MICROBIOLOGICAL PATTERN IN CASES OF PRETERM PREMATURE RUPTURE OF FETAL MEMBRANES (PPROM): A CASE-CONTROL STUDY

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MAY 2013
DECLARATION

This dissertation is done at Obafemi Awolowo University Teaching Hospitals Complex and to the best of my knowledge, it contains no material previously published or written by another person nor material which to a substantial extent has been accepted for the award of any other degree or diploma of the university or other institute of higher learning, except where due acknowledgement has been made in the text.

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DEDICATION

To the Almighty God, the one that gives wisdom!

My loving family whose encouragement and support I have enjoyed.
ABSTRACT

BACKGROUND: Preterm premature rupture of fetal membranes (PPROM) is a significant contributor to adverse obstetric outcome. The need for a continuous search for the aetiological factors to enable its prevention and proper management if it occurs cannot be overemphasized. Empirical antibiotic prescription is often based on the common pathogens and sensitivity pattern from studies done in developed countries and it is very likely that these pathogens would be different from those in our environment.

OBJECTIVE: To determine the pattern of micro – organisms implicated in cases of preterm premature rupture of fetal membranes and the antimicrobial sensitivity pattern at Obafemi Awolowo University Teaching Hospitals Complex, Ile – Ife.

METHOD: This was a case-control study of 56 cases of PPROM between 24 weeks and 36 weeks gestation versus controls matched for age, gestation age and parity. Endocervical swab and high vaginal swab were taken from both cases and control and sent for microscopy, culture and sensitivity.

RESULT: The overall incidence of PPROM was 5.7%. The cases of PPROM had significantly more positive cultures than controls (83.9% versus 8.9% P = 0.001). The common pathogens include klebsiella (32.1%), Escherichia coli (19.6%), Proteus (14.3%), and Staphylococcus aureus (10.7%). Others which are also isolated in the controls were Streptococcus pyogenes (7.1%), Coagulase negative Staphylococcus (3.6%), Bacteriodes (5.4%) and β haemolytic Streptococcus (3.6%). The organisms showed very good sensitivity to Ciprofloxacin (96.3%), Ceftriaxone (92.6%), Amoxiclav (94.4%), Cefuroxime (90.7%), Erythromycin (88.9%), Gentamicin(70.4%) and Chloramphenicol (63%). Cloxacillin only showed moderate sensitivity (50%) while Ampicillin, Co-trimoxazole and Amoxicillin all had low sensitivity. Low socio-economic class was associated with PPROM (P < 0.001).

CONCLUSION: Positive cultures are present in most cases of PPROM and Klebsiella is the commonest pathogen identified.
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CHAPTER ONE

INTRODUCTION

Premature rupture of membranes (PROM) is defined as the rupture of fetal membranes before the onset of labour, after the age of viability. It is a common obstetric problem occurring in about 10% of pregnancies. Preterm premature rupture of membranes (PPROM) is rupture of fetal membranes prior to 37 weeks gestation. PPROM complicates 3% to 4.5% of all pregnancies and is responsible for 40% of all preterm births with attendant high perinatal mortality rate of 60-80%.

Rupture of fetal membranes occurring less than one hour before onset of labour is regarded as part of labour events. However, when fetal membrane rupture occurs more than one hour before onset of labour it is Pre-Labour Rupture of Fetal Membranes.

At term, programmed cell death and activation of catabolic enzymes such as collagenase and mechanical forces result in rupture of membranes. PPROM occurs probably due to the same mechanisms and premature activation of these pathways. However, early PROM also appears to be linked to underlying pathologic processes, most likely due to inflammation and/or infection of the membranes. Risk factors implicated or associated with aetiology of PPROM include low socioeconomic status, low body mass index, tobacco use, history of preterm labour, urinary tract infection, vaginal bleeding at any time in pregnancy, cerclage, and amniocentesis.

In recent years, the role of infection with lower genital tract organism in precipitating PPROM and preterm labour has come under considerable scrutiny. Although, the aetiology of PPROM is multifactorial, increasing evidence regarding
clinical risk factors, membrane histology and amniotic fluid microbiology shows a strong association with infection leading to amniorhexis. There is evidence that microorganisms can penetrate intact fetal membranes. Several studies have shown that women with low socio-economic status are at higher risk of PPROM and are more likely to develop chorioamnionitis as a complication of PPROM.

When PPROM occurs before 34 weeks gestation, conservative management is advocated to ensure fetal lung maturity. It is possible to successfully prolong the latency from membrane rupture to delivery but it is associated with development of maternal and foetal infection. Recommended management strategy includes the use of corticosteroids, tocolytics and antibiotics. Early studies suggested that prophylactic antibiotics could be beneficial in cases of idiopathic PPROM and preterm labour. There is prolongation of latency period, reduction in chorioamnionitis and possible reduction in gestational age dependent morbidity and neonatal infections in PPROM when antibiotics are used. Appropriate antibiotic therapy is instituted following culture and sensitivity results of amniotic fluid and/or endocervical swabs.

This study is relevant in our environment. In particular, the lack of rapid diagnostic method for confirmation of organisms implicated inevitably leads to inappropriate use of antibiotics. Broad spectrum antibiotics are often prescribed in this situation without microbiological studies. The lack of adequate microbiological studies prior to commencement of antibiotics in cases of PPROM and non-availability of laboratory backup in many secondary and primary level health care facilities creates the need to study the local microbiological pattern and their sensitivity in order to rationally
suggest a first line choice for empirical treatment. Such treatment becomes invaluable not only in the institution of study but also in other neighbouring secondary and tertiary centres where this type of study has not been performed or laboratory facilities are lacking.
CHAPTER TWO

LITERATURE REVIEW

Introduction

PPROM is the most common cause of preterm delivery which is the leading cause of perinatal morbidity and mortality. PPROM is implicated in 40% of preterm births. Fetal membranes rupture is a serious tissue failure, an exclusive event that is either spontaneous or occurs prior to onset of regular uterine contraction. It is diagnosed by visualization of liquor by sterile speculum vaginal examination.

Anatomy of Fetal Membranes

Fetal membranes are made up of amnion and chorion which are closely adherent layers consisting of several cell types, including epithelial cells, mesenchymal cells, and trophoblast cells, embedded in a collagenous matrix. They retain amniotic fluid, secrete substance both into the amniotic fluid and towards the uterus, and guard the fetus against infection ascending the reproductive tract. The human fetal membranes are composed of five layers; it contains no blood vessels or nerves, the nutrient it requires are supplied by the amniotic fluid. The innermost layer, nearest the fetus, is the amniotic epithelium. Amniotic epithelia cells secrete collagen types III and IV and noncollagenous glycoprotein, (laminin, nidogen, and fibronectin) that form the basement membrane, the next layer of the amnion.

The compact layer of connective tissues adjacent to the basement membrane forms the main fibrous skeleton of the amnion. The collagens of the compact layer are secreted by mesenchymal cells in the fibroblast layer. Interstitial collagens (types i and iii)
predominate and form parallel bundles that maintain the mechanical integrity of the amnion\textsuperscript{25} Collagen types V and VI form filamentous connection between the interstitial collagens and the epithelial basement membrane.\textsuperscript{25} There is no interposition of amorphous ground substance between collagen fibrils in amniotic connective tissues at term, so the amnion maintains its tensile strength throughout the late stages of normal pregnancy. Break down of membranes occurs before term (PPROM) due to genital infection that causes release of collagenase and proteinase which leads to the breakdown of membrane.

**Genital tract infection and PPROM**

Subclinical genital tract infection has been linked with preterm birth and PPROM especially when the gestational age is less than 34 weeks.\textsuperscript{4,6,10,11} Lower genital tract infection not only causes PPROM and preterm birth but also results in serious maternal and fetal infection; thus making it a major cause of perinatal morbidity and mortality especially in PPROM that is remote from term in which conservative management is instituted.\textsuperscript{12,14,16,20,26} Neonatal infection\textsuperscript{2} and endometritis\textsuperscript{28} are commoner in patient with preterm delivery.

There is increasing evidence that links genital tract infection and preterm birth which now provides an exciting potential for the development of sensitive new markers to identify women at risk and effective interventions to prevent PROM/birth before term. Microorganisms have been isolated from the amniotic fluid of women who experienced preterm labour with or without PPROM, although the rate of positive cultures are higher in women who have PPROM (approximately 32.4\%) than in those with preterm
labour with intact membranes (approximately 12.8%)\textsuperscript{29}. Infection can be associated with PPROM as either a cause or a consequence. Infection preceding PPROM is often subclinical and thought to ascend from the lower genital tract\textsuperscript{30,31}. Following rupture of the membranes ascending bacterial invasion can lead to intrauterine infection in up to 60\% of cases in the absence of antibacterial therapy.\textsuperscript{32}

Administration of antibiotics after PPROM is associated with prolongation of pregnancy and reduction in maternal and neonatal morbidity.\textsuperscript{33,34} Genital tract organisms have been found to penetrate intact fetal membranes\textsuperscript{6} and subsequently result in PPROM through mechanisms that have been studied but not clearly understood.\textsuperscript{35,36}

Presence of periodontal disease has been linked with PPROM and preterm birth.\textsuperscript{37} Oral opportunistic pathogens and/or their inflammatory products may also have a role in PPROM/preterm birth through haematogenous route. Fusobacterium nucleate, a common oral species is the most frequently isolated species from amniotic fluid cultures among women with preterm labour and intact membrane.\textsuperscript{13,37,38} Proper understanding of how pathophysiologic mechanism by which genital tract infection results in PPROM will give us a better insight to the role of infection and so help initiate treatment to reduce the perinatal mortality and morbidity associated with PPROM.\textsuperscript{39}

The putative mechanism underlying infection and PPROM requires intrauterine bacterial invasion, which activate the decidua and fetal membranes to produce pro-inflammatory cytokines. This in turn leads to the release of prostaglandins, metalloprotease and other bioactive substances. The prostaglandins stimulate uterine contractions and metalloprotease soften the cervix and target the membrane leading to
rupture. The role of humoral factors such as interleukin 1, neutrophil activating peptide-1 in idiopathic preterm labour/PPROM may allow us to determine the physiologic mechanism that leads to PPROM.37,39

Bacterial infection and the host inflammatory response also induce the fetal membranes to release prostaglandins which is thought to increase the risk of preterm premature rupture of the membranes by causing uterine irritability and collagen degradation within the membranes. Certain strains of vaginal bacteria produce phospholipase A₂, which mediates the releases of prostaglandin precursor arachidonic acid, from membrane phospholipids. Furthermore, the immune response to bacterial infection includes the production of cytokines by activated monocytes that increase prostaglandin E₂ production by chorionic cells.41 Cytokine stimulation of prostaglandin E₂ production by the amnion and chorion appears to involve induction of cyclooxygenase II, the enzyme that converts arachidonic acid to prostaglandin.42

The precise regulation of prostaglandin E₂ synthesis in relation to bacterial infection and the host inflammatory response is not understood and direct link between prostaglandin production and premature rupture of the membrane has not been established. However, prostaglandin (specifically prostaglandin E₂ and prostaglandin F₂α) are considered to be mediators of labour in all mammals, and prostaglandin E₂ diminishes collagen synthesis in fetal membranes and increases MMP-1 and MMP-3 expression in human fibroblast.43,44

Another component of the host response to infection is the production of glucocorticoids. In most tissues the anti-inflammatory action of glucocorticoids is
mediated by suppression of prostaglandin production. However, in some tissues, including the amnion, glucocorticoids paradoxically stimulate prostaglandin production. Furthermore, dexamethasone reduces the synthesis of fibronectin and type III collagen in primary cultures of amniotic epithelial cell\textsuperscript{45}. These findings suggest that glucocorticoids produced in response to the stress of microbial infection facilitate rupture of the fetal membranes.

The high concentration of potentially pathogenic microorganism in the vaginal and the cervix of pregnant woman with bacterial vaginosis may increase the possibility of an ascending infection via the cervix, decidua, fetal membranes, maternal placenta, and amniotic fluid\textsuperscript{36}. Some of the bacterial vaginosis such as Bacteroides species are particularly important, certain bacteria produce enzymes that potentially could affect the fetal membranes or maternal decidua. Bacteroides species and group B streptococcus produce proteases\textsuperscript{36, 46, 47, 48}. Protease enzymes reduce the chorioamniotic membrane strength in vitro. It is even possible that a high concentration of bacteria in the lower genital tract could produce enough proteases to weaken the fetal membrane strength, causing premature rupture of the membranes. Bacteria lipases could also cause tissue injury. Lysosomes within fetal membrane cells contain phospholipase A\textsubscript{2} in high concentration. Phospholipase A\textsubscript{2} is a precursor of prostaglandin synthesis and the destruction of lysosomes within decidua or chorioamniotic cells may induce prostaglandin synthesis resulting in uterine contraction\textsuperscript{8,37}.

In some studies, a high rate of phospholipase A\textsubscript{2} production was found to be associated with bacteroides species, anaerobic Streptococci, Fusobacterium species, and
Gardnerella Vaginalis. It was also demonstrated that bacteria product of group B Streptococci, Viridians Streptococci, Escherichia Coli, Bacteroides fragilis but not lactobacillus species increase the synthesis of prostaglandins in the membranes. Thus selected bacteria, including some closely related to bacteria vaginosis may play a role in the initiation of uterine contraction by stimulating prostaglandin synthesis.

The common pathogens associated with PPROM and preterm labours are Bacterial Vaginosis Complex, Group B Streptococci, E. Coli, Bacteroides, Viridians Streptococci and an unusual organism fusobacterium. The Bacterial Vaginosis complex include organisms such as Gardnerella Vaginalis, anaerobic species primarily among Prevotella, Peptostreptococcus and Mobiluncus, Mycoplasma Hominis and ureaplasma Urealyticum. It is interesting that candida species, common in the vagina, is an unusual pathogenic cause of preterm labour/PPROM and Haemophilus influenza has also reportedly been found in women presenting with PPROM. The role of Chlamydia trachomatis and viruses in PPROM/preterm labour remains to be determined. Use of molecular microbiology techniques to diagnose intrauterine infection may uncover role of fastidious microorganisms that have not yet been discovered.

In a study in Saudi Arabia, Bahar et al found a verity of aerobic or anaerobic organism or both in cases of PPROM. Shaarawy et al found mycoplasma Hominis and Ureaplasma Urealyticum in addition to aerobic and anaerobic organisms in Egypt. This was similar to the findings of Abd El et al in another study in Egypt. In a study in Brazil; Silva et al isolated Staphylococcus aureus in addition to a wide diversity of microorganisms. They found an intense inflammatory infiltrate in membranes which
they linked to the rupture of membranes. With the strong link between infection and PPROM, research has focused on the use of antibiotics in PPROM for the purpose of decreasing the complications associated with infection.

**Antibiotic Therapy in PPROM**

Antibiotic therapy could improve outcome PPROM in two ways. First, the prevention or treatment of infection may reduce maternal or fetal/neonatal morbidity. Second, by treating or preventing ascending infection, antibiotic therapy may prolong pregnancy and delay the progression to preterm birth.\(^{32,34}\) Many studies assessing the effect of antibiotics following PPROM have been published. Most of these are small.

However, there are two large randomized controlled trials; the first is the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network Trial, which enrolled 614 women with PPROM from 24 to 32 weeks’ gestation;\(^ {56}\) the other is the ORACLE I trial, which enrolled 4826 women.\(^ {57}\) In the first trial, women were randomized to receive antibiotics or placebo for a total of seven days. The antibiotic regimen used 48 hours of intravenous therapy followed by five days of oral medications. The initial phase involved the use of ampicillin 2 g IV every 6 hours and erythromycin 250 mg IV every 6 hours. After 48 hours, these medications were changed to amoxicillin 250 mg orally every 8 hours and erythromycin 333 mg orally every 8 hours. Antibiotic therapy did prolong pregnancy, with a two-fold likelihood that patients would not deliver after seven days of treatment. Treated women were more likely to remain pregnant for up to three weeks after randomization.
In the ORACLE I trial, 4826 women with PPROM at < 37 weeks’ gestation were enrolled and randomized into one of four oral treatment groups: (1) 325 mg co-amoxiclav (250 mg amoxicillin and 125 mg clavulanic acid) plus 250 mg erythromycin, (2) co-amoxiclav plus erythromycin placebo, (3) erythromycin plus co-amoxiclav placebo, or (4) co-amoxiclav placebo plus erythromycin placebo. All medications were taken four times daily for 10 days or until delivery. For the composite primary outcome of death or major adverse outcome in the baby before discharge from hospital, there were no statistically significant reductions for any of the comparisons. However, oral erythromycin was associated with prolongation of pregnancy for 48 hours when erythromycin only was compared with placebo (34.8% vs. 40.7%, P = 0.004) and for 7 days when any erythromycin was compared with no erythromycin (57.7% vs. 60.5%, P = 0.05). The combination of drugs (erythromycin and co-amoxiclav) led to similar findings. The authors concluded that erythromycin has a range of neonatal health benefits when administered to women with PPROM, but that co-amoxiclav should not be used because of its association with NEC. The study has been criticized because there were no differences in the composite primary outcome for any of the treatment groups when compared with placebo.

However, there were many significant differences in subgroup analyses (presented above). Data on long-term outcomes among children from this trial were published in 2008. After seven years of follow-up, there was no difference in the proportion of children with any functional impairment in the group born to women who received erythromycin, with or without co-amoxiclav, and in the group born to women who received
Erythromycin, with or without co-amoxiclav, and in group born to women who received no erythromycin.\textsuperscript{59}

In addition to these two trials, many other studies have been published assessing the efficacy of antibiotics following PPROM for pregnancy prolongation and reduction of maternal and neonatal morbidity, with different regimens and duration of treatment. They include studies documenting an increase in the latency period in women who received imipenem/cilastatin\textsuperscript{60} and mezlocillin\textsuperscript{61} In a study comparing duration of therapy, all patients received 48 hours of parenteral ampicillin and were then randomized to receive either three or seven days of oral ampicillin following PPROM. There was no difference between the two regimens in the ability to achieve a seven-day latency period, and no difference in the incidence of maternal or neonatal morbidity.\textsuperscript{62}

Larger reviews have also been performed to assess the effects of antibiotic administration in women with PPROM on maternal and perinatal morbidity and mortality, and to attempt to identify the antibiotic(s) of choice. Kenyon and colleagues published a systematic review of 19 trials involving 6951 women, of which 14 were randomized controlled trials.\textsuperscript{34} Participants were enrolled from 21 to 37 weeks’ gestational age, and several different antibiotic regimens were used.

In terms of specific antibiotics, benefits were seen (pregnancy prolongation and decreases in neonatal morbidity) in trials using penicillins and erythromycin. In two trials enrolling a total of 4888 women, the authors concluded that the data supported the use of antibiotics (erythromycin and penicillins) for women following PPROM to delay delivery and decrease maternal and neonatal morbidity. The strength of evidence was greater for
erythromycin, as it was used in larger trials than penicillins; however, the optimal antibiotic regimen is unclear, because equivalency/superiority trials have not been done. It was recommended that amoxicillin/clavulanic acid not be used because of the increased risk of NEC (RR 4.60; 95% CI 1.98 to 10.72).34

Finally, in 2008, the Cochrane Collaboration published a review by Kenyon and colleagues of the use of antibiotics following PPROM.63 This systematic review consisted of 22 trials with over 6000 women. It included the randomized controlled trials that were part of the 2004 review by Kenyon et al., and the findings therefore mirrored those of the earlier review.34 Once again, the use of antibiotics was associated with a prolongation of pregnancy for both 48 hours (RR 0.71; 95% CI 0.58 to 0.87) and 7 days (RR 0.80; 95% CI 0.71 to 0.90), and with a decrease in chorioamnionitis and several markers of neonatal morbidity.59 Amoxicillin/clavulanic acid was again associated with a significantly increased risk of NEC (RR 4.60; 95% CI 1.98 to 10.72).63 The authors concluded that antibiotic administration following PPROM is associated with a delay in delivery and a reduction in markers of neonatal morbidity and that the data support the routine use of antibiotics in PPROM.63

At gestational ages between 32 and 34 weeks, if fetal lung maturity can be documented, delivery is suggested, as conservative management has been shown to prolong pregnancy only briefly (36 vs. 14 hours, P < 0.001) and to increase the risk of amnionitis (27.7% vs. 10.9%, P = 0.06).64 If fetal lung maturity cannot be proven, then administration of antibiotics to prolong the latency period is recommended.
Antibiotic treatment for women with PPROM especially remote from term, offers significant benefit with respect to pregnancy prolongation of interval from rupture of membranes to delivery and improvement in neonatal outcome\textsuperscript{65, 66, 67, 68} with reduced risk of maternal infection.
CHAPTER THREE

OBJECTIVES

GENERAL OBJECTIVE

To determine the microbiological pattern in cases of PPROM at OAUTHC, Ile-Ife

SPECIFIC OBJECTIVES

- To determine the incidence of PPROM
- To identify the common micro organism in cases of PPROM
- To determine the antibiotic sensitivity pattern of these organisms.
- To suggest from the findings, first line antibiotic regimen for empirical use while awaiting culture sensitivity result.

NULL HYPOTHESIS

- The pattern of microorganisms found in patients with PPROM is not significantly different from those without PPROM.
JUSTIFICATION OF THE STUDY

Preterm premature rupture of fetal membranes is a significant cause of preterm delivery which accounts for about 60-80% of perinatal mortality.\textsuperscript{4,5,6} Available evidence implicates urogenital tract infections as a major contributor to the aetiology of PPROM which could also predispose to further infections. A combination of PPROM, preterm delivery and infections could worsen both fetal and maternal outcome. There is paucity of data on microbiological pattern of the organisms implicated in our environment.

Empirical antibiotic prescription is often based on the common pathogens and sensitivity pattern from studies done in developed countries and it is very likely that these pathogens would be different from those in our environment. In view of this, a local study of microbiological pattern and antibiotic sensitivity will not only help identify the appropriate first line choice of antibiotics for empirical treatment but this will also help prolong latency period and improve the fetal and maternal outcome as well as prevent wastage of resources and antibiotic abuse.
CHAPTER FOUR

METHODOLOGY

SITE

The study was carried out at the obstetrics, gynaecology and perinatology department of the Obafemi Awolowo University Teaching Hospital Complex, Ile-Ife, Osun State, Nigeria, comprising two obstetric units: Ife Hospital Unit (IHU) and Wesley Guild Hospital (WGH), Ilesha.

These hospitals serve as tertiary referral centres for secondary and primary tiers of hospitals in Osun, Ondo and Ekiti zones of the country. The two obstetric units conduct an average of 2,750 deliveries every year with antenatal booking clinic attendance of an average of 3,050 per year.

STUDY DESIGN

It is a case control study

TARGET POPULATION

Pregnant women in the Obstetric Unit of Ile-Ife and Wesley Guild Hospital Ilesha.

INCLUSION CRITERIA

1) Patients with rupture of fetal membranes before 37 weeks gestation and less than 24 hours duration.

2) Patients with an ongoing pregnancy without ruptured membranes matched for parity (+ or -2), age (+ or -2 years) and gestational age (+ or -2 weeks).
EXCLUSION CRITERIA

1) Patients with rupture of membranes less than 24 weeks or after 37 completed weeks.

2) Patients with PPROM more than 24 hours.

3) Patients with PPROM and pyrexia-temperature of 38°C and above.

4) Patients with PPROM who have taken antibiotics within the past 7 days.

5) Patients with malpresentation, polyhydraminos or cervical incompetence who presented with PPROM.

SAMPLE SIZE DETERMINATION:

The sample size was calculated using the upper limit of the incidence of PPROM of 3-4.5%. Using the incidence of 4.5% from the above study, and accepting a study power of 80%, confidence interval of 95%, case to control ratio of 1:1; the sample size of each group is determined using the statistical formula for the comparison of categorical variables in case control study.\(^69\)

\[
n = \left[ \frac{2 \times (Za + Zb)^2 \times P \times (1 - P)}{(P_0 - P_1)^2} \right]
\]

- \(P_0\) = percentage of patients with PPROM. i.e. 4.5% or 0.045.
- \(P_1\) = the proportion of patients with PPROM. This is usually set relative to \(P_0\), and with proposed effect size of 30%; \(P_1 = 0.045 + 0.30\) (effect size) = 0.345.
- $Z_\alpha$ was determined from statistical tables based on the value of the level of significance 0.05 for this study. Therefore, $Z_\alpha = 1.96$.

- $Z_\beta$ was determined from statistical tables based on the acceptable power of comparison i.e. 80% between the two groups. Therefore, $Z_\beta = 0.84$.

$$P = \frac{P_0 + P_1}{2} = \frac{0.045 + 0.345}{2} = 0.2$$

Therefore, sample size $n$

$$n = \left[ \frac{2 \times (1.96 + 0.84)^2 \times 0.2 \times (1 + 0.2)}{(0.045 - 0.345)^2} \right]$$

$n \approx 28$ participants per group approximately.

The sample size was increased with over 100% (i.e 56 participants per group) to increase the statistical power and weight of the study.

**Training**

Prior to commencement of the study, a training session was conducted for ten resident doctors (five each from Wesley Guild and Ife hospital units) who were involved in the study, both the inclusion and exclusion criteria of the study was explained. Diagnosis of PPROM and methods of sample collection was discussed and any ambiguity clarified. The participating doctors were involved in the diagnosis of PPROM and in sample collection.
**Study procedure**

Upon completion of informed consent, all study participants baseline data including the admission vital signs were recorded in the study proforma. Diagnosis of PPROM was confirmed by seeing a pool of amniotic fluid in the posterior fornix of the vagina and observing its egress from the cervix with or without valsava manoeuvre. Endocervical and high vaginal swabs were taken from one hundred and twelve participants (56 participants each for cases and control) who met the criteria for the study. The controls were pregnant women without PPROM recruited from ante natal clinics of the Hospital wings.

Two qualified microbiologists were responsible for the processing of all the samples (One in Ife hospital unit and the other in Ilesha Hospital Unit) The high vaginal swab and the endocervical swab from both the cases and controls were quickly transferred into the Stuart transport medium in which they were transported to the laboratory. All swabs in the transport medium were processed within four (4) hours of sample collection.

Each sample was inoculated into blood agar, maconkay agar, chocolate agar, and gentamicin blood agar. All the inoculated agars were incubated for 24hours at 37°C. Anaerobic jar was used with gentamicin blood agar while incubating at 37°C. Wet mount was done with both high vaginal and endocervical swab of both cases and controls, smeared on a slide and examined microscopically for fungal elements, Trichomonal and Gardnerella vaginalis. Gram staining of all specimens was done and examined for intracellular Gram-negative diplococci. Three drops of 10% potassium hydroxide (KOH)
were also added separately for whiff test as part of criteria to diagnose bacteria vaginosis.

**STATISTICAL ANALYSIS**

Data obtained was analysed using the computer software SPSS version 16. Frequency tables were made and results tested for significance using the student t-test for continuous variables and Chi square test for categorical variables with level of significance (p) less than 0.05.

**LIMITATIONS OF THE STUDY**

Gestational age estimation was a problem for those who could not remember their last menstrual period and did not have early ultrasound scan. Late ultrasound scan estimation was used to estimate the gestational age. There is no objective way to know the duration of membrane rupture but good history taking helped in reducing the effect of this limitation. Mycoplasma hominis and Ureaplasma were not tested for in this study because of non-availability of the materials needed to isolate them. Also, the presence or isolation of a microorganism in a patient with PPROM might not necessarily be the cause of membrane rupture.
ETHICAL CONSIDERATION

Ethical clearance was obtained for this study from the ethical clearance committee of the Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife. All participants were fully informed about the study. The information obtained from them was kept in a personal computer with a pass word and reserved the right to decline being co-opted for whatever reasons without penalty.
CHAPTER FIVE
RESULT

A total of 56 patients with PPROM were matched with 56 pregnant women without PPROM, table 1 shows the socio demographic data of the studied population.

The overall incidence of PPROM was 5.7% (88 of 1,540 pregnant women)

Table 1
Socio Demographic Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cases n=56 (%)</th>
<th>Controls n=56 (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (Years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>1 (1.8)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>20 – 24</td>
<td>8 (14.3)</td>
<td>4 (7.1)</td>
<td></td>
</tr>
<tr>
<td>25 – 29</td>
<td>18 (32.1)</td>
<td>26 (46.4)</td>
<td>0.35</td>
</tr>
<tr>
<td>30 – 34</td>
<td>26 (46.4)</td>
<td>21 (37.5)</td>
<td></td>
</tr>
<tr>
<td>35 and above</td>
<td>3 (5.4)</td>
<td>5 (9)</td>
<td></td>
</tr>
<tr>
<td><strong>Mean age in years</strong></td>
<td>29.11±4.11</td>
<td>29.45±4.07</td>
<td>0.66</td>
</tr>
<tr>
<td><strong>Parity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>12 (21.4)</td>
<td>8 (14.3)</td>
<td></td>
</tr>
<tr>
<td>1-2</td>
<td>24 (42.9)</td>
<td>34 (60.7)</td>
<td>0.17</td>
</tr>
<tr>
<td>3-4</td>
<td>20 (35.7)</td>
<td>13 (23.2)</td>
<td></td>
</tr>
<tr>
<td>5 and above</td>
<td>0 (0)</td>
<td>1 (1.8)</td>
<td></td>
</tr>
<tr>
<td><strong>Mean parity</strong></td>
<td>1.82±1.29</td>
<td>1.77±1.17</td>
<td>0.82</td>
</tr>
<tr>
<td><strong>Social class</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (4-5)</td>
<td>37 (66.1)</td>
<td>13 (23.2)</td>
<td></td>
</tr>
<tr>
<td>Middle (3)</td>
<td>11 (19.6)</td>
<td>33 (58.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>High (1-2)</td>
<td>8 (14.3)</td>
<td>10 (17.9)</td>
<td></td>
</tr>
<tr>
<td><strong>Mean social class</strong></td>
<td>4.05±0.86</td>
<td>3.02±0.92</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Estimated gestational age(wks)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-27</td>
<td>3 (5.3)</td>
<td>3 (5.3)</td>
<td></td>
</tr>
<tr>
<td>28-30</td>
<td>14 (25)</td>
<td>20 (35.7)</td>
<td></td>
</tr>
<tr>
<td>31-33</td>
<td>29 (51.8)</td>
<td>16 (28.6)</td>
<td>0.086</td>
</tr>
<tr>
<td>34-36</td>
<td>10 (17.9)</td>
<td>17 (30.4)</td>
<td></td>
</tr>
<tr>
<td><strong>Mean EGA(wks)</strong></td>
<td>31±2.32</td>
<td>31±2.67</td>
<td>0.99</td>
</tr>
</tbody>
</table>

Wks=Weeks, < = Less than, EGA = Estimated Gestational Age
The age distributions in the case and control groups were homogenous (p=0.35). The study population consisted mainly of those with parous experience (78.6% and 85.7%) for cases and control. No statistical significant difference was found in age and parity between cases and control (P = 0.35 and 0.17 respectively).

A high percentage of the cases of PPROM (51.8%) occurred at estimated gestational age of 31-33 weeks followed by cases that occurred between 28-30 weeks gestation with 25% occurrence. The occurrence of PPROM at estimated gestational age of 34-36weeks is 17.9% while only 5.3% of cases occurred between 24-27 weeks of gestation. There is however no statistical difference in the estimated gestational age at which PPROM occurred (P = 0.087). It was found that about two third of the cases of PPROM occurs in patients with low socio-economic status. This is statistically significant when compared with control which account for about one fourth of the controlled population (p=0.001)
### Table 2
**Isolates from cases and controls**

<table>
<thead>
<tr>
<th>Isolates</th>
<th>Isolates from cases n=56</th>
<th>Controls n=56</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HVS</td>
<td>ECS</td>
</tr>
<tr>
<td>Klebsiella</td>
<td>12</td>
<td>21.4</td>
</tr>
<tr>
<td>E. coli</td>
<td>9</td>
<td>16.1</td>
</tr>
<tr>
<td>Proteus</td>
<td>3</td>
<td>5.3</td>
</tr>
<tr>
<td>Staph aureus</td>
<td>6</td>
<td>10.7</td>
</tr>
<tr>
<td>Strept. pyogenes</td>
<td>4</td>
<td>7.1</td>
</tr>
<tr>
<td>CONS</td>
<td>2</td>
<td>3.6</td>
</tr>
<tr>
<td>Bacteroides</td>
<td>3</td>
<td>5.4</td>
</tr>
<tr>
<td>β haemolytic strept.</td>
<td>2</td>
<td>3.6</td>
</tr>
</tbody>
</table>

E.coli= Escherichia coli.  Strept. Pyogenase = streptococcus pyogenase ,  β haemolytic strept. = β haemolytic streptococcus.  HVS = High vaginal swab.  ECS = Endocervical swab.  CONS= Coagulase negative staphylococcus.  Staph. aureus = Staphylococcus aureus

- Gardnerella vaginalis was demonstrated microscopically and whiff test positive in 3(5.3%) of PPROM but 1(1.8%) in the control group.

- Trichomonas vaginalis was seen microscopically in 3(5.3%) of PPROM but 2(3.6%) in the control group.

- Candida albicans was seen in 2(3.6%) of the cases but 7(12.5%) in the control group.

These three occurred mixed with some of the positive bacterial cultures.
A total of fifty four pathogens were isolated from forty seven patients out of the fifty six cases of PPROM while only five pathogens were isolated from the controls.

The occurrence of various organisms isolated from both HVS and ECS of cases and controls were as shown above (Table 2). No organism was isolated from the ECS of the controls but five of the controls had positive culture from HVS. There is substantial positive culture from both the ECS (71.3%) and HVS (73.2%) of the cases. Gardnerella vaginalis, Trichomonas vaginalis and Candida albicans occurred with some positive bacterial cultures in a mixed fashion.
Table 3
Frequency of isolates of various organisms

<table>
<thead>
<tr>
<th></th>
<th>Cases n=56</th>
<th>Controls n=56</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Klebsiella</td>
<td>18</td>
<td>32.1</td>
<td>-</td>
</tr>
<tr>
<td>E. coli</td>
<td>11</td>
<td>19.6</td>
<td>-</td>
</tr>
<tr>
<td>Proteus</td>
<td>8</td>
<td>14.3</td>
<td>-</td>
</tr>
<tr>
<td>Staph. aureus</td>
<td>6</td>
<td>10.7</td>
<td>-</td>
</tr>
<tr>
<td>Strept. pyogenes</td>
<td>4</td>
<td>7.1</td>
<td>2</td>
</tr>
<tr>
<td>CONS</td>
<td>2</td>
<td>3.6</td>
<td>1</td>
</tr>
<tr>
<td>Bacteroides</td>
<td>3</td>
<td>5.4</td>
<td>1</td>
</tr>
<tr>
<td>β haemolytic strept.</td>
<td>2</td>
<td>3.6</td>
<td>1</td>
</tr>
<tr>
<td>Total pathogens isolated</td>
<td>54</td>
<td>96.4</td>
<td>5</td>
</tr>
</tbody>
</table>

E. coli = Escherichia coli. Strept. Pyogenase = streptococcus pyogenase. β haemolytic strept. = β haemolytic streptococcus. CONS = Coagulase negative staphylococcus. Staph. aureus = Staphylococcus aureus
The prevalence of various organisms isolated is shown above (Table 3). There were fifty four (54) bacteriological isolates from the HVS and ECS of the cases. Klebsiella was the commonest organism isolated accounting for 32.1%, the other organisms isolated include Escherichia coli (19.6%), Proteus (14.3%), Staphylococcus aureus (10.7%), Streptococcus pyogenes (7.1%), Bacteroides (5.4%), Coagulase negative staphylococcus (3.6%) and β haemolytic Streptococcus (3.6%). Total positive cultures were 83.9% and 8.9% for case and control respectively giving a P value of 0.001.
<table>
<thead>
<tr>
<th>Drugs</th>
<th>E.coli n=11 (%)</th>
<th>Klebsiela n=18 (%)</th>
<th>S.pyogenes n=4 (%)</th>
<th>Proteus n=8 (%)</th>
<th>CONS n=2 (%)</th>
<th>S.aureus n=6 (%)</th>
<th>β.H.strept n=2 (%)</th>
<th>Bacteriodes n=3 (%)</th>
<th>Total number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloramphenicol</td>
<td>6 (54.5)</td>
<td>12 (66.7)</td>
<td>3 (75)</td>
<td>4 (50)</td>
<td>1 (50)</td>
<td>6 (100)</td>
<td>1 (50)</td>
<td>1 (33.3)</td>
<td>34 (63%)</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>8 (72.7)</td>
<td>16 (88.9)</td>
<td>3 (75)</td>
<td>4 (50)</td>
<td>2 (100)</td>
<td>3 (50)</td>
<td>1 (50)</td>
<td>1 (33.3)</td>
<td>38 (70.4)</td>
</tr>
<tr>
<td>Co-trimoxazole</td>
<td>3 (27.3)</td>
<td>5 (27.8)</td>
<td>2 (50)</td>
<td>5 (62.5)</td>
<td>0 (0)</td>
<td>2 (33.3)</td>
<td>1 (50)</td>
<td>0 (0)</td>
<td>18 (33.3)</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>2 (18.2)</td>
<td>4 (31.3)</td>
<td>0 (0)</td>
<td>4 (50)</td>
<td>1 (50)</td>
<td>3 (50)</td>
<td>1 (50)</td>
<td>0 (0)</td>
<td>15 (27.8)</td>
</tr>
<tr>
<td>Cloxacillin</td>
<td>6 (54.5)</td>
<td>9 (50)</td>
<td>3 (75)</td>
<td>4 (50)</td>
<td>1 (50)</td>
<td>2 (33.3)</td>
<td>1 (50)</td>
<td>1 (33.3)</td>
<td>27 (50)</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>10 (90.9)</td>
<td>16 (88.9)</td>
<td>4 (100)</td>
<td>6 (75)</td>
<td>2 (100)</td>
<td>5 (83.3)</td>
<td>2 (100)</td>
<td>2 (66.6)</td>
<td>47 (88.9)</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>11 (100)</td>
<td>18 (100)</td>
<td>4 (100)</td>
<td>8 (100)</td>
<td>2 (100)</td>
<td>6 (100)</td>
<td>2 (100)</td>
<td>1 (33.3)</td>
<td>52 (96.3)</td>
</tr>
<tr>
<td>Amoxiclav</td>
<td>11(100)</td>
<td>16 (88.9)</td>
<td>4 (100)</td>
<td>8 (100)</td>
<td>2 (100)</td>
<td>6 (100)</td>
<td>2 (100)</td>
<td>2 (66.6)</td>
<td>51 (94.4)</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>10(90.9)</td>
<td>17 (94.4)</td>
<td>4 (100)</td>
<td>8 (100)</td>
<td>2 (100)</td>
<td>6 (100)</td>
<td>2 (100)</td>
<td>1 (33.3)</td>
<td>50 (92.6)</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>11(100)</td>
<td>17(94.4)</td>
<td>3 (75)</td>
<td>8 (100)</td>
<td>2 (100)</td>
<td>5 (83.3)</td>
<td>2 (100)</td>
<td>1(33.3)</td>
<td>49 (90.7)</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>5 (45.5)</td>
<td>7 (38.9)</td>
<td>2 (50)</td>
<td>3 (37.5)</td>
<td>0 (0)</td>
<td>3 (50)</td>
<td>1 (50)</td>
<td>1 (33.3)</td>
<td>22 (40.7)</td>
</tr>
</tbody>
</table>

E.coli= Escherichia coli.  Strept. Pyogenase = streptococcus pyogenase,  β haemolytic strept. =β haemolytic streptococcus. CONS= Coagulase negative staphylococcus. Staph. aureus = Staphylococcus aureus
Table 4 shows the antibiotic sensitivity pattern of the organisms isolated; the drug that showed the highest sensitivity was Ciprofloxacin (96.3%). This was followed by Amoxiclav (94.4%), Ceftriaxone (92.6%) and Cefuroxime (90.6%), others that showed good sensitivity were Erythromycin (88.9%) Gentamicin(70.4) and Chloramphenicol (63%). Fair sensitivity was showed by Cloxacillin (50%) while Amoxicillin (40.7%), Cotrimoxazole (33.3%) and Ampicillin (27.8%) all showed low effectiveness, sensitivity less than (50%). The common pathogens isolated in this study were Klebsiela, E.coli, Proteus, Staphylococcus aureus and Strptococcus pyogenase. They showed good sensitivity to Ciprofloxacin, Amoxiclav, Ceftriaxone, Cefuroxime, Erythromycin and Gentamicin.
CHAPTER SIX

DISCUSSION

This study demonstrated an overall incidence of 5.7%; this is higher than the value obtained in a study done by Obi et al\textsuperscript{72}, which was 2.5%. This could be partly due to the fact that this study was a prospective study with proper record keeping and documentation, unlike the Obi’s study which was a retrospective study.

In this study, fifty six (56) cases of PPROM matched with fifty six (56) controls without PPROM revealed a positive culture rate of 83.9%. There was statistically significant difference between the cases and controls which suggests a strong link of genital tract infections with the occurrence of PPROM. There was no statistically significant difference in the sociodemographic characteristics (mean age, mean gestational age, mean parity), except for mean social class (P = 0.001). It can therefore be said that the occurrence of PPROM is strongly associated with low socio–economic status. (P=0.001). This agrees with findings of previous studies by Okonofua et al\textsuperscript{18} and Savitz et al.\textsuperscript{71} Association of PPROM with low socio–economic class could be a reflection of the personal hygiene of women in this group.

Klebsiella spp. was the commonest organism isolated (32.1%). This gram negative aerobic organism has been implicated as part of wide variety of microbes in association with PROM cases in previous studies by Aboyeji et al\textsuperscript{73} and Asindi et al\textsuperscript{74}. The significance of this finding is more pronounced when consideration is given to the fact that no klebsiella spp was isolated among the 56 controls. Escherischia coli accounts for 19.6% of the organism isolated from cases and non in the control group. This gram
negative aerobic organism has been found in previous studies to penetrate intact fetal membranes, cause intra-amniotic infection and subsequent amniorhexis\textsuperscript{14,35}. Proteus is a gram negative aerobes while Staphylococcus aureus is gram positive aerobes with prevalence of 14.3\% and 10.7\% respectively in this study. Bahar et al\textsuperscript{52} reported Proteus as part of wide variety of microbes that was implicated in PPROM while isolation of Saphylococcus aureus in this study is also similar to the findings of Silva et al\textsuperscript{55} who found a wide diversity of aerobic and anaerobic organisms. The presence of an intense inflammatory infiltrate in the membranes in their study was linked with the rupture of membranes as the aetiologial factor.

Streptococcus Pyogenase (7.1\%), Coagulase negative Staphylococcus (3.6\%) and Bacteriodes (5.4\%) were both isolated in cases and controls in this study. These organisms may be part of wide variety of microbes in association with prelabour rupture of membranes as demonstrated by Aboyeyeji et al\textsuperscript{73} in their study. β haemolytic streptococcus has also been implicated in some studies\textsuperscript{51,52,53,54} as part of organisms involved in PPROM though, the prevalence is low in this study.

Gardnerella vaginalis was demonstrated in 3 cases (5.3\%) and 1 (1.8\%) in the control group, all occurred in cases where Bacteriodes spp was isolated. This is worthy of note as this organism which is part of the bacterial vaginosis complex is often associated with anaerobic bacteria such as Bacteriodes as demonstrated in this study and their role in the aetiology of PPROM is already well documented\textsuperscript{36,48,67}. Microscopic isolation of candida spp in 7 out of the 56 controls (12.5\%) as against 2 in the cases (3.5\%) in this study is worthy of note. There appears to be an inverse relationship between the presence
of candida spp and the occurrences of PPROM, reason for this is not known. This finding is at variance with that previously documented by Chaim W. et al\textsuperscript{13}.

The sensitivity pattern in this study revealed that ciprofloxacin had the highest sensitivity (96.3\%) with almost all the isolated organisms sensitive to it. However, this drug which is a quinolone is not safe in pregnancy; other drugs that showed excellent sensitivity include Amoxiclav (94.4\%), Ceftriaxone (92.6\%), Cefuroxime (90.7\%) Erythromycin (88.9\%) and Gentamicin (70.4\%). All these drugs are safe in pregnancy except Gentamicin. Bacteroides spp, a gram negative anaerobic organism was found in association with Gardnerella vaginalis (one of the organism implicated in Bacterial vagnosis complex) in this study. This had poor sensitivity to almost all the antimicrobial agents except Erythromycin and Amoxiclav that had 66.6\% sensitivity each.

Metronidazole sensitivity was not tested in this study as the disc was not available. Amoxiclava has been found to cause neonatal necrotising enterocolitis in the ORACLE trial 2001\textsuperscript{57}. Chloramphenicol showed good sensitivity but is contra-indicated in pregnancy. The common antibiotics used in our general practice; Ampicillin, Co-trimoxacole and Amoxicillin all showed low sensitivity to the bacterial isolates in this study.

Two of the largest studies that looked at the effectiveness of antibiotics use in PPROM are the national institute of child health and human development maternal-fetal medicine units, (NICID-MFMU) study on PPROM\textsuperscript{56} and the ORACLE trial\textsuperscript{57}. In the NICID-MFMU study, intravenous antibiotics; Ampicillin 2gms 6 hourly and Erythromycin 250mg 6 hourly were used for 48 hours. The patients were then placed on
oral Amoxicillin 250mg 8hourly and enteric coated Erythromycin- base 333mg every 8 hours to complete the course of antibiotic therapy for seven days. In this trial, the antibiotic group had a significantly longer duration of pregnancy than the control group.

The antibiotic group was twice as likely to remain undelivered after 7 days of treatment with increased latency period which continued up to 3 weeks after discontinuation of antibiotics. Composite primary outcome and morbidities for the neonates were lower in the antibiotic group. Incidence of chorioamnionitis and neonatal sepsis, including group B streptococcal sepsis was decreased. In the ORACLE trial; where Amoxiclav was used either alone or in combination with Erythromycin, an increased risk of necrotising enterocolitis occurred and there was no significant difference in latency and morbidity between the antibiotic group and controls.

Based on current evidence, seven days of antibiotics as proposed by the NICID-MFMU is being recommended for PPROM cases that are being managed conservatively. In this study concluded at Obafemi Awolowo University Teaching Hospitals Complex, Ile Ife, the sensitivity of most of the bacterial isolates to Ampicillin was very poor (27.8%). The sensitivity to Ceftriaxone (92.6%), Cefuroxime (90.7%) and Erythromycin (88.9%) were excellent and any of these can be substituted for Ampicillin. The sensitivity of Amoxicillin was also poor (40.7%). Cephalosporins are found to be very sensitive to isolated organisms in this study; ceftriaxone and Cefuroxime are readily available in parenteral and oral formulation and either can be used to replace Ampicillin and Amoxicillin.
The regimen suggested based on findings in this study is intravenous Ceftriaxone 1gram daily and intravenous Erythromycin 250mg 8hourly for 48hrs; then, oral Ceftriaxone 400mg daily and Erythromycin 500mg 8hourly to complete a 7 day course. Oral Erythromycin could be started for the first 48hours with parenteral ceftriaxone and then continue to complete 7 days course in environment where parenteral Erythromycin is not available.
CONCLUSION

Low socio-economic status is a significant risk factor demonstrated in this study.

Genital tract infection is found to be related to the occurrence of preterm premature rupture of fetal membranes (PPROM) and it is one of the major aetiologic factors in our environment with Klebsilla being the commonest organism isolated. Antibiotic of choice in the expectant management of PPROM include Cerftriaxone, Cefuroxim, Amoxiclav and Erythromycin.

RECOMMENDATION

Based on the findings of the present study, it is recommended that improvement in general socio-economic condition of women is likely to have a significant impact in reducing PPROM/preterm birth with subsequent reduction in maternal and perinatal morbidity and mortality. Also, prophylactic use of antibiotics in the management of PPROM should be based on the demonstrated microbiological pattern and their sensitivity in this centre.
REFERENCES


MICROBIOLOGICAL PATTERN IN CASES OF PRETERM PREMATURE RUPTURE OF FETAL MEMBRANES (PPROM) IN OAUTHC, ILE-IFE STUDY PROFORMA

DATE: ..........................  SERIAL NO:

..............

NAME: .........................  HOSPITAL NO:

..............

AGE: ...........................  BOOKING STATUS:

..............

PARITY: .......................  LMP:

............................

SOCIO ECONOMIC DATA:
EDUCATIONAL STATUS: ..........................  SCORE:

..............

HUSBAND OCCUPATION: ..........................  SCORE:

..............

SOCIAL CLASS: .............................
DURATION OF MEMBRANE RUPTURE:

............................

HISTORY OF FEVER: (YES/NO)  TEMPERATURE AT PRESENTATION:

..............

ANTIBIOTIC USE WITHIN LAST 7 DAYS (YES/NO)
ORGANISM ISOLATED: (YES/NO)
TYPES OF ORGANISM ISOLATED: .............................
ANTIBIOTIC SENSITIVITY PATTERN:

.............................
STUDY PROTOCOL

DATE: 
HOSPITAL NUMBER: 
BOOKING NUMBER: 
AGE: 
PARTY: 
STATE: 
EDUCATIONAL STATUS: 
SCORE: 
HUSBAND OCCUPATION: 
SOCIAL CLASS: 
QUALIFICATION OF MEMBRANE RUPTURE: 
TERM AT RESISTANCE:
BIRTHWEIGHT LAST 10 YEARS (YES/NO) 
ORGANISATION/INSTITUTION (YES/NO)

ANTIBIOTIC SENSITIVITY PATTERN

MICROBIOLOGICAL PATTERN IN CASES OF PRETERM PREMATURE RUPTURE OF FETAL MEMBRANES (PPROM) IN CAUTIOUS LIFE

ETICS AND RESEARCH COMMITTEE
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CHAIRMAN: Prof. (Mrs) E. A. Adeyemo
REGISTRATION NUMBER:
INTERNATIONAL: 163741
NATIONAL: NERC/2007/CRC/13

CLEARANCE CERTIFICATE

PROTOCOL NUMBER: ERGC/2011/002
PROJECT TITLE: PATTERN OF MICRO ORGANISM ISOLATED FROM PRETERM PREMATURE RUPTURE OF FETAL MEMBRANES (PPROM)
INVESTIGATOR: Dr. Abisoye Obasekri Adekunle
DEPARTMENT/INSTITUTION: Department of Obstetrics & Gynaecology, LAUTECH, Ogbunike
DATE CONSIDERED: 27/09/2011
DURATION OF APPROVAL: Six (6) Months

This is to inform you that the research described in the submitted protocol and all relevant information have been reviewed by the LAUTECH Ethics and Research Committee.

The approval is from 27/09/2011 to 27/03/2012. You are advised to submit the consent form to the investigator as soon as possible. Consent shall be obtained within 10 days of the date of approval. Any deviation from the approved protocol shall require written approval from the Ethics Committee.

The National Code of Health Research Ethics requires that you follow all guidelines, rules and regulations including ensuring that all relevant changes and developments are communicated to the LAUTEHCRC. The LAUTEHCRC reserves the right to withhold research funds without prior notification.