Evaluation of pregnant women admitted with prelabour rupture of membranes (PROM)

Research Report for
M Med (Obstetrics and Gynaecology)

Dr N E Iloanusi

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Dedicated to my son, Master Kelvin Chukwuemeka, jnr. and my father, the late Mr R A Iloanusi.

Evaluation of pregnant women admitted with prelabour rupture of membranes (PROM)

Dr Nicholas Emeka Iloanusi

Current Qualifications: B.Sc (Physiology); MBBS; FCOG(SA)

Student Number: 384066

Department of Obstetrics and Gynaecology,
Faculty of Health Sciences, University of the Witwatersrand,
Johannesburg

Tel: +27 72 446 1869.

Degree for which dissertation is submitted: MMed (O&G)

Supervisor's Details

Prof Eckhart Buchmann MBBCh; MSc(Med); FCOG(SA); PhD, MSc (Epidemiology).

Head, Department of Obstetrics and Gynaecology
Chris Hani Baragwanath Academic Hospital
Johannesburg
Tel. +2711933 8156.

ABSTRACT

Background and objectives

Prelabour rupture of the membranes (PROM) is a major obstetric problem affecting about 20% of pregnancies. Complications include preterm labour, ascending intrauterine and perinatal infections, and neonatal mortality. Standard guidelines are formulated and continually reviewed to improve the clinical management of PROM and to reduce poor perinatal outcomes associated with this condition. The objectives of this study, conducted using women in Johannesburg as a sample population, were: 1) to audit the implementation of the standard protocol on management of PROM, and 2) to determine the maternal and fetal outcomes of this condition.

Methods

A cross-sectional descriptive study was done on women admitted to the antenatal wards of Chris Hani Baragwanath Academic Hospital with PROM. Inclusion criteria were that PROM was the main reason for admission, gestation ≥24 weeks, and maternal age 18 years or more. Hospital clinical files were studied for obstetric and clinical characteristics, adherence by doctors to the management protocol, and final outcome including latency period, induction rate, mode of delivery, and neonatal outcome.

Results

Ninety-seven women participated in the study. Their mean age was 27.0 years, and 37 (38%) were nulliparous. Eighty-five (87%) had attended antenatal clinic. Twenty-nine (30%) were HIV-infected, 23 (79%) of them on highly active antiretroviral treatment.

The mean gestational age on admission was 32.8 weeks, with 78 (80%) women having preterm PROM at GA<37 weeks and 52 (54%) at GA <34 weeks. The most frequent methods of diagnosis were visual inspection in 77 (79%), speculum examination in 49 (51%) and ultrasound scan in 81 (84%) of the women. Antibiotics were given to 96 women (99%), and antenatal corticosteroids were used in all women <34 weeks pregnant. No cases of clinical chorioamnionitis were detected. The mean latency from PROM to delivery for women <37 weeks pregnant was 15 days, and for those <34 weeks, it was 19 days. Twenty-nine women (30%) required induction of labour, and 25 (25.8%) had caesarean sections. There were 12 perinatal deaths (with the exclusion of three late neonatal deaths), resulting from prematurity (n=4), congenital anomalies (n=2), neonatal jaundice (n=2), respiratory distress syndrome (n=2) and perinatal asphyxia / hypoxic ischaemic encephalopathy (n=2). There were no recorded cases of either neonatal or puerperal sepsis.

Conclusion

The study may have under-represented term PROM, so the findings are most applicable to preterm PROM. The condition was mostly managed appropriately within the local protocol, especially in terms of corticosteroid and antibiotic use. Overt or clinically evident chorioamnionitis was not detected. However, the perinatal mortality rate was high, and whatever the causes of perinatal death in this group, it is clear that PROM is a high-risk condition deserving of close clinical attention.

DECLARATION

I, Dr Nicholas Emeka Orlando Iloanusi declare that this research report is my original work. It is being submitted for the degree of Master of Medicine in Obstetrics and Gynaecology in the University of Witswatersrand, Johannesburg.

It has not been reproduced from any previous work or submitted before for any degree or examination in this or any other university

Signed……

This 18th day of January, 2013

ABBREVIATIONS

ACOG	American Congress of Obstetrics and Gynecology
AFI	Amniotic fluid index
ARV	Antiretroviral drugs
BMI	Body mass index
CS	Caesarean section
CHBAH	Chris Hani Baragwanath Academic Hospital
CI	Confidence interval
CRP	C-reactive protein
D&C	Dilatation and curettage
DROM	Duration of rupture of membranes
EFW	Estimated foetal weight
FBC	Full blood count
FHR	Fetal heart rate
G	Gravidity
GA	Gestational age
GBS	Group B Streptococcus
GDM	Gestational diabetic mellitus
HAART	Highly active anti-retroviral treatment
HIV	Human immunodeficiency virus
HMD	Hyaline membrane disease
HVS	High vaginal swab
IOL	Induction of labour
IL-GFBP	Insulin-like growth factor binding protein
IVH	Intraventricular haemorrhage
L/S	Lecithin / Sphingomyelin
MCS	Microscopy, culture and sensitivity
MFMUN	Maternal Fetal Medicine Units Network
MTCT	Maternal to child transmission
NEC	Necrotising enterocolitis
NICU	Neonatal intensive care unit
NND	Neonatal deaths
NST	Non-stress test
NVD	Normal vaginal delivery
O&G	Obstetrics and Gynaecology
OR	Odds ratio
P	Parity
PAMG	Placental α-microglobulin
PR	Pulse rate
PROM	Prelabour rupture of membranes
PTD	Preterm delivery
RDS	Respiratory distress syndrome
RR	Relative risk
SFH	Symphysis-fundal height
STI	Sexually transmitted infection
WCC	White cell count

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INTRODUCTION AND LITERATURE REVIEW

Definition

Prelabour rupture of membranes (PROM) is spontaneous rupture of membranes before onset of labour; this is, therefore, defined in the absence of any obvious cervical changes or contractions consistent with established labour. Although there is no specific time frame, labour is expected to commence within 1 or 2 hours after PROM,[1] but according to Pernoll,[2] in the book 'Current Obstetric & Gynecologic Diagnosis & Treatment', PROM is considered to be prolonged if it occurs more than 24 hours before the onset of labour.

In technical terms, PROM is defined along viability lines and should be used only for viable pregnancies (approximately 24 weeks' gestation or more). Any rupture of membranes before viability is considered and treated as inevitable abortion. Some authors, however, reserve the use of PROM exclusively for term pregnancies at 37 completed weeks or more, using 'preterm PROM' to define pregnancies from viability to less than 37 completed weeks. In this dissertation, 'PROM' is used to cover all pregnancies considered viable within the context of this study, with 'term PROM' and 'preterm PROM' used specifically when and where necessary. PROM and viability are limited to pregnancies at 24 weeks' gestation and above, and/or birth weight of 600 g or more.

Incidence

PROM affects 10% to 20% of all pregnancies, but frequencies as high as 40% have been reported, with possible inclusion of non-viable pregnancies. Pernoll noted in his textbook chapter "Untimely termination of pregnancies" that in about 94% of cases of PROM, the fetus

is mature, with about 50% experiencing membrane rupture less than 24 hours before the onset of labour. Approximately 90% of women with PROM go into labour within 1 week.[3] Five per cent of cases of PROM involve fetuses in the 1000 g to 2500 g weight category, while those weighing less than 1000 g constitute less than 0.5%. Preterm PROM, while affecting about 5% of all pregnancies,[2,3] accounts for up to 30% of all preterm deliveries.

Aetiology and predisposing factors

The exact cause of PROM is unknown but a multifactorial association has been made with the condition which could be either maternal or fetal in origin or both. Intrauterine infection or chorioamnionitis which could be clinical or sub-clinical, remains the single most important factor implicated in the aetiology and pathophysiology of PROM. Chorioamnionitis is presumed to be the result of ascending bacterial infection or overgrowth of pathogens in the lower genital tract, such as sexually transmitted infection or bacterial vaginosis, but at times occurs for no apparent reason. Sexual intercourse in pregnancy may pose an increased risk for chorioamnionitis[4,5] and subsequently, PROM, especially in the presence of predisposing factors like underlying lower genital tract infection and incompetent cervix.[6] These findings are supported by Harmanli et al. who, in their study of the effects of the human ejaculate on the biomechanical properties of the chorioamnionitic membranes, noted that in vitro exposure of the fetal membranes to ejaculate for an hour significantly weakened the membranes.[7] However, two other studies, by Riss et al.[8] in Germany and Ekwo et al.[9] in the USA, failed to establish an association between coitus and its frequency during pregnancy and any adverse pregnancy or fetal outcome. However, coitus can cause genital tract infections which themselves may predispose to chorioamnionitis and PROM. Maternal urinary tract infection is also a frequently noted associated factor, especially with concomitant bacterial vaginosis.[10,11]

Multiple pregnancy and polyhydramnios cause overdistension of the uterus and thus test the tensile limit of the chorioamniotic membranes, with a relatively high chance of rupture especially in the presence of inflamed membranes and incompetent cervix. Incompetent cervix can be a congenital uterocervical anomaly, or may be acquired from previous traumatic gynecological maneuvers such as dilatation and curettage, poorly treated lower genital tract infections, or uterocervical fibroids. Congenital fetal anomalies, especially neural tube and gastrointestinal tract defects, have the tendency to cause polyhydraminos as well as abnormal fetal lies and positions resulting from uterine or placental factors, which also predispose to PROM.

Other factors implicated in PROM are nutritional deficiency, poor socioeconomic status, lack of antenatal care, placenta praevia, use of tobacco and other drugs of addiction.[12,13,14,15]

Also noteworthy are both the previous personal and family histories of PROM. It is generally acknowledged that the risk of PROM is higher among women who have had the condition in their previous pregnancies.[16,17] In an American College of Obstetrics and Gynecology (ACOG) review,[17] Mercer noted that cigarette smoking, prior preterm deliveries, preterm labour in the same pregnancy, low body-mass index (BMI), work during pregnancy and cervical cerclage are all possible associations in the pathogenesis of PROM. Preterm PROM is said to complicate 25% of all pregnancies with cervical cerclage.[16,17] Direct abdominal trauma, be it accidental or iatrogenic as during amniocentesis, can also disturb the integrity of the chorioamniotic membranes, leading to subsequent rupture.

Pathogenesis and complications

The pathophysiology of PROM is an inter-play of the many aetiologic and predisposing factors discussed above, but with a frequent common pathway involving a subclinical or clinical chorioamnionitis from ascending infection of the lower genital tract. Chorioamnionitis is both a cause and important consequence of PROM. According to a review by Parry,[3] ascending infections cause a loss of cervical canal integrity, leading to a cascade of biochemical changes in the fetal membranes and deciduas, with release of prostaglandins and cytokines, and up-regulation of intracellular messengers. This results in cervical ripening, membrane disruption and PROM. This inflammatory process involving the membranes forms the basis for development of PROM and can also follow amniocentesis and subchorionic bleeds, both implicated in PROM. Membrane disruption and rupture is also attributed to the actions of some enzymes, proteases and metalloproteinases, produced by bacteria that colonize the chorioamniotic membranes from the genital tract, and weaken the membranes.[18]

Chorioamnionitis and preterm delivery (PTD) are two direct and most important complications of PROM, with their attendant maternal and neonatal morbidities (endometritis, puerperal sepsis, neonatal respiratory distress syndrome (RDS), congenital infections like pneumonia and intraventricular haemorrhage (IVH) and increased neonatal mortality.[19,20,21]

The exact cause of chorioamnionitis and its predisposing factors remain a case for clarification, but one fact is certain: it is highly implicated in the aetiology of neonatal sepsis. Many researchers believe that either pre-existing lower genital tract infections or those introduced during vaginal examinations, after PROM, could be responsible, especially if conservative management was the option.

Seaward et al.[22] in their article "Evaluation of predictors of clinical chorioamnionitis and postpartum fever in patients with PROM" in 1997, noted that chorioamnionitis increased with number of digital vaginal examinations independent of other factors; the odds ratio (OR) climbed from a 2-fold increase for 3-4 examinations to a 5-fold increase with >8 examinations. Similar findings were made the following year when the same authors evaluated possible predictors of neonatal infections in infants born to patients with PROM. They noted that the percentage of neonatal infection also increased with number of digital examinations and that chorioamnionitis had the strongest independent association with neonatal infections, with a neonatal infection rate of 16% among those with chorioamnionitis, a 6-fold increase compared with those without it.[23] At about the same time, Hannah et al. assessed women with PROM for Group B streptococcus (GBS) colonization and, while acknowledging the fact that vaginal examination during PROM increased the risk of neonatal infection, also noted that one-third of neonatal infections among women with PROM were seen in those who tested positive for GBS, and 25% of neonatal deaths found in women managed conservatively (without immediate delivery) were due to GBS.[24]

Chorioamnionitis, like PROM itself, has been shown in many studies to have some beneficial effects on perinatal outcomes. For example, it is postulated to cause accelerated lung maturity and hence decreases RDS in low birth weight infants.[25,26] It is also believed that during prolonged PROM or chorioamnionitis, the placenta produces interleukin-1B and other mediators of inflammation, which stimulate the release of fetal hypothalamic corticosteroid releasing factor with subsequent secretion of adrenocorticotropic hormone and cortisol.

The high level of cortisol seen in the infants immediately after birth and which continues through their first week of life, is invariably responsible for the decrease in need for acute respiratory support or ventilation, supplemental oxygen and surfactant.[19,25]

The question arises whether the amount of cortisol produced is sufficient to stimulate lung maturity and if so, would there be any need for giving exogenous steroids to women with PROM? Or do the antibiotics given in PROM protect against maternal and neonatal infections, at the same time suppressing this seemingly natural protective mechanism? All the same, the effects of chorioamnionitis on the incidence and severity of acute RDS in premature infants remain unclear and controversial.

Preterm delivery (PTD) following PROM can occur due to spontaneous labour or be induced for any PROM-associated complication like chorioamnionitis, cord prolapse, oligohydraminos and fetal distress. But whatever the reason, PTD has a strong association with chorioamnionitis and frequently results in perinatal morbidities and mortality, mostly from fetal immaturity. Guzick et al[27] established that the incidence of PTD was 5.4% in the absence of PROM and chorioamnionitis, up to 11% in chorioamnionitis alone without PROM, and as high as 57% if both chorioamnionitis and PROM were present.

Cord prolapse is a rare complication of PROM with a closed cervix, but carries a high perinatal mortality rate when it occurs. The incidence following preterm PROM in pregnancies <34 weeks was said to be 7.0%, and be it occult or overt, it is associated with poor perinatal outcome including stillbirth.[28] Among surviving infants, asphyxia and Respiratory distress syndrome (RDS) are the most common acute morbidities at any gestational age.

However, IVH, necrotising enterocolitis (NEC), neonatal sepsis and seizures, and retinopathy of prematurity are all rare after 32 weeks' gestation.[29]

Abruptio placentae is also said to complicate 1-6% of cases of PROM occurring at <34 weeks,[30,31] with higher values if term pregnancies are included, although cause and effect seem difficult to disentangle. Chorioamnionitis may provide a cause for both abruptio placentae and PROM.

Predictability of preterm PROM and preterm labour

The National Institute for Child Health and Human Development Maternal Fetal Medicine Units Network (MFMUN),[16] in a large study on the predictability of preterm PROM found that a short cervical length (<25 mm) and a positive cervico-vaginal fetal fibronectin test were good predictive indicators, in close association with parity and in the presence of known predisposing factors. The authors noted that previous preterm birth and preterm birth due to preterm PROM were associated with subsequent PTD due to preterm PROM and that a patient with a previous history of PTD at 23–27 weeks had a 27.1% risk of PTD while those with a history of preterm PROM had a 14% risk of PTD due to preterm PROM in a subsequent pregnancy and a 13.5-fold higher risk of preterm PROM at less than 28 weeks in the subsequent pregnancy.

In the same study, nulliparous women with a positive cervico-vaginal fetal fibronectin test and a short cervix were found to have a 17% risk of PTD due to preterm PROM, whereas a combination of multiparity, previous history of PROM and PTD due to PROM, a short cervical length (<25mm) and a positive fetal fibronectin posed a 25% risk of preterm PROM in

subsequent pregnancy. Thus, multiparous women with all 3 risk factors had a 31-fold increased risk of PROM with delivery before 35 weeks relative to those without these risk factors.[16,17]

Diagnosis and management

Good history-taking is the key to the diagnosis of PROM, with most women describing a sudden, usually unprovoked, gush of fluid from the vagina, followed at times by continuous leakage. Occasionally, only gradual continuous leakage is the presenting symptom. Physical examination involves visual inspection of the vulva and vagina to confirm leakage. The fluid is examined for colour (usually clear and colourless but may be pink or meconium-stained), and for flecks of vernix. Visual examination can also be accomplished with insertion of a vaginal speculum to confirm the origin of the fluid and to rule out cord prolapse. When leakage is only slight or in doubt, a Valsava manoeuvre, coughing, or application of fundal pressure to the uterus can be used to provoke and confirm leakage.

If there is also doubt about the origin of the leaking fluid, the fluid collected may be subjected to litmus testing. Amniotic fluid (AF) usually has a pH >7.0 and tests alkaline to litmus paper to differentiate it from normal acidic vaginal secretions. During speculum examination, the fluid may be collected for potassium hydroxide and wet mount examination, fern test (for arborisation on sliding glass under light microscope) and for determination of the lecithin:sphyngomyelin ratio, rapid surfactant test or the presence of phosphatidyl glycerol. Cervical secretions or a high vaginal swab may be taken to rule out GBS and other infections.

An abdominal examination may show a decrease in uterine size and easily palpable fetal parts. Occasionally, tenderness is elicited which could be a pointer to chorioamnionitis, with possible maternal pyrexia and tachycardia. Digital vaginal examination is discouraged, to prevent introduction of bacteria into the cervical opening, but can be done if immediate delivery is planned.

An ultrasound scan may be done to assess amniotic fluid volume, and estimate gestational age (GA) and fetal weight. Although not commonly practiced nowadays, in cases of uncertainty, amniocentesis may be done and a dye (Evans blue or indigo) injected after collecting amniotic fluid for lung maturity tests, microbiological analysis and white cell count. Thereafter, a vaginal speculum is inserted to confirm the presence of dye in the vagina. Maternal tests that may be considered include white cell count (WCC), C-reactive protein (CRP), and urine culture.

The TermPROM study by Hannah et al.[20] on "Induction of labour compared to expectant management for prelabour rupture of membranes at term" is the largest randomized, controlled trial ever done on this condition. This multicentre, multinational trial, using 5041 women with confirmed PROM at ≥37 completed weeks of pregnancy, remains the reference guide for most clinicians in the management of term PROM.

The GA at which membrane rupture occurs is an important predictor of the consequences of PROM and forms the basis of decisions for further management of the pregnancy and PROM. When PROM occurs at or near term (≥34 weeks and/or estimated fetal weight (EFW) ≥2 kg), at which point fetal lung maturity is assumed to have occurred and extra-uterine survival is

more likely, it poses no serious problem in terms of management because delivery is imminent, be it by induction of labour (IOL), caesarean section (CS) or allowing spontaneous labour.

The ACOG committee recommends immediate intervention by IOL with oxytocin for women with term PROM, with a view to decreasing chorioamnionitis, febrile morbidity and neonatal antibiotic treatment, without increasing CS rate.[32,33]

However, the Cochrane review on this subject noted, with particular reference to the TermPROM study, that immediate IOL does not decrease the risk of neonatal infection.[34] The Cochrane review further stated that the difference in outcome between early and planned or expectant management may not be substantial and choice of management can be individualized with adequate informed consent. In terms of method of IOL, the TermPROM study established no difference in maternal and neonatal outcomes, using either oxytocin or prostaglandins, and irrespective of favorability of the cervix.[3,20]

The Cochrane review noted that planned early IOL decreased the risk of maternal infection without increasing CS or operative vaginal birth rates and fewer infants were admitted to the neonatal intensive care unit (NICU) under such a condition. In line with the above findings, it was postulated that 1 case of chorioamnionitis would be avoided for every 50 women with term PROM started on immediate or early IOL, and 1 less newborn would be admitted to the NICU for every 20 induced deliveries.[34,35]

PROM is of particular clinical importance or concern if it occurs before 34 weeks (preterm PROM). Conservative management remains the preferred option for such pregnancies,

especially if EFW <2 kg, with the intention of improving perinatal outcome, while delivery is planned at around 34 weeks, in the absence of any indication for urgent intervention. Most studies have reported an increase in chorioamnionitis with conservative management but there is an overall decrease in morbidities related to PTD. On confirmation of preterm PROM, the patient is admitted to the ward after due counseling, and started on antibiotics and corticosteroids, while fetal and maternal monitoring is done for symptoms and signs of infection and fetal distress. Observation includes 4-hourly maternal pulse rate (PR), temperature and fetal heart rate (FHR), daily abdominal examination, non-stress testing (NST) and pad checks. Daily or alternate-day WCC and CRP may be done,[3] but these are probably no better at detecting early chorio-amnionitis than meticulous physical examination.[1]

Stewart et al.,[36] from Cape Town, evaluated women with preterm PROM before 28 weeks gestation and reported a "better than feared outcome" of expectant management of the condition at their institution. The authors found that conservative management of extreme preterm PROM offered a survival rate of at least 40% with no serious complications. The mean (GA) at delivery was 26.7 ± 3.92 weeks, with a latency period of 24.1 ± 29.1 days (range 1.5-154 days). They concluded that fetal survival is directly proportional to the latency period, fetal weight gain and increase in GA.

Occasionally, patients with adequate amniotic fluid volume on ultrasound scan, good fetal and maternal condition, and no longer draining liquor, are discharged home on antibiotics, with advice on fetal kick counts, abstinence from sexual intercourse, and avoidance of sitz-baths. They are then followed up weekly with ultrasound scans for biometry and liquor volume.

Abou et al. reviewed "Planned home versus hospital care for preterm PROM prior to 37 weeks gestation" and noted that while there was no evidence to prove that perinatal morbidity and mortality differed between the two groups, there was evidence that hospital managed patients were more likely to give birth by caesarean section.[37]

Home-based management may be more cost-effective because it decreases hospital stay and associated expenses, and reduces CS rate and PTDs resulting from over-zealous monitoring and intervention. However, most of the studies done in this regard may have been carried out in centres with people likely of higher socio-economic class.

In more poorly-resourced areas, there is concern that lower levels of nutrition, difficult living conditions and transport difficulties could easily predispose to infection with maternal and fetal complications. So, except for a few cases where discharges are made from the hospital because drainage of liquor has stopped and amniotic fluid index (AFI) shows adequate liquor volume, hospital-based management may be chosen with patients' socio-economic background in mind.

The use of drugs for PROM, especially antibiotics and steroids, has been widely studied and reviewed at different centres. Corticosteroids for accelerating fetal lung maturity in women before anticipated preterm birth have been globally accepted for use in pregnancies <34 weeks. One of the most important studies with regard to antenatal steroid use in preterm PROM was done in South Africa. Pattinson et al.,[38,39] for the DEXIPROM study group, evaluated the use of dexamethasone in women with preterm PROM in a multicentre, double-blind placebo-controlled randomized trial, and published their findings in 1999.

Women whose pregnancies were complicated by PROM at 28-34 weeks or had an EFW of 1000 – 2000 g (if GA unknown) were recruited from 6 public hospitals, given 2 doses of dexamethasone (12 mg 24 hours apart), or no treatment, with concomitant amoxicillin and metronidazole antibiotic cover.

On the basis of the initial fear that steroid use could cause or worsen maternal infection especially in developing countries, the authors not only confirmed that corticosteroids used at the minimal standard doses improved overall perinatal outcome, they also showed that maternal infectious morbidity was not affected. They then advised against restricting steroids in women with preterm PROM in developing countries, also suggesting concomitant antibiotic use in any preterm PROM management protocol.

A Cochrane review, by Roberts and Dalziel,[21] assessed the effects of antenatal corticosteroids given to pregnant women expected to deliver early due to preterm PROM. They noted that corticosteroid administration, contrary to expectations, did not increase maternal risk of infections, chorioamnionitis, puerperal sepsis or perinatal death. Rather, steroid use was associated with an overall decrease in neonatal death (relative risk (RR) 0.69; 95% CI 0.58-0.81); RDS (RR 0.66; 95% CI 0.59-0.73); IVH (RR 0.54; 95% CI 0.43-0.69); NEC (RR 0.46; 95% CI 0.39-0.74); and systemic infection within 48 hours of life (RR 0.56; 95% CI 0.58-0.85). Antenatal steroids are thus confirmed to be beneficial for women with preterm PROM at <34 weeks.[21,38,39]

The value of routine antibiotic use in preventing infections and improving perinatal outcome in PROM has also been globally acknowledged. A Cochrane review by Kenyon et al. evaluated

the effects of immediate and long-time use of antibiotics in women with PROM at <37 weeks on maternal morbidity, neonatal morbidity and mortality, and childhood developmental outcome.[40,41] The authors noted that antibiotic use increased intrauterine stay, decreased infection, and decreased the number of babies with potential developmental problems, although it did not prevent perinatal death. The authors of the review found that use of antibiotics was associated with a decreased risk of chorioamnionitis (RR 0.57; 95% CI 0.37-0.86); number of babies born within 48 hours (RR 0.71; 95% CI 0.58-0.89); neonatal infection (RR 0.68; 95% CI 0.53-0.87); use of surfactant (RR 0.83; 95% CI 0.72-0.96); oxygen therapy (RR 0.88; 95% CI 0.81-0.96); and abnormal cerebral ultrasound scan prior to discharge from hospital (RR 0.82; 95% CI 0.68-0.98).

The results of the ORACLE1 randomised trial, the largest trial on antibiotics for preterm PROM, suggest that a 10-day course of oral erythromycin is effective in decreasing neonatal morbidity,[42] although the MFMUN recommends 48 hours of parenteral antibiotics (ampicillin and erythromycin), followed by a course of oral amoxicillin and erythromycin for 5 days or up to delivery.[16] If delivery does not occur within few days, antibiotics should be continued for at least 1 week.[40] Erythromyin is the drug of choice, even in GBS-infected patients. The amocycillin/clavulanate combination has been implicated in neonatal NEC (RR 4.60; 95% CI 1.98-10.72),[41,43] and should be avoided.

Recent studies and advances in management of PROM

Researchers are continually making advances towards finding possible predictive or early diagnostic factors to avoid or minimize complications of PROM. Williams et al.[44] recently reported on "The effects of prolonged oligohydraminos following mid-trimester rupture of

membranes: antenatal and postnatal management." The authors noted that the true risk-benefit ratio of antibiotics, tocolysis and strategies to normalize amniotic fluid volume remained unclear, and that there was no consensus regarding the optimal ventilation strategy to support infants with pulmonary insufficiency following long-standing PROM.

The accuracy of imaging modalities in the prediction of pulmonary hypoplasia secondary to mid-trimester preterm PROM has been reviewed, with the use of chest and abdominal circumference ratio and other parameters in this regard showing only limited accuracy.[45]

The diagnostic efficacies of two relatively new bedside (rapid) immunoassay strip tests have been compared with the combined clinical and conventional methods of diagnosis of PROM: The use of the immunoassay of placental α-microglobulin-1 (PAMG-1) and insulin-like growth factor binding Protein-1 (IL-GFBP-1) is allegedly more accurate.[46] PAMG-1 (trade-name Amnisure) has, in another study by Neil et al. in Australia, been found to be clinically useful especially if the diagnosis of PROM is in doubt.[47]

Osaikhuwuomwan et al.[15] conducted an index cross-sectional study in Nigeria, trying to establish a link between plasma vitamin C levels and the risk of preterm PROM. The findings, published in 2011, suggested that that plasma vitamin C levels were lower in women with PROM and that a significant association existed between low vitamin C levels and the occurrence of preterm PROM (95% CI 1.53-11.88; P=0.008). However, a true causal link could not be established with certainty.

Actin A, an early phase reactant, has been evaluated as a possible marker of intrauterine infection but was found not to be of any significance.[48]

The concentration of vaginal fluid lactate in women with PROM has also been studied as a possible predictor of early onset of labour by Wiberg et al., in Stockholm, Sweden. The authors concluded that a high lactate concentration in the vagina is associated with early onset of labour within 48 hours, and may be a good tool in bedside obstetric practice as a good predictive test.[49]

PROM in the presence of maternal human immunodeficiency virus infection

Infection with human immunodeficiency virus (HIV) remains the single most important factor implicated in maternal mortality in South Africa. Apart from increasing the risk of both maternal and fetal morbidity and mortality, HIV has made questionable the conservative management of PROM to improve perinatal outcome, with the evidence-based fact that the risk of maternal-to-child transmission (MTCT) of HIV infection increases with duration of rupture of membranes (DROM).[50,51]

There have been contradictory findings on the relationship between PROM, the DROM, chorioamnionitis, duration of labour and HIV transmission. Minkoff et al., in 1995, following a cohort analysis of HIV-infected women with pregnancies complicated by PROM, noted that women with low CD4 counts (<20%) were more likely to transmit HIV to their babies if the DROM was ≥4 hours (RR 4.53, 95% CI 1.14-1.81). There was no association between HIV transmission and duration of labour and mode of delivery.[50]

A similar retrospective cohort study by Garcia-Tejedor et al., published in 2003, found that prolonged DROM increased the risk of HIV transmission especially when associated with prolonged labour, and estimated a critical cut-off point at 6 hours for DROM and 5 hours for duration of labour.[51] The above findings were recently refuted by Alvarez et al., who stated that the mother-to-child transmission (MTCT) rate of HIV was not related to the DROM prior to onset of labour.[52]

The risk of perinatal transmission of HIV-1 following acute and chronic chorioamnionitis, a known predisposing factor and complication of PROM, was evaluated by Chi et al.[53] Their findings, published in 2006, found a positive correlation between intrauterine HIV-1 transmission (OR 7.61; 95% CI 1.04-85.5) and the following: 1) acute chorioamnionitis in the presence of prolonged labour ($r=0.208$, $p=0.002$); 2) DROM ($r=0.177$; $p=0.008$); and 3) chronic chorioamnionitis in the presence of high viral load ($p=0.05$). There was no correlation between acute chorioamnionitis alone and vertical transmission.

Goldenberg et al.,[54] in 1998, discussing choriodecidual inflammation and PROM, stated that prolonged PROM is a risk factor for perinatal HIV transmission, because increased amniotic fluid cytokine activity during PROM and intrauterine infection attract maternal HIV-infected leucocytes into the amniotic cavity and increase the replication of HIV-1. The authors suggested that the risk of MTCT in these circumstances could be prevented by the use of antibiotics during PROM. However, Taha et al., in their double-blinded, placebo-controlled clinical evaluation of the efficacy of antibiotics in reducing chorioamnionitis-related MTCT of HIV-1, in 2006, noted that simple antepartum and peripartum antibiotic regimens did not reduce the risk of vertical transmission of HIV infection.[55]

Most conclusions on duration of rupture of membranes and its relationship to MTCT have been based on intrapartum data. It is not known whether PROM with a closed cervix carries increased risks of MTCT, although it seems likely that transmission rates are lower and that the 4-hour cut-off is not relevant before the onset of labour.

Aagaard-Tillery et al. in a retrospective study on the management and outcomes of 291 HIV-infected women with pregnancies complicated by preterm PROM, noted in 2006 that, in spite of conservative management, no vertical transmission occurred in all women who were already on highly active antiretroviral therapy (HAART) at the time of PROM, even among those who had CS with viral load >1000 copies/ml.[56] Only 2 instances of MTCT were observed: one in a patient on a single-drug regimen with zidovudine and the other on no medication at all. The authors suggested that conservative management could proceed with preterm PROM if patients were already on HAART.

Irrespective of the controversies and contradictions about DROM, duration of labour and timing of delivery, it is still generally accepted that PROM increases the risk of MTCT of HIV. Whether delivery should be effected immediately or sooner than is conventional in cases of preterm PROM at <34 weeks gestation, considering maternal immune status and the use of HAART, remains an issue of concern, and a topic for future interventional research.

Management of PROM at Chris Hani Baragwanath Academic Hospital

PROM is a common presenting complaint among pregnant women admitted at Chris Hani Baragwanath Academic Hospital (CHBAH). Its management at CHBAH and, of course, South Africa as a whole, is not different from what is taught and practised globally.

However, the prevalence of HIV infection can be said to have an impact on the incidence of PROM and its management locally. The PROM management protocol is partly stipulated in the guidelines booklet[57] of the Department of Obstetrics and Gynaecology, as follows:

The diagnosis must be confirmed by any or combination of the following: visual inspection, speculum examination, pH testing of vaginal fluid or, if necessary, by liquor volume assessment on ultrasound. Management depends on gestational age and/or estimated fetal weight (by palpation or ultrasound).

Gestational age ≥34 weeks or estimated fetal weight ≥2kg:

1. *Give ampicillin 1g IV 6 hourly and metronidazole 400mg orally 8 hourly.*
2. *Allow labour to proceed.*
3. *If the mother is not in labour within 12-24 hours, induce labour with oxytocin or oral misoprostol.*

Gestational age 24-33 weeks or estimated fetal weight 600g-1999g:

1. *Admit to hospital.*
2. *Do not do digital vaginal examination as this may contribute to chorioamnionitis.*
3. *Give erythromycin 250mg orally 4 times daily and metronidazole 400mg orally 3 times daily for 7 days orally*
4. *Give betamethasone 12mg IM 12 hourly for 2 doses.*
5. *Give hexoprenaline/salbutamol or nifedipine regimen if contractions start in first 24 hours after admission.*
6. *Observe temperature, pulse rate, fetal heart rate, and pad checks 4 hourly*
7. *Palpate daily for evidence of chorioamnionitis (irritable or tender uterus)*
8. *Do CTG daily if possible*
9. *Induce labour at 34 weeks or 2kg or if there are signs of chorioamnionitis*
10. *During labour, give ampicillin 1g IV 6 hourly.*

Gestational age <24 weeks or estimated fetal weight <600g:

1. *Ensure that the membranes have definitely ruptured (reduced liquor volume on ultrasound). If in doubt, admit to hospital to observe for passage of liquor.*
2. *If rupture of membranes has been confirmed, induce labour with oxytocin 10-20 units in 1 litre Ringer's Lactate at 120ml/hr, after full discussion of problem with the mother.*

PROBLEM STATEMENT AND OBJECTIVES

PROM is a frequent but worrisome obstetric and paediatric problem, especially if it occurs at <34 weeks gestation, with its associated perinatal morbidity and mortality. Although there is global understanding about its management to improve perinatal outcome, differences in socioeconomic backgrounds of patient populations, the obstetric centres, and their types of facilities, all allow for the current diverse approaches to the management. The consensus on the use of antibiotics and antenatal corticosteroids in preterm PROM is universal, but some controversies still exist regarding the duration of use of antibiotics, the management of preterm PROM in absence of further drainage of liquor, and the timing of delivery, among other factors.

The differences in choice of either conservative management or immediate delivery in this study, go beyond official protocols to doctors' personal discretion. For those who opt for immediate delivery, the major issue of concern remains prematurity-related problems, and if conservative management is the option, problems border principally on finance due to prolonged hospital stay and antibiotic use and, of course, possible complications of chorioamnionitis.

Although there have been no studies directly implicating HIV infection as a major predisposing factor or cause of PROM, irrespective of purported increase in its vertical transmission in presence of PROM, the South African HIV epidemic has, nonetheless, caused some distortions in the management of PROM. Local research is needed to highlight the problems associated with the management of PROM, the differences in the approach to the management and the reasons for such, and to find a basis for further clinical evaluations of some confounding

problems, hence the need for this study, aiming to understand PROM and its management at CHBAH.

Specific objectives of the study

1. To audit the implementation of the local protocol on diagnosis and treatment of PROM at CHBAH.

2. To determine the outcome of pregnancies admitted with PROM with respect to induction of labour, mode of delivery, and maternal and perinatal morbidity and mortality.

METHODS

Setting

This study was performed at the maternity unit of CHBAH which is one of the hospitals attached to the University of the Witwatersrand's Department of Obstetrics and Gynaecology, and serves as referral centre for many other hospitals and clinics in and around Johannesburg.

Study Design

The study involved a descriptive design for characteristics and outcomes of PROM, and a clinical audit of the implementation of the local protocol for the management of PROM, by prospective review of files of women admitted with PROM, both term and preterm.

Study population

The study population was pregnant women diagnosed and admitted with PROM from November 2010 to May 2011. The primary reason for admission had to be PROM, with criteria as follows:

Inclusion Criteria:

- All women who gave a history of PROM <24 hours before presentation.
- GA ≥24 weeks and EFW ≥600 g.
- Clinical certainty about the diagnosis of PROM.
- Women above 18 years of age

Exclusion Criteria:

- Women in established labour on admission.
- Clinical features of chorioamnionitis, or evidence of fetal compromise necessitating delivery.
- Intrauterine fetal death at the time of presentation
- Women with other significant obstetric problems in the current pregnancy, such as multiple pregnancy, breech presentation, hypertension in pregnancy, cardiac disease, diabetes mellitus, and antepartum haemorrhage.
- Women who had not given birth by the time of data analysis and closure of the study.
- Cases of PROM confirmed to be iatrogenic or secondary to trauma.
- Women on conservative management for PROM lost to follow-up because clinical files not found.

Sampling and data collection

The researcher was a registrar in the obstetric department at the time of the study. Data collection was not done on regular basis but on days where the researcher was available to collect data, during which all eligible patients admitted with PROM were selected, constituting a convenience sample. Only women with PROM for <24 hours included, to prevent over-selection of women with long latency periods from PROM to delivery.

To maintain strict exclusion and inclusion criteria, the initial sample selected was re-scrutinised to obtain the final number used for data analysis. This was necessitated by the fact that some women were admitted for PROM but later found to have some underlying co-existing

conditions, previously mentioned, that disqualified them for the study, especially if delivery was made for indications related more to the co-morbid factors than to PROM. However, women admitted for PROM and later diagnosed with other problems like mild hypertension or gestational diabetes mellitus (GDM), which eventually were not part of the indications or consideration for delivery were included; so also were women admitted for some other conditions but developed PROM while on admission, when this became the primary reason for staying in hospital.

Eligible women were traced to the antenatal wards with their names and other details from the maternity admissions register. They were handed the information leaflets to read after the study was explained to them. This was followed by signing the informed consent form to participate (Appendix A). Women admitted and sent directly to labour ward and started on induction of labour were also traced and recruited, but this proved difficult because some had given birth and been discharged by the time the researcher identified them as eligible participants.

All recruited women were followed through pregnancy, delivery and the puerperium by review of their hospital files. The hospital numbers of all selected patients were kept and used to trace their files in the wards and records office when needed. Relevant personal details, clinical findings on management of their condition and outcomes of the pregnancies were noted for data analysis. Both booked and unbooked women were recruited. Those who claimed to have been booked or were attended to by private doctors but had no documented proof or antenatal clinic cards to show were considered as unbooked. Booking blood tests (rhesus group, rapid plasma reagin, haemoglobin) and HIV (with CD4 count) were done for all such women according to the departmental routine.

Methods of diagnosis of PROM were sought. These involved visual inspection of the vulva or vagina, digital vaginal examination, or speculum vaginal examination. The number of digital vaginal examinations was recorded in each case, with women who had more than 4 examinations recorded as having 5 examinations, including those done at presentation and during labour. Women were asked the estimated time of PROM, and this, not the time of admission, was taken as the reference for DROM.

Other modalities of management in the ward in terms of fetal and maternal monitoring, and use of drugs like antibiotics and steroids were reviewed and noted. The use and frequency of NSTs, maternal vital signs, WCC, CRP, pad checks and abdominal examination in evaluating chorioamnionitis were all considered. Maternal vital signs were as a routine charted in the ward every 4 hours unless otherwise instructed. Maternal tachycardia and pyrexia were considered significant if >90 beats/minute and >37.5^{o}C respectively in ≥75% of times recorded, in the absence of any other known medical condition.

Implementation of the departmental protocol by the clinical staff was assessed from the case-notes. Direct interactions with, and interrogations of patients about PROM management were made minimal, with information mostly sourced from their files. Maternal morbidity like chorioamnionitis and puerperal sepsis encountered in the course of management was noted. Delivery modes, times between onset of PROM and delivery, as well as IOL methods were all noted.

Babies were followed from delivery, through the neonatal nursery or neonatal care unit, to final discharge. This was done using the mothers' and babies' file numbers.

Some women whose telephone numbers were taken during data collection were contacted directly, where the babies files could not be reached easily, to give information on the perinatal outcome. Perinatal outcome data included birth weights, Apgar scores at 1 and 5 minutes, admission to neonatal unit with reasons, perinatal disorders and mortality. All data was entered on a study data sheet (Appendix B)

Data management and analysis

Information from the study data sheet was entered into Epi-Info software and then exported into Stata 11 software for analysis. Descriptive analysis of all categorical data involved expression of simple proportions and percentages. For frequency distributions, means ± standard deviations (SDs), medians and ranges were calculated.

ETHICS

The conduct of this research was approved by the Human Research Ethics Committee of the University of Witwatersrand (Appendix C). Only women who were duly informed, above the age of 18 years, and who willingly gave their informed, written and signed consent, were recruited for the study (Appendix A). Anonymity was maintained in respect of the women and all the health personnel involved in their management. Participating women were given anonymous sequence numbers, while a master list of their hospital numbers was kept with the researcher for reference purposes. No information other than necessary for evaluation of PROM was extracted from patients' files.

RESULTS

A total of 122 women admitted for PROM were initially selected for the study. To maintain strict exclusion and inclusion criteria, and ensure that certain obvious predisposing factors were excluded, as explained in the methods, the sample was re-scrutinized to obtain the 97 women used for final data analysis.

The reasons for exclusion were as follows: 6 women were eliminated on account of being less than 18 years old. These women approximated their ages to 18 years and consented to participate in the study but were found to be less than 18 years by the dates of birth on their files. Eight were left out on follow-up because they had not given birth by the time of data analysis or their files were not found. Three had placenta praevia, 3 had PROM for more than 24 hours before presentation, 2 were multiple pregnancies, 1 was a pregestational diabetic, and 2 had PROM preceded by trauma (one cordocentesis for investigation of fetal abnormality, the other an attempted illegal termination of pregnancy).

The demographic and obstetric characteristics of the 97 eligible women evaluated are shown in Table 1. Their ages ranged from 18 to 43 years with mean of 27.0 ±6 .4 years; 85.5% were aged <35 years. Their parities ranged from 0 to 5, with primigravidas constituting 38% of the sample. Eighty-four women (86.6%) had attended antenatal clinic at least once. Four had a positive previous history of PROM. Twenty-nine women (29.9%) were HIV-infected while 66 (68%) were HIV-negative; 2 women were not tested. Nineteen (65.5%) of the HIV-infected women had known CD4 counts, ranging from 74 to 503/mm^3 with a mean of 227. Twenty-three (79.3%) of all HIV-infected women were on HAART. Of the remaining 6 women not on HAART, 4 had unknown CD4 counts. The duration of HAART ranged from 1-14 months.

All HIV-infected patients on dual therapy received antenatal zidovudine and intrapartum nevirapine, and also intrapartum of Truvada as per protocol, along with all whose CD4 counts were unknown. It is, however, not known from the records if the two patients with unknown HIV status were offered rapid HIV testing before delivery or they refused.

Table 1. Demographic, clinical and obstetric characteristics of women with PROM (n=97).

Age in years (mean ± SD; range)		27.0 ± 6.4; 18-43
Parity:	0	37 (38.1%)
	1	25 (25.8%)
	2	23 (23.7%)
	3	8 (8.2%)
	4	3 (3.0%)
	5	1 (1.0%)
Attended antenatal clinic at least once		84 (86.6%)
HIV Status:	Positive	29 (29.9%)
	Negative	66 (68.0%)
	Unknown	2 (2.1%)
CD4 count (n=29)	Known	19 (65.5%)
On ARVS (n=29)	Yes	23 (79.3%)
Previous PROM (n=97):	Yes	4 (4.1%)
	No	30 (30.9%)
	Unsure or unknown	63 (64.9%)

The distribution of women according to the GAs at which PROM occurred, and the methods of diagnosis, are shown in Table 2. The range of GAs was 24-43 weeks. Thirty-four women (35.1%) had digital examination done ≥5 times while 39 (40.2%) had it done 2-3 times. The use of speculum examination in diagnosis was nonetheless upheld, with 49 (50.5%) patients having this done as part of the diagnostic approach where visual inspection alone (79.0%) could not confirm the diagnosis.

Eighty-one women (83.5%) had at least 1 ultrasound evaluation done on admission while 16 had follow-up scans. Only 21 women (21.6%) had an antenatal ultrasound scan before PROM occurred.

Table 2. Onset and diagnosis of PROM on admission (n=97)

Mean onset before admission in hours ±SD		7.0 ± 5.6
Mean gestational age at onset of PROM in weeks ±SD		32.8 ± 4.3
GA bands in weeks: (N(%) and mean):	24-27 (conservative, < 1 kg)	14 (14.4%); 25.2
	28-33 (conservative)	38 (39.2%); 31.1
	34-36 (immediate delivery)	26 (26.8%); 35.0
	24-36 (all preterm)	78 (80.4%); 31.4
	≥37 (term PROM)	19 (19.6%); 38.5
Methods of diagnosis:	Visual assessment	77 (79.4%)
	Speculum examination	49 (50.5%)
	Digital examination (all GAs)	48 (49.5%)
	Digital examination (GAs <34 weeks; n=52)	20 (38.5%)
	Litmus paper/ nitrazine test	0
	Ultrasound scan	81 (83.5%)

The management in the wards in terms of clinical assessment and medication given to prevent intrauterine infection, increase intrauterine stay and prevent poor perinatal outcome generally, is shown in Table 3. In terms of diagnosis, 48 women (49.5%) had digital examination done as part of diagnostic approach on presentation, 20 of them with pregnancies < 34 weeks. Eighty-eight women (90.7%) had a digital vaginal examination done at one point or the other in the course of their pregnancy. Thirty-four women (35.1%) had digital examination done ≥5 times while 39 (40.2%) had it done 2-3 times. Seventy women (72%) received bethamethasone, which is more than the 52 patients assessed to be <34 weeks or with EFW <2000 g. All women at less than 34 weeks received betamethasone. Sixty-six women received the usual 2 doses at 12-hourly intervals according to the local protocol. One patient received a single dose before delivery while one received 3 and another received 4 doses.

Ninety-six women (99%) were found to have been started on intravenous antibiotics immediately on admission. The duration of antibiotic use, be it prophylactic or therapeutic, ranged from 0-18 days (median 6). NSTs were done in 96 women (99.0%). Thirteen (13.4%) and 2 (2.1%) women were found to have a recorded increase in maternal heart rate and temperature respectively.

Table 3. Clinical assessment and management in the antenatal ward (n=97).

Follow-up ultrasound scans done		16 (16.7%)
Antibiotics given		96 (99.0%)
Betamethasone received:	Total number given	70 (72.2%)
	<34 weeks (n=52)	52 (100%)
Doses of betamethasone received:	1	1 (1.0%)
	2	66 (68.0%)
	3	1 (1.0%)
	4	1 (1.0%)
Monitoring:	NST	96 (99.0%)
	Maternal WCC or CRP	72 (74.2%)
	Maternal heart rate, temperature	97 (100%)
Increase in maternal:	Pulse rate (≥90 bpm)	13 (13.4%)
	Temperature (≥37.5^{o}C)	2 (2.1%)
Digital examinations done:	0	9 (9.3%)
	1	6 (6.2%)
	2	23 (23.7%)
	3	16 (16.5%)
	4	9 (9.3%)
	≥5	34 (35.1%)

Details of different gestational ages at which deliveries occurred and the modes of deliveries are shown in Table 4. Fifty-six (57.7%) women went into spontaneous labour, and 48 of them went on to have normal vaginal delivery (NVD), 7 after augmentation with oxytocin. Eight required emergency CS for different reasons. Twenty-nine (29.9%) women had labour induced at different points and for different reasons, out of whom 24 (82.8%) went on to NVD, 3 after augmentation, with 5 having emergency CS.

Eleven women had emergency CS while undergoing conservative management, for reasons ranging from suspicious NST, cord prolapse, oligohydraminos, fetal growth restriction, to suspected chorioamnionitis with prematurity not fit for induction of labour. Hence, a total of 72 women (74.2%) had NVD and 24 (24.7%) had emergency CS. Only 1 woman had an elective CS. Low-dose oral misoprostol was used for 27 of the 29 IOLs (93.1%).

Table 4. Gestational ages at labour and delivery, with modes of delivery and indications (n=97)

GA bands in weeks: (N(%); mean)		24-27	8 (8.2%); 28.4
		28-33	26 (26.8%); 33.8
		34-36	35 (36.1%); 35.8
		24-36	69 (71.1%); 33.5
		≥37	28 (28.9%); 38.5
Labour induced			29 (29.9%)
Delivery by emergency CS			25 (25.8%)
Reasons for IOL (n=29):	GA ≥34 weeks		27 (93.1%)
	Others		2 (6.9%)
Indications for CS (n=25):		Combined as below	9 (36.0%)
		Fetal distress/suspicious NST	7 (28.0%)
		Previous caesarean section	5 (20.0%)
		Failed induction of labour	4 (16.0%)

The gestational ages of women presenting with PROM ranged from 24 to 43 weeks and those at delivery from 25 to 43 weeks. The latency period ranged from 0.5 to 106 days, with a mean of 12.5 days. The highest mean latency period of 21.4 days was seen in the lowest gestational age group of <28 weeks, reducing to 18.0 days at 28-33 weeks and 6.5 days at 34-36 weeks. The mean latency period for the GA 24-34 weeks, the group of concern that would require for conservative management, was 19 days.

Table 5. Mean latency periods (days) according to gestational ages (weeks) from presentation with PROM to delivery (n=97).

GA range	GA at PROM		GA at Delivery		Mean latency period (days)
	(N, %)	Mean	(N, %)	Mean	
24-43 (all)	97 (100%)	32.8	97 (100%)	34.5	12.3
24-27	14 (14.4%)	25.2	8 (8.2%)	28.4	21.4
28-33	38 (39.2%)	31.1	26 (26.8%)	33.8	18.0
34-36	26 (26.8%)	35.0	35 (36.1%)	35.8	6.5
24-34	52 (53.6%)	29.5	34 (35.1%)	32.4	19.0
24-36	78 (80.4%)	31.4	69 (71.1%)	33.5	14.8
≥ 37	19 (19.6%)	38.5	28 (28.9%)	38.5	2.0

Of the 14 women whose PROM occurred at <28 weeks, 6 carried their pregnancies beyond 28 weeks. Twenty-six of the 38 women who had PROM between 28 and 34 weeks delivered within the same period and 12 went up to and beyond 34 weeks. Fifty-two (53.6%) cases of PROM involved GAs <34 weeks; 45 women (46.4%) had PROM at ≥34 weeks gestation but a total of 63 deliveries were recorded at and beyond this GA. This means that 18 women accounted for PROM that occurred at <34 weeks and continued beyond 34 weeks, with only 9 carrying their pregnancies up to term, and probably were not induced for PROM >34 weeks. Comparing preterm and term PROM, 78 (80.4%) cases of PROM occurred at GA<37 weeks and 19 (19.6%) involved pregnancies ≥37 weeks. The mean GA at delivery for preterm PROM (<37 weeks) was 33.5 weeks, and for term PROM, 38.5 weeks.

Table 6 shows the distribution of modes of labour and delivery based on borderline gestational age (34 weeks) at which conservative management, as widely accepted, is either continued or discarded. Of the 34 (35.1%) women who delivered at GAs <34 weeks, 24 (24.7%) went into spontaneous labor and 2 had labour induced.

Twenty-five (25.8%) had NVD and 9 (9.3%) were delivered by CS. Forty-seven patients (48.5%) had NVD at GAs ≥34 weeks and 16 were delivered by CS, giving a total of 63 (64.9%) deliveries ≥34 weeks' gestation.

Table 6. Modes of delivery according to gestational ages (GAs) at or above and below 34 weeks (n=97)

Gestational ages (wks)	Spontaneous labour	Labour induced	Vaginal birth	Caesarean section
< 34	24 (24.7%)	2 (2.1%)	25 (25.8%)	9 (9.3%)
≥ 34	32 (33.0%)	27 (27.8%)	47 (48.5%)	16 (16.5%)
Total	56 (57.7%)	29 (29.9%)	72 (74.2%)	25 (25.8%)

Perinatal outcomes are shown in Table 7. All babies were born alive. The birth weights ranged from 720-3940 g with a mean of 2230 ± 717 g. Sixty-three babies (64.9%) weighed <2500 g at birth. Ninety (93.8%) babies had Apgar scores ≥5 at 1 minute and an equal number had scores of ≥7 at 5 minutes. Forty-two infants (43.8%) were admitted to the neonatal unit. Fifteen neonatal deaths (NNDs), (15.5% of all births) were recorded with 12 (80%) of them being early NNDs (occurring within the first week of life).

The distribution of perinatal deaths by birth weight is shown in Table 8. Six NNDs occurred in babies<1000 g, and 3 occurred in babies ≥2500 g. The perinatal mortality rate for babies≥500g was 123.7 per 1000 births, and that for babies ≥1000 g was 82.5 per 1000 births.

Table 7. Perinatal outcome after PROM (n=97)

Birth weight (g) distribution:	500-999	9 (9.3%)
	1000-1499	6 (6.2%)
	1500-1999	19 (19.6%)
	2000-2499	25 (25.8%)
	≥2500	38 (39.2%)
Live births		96 (99.0%)
Apgar scores ≥ 5 at 1 minute		90 (93.8%)
≥ 7 at 5 minutes		90 (93.8%)
Admitted in neonatal unit various reasons:		42 (43.8%)
*Precautionary observation in neonatal unit (n=42)		28 (66.7%)
Poor Apgar scores (n=42)		5 (11.9%)
Respiratory distress syndrome (n=42)		2 (4.8%)
Other reasons (n=42)		7 (16.7%)
Neonatal deaths (NNDs):		15 (15.6%)
Early NND		12 (12.5%)
Late NND		3 (3.1%)

*Precautionary observation for maternal chorioamnionitis, maternal HIV, moderate prematurity

Table 8. Distribution of perinatal deaths according to birth weights

Birth weight (g)	Early Neonatal death	Late neonatal deaths	Stillbirths
500-999	4	1	
1000-1499		1	
1500-1999	4	1	
2000-2499	1		
≥2500	3		

Five (n=5) neonatal deaths were strongly related to prematurity. Two (n=2) early NNDs, 1 in the 1500-1999 g category, and 1 in the 2000-2499 g category, had major congenital abnormalities. Other causes of neonatal death included respiratory distress syndrome (n=3), neonatal jaundice (n=2), and birth asphyxia / hypoxic ischaemic encephalopathy (n=3)

The 3 early neonatal deaths recorded in the birth weight group of ≥2500 g cannot be directly attributed to any PROM-related factor. All 3 babies were born by CS done for fetal distress, one after IOL. One, weighing 2575 g, was born with a good Apgar score (10 at 5 minutes), but developed acute respiratory distress of uncertain cause shortly afterwards. The other 2, with weights 2780 g and 3135 g, had low Apgar scores (both 6 at 5 minutes) and died from complications of perinatal asphyxia, having developed hypoxic ischaemic encephalopathy.

Nine (60%) neonatal deaths involved babies of women with low latency periods of about 7 days. Two of the deaths were in women with PROM who stayed in hospital for 5 and 6 weeks respectively. Only one NND was associated with maternal increase in temperature prenatally but was not delivered for intrauterine infection; the woman went into spontaneous labour at 26 weeks and was allowed to proceed, having been admitted at 25 weeks and given antenatal corticosteroids. However, tocolysis would not have been offered in the presence of the maternal pyrexia.

Seven (46.7%) of the perinatal deaths involved HIV-exposed babies while 1 had unknown HIV status. Unfortunately, it was difficult to follow patients up to 6 weeks post-delivery to further evaluate perinatal outcomes, especially neonatal HIV status because most patients could not be reached and neither could the babies' files. The study, basically involved the review of patients' file with minimal direct interactions with the patients.

DISCUSSION

This study has, as intended, described the characteristics of women and pregnancies with PROM, and attempted to investigate the clinical management at this referral hospital. From the data analysis made, this study has not only confirmed some pre-existing facts about PROM but has also posed some questions about this condition that warrant further evaluation.

37 cases of PROM occured among primigravidas, 48 among women of para 2-3 and 12 among women, para 4 and above. By age strata, 83 patients with PROM were between ages 18-35 years old and only 14 patients above 35 years were affected. These findings cannot establish any strong association between patients' ages, parity and PROM.[58] Most of the patients used in the study were booked, had normal or routine antenatal reviews as per schedule, with no suggestion of any link between PROM and poor antenatal care. The HIV seropositivity rate of 30% was similar to current rates known from antenatal clinics in and around Soweto (personal communication – Prof E Buchmann).

In terms of diagnosis, more than one method was used in many instances to reach a conclusion. It was found that the avoidance of digital examination in situations where conservative management is considered, was not strictly observed because 38.5% of the patients who had digital examination done on them as part of the diagnostic approach had PROM <34 weeks. The highest frequencies of digital examinations (≥5 times) occurred among women who either underwent IOL or went into spontaneous labour that became prolonged, requiring repeat evaluations for cervical changes and labour progress. Also, more digital exams were seen among cases referred from the clinics where midwives had done digital vaginal examinations before referring patients to hospitals, repeated by doctors on patients' arrival at CHBAH.

Most patients affected in this latter instance were found to have been wrongly assessed as >34 weeks pregnant before ultrasound scanning proved otherwise. However, while some studies have implicated frequent digital examination in the pathophysiology of chorioamnionitis and neonatal infection,[22,23] this study was unable to (and was not powered to) establish any association between poor perinatal outcome and frequent digital examination.

The use of speculum examination in diagnosis was nonetheless upheld, especially in cases of PROM involving GA<34 weeks. Cases where it was not done as a routine included pregnancies that were obviously above term on presentation or where visual diagnosis of passage of liquor was established without doubt, or wrong assessment made by palpation with overestimation of actual GA. Vaginal fluid pH assessment was not performed in any of the patients in the study. This simple and potentially useful test has, in the author's experience, disappeared from practice at CHBAH, with no clinician currently advocating for its use, despite its place in the clinical protocol for diagnosis of PROM.

The strict and consistent use of antenatal corticosteroids for fetal lung maturation and improved neonatal outcome was evidenced by the fact that more women with PROM got Steroids (72.2%) than had pregnancies <34 weeks or EFW <2000g (53.6%). For reasons of uncertainty and safety, some doctors still chose to give steroid at borderline GA of 34 weeks and/or EFW of 2000g, on assumption that the minimal doses used could do no harm while some patients received due to initial wrong underestimation of GA. All women with pregnancies <34 weeks received steroids, and some received more than the usual 2 doses. The latter represented those who had been admitted earlier, confirmed to have PROM but stopped draining, were discharged home and readmitted more than 4 weeks later, still at <34 weeks' gestation.

Some other patients received the first dose at the referring clinics and completed the course on arrival at CHBAH.

The absence or rarity of clinical chorioamnionitis, evidenced by almost universal normal maternal vital signs, and absence of infective neonatal morbidity even with multiple digital vaginal examinations, could perhaps be attributed to the conventional practice of immediate initiation of antibiotics on admission, without waiting for ominous symptoms and signs or the laboratory markers of infection. This might have helped also in prolonging intrauterine stay and the latency period, according to previous work,[40,41] owing to treatment of subclinical infections which could have become overt and evoked preterm labour. However, the role of subclinical chorioamnionitis may have been underestimated in this study, as bacteriological and histological evidence was not obtained for any of the women studied.

CRP and WCC were used to monitor for intrauterine infection, along with maternal examination. Among the few patients found to have isolated slight increases in either their temperature or pulse rate, no strong associations were made with WCC and CRP and since no case of chorioamnionitis was diagnosed or any delivery indicated by these findings, it is difficult to ascertain the usefulness of these surrogate markers from the results of the study. The use of WCC and CRP in monitoring for intrauterine infection was, however, inconsistent, depending largely on doctors' choice and perhaps on patients' clinical indications. It remains surprising that CRP and WCC were used as often as they were, given that they are not part of the protocol for conservative management of PROM in this clinical department.

It was notable that the highest gain in latency period of 21.4 days occurred in the lowest GA group of <28 weeks, with mean GA at delivery, of 28.4 weeks. These findings are similar to those made in a study in Cape Town, with values of 24.1 days and 26.7 weeks respectively.[36]

The latency period, expectedly, was inversely proportional to GA, decreasing from 21 days for PROM occurring at ≥24 weeks to 19 days at 33 weeks, and down to 2 days for PROM at term. This was due, in part, to the decision to discontinue conservative management and deliver PROM pregnancies at GA ≥34 weeks.

From analysis of the latency periods, it was realized that pregnancies complicated by preterm PROM could actually be managed up to term if liquor drainage stopped and patient still has enough amniotic fluid volume to continue the pregnancy with good antibiotic cover.[56] In this study, one such remarkable case of PROM occurred at 26 weeks gestation and, following a spontaneous labour at 41 weeks, the patient was eventually delivered of a healthy baby, gaining the longest latency period of 2562 hours (106.75 days). Excluding this as an outlier, the mean latency period becomes 11.2 days. The median latency is 103 hours (4.3 days)

With over 70% of deliveries made at GA<37 weeks in this studies, it can be said that PTD remains a major complication of PROM with or without chorioamnionitis. Though, in line with findings of previous studies, this finding is confounded by the fact that most pregnancies complicated by PROM at GA ≥34 weeks were, as a matter of protocol, not given a chance of conservative management.

Most neonatal morbidities were preterm-related. Perinatal mortality rates were high, well above the hospital perinatal mortality rate. Although most of the deaths appeared to be prematurity-related, there were neonatal deaths related to severe perinatal asphyxia in term infants, and unavoidable causes like severe congenital anomalies not compatible with life.

As mentioned earlier, it not possible to exclude a role for subclinical chorioamnionitis in some of these deaths in the absence of bacteriological or histopathological evidence. Most neonatal deaths involved babies of patients with low latency periods of less than 7 days. Only 2 of the patients had PROM for 5 or more weeks. This may suggest that conservative management, with good antibiotic cover, not only prolongs intrauterine stay, but also improves perinatal outcome.[36]

Though outside the protocol, some doctors decided to keep and observe some pregnancies further and beyond the recommended 34 weeks for delivery, in the absence of chorioamnionitis or any other form of fetal or maternal morbidity, coupled with adequate liquor volume. The fact that half (50%) of the 18 patients who presented with PROM at <34 weeks and continued beyond 34 weeks, carried their pregnancies till term, means conservative management towards term should be aimed at and encouraged.

On this note, I recommend follow-up research. Also necessary is a study comparing perinatal and maternal morbidities outcomes between patients presenting with PROM before and after 24 hours, which this study did not address. Another area that was not addressed was the HIV vertical transmission transmission rate, an area of concern with PROM.

Further studies on PROM in South Africa should take advantage of current high infant testing rates for HIV, to determine risks of PROM with extended antiretroviral cover for pregnant women.

LIMITATIONS

The inconsistencies in the method of sample collection make it difficult to conclude that the sample population is truly representative of all pregnancies complicated by PROM during the period of study. The times of data collection and subject recruitment allowed for selection bias which would affect measures like latency period and even neonatal outcome. The number of 97 women does not represent all women with PROM during the time period of the study. Also, the convenience sample could not be said to be truly representative of the overall PROM population Women admitted for PROM who were immediately subjected to IOL and gave birth soon after might easily have been missed, and these women were likely to differ from those with longer latency periods, especially in gestational age. The sample in this study best represents preterm PROM in women who had longer than average latency periods.

As with most record reviews, some patients' clinical notes and supposedly done, NSTs could not be seen and were assumed to have been lost due to poor filing and record keeping. There may also have been omissions in note-keeping, for example speculum examination done but not noted.

CONCLUSION

This study has shown that PROM, at least that with long latency period, is mostly managed appropriately within the local protocol, especially in terms of corticosteroid and antibiotic use. Overt or clinically evident chorioamnionitis was not detected. However, the perinatal mortality rate was high, and whatever the causes of perinatal death in this group, the unavoidable conclusion must be that PROM is a high-risk condition deserving close clinical attention.

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APPENDIX A

INFORMATION LEAFLET AND INFORMED CONSENT

Study: Evaluation of pregnant women amitted with Prelabour rupture of membranes

Researcher: Dr NE Iloanusi
Dept. of Obstetrics & Gynaecology, Chris Hani Baragwanath Hospital and Faculty of Heath Sciences, University of Witwatersrand,
Johannesburg, South Africa
072 446 1869
Supervisor: Prof E Buchmann
HOD, Obs/Gynae Dept. CHBH
011 933 8156

To The Potential Participant,

Good day. My name is Dr Nick Iloanusi and I am doing a research project for my Master's degree as a specialist in obstetrics and gynaecology. I am asking you to be part of my research project.

This information leaflet is to briefly explain to you the research project I want to do on pregnant women with breaking of the water before labour starts (also called by us 'prelabour rupture of membranes' or 'PROM' for short. This means the drainage of liquor before labour starts, and is a major problem that can affect both the pregnant mother and her unborn or born child. The most important problems are 1) that labour can start soon after, which is a serious matter before 9 months of pregnancy, and 2) that infection might enter into the baby's bag of waters, because it is no longer sealed. We usually treat women with PROM by admitting them to hospital and starting labour if the pregnancy is 9 months or close to 9 months, or observing them for signs of infection if the pregnancy is less than 8 months. I want to observe what happens to women who get PROM and who are treated in the hospital. I am also interested in knowing if the doctors are exactly following our hospital guidelines for treatment of PROM. By making these observations, I want to help the hospital to improve the treatment of PROM for women who come here.

This study will only involve a review of your hospital file, and I will write down information from your file onto my data sheet. This will not interfere or influence your treatment at all. Your doctors are treating you as an individual patient and I will not be involved with changing your treatment. All information collected from your files will be strictly confidential; the use of names and hospital numbers will be avoided on my data sheet and no information other than is needed for the study will be extracted from your file. Your participation in this research is completely voluntary, and I will not try to force you to participate. If you do not participate in the study, this will not cause me or the hospital to change your treatment or hold it against you. Even if you agree to be on the study, you are free to withdraw at any point if you do not feel comfortable about participating. You should also know that if you participate in the study, there is no reward or payment or benefit for you. This is just for research.

Please read this form thoroughly or ask me or my assistant to explain it to you. Ask for further explanations where necessary before giving your consent and signing to participate.

The approval for this study is obtained from the Human Research Ethics Committee, HREC, of the University of Witwatersrand. This committee has its offices at the University, telephone number 0117171234. If you need any information or clarity, feel free to contact me directly on 0724461869 or my supervisor, Professor E Buchmann on 083408777 or 0119338155.

Thanks for your anticipated co-operation.

INFORMED CONSENT

I hereby confirm that the nature, conduct, aims and objectives of the study, "Evaluation of Pregnant women admitted with Prelabour Rupture of Membranes" have been duly explained to me by the researcher, Dr N.E Iloanusi.

I have read through, and understand the information leaflet given to me. I have also been given the right to ask questions for clarity, to withdraw from participation at any time I want, and to re-enter if I so wish and am still needed.

Having been made aware of the above conditions, I herein consent and sign, of my own will, to be a part of the intended study.

Participant: signature/thumbprint……..

Full Names……

.

Date……

Researcher: sign…….

Full Names: Dr. Nicholas Emeka Iloanusi

Date……..

Translator: signature……

Profession/Designation…….

Full Names……

Date……

APPENDIX B

Data collection sheet

1. Patient's Details: ID No. ☐☐☐

Study/S.No ☐ Date data taken ☐☐☐

Age (yrs); Gravidity; Parity ☐ ☐ ☐

Booked? ☐

HIV status ; CD4 count ☐ ☐☐☐☐

ARV ; For (months) ☐ ☐☐☐

Gestational age @ PROM (weeks) ☐☐

Previous history of PROM? ☐

2. Present PROM:

a) Onset/Time before presentation (hours) ☐☐

b) Admission Date ☐☐☐ Time ☐☐

c) Method of diagnosis

Visual inspection ☐

Speculum exam ☐

Litmus paper/PH ☐

Digital exam ☐

d) How many digital exams: 1, 2, 3, 4, ≥5 ☐

e) Sonar done ☐

Before PROM @ GA (weeks) ;EFW(g). ☐☐ ☐☐☐☐

At PROM/admissn;GA (wks) ;EFW(g) ☐☐ ☐☐☐☐

Follow-up sonar ☐☐☐

No sonar at all

GA by palpation (weeks); EFW (g) ☐☐ ☐☐☐☐

f) Medications given: Steroids?; Doses ☐ ☐

If ' No',reason……

Antibiotics ☐

Given for(days) ☐☐☐

If 'No antibiotics', reason……

g) NST per day (average) ☐

h) WCC/ CRP: Every 1) 24hrs; 2) 48hrs; 3) week; 4) 2weeks; 5) PRN ☐

i) Maternal Temperature & PR; Every 1) 2hrs; 2) 4hrs; 3) >4hrs ☐

3. Delivery details:

a) Spontaneous labour: onset after PROM/admission (hours) ☐☐☐ ☐☐☐

b) Induced ☐ At Gestational age ☐☐

Reason/indication ☐

Method i, Misoprostol: Oral ☐ Per Vagina ☐

ii. Oxytocin infusion ☐

c) Delivery: NVD ☐ Emergency C/S ☐ Elective C/S ☐

Reason/indication for C/S ☐

Delivery Date ☐☐☐ Time ☐☐

Period between PROM & Delivery: Days/Hours ☐☐ ☐☐

4. Perinatal outcome:

a) Birthweight (g) ☐☐☐☐ Apgar scores @ 1, 5, 10 mins ☐☐☐

b) Resuscitation ☐ Sillbirth ☐ Early Neonatal death ☐

c) Admission in NICU ☐ Reason ☐ How long (days) ☐☐

5. Maternal morbidity & mortality ☐ ☐

If yes, state……

Codes for

1. Indications for Caesarean section:
   Fetal distress/ suspicious NST……1
   Previous C/S……2
   Prematurity/ chorioamnionitis……..3
   GA≥34 weeks and/or EFW≥2000g…….4
   Failed IOL/ augmentation……....5
   Others……..6

2. Indications for IOL:
   GA≥34 weeks andor EFW≥2000g……...1
   Suspicious NST……....2
   Suspected chorioamnionitis……..3
   Others……...4

3. Admission of neonate:
   For observation……..1
   (due to prematurity; suspected intrauterine infection; maternal HIV, DM, etc)
   Poor Apgar score……2
   Birth asphyxia…….3
   Respiratory Distress Syndrome……..4
   Congenital Pneumonia……....5
   Others…….....6

APPENDIX C

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr NE ILoanusi

CLEARANCE CERTIFICATE	**M101033**
PROJECT	Evaluation of Pregnant women admitted with prelabour rupture of membranes (PROM).
INVESTIGATORS	Dr NE ILoanusi.
DEPARTMENT	Department of Obstetrics & Gynaecology
DATE CONSIDERED	29/10/2010
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 29/10/2010 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Prof E Buchmann

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...