and 91 (0.8%) was twin deliveries. NICU admission for 2011 was 1324 cases.

The antenatal wards have 28 beds with major antenatal admission was premature rupture of membrane (PROM), pregnancy induced hypertension (PIH), post-term pregnancy, gestational diabetes mellitus (GDM), premature labour, antepartum hemorrhage (APH) and reduced fetal movement.

The labour suite is situated on the fourth floor of the main block. It has 17 beds. There are four beds which act as a high dependency ward for high-risk cases such as pre-eclampsia, postpartum hemorrhage or eclampsia cases. Fourteen beds are reserved for husband friendly for husband or companion to accompany the laboring women in the process of labour. Epidural services are provided on needed basis. Main operation theatre is situated on the fifth floor connecting to labour room via four available lifts, where all caesarean sections are performed. Adjoining labour ward is the patient assessment centre (PAC), it functions as day care center for assessment of early labour, scanning or some

minor procedure to be done examples external cephalic version (ECV), intravenous inferon, injection of Ovidrel (ovarian stimulation) etc.

The post natal ward has two separating ward, high risk and low risk cases, equipped 28 beds each ward. Breast feeding policies is fully implemented and HSI is recognized as a Baby Friendly Hospital.

The Neonatal Intensive Care Units (NICU) is situated at the same floor to labour room. It is equipped with modern facilities for the care of troubled newborn babies. The consultant neonatologists supervise the running of its care and services.

Gynaecological ward has a total of 28 beds and it located in the fourth floor. All gynaecological cases are managed here. Patients are admitted through the casualty department, gynaecology clinic, outpatient clinic and direct referrals from other hospitals. There are several gynaecological operations were performed such as transabdominal hysterectomy (TAH), vaginal hysterectomy with or without pelvic floor repair, Wertheim's hysterectomy, cystectomy, oophorectomy, myomectomy, salphingectomy, cervical cerclage, evacuation of product of conception, marsupilization, sterilization, diagnostic laparascopic, and hysteroscopy.

House officers, medical officers and registrars on duties are provided with comfortable on-call rooms. A minimum of eight calls per months is rota for gaining sufficient experience in emergency obstetrics and gynaecology under supervision of the specialist on-call.

Clinic scheduled as below

	Morning	Afternoon
Monday	Urgent clinic	1st and 3rd week: Combined 2nd and 4th week: Colposcopy
Tuesday	Gynae	Infertility and Menopause
Wednesday	Antenatal	Gynaeoncology
Thursday	Urgent	Colposcopy
Friday	Booking	

*Urgent clinic will see referred cases which need immediate or within a week for assessment mostly from obstetric cases.

Regular post-graduate teaching sessions were conducted example Journal club meeting, pre operation assessment, clinical presentation. Caesarean census and perinatal morbidity/ mortality review audit were performed monthly. Daily census is done in every morning at 8 am at meeting room in the Labour room.

1.4 Introduction of study

Prelabour rupture of the membranes at or near term (term PROM) increases the risk of infection for the woman and her baby, therefore routine use of antibiotics for women at the time of term PROM may reduce this risk.

This truth becomes the foundation for the recommendation by the Centers for Disease Control and Prevention (CDC) that antibiotic prophylaxis should be given to women in labour who either have been shown to carry group B streptococci by culture or who develop risk factors for transmission of the organism (Centres for Disease Control and Prevention, 1996) and these guidelines were revised in 2002. The American Academy of Paediatrics (1992) and the American College of Obstetricians and Gynaecologists (1992) also have authorized the same strategy.

The principle of prophylactic antibiotic is to diminish the colonization pressure of microorganism, not to sterile tissue, Mangram et al (1999) and it needs to be safe, inexpensive and effective against pathogens.

.

Several well-designed studies have reported the benefit of prophylactic antibiotic in lowering the rate of postpartum endometritis, wound infection, risk of febrile morbidity and urinary tract infection in all high risk patients went for caesarean section (ACOG, 2004).

Therefore, Hopkins and Smaill (2002) also assured that intrapartum treatment with antibiotics was associated with a “significant” clinical reduction in neonatal sepsis (relative risk [RR] =0.08; 95% confidence interval [CI], 0.00–1.44) and pneumonia (RR=0.15; 95% CI, 0.01–2.92) compared with treatment given immediately postpartum.
Nevertheless, through data from Cochrane review summarized that neither value was truly statistically significant.

However, Synder and Jamieson (2007) accounted intrapartum antibiotic treatment is not superior to postpartum antibiotics for reducing neonatal sepsis and pneumonia with strength of recommendation is C which based on patient-oriented, underpowered randomized trials.

2.0 LITERATURE REVIEW

Penicillins group (including ampicillin) is a renowned antibiotic used in pregnancy. Many studies have revealed their safety by lack of fetal adverse effects, even though it has been proved that they accumulate in the amniotic fluid (Heinonen, 2008).

Penicillins, is a β-lactam antibiotic which inhibit cell-wall synthesis in bacteria and have bactericidal properties. When used in therapeutic doses, they have a low toxicity profile for both, the pregnant woman and the fetus. Penicillins cross the placenta in low concentrations, and can be detected in amniotic fluid. Heikkla (2004), plotted that the dosage or dosage intervals should be adjusted if necessary since the elimination is more rapid in pregnant women. There is no evidence that penicillins have teratogenic or embryo/fetotoxic properties (Berkowitch et al, 2004). Nevertheless, a higher prevalence of cleft palate after prenatal exposure to ampicillin in the second and third month of pregnancy was revealed though a study by Czeizel et al (2007).

The CDC suggested the use of penicillin G preferentially for antibiotic prophylaxis (antibiotic started from onset of PROM >18 hours) because, theoretically, it was less likely to select for β- lactam antibiotic- resistant organisms because of its narrow spectrum of activity (Centres for Disease Control and Prevention, 1996).

Furthermore, although the CDC recommended penicillin G over ampicillin (which was referred to as an “acceptable alternative”), most clinical studies appraising intrapartum antibiotic prophylaxis have employed ampicillin (Allardice et al, 1982; Boyer, 1986, and Matorras et al,1990) and, at least in part because of this fact, ampicillin is used extensively for this principle. In addition to having antimicrobial activity against aerobic streptococci, such as group B streptococci, ampicillin is also bactericidal for many of the aerobic gram-negative bacilli, especially the family Enterobacteriaceae (Rodney et al, 2002).

Approximately 8% of women at term experience spontaneous rupture of the membranes prior to the onset of labour (Cammu 1990). Spontaneous labour follows term PROM at 24, 48 and 96 hours in 70%, 85% and 95% of women, respectively (Keirse et al, 1996 and Hannah et al, 1996).

Subclinical ascending infection is thought to play a role and has been identified in up to one third of women with term PROM (Romero 1992). Despite the antibacterial properties of amniotic fluid, there is an increased risk of infection for the woman and her infant following term PROM (Newton 1993). Therefore, the use of antibiotics may reduce the risk of infection for the woman and her baby.

Despite the advantages of use antibiotic prophyaxis in patient with PROM more than 18 hours, it is important to ensure judicious use of antibiotics. This is due to increasing dilemma with bacterial resistance (Lin 1999) and the risk of rare but potentially life threatening risk of maternal anaphylaxis with antibiotic use, Heim (1991).

According to RCOG Guideline 2003, the incidence of severe anaphylaxis associated with the use of penicillin in labour has been estimated at 1/10 000 women treated. Fatal anaphylaxis has been estimated to occur in as many as 1/100000 women treated (Weiss, 1988). The fetal effects of severe anaphylaxis have not been well described.

The widespread use of antibiotics is known to contribute to the development of resistant organisms particularly in broad-spectrum antibiotics such as ampicillin (Moore et al, 2003 and Stoll et al, 2002) and also when using penicillin.

Furthermore, recent clinical trial by Edwards et al (2003) also reported that intrapartum antibiotic prophylaxis (with either ampicillin or penicillin) may increase the likelihood of neonatal infection with ampicillin resistant Gram-negative organisms.

There is also a possibility that exposure to antibiotics in the neonatal perinatal period may affect neonatal faecal flora, with a subsequent impact on immune development and later allergy (Murch 2001).

Despite these possible problems, antibiotic prophylaxis remains the treatment of choice for pregnancies thought to be at risk. According to Green top Guideline No 36, number need to be treated approximately 625 women to prevent 1 case and 5882 women to prevent one death.

3.0 OBJECTIVES OF THE STUDY

3.1 General objective

To evaluate the differences in sepsis outcome (maternal and neonatal) comparing between 2 antibiotic prophylaxis regimes (2 grams stat followed by 1 gram 4 hourly versus 1 gram stat followed by 500 milligrams 6 hourly) in patient with PROM ≥ 18 hours.

3.2 Specific objectives

3.2.1 To compare the maternal outcome between these 2 antibiotic prophylaxis regimes

3.2.1.1 Choriamnionitis

3.2.1.2 Endometritis within 7 days postpartum

3.2.1.3 Allergic reaction

3.2.2 To compare the neonatal outcome between these 2 antibiotic prophylaxis regimes

3.2.2.1 Apgar score at 1 and 5 minutes

3.2.2.2 NICU admission

3.2.2.3 Early onset of sepsis

3.2.2.4 Neonatal mortality

3.2.3 To compare the association between these 2 antibiotic prophylaxis regimes and chorioamnionitis and early onset of sepsis in term of:-

3.2.3.1 Duration of PROM

3.2.3.2 Prostin insertion

3.2.3.3 Level of white cell count

3.2.3.4 Temperature

3.2.3.5 Vaginal examination prior to delivery

3.2.3.6 Dosage of intrapartum antibiotics

4.0 DEFINATION OF CLINICAL VARIABLE AND OUTCOMES

Gestational age	Estimated from the date of last menstrual period or amended by means of ultrasonography in some women in week 16-20 for those who are unsure of dates.
Term pregnancy	Gestational age from 37 completed weeks of gestation to 42 weeks
PROM	Complaining of rupture of membrane (sudden gushing of fluid and/or dribbling) before onset of labour (RANZCOG, 2014) and confirmation done by using a standardized evaluation local hospital protocol that consist of assessment for vaginal fluid fool and/or positive cough impulse by sterile speculum examination and secondary evaluation by amniocator. (AJOG, 2005; HSIJB Labour protocol, 2013).
Antibiotic prophylaxis	• Based on local protocol used of Ampicillin of 1 gram stat followed by 500 milligram 6 hourly from the onset of PROM more than 18 hours until delivery of baby (HSIJB Labour protocol, 2013). • Recommended Ampicillin of 2 gram stat followed by 1

gram 4 hourly from the onset of PROM more than 18 hours until delivery of baby (CDC, 2010).

- Antibiotic prophylaxis is given to patient with term PROM more than 18 hours including with membrane intact or absent.

Apgar score

A method of determining an infant's condition at birth by screening heart rate, respiratory effort, muscle tone, reflex and colour. The infants is rated from 0 to 2 on each of the five items, the highest possible is being 10

Apgar score	0	1	2
Heart rate (beats/min)	Absent	Less than 100	More than 100
Respiratory effort	Absent	Slow, irregular	Good cry
Muscle tone	Limp	Some flexion	Active
Reflex	No response	Grimace	Cry
Colour	Pale	Body pink, extremities blue	All pink

Early-onset neonatal sepsis (EOS)

- Infection with onset within 72 hours of birth, mainly due to bacteria acquired before and during delivery (Kaftan and Kinney, 1998; S Vergnano *et all*, 2005)
- Defined by both clinically and/or microbiologically, by positive blood and/or cerebrospinal fluid/ urine culture
- Clinical criteria for diagnosis of sepsis

	IMCI criteria for severe bacterial infection*	WHO young infant study group+
Convulsion	X	X
Respiratory rate >60 breath/min	X	X (divided by age group)
Severe chest indrawing	X	X
Nasal flaring	X	
Grunting	X	
Bulging fontanelle	X	
Pus draining from ear	X	
Redness around umbilicus extending to the skin	X	
Temperature >37.7^{o}C (or feels hot) or <35.5^{o}C (or feels cold)	X	X
Lethargic or unconscious	X	X (not aroused by minimal stimulus)
Reduced movements	X	X (change in

		activity)
Not able to feed	X	X (not able to sustain suck)
Not attaching to the breast	X	
Not suckling at all	X	
Crepitations		X
Cyanosis		X
Reduced digital capillary refill time		

*any of the signs listed implies high suspicion of serious bacterial infection.

+each symptom or sign is associated with a score. The score indicates the probability of disease.

IMCI, Integrated Management of Childhood Illness

(S Vergnano *et all*, 2005)

Clinical chorioamnionitis	Presence of uterine tenderness and/or purulent or foul smelling amniotic fluid with any 2 of following:- • Antepartum/intrapartum temperature of 37.8 ^{o}C (100.4^{o}F) or more • Maternal tachycardia (more than 120 beats/min) • Maternal leukocytosis (more than 18,000 cells/mm^{3}) • Fetal tachycardia (more than 160 beats/min) (AJOG, 2005)
Postpartum endometritis	Patient presented with fever with 38^{O}C, abdominal tenderness, leukocytosis (more than 12,000/ml) or foul smelling lochia or purulent vaginal discharge within 1 week following the delivery (Chaim W *et al*, 2000).

5.0 BACKGROUND OF THE STUDY

According to NICE guideline 2012 and Centers for Disease Control and Prevention (CDC, 2010) recommended antibiotic prophylaxis of 2 grams IV Ampicillin in the initial dose of PROM ≥ 18 hours followed by 1 gram IV every 4 hours until delivery.

Unfortunately, this regime is not standardized thorough out hospitals in this country as some hospitals use a regime of 1 gram IV Ampicillin from the onset of PROM ≥ 18 hours followed by 500 milligrams every 6 hours until delivery. This disparity of the Ampicillin regime that exist aiming to reduce risk of drug resistance, cost effective reason or could be already established treatment and practice.

1 vial of Ampicillin contain 500mg cost RM 2.32

	2 grams IV STAT then 1 grams every 4 hour until delivery	**1 grams IV STAT then 500 milligrams every 6 hours until delivery**
Starting the antibiotic	RM 9.28	RM 4.64
4 hours in labour	RM 4.64	
6 hours in labour		RM 2.32

8 hours in labour	RM 4.64	
TOTAL	RM 18.56	RM 6.96

Based on the cost calculation, if patient delivered after 8 hours in labour, there is difference about RM 11.60 between these two drug regimes. Even though the cost analysis in favour of lower dose regime, there is no proper literatures that recommend this dose regime for practical usage.

In this study hospital, since established we are using standard dose antibiotic of 1 gram stat then 500 milligrams 6 hourly and data of neonatal mortality in 2011 noticed that the most common causes was neonatal sepsis (28%) followed by prematurity (19%) and birth asphyxia (13%).

Hence, this research is embarked to justify the optimal regimen for Ampicillin when used as antibiotic prophylaxis to prevent early-onset neonatal infection and furthermore to consider the clinical maternal and neonatal outcomes.

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6.0 METHODOLOGY

6.1 Study setting

The study was conducted in Hospital Sultan Ismail, Johor Bahru (HSIJB). It is a well-equipped tertiary hospital with excellent quality of services and latest technology.

6.2 Study design

This was a prospective randomized controlled study, involving 292 patients who were admitted to labour room or antenatal ward and were randomized into these two regimes of antibiotic (as defined before) using randomization blocks.

6.3 Study population

All term pregnancy presented or been referred for PROM ≥ 18 hours in Hospital Sultan Ismail, Johor Bahru were recruited in the study.

6.4 Sample size calculation

Sample size was determined using P+S Software prior to the commencement of the study in consultation with the university statistician. Estimation of the sample size used the single proportion formula with 95% confidence interval.

Two formulas were tested to estimate the largest sample size needed.

- **Objective 1**
    - α=0.05

- Power= 0.9
- P0= 0.26
    - 26% risk of neonatal infection in Malaysia according to Lim NL *et al* (1995)
- P1= 0.43
- n= 122
- n + 20% (drop out) = 146
- Each arm trials would require 146 patients (total sample size of 292)

- **Objective 2**
    - α=0.05
    - Power= 0.9
    - P0= 0.2
        - 20% overall maternal infection (J Psychiatry Neurosi, 2008)
    - P1= 0.37
    - n= 110
    - n + 20% (drop out) = 132
    - Each arm trials would require 132 patients (total sample size 264)

Therefore, we established a target sample size of 292 patients.

6.5 Inclusion/ Exclusion criteria

Inclusion criteria

- All term singleton pregnancy.
- Presented with PROM more than 18 hours.
- Cephalic presentation.

Exclusion criteria

- Known case of allergic to Penicillin.
- Received an antibiotic within the preceding 7 days.
- In advanced labour with cervical opening more than 7 cm.
- Patient with chronic medical conditions that would interfere with study participation or evaluation of the treatment (e.g. seizures, psychiatric disorders, uncontrolled chronic hypertension, congestive heart failure, chronic renal failure, uncontrolled diabetes mellitus with end-organ dysfunctions, active thrombophlebitis or a thromboembolic disorder, history of hormone-associated thrombophlebitis or thromboembolic disorders, active liver disease, known or suspected malignancy of the breast or genital organs).
- Diagnosed to have major fetal anomaly.

6.6 Study period

The study was conducted in the Obstetrics and Gynecology Unit, HSIJB for a period of 7 months duration from 1st Mac 2014 until 30th September 2014 inclusive in accordance with the principles outlined in the Good Clinical Practice.

6.7 Sampling methods/ Data collection

All patients who presented or been referred for PROM ≥ 18 hours to Hospital Sultan Ismail during the study period, who fulfilled the inclusion and exclusion criteria were identified and recruited into the study.

Investigation such as full blood count and high vaginal swab for culture and sensitivity were taken from this patients. Four hourly vital signs such as temperature monitoring, pulse rate monitoring and pad charting were recorded.

Each participant was briefed on the study's background and objectives. Informed consent was obtained prior to their inclusion in the study (Appendix 1). Patient's demographic data and information were kept confidential. If they agreed to participate into the study, written informed consent were taken.

The patients were recruited by randomization using block the number of participants to avoid major imbalance of participants for each two different regimes. The patients picked one envelope from studied box (Double blinded study). They were subsequently grouped into 2 different antibiotic regimens; 2 gram Ampicillin stat followed by 1 gram 4 hourly (2

gram group) and 1 gram Ampicillin stat followed by 500 milligram 6 hourly (1 gram group).

Based on local protocol, patient who presented with PROM ≥ 18 hours were started on intravenous 1 gram of Ampicillin stat then 500 milligram for 6 hours until delivery. At any time patient developed clinical chorioamninitis, antibiotic was changed to third generation of cephalosporins group and the intravenous antibiotic was continued till day 3 of delivery and patient was discharged with oral Cefuroxime and Metronidazole for another 1 week. Placenta swab for culture and sensitivity were taken intraoperatively. Those patients who underwent Caesarean delivery for obstetrics indication the were given stat dose third generation of cephalosporin as a prophylaxis for surgical site infection and for those patient who underwent manual removal of placenta, intravenous Ampicillin for 1 day plus an intravenous Metronidazole 500mg TDS for 1 day post-delivery were given.

Once knowing the regime of antibiotic prophylaxis group, the Ampicillin was given to patient. The data collecting form or patient's information sheet was designed to meet the objective for this study. The demographic data of the participants were collected using this patient's information sheet (Appendix 3).

In patients with unfavorable cervix of PROM after 24 hours, they were induced with prostaglandin E2 pessary (Dinoproston/Prostin). Based on local protocol, prior to induction, cardiotocograph (CTG) was done to ascertain fetal heart. The patient emptied her bladder first. This pessary was inserted during vaginal examination at posterior fornix. 3 milligram