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MATERNAL AND NEONATAL OUTCOMES IN LATE PRETERM PRELABOUR RUPTURE OF MEMBRANES
A Retrospective Study

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DECLARATION

I, Dr Leelodharry Vakil Kumar, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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ABSTRACT

Background:

The management of late preterm prelabour rupture of membranes (PPROM) is associated with an increased risk of neonatal prematurity related morbidity due to many obstetric care guidelines which favour delivery at 34 weeks or immediately upon diagnosis of ruptured membranes after 34 weeks gestation. However, expectant management of this group of patients (i.e delayed delivery) between 34^{+0} and 36^{+6} weeks of gestation is associated with an increased risk of neonatal and maternal infectious morbidities.

Aim of Study:

The aim of this study was to evaluate the impact of the latency period on maternal and neonatal outcomes in late preterm prelabour rupture of membranes in a regional perinatal service in Cape Town, South Africa. The latency period was defined as the time from rupture of membranes to the time of delivery. In addition, we sought to investigate whether immediate induction of labour in the absence of overt signs of infection or fetal compromise should be prioritised in women who present with late preterm prelabour rupture of membranes.

Methods:

This was a retrospective cohort study carried out over a period of two years in two secondary level hospitals of the Metro West area of Cape Town. The subjects were low risk HIV negative women with singleton pregnancies with ruptured membranes in the late preterm period. Maternal and neonatal outcomes were studied between two latency periods, namely short latency (< 48 hours) and long latency period (≥ 48 hours) after ruptured membranes.

Results and Conclusion:

There were no significant differences in maternal and neonatal outcomes between the two groups of latency periods when latency was defined as the time from ruptured membranes to delivery. The study favoured a delayed induction thereby improving neonatal outcomes by decreasing the complications of prematurity. There were more adverse maternal outcomes, including an increase likelihood of augmentation of labour and more operative delivery along with its major risk, that of obstetric haemorrhage, were noted in the short latency period group. Therefore, a delayed induction policy appeared to be more appropriate.

Preterm delivery places the newborn at risk of prematurity. Therefore, the risk of prematurity must be balanced with the risks of intrauterine infection and antepartum haemorrhage, the two major complications of expectant management if delayed induction is to be adopted. Proper monitoring of both the pregnant woman and fetus is essential when expectant management is carried out to avoid these adverse maternal and neonatal outcomes.

LIST OF ABBREVIATIONS

ACOG	-American College of Obstetrician and Gynaecologist
AFP	-Alpha feto Protein
ß-hCG	-Beta Human Chorionic Gonadotropin
CRP	-C Reactive Protein
EFW	-Expected fetal weight
EM	-Expectant Management
FHR	-Fetal Heart Rate
HIV	-Human Immunodeficiency Virus
HREC	-Human Research Ethics Committee
IGT	-Impaired Glucose Tolerance
IV	-Intravenous
IVH	-Intraventricular haemorrhage
IOL	-Induction of Labour
MMH	-Mowbray Maternity Hospital
MOU	-Midwife Obstetric Unit
NEC	-Necrotising Enterocolitis
NICU	-Neonatal Intensive Care Unit
NSH	-New Somerset Hospital
PI	-Principal Investigator
PMTCT	-Prevention of Mother to Child Transmission
PROM	-Prelabour Rupture of Membranes
PPROM	-Preterm Prelabour Rupture of Membranes
PPROMT	-Preterm Prelabour Rupture of Membranes Trial
PVL	-Periventricular Leukomalacia
RCOG	-Royal College of Obstetrician and Gynaecologist
RDS	-Respiratory Distress Syndrome
UCT	-University of Cape Town

CHAPTER 1: INTRODUCTION AND LITERATURE REVIEW

Prelabour rupture of membranes (PROM) is defined as the rupture of the fetal membranes before the onset of uterine contractions. Term PROM complicates approximately 8% of all pregnancies.

When PROM occurs before 37 completed weeks of pregnancy, it is referred to as preterm prelabour rupture of membranes (PPROM). PPROM complicates only 2% of all pregnancies but it is associated with 40% of preterm deliveries, thus resulting in significant neonatal morbidity and mortality.[1]

The aetiology of PPROM is obscure. Evidence suggests that there is an association between ascending infection from the lower genital tract and PPROM. About one third of pregnancies have positive amniotic fluid cultures and studies have shown that bacteria have the ability to cross intact fetal membranes.[2,3] Hence PPROM is associated with significant maternal, fetal and neonatal risks.

The maternal risk associated with PPROM include subclinical chorioamnionitis (30%), abruptio placenta, psychosocial sequelae as a result of prolonged hospitalisation and uncertain neonatal prognosis and increase in operative intervention.[4,5,6,7]

Prematurity is the major cause of neonatal morbidity and mortality. The major morbidities include respiratory distress syndrome (RDS), cerebral palsy, necrotising enterocolitis (NEC), intraventricular haemorrhage (IVH) and neonatal sepsis (2-4%).[8]

1.1 DIAGNOSIS OF PROM:

The diagnosis of PROM should be done judiciously. The history of passing a gush of fluid, feeling constantly wet and fluid draining down the legs is very common. In most cases, the ruptured membranes is confirmed by documenting amniotic fluid leakage from the cervical os with visualisation of pooling of fluid in the posterior fornix of the vagina on a sterile speculum examination.

Other methods for the diagnosis of PROM include a combination of diagnostic tests:[9]

1. Litmus paper and pH testing
2. Nitrazine paper test
3. Amniotic fluid crystallisation (Ferning test)
4. Ultrasound assessment of amniotic fluid
5. Intra-amniotic dye injection
6. Other methods such as:
    a. Determination of certain markers in amniotic fluid such as Alpha-feto Protein (AFP), Beta hCG, fetal fibronectin, lactate, creatinine and urea.
    b. Determination of Alpha-1 microglobulin by amnisure ROM immunoassay test.

It must be noted that digital vaginal examination is best avoided because this may introduce infection and possibly stimulate labour.

1.2 LITERATURE REVIEW OF THE MANAGEMENT OF PPROM:

When prelabour rupture of membranes occurs at term, Hannah et al[10] in the TERMPROM study provided good evidence for early delivery in view of a lower incidence of maternal infection and increased maternal satisfaction as compared with expectant management.

Similarly, for gestation before 34 weeks, most existing guidelines recommend expectant management for further fetal maturation.[1,8,11]

The American College of Obstetricians and Gynaecologists (ACOG) guidelines recommend induction of labour (IOL) if PPROM occurs at or beyond 34^{+0} weeks of gestation.[8] The Royal College of Obstetricians and Gynaecologists (RCOG) guideline states that delivery should be considered at 34^{+0} weeks of gestation and recommends that women with PPROM who are managed expectantly beyond 34 weeks of gestation should be counselled about the increased risk of chorioamnionitis and the presumed decreased risk of neonatal respiratory problems, admission for neonatal intensive care, and caesarean section.[1]

The current standard of care as recommended by the Maternal Obstetric Guidelines for South Africa is to induce labour within 12 to 24 hours and in patients who are HIV positive, delivery should ideally occur within 4 hours from the time of rupture of membranes.[11] The latter may however change with the recent National Consolidated Guidelines for PMTCT[12] (Prevention of Mother to Child Transmission) in South Africa which puts emphasis on viral load monitoring every 3 months in pregnancy hence ensuring that pregnant women are fully suppressed at the time of labour to prevent mother to child transmission of HIV.

Therefore, the management of PPROM between 34^{+0} and and 36^{+6} weeks still remains a dilemma because of numerous morbidities associated with late preterm birth.

Late Preterm births constitute the group of neonates who are born between 34^{+0} to 36^{+6} weeks. They are considered to be physiologically immature and have limited compensatory responses to extrauterine life. They are at risk of major complications, including respiratory distress, apnoea, temperature instability, sepsis, metabolic complications like hypoglycaemia and hyperbilirubinaemia and poor feeding.
Furthermore, infants born during the late preterm period compared with term infants are at an increased risk of developing cerebral palsy due to the fact that the last six weeks of gestation represent a critical period of brain growth and development.[13]

However, in PPROM, these neonatal morbidities and risks need to be balanced against the increased incidence of chorioamnionitis, which can be up to 30% with the expectant management of late preterm PPROM.[10] Although there is a low incidence of neonatal sepsis (about 2-4%), chorioamnionitis is a known risk factor for the development of neurological sequelae such as cerebral palsy.[14,15]

While immediate delivery of the fetus above 34 weeks of gestation in patients with PPROM may protect the neonate from infection, prolonging the pregnancy may allow the fetus to mature, thus reducing the risk of much more prematurity-related morbidity.

In PPROM, the optimal interval for delivery occurs when the risks of immaturity are outweighed by the risks of pregnancy prolongation such as infection, placental abruption and cord accidents.

A further search of the literature, including Cochrane reviews, Medline, and Pubmed, found very few studies done to provide evidence on the care of patients with PPROM between 34^{+0} and 36^{+6} weeks of gestation. The following are a few of the trials and studies which have been done on the management of PPROM.

PPROMEXIL (PPROM Expectant Management versus Induction of Labour) trial was done from January 2007 to September 2009, as a randomized controlled trial in 60 hospitals with 536 patients in The Netherlands. The trial included non-labouring women with more than 24 hours of PPROM between 34^{+0} and 37^{+0} weeks of gestation with the main outcome being neonatal sepsis. Neonatal sepsis occurred in seven (2.6%) newborns of women in the IOL group and in 11 (4.1%) neonates in the expectant management group (relative risk [RR] 0.64; 95% confidence interval [CI] 0.25 to 1.6). RDS was seen in 21 (7.8%, IOL) versus 17 neonates (6.3%, EM) (RR 1.3; 95% CI 0.67 to 2.3), and a caesarean section was performed in 36 (13%, IOL) versus 37 (14%, EM) women (RR 0.98; 95% CI 0.64 to 1.50). The risk for chorioamnionitis was reduced in the IOL group. No serious adverse events were reported.

Because the PPROMEXIL trial was underpowered and because of a lower than expected incidence of neonatal sepsis, another trial was performed PPROMEXIL-2 between December 2009 until January 2011 as a randomised controlled trial of 200 patients in the Netherlands. The investigators found that induction of labour did not reduce the incidence of neonatal sepsis and therefore concluded that expectant management seemed to be a safe strategy with respect to neonatal sepsis (3.0% in the induction group versus 4.1% in the expectant group). The relative risk of neonatal sepsis was 0.74; 95% confidence interval, 0.17-3.2.[16]

A randomised trial done by Mercer et al[17], with 93 patients with PPROM between 32 to 36^{+6} weeks of gestation who were assigned to either immediate or delayed delivery, showed that the incidence of respiratory distress syndrome, intraventricular haemorrhage and confirmed neonatal sepsis was not significantly different in the two groups. They however observed that expectant management had prolonged maternal and neonatal hospitalisation and an incidence of chorioamnionitis (27.7%) which was higher than the 10.9% in the induced group. They concluded that immediate induction should be considered in mature surfactant profiles.

Naef et al[18] did a prospective study of 120 women with PPROM between 34 to 37 weeks of gestation at the University of Mississippi and found that the expectantly managed group had a higher incidence of chorioamnionitis (16%) compared with the immediate delivery group (2%). The incidence of neonatal sepsis was 5% in the expectantly managed group compared to none in the immediate delivery group. The results were not statistically significant.

Neerhof et al[19] did a retrospective study examining the neonatal outcome following cases with PPROM between 32 to 36 weeks of gestation which showed that the specific gestation for reduced morbidity was 34 weeks. They showed a reduced incidence of respiratory distress syndrome of 22.5% and 5.8% at 33 and 34 weeks of gestation respectively. However, although the incidence of RDS beyond 34 weeks was relatively low, the condition still affected newborns at 36 weeks, with incidences of 10.4 % and 1.5 % at 35 and 36 weeks respectively.

A large international multi-centre, randomised controlled trial (PPROMT Trial) with 1835 recruits from 65 centres in 11 countries was carried out. The PPROMT trial, (Preterm prelabour rupture of membranes close to term) finished in December 2013. The aim was to evaluate the effectiveness of early planned birth compared with expectant management for women with PPROM between 34^{+0} weeks to 36^{+6} weeks of gestation. The primary outcome was neonatal sepsis. In this trial, 924 women were randomised to early delivery and 915 to expectant management. Neonatal sepsis occurred in 23 (2%) in the immediate delivery group and in 29 (3%) of the neonates in the expectant management group. However, 8% of the neonates in the immediate delivery group had respiratory distress syndrome and 5% developed the condition in the expectant management group. Compared to women assigned to the immediate delivery group, those who were managed expectantly had higher risks of antepartum haemorrhage, intrapartum fever and the use of postpartum antibiotics along with a longer duration of hospital stay.[20,21,24]

1.3 MANAGEMENT OF PPROM IN WESTERN CAPE SOUTH AFRICA

The Maternal Obstetric Care Guidelines for South Africa (4th edition 2015), recommends that induction of labour should be carried out within 12-24 hours if the gestational age is above 34 weeks or estimated fetal weight (EFW) is above 2 kg in women with PPROM. The Western Cape protocols for maternal care at district hospitals does not stipulate immediate delivery for these patients. Thus, the Metro West maternal and neonatal service presents an opportunity to investigate if differences in maternal and neonatal outcomes exist between active and conservative management of late preterm PPROM.

The management options, as supported by the evidence, do not clearly favour either expectant management or immediate delivery. There is no local data to indicate whether either of these methods results in a better outcome. The generally accepted management of confirmed PPROM above 34 weeks is to wait for 24 hours for the spontaneous onset of labour and then induce if it does not occur. This is based on two assumptions:

1) Seventy percent of women will go into spontaneous labour within the first 24 hours after PPROM.[8,10,22]
2) Lung maturity has usually occurred by 34 weeks and after that there should be good fetal outcome.

A longer latency interval with expectant management may allow time for clinical chorioamnionitis, which either is subclinical at the time of membrane rupture or develops with ascending bacterial infection subsequent to membrane rupture.

Proponents of delivery at 34 weeks argue that because of the lack of significant neonatal benefits with the prolongation of pregnancy until 37 weeks, early delivery is justified to reduce the risk of chorioamnionitis and neonatal sepsis. In Australia, a survey was conducted in women with PPROM above 34 weeks. In the survey, 49% of obstetricians indicated that they would manage these patients expectantly with the women staying in hospital and 51% would plan to deliver these women prior to term.[23]

It would appear that the relative benefits and risks of active versus expectant management after PROM in late preterm is not clear and this would justify further research.

South Africa is a low income country and has a high rate of neonatal infection in view of the low socioeconomic conditions which prevail among the high risk population. Furthermore, with the high prevalence of HIV, the incidence of chorioamnionitis and the risks of HIV transmission to neonates in patients with unsuppressed viral load could be high in cases of PPROM. The current standard of care as recommended by the Maternal Guidelines for South Africa is to induce labour within 12-24 hours. In patients who are HIV positive, delivery should occur within 4 hours from the time of rupture of membranes to reduce the risk of mother to child transmission of HIV. These patients are usually managed at level 2, regional referral hospitals with neonatal ICU facilities. However due to bed constraints and other operational issues, patients often wait longer before being induced and thus the latency period which is defined as the time between rupture of membranes and delivery may have an impact on both maternal and neonatal outcomes.

In view of the above, several questions remain:

- Can we manage patients with PPROM near term expectantly to reduce the risk of prematurity-related comorbidities?
- Should we offer an early delivery to reduce the risk of chorioamnionitis, neonatal and maternal sepsis?
- What is the optimal delivery time in patients with late preterm prelabour rupture of membranes?

CHAPTER 2: METHODS

2.1 Aim of the study:

The aim of this study was to determine whether delayed delivery compared with early planned delivery was associated with more neonatal and maternal morbidities in women with PPROM between 34^{+0} to 36^{+6} weeks of gestation.

2.2 Hypothesis:

For the purpose of the study, a latency period of 48 hours was taken to separate patients into two groups namely early delivery group (latency period < 48 hours) and delayed/late delivery group (latency period ≥ 48 hours). We anticipated that there would be a higher rate of composite neonatal and maternal infectious morbidities in the late delivery group. We further anticipated less neonatal prematurity related morbidities in the late delivery group.

The null hypothesis and sample size calculation was based on the primary outcomes that there will be no differences in the rate of maternal and neonatal infectious morbidities and prematurity related morbidities between the two groups of patients with PPROM at 34^{+0} to 36^{+6} weeks of gestation that are delivered before and after 48 hours.

2.3 Study Design:

The study was a retrospective observational cohort study to assess the impact of early delivery (< 48 hours) versus late delivery (≥ 48 hours) on the maternal and neonatal outcomes for women with Preterm PROM between 34^{+0} to 36^{+6} weeks of gestation. The cut-off point of 48 hours was taken to differentiate the two groups of patients based on the Maternal Obstetric Care Guidelines of South Africa that induction of labour must occur within 12 to 24 hours in this category of patients.

2.4 Study Setting:

The study was conducted at Mowbray Maternity Hospital (MMH) and New Somerset Hospital (NSH). These are urban Metro West level 2 regional referral hospitals. Both hospitals are public maternity hospitals. These secondary hospitals receive patients from primary care Midwife Obstetric Units (MOU) and from the surrounding residential areas. The MOUs include Gugulethu (GMOU), Hanover Park (HPMOU), Retreat (RMOU), Mitchell's Plain MOU (MPMOU), Vanguard MOU (VMOU), as well as Westfleur and False Bay hospitals.

2.5 Patient selection:

The patient population consisted mostly of the lower to middle socio-economic status with patients of mixed ethnicity and a large migrant population. The patients were selected according to a set of inclusion and exclusion criteria as shown in the table below. The names and folder numbers of eligible subjects were identified in the admission suite and antenatal ward registers of Mowbray Maternity and New Somerset Hospitals. The patient folders were then retrieved from the appropriate records department and screened for eligibility.

As per the Western Cape protocol, any pregnant woman with PPROM below 37 weeks is referred to a district or secondary level hospital for further management. Therefore, recruitment was not necessary from the level 1 (MOU and district Hospital) facilities.

Table 2.1: Inclusion and Exclusion Criteria

Inclusion criteria	Exclusion criteria
Pregnant woman between 34^{+0} to 36^{+6} weeks gestation with a live fetus	HIV positive patients
Singleton pregnancy with no major congenital anomalies	Fetal demise
	Non reassuring CTG on admission
	Meconium Stained Liquor with an abnormal CTG
	Patients in established labour on admission
	Patients with clinical evidence of chorioamnionitis on admission
	Antepartum haemorrhage on admission
	Abnormal presentation
	Active Genital herpes
	Placenta praevia
	Multiple pregnancy

- Since the study was carried out in a low risk population, patients with maternal medical diseases were excluded. Furthermore the study was carried out in secondary level hospitals and most patients with medical diseases are managed at our tertiary level of care in the Metro West of Cape Town.

2.6 Outcomes:

The outcomes of the study were divided into primary and secondary maternal and neonatal outcomes.

2.61 Primary outcomes

The primary outcome associated with the latency period of 48 hours were described as follows:

- Composite Neonatal Infectious Morbidity
- Composite Neonatal Prematurity Morbidity
- Composite Maternal Infectious Morbidity

1) Composite Neonatal Infectious Morbidity:

This was defined as any one of the following:

a. A diagnosis of sepsis (A positive blood or CSF culture with an identified organism)
b. Pneumonia
c. Necrotising Enterocolitis

The clinical signs of neonatal sepsis include respiratory distress, apnoea, lethargy, abnormal level of consciousness, circulatory compromise needing support, poor feeding and/or temperature instability.

2) Composite Neonatal Prematurity Morbidity:

This was defined as a diagnosis of any one of moderate or severe Respiratory distress syndrome, Bronchopulmonary Pulmonary Dysplasia, Intraventricular Haemorrhage, Periventricular leukomalacia or Retinopathy of Prematurity.

3) Composite Maternal Infectious Morbidity:

This was defined as a diagnosis of any puerperal sepsis which included endometritis, septicaemia, peritonitis or wound infection.

2.62 Secondary Outcomes:

These were grouped into secondary neonatal and maternal outcomes as described in detail in Appendix 2.

Table 2.2: Secondary Neonatal & Maternal Outcomes

SECONDARY NEONATAL OUTCOMES	SECONDARY MATERNAL OUTCOMES	
	Antepartum & Intrapartum	Postpartum
Apgar Scores at 1 and 5 minutes intervals	Intrapartum fever	Puerperal sepsis
Birth Weight	Chorioamnionitis	Hysterectomy
Metabolic complications	Antepartum haemorrhage	Antibiotic requirement
Admission to NICU or high care unit	Spontaneous onset of labour	Duration of maternal admission
Duration of neonatal admission	Augmentation of labour	
	Mode of delivery	

2.7 Data Collection:

A data collection sheet (Appendix 1) was designed to capture baseline demographic and medical information as well as the method of delivery.
The data collection consisted of two parts. The first part included the demographic details, booking details of the index pregnancy, and important clinical information during the antenatal period. The second part included maternal and neonatal outcomes. Data from the data collection sheets were transcribed into an MS-Excel spreadsheet. All patient identification information was removed from the spreadsheet, and the computer had a lock and access code which was known only to the Principal Investigator (PI).

2.8 Statistical Methods for Data Analysis:

This study was designed to demonstrate that managing PPROM patients between 34^{+0} to 36^{+6} weeks with early delivery defined as a latency period < 48 hours would result in less neonatal and maternal infectious morbidities compared to those delivered after 48 hours. We estimated that the risk of adverse outcomes in the early delivery group would be 4% and that in the late delivery group 20%.

As per the Maternal Obstetric Care Guidelines for South Africa, we expected that 75% of the patients would have been delivered before 48 hours and that 25% delivered after 48 hours.[23] We calculated a sample size of 122 patients with 80% power and a significance level of $p = 0.05$.

Demographic data were presented in tabular and descriptive formats. Data were presented in descriptive form with appropriate statistical inference as applicable. Continuous numerical data was analysed using the t-test. Non parametric numerical data was analysed using the Wilcoxon sum-rank test. Categorical data was analysed statistically using Chi-square test, with Friedman test being used for any data with fewer than 5 events in any given category. Statistical analysis was performed using Stata® version 13.

2.9 Ethical considerations:

Following approval by the Departmental Research Committee, the study protocol was submitted to and approved by the Human Ethics Research Committee (HREC) of the University of Cape Town (Appendix 3). Informed consent was not required for the study since all data were retrieved by folder review. All information was kept confidential. Further approval was obtained from the facility based research committees of Mowbray Maternity Hospital and New Somerset Hospital.

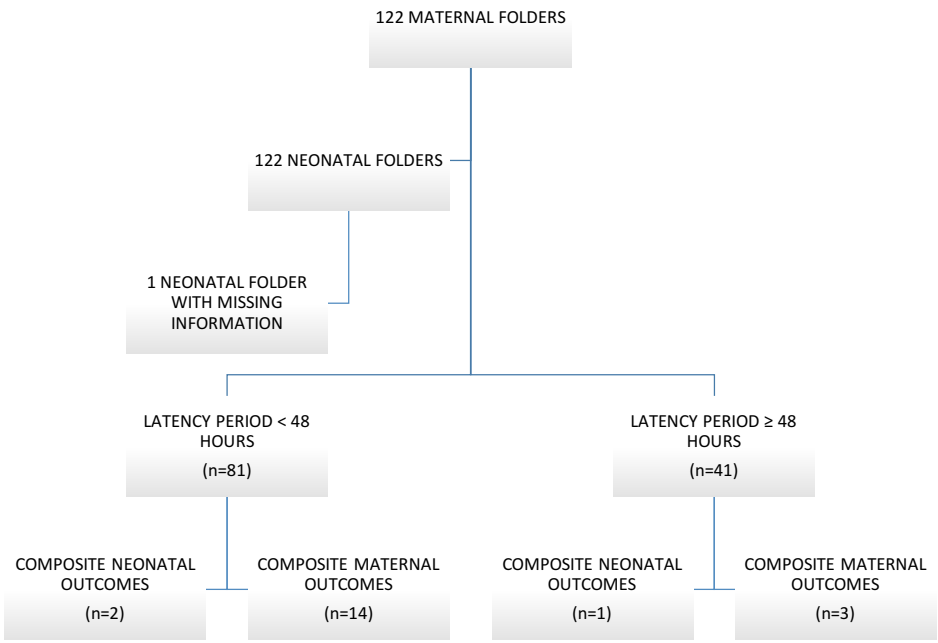
CHAPTER 3: RESULTS

The folders of 122 patients were retrieved from Mowbray Maternity and New Somerset Hospitals for the study of the effect of latency period on maternal and neonatal outcomes in women who had ruptured membranes between 34^{+0} to 36^{+6} weeks of gestation. Latency period was defined as the duration from the time of rupture of membranes until the time of delivery.

There were two latency periods, a shorter latency period which was before 48 hours and a longer which was at or beyond 48 hours.

All of these patients delivered between January 2014 to June 2016. They were all low risk patients and there were no other indications for induction of labour. In addition, the patients were all HIV negative.

Figure 3.1: Study Profile



1.1 Demographic Details:

Table 3.1: Table of Demographics

	MINIMUM	MAXIMUM	MEAN/MEDIAN
AGE	15	41	25.8
GRAVIDA	1	6	2
PARITY	0	4	1
SOCIOECONOMIC STATUS n(%)	LOW	AVERAGE	UNKNOWN
	60(49.2)	57(46.7)	5(4.1)
ETHNICITY n(%)	BLACK	COLOURED	WHITE
	30(24.6)	80(65.6)	12(9.8)

3.11 Maternal Age/ Gravidity/Parity

The minimum age in the study was 15 and the maximum age was 41 with a mean age of 25.8 years old.

Gravida is defined as the number of times a woman has been pregnant regardless of whether these pregnancies were carried to term. In the study the minimum gravidity was 1 and the maximum was 6 with a median gravidity of 2.

Parity is defined as the number of times a woman has given birth to a viable fetus that is above 28 weeks of gestation. The median parity was 1.

Table 3.2: Comparison of Demographics between the two latency periods

	LATENCY PERIOD < 48 HOURS (n=81)	LATENCY PERIOD ≥ 48 HOURS (n=41)	SIGNIFICANCE
MATERNAL AGE	26.0	25.4	P=0.61
GRAVIDA	2	2	P=0.77
PARITY	1	1	P=0.56

Most women in the study were between gravida 1 to gravida 3 (78.7%). This was consistent between the short and long latency groups. In both groups most patients were either nulliparous or primiparous (71.3%).

There were 81 patients in the short latency group and 41 patients in the long latency group. There was no statistical difference in the means and distribution of maternal ages between the two groups, short latency period and long latency period (p=0.61).

3.12 Socioeconomic Status:

Socioeconomic status was defined in terms of monthly revenue which was less than R2000 in low socioeconomic groups and between R2000 to R4000 in the average socioeconomic groups

The number of patients with preterm prelabour rupture of membranes was found to be nearly equally distributed between low and average socioeconomic status. It should be noted that the study was carried out in public hospitals that provide free health care services. The monthly income of approximately 4% of the study population could not be found.

3.13 Ethnicity:

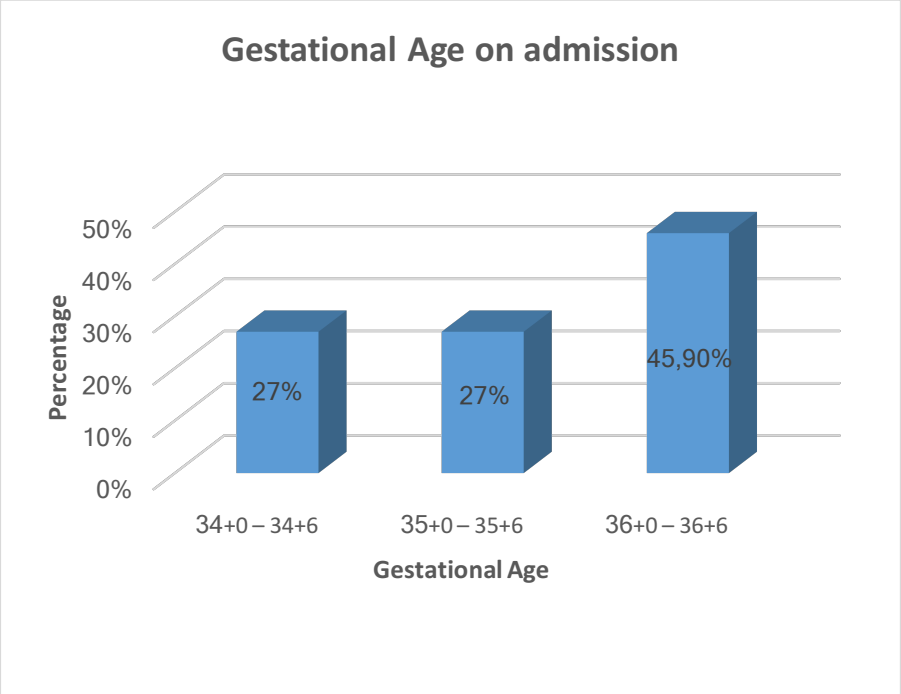
Out of the 122 folders that were retrieved, 65.6% of the patients were found to be coloured, 24.5% were black African and 9.8% were white when grouped under major racial categories in the Republic of South Africa. In the short latency period, there were 27.2% black, 63.0% coloured and 9.9% white patients. In the long latency period, there were 19.5% black, 70.7% coloured and 9.8% of black patients. There was no statistical difference between the two groups in terms of ethnicity. (p=0.64)

Table 3.3: Comparison of ethnicity between Latency period

	BLACK	COLOURED	WHITE
LATENCY PERIOD < 48 HOURS (N=81)	22/81 (27.2%)	51/81 (63.0%)	8/81 (9.9%)
LATENCY PERIOD ≥ 48 HOURS (n=41)	8/41 (19.5 %)	29/41 (70.7%)	4/41 (9.8%)

1.2 Gestational Age:

Figure 3.2: Distribution of patients with PPROM according to Gestational Age



The majority of patients, about 45.9% who ruptured membranes during the late preterm period, were found to be between 36^{+0} to 36^{+6} weeks of gestation. There were 27% of patients in each of the gestation age groups, between 34^{+0} to 34^{+6} weeks and 35^{+0} to 35^{+6} weeks.

Table 3.4: Comparison of Gestational Age & Latency period

GESTATIONAL AGE AT TIME OF RUPTURED MEMBRANES	LATENCY PERIOD < 48 HOURS (n=81)	LATENCY PERIOD ≥ 48 HOURS (n=41)	p value
$34^{+0} – 34^{+6}$	21/81(25.9%)	12/41(29.3%)	0.69
$35^{+0} – 35^{+6}$	16/81(19.8%)	17/41(41.4%)	0.01
36^{+0} - 36^{+6}	44/81(54.3%)	12/41(29.3%)	0.01

The latency period was compared in the 3 different gestational age groups. Between 34^{+0} to 34^{+6} weeks of gestation, 25.9% patients were in the shorter latency group as compared to 29.3% in the longer latency group. This was not statistically significant. However, in the gestational age group of 36^{+0} to 36^{+6} weeks, 54.3% of patients had a latency period of less than 48 hours compared to 29.3% with a latency period of greater or equal to 48 hours and this was statistically significant suggesting that the greater the gestational age, the shorter was the duration between the time of rupture of membranes and time of delivery.

1.3 Obstetric risk factors:

The obstetric risk factors consisted of the booking details of the patient, any history of previous caesarean section, the administration of antenatal corticosteroids and any medical comorbidities that can affect the management of patients with preterm prelabour rupture of membranes.

3.31 Booking Details:

Table 3.5: Representation of booking details of patients with PPROM

BOOKING	FREQUENCY (n%)
BOOKED + ANC	114(93.4)
BOOKED NO ANC	1(0.8)
UNBOOKED	7(5.7)

There was 93.4% of patients booked, with regular antenatal care follow up either at their respective Midwife Obstetric Units or the two secondary level hospitals. Only one patient was found to default antenatal care while 5.7% were unbooked.

3.32 Previous caesarean section:

About 9.8% of the patients in the study had only one previous caesarean section and these patients were included in the study. These patients were admitted to the antenatal ward awaiting spontaneous labour. If they were undelivered after 24 hours, they had a caesarean section as per protocol.

Figure 3.3: Patients with Previous caesarean section

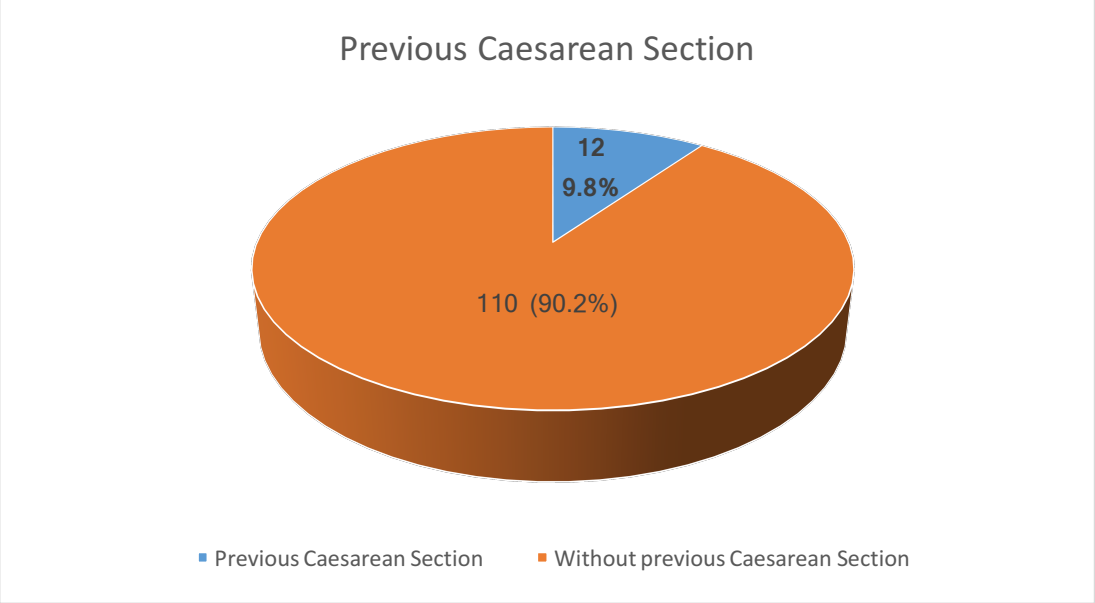


Table 3.6: Representation of Obstetric risk factors

OBSTETRIC RISK FACTOR	FREQUENCY n(%)	
	YES	NO
PREVIOUS CAESAREAN SECTION	12 (9.8%)	110 (90.2%)
ANTENATAL STEROIDS	23 (18.8%)	99 (81.2%)
MEDICAL COMORBIDITIES	7 (5.7%)	115 (94.3%)

3.33 Antenatal Corticosteroids:

Antenatal corticosteroids are usually given prior to 34 weeks of gestation. However, in the study, it was found that 18.8% of patients had received corticosteroids either before 34 weeks of gestation due to preterm labour or it was given when the gestational age was close to 34 weeks.

3.34 Medical Comorbidities:

Medical comorbidities can alter the course of the index pregnancy and also affect the timing of delivery. In the study, 5.7% of patients were found to have associated medical complications which either were present prior to pregnancy such as Hypertension or Bronchial Asthma or developed during the course of pregnancy such as Impaired Glucose Tolerance(IGT). It should be noted that patients with other medical comorbidities such as Diabetes Mellitus, cardiac or neurological patients were not included in the study as they are managed at a tertiary hospital namely Groote Schuur Hospital in the Metro West Obstetric Service in the Western Cape. It should also be noted that all patients in the study were HIV negative. HIV positive patients were considered as an exclusion criteria after review of the original protocol of the study by the HREC (Human Subjects Research Ethics Committee) of the University of Cape Town.

Table 3.7: Comparison of Obstetric Risk Factors and latency period

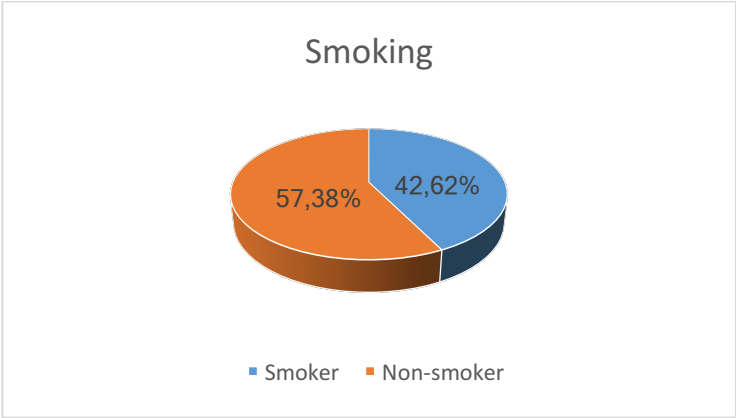
OBSTETRIC RISK FACTOR	LATENCY PERIOD < 48 HOURS (n=81)	LATENCY PERIOD ≥ 48 HOURS (n=41)	p value
PREVIOUS CAESAREAN SECTION	9/81(11.1%)	3/41(7.3%)	0.506
MEDICAL COMORBIDITIES	3/81(3.7%)	4/41(9.8%)	0.174
ANTENATAL STEROIDS	15/81(18.5%)	8/41(19.5%)	0.895

When the obstetric risk factors were analysed between the two groups of patients, there was no statistical differences noted in terms of previous caesarean section, medical comorbidities and the use of antenatal corticosteroids.

3.4 Factors related to ruptured membranes:

3.41 Smoker:

Figure 3.4: Representation of smokers in the population



Smoking is considered to be a major risk factor in patients with Preterm prelabour Rupture of membranes. Of all women in the study, 42% were smokers with 37 patients in the short latency group and 18 patients in the long latency group. The majority of them were in the coloured ethnic group. About 58% of patients were non-smokers.

3.42: Use of Antibiotics:

Table 3.8: The use of Antibiotics in Patients with PPROM

USE OF ANTIBIOTICS	ANTIBIOTICS				TOTAL (n%)
	AZITHROMYCIN	PENICILLIN	PENICILLIN & FLAGYL	UNSPECIFIED OR NONE	
NONE	0	0	0	26	26(21.3)
ORAL ANTIBIOTICS	16	1	1	0	18(14.8)
IV ANTIBIOTICS	0	74	2	2	78(63.9)

In the study, antibiotics were given during the first 24 hours and intrapartum as recommended by the Guidelines for Maternity Care in South Africa 3rd edition 2007 and the updated guidelines 4th edition 2015[11]. Twenty-six patients did not receive antibiotics and 18 patients received oral antibiotics mainly Azithromycin. Seventy-eight patients received intravenous antibiotics mainly Ampicillin. Two of them received both Ampicillin and Metronidazole and 2 of them were unspecified.

Table 3.9: Use of Antibiotics and Latency Period

	LATENCY PERIOD < 48 HOURS (n=81)	LATENCY PERIOD ≥ 48 HOURS (n=41)	p value
NO ANTIBIOTICS	24/81(29.6%)	2/41(4.9%)	0.002
ORAL ANTIBIOTICS	11/81(13.6%)	7/41(17.1%)	0.607
IV ANTIBIOTICS	46/81(56.8%)	32/41(78.0%)	0.021

Fifty-six percent of the patients in the short latency period and 78% of patients in the long latency period required IV antibiotics. The difference between the proportions was statistically significant (p value= 0.021). In the short latency period, 29.6% of patients received no antibiotics and 4.9% in the longer latency period did not receive antibiotics. This finding is consistent with there being need for antibiotics when delivery is imminent and this finding was statistically significant (p = 0.002). Antibiotics were prescribed in accordance with the recommendations in the Guidelines for Maternity Care in South Africa.

3.5 Neonatal Outcomes:

The neonatal outcomes were divided into primary and secondary outcomes. Primary outcomes included both composite neonatal infectious morbidity and composite neonatal prematurity morbidity.

Table 3.10: Representation of secondary Neonatal outcomes

APGAR SCORE	TOTAL (n=122)	
	1 MINUTE	5 MINUTES
NORMAL	116/122(95.1%)	121/122(99.2%)
LOW	2/122(1.6%)	0
CRITICAL	1/122(0.8%)	1(0.8%)
HIGH CARE ADMISSION (n=122)		
METABOLIC COMPLICATIONS	11/122(9.0%)	
RESPIRATORY COMPLICATIONS	2/122(1.6%)	
NOT ADMITTED	109/122(89.3%)	
LENGTH OF NEONATAL STAY (Days) TOTAL (n=121)		
> 7 DAYS	1/121(0.8%)	

Table 3.11: Comparison of Neonatal Outcomes between the two latency periods

	LATENCY PERIOD < 48 HOURS (n=81)	LATENCY PERIOD ≥ 48 HOURS (n=41)
PRIMARY OUTCOME		
NEONATAL SEPSIS	1/81(1.2%)	0
SECONDARY NEONATAL OUTCOMES		
COMPOSITE NEONATAL PREMATURITY COMPLICATIONS	1/81(1.2%)	1/41(2.4%)
BIRTHWEIGHT	2569(329.4)	2432(289.3)
APGAR SCORE < 4 AT 5 MINUTES	1/81(1.2%)	0
ADMISSION TO HIGH CARE		
METABOLIC COMPLICATIONS	*6/80(8.8%)	4/41(9.8%)
RESPIRATORY COMPLICATIONS	*1/80(1.3%)	1/41(2.4%)
NEONATAL STAY > 7 DAYS	0	1/41(2.4%)

*one neonatal folder had missing information(n=80)

3.51 Neonatal Infectious Morbidity:

Neonatal infectious morbidity was defined as any one of the following:

- A diagnosis of sepsis (A positive blood or CSF culture with an identified organism)
- Pneumonia
- Necrotising enterocolitis

The clinical signs of neonatal sepsis included respiratory distress, apnoea, lethargy, abnormal level of consciousness, circulatory compromise needing support, poor feeding and/or temperature instability.

Any preterm baby delivered in a woman with Prelabour rupture of membranes of more than 18 hours was empirically started on Intravenous ceftriaxone for a minimum of 2 to 3 days and a Full blood count along with Blood culture and CRP were done as part of the protocols at both secondary level hospitals.

In our study, only one neonate was found to have neonatal sepsis in the short latency group. This was based on a positive blood culture and a high CRP.

There were no neonatal deaths in the study.

3.52 Neonatal Prematurity Morbidity:

Neonatal prematurity morbidity was defined as a diagnosis of any one of moderate or severe Respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular haemorrhage, periventricular leukomalacia or retinopathy of prematurity. There were 2 cases of respiratory distress syndrome that were admitted to high care and these accounted for 1.6% of the neonatal prematurity complications. There were no cases of bronchopulmonary dysplasia, intraventricular haemorrhage, periventricular leukomalacia and retinopathy of prematurity as these complications are rare after 34 weeks of gestation.

3.53 Secondary Neonatal Complications:

This included Apgar scores at one and five minute intervals, birth weight, metabolic complications (hypoglycaemia, hyperbilurubinaemia), NICU admission and length of stay in NICU or high care.

Apgar Scores:

There were 95.1% and 99.2% of neonates who had normal Apgar scores, that is 7 out of 10 at 1 minute and 5 minutes after birth respectively. In the whole of the study only one neonate had a critically low Apgar score and was admitted to NICU. (Appendix 2)

Metabolic Complications:

Nine percent of the neonates had metabolic complications such as hypoglycaemia and hyperbilirubinemia which were most common. One folder was missing from our records.

Admission to NICU/HIGH CARE:

Table 3.12: Comparison of Metabolic complications between Latency period

	METABOLIC COMPLICATIONS	
	PRESENT	ABSENT
LATENCY PERIOD < 48 HOURS (n=80)*	7/80(8.7%)	73/80(91.3%)
LATENCY PERIOD ≥ 48 HOURS (n=41)	4/41(9.8%)	37/41(90.2%)

*one neonatal folder had missing information (n=80)

Table 3.13: Comparison of Respiratory complications between Latency period

	RESPIRATORY COMPLICATIONS	
	PRESENT	ABSENT
LATENCY PERIOD < 48 HOURS (n=80)*	1/80(1.3%)	79/80(98.6%)
LATENCY PERIOD ≥ 48 HOURS (n=41)	1/41(2.4%)	40/41(97.6.%)

*one neonatal folder had missing information

Thirteen neonates were admitted to high care out of which 2 had respiratory complications one in the short latency period and one in the long latency period. Eleven of them had metabolic complications. There was no statistical difference between the two groups in terms of metabolic complications. About 89.3% of the neonates were allowed to be transferred to their mothers and all of them were considered to be well enough to stay in the postnatal ward. They were all given intravenous ceftriaxone empirically.

Duration of Neonatal stay:

Only one neonate stayed in high care for more than 7 days and that was related to metabolic complication. (The denominator was n = 121 for this factor as one neonatal folder had missing information).

3.6 Maternal Outcomes:

The maternal outcomes were divided into a primary composite infectious maternal morbidity and secondary maternal outcomes.

3.61 Composite Maternal Infectious Outcomes:

Composite maternal infectious outcome was defined as a diagnosis of any puerperal sepsis which included endometritis, septicaemia, peritonitis or wound infection.

Table 3.14: Representation of Maternal Infectious Outcomes

	TOTAL (n=122)	
	FREQUENCY (n)	PERCENTAGE(n%)
COMPOSITE MATERNAL INFECTIOUS MORBIDITY	0	0
CHORIOAMNIONITIS	1	0.82
INTRAPARTUM PYREXIA	1	0.82
USE OF INTRAVENOUS ANTIBIOTICS INTRAPARTUM	1	0.82
POST PARTUM INTRAVENOUS ANTIBIOTICS	12	9.84
PUERPERAL SEPSIS	0	0

There were no cases of composite infectious maternal morbidity such as endometritis, septicaemia, peritonitis or wound infection. However, one case of chorioamnionitis was noted that required triple antibiotics intrapartum. Only 12 patients were given intravenous antibiotics postpartum and all of them had a caesarean section. All the patients were discharged home on oral antibiotics namely Amoxicillin and Metronidazole for a week.

3.62 Secondary Maternal Outcomes:

The secondary maternal outcomes were grouped into antepartum, intrapartum and postpartum outcomes.

1. Antepartum and Intrapartum Outcomes were:
   Intrapartum pyrexia, chorioamnionitis, antepartum haemorrhage, spontaneous onset of labour, use of augmentation of labour, mode of delivery and failed induction requiring caesarean delivery.
2. Postpartum outcomes were
   Puerperal sepsis, hysterectomy, requirement of antibiotics and length of hospital stay.

3.63 Labour and Delivery:

Table 3.15: Representation of Secondary Maternal Outcomes

OUTCOME	TOTAL (n=122)
SPONTANEOUS ONSET OF LABOUR	42/122 (34.4%)
INDUCTION OF LABOUR	80/122 (65.6%)
AUGMENTATION OF LABOUR	17/122 (13.9%)
FAILED INDUCTION OF LABOUR	12/122 (9.8%)
VAGINAL DELIVERY	92/122 (75.4%)
CAESAREAN SECTION	30/122 (24.6%)
ANTEPARTUM HAEMORRHAGE	2/122 (1.6%)
HYSTERECTOMY	1/122 (0.8%)

About 34.4% of women with Prelabour rupture of membranes had spontaneous onset of labour before 24 hours while 80 women out 122 were induced after 24 hours. During labour, 13.9% required augmentation with intravenous oxytocin while 12 of them had a failed Induction of labour and needed an operative delivery.

Mode of Delivery:

Table 3.16: Mode of Delivery

MODE OF DELIVERY	TOTAL (n=122)	
	FREQUENCY (n)	PERCENTAGE(n%)
VAGINAL DELIVERY	92	75.4
CESAREAN DELIVERY	30	24.6

Ninety-two women in the study had a normal vaginal delivery. Thirty women (24.6%) had a caesarean section and the indications were mostly failed induction of labour which constituted 9.8%. Other indications for caesarean section were failed VBAC and fetal distress.

Table 3.17: Comparison of Labour characteristics and Latency period

	LATENCY PERIOD < 48 HOURS (n=81)	LATENCY PERIOD ≥ 48 HOURS (n=41)	RELATIVE RISK (95 % CI)	p value
SPONTANEOUS ONSET OF LABOUR	36/81(44.4%)	6/41(14.6%)	3.0(1.4-6.6)	0.001
INDUCTION OF LABOUR	45/81(55.6%)	35/41(85.4%)	0.7(0.5-0.8)	0.001
AUGMENTATION OF LABOUR	7/81(8.6%)	10/41(24.4%)	0.4(0.2-0.9)	0.018
VAGINAL DELIVERY	58/81(71.6%)	34/41(82.9%)	0.8(0.7-1.1)	0.170
CAESAREAN DELIVERY	23/81(28.4%)	7/41(17.1%)	1.6(0.8-3.5)	0.170

Women in the short latency period were more likely to have a spontaneous onset of labour. This finding was statistically significant.

About 55.6% of women in the short latency period had an induction of labour after 24 hours out of which 71.6% had a normal vaginal delivery and 28.4% had a caesarean section. Compared to women who were induced in the long latency period, 82.9% delivered vaginally and 17.1% had a caesarean section. This latter finding was not statistically significant.

3.64 Secondary Maternal Complications:

There were 2 reported cases of antepartum haemorrhage. There was one hysterectomy as a result of postpartum haemorrhage.

Table 3.18: Secondary Antepartum complications during IOL in late PPROM

	TOTAL (n=122)	
	FREQUENCY (n)	PERCENTAGE(n%)
Antepartum Haemorrhage	2	1.64
Hysterectomy	1	0.82

3.7 Comparison of Composite Maternal and Neonatal Outcomes at different Gestational Age Groups:

Table 3.19: Comparison of Maternal and Neonatal outcomes at different Gestational Ages

GESTATIONAL AGE	COMPOSITE NEONATAL OUTCOMES n(%)		COMPOSITE MATERNAL OUTCOMES n(%)	
	ABSENT	PRESENT	ABSENT	PRESENT
$34^{+0} – 34^{+6}$	33(100)	0	28(84.6)	5(15.2)
$35^{+0} – 35^{+6}$	32(97.0)	1(3.0)	26(78.8)	7(21.2)
$36^{+0} – 36^{+6}$	54(96.4)	2(2.5)	51(91.1)	5(8.9)
TOTAL	119(97.5)	3(2.5)	105(86.1)	17(13.9)
P value	0.56		0.26	

The composite maternal and neonatal outcomes were analysed at different gestational ages in the late preterm population. There were more maternal outcomes (13.9%) compared to the neonatal outcomes (2.5%) during the study.

There were no complications in 97.5% of the neonates born between 34^{+0} to 36^{+6} weeks of gestation in pregnant women who had prelabour rupture of membranes. Of the 2.5% of neonates who were affected, there was one case of neonatal sepsis and two cases of respiratory complications, namely respiratory distress syndrome. The p value when neonatal outcomes were compared to the gestational age was 0.56 and was not statistically significant. About 13.9% of the pregnant women in the study had an adverse maternal outcome between this specific gestational age of 34^{+0} to 36^{+6} weeks. The p value when maternal outcomes were compared to gestational age was 0.26 and was not statistically significant.

3.8 Comparison of Composite Maternal and Neonatal Outcomes between the two latency periods:

Table 3.20: Comparison of Composite Neonatal Outcomes between the two latency periods

LATENCY PERIOD	COMPOSITE NEONATAL OUTCOMES n(%)	
	PRESENT	ABSENT
LESS THAN 48 HOURS	2(2.5)	79(97.5)
MORE THAN OR EQUAL TO 48 HOURS	1(2.4)	40(97.6)
TOTAL	3(2.5)	119(97.5)
P value	0.99	

Table 3.21: Comparison of Composite Maternal Outcomes between the two latency periods

LATENCY PERIOD	COMPOSITE MATERNAL OUTCOMES n(%)	
	PRESENT	ABSENT
LESS THAN 48 HOURS	14(17.3)	67(82.7))
MORE THAN OR EQUAL TO 48 HOURS	3(7.3)	38(92.7)3(7.3)
TOTAL	17(13.9)	105(86.1)
P value	0.13	

The effect of latency period was analysed with respect to maternal and neonatal outcomes. The risk of having an adverse neonatal outcome between the two latency periods was negligible and the p value was 0.99 which was statistically not significant.

There were more secondary maternal outcomes in the short latency period, that is latency period before 48 hours which might have been related to failed induction of labour leading to caesarean section. This finding is possibly also an indication that the pregnancy was not prolonged in patients who developed or were at risk of adverse outcomes. The p value between the 2 groups was 0.13 which was not statistically significant.

3.9 Comparison of Maternal and Neonatal Outcomes in both Latency Periods:

Table 3.22: Comparison of Outcomes with Latency period

	LATENCY PERIOD < 48 HOURS (n=81)	LATENCY PERIOD ≥ 48 HOURS (n=41)	RELATIVE RISK (95 % CI)	p value
PRIMARY OUTCOME				
NEONATAL SEPSIS	1/81(1.2%)	0	N/A	N/A
SECONDARY NEONATAL OUTCOMES				
COMPOSITE NEONATAL PREMATURITY COMPLICATIONS	1/81(1.2%)	1/41(2.4%)	0.5(0.03-7.89)	0.62
BIRTHWEIGHT	2569(329.4)	2432(289.3)		
APGAR SCORE <4 AT 5 MINUTES	1/81(1.2%)	0	N/A	N/A
ADMISSION TO HIGH CARE				
METABOLIC COMPLICATIONS	7/80(8.7%)	4/41(9.8%)	0.90(0.28-2.89)	0.86
RESPIRATORY COMPLICATIONS	1/81(1.2%)	1/41(2.4%)	0.50(0.03-7.80)	0.63
NEONATAL STAY > 7 DAYS	0	1/41(2.4%)	N/A	N/A
SECONDARY MATERNAL OUTCOMES				
ANTEPARTUM HEMORRHAGE	1/81(1.2%)	0	N/A	N/A
INTRAPARTUM FEVER	1/81(1.2%)	0	N/A	N/A
CHORIOAMNIONITIS	1/81(1.2%)	0	N/A	N/A
HYSTERECTOMY	1/81(1.2%)	0	N/A	N/A
POST PARTUM ANTIBIOTICS	10/81(12.3%)	2/41(4.9%)	2.5(0.58-11.0)	0.19
MATERNAL HOSPITALISATION > 7 DAYS	5/81(6.2%)	1/41(2.4%)	2.5(0.31-21.0)	0.37

* N/A: The relative risk is not reported when there was no events in any of the two groups

The primary outcome of neonatal sepsis occurred in only one neonate which was in the short latency period and there was none in the longer latency period. There were no statistical differences between the composite neonatal prematurity complications, critical Apgar scores at 5 minutes, admission to high care unit as a result of metabolic or respiratory complications and the duration of neonatal stay in hospital between the two groups.

When the secondary maternal outcomes were analysed, there was only one case of antepartum haemorrhage, intrapartum pyrexia and chorioamnionitis which was in the short latency period compared to none in the longer latency period and this was not statistically significant.

There was also one case of hysterectomy which was related to postpartum haemorrhage and was also not statistically significant.

About 12.3% of women in the shorter latency period required postpartum antibiotics compared to 4.9% in the longer latency period and this was also not statistically significant (p=0.190).

There was no statistical difference between the length of maternal hospitalization between the two groups (p=0.367).

3.10 Comparison of Birth weight and Latency period:

Table 3.23: Distribution of Birth weight and Latency period

GROUP	OBSERVATION	MEAN	STANDARD ERROR	STANDARD DEVIATION	95 % CI
Short Latency (< 48 hours)	80	2543.6	46.9	419.7	2450.2-2637.1
Long Latency (≥ 48 hours)	41	2423.6	45.2	289.3	2332.3-2514.9
P value	0.10				

This table represents t-test for the distribution of birth weight between the two groups, short latency period (< 48 hours) and long latency period (≥ 48 hours). There were 80 patients in the short latency group and 41 patients in the long latency group. The p value was 0.10, i.e there was no statistical differences between the mean birth weight in the two groups.

Summary of Results of the study:

There were 122 patients in the study of maternal and neonatal outcomes in late preterm prelabour rupture of membranes between two different latency periods. All of the patients were HIV negative. The short latency period was defined as the time from the rupture of membranes until birth and was less than 48 hours. The long latency period was considered if there was more than 48 hours between rupture of membranes and time of delivery.

- There was no statistical difference in the means and distribution of maternal ages between the two groups.

- In patients who were between 34^{+0} to 34^{+6} weeks of gestation, the proportion of patients between the short and long latency groups was the same. Between 35^{+0} to 35^{+6} weeks, there was a difference in proportion of patients between the two groups of latency period. This is an unusual finding and is probably related to an inadequate sample size of our study. However, between 36^{+0} to 36^{+6} weeks of gestation, there was a difference in the proportion of patients between the short and long latency period and more was in the former. This finding explained that the further the gestational age is closer to term, the more likely the patients were to be induced and hence a shorter latency period.

- In terms of obstetric risk factors which included a history of previous caesarean section, medical comorbidities and the use of antenatal corticosteroids, no statistical difference was noted between the two groups.

- There was no statistical difference in patients who required antibiotics in both groups.

- There was no statistical difference noted in terms of both maternal and neonatal outcomes when they were compared in both groups.

- There was no statistical difference noted in when maternal and neonatal outcomes at different gestational age groups were compared. It was noted however that there were more adverse maternal outcomes than neonatal outcomes.

- There was no statistical difference when the mean birth weight was compared in the two groups.

CHAPTER 4: DISCUSSION

The study was carried out on patients who presented with late preterm prelabour rupture of membranes by dividing the patients between two groups according to the latency period. The first group was that of short latency which was less than 48 hours and the second was the long latency period group which was 48 hours or more.

Most major published studies addressing the clinical question of immediate induction versus expectant management of patients with late preterm PPROM include patients who are delivered only for obstetric reasons or once they reach 37 completed weeks gestation. This was not the case in our study where the decision to deliver was either taken based on the National Maternity Guideline or clinician preference. Another possible reason for this discrepancy is that our study was not a randomised trial. We believe that this is a limitation of our study.

Based on the result of this study of pregnant women who had ruptured membranes between 34^{+0} to 36^{+6} weeks of gestation, expectant management was safe with reduced risk of adverse neonatal outcomes. It was also noted that the latency period was even shorter as the gestational age was close to term. This finding is not surprising as most clinicians would deliver at or close to 37 completed weeks of gestation.

It was initially anticipated that there will be a higher rate of composite maternal and neonatal infectious morbidity in the study population. However, we found only one case of neonatal sepsis and this was seen in a patient who had an early induction of labour. It was also noted that there were no cases of maternal sepsis in either of the two groups. Thus, there was no difference between the two groups (short versus long latency period) in terms of maternal and neonatal infectious morbidity outcome.

It was also hypothesized that there will be more composite prematurity complications when delivery would have occurred in the early latency period. However, no significant differences were found between the two groups. This is probably because the maximum latency period in this study was not more than 96 hours. This was a limitation in the study as compared to the PPROMT trial since the

current standard of care recommended in South Africa is to induce labour within 12 to 24 hours after rupture of membranes above 34 weeks of gestation. Since this study was carried out in low risk patients and excluding HIV patients, it is probable that expectant management would have decreased prematurity complications if the latency period was defined as that of the PPROMPT trial.

There were more adverse maternal outcomes noted in the study compared to neonatal outcomes. This was related mostly to the mode of delivery and it was noted that patients in the early delivery group had a higher incidence of operative delivery. About 24.6% of women in the study had a caesarean section and the incidence was higher in those patients who had a latency period within 48 hours (28.4%) compared to those whose latency period was more than 48 hours (17.1%). It was mostly as a result of failed induction of labour or due to fetal distress associated with augmentation of labour. Hence it can be concluded that early induction in patients with ruptured membranes in the late preterm period was associated with more intervention and an increased likelihood of caesarean section.

The PPROMT trial showed that antepartum haemorrhage was one of the main adverse maternal outcomes in patients who were in the expectant management group. There were no cases of antepartum haemorrhage noted in our study. This was probably because the latency period was not long as in the PPROMT trial and hence patients were delivered early. It can be concluded that if expectant management is to be observed, then the increased risk of antepartum haemorrhage needs to be taken into consideration and patients need close monitoring.

The study by Mercer et al[17] after randomising 93 patients with ruptured membranes and documented lung maturity between 32 to 36 weeks of gestation concluded that expectant management was associated with prolonged maternal and neonatal hospitalisation along with an increase incidence of chorioamnionitis and the requirement of antibiotics. Similarly, another study by Naef et al[18] among patients with PPROM between 34 to 37 weeks of gestation also reported a higher incidence of chorioamnionitis and increased duration of maternal and neonatal stay in hospital. When both studies were taken together, they both supported immediate induction as

compared to delayed induction of labour. However, they do not provide guidance regarding the timing of induction when compared to the neonatal outcomes.

Expectant management is associated with higher chances of spontaneous onset of labour and allowing adaptive changes to occur in the neonate resulting in less neonatal prematurity complications mostly respiratory distress. As a result, more neonates will be of older gestation and hence fewer will require admission to nursery or high care. This will also allow more bonding between mothers and neonates, as well as improving the rate of breast feeding which is of utmost importance on the African continent where many neonates are at risk of adverse childhood outcomes.

The findings of the largest trial carried out to date on late preterm prelabour rupture of membranes, the PPROMT trial, clearly favours expectant management. The adoption of such a practice in our setting, at level 2 hospitals, with careful monitoring of both the mother and the fetus such as monitoring for fever or other signs of chorioamnionitis and antepartum haemorrhage can decrease maternal and neonatal adverse outcomes. One of the drawbacks of expectant management in these low risk pregnant women will be an impact on the economy of the health care system in view of longer maternal admission. However, spending more money on maternal admission is more acceptable than using resources on the management of adverse neonatal complications in ICU or a neonatal high care which is much more expensive and has potential longer term sequelae.

CHAPTER 5: CONCLUSION

This retrospective observational study was carried out in low risk HIV negative women with singleton pregnancies with ruptured membranes in the late preterm period. It has been shown that there were no significant differences in both maternal and neonatal outcomes between the two groups of latency periods when latency was defined as the time from ruptured membranes to delivery. Hence prioritising a delayed induction of labour in low risk HIV negative patients with careful maternal and fetal monitoring can be beneficial to the newborn babies as well as to the health care system.

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APPENDIX 1:DATA COLLECTION SHEET LATE PPROM STUDY

STUDY NUMBER	
FOLDER NUMBER	
AGE	
GRAVIDITY	
PARITY	
GESTATIONAL AGE (WEEKS) 1=34^{+0}-34^{+6} 2=35^{+0}-35^{+6} 3= 36^{+0}-36^{+6}	
HIV STATUS 1= Positive on Rx 3=Negative 2=Positive not on Rx 4=Unknown	
SOCIOECONOMIC STATUS 1=Low 2=Average 3=Unknown	
ETHNICITY 1=Black 3=White 2=Coloured 4=Others	
SMOKER 1=Yes 2=No	
PREVIOUS C/S 1=Yes 2=No	
MEDICAL COMORBIDITIES 1=Yes 2=No	
BOOKING 1= Booked + ANC 2= Booked but no ANC 3= Unbooked	
USE OF ANTIBIOTICS 1=None 2=Stat dose only 3=Oral Antibiotics 4=Intravenous Antibiotics	
TYPE OF ANTIBIOTICS USED 1=Azithromycin 4= None 2=Penicillin 3=Penicillin and Flagyl	
ANTENATAL CORTICOSTEROIDS 1=Yes 2= No	
LATENCY PERIOD 1= <24 hours 3= 48 hours- 7 days 2=24 -48 hours 4= > 7 days	

PRIMARY OUTCOMES

COMPOSITE NEONATAL INFECTIOUS MORBIDITY

NEONATAL SEPSIS 1=Yes 2=No	
PNEUMONIA 1=Yes 2=No	
NECROTISING ENTEROCOLITIS 1=Yes 2=No	
NEONATAL DEATH 1=Yes 2=No	

COMPOSITE NEONATAL PREMATURITY MORBIDITY

RESPIRATORY DISTRESS SYNDROME 1=Yes 2=No	
BRONCHOPULMONARY DYSPLASIA 1=Yes 2=No	
INTRAVENTRICULAR HEMORRHAGE 1=Yes 2=No	
PERIVENTRICULAR LEUKOMALACIA 1=Yes 2=No	
RETINOPATHY OF PREMATURITY 1=Yes 2=No	

COMPOSITE MATERNALINFECTIOUS MORBIDITY

ENDOMETRITIS 1=Yes 2=No	
SEPTICAEMIA 1=Yes 2=No	
PERITONITIS 1=Yes 2=No	
WOUND INFECTION 1=Yes 2=No	

SECONDARY OUTCOMES

MATERNAL OUTCOMES

INTRAPARTUM PYREXIA 1=Yes 2=No	
CHORIOAMNIONITIS 1=Yes 2=No	
ANTEPARTUM HEMORRHAGE 1=Yes 2=No	
TRIPLE ANTIBIOTICS INTRAPARTUM 1=Yes 2=No	
SPONTANEOUS ONSET OF LABOUR 1=Yes 2=No	
AUGMENTATION OF LABOUR 1=Yes 2=No	
VAGINAL DELIVERY 1=Yes 2=No	
FAILED INDUCTION 1=Yes 2=No	
CAESAREAN DELIVERY 1=Yes 2=No	
PUERPERAL SEPSIS 1=Yes 2=No	
HYSTERECTOMY 1=Yes 2=No	
POSTPARTUM INTRAVENOUS ANTIBIOTICS 1=Yes 2=No	
LENGTH OF MATERNAL HOSPITALISATION 1=> 7 Days 2= ≤ 7 Days	

NEONATAL OUTCOMES

APGAR SCORE 1 MINUTE	
APGAR SCORE 5 MINUTES	
BIRTH WEIGHT 1= ≤ 2 Kg 2= > 2 kg	
METABOLIC COMPLICATIONS 1=Yes 2=No	
ADMISSION TO NICU 1=Yes 2=No	
LENGTH OF NICU ADMISSION 1=> 7 Days 2= ≤ 7 Days	

APPENDIX 2: Data Collection Sheet (Definition of components)

1. Chorioamnionitis[11]:

It is defined as the acute inflammation of the fetal membranes and chorion of the placenta, typically due to ascending polymicrobial bacterial infection in the setting of membrane rupture. When clinical signs are present, the condition is referred to as clinical chorioamnionitis. It is characterised by the following:

- Fever (Temperature > 38^{o}C)
- Maternal tachycardia (Pulse ≥ 100 beats/minute)
- Fetal tachycardia (FHR ≥ 160 beats/minute)
- Uterine fundal tenderness/ Irritability
- Offensive smell of liquor

Leucocytosis and raised CRP for the diagnosis or prediction of chorioamnionitis as part of routine clinical practice is not established as it is common during labour and with the use of steroids.

2. Apgar Score:

The test is generally done at one and five minutes after birth, and may be repeated later if the score is and remains low. Scores 7 and above are generally normal, 4 to 6 fairly low, and 3 and below are generally regarded as critically low.

Components of Apgar score are listed as follows:

SCORE	0	1	2
APPEARANCE	Complete cyanosis	Blue at extremities pink body	No cyanosis /pink extremities
PULSE	absent	< 100/min	>100/min
REFLEX	No response to stimulation	Grimace on stimulation	Cry on stimulation
ACTIVITY	none	Some flexion	Flexed arms/legs resisting extension
RESPIRATION	absent	Weak,irregular,gasping	Strong,lusty cry

3. Latency Period:

It is defined from the time of rupture of membranes to the time of delivery of the baby.

4. Use of Antibiotics[11]:

In our setting, once the woman is induced she is given a stat dose of 2 gm of Ampicillin followed by 1 gm 6 hourly. If the patient is allergic to penicillin, she is given Clindamycin 600 mg 8 hourly.
In case of chorioamnionitis, triple antibiotics with Ampicillin, Gentamycin and flagyl are administered.

5. Neonatal Infectious Morbidity[25]:

Neonatal sepsis:

This is defined as signs and symptoms of infection and a positive culture of a known pathogen from blood or cerebrospinal fluid. The clinical signs of infection include respiratory distress, apnoea, lethargy, abnormal level of consciousness, circulatory compromise needing support, poor feeding and/or temperature instability.

Necrotising Enterocolitis:

The disease is characterised by various degrees of mucosal or transmural necrosis of the intestine as a result of intestinal immaturity. The first signs of impending disease may be nonspecific, including lethargy and temperature instability, or related to gastrointestinal pathology, such as abdominal distension and gastric retention. Bloody stools is seen in about 25% of patients.

6. Secondary Neonatal Outcomes[25]:

Respiratory Distress Syndrome:

It is also known as hyaline membrane disease and its incidence is inversely related to the gestational age and birth weight. It occurs as a result of surfactant deficiency and has a 15-30% incidence between 32-36 weeks of gestation. It is usually characterised by tachypnoea, grunting, intercostal and subcostal recession and nasal flaring. Its definitive diagnosis is by a Chest X-ray and Arterial blood gas which shows hypoxemia, hypercapnia and metabolic acidosis.

Bronchopulmonary Dysplasia:

This is a pathological process which leads to chronic lung disease in the neonatal period. The current accepted definition involves oxygen requirement for 28 days or more postnatally. It is typically characterised by tachypnoea, mouth breathing due to narrowed air passages and high arched palate.

Intraventricular Haemorrhage and Periventricular Leukomalacia:

When intracranial haemorrhage involves the ventricles, it is known as intraventricular haemorrhage (IVH). Venous obstruction as a result of IVH will result in decreased perfusion leading to necrosis and focal necrotic areas in the brain is known as periventricular leukomalacia (PVL). Both conditions are very common in premature infants because of immature blood vessels in the region of the developing brain combined with poor tissue vascular support. Neurological manifestations will be seen shortly after birth and in case of PVL, it is usually asymptomatic until the neurological sequelae of white matter damage become apparent in later infancy as spastic motor deficits.

Retinopathy of Prematurity:

Usually detected late in infancy, it occurs as a result of injury to the retinal angiogenesis process which starts early in prenatal life from the region of the optic disc and proceeds to the periphery around 36-40 weeks of gestation.

7. Composite Maternal Infectious Morbidity:[26]

This was defined as any postpartum patient who presented with puerperal pyrexia with a temperature above 38^{o} C on any two days of the first ten days of puerperium, exclusive of the first 24 hours. Patients who presented with wound infection post caesarean section, endomyometritis, pelvic abscess and peritonitis after prolonged rupture of membranes were included under this outcome variable.

Endomyometritis has an incidence in excess of 30% in patients in patients with prolonged rupture of membranes after a caesarean section. The above 4 conditions will usually manifest with fever, abdominal pain, offensive lochia, purulent discharge from a caesarean section wound and toxic looking patient.

APPENDIX 3: HREC APPROVAL LETTER

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

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Observatory 7925
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31 May 2016

HREC REF: 156/2016

Dr G Petro
Division of Obstetrics & Gynaecology
H-Floor
OMB

Dear Dr Petro

PROJECT TITLE: MANAGEMENT AND OUTCOMES OF PRE LABOUR RUPTURE OF MEMBRANES IN LATE PRE TERM IN THE METRO WEST OF CAPE TOWN (MMed-candidate-Dr V Leelodharry)

Thank you for your response letter dated 23 May 2016, addressing the issues raised by the Human Research Ethics Committee (HREC).

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 June 2017.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

We acknowledge that the student, Dr Vakil LeelodHarry will also be involved in this study.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938