LATENCY, PERINATAL AND MATERNAL OUTCOMES IN CONSERVATIVELY MANAGED PATIENTS WITH PRETERM PREMATURE RUPTURE OF MEMBRANES AT 24-34 WEEKS GESTATION AT KENYATTA NATIONAL HOSPITAL.

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Dissertation submitted for examination in part fulfilment of the requirements for an award of the degree Masters in Medicine, Department of Obstetrics and Gynecology, Faculty of health sciences, University of Nairobi.

2023

DECLARATION

I declare that this dissertation 'Latency, perinatal and maternal outcomes in conservatively managed patients with preterm premature rupture of membranes at 24-34 weeks' gestation at Kenyatta national hospital; a retrospective cohort study' is my original work, done under the supervision of my supervisors and it has not been presented anywhere for a degree.

All resources used or quoted have been indicated and acknowledged by referencing.

I further declare, this work has not been submitted to any institution or university for the award of any other degree.

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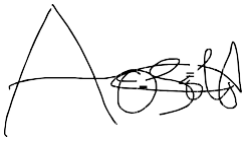
Signature:  **Date:** 08/06/2023

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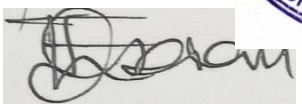
Signature:  **Date: 14th June 2023**

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LIST OF ABREVIATIONS AND ACRONYMS

AOR: Adjusted Odds Ratio

ANC: Ante Natal Care

APGAR: Appearance, Pulse, Grimace, Activity, Respiration

APH: Ante partum hemorrhage

CI: Confidence interval

C/S: Caesarean Section

EOS: Early onset sepsis

FSB: Fresh still birth

GA: Gestation age

IUGR: Intrauterine growth restriction

IVH: Intra ventricular hemorrhage

KNH: Kenyatta National Hospital

MSB: Macerated still birth

NBU: New born unit

NNS: Neonatal sepsis

NND: Neonatal death

NICU: Neonatal Intensive Care Unit

NRFHT: Non reassuring fetal heart tracing

OR: Odds Ratio

PPH: Postpartum hemorrhage

PROM: Premature rupture of the membranes

PPROM: Preterm premature rupture of the membranes

PVL: Periventricular Leucomalacia

RDS: Respiratory Distress syndrome

SD: Standard deviation

SPSS: Statistical package for social sciences

SVD: Spontaneous vertex delivery

LMP: Last menstrual period

DEFINITIONS

- **Premature rupture of the membranes:** defined as spontaneous rupture of membrane that occurs before the onset of labor.
- **Preterm PROM:** spontaneous membrane rupture occurring before 37 weeks' gestation.
- **Latency period:** refers to the time from membrane rupture to delivery.
- **Conservative/ expectant management**: defined as treatment directed at continuing the pregnancy to improve neonatal outcome. It in cooperates use of adjunct antibiotics and induction of fetal lung maturation, while monitoring fetal and maternal status.
- **Preterm birth:** any birth before 37 completed weeks of gestation, or fewer than 259 days since the LMP. Its further subdivided on basis of gestation age;
- **Extremely preterm:** birth after 24 weeks to 28 weeks,
- **Very preterm:** birth between 28-32 weeks,
- **Moderate or late term preterm:** birth between 32- <37
- **Neonatal mortality:** death that occurs from birth up to 28 days of life
- **Perinatal mortality:** death that occurs after 28 weeks' gestation and up to 7 days of life
- **Early neonatal outcomes**: illnesses occurring within the first 7 days
- **Morbidity**: condition of suffering from a disease
- **Mortality**: death

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Abstract

Background: Preterm premature rupture of membranes (PPROM) complicates 3%-8% of all pregnancies and is associated with 30–40% of preterm births, perinatal and maternal morbidities, and mortality. At 24-34 weeks, PPROM is conservatively managed if there are no indications for immediate delivery. Although latency period, time from PPROM to delivery for conservatively managed PPROM determines the perinatal and maternal outcomes, this has not been evaluated at Kenyatta National Hospital (KNH). Information on latency and associated pregnancy outcomes can inform patient guidance on expectations and likely maternal and perinatal outcomes.

Objective: To describe the latency period, perinatal and maternal outcomes in conservatively managed patients with PPROM at 24-34 weeks of gestation at KNH in 2019.

Methods: This was a retrospective descriptive cohort study in which records of conservatively managed patients with PPROM at 24-34 weeks at KNH from 1st January to 31st December 2019 were reviewed. Latency was defined as the time from spontaneous rupture of membranes to delivery. The mean (standard deviation) and median (interquartile range) latency period was estimated. Perinatal morbidity was summarized as percentages, while the perinatal mortality rate was calculated as the number of fetal and early neonatal deaths/per 1000 total births following PPROM. We evaluated the association between latency period (of > 72 hours and > 7 days) with adverse perinatal and maternal outcomes. A p-value of < 0.05 was considered statistically significant.

Results: Between January 2019 and December 2019, we screened 514 files of which 143 (27.8 %) maternal files (122 singletons and 21 multiple pregnancies) and 165 (95%) neonatal files were eligible. The mean age of participants was 28.4 (± 6.3) years. The mean gestation at PROM and at delivery was 30.1 (± 2.7) and 31.1 (± 2.3) weeks respectively. The overall mean latency was 6.7 (± 8.5) days and 15.1 (± 13.2) ,6.1 (± 6.7) and 3.1 (± 2.4) days at 24 – 28 weeks, 28+1 – 32, and 32+1 – 34 weeks of gestation respectively. The perinatal morbidity rate was 63% (95% Confidence Interval (CI), 55.4% – 70.0%) due to respiratory distress syndrome 38.2% (CI, 31.1% – 45.8%), neonatal jaundice 32.7% (CI, 26.0% – 40.2%), neonatal sepsis 26.7% (CI, 20.5% – 33.9%) and necrotizing enterocolitis 3.6% (CI, 1.7% – 7.7%). The Perinatal Mortality Rate was 194/1000 live births. The incidence of maternal morbidity was 18.9%, due to abruptio placentae 4.9% (CI,0.7%-6.0%), chorioamnionitis 6.3% (CI,3.4%-11.5%), cord prolapse 3.4%(CI,2.4%-9.8%), retained placenta 0.7%(0.1%-3.9%) and postpartum hemorrhage 2.1% (CI, 0.7%-6.0%) the use of steroids and antibiotic were associated with latency of >72hours, while prolonged latency of >7 days was associated with early gestation at PPROM, gestation at birth at 28+1-32 weeks, use of steroids and antibiotics. Prolonged latency of > 72 hours was associated with hyperbilirubinemia and necrotizing enterocolitis, however latency of > 7 days was not associated with any adverse perinatal and maternal outcomes.

Conclusion: The mean latency of pregnant women who had PPROM at 24-34 weeks, was 6.7 days, and was highest at 24-28 weeks' gestation. Perinatal morbidity and mortality was high. Maternal morbidity was 18.9% with leading morbidity being chorioamnionitis. There was no maternal death. Prolonged latency was associated with necrotizing enterocolitis(NEC) and hyperbilirubinemia and was not associated with any adverse maternal outcomes.

Recommendations: When not contraindicated, conservative management of PPROM at 24-34 weeks is safe can be offered to eligible women to prolong latency. Interventions that can increase latency and improve neonatal survival should be assessed and instituted. These study findings can be used to generate statements for future references.

1.1 INTRODUCTION

Preterm prelabor rupture of membranes (PPROM) is defined as the spontaneous membrane rupture that occurs before 37 weeks' gestation. It complicates 3%-8% of pregnancies worldwide. The prevalence of PPROM varies between different regions due to different population risk factors. Different studies revealed a prevalence of 2.3% in Canada, 3-10% in India, 2.4-4.7% in Egypt, 3.3% and 3.1% in Nigeria, 13.7%, and 14.6% in Ethiopia and Uganda reported 13.8%. From this literature, we see a higher prevalence is recorded in Africa (1–7) 30–40% of preterm births are attributed to PPROM (4,8). Prematurity related morbidity and mortality accounts to 85%, while other causes of adverse outcomes include sepsis, cord accidents, pulmonary hypoplasia, and maternal adverse outcomes like chorioamnionitis and placental abruption (4,8). Preterm delivery affects 10% of births in the USA and the rate in developing countries is higher. No study on the prevalence of PPROM has been done in Kenya however the prevalence of preterm birth is 18.3% (9) and statistics show neonatal mortality of 24.6% from prematurity (10).

Premature infants put a great strain on the health care resources of a country and its overall economy. Therefore, the decision to continue a pregnancy or deliver expeditiously following PPROM should be done following an accurate diagnosis and a thorough evaluation of the risks and benefits of each option of management (10). The disease burden includes adverse maternal and neonatal outcomes, a country's economic drain due to the expense of drugs and specialized equipment, prolonged hospitalization, caretakers' absence from their workplaces, and cost of the health care professionals.

The pathophysiology of PPROM is multifactorial in nature, with one or more factors being evident in any given patient. Choriodecidual inflammation or infection is a key implication in the etiology of PPROM, especially at early gestational ages. Low content of membrane collagen has been noted in the presence of PPROM and commonly with higher gestational age. In confirming this, increases in matrix metalloproteases in amniotic fluid and decreasing tissue inhibitors of matrix metalloproteases (1and 2) have been ascertained in women with PPROM.(11)

The incidence of PPROM in African and African-American women appears to be higher than in Caucasian women. Malnutrition, deficiencies in hydroxyproline, copper, zinc, and vitamin C have also been evidenced to predispose pregnant women to PPROM. A strong correlation exists between smoking and PPROM (12).Studies show an increased risk for PPROM in patients with abnormal vaginal discharge, history of abortion, history of prior cesarean section (5,10,12–14) , urinary tract infection (15), previous PROM, vaginal bleeding (3,7,13,14,16), mid-upper arm circumstance <23cm, history of preterm delivery (5,17,18), twin gestation(19), cervical incompetence and cervical cerclage (12). The frequency of PPROM in those aged 15–25 years is high (18).

Other significant risk factors include low socioeconomic status, inadequate antenatal care, and sexually transmitted infections (20). One study showed no association of PPROM with carrying heavy objects, sexual intercourse, smoking, gravidity and parity (14).

The exact cause of PPROM is not known, however postulated factors are: previous PPROM, membrane defects, infections of the genital tract like Chlamydia trachomatis, Neisseria gonorrhea, Bacterial vaginosis, Group B streptococcus and Gardnerella vaginalis (13,15), an insufficient or short cervix, multiple gestation, polyhydramnios, abruption placentae and abnormal placentation have been considered to have a causal role. Fetal blood sampling and amniocentesis, fetal malformations, positive fetal Fibronectin, IUFD, injuries, poor socio-economic status have been implicated as causal associations of PPROM(20)

The clinical presentation of PROM entails a history of an abnormal watery discharge per vaginally, flowing down the feet or a sudden fluid gush per vagina. The fluid may appear clear, brown, green or pink, yellow and may have a mal odor. The fluid may leak constantly or on exertion. In addition, fever, chills or abdominal pains may be present (20).

The diagnosis of PROM is confirmed by pooling of fluid in the vagina on speculum examination, and once this is evident, no more diagnostic tests are required. When there is no clear observation of the fluid, it is necessary to test for IGFBP-1 or PAMG-1 where possible, since the markers have a high sensitivity and specificity(21). The results should be well correlated with the patient's history, and gestation. Testing using Nitrazine is not recommended, and when the woman is in established labor, then there is no need for further testing (22).

Baseline workups include; complete blood count, Erythrocyte Sedimentation Rate, Amniotic fluid for microbiologic assay, a bubble test to check for maturation of the lungs and urine analysis. An obstetric ultrasound is useful to determine fetal viability, gestation, liquor volume, fetal anomalies and fetal presentation(20). An ultrasound showing oligohydramnios can support the clinical diagnosis but not to make a diagnosis of PPROM.(8)

Differential diagnosis of PPROM include excessive normal or abnormal vaginal secretions, cervicitis, bloody show, urinary incontinence or postcoital semen discharge.(1)

For optimal management of the newborns, once a diagnosis of PPROM is established and there is imminent need for delivery. The Newborn unit should be alerted for appropriate preparation for the neonate. The couple should meet a neonatologist to discuss the management plan(8).

There are limited data on latency, perinatal and maternal outcomes of conservative management of PPROM locally and the findings of these study are to fill in this gap in information.

2.0 LITERATURE REVIEW

Preterm newborns account for 8-10% of live births but are accountable for 90% of neonatal morbidity. The 24-34 weeks' gestation preterm is an important population of study due to the associated morbidity and mortality in this age group, the need to delay the delivery i.e. to prolong the latency period in order to improve the neonatal outcomes becomes an important factor. Evidence demonstrates the use of antibiotics in a patient with PPROM prolong the latency period and therefore improve outcomes. Corticosteroids use in PPROM at 24-34 weeks have demonstrated a decreased risk of IVH, RDS and NEC(23)

Latency duration and factors associated with short and prolonged latency periods

Latency is the time from rupture of membranes to delivery; it is generally inversely proportional to the gestational age at which PROM occurs.

Inaccuracy in the prediction of the latency period and its course for women with PPROM is a challenge and hence consulting these women about their predicted latency period is a difficult task.

The mean latency duration following PPROM range between 3.6-7.8 days (19,24–29).

Different studies have been done to identify the predictors of latency period and find the factors associated with either shortening or prolonging latency in a bid to improve care for the women with PPROM. Predictors include a woman's age, parity, number of gestations, gestation age at onset of PPROM, volume of liquor, presence or absence of chorioamnionitis.

Factors associated with a short latency period include multiple gestation, digital cervical examination, cervical dilation >2 cm at admission, presence of uterine contraction at admission and advanced gestation at the onset of PPROM (22,28,44). In addition, IUGR and oligohydramnios have been associated with a short <48hrs latency (30).

Mixed findings on the association of these factors and latency have been highlighted and include nulliparity, multiparity, oligohydramnios, maternal age and history of PPROM and PTD (24,30,31).

Factors associated with prolonged latency period include advanced maternal age >30 years, an earlier gestation age at onset of PPROM, use of prophylactic antibiotics, use of tocolytics and avoidance of digital cervical examination (25,31,32).

Prolonged latency, its benefits and adverse outcomes

Many studies agree that prolonged latency periods, do not worsen the prognosis of neonates and therefore noted a low association with adverse neonatal outcomes however they differed on maternal outcomes having adverse effects.

Frenette et al demonstrated that prolonged latency of more than 2 days was beneficial in that it decreased prematurity related morbidity and no association with neonatal infectious morbidity. She further noted NICU length of stay decreased for neonates who had a latency period of more than 7 days. These findings were similar to what Sighal et al who demonstrated no influence in neonatal infectious morbidity with prolonged latency. In addition, Sighal found the mean birth weights increased and there was a reduction of NICU length of stay in patients with prolonged latency.

Lorthe et al found prolonged latency did not worsen the prognosis of neonates, had no association with early onset sepsis (EOS) or survival without severe morbidity. Nayot noted both severe and moderate neonatal morbidity's incidence reduced after 72 hours of latency. Drassinamer was unable to link increased risk of NNS with prolonged PPROM, on the contrary 4 weeks and more of latency was associated with a significant decrease in NNS therefore he concluded that increasing latency improved prognosis.(26,28,31,33).

Commonest maternal outcomes reported with prolonged latency are an increase in febrile morbidity and chorioamnionitis a finding by Kahramanoglu et al; he however found no effect on incidence of PPH and placenta abruption with prolonged latency. Yu et al concluded that the fewer weeks of gestation at onset of PPROM was associated with a diagnosis of chorioamnionitis but this did not demonstrate an association with neonatal morbidity and mortality (19,25).

Shukla et al demonstrated that 72 hours or more of latency was actually associated with a 50% increase in abruption placentae, 37% increase in puerperal pyrexia and 60% of patients had chorioamnionitis (10).

Monitoring for any clinical evidence of infection is paramount since this patients are at risk of infection, all vital signs should be recorded on the obstetric early warning chart i.e. pulse, blood pressure, respiratory rate and temperature (22).

Factors that prolong latency

Evidence show that use of antibiotics prolong latency in most cases by reducing gestational age dependent and infectious infant morbidity (34), hence conservative management result in fewer morbidities at the time of delivery.
Digital cervical examination should be avoided during the evaluation of a patient with PPROM, studies have shown it precipitates labor and delivery and lead to increased morbidities to neonates (22,31).

Evidence also suggests that use of corticosteroid during conservative management improve neonatal outcome without potentiating risk of infection during the perinatal period (34). Steroids should only be administered once there is confirmation that the patient has no infection.

Evidence disagrees on the benefit of tocolytics in PPROM remote from term (34).

Magnesium sulfate and corticosteroids should be issued to PPROM patients above 23 weeks and have no infection, some studies show evidence of prolonged latency although some studies show no benefit in use of tocolytics (35).

Medications used during conservative management

a) Antibiotics

A study combination of 22 trials which included 6872 participants of women and babies revealed the usefulness of antibiotics in management of PPROM. Antibiotics reduced the rate of babies born within 48 hours and seven days of randomizing and the incidence of chorioamnionitis reduced significantly. There was a notable reduction in neonatal infection, need for surfactant and oxygen therapy, and reduction in number of abnormal cerebral ultrasound prior to hospital discharge. The study highlighted an increased risk of NEC with use of Co-amoxiclav. Minimal health effects were noted in the children seven years later from use of antibiotics and with the many advantages in the short term the antibiotics were recommended for routine use (36).

The ORACLE 1 trial revealed Erythromycin has been found to be beneficial in PPROM management; it prolongs latency and reduces the neonatal mortality and morbidity due to major cerebral abnormality and chronic lung disease (37). As compared to Co-amoxiclav, its risk causation of NEC is low. The recommended dose for prophylactic use in PPROM is 250mg six hourly for ten days or until delivery and Amoxicillin can be used if erythromycin is unavailable (37)

Recommendations in use include Intravenous Ampicillin 2 g 6 hourly and Erythromycin 250 mg 6 hourly for 2 days. Thereafter, an oral combination of Amoxicillin 250mg and Erythromycin 250mg 8 hourly for 5 days.

Patient who are allergic to penicillin can use clindamycin 900 mg 8 hourly for 2 days and gentamicin 7 mg/ kg once a day for 2 days. Thereafter oral clindamycin 300 mg eight hourly for 5 days (23).

Patients with chorioamnionitis should have IV broad spectrum antibiotics and support measures like IV fluids(20).

b) Corticosteroids

From a meta- analysis done, corticosteroids have proved helpful in decreasing risk of RDS and IVH. Evidence show no associated maternal infection or NNS with use of antenatal steroids. When administering corticosteroids, the following should be considered; gestation age, delivery likelihood in 48 hours and the interval between the last course of steroids in case of the need of a repeat course of corticosteroids (20,22).

Betamethasone is given 12mg once a day for 48 hours while dexamethasone is administered 6 mg every 12 hours for 48 hours (22).

c) Neuroprotection

Evidence from Meta-analyses revealed that women who had established preterm labor or elective preterm delivery in 24 hours, who used Magnesium sulphate for Neuroprotection had decreased incidence of cerebral palsy and motor dysfunction in the neonates. The drug is recommended in women likely to deliver before 30 weeks of gestation, NG255 recommends use in 30-34 weeks gestation (35).

d) Tocolytics

Following a review by Cochrane, evidence show that while tocolytics prolong latency by 73 hours on average, tocolytics were found to increase poor Apgar score of less than 7 at the 5^{th} min with newborns requiring ventilation and the women who were less than 34 weeks getting chorioamnionitis. With the evidence, a conclusion of no benefit in use of tocolytics was made. That said, tocolytics have been offered to women with uterine contractions and need to be referred to a center with a NICU facility or when delivery needs to be delayed for purposes of allowing time for steroids to function (23,35).

Maternal Complications of PPROM

Among maternal complications, the most common reported is chorioamnionitis with an incidence of 13-69% (38). Some have studied histopathology evidence in the placentas and found chorioamnionitis in 53% and 69% (1,17). For clinical chorioamnionitis 4.3%,12% and 17.8% were demonstrated (1,2,17), several other studies recording positive findings (4,10,18,39).

Postpartum hemorrhage has also been noted as a complication in 3% -12 % of patients, it has been attributed to chorioamnionitis or retained placental products. (4,10,17).

Cesarean section rate have been reported as increased in PPROM patients as revealed in some studies with ranges between 14%-49%(3,7,10,18), the indications are mainly due to malpresentation, fetal compromise, or failed or delayed progress of labor.

Other maternal complications include abruption placenta (10),a prolonged hospital stay (4) and Post-traumatic stress syndrome. Cases of umbilical cord compression, preterm delivery and prolapsed cord have also been reported as to complicate PPROM.(40).

A prospective cohort study by Stamrood et al, who compared post-traumatic stress disorder in women with PPROM and women without complications in pregnancy, found the disorder was more in the PPROM group than the controls. Therefore, it is important to give additional physiological support to the affected couples during and after delivery (20,35).

Perinatal complications of PPROM

These complications are dependent on the gestation at which PPROM occurs. Studies show that PPROM is associated with a four and a threefold increase in perinatal mortality and neonatal morbidity respectively.(40)

The neonatal mortality for PPROM has been noted to be between 7%-10% (4,7,19,40,41). While considering the very remote from term gestation that is 14-23+6 weeks, the neonatal mortality was noted to be at 95%.(17)

Neonatal morbidity has been recorded ranging from 8%-61% (2,7,10,19) with the commonest morbidities being neonatal sepsis, RDS, NEC, hyperbilirubinemia, PDA and IVH. Other complications include pulmonary hypoplasia, fetal infection, low birth weights (LBWs) and fetal deformation(40).

Other parameters determining neonatal mortality include APGAR scores at 5min of less than 7 (3,13), need for surfactant and ventilator support and NICU admission rates which range from 20%-72.9% (2,13,19).

RDS is a common complication accounting 11-54% of the neonatal morbidities (2,19,42).

2.1 CONCEPTUAL FRAMEWORK

2.1.1. NARRATIVE

Preterm newborns account for 8-10% of live births but are accountable for 90% of neonatal morbidity. The 24-34 weeks' gestation preterm is an important population of study due to the associated morbidity and mortality in this age group, the need to delay the delivery i.e. to prolong the latency period in order to improve the neonatal outcomes becomes an important factor.

Studies have demonstrated several risk factors associated with the causation of PPROM however there still remains a challenge in prevention of PPROM because of its multifactorial causation. Factors that have been investigated and therefore associated with occurrence and duration of PPROM are low socioeconomic status, cervical insufficiency, ante partum bleeding, previous history of PPROM, caesarean section, abortions & preterm births.

The underlying factor influencing the duration of latency being dependent on the gestation, parity, degree of oligohydramnios, cervical dilation on admission, presence of uterine contractions, presence of infection and also to some extent the interventions employed in its management.

Interventions have been made to better the outcomes of patients managed with PPROM and this is a great step however the morbidity and mortality in the study groups still remain high and more exploration in terms of local studies remain needful.

Evidence demonstrates the use of antibiotics in a patient with PPROM prolong the latency period and therefore improves outcomes. Corticosteroids use in PPROM at 24-34 weeks have demonstrated a decreased risk of IVH, RDS and NEC.

Exploration of the associated risk factors for causation, the course of latency and its outcomes both to the mother, fetus and neonate will bring to light some information that can be useful in the future management of this patients.

2.1.2. SCHEMATIC CONCEPTUAL FRAMEWORK

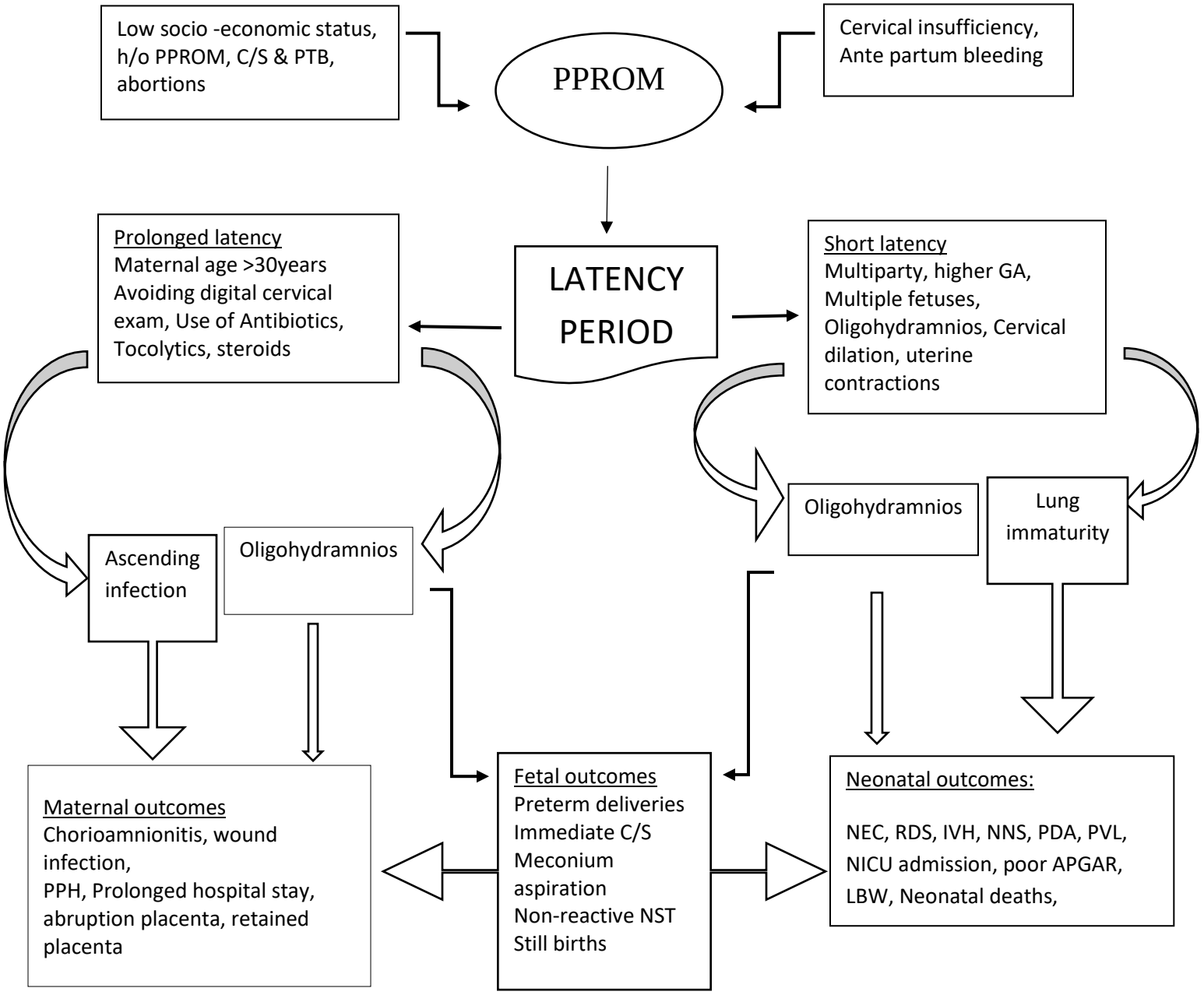


Figure 1: Conceptual Framework

2.2. STUDY JUSTIFICATION

Latency duration is important for it determines the maternal and neonatal outcomes.

Latency in other settings range from 3.6- 7.8 days (SD 8.5). This information is missing in our setting.

Inaccuracy in the prediction of the latency period for women with PPROM is a challenge and hence consulting these women on their expected latency is a hard task. It is therefore important to have a study that would estimate the overall duration of latency and also per the gestation age in order to have some data that would be useful to advice accordingly.

Patients with PPROM are advised to record a fetal kick chart and to monitor vulval pads for fluid amount, color and smell. These measures among others are to aid identify possible complications during their management and knowledge of the various outcomes of management in our region would guide the clinicians to enlighten the patients on the likely outcomes and complications.

The study will reveal some data on perinatal outcomes with age specific perinatal mortality rates which would be helpful in the counseling of these patients.

Most references on latency period, perinatal and maternal outcomes are from studies done abroad and there is paucity of local data.

Several interventions have been instituted to manage PPROM in our institution and locally. It is important to know how we fare in terms of our interventions. The findings of this study will seek to answer how helpful these interventions have been.

Further, no prior studies have been done to determine factors of association in relation to prolonged latency in this setting. So this study will enlighten us on any key associations.

2.4. RESEARCH QUESTION

What is the latency period, perinatal and maternal outcomes in conservatively managed patients with PPROM at 24-34 weeks' gestation at KNH?

2.5. OBJECTIVES OF STUDY

2.5.1 Broad objective

To describe the latency period, perinatal and maternal outcomes in conservatively managed patients with PPROM at 24-34 weeks' gestation at KNH in 2019.

2.5.2 Specific Objectives

Among conservatively managed patients with PPROM at 24-34 weeks of gestation at KNH in 2019,

- **Primary objectives**

1. To estimate the overall mean latency period and the mean by gestation at which PPROM occurred.

2. To determine the perinatal morbidity and mortality rate

3. To determine the incidence of maternal morbidity and mortality

- **Secondary objectives**

1. To determine factors associated with prolonged latency at > 72 hours and > 7 days

2. To determine if prolonged latency at > 72 hours and > 7 days is associated with adverse perinatal and maternal outcomes

3.0 CHAPTER THREE: METHODOLOGY

3.1. STUDY DESIGN

This was a retrospective descriptive cohort study in which records of 143 women who were managed conservatively for PPROM at 24-34 weeks and 165 neonates born to these mothers between 1st January-31st December 2019 were reviewed. The retrospective cohort nature was very efficient in the study as a large number of paired maternal and neonatal files were studied within a short while. Additionally, since we dealt with files, the participants had no intervention instituted, therefore giving a true representation of the study findings. Conservative management entailed use of adjunct antibiotics, induction of fetal lung maturation and use of tocolytics while monitoring for any fetal or maternal compromise.

3.2. STUDY AREA DESCRIPTION AND SPECIFIC STUDY SITE

KNH is the national referral hospital in Kenya and it is situated in the capital city, Nairobi. Other than being the primary hospital for many locals of Nairobi, it receives referrals for complicated obstetric conditions, including PPROM from the entire country. KNH is the training facility for postgraduate and undergraduate students of the college of health sciences, of University of Nairobi. The Kenya Medical Training College (KMTC) also trains students undertaking various diploma courses in the medical field at KNH.

The study site was at the Kenyatta National Hospital's Record's department.

KNH has one labor unit, three antenatal/post-natal units (GFA, GFB and 1A) and a newborn unit. The labor unit has a capacity of 50 beds, while the antenatal/Postnatal units each has a capacity of 50 beds. Labor unit provides delivery services to about 1300 women per month. The number of PPROM patients at 24-28 weeks is averaged at 12 per month and 144 per year.

It is in labor ward that all pregnant women at 20 weeks and above are triaged for admission to either labor ward or the antenatal wards depending on their diagnoses.

A nurse at triage takes vitals and fetal assessment and works in consultation with the registrar in labor ward. For PROM patients, a sterile speculum examination is done at the triage room and further review is done and treatment instituted. Patients in labor or in need of acute care are admitted to labor ward. It is at this point that a patient is assigned to a nurse; one nurse can be assigned 7-10 patients per shift. Management is further based on the standard practice of

management of PPROM at KNH. Following delivery, the neonates are examined by a pediatric registrar in consultation with a neonatologist on call concerning further management including admission to NBU.

NBU has a capacity of 50 beds and reports 1000 admissions per month. All preterm newborns with a birth weight short of 2000 grams, neonates with morbidities like RDS, NEC and neonatal sepsis are admitted to NBU.

At KNH, the laboratory and radiologic services are provided 24 hours in a day, so any investigation can be effected upon admission or when deemed necessary in the course of patient management in the unit. This collaborative support from different departments and its expertise make the site suitable for my study.

3.3. STUDY POPULATION

3.3.1 Population characteristic and definition of cohort

The study population included patients who were conservatively managed for PPROM at 24-34 weeks' gestation. This included both the singleton and multiple gestation. The neonates of this women were also followed up.

The gestation was established from LMP and a 1st or early 2nd trimester scan. Pregnant women with drainage of liquor, confirmed by speculum examination by a clinician, and admitted for conservative management of PPROM were followed up till delivery and their neonates followed up during their neonatal period. Ultrasound findings on amount of liquor, gestation and cervical status like dilatation and length were documented.

3.3.2. Inclusion criteria

For a patient's record to be eligible for inclusion, these characteristics must have been present

- Spontaneous membranes rupture at 24-34 weeks of gestation
- Singletons and multiple gestations
- Confirmed fetal viability when decision was made for conservative management

3.3.3. Exclusion criteria

Those excluded from the study were

- Patients presenting with chorioamnionitis, APH, NRFS, Abruptio placentae, cord prolapse or active labor

- Incomplete records for key variables
- Delivery within 4 hours of admission
- Patients whose diagnosis of PPROM was ruled out during the course of admission

3.4. SAMPLE SIZE DETERMINATION

3.4.1 Sample Size determination from objective 1 on establishing mean latency period.

The Fisher's formula (Daniel, 1999), was used to calculate the sample size.

$$\boldsymbol{n = \frac{(Z_{1-\propto/2})^2 SD^2}{d^2}}$$

Where,

n = Desired sample size

$\boldsymbol{Z_{1-\frac{\alpha}{2}}}$ = value from standard normal distribution corresponding to desired confidence level (Z=1.96 for 95% CI)

$\boldsymbol{SD}$ = Standard deviation taken from a study (Seema *et al (2012)* India, study found a mean latency period of 4.8 days and standard deviation of 6.6)

$\boldsymbol{d}$ = Precision (the average differences of the means from various studies looking at latency period)

$$\boldsymbol{n = \frac{(1.96)^2(6.6)^2}{2^2} = 42}$$

42+4.2 (10%) = 46

A sample size of **46** patients was required for the study after an addition of 10% attrition rate for patient's files with incomplete data.

3.4.2. Sample size determination from objective 2 looking at perinatal mortality and morbidity

The Fisher's formula (Daniel, 1999), was used to calculate the sample size.

$$n = \frac{Z^2 xP(1-P)}{d^2}$$

Where,

n = Desired sample size

Z = value from standard normal distribution corresponding to desired confidence level (Z=1.96 for 95% CI)

P = expected true proportion (estimated at *7.4* %, from a study conducted by Yu et al (2014) China; looking at 624 neonates born to women with PPROM, found *46* were neonatal deaths).

d = desired precision (0.05)

$$n_0 = \frac{1.96^2 x\ 0.074(1-0.074)}{0.05^2}$$

N=105+11(10%) = 116

A Sample size of **116** was required for the study after an addition of 10% attrition rate for patient's files with incomplete data.

3.4.3 Sample size determination from objective 3, looking at maternal morbidity and mortality

The Fisher's formula (Daniel, 1999), was used to calculate the sample size.

$$n = \frac{Z^2 xP(1-P)}{d^2}$$

Where,

n = Desired sample size

Z = value from standard normal distribution corresponding to desired confidence level (Z=1.96 for 95% CI)

P = expected true proportion (estimated at *9* %, from a study conducted by Frenette et al (2013), France; looking at 866 women with PPROM, found *78* of them had chorioamnionitis).

d = desired precision (0.05)

$$n_0 = \frac{1.96^2 x\ 0.09(1-0.09)}{0.05^2}$$

N=125.8 plus 12.5 (10%) = 138

A Sample size of **138** was required for the study after an addition of 10% attrition rate for patient's files with incomplete data.

CONCLUSION

Consideration of the 3 samples established from the three objectives, the largest sample size was considered for the study so that it was sufficient to analyze the other objectives. Sample size was **138**, and we studied **143 files.**

3.5. SAMPLING PROCEDURE

Consecutive sampling method was used to achieve the study sample.

A sampling frame was used containing inpatient numbers of all patients who were admitted and managed conservatively for PPROM at 24-34 weeks of gestation during the retrospective study period. These files were retrieved for data collection. All files that fit the inclusion criteria were considered starting from 31st December 2019 backwards.

The in-patient numbers of the files that fit the inclusion criteria were recorded and these numbers were matched to the newborn in patient numbers manually from the newborn registers or electronically from the mother's electronic record. These numbers were recorded into a sampling frame and retrieval was done from the records department.

3.6 SOURCES AND METHODS OF RECRUITMENT

3.6.1. SOURCES OF RECRUITMENT

Study participants were identified from the Labor wards triage and admission registers because all women requiring admission at KNH and are above 20 weeks of gestation are admitted through labor ward. In-patient numbers of all patients who had PPROM at 24-34 weeks were recorded and submitted to the records department for retrieval of the files upon Ethical approval, obstetrics, Paediatric and health records department approval to access patient's records. The files were checked for eligibility into the study. Pairing of neonatal files for patients who qualified for the study was done and the files were retrieved from the records department for data collection.

3.7. VARIABLES MEASURED

The study variables were summarized in the following table

Independent variables			**Dependent variables**	
1.	Socio-demographic characteristics:		1.	Latency period
	Maternal age, Parity, Marital status, Educational level.			Latency at <72 hours, Latency 72 hours- 7 days, Latency of > 7 days
2.	Gestation age		2.	Perinatal outcomes
	24-28 weeks 28+1 -32 weeks 32+1 -34 weeks			APGAR at 5 min, birth weight, gender, admission to NBU NEC, RDS, IVH, NNS, Hyperbilirubinemia, PVL, NICU admission, neonatal deaths and Still births (MSB, FSB)
3.	Conservative management		3.	Maternal outcomes
	Antibiotics Tocolytics, Corticosteroids Magnesium sulphate			Maternal sepsis; (Chorioamnionitis, septicemia, peritonitis, wound infections), PPH, abruption placenta, retained placenta, C/S rates, hospital admission stay.

3.7.1 Outcome variables study definitions

Dependent variable	**Study definition**
NEC	History of inability to tolerate feeds, bloody stools, or abdominal distention. Abdominal x-ray; bubbly appearance/air in peritoneal cavity/lack of gas in abdomen

RDS	Chest in drawing, grunting, cyanosis, tachypnea, infants who required ventilator support for at least 24 hours. Those in needing oxygen therapy and those who had positive CXR findings
IVH	Apnea, bradycardia, cyanosis, Neonatal cranial ultrasound revealing bleeding.
NNS	2 signs of either temperature >38/ <36.5, tachycardia of >200b/min and Increased oxygen requirement/ Positive blood cultures/ CSF cultures/ and treatment with antibiotics for 5 days /positive CRP
Hyperbilirubinemia	Jaundice requiring phototherapy and or exchange transfusion, bilirubin levels per bilirubin percentile chart.
PVL	Periventricular white-matter; echolucencies on ultrasonography
Maternal sepsis; Chorioamnionitis	Any 3 of the following Temperature > 38°C/ Tachycardia >110/ Persistent fetal tachycardia> 160/ Bradycardia of <120/ tender uterus. Raised CRP levels / Foul smelling vaginal discharge/ Leukocytes of >15,000 cells /mm3
Septicemia	Positive blood cultures
Peritonitis	Tender abdomen, abdominal distension, reduced or absent bowel sounds
Wound sepsis	Purulent discharge from wound site/ Surgical wound requiring exploration
PPH	Blood loss of > 1000 following SVD or C/S

For neonatal diagnosis: The study used the doctor's diagnosis recorded in the case notes or cardex.

For maternal diagnosis: The study considered the doctor's diagnosis or the above diagnostic criteria.

3.8. DATA COLLECTION PROCEDURE AND INSTRUMENTS

3.8.1. Data collection procedure

All patients' case notes were in the health records department. Following approval by the Ethics and review committee, approval was sought from the departments i.e. pediatrics and reproductive health who gave approval letters to be submitted to the health records department. A record officer was assigned to retrieve the files for the principal investigator and research assistant.

3.8.2. Data collection instruments

Data on all exposure variables and outcomes of interest were extracted from the patients records; maternal and neonatal case notes, nursing cardex, treatment sheets and laboratory report forms. Antenatal, delivery and nursery admission books were checked for any additional information.

A data abstraction form was used to collect data. The form contained the key variables for the study; the patient's particulars, the clinical and obstetric characteristics, the neonatal outcomes and the management administered. For every patient's case note retrieved, the principal investigator and research assistants filled in data based on information obtained from the patients' records.

3.9. DATA MANAGEMENT AND DATA ANALYSIS METHODS

3.9.1. Data management

The principal researcher worked with two research assistants to collect data, these were a registered clinical officer and a registrar in obstetrics and gynecology whom both had experience with managing obstetric women.

3.9.2 Quality assurance

Quality assurance was ensured by the principal investigator training the research assistants on study protocol and procedures before commencement of data collection and entry. This was done a week prior to commencement of data collection and continued during the data collection time till the principle investigator was confident about their competence in data collection and entry.

3.9.3 Data validation and reliability

Information collected from the data abstraction forms was double checked for completeness.

The principal investigator rechecked every tenth abstraction form filled by the research assistants to ensure optimal standards of data entry.

Any missing data were completed by rechecking the patient case notes. All collected data were de-identified and anonymized. Data were then entered into Microsoft excel spread sheet.

It was cleaned using statistical software to inspect each variable in the database for completeness, validity and cross validation of entries in related variables.

3.9.4 Data storage

All filled abstraction forms were stored safely. Data was stored in a password protected external storage device and only the principal investigator and statistician and the supervisor had privy to the information. The data will be stored and accessed for a period of 3 years from time of data collection. Thereafter the data will be discarded after 3 years' period has elapsed.

3.9.5 Data sharing and access

Data will be shared with uttermost confidentiality. Once it is processed, the principal investigator plans to publish the findings and this will then be accessed from medical journal sites.

3.9.6 Data analysis

Data were analyzed using Statistical Package for Social Sciences.

Latency was defined as the time from spontaneous rupture of membranes to time of delivery. The mean and median latency period was estimated as a mean with standard deviations or a median with an interquartile range.

Perinatal morbidity was estimated as the total morbidity per the total study population, while the perinatal mortality rate was calculated as the number of fetal and early neonatal deaths (within 7 days of life)/per 1000 total births following PPROM.

In addition, we evaluated factors associated with prolonged latency (at a cut-off of > 72 hours and > 7 days) and if prolonged latency was associated with adverse perinatal and maternal outcomes. A p-value of <0.05 was considered statistically significant.

Categorical data were analyzed and presented as percentages and frequencies.

Continuous variables were summarized and presented in the form of means with standard deviations or medians with an interquartile range where applicable.

Factors associated with the latency period were subjected to bivariate analysis using the Chi-squared test and t-test for categorical and continuous variables respectively. The odd ratios and the corresponding 95% Confidence Interval were obtained. Multivariate analysis, adjusted odds ratio and corresponding (95% CI) was obtained.

Statistical significance was only regarded if the P-value was < 0.05. Data presentation was in the form of charts, box plot, graphs, and tables.

A summary of data analysis is presented in the following table

Objectives		**Analysis**
1	Latency period	Summarized and presented as means with standard deviations
2	a) Perinatal morbidities	Total no. of a morbidity/Total morbidities*100 Morbidities include NEC, RDS, IVH, NNS, Hyperbilirubinemia, PVL and PDA

	b) Perinatal mortality rate	PMR= Fetal (>28/40) and early neonatal deaths (<7/7)/total births (live and dead) *1000
3	a) The incidence of maternal morbidity	I= No. of patients with morbidities/ Total No. of patients*100 Morbidities; Sepsis, PPH, abruption placenta, retained placenta.
	b) The incidence of maternal mortality	I= No. of patients who died/total No. of patients*100 NB; This is during the 1 year study period
4	Factors of association	Bivariate analysis using the Chi-squared test and t-test for categorical and continuous variables respectively to obtain odds ratio and corresponding 95% CI
5		A multivariate analysis using general linear regression models to obtain adjusted odds ratio and corresponding 95% CI

3.10. ETHICAL CONSIDERATION

Data collection was commenced after Permission to conduct study was granted from KNH-UoN Ethics and Research committee.

Permission was also sought from KNH Reproductive health, Paediatrics department and Heath records department after ERCs approval.

The records were stored in the health records department and were only accessible to principal investigator and the research assistants.

The data collection took place within the health records' department premise. No one was allowed to leave with any case notes. The collected data were kept in a computer with a password lock and the data were only accessed by the principal investigator, research assistants, statistician and supervisors.

Analyzed data were kept with strict compliance of confidentiality.

Confidentiality was maintained at all times with anonymity to patient details and abstraction forms allocated study numbers. Only the investigators accessed data for the purpose of the study.

3.11. STUDY RESULTS DISSEMINATION PLAN

On completion of the study, the results were first presented at the department of Obstetrics and gynecology for review. Feedbacks will be shared with the study facility stakeholders through a CME. The recommendations from the feedbacks will be incorporated in the final report before publishing of the manuscript in peer reviewed journal.

4.0 RESULTS

Between January and December 2019, 514 files for women who had PPROM in 2019 were screened. A total of 143 (27.8 %) maternal files and 165 neonatal files were eligible. Of these eligible files 122 were singletons and 21 were multiple pregnancies.

The ineligible files were 371, these comprised of those who had PPROM at less than 24 weeks or more than 34 weeks, those who had emergent need for delivery, those with incomplete records,

those who were managed for PPROM beyond 34 weeks, some patients were lost to follow up and some did not have conservative management, and some the neonatal files were missing or had incomplete data thus these were excluded too.

Participants were recruited as per the flow chart below

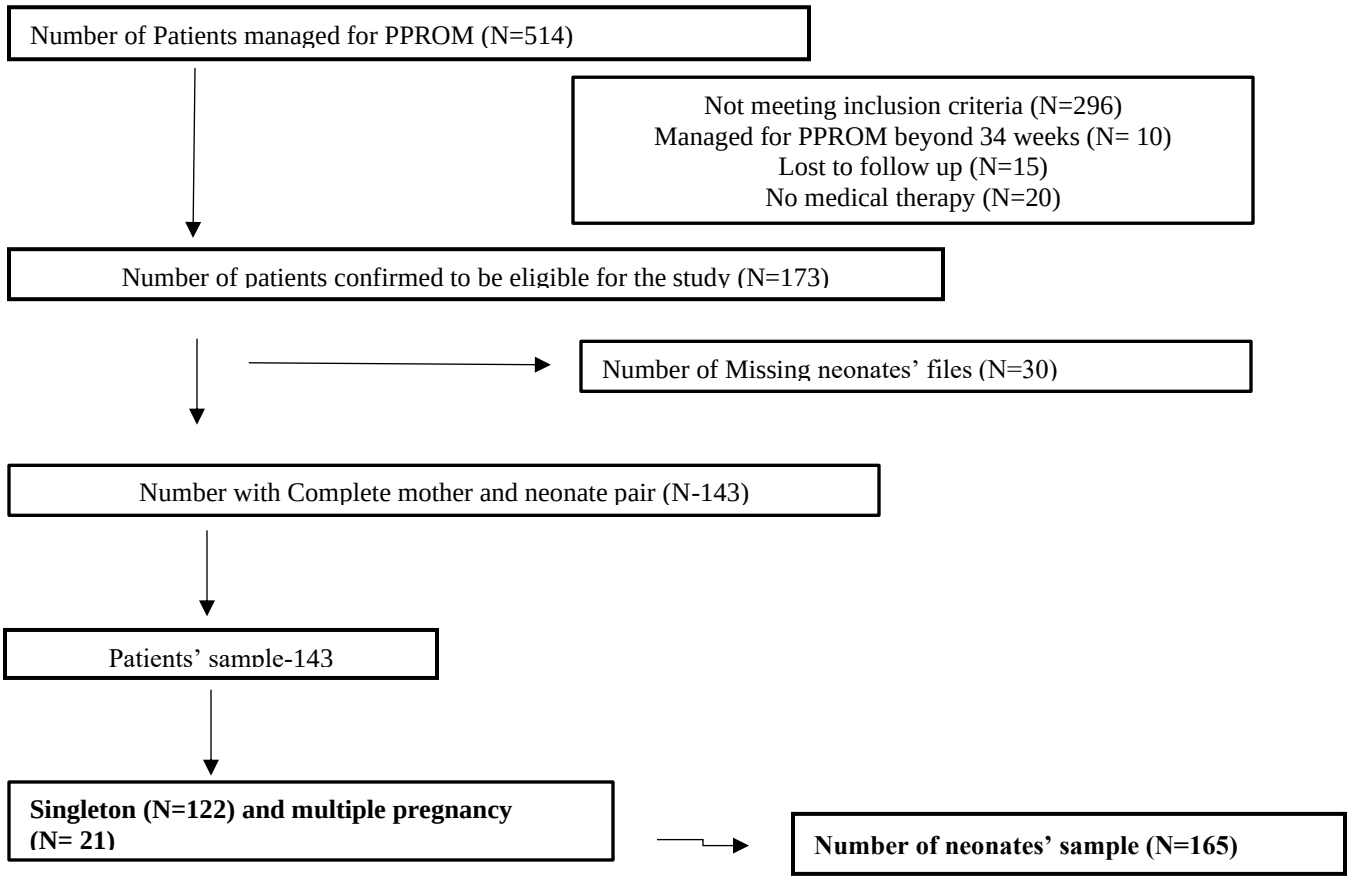


Figure 2: Flow chart showing recruitment of participants

4.1. Socio-demographic characteristics of patients managed conservatively for PPROM at 24-34 weeks' gestation at KNH in 2019.

Table 1:Maternal socio-demographic characteristics of patients managed conservatively for PPROM at 24-34 weeks' gestation at KNH in 2019.

Socio-demographic characteristics		**Frequency (n=143)**	**Percent (%)**
Age	<20	7	4.9
	20-29	82	57.3
	30-39	46	32.2
	40+	8	5.6
Marital status	Single	22	15.4
	Married	121	84.6
Education	None	2	1.4
	Primary	25	17.5
	Secondary	53	37.1
	Tertiary	63	44.1

The mean age of participants was 28.4 (± 6.3) years while the median age was 27 (IQR 23.0 – 33.0) years.

As shown in table 1 above, the women aged 20-29 were the majority at 82 (57.3%), the least number of women was noted at 40 years and above age group who were only 8 (5.6%). The majority of the women were married 121(84.6%) and more women had tertiary education 63 (44.1%).

4.2 Clinical characteristics of patients managed conservatively for PPROM at 24-34 weeks' gestation at KNH in 2019

Table 2: Clinical characteristics of patients managed conservatively for PPROM at 24-34 weeks' gestation at KNH in 2019

Clinical characteristics		Frequency (n=143)	Percentage (%)
Parity	Primiparous	54	37.8
	Multiparous	89	62.2
Gestation	Singleton	122	85.3
	Multiple	21	14.7
Gestation age at PROM	24 – 28	27	18.9
	28+1 – 32	63	44.1
	32+1 – 34	53	37.1
Gestation age at birth	24 – 28	14	9.8
	28+1 – 32	60	42.0
	32+1 – 34	69	48.3
Mode of delivery	SVD	68	47
	CS	75	53

The mean gestation at PPROM and at delivery was 30.1 (± 2.7) and 31.1 (± 2.3) weeks respectively.

As shown in table 2 above, the gestation age at PROM between 28+1- 32 weeks was 63 (44%), at 24-28 weeks and 32+1-34 weeks were 27(18.9%) and 53(37.15) respectively. This pattern of occurrence changed when it was time for delivery whereby those between 32+1-34 had a bigger population 69 (48.3%) and the least number were those at 24-28 weeks who were 14 (9.8%).

The mode of delivery differed with a small margin as the SVD were 68(47%) and cesarean delivery were 75(53%).

The multiparous women were the majority at 89 (62.2%) while the primiparous were 54 (37.8%)

4.3 Latency in patients managed conservatively for PPROM at 24-34 weeks' gestation at KNH in 2019

Table 3:The mean and median duration of latency by gestation of patients managed conservatively for PPROM at 24-34 weeks at KNH in 2019 stratified by preterm gestational age.

Gestation at PROM	Frequency (n=143)	Mean (SD)	Median (IQR)	Min days	Max days
24-34	143	6.7 (± 8.5)	(IQR 1.2 – 7.5)	0.2	56
24 – 28	27	15.1 (13.2)	11.0 (4.5 – 24.5)	1.0	56.0
28+1 – 32	63	6.1 (6.7)	4.0 (1.5 – 7.5)	0.2	31.0
32+1 – 34	53	3.1 (2.4)	1.0 (1.2 – 5.0)	0.3	10.0

As shown in table 3 above, the overall mean latency in patients managed conservatively for PPROM at 24-34 weeks' gestation at KNH in 2019 was 6.7 (± 8.5) days while the median latency was 4.0 (IQR 1.2 – 7.5) days.

Stratification by preterm gestational age was done. The longest latency was in the lowest gestation of 24-28 weeks, which was 15.1 (± 13.2). Of note the longest latency was 56 days. At 28+1-32 weeks; the mean latency at this gestation was 6.1 (± 6.7) and the longest latency was 31days. The shortest latency was noted in the highest gestation 32+1 – 34 weeks, it was 3.1 (± 2.4) days with the longest latency of 10 days.

Box plots showing the distribution of patients at PRROM and at delivery in the different gestations when PPROM occurred.

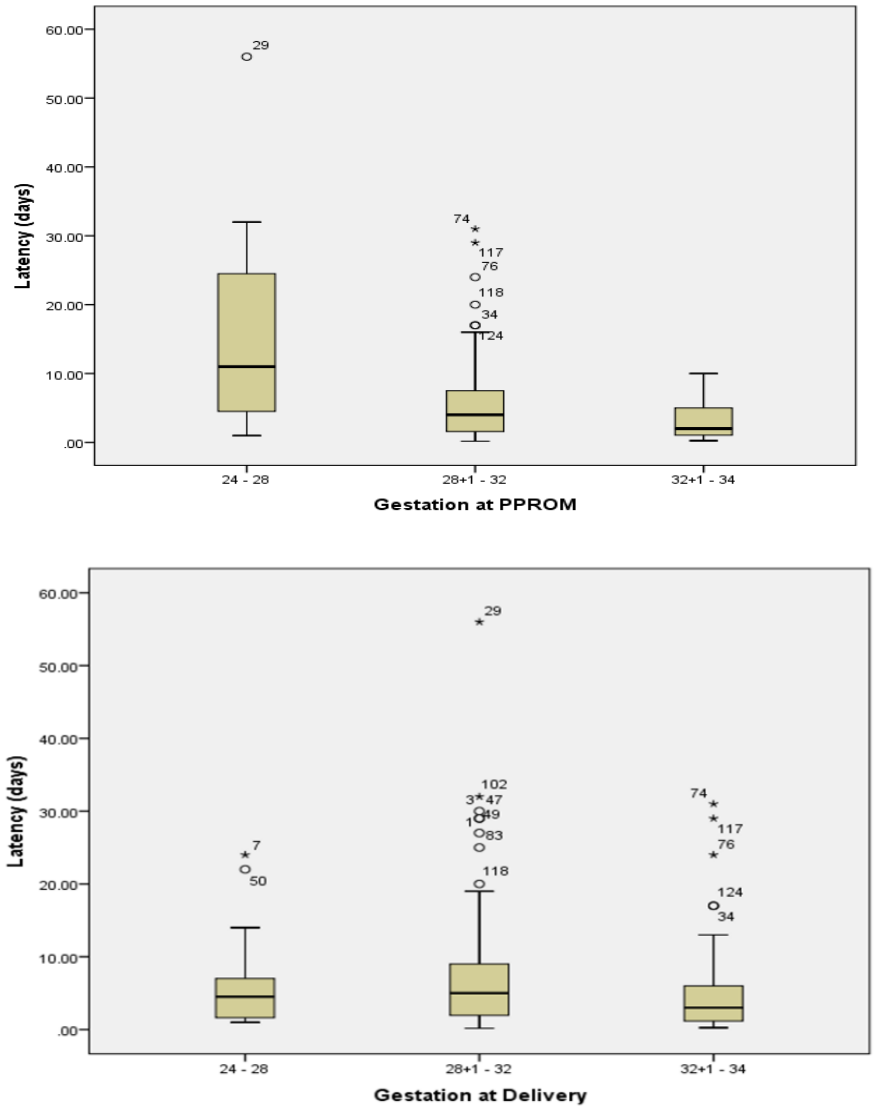


Figure 3: Box plot figure showing latency in days per gestation at PPROM and at delivery

The box plots illustrate the distribution of patients in the different gestation at the point of PPROM and at delivery. Of note are the few outliers that are represented by numbers.

4.4. Perinatal outcomes of patients managed conservatively for PPROM at 24-34 weeks' gestation at KNH in 2019

Table 4: Perinatal outcomes of patients managed conservatively for PPROM at 24-34 weeks' gestation at KNH in 2019.

Perinatal outcome		N 165	% percentage
Neonatal sex	Male	91	55.2
	Female	73	44.2
	Ambiguous genitalia	1	0.6
Status at birth	Live births	152	92.1
	Still births	13	7.8
Status at discharge	Alive	113	68.4
	NND	39	23.6
	Still births	13	7.8

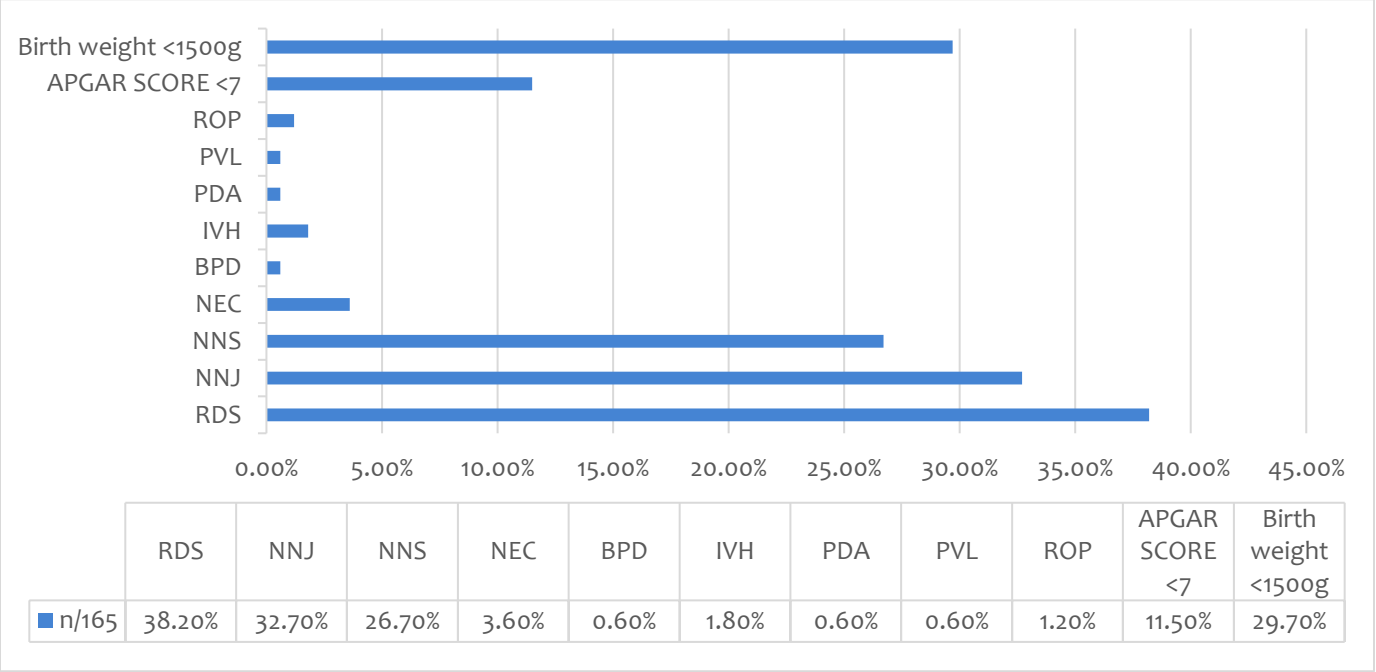
The perinatal outcomes are as shown on table 4 above. Majority were male 91 (55.2%) and there was one case of ambiguous genitalia. There were 152 (92.1%) neonate live births. Of these, 113 (68.4%) were discharged alive while 39 (23.6%) ended as neonatal deaths. There were 13 stillbirths 13 (7.8%).

NICU admission days	Mean	4.0 days	(SD 3.3)
	Median	3 days	(IQR 1.0 – 6.0)
NBU admission days	Mean	17.4 days	(SD 15.4)
	Median	13 days	(IQR 5.5)

The mean (±standard deviation) stay in NICU was 4(± 3.3) days, while mean stay at the New Born Unit was 17.4 (± 15.4) days

4.5. Perinatal morbidity outcomes in patients managed conservatively for PPROM at 24-34 weeks' gestation at KNH in 2019

The overall perinatal morbidity was 104 (63 %) and the specific perinatal morbidities as shown in the bar graph below.



	RDS	NNJ	NNS	NEC	BPD	IVH	PDA	PVL	ROP	APGAR SCORE <7	Birth weight <1500g
n/165	38.20%	32.70%	26.70%	3.60%	0.60%	1.80%	0.60%	0.60%	1.20%	11.50%	29.70%

Figure 4: Perinatal morbidities in patients managed conservatively for PPROM at 24-34 weeks' gestation at KNH in 2019

Specifically, 63(38.2%,) neonates had Respiratory Distress Syndrome (RDS), 54(32.7%) neonates had Neonatal Jaundice (NNJ), 44(26.7%) neonates had Neonatal Sepsis (NNS), 6(3.6 %,) neonates had Necrotizing enterocolitis (NEC), 1(0.6%,) neonates had Bronchopulmonary Dysplasia (BPD), 3(1.8%,) neonates had Intraventricular hemorrhage (IVH), 1(0,6%,) neonate had Patent ductus arteriosus (PDA), 1 (0.6%,) neonate had Periventricular Leucomalacia (PVL) and 2 (1.2%,) neonates had retinopathy of prematurity (ROP). There were 19(1.5%) of neonates who had an APGAR score of <7 and 49(29%) neonates had a birth weight of <1500g.

4.6. Perinatal mortality in patients managed conservatively for PPROM at 24-34 weeks' gestation at KNH in 2019.

Table 5: Perinatal mortality rate per gestation groups of patients managed conservatively for PPROM at 24-34 weeks at KNH in 2019 stratified by preterm gestational age.

Gestation	No. dead	PMR
24-34	41	193 (CI, 171-220) * 248 (CI,211-273)
24-28	11	66
28+1 -30	9	54
30+1 -32	12	68
32+1 -34	9	54
Total	41	248 (CI,211-273)

*Considering WHO recommended cut off at >28 weeks' gestation; Perinatal Mortality Rate (PMR) = 193/1000 (Confidence interval (CI), 171 - 220)

Considering the cut off >24 weeks' gestation; Perinatal Mortality Rate (PMR) = 248/1000 (Confidence interval (CI), 211 - 273).

Neonatal Mortality Rate (NMR) = 212/1000 (CI, 157 -271)

Still Birth Rate =78/1000 (CI, 64 -92)

4.7. Adverse maternal outcomes in patients managed conservatively for PPROM at 24-34 weeks' gestation at KNH in 2019.

The overall maternal morbidity was 18.9%. There was no maternal mortality recorded.

The specific maternal morbidities of interest and the incidence is shown in the pie chart below. The leading morbidity was chorioamnionitis 9(6.3%) followed by cord prolapse7(4.9%) and Abruptio placentae at 3(3.4%). Other morbidities included post-partum hemorrhage 3(2.1%) and retained placenta1(0.7%).

The mean (±standard deviation) hospital stay for the women managed conservative for PROM was 7.8 (±7.2) days, and the median (IQR) was 5.0 (4.0 – 9.0) days.

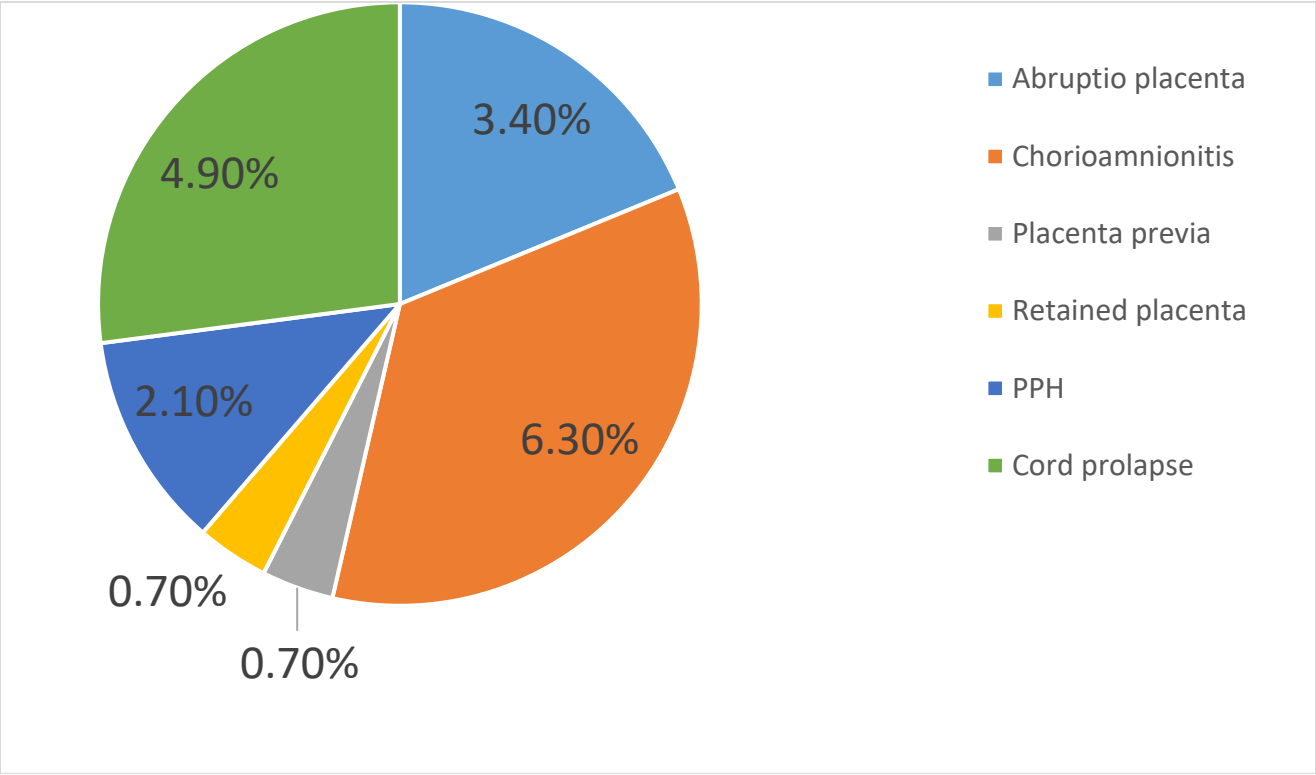


Figure 5: Maternal morbidities in patients managed conservatively for PPROM at 24-34 weeks' gestation at KNH in 2019.

4.8. Factors associated with prolonged latency at > 72 hours and > 7 days in patients managed conservatively for PPROM at 24-34 weeks' gestation at KNH in 2019

4.8.1 Maternal sociodemographic factors associated with prolonged latency at > 72 hours and > 7 days in patients managed conservatively for PPROM at 24-34 weeks' gestation at KNH in 2019

Table 6: maternal sociodemographic factors associated with prolonged latency of > 72 hours and > 7 days

		n	≥72hrs	<72hrs	COR(95% CI)	p-value	AOR(95% CI)	p-value
Age	<20	7	5 (5.6)	2 (3.7)	Reference		Reference	
	20-29	82	53 (59.6)	29 (53.7)	0.7 (0.1 – 4.0)	0.718	1.0(0.1-7.1)	0.988
	30-39	46	27 (30.3)	19 (35.2)	0.6 (0.1 – 3.2)	0.525	0.7(0.1-5.8)	0.741
	40+	8	4 (4.5)	4 (7.4)	0.4 (0.1 – 3.4)	0.403	0.5(0.1-5.9)	0.575
Marital status	Single	22	16 (18.0)	6 (11.1)	1.8 (0.6 – 4.8)	0.274	17(0.6-5.5)	0.338
	Married	121	73 (82.0)	48 (88.9)	Reference		Reference	
Parity	Primiparous	54	34 (38.2)	20 (37.0)	1.1 (0.5 – 2.1)	0.889	0.8(0.3-1.9)	0.593
	Multiparous	89	55 (61.8)	34 (63.0)	Reference		Reference	
Education	None	2	2 (2.2)	0 (0.0)	-		-	
	Primary	25	16 (18.0)	9 (16.7)	1.2 (0.4 – 3.1)	0.749	1.1(0.4-3.1)	0.823
	Secondary	53	33 (37.1)	20 (37.0)	1.1 (0.5 – 2.3)	0.830	1.0(0.5-2.2)	0.927
	Tertiary	63	38 (42.7)	25 (46.3)	Reference		Reference	

The maternal socio-demographic factors namely age, marital status, parity and level of education were not associated with latency of >72 hours and of >7 days.

4.8.2 Clinical characteristic factors associated with prolonged latency at > 72 hours in patients managed conservatively for PPROM at 24-34 weeks' gestation at KNH in 2019

Table 7: clinical characteristics associated with prolonged latency of > 72 hours in patients managed for PPROM at 24-34 weeks' gestation

		n	≥72hrs	<72hrs	OR(95% CI)	p-value	AOR	P-value
Parity	Primiparous	54	34 (38.2)	20 (37.0)	1.1 (0.5 – 2.1)	0.889	0.8(0.3-1.9)	0.593
	Multiparous	89	55 (61.8)	34 (63.0)	Reference		Reference	
Gestation age at PROM	24 – 28	27	23 (25.8)	4 (7.4)	6.4 (2.0 – 21.2)	**0.002**	-	
	28+1 – 32	63	41 (46.1)	22 (40.7)	2.1 (1.0 – 4.4)	0.054	3.6(0.7-17.3)	0.111
	32+1 – 34	53	25 (28.1)	28 (51.9)	Reference		Reference	
Gestation age at delivery	24 – 28	14	10 (11.2)	4 (7.4)	2.0 (0.6 – 7.1)	0.265	-	
	28+1 – 32	60	41 (46.1)	19 (35.2)	1.8 (0.9 – 3.6)	0.125	0.6(0.1-2.7)	0.466
	32+1 – 34	69	38 (42.7)	31 (57.4)	Reference		Reference	
Steroid use	Complete	103	81 (92.0)	22 (40.7)	16.8 (6.5 – 43.2)	**<0.001**	14.5(4.9-42.8)	**<0.001**
	Incomplete	39	7 (8.0)	32 (59.3)	Reference		Reference	
Antibiotic use	Yes	122	85 (95.5)	37 (68.5)	9.8 (3.1 – 31.0)	**<0.001**	7.4(1.7-30.9)	**<0.001**
	No	21	4 (4.5)	17 (31.5)	Reference		Reference	
Tocolytics use	Yes	42	27 (30.3)	15 (27.8)	1.1 (0.5 – 2.4)	0.745	0.7(0.3-1.8)	0.418
	No	101	62 (69.7)	39 (72.2)	Reference		Reference	

Regarding latency >72 hours, there was a statistically significant association between Steroid use and antibiotic use with prolonged latency >72hours with a P value of <0.001 following bivariate and multivariate analysis, of note no adjustments for confounders was made in the multivariate analysis. Prolonged latency >72hours showed a statistically significant association with gestation at PROM in bivariate analysis with a p value of <0.002. Parity, gestation age at birth and tocolytic use were not associated with prolonged latency of >72hours.

4.8.3 Clinical characteristics factors associated with prolonged latency of> 7 days in patients managed conservatively for PPROM at 24-34 weeks' gestation at KNH in 2019

Table 8: clinical characteristics associated with prolonged latency of > 72 hours in patients managed conservatively for PPROM at 24-34 weeks' gestation

		n	≥7 days	<7 days	OR (95% CI)	p-value	AOR(95%CI)	P-value
Gestation age at PROM	24 – 28	27	17 (41.5)	10 (9.8)	20.8(5.8– 75.2)	**<0.001**	-	
	28+1 – 32	63	20 (48.8)	43 (42.2)	5.7 (1.8 – 18.0)	**0.003**	16.5(3.6-75.4)	**<0.005**
	32+1 – 34	53	4 (9.8)	49 (48.0)	Reference		Reference	
Gestation age at delivery	24 – 28	14	4 (9.8)	1	1.7 (0.5 – 6.4)	0.415	-	
	28+1 – 32	60	24 (58.5)	36 (35.3)	2.9 (1.3 – 6.4)	**0.009**	0.2(0.1-0.9)	**0.028**
	32+1 – 34	69	13 (31.7)	56 (54.9)	Reference		Reference	
Steroids use	Complete	103	36 (90.0)	67 (65.7)	4.7 (1.5– 14.3)	**0.006**	2.5(0.6-9.9)	0.198
	Incomplete	39	4 (10.0)	35 (34.3)	Reference		Reference	
Tocolytics use	Yes	42	12 (29.3)	30 (29.4)	1.0 (0.4 – 2.2)	0.986	0.8(0.3-2.4)	0.715
	No	101	29 (70.7)	72 (70.6)	Reference		Reference	
Antibiotics use	Yes	127	41(100.0)	81 (79.4)	-		-	
	No	17	0 (0.0)	21 (20.6)				
Magnesium sulphate use	Yes	19	5 (12.2)	14 (13.9)	0.9 (0.3 – 2.6)	0.792	1.2(0.2-5.6)	0.830
	No	123	36 (87.8)	87 (86.1)	Reference		Reference	

Regarding latency at >7days; there was a statistical significance between the gestation at PPROM, the gestation at delivery and steroid use on the bivariate analysis however, on multivariate analysis, latency of >7days had a statistical significance association with the gestation at PROM and the gestation at delivery. No adjustments were made for confounders in the multivariate analysis.

There was no association between latency of > 7 days and tocolytics use, magnesium sulphate use or antibiotic use.

4.9 Adverse maternal and perinatal outcomes associated with Prolonged latency of > 72 hours and > 7 days in patients managed conservatively for PPROM at 24-34 weeks' gestation at KNH in 2019

4.9.1 Adverse maternal outcomes associated with Prolonged latency of > 72 hours in patients managed conservatively for PPROM at 24-34 weeks' gestation at KNH in 2019

Table 9: Adverse maternal outcomes associated with Prolonged latency of > 72 hours in patients managed conservatively for PPROM at 24-34 weeks' gestation at KNH in 2019

		N	**≥7days**	**<7days**	**OR (95% CI)**	**P-value**	**AOR (95%)**	**P-value**
Chorioamniotis	Yes	9	3 (7.3)	6 (6.0)	1.2 (0.3 – 5.2)	0.719	2.1(0.4-11.1)	0.384
	No	132	38 (92.7)	94 (94.0)	Reference		Reference	
Abruptio placentae	Yes	3	2 (4.9)	1 (1.0)	5.1 (0.4 – 57.6)	0.203	1.2(0.1-14.1)	0.864
	No	138	39 (95.1)	99 (99.0)	Reference		Reference	
Still birth	Yes	13	4 (9.3)	9 (7.8)	1.2 (0.4 – 4.2)	0.750	1.1(0.3-3.7)	0.890
	No	146	39 (90.7)	107 (92.2)	Reference		Reference	
Cord prolapse	Yes	7	1 (2.4)	6 (6.0)	0.4 (0.1 – 3.4)	0.673	0.4(0.1-2.0)	0.264
	No	134	40 (97.6)	94 (94.0)	Reference		Reference	

Latency of > 72 hours, showed no statistically significant association with adverse maternal outcomes like Chorioamnionitis, Abruptio placentae, still birth, cord prolapse and post-partum hemorrhage.

4.9.2 Adverse perinatal outcomes associated with Prolonged latency of > 72 hours in patients managed conservatively for PPROM at 24-34 weeks' gestation at KNH in 2019

Table 10: Adverse perinatal outcomes associated with Prolonged latency of > 72 hours in patients managed conservatively for PPROM at 24-34 weeks' gestation at KNH in 2019

Adverse outcomes	With/without adverse outcomes		Latency period		OR (95% CI)	p-value	AOR(95%)	P value
		N	≥72 hours	< 7Hours				
NNS	Yes	44	28 (30.8)	16 (25.8)	1.3 (0.6 – 2.6)	0.506	0.9(0.4-2.2)	0.780
	No	109	63 (69.2)	46 (74.2)	Reference		Reference	
Neonatal death	Yes	39	22 (24.4)	17 (27.4)	0.9 (0.4 – 1.8)	0.680	1.1(0.5-2.3)	0.902
	No	113	68 (75.6)	45 (72.6)	Reference		Reference	
RDS	Yes	63	42 (46.2)	21 (33.9)	1.7 (0.9 – 3.3)	0.130	1.3(0.6-2.7)	0.506
	No	90	49 (53.8)	41 (66.1)	Reference		Reference	
PVL	Yes	1	0 (0.0)	1 (1.6)	-		-	
	No	152	91 (100)	61 (98.4)				
ROP	Yes	2	2 (2.2)	0 (0.0)	-		-	
	No	151	89 (97.8)	62 (100.0)				
NEC	Yes	6	1 (1.1)	5 (8.1)	0.1(0.01 – 1.1)	**0.040**	0.1(0.01-0.9)	**0.036**
	No	147	90 (98.9)	57 (91.9)	Reference		Reference	
Hyperbilirubinemia	Yes	53	38 (41.8)	15 (24.2)	2.2 (1.1 – 4.6)	**0.025**	2.7 (1.1-6.6)	**0.032**
	No	100	53 (58.2)	47 (75.8)	Reference		Reference	

Regarding latency >72 hours, there was a statistically significant association between latency of > 72 hours and Necrotizing enterocolitis with a p-value of 0.040 on bivariate analysis and a p-value of 0.036 on multivariate analysis. Hyperbilirubinemia also had a statistically significant association with latency of > 72 hours. neonatal death, neonatal sepsis, Respiratory distress syndrome (RDS), Periventricular Leucomalacia (PVL)and retinopathy of prematurity did not have any statistically significant association with latency at >72 hours.

4.9.3 Adverse maternal outcomes associated with Prolonged latency of > 7 days in patients managed conservatively for PPROM at 24-34 weeks' gestation at KNH in 2019

Table 11: Adverse maternal outcomes associated with Prolonged latency of > 7 days in patients managed conservatively for PPROM at 24-34 weeks' gestation at KNH in 2019

Adverse outcome	With/without Adverse outcome		Latency period					
		N	**≥7 days**	**<7days**	**OR (95% CI**	**p-value**	**AOR(95%)**	**P-value**
Chorioamniotis	Yes	9	3 (7.3)	6 (6.0)	1.2 (0.3 – 5.2)	0.719		0.522
	No	132	38 (92.7)	94 (94.0)	Reference		Reference	
Abruptio placentae	Yes	3	2 (4.9)	1 (1.0)	5.1 (0.4 – 57.6)	0.203	5.0(0.4-57.2)	0.194
	No	138	39 (95.1)	99 (99.0)	Reference		Reference	
Still birth	Yes	13	4 (9.3)	9 (7.8)	1.2 (0.4 – 4.2)	0.750	1.2(0.3-4.3)	0.766
	No	146	39 (90.7)	107 (92.2)	Reference		Reference	
Cord prolapse	Yes	7	1 (2.4)	6 (6.0)	0.4 (0.1 – 3.4)	0.673	0.4(0.1-3.2)	0.364
	No	134	40 (97.6)	94 (94.0)	Reference		Reference	

Prolonged latency of>7 days depicted no statistical significant association with adverse maternal outcomes like Chorioamnionitis, Abruptio placentae, still birth or cord prolapse.

4.9.4 Adverse perinatal outcomes associated with Prolonged latency of > 7 days in patients managed conservatively for PPROM at 24-34 weeks' gestation at KNH in 2019

Table 12: Adverse perinatal outcomes associated with Prolonged latency of > 7 days in patients managed conservatively for PPROM at 24-34 weeks' gestation at KNH in 2019

Adverse outcomes	**With/without adverse outcomes**		**Latency period**		**OR (95% CI)**	**p-value**	**AOR(95 %)**	**P value**
		N	**≥7days**	**<7days**				
NNS	Yes	42	9 (23.1)	33 (28.9)	0.7 (0.3 – 1.7)	0.478	0.6(0.2-1.5)	0.253
	No	111	30 (76.9)	81 (71.1)	Reference		Reference	
Neonatal death	Yes	39	11 (28.2)	28 (24.8)	1.2 (0.5 – 2.7)	0.673	1.2(0.5-2.8)	0.696
	No	113	28 (71.8)	85 (75.2)	Reference		Reference	
RDS	Yes	62	20 (51.3)	42 (36.8)	1.8 (0.9 – 3.8)	0.113	2.1(1.0-4.7)	0.067
	No	91	19 (48.7)	72 (63.2)	Reference		Reference	
PVL	Yes	1	0 (0.0)	1 (0.9)	-	-	-	
	No	152	39 (100)	113 (99.1)	Reference			
ROP	Yes	2	0 (0.0)	2 (1.8)	-	-	-	
	No	151	39 (100)	112 (98.2)	Reference			
NEC	Yes	6	0 (0.0)	6 (5.3)	-	-	-	
	No	147	39 (100)	108 (94.7)	Reference			
Hyperbilirubinemia	Yes	53	15 (38.5)	38 (33.3)	1.3 (0.6 – 2.7)	0.561	1.3(0.5-3.2)	0.619
	No	100	24 (61.5)	76 (66.7)	Reference		Reference	

Regarding latency at > 7 days, there was no statistically significant association between the adverse outcomes namely neonatal death, neonatal sepsis(NNS), respiratory distress syndrome (RDS), Periventricular Leucomalacia (PML), retinopathy of prematurity(ROP), necrotizing enterocolitis(NEC) and hyperbilirubinemia.

5.0. DISCUSSION

In this study, the mean gestation at PPROM and at delivery was 30.1 (± 2.7) and 31.1 (± 2.3) weeks respectively. These findings were comparable to those found by Haiyan Yu in China who found a gestation at PPROM and at delivery to be 31.1 (± 2.2) and 32.1 (± 2.0) respectively (19)

Latency: In this study we found that the mean latency following PPROM at 24-34 weeks at KNH in 2019 was 6.7 (SD 8.5) days and this is consistent with findings of other studies which reported a mean latency range of 4 -7.8 days. This finding of mean latency of 6.7 (SD 8.5) days is consistent with findings Kahramanoglu in a study in Turkey found a mean of 5.7±6.2 and a study by Avirtal in Israel found a mean of 6.1875 ± 11. 033.This could be explained by the similarity in the study group despite difference in geographical localities noted. This study finding had a varied difference when compared to findings by Seema in a study done in India found a mean of 4.8439 ± 6.55684, and Dusingizimana from Rwanda who did a retrospective and prospective study found a mean of 7.8 ± 8.5, this could be attributed to the fact that the study population and methodology was different. In addition, the study by Dusingizimana found a maximum latency period of 7 weeks which was comparable with our finding of 8 weeks, this finding could be attributed to similar characteristics in patient population and to some extent in similarity of the management. (19,29,31,43)

This study found a median of 4.0 (IQR 1.2 – 7.5), This finding was lower compared to finding by Lorthe in a study done in France that found a median of 6.1 days (IQR 3-12.1). The difference in the median could be attributed to difference in the level of care in high income countries who have adequate personnel, drugs and infrastructure (43).

This study found latency per gestation of 15.1 (± 13.2) in the extremely preterm(24-28week),6.1 (± 6.7)days in the very preterm (28+1 – 32weeks) and 3.1 (± 2.4) days in the moderate preterm at (32+1 – 34weeks) following PPROM, depicting an inverse relationship between gestation age at PPROM and latency. This finding was similar to Kahramanoglu ‘s finding of mean latency of 5.7±6.2 days at < 30 weeks’ and 30-34 weeks’ gestation with means of 6.8 ± 7.1 and 4.6±5.5 respectively and findings from Avital’s study in Israel found similar findings of latency of 14.6 days between 23-26 weeks and 3.3 days between 30-33 weeks and the study showed an inverse relationship between gestation age at PPROM and latency period. Similarities in findings could be due to similarity in study participants and geographical distribution. (44,45)

Adverse Perinatal outcomes in patients managed conservatively for PROM at 24-34 weeks' gestation:

The overall perinatal morbidity was 63%, this finding from our study was high compared to the findings from other studies like Haiyan from China who recorded 40% morbidities, Shehla in a study at Pakistan who found a rate of 28.3% and Shweta in a study in Bombay who found an overall morbidity of 33%.(19,42,46) this high rate could be attributed to different geographical distribution, probable difference in management and our high patient load since our facility is the national referral hospital.

The incidence of specific morbidities among patients managed conservatively for PPROM at 24-34 weeks' gestation was: Neonatal jaundice 32.7%, neonatal sepsis 26.7% and necrotizing enterocolitis 3.6%.this rates were comparable to those reported by studies done in high and low income setting.(2,19,45,47–49).

Notably the incidence of Retinopathy of Prematurity 1.2%, Peri Ventricular Leucomalacia 0.6%, Intra Ventricular Hemorrhage 1.8% and Patent Ductus Arteriosus 0.6% had lower rates recorded. This low rates could be attributed to lack of screening for all patients in our setting, unlike routine screening in high income settings for these morbidities.(19,42,47).

This study found NICU to be low at 15%, compared to studies by Haiyan in China who found NICU admissions of 72.9%, and Yasser in a study in Egypt recorded a NICU admission of 62.5%. This finding is mainly a factor of limited bed capacity as opposed to the lack of neonates in need of NICU care in our setting. (19,42,47).

Perinatal mortality: this study found a PMR of 19.3, a NMR of 21.2 and Still Birth Rate of 7.8 among patients managed for PROM at 24-34 weeks' gestation. These findings were comparable to a large extent to studies especially in low income setting. Our findings were lower compared to studies by Dusingizimana in Rwanda who found a PMR of 38.5, NMR of 23.8 and Yasser in Egypt who found a PMR of 38.6, and still birth rate of 15.9 (29,47). This could be attributed to similarity in the patient population and level of care in the low income setting. The findings were very high compared to high income setting like America where Yair in a study found a PMR of 7.4, Lorthe in a study in France who found a NMR of 5.5 and still birth rate of 1 and Haiyan in a study in China who found a NMR of 7.4 and still birth rate of 0.6(19,43,50).

This high PMR of 19.3, NMR of 21.2% and Stillbirth rate of 7.8% among patients managed for PROM at 24-34 weeks' gestation could be attributed to RDS, the commonest morbidity leading to mortality could be responsible for the high morbidity as some patients didn't complete the antenatal steroid doses. Antenatal steroids reduce incidence of RDS, NEC and IVH and in turn reduce on the perinatal and neonatal morbidity and mortality rates. Other contributory factors of note could be lack of new born unit capacity and limited advanced perinatal care, in addition to maternal factors like inadequate inpatient monitoring due to the high patient number.

Adverse maternal outcomes in patients managed for PROM at 24-34 weeks in KNH in 2019.

Maternal mortality**:** This study recorded no maternal death, similar findings were recorded by Yasser in a study done in Egypt (47), however on the contrary were findings by Okeke in Nigeria who found 1 maternal mortality accounting to 1.2%(4). This study followed up patients until delivery-meaning women delivered due to sepsis may have developed chorioamnionitis related complications and died beyond the duration of review in puerperium and could have been missed out.

Maternal morbidity: The overall morbidity of patients managed conservatively for PROM at 24-34 weeks gestation at KNH was 18.9 % this was comparable with that of a study by Okeke in a study done in Nigeria that recorded a morbidity rate of 20%(4)**.**

The Chorioamnionitis rate from this study was 6.3%, this rate was low compared to other studies where the range was 2.5-48.9%,(4,10,19,27,45) these low rate of chorioamnionitis could be attributed to lack of routine diagnostic measures like high vaginal swabs and culture for all women with PROM and assessment of placental histopathology. This measures are employed in high income setting and were not instituted in our study and therefore some cases of chorioamnionitis could have been missed.

Post-partum hemorrhage (PPH) rates were low 2.1% compared to other settings where the range was 3-15.1%,(4,10). The findings likely due PPH prevention and active management of third stage of labor measures instituted at KNH, or could in a small extent to inaccurate estimation of blood loss and our cut off for PPH diagnosis being 1000mls of blood.

The caesarean rate was 52 %, other studies had a range of 14.5-85%, with some recording a low rate while others a high rate. (2,10,19,45,49). This wide range difference in the rates of cesarean delivery could be attributed to institutional guidelines in delivery of patients with PROM and its related complications.

Factors associated with prolonged latency: In this study there was no noted association between maternal socio-demographic factors like age, marital status, level of education and prolonged latency of more than 72 hours and more than 7 days.

Clinical characteristics like parity, digital examination, twin gestation, and history of abortion or previous CS, male infant gender were not found to have any association with prolonged latency of 72 hours or 7 days. This finding were contrary to findings by Melamed in a study in Israel who found that short latency was associated with cervical dilatation, higher gestational age at admission and uterine contractions at admission. However he found no association with maternal age, history of preterm delivery, preterm PROM, nulliparity, oligohydramnios or uterine anomalies and therefore some findings were consistent with this study(30)

Prolonged latency has been associated with Maternal age >30 years, avoiding digital cervical exam and use of tocolytics and prophylactic antibiotic use, this findings were not consistent with this current study (31).

This study found that steroid use, antibiotic use and extreme prematurity (24-28 weeks) had a statistically significant association with prolonged latency. This findings consistent with those by Duzingizimana in a study in Rwanda which showed that antibiotics benefits in prolonging latency, treating chorioamnionitis and was associated with good fetal outcomes (29)

This study found prolonged latency was noted in those with extreme prematurity (24-28 weeks gestation) and these findings were consistent with those found by Dusingizimana that prolonged latency of more than 2 weeks was common in 24-28 weeks gestation (29) he also found that use of antibiotics regardless of the dose was significantly associated with prolonged latency (29).

Prolonged latency and associated adverse maternal and perinatal outcomes:

This study finding showed that prolonged latency of > 72 hours was statistically associated with adverse perinatal outcome namely necrotizing enterocolitis and hyperbilirubinemia in patients managed conservatively for PROM at 24-34 weeks' gestation. Prolonged latency of more than 7 days was not associated with adverse perinatal outcomes. This findings were inconsistent with a study by Nayot in Canada who found that the incidence of severe and moderate neonatal morbidity was reduced with Latency of more than 72 hours for infants at 24-34 weeks(28) and latency of > 2 days decreased premature related morbidity and was not associated with increased infectious morbidity (27).

This study found no adverse maternal outcomes with prolonged latency this finding was contrary to findings studies showed prolonged latency was associated with increased febrile morbidity and chorioamnionitis and was not associated with increased incidence of PPH and retained placenta (45)

Haiyan in a study in China found fewer weeks at PPROM were associated with clinical chorioamnionitis and that there was no association between clinical chorioamnionitis with neonatal mortality and morbidity.(19)

Lorthe in a study in France found that at any gestation at PPROM prolonged latency was not associated with worsening neonatal prognosis and prolonged latency was not associated with survival without severe morbidity or early onset sepsis.(43)

Prolonged exposure to intra uterine environment of PPROM does not increase the risk of NNS, in fact Drassinower found that at 4 weeks was associated with decreased risk of NNS (51)

Yair in a 17,501 neonates study to establish the effect of PPROM on NNM, noted prolonged PPROM was associated with reduced neonatal mortality, however the study noted that early sepsis was significantly higher in the prolonged preterm PROM group as compared to the no PPROM at gestation of 26-34 weeks. (50)

Frenette noted latency of more than 48 hours was associated with decreased prematurity related morbidity and longer latency was not associated with increase in composite neonatal infectious morbidity(27).

Our study found prolonged latency was not associated with adverse maternal outcomes in patients managed conservatively for PROM at 24-34 weeks gestation, these findings agreed with those of Kahramanoglu (45).

Our findings showed no association between prolonged latency with chorioamnionitis and abruptio placentae, however different studies have differed if prolonged latency was associated with increased febrile morbidity and chorioamnionitis and Abruptio placentae(10,45).

6.0. CONCLUSION

The mean latency among patients managed for PPROM at 24-34 weeks' gestation at KNH in 2019 was 6.7 days. The latency period per the different gestation varied as follows, at 24 – 28 weeks was 15.1 (± 13.2) days, at 28+1 – 32 was 6.1 (± 6.7) days and at 32+1 – 34 weeks it was 3.1 (± 2.4) days.

Among the patients managed conservatively for PPROM at 24-34 weeks' gestation, we established high mortality rates namely the Perinatal Mortality Rate at 19.3 %, the Neonatal Mortality Rate at 21.2% and the Still Birth Rate at 7.8 %.

The most common perinatal morbidities included respiratory distress syndrome at 38.2%, hyperbilirubinemia at 32.7% and neonatal sepsis at 26.7%.

The overall maternal morbidity was 18.3% and the specific morbidities that were predominant were chorioamnionitis 6.3%, cord prolapse 4.9% and abruptio placenta 3.4%.

There was no maternal mortality reported in the study participants.

The factors that were associated with prolonged latency were namely; early gestation PPROM at 24-28, the gestation at delivery at 28.1-32, the use of steroids and antibiotics.

Prolonged latency of > 72 hours was associated with development of necrotizing enterocolitis (NEC) and hyperbilirubinemia. No association was noted with any studied adverse maternal outcomes.

Prolonged latency of > 7days was not associated with any adverse perinatal or maternal outcomes in patients managed conservatively for PPROM at 24-24 weeks

7.0. RECOMMENDATIONS

The study findings can be used to generate statements for future references namely;

- Patients can be counseled on latency and their possible outcomes in their management
- Clinicians can use the established latency duration to counsel patients on their expected latency.

Focused antenatal visits and increased fetal surveillance of patients with PPROM to aid reduce the high perinatal mortality rate.

Increase of capacity in NICU to meet the high demand of neonates considering KNH is a National referral facility.

Screening for hyperbilirubinemia should be increased and the use of antenatal steroids to reduce the incidence of necrotizing enterocolitis

Conservative management should be offered to patients with PPROM at 24-34 weeks excluding those who need immediate delivery.

8.0. STUDY LIMITATIONS

The design of the study being retrospective, there was a limitation in having missing data and hence exclusion of some files from the study during the set study period. This limitation was mitigated by increasing the sample size, and only case notes with complete data were analyzed prospectively until adequate sample size was achieved, the challenge with this was the time spent in the data collection phase.

Due to the retrospective design of the study, we could not objectively interview the study participants. In addition, interventions like High Vaginal Swabs for culture and sensitivity or placental histopathology could not be instituted and therefore we could have missed some patients with chorioamnionitis.

The study assessed factors of associations, these were secondary objectives, however the study sample size might have lacked enough power to asses for association.

Prospective studies can mitigate these limitations as they would interview patients and do the specific investigations and further make interventions in the management of the study participants.

STUDY TIMELINE

PROJECT	**Aug '2019**	**Sept'-May 2019**	**May 2020**	**June' 2020**	**July-Nov' 2020**	**Dec'2020 – April '2021**	**April-May' 2021**	**June 2021**	**July-Sept' 2021**	**Dec 2021 – July 2022**	**Oct' 2022**
Concept note presentation											
Proposal development											
Proposal marking by 2 internal examiners											
Power point presentation to department											
Ethical approval											
Data collection											
Data analysis											
Results presentation to department											
Manuscript writing											
Internal marking											
Submission of manuscript to peer reviewed journal											

BUDGET

		UNITS	UNIT COST	TOTAL
Proposal development	Photocopying	2	500	1000
	Printing charges	200	10	2000
	Binding charges	3	300	900
Data collection	Photocopying	1000	3	3000
	Stationary i.e. pens,	30	10	300
	Printing	300	10	3000
	Internet		15000	15000
	Research assistance levy	2	10000	20000
Data analysis	Statistician's fees	1	30000	30000
Thesis write up	Stationary	80	10	800
Miscellaneous	Transport, communication and logistics		10000	10000
TOTAL				85,000

Budget justification

This being a retrospective study, the budget was mainly for stationary and human resource for the study.

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APPENDICES

1. DATA ABSTRACTION TOOL

1) Identification number [ ]

1) Age [ ] years

2) Marital status

   a) Single [ ]
   b) Married [ ]
   c) Separated [ ]

3) Parity [ ] + [ ]

4) Level of education.

   a) None [ ]
   b) Primary [ ]
   c) Secondary [ ]
   d) Tertiary [ ]

5) ANC Visits:

   a) None [ ]
   b) 1-3times[ ]
   c) 4-6times[ ]
   d) > 7

6) Gestation at PPROM [ ] weeks

7) Gestation at delivery [ ] weeks

8) Mode of delivery

   a) Spontaneous vaginal delivery [ ]
   b) Cesarean section [ ]
   c) Assisted delivery [ ]

9) History of previous cesarean section a) yes [ ] b) No [ ] If yes, how many? [ ]

10) History of preterm delivery a) yes [ ] b) No [ ] If yes, how many? [ ]

11) Cervical dilatation on admission [ ] cm

12) Presence of chorioamnionitis yes [ ] No [ ]

13) Neonatal admission ; No admission [ ] Bedside with mother [ ] or Nursery admission [ ]

14) Perinatal outcome:

a) Live birth [ ]
b) FSB [ ]
c) MSB [ ]
d) NND [ ]
e) Birth weight [ ] grams
f) APGAR score ; 1 min [ ] 5 min [ ] 10 min [ ]

15) Perinatal morbidity:

a) RDS a) present [ ] b) absent [ ]
b) IVH a) present [ ] b) absent [ ]
c) NNS a) present [ ] b) absent [ ]
d) PDA a) present [ ] b) absent [ ]
e) Hyperbilirubinemia a) present [ ] b) absent [ ]
f) NICU length of stay [ ] days
g) NBU length stay [ ] days

16) Presence or absence of

a) Clinical chorioamnionitis [ ] abdominal tenderness[ ]fever /Temp > 38.2 o C[ ] WBC >15 * 109[ ] foul smelling liquor [ ]
b) Placenta abruption a) present [ ] b) absent [ ]
c) Umbilical prolapse a) present [ ] b) absent [ ]
d) PPH a) present [ ] b) absent [ ] [ ]
e) Retained placenta a) present [ ] b) absent [ ]
f) Wound infection a) present [ ] b) absent [ ] SSI grade 1 [ ], 2 [ ], 3 [ ]
g) Endometritis a) present [ ] b) absent [ ]
h) Peritonitis a) present [ ] b) absent [ ]
i) Other maternal morbidities a) present [ ] b) absent [ ] Details……

17) Total maternal hospital stay [ ]days

18) Maternal status at discharge ; Alive [ ] dead [ ]

19) Cause of death where applicable ……

20) Indications for delivery

a) Chorioamnionitis [ ]
b) Fetal complication [ ] a) NRFHT [ ] b) Reduced fetal movements [ ] c) Cord prolapse [ ] d) Fetal death [ ]
c) Maternal complication [ ] Abruptio placenta [ ]
d) Gestation 34 weeks [ ]
e) Other indication [ ].Details…….

21) Antenatal management:

a) Corticosteroids [ ]
b) Antibiotics ; prophylactic [ ] or therapeutic [ ]
c) Tocolytics [ ]

22) Corticosteroid use

a) yes [ ] b) no [ ]

23) Antibiotics used

a) Erythromycin [ ]
b) Amoxicillin [ ]
c) Amoxicillin +erythromycin [ ]
d) Augmentin [ ]
e) Ceftriaxone [ ]
f) Others [ ]

24) Tocolytics yes [ ] no [ ]

a) Tocolytics salbutamol[ ]
b) Magnesium sulphate[ ]
c) Nifedipine [ ]

25) Neuroprotection

a) Yes [ ]
b) No [ ]

2. KNH-UON ERC APRROVAL LETTER

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Ref: KNH-ERC/A/395

12th November 2020

Dr. Makau Peninnah Mwikali
Reg. No.H58/11320/2018
Dept.of Obstetrics and Gynaecology
School of Medicine
College of Health Sciences
University of Nairobi

Dear Dr. Makau

RESEARCH PROPOSAL – LATENCY, PERINATAL AND MATERNAL OUTCOMES IN CONSERVATIVELY MANAGED PATIENTS WITH PPROM AT 24-34 WEEKS GESTATION AT KENYATTA NATIONAL HOSPITAL (P403/07/2020)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and **approved** your above research proposal. The approval period is 12th November 2020 – 11th November 2021.

This approval is subject to compliance with the following requirements:

a. Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b. All changes (amendments, deviations, violations etc.) are submitted for review and approval by KNH-UoN ERC before implementation.
c. Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
d. Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
e. Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
f. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
g. Submission of an *executive summary* report within 90 days upon completion of the study. This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/ or plagiarism.

Protect to discover

For more details consult the KNH- UoN ERC website**http://www.erc.uonbi.ac.ke**

Yours sincerely,

PROF. M. L. CHINDIA
SECRETARY, KNH-UoN ERC

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The Senior Director, CS, KNH
The Chairperson, KNH- UoN ERC
The Assistant Director, Health Information Dept, KNH
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