University of Nairobi

EARLY NEONATAL OUTCOMES AMONG MOTHERS RECEIVING VARIABLE DOSES OF DEXAMETHASONE FOR MANAGEMENT OF PRETERM PREMATURE RUPTURE OF MEMBRANES AT KENYATTA NATIONAL HOSPITAL BETWEEN 2011 AND 2015: A RETROSPECTIVE COHORT STUDY

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Dissertation Submitted for examination in Part Fulfillment of the requirements for Award of the Degree of Master of Medicine

in Obstetrics and Gynaecology

College of Health Sciences

University of Nairobi

2018

DECLARATION

I declare that this dissertation, 'A study on early neonatal outcomes among mothers receiving variable doses of dexamethasone for Preterm Premature Rupture of Membranes at Kenyatta National Hospital', a retrospective cohort study, is my own original work and has not been submitted elsewhere for examination or award of degree. All resources and materials I have used or quoted have been indicated and acknowledged by means of reference. I further declare that this dissertation has not been submitted for the award of any other degree or to any university or institution.

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CERTIFICATE OF AUTHENTICITY

This is to certify that this dissertation is the work of Dr. Scholastica Akinyi Odhiambo, Master of Medicine student in the Department of Obstetrics and Gynaecology, School of Medicine, University of Nairobi, Registration number H58/76608/14.

The study was carried out at Kenyatta National Referral Hospital, Reproductive Health unit under the supervision of the department of Obstetrics and Gynaecology, School of Medicine, College of Health Sciences, University of Nairobi. It has not been presented to any other university for award of degree.

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ACKNOWLEDGEMENTS

This dissertation would never have seen the light of day without the support of a number of people and departments, and to whom I am eternally grateful

To my supervisors, Drs. Anne-Beatrice Kihara and Rose J. Kosgei, I sincerely acknowledge your unwavering support and input, from the inception to completion of this study. Your insights, wealth of knowledge, vibrancy and encouragement is appreciated

Mr. Philip Ayieko, my statistician from London School of Hygiene and Tropical Medicine who put his effort and time in part realization of this research proposal.

I would also like to thank my able and diligent research assistants; E.Hans Odhiambo, Jackline Wanjiku, Shirlene Lang'at and Becky Wanjiku. Thank you for the time you put into this. To my colleagues, for the lessons taught and the insights offered, I am grateful. Many thanks to the Department of Obstetrics and Gynaecology, University Of Nairobi; all the lecturers for their various input at different stages of development of this study; Reproductive health department and staff at records department, Kenyatta National Hospital. May God bless you all

DEDICATION

I dedicate this dissertation to Almighty God for life, strength and wisdom.

I also dedicate this work to my dear husband, Nicholas Airo (Jalife), who has been a pillar and a great support system for the four years during the period of study. Thank you for the push towards realization of my life goals and for your practical and emotional support in pursuit of this path.

To my children: Krystina Amor, Justin Hawi and Jennifer Solidad, for being patient and understanding during the entire process. Thank you. You are the inspiration behind

God bless you.

ABBREVIATIONS

ACOG	American Congress of Obstetricians and Gynaecologists
CPAP	Continuous Positive Airway Pressure
GDM	Gestational Diabetes Mellitus/Diabetes Mellitus
IUGR	Intrauterine Growth Restriction
KNH	Kenyatta National Hospital
MOH	Ministry of Health
NEC	Necrotizing Enterocolitis
NMR	Neonatal Mortality Rate
NIH	National Institute of Health
Pre term PROM	Preterm Premature/Prelabour Rupture of Membranes
RANZCOG	Royal Australian and New Zealand College of Obstetricians and Gynaecologists
RCOG	Royal College of Obstetricians and Gynaecologists
RDS	Respiratory Distress Syndrome
SVD	Spontaneous Vertex Delivery
WHO	World Health Organization

DEFINITIONS

Preterm premature/prelabour rupture of the fetal membranes (PROM): the rupture of the amniotic membranes with release of the amniotic fluid more than 1 hour prior to the onset of labour prior to 37 weeks of gestation. Live birth is the complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of the pregnancy, which, after such separation, breathes or shows any other evidence of life, such as beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles.

Neonatal mortality*:* death that occurs from birth to 27th day of life.

Early neonatal period: the period from birth to day 7 of life.

Early neonatal outcomes: outcomes are deemed to occur within the first 7 days of life of a neonate.

Respiratory distress syndrome*:* the presence of cyanosis, grunting, inspiratory stridor, nasal flaring and tachypnoea caused by developmental insufficiency of surfactant production and structural immaturity of the lungs.

Necrotizing enterocolitis*: a* medical condition primarily seen in premature infants, where portions of the bowel undergo tissue death (necrosis)

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ABSTRACT

Background: Antenatal corticosteroids reduce neonatal complications that arise in preterm births. Globally, the prevalence of preterm birth is 11%. In Sub-Saharan Africa and in Kenya, the preterm birth rate is 18% and 12% respectively. Of the Neonatal deaths which arise from preterm birth, 75% occur in the developing countries. There is no consensus on the optimal dosing of antenatal corticosteroids. However, authors agree that they should be administered even when delivery is anticipated within 12 hours. Therefore does incomplete dosing of dexamethasone confer any benefit to premature neonates?

Objective: To compare the early neonatal outcomes among mothers who had preterm PROM and received two doses of 12 mg dexamethasone to those who received one 12-mg dose of dexamethasone between 28 to 34 weeks gestation at Kenyatta National Hospital

Methods: This was a retrospective cohort study where the study participants were consecutive neonates of mothers who had preterm premature rupture of membranes (PPROM) at 28 to 34 weeks gestation in KNH in the period between January 1, 2011, and December 31, 2015 and received dexamethasone (either two 12-mg dose-exposed group or one 12-mg dose-unexposed group). Data was collected from 328 neonates with 164 neonates in each arm to detect either a decrease in early neonatal morbidity or mortality with two 12-mg doses of dexamethasone compared with a single 12-mg dose of dexamethasone. The groups were compared for early neonatal outcomes such as Respiratory Distress Syndrome (RDS), Necrotizing Enterocolitis (NEC, neonatal septicaemia, neonatal mortality and duration of hospital stay. Univariate comparison of the socio-demographic and reproductive characteristics of the two 12-mg dose group (exposed) versus one12-mg dose dexamethasone treatment was conducted using proportions. Bivariate analysis of relative risk for the different neonatal outcomes was calculated. A multivariate logistic regression was calculated with early neonatal outcome as the dependent variable. P value was set at <0.05, precision at 95% confidence intervals and 80% power.

Results: There was a difference in the gestational ages at delivery; 30-31 weeks versus 32-34 weeks for mothers who received single 12-mg versus two 12-mg dexamethasone doses respectively. The incidence of neonatal septicemia was lower in the single 12-mg cohort (RR 0.78, 95% CI 0.62 to 0.99; p=0.039), however there were no differences in the other early neonatal outcomes studied (Apgar score <7 at 5 minutes, RDS, NEC, mortality and duration of hospital stay). Subgroup analysis by gestational ages showed increased neonatal mortality in the single 12-mg dose group (RR 2.09 95%CI 1.11-3.93; p=0.023).

Conclusion: The incidence of early neonatal outcomes of mothers with preterm PROM at 28 to 34 weeks gestation at KNH in 2011 to 2015 were similar for mothers who received two doses of 12 mg dexamethasone and those who received single dose dexamethasone dose apart from early neonatal septicemia which was increased in the two 12 mg dexamethasone group

Recommendations: A single dose of dexamethasone reduces some adverse early neonatal outcomes in mothers with preterm PROM at 28 to 34 weeks gestation and it should be given at the earliest opportunity even when the standard two 12 mg doses of dexamethasone may not be completed. Further studies are needed on the association of two 12-mg dexamethasone doses with neonatal septicemia

1 INTRODUCTION

The burden of preterm birth is estimated to be 11.1% worldwide; 18% in sub-Saharan Africa and 12% in Kenya (1,2). Over 1 million of these babies die secondary to preterm birth complications with the commonest being Respiratory Distress Syndrome (RDS) (3,4). Antenatal corticosteroids have been shown to prevent its occurrence (5). United Nations (UN) on life-saving commodities states that antenatal corticosteroids can save half a million neonatal lives if given to women at risk of preterm birth (3,6).

Despite the availability of evidence on the role of antenatal corticosteroids, its uptake remains low in low and middle income countries (7). Systematic reviews conducted have shown beneficial effects beyond prevention of RDS: they reduce severe neonatal morbidities (necrotizing enterocolitis, intraventricular hemorrhage, neonatal septicemia and need for ventilator support) and mortality associated with prematurity in neonates born prior to 34 weeks gestation (5)(8).

Many studies have demonstrated the benefit of single course antenatal corticosteroids (24 mg of betamethasone or dexamethasone intramuscular) with similar efficacy (9). Betamethasone is administered as 12-mg once daily over 48 hours and dexamethasone as 6-mg twice daily over 48 hours (this is the recommended dosage in multiple guidelines and dosage used in various studies) (5,10,11). In Kenyatta National Hospital (KNH), dexamethasone is the antenatal corticosteroid in use and is commonly administered intramuscularly as 12-mg twice over 24 hours due to the 4mg vials provided by the hospital (12). The existing protocol on preterm labour and preterm PROM (SOP/KNH/OBS/GYN/059) does not specify the antenatal corticosteroids to administer and the dosage (see appendix 3).

Anecdotal evidence shows a lack of consensus on the dosing schedule for antenatal corticosteroids. The optimal time when benefits accrue is not known and time of delivery cannot be predicted. However, there is agreement to administer corticosteroids even if delivery is anticipated before 12 hours regardless of the dosing schedule chosen (13,14). Few studies on the benefits of incomplete antenatal corticosteroids have been conducted in the developed world (15–17). This is significant because it is not always possible to complete the course of antenatal corticosteroids (18). This study aims to determine if single 12 mg dexamethasone dose is as efficacious as two doses of 12mg dexamethasone. Knowledge on whether a single dose of dexamethasone is as efficacious as multiple doses could even enhance utilization of this essential commodity in our set up and be cost effective to the health system.

2 LITERATURE REVIEW

Preterm birth does not only have negative psychological impact on families but it affects the newborn in the early neonatal period and in the long term (5,19). Moreover, a country's economy is affected because of the need for neonatal intensive care to treat the newborn (20,21). Preterm birth complications arise from poor lung development as well as the development of other organs (5,22).

A cross sectional study in 2013 by Wagura et al in KNH showed that the prevalence of preterm birth stood at 18.3% (23). Globally, 15 million live births are preterm, giving a prevalence of 11%. Over 1 million of these babies die annually (1,4). Preterm births rates are on the rise and will continue to rise even beyond 2030 (4). Preterm birth is the leading cause of perinatal morbidity and mortality contributing to 75% of morbidity and mortality in the perinatal period (1,24).

The three causes of preterm births are spontaneous preterm labor (40-45%), delivery for maternal or fetal indications (30-35%) and preterm premature rupture of membranes (preterm PROM). The latter account for 1 out of 4 babies who are born too soon (24).

Risk factors for Preterm PROM include: previous history of preterm PROM, genital tract infection, antepartum bleeding, cigarette smoking and genetics, while the associated obstetric complications are maternal and neonatal infection, cord compression or prolapse, non-reassuring fetal status, oligohydramnios, malpresentation and preterm birth (24,25). The clinician has to balance on when to deliver in order to avoid the risks of prematurity visa a vie encountering the complications.

Administration of a single course of antenatal corticosteroids has been shown to reduce preterm birth complications in preterm PROM without infection (5). Additionally, prophylactic antibiotics are given if there is preterm PROM at a lower gestation (less than 34 weeks). Kenyon et al demonstrated the benefit of antibiotics in reducing the risk of early onset of neonatal infection and prolonging the latency thus allowing administration of antenatal corticosteroids in a systematic review (26).

Known mitigating factors for perinatal morbidities and mortality resulting from preterm birth include administration of antenatal corticosteroids and kangaroo mother care for stable neonates weighing 2000g or less (5,13). Studies have demonstrated a rise in cortisol in the fetal circulation near term with maturational effects in the fetus, essential for successful transition to extra uterine life (5). The rise in cortisol is in conjunction with other hormones such as estrogen, thyroid hormones and prolactin. These hormones not only promote lung development but also development of other organ systems (22).

In addition, endogenous and synthetic glucocorticoids stimulate maturation of certain structural aspects in the fetal lungs, including alveolarisation, thinning of the alveolar septae and increasing pulmonary collagen and elastin content (27). They also activate synthesis of both the lipid and protein components of surfactant and its secretion from type II pneumocytes in the alveoli together with other hormones (28,29).

Antenatal corticosteroids play a big role in the prevention of neonatal morbidities and mortalities that arise due to preterm birth. Antenatal corticosteroids in preterm birth are given to reduce respiratory distress syndrome, necrotizing enterocolitis, neonatal mortality up to day 28 of life, systemic infection, intraventricular hemorrhage, patent ductus arteriosus, neonatal intensive care admissions, need for ventilatory support and in the long term prevent cerebral palsy, mental retardation as well as retinopathy of prematurity (5,9,10).

Numerous studies have been done on the prevalence of preterm birth and the preterm birth complications (RDS, NEC, neonatal septicemia, neonatal mortality); when they occur, to demonstrate the magnitude of the burden of preterm birth and its' complications. A systematic analysis on causes of under 5 mortality globally, carried out between 2000 to 2013 and included 166 countries in different regions, found out that over two-fifths of the deaths occurred in the neonatal period with preterm birth complications as the leading cause (15.4%) and a global cause-specific mortality rate of 7 per 1000 live births. The deaths were mostly in sub-Saharan Africa and Southern Asia (>80%) (4). A study in KNH showed that only a third of neonates born between 28 to 31 weeks gestation survived and that 70% of neonatal deaths occurred in the early neonatal period (30). Similar findings on timing of most neonatal deaths were observed in a 2006 study estimating neonatal mortality in 188 countries (31). Whereas the neonatal mortality rate in Kenya as per the Kenya Health Demographic Survey, 2014 is 22 per 1000 live births is below the WHO estimates of neonatal mortality rates for developing countries and Africa (33 per 1000 live births and 41 per 1000 live births respectively), the rate falls way below the figures reported in developed countries (5 per 1000 live births) (31,32). Jennifer et al in a study described even lower values for 18 European countries (1.2-4 per 1000 live births) as at the year 2000 (33).

Simiyu and Were et al, while looking at neonatal morbidity and mortality of low birth weight infants at KNH, established that RDS was the leading cause of death contributing between 43-69% (30,34). In the United States less than a third of premature neonates born at 30-31 weeks' gestation develop RDS. Global RDS-specific mortality rates could not be established.

Neonatal infections contribute up to 26% of deaths in the neonatal period and preterm PROM is a known risk factor (35). Suspected neonatal sepsis contributed between 37-41% of neonatal deaths in KNH with a case fatality rate of 36.5% (30,34). In a global cause-specific mortality estimate of under 5 in 2013, neonatal sepsis lead to 7% of neonatal deaths (4). Necrotizing enterocolitis is estimated to develop in nearly 3% of infants born at 27 weeks gestation or more with an incidence rate of four neonates per 1000 live births for those born weighing between 1501 to 2500g. Its prevalence is directly proportional to the number of premature births in a country. A systematic review by Gephart et al, found prematurity was a major risk factor to development of NEC (36).

While the role of antenatal corticosteroids on fetal lung maturation have been known for over four decades (37) little has been done to improve utilization of these essential commodities particularly in low and middle income countries (38). Gwako et al in a cross-sectional study at KNH in 2013 revealed that only 46% of the patients who were at risk of preterm delivery before 34 weeks gestation and needed antenatal corticosteroids got treatment. A study by WHO in 29 low and medium income earning countries showed utilization of antenatal corticosteroids in Kenya to be 32%. Only 52% of women who gave birth at 26–34 weeks' gestation received antenatal corticosteroids in these countries. The study showed a wide range in rates of antenatal corticosteroid between the countries; 16-91% and a median of 54% (12,39).

Systematic reviews and other studies have demonstrated neonatal benefits conferred by a single course of antenatal corticosteroids with no fetal adverse effects for pregnancies at risk of preterm birth between 23 to 34 weeks gestation (5,10). A Cochrane review by Robert et al provided strong evidence that respiratory distress syndrome (RDS) in 21 studies, necrotising enterocolitis (NEC) in eight studies, neonatal death in 18 studies, intensive care admissions in two studies and systemic infections in the first 48 hours of life in 5 studies are significantly reduced when corticosteroids are given at 26 to 34 weeks of gestation. Rates of neonatal mortality were reduced by 31-34% and morbidity by 37% with higher reduction in the rates observed in trials conducted in middle income countries (5). There were no demonstrable adverse effects on the infants born before 34 weeks gestation. The study showed that antenatal corticosteroids were effective in women with preterm premature rupture of membranes as well. Another study did not report increased risk of infection with even repeat antenatal corticosteroids even in women with preterm PROM, Gyamfi et al (5,40).

2.1 Use of corticosteroids in pregnancy

WHO recommends antenatal corticosteroids to pregnant women at risk of preterm birth between 24 to 34 weeks gestation; women with hypertensive disorders, Gestational Diabetes Mellitus (GDM) or Diabetes Mellitus (DM), Preterm PROM without infection, with Intra Uterine Growth Restricted (IUGR) fetus and singleton or multiple pregnancies. Antenatal corticosteroids should be used if preterm birth is anticipated within 7 days and should be given even if birth will occur within 12 hours(13).

Antenatal corticosteroids (dexamethasone or betamethasone) are beneficial for neonates of women at risk of preterm birth between 24 to 34 weeks gestation in improving neonatal outcomes; if the women are at risk of preterm birth within 7 days and even if delivery is to occur in the next 12 hours (WHO and different international society guidelines). This is because little is known on the optimal timing when benefits start to accrue and the delivery time cannot be predicted (5,14,40).

Areas of controversy include: optimal dosing interval, optimal time interval, repeat course and benefits of antenatal corticosteroids below 24 weeks gestation and beyond 34 weeks gestation. Canadian committee on antenatal corticosteroid for fetal maturation agrees with the National Institute of Health (NIH) Consensus statement and only gives antenatal corticosteroids to women with preterm PROM without infection if they are less than 30 to 32 weeks gestation while still skeptical with regards to risk of infection (40,41).

American Congress of Obstetricians and Gynaecologists (ACOG) 2017 interim update recommends single course of antenatal corticosteroids for pregnant women at risk of preterm birth between 24 weeks and less than 34 weeks gestation, including those with preterm PROM. ACOG states administration of betamethasone may be considered in women with a singleton pregnancy at 34 to 37 weeks of gestation at imminent risk of preterm birth (11). It also recommends repeat single course of antenatal corticosteroids to women at risk of preterm birth and less than 33 weeks gestation (11).

Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) recommend a single course of 12 mg of betamethasone in divided doses completed between 12

and 36 hours or 12 mg of dexamethasone in divided doses completed between 12 and 40 hours, a repeat course in case of continued risk beyond the 7 days and for planned caesarean delivery beyond 35 weeks if there is confirmed fetal lung immaturity (42).

Royal College of Obstetricians and Gynaecologists (RCOG) states that antenatal corticosteroids can be considered for women between 23 weeks and 24 weeks gestation at risk of preterm birth by a senior; planned caesarean delivery if at less than 39 weeks gestation and a repeat course if the first course was given at less than 26 weeks gestation in the event of a new obstetric indication (14).

NIH consensus statement agrees that both surfactant and antenatal corticosteroids have additive effects. Postnatal surfactant administration is not a substitute for antenatal corticosteroid therapy (41,43).

In a randomized controlled study, only 25% of women delivered within the optimal window of steroid administration: 12 hours to 7 days after the second dose (37). Makhija et al discovered that only 26.5 to 28.5% of women delivered within the optimal window defined as 48 hours to 7 days after the first dose or third dose and only 32.1% of women with preterm premature rupture of membranes delivered within the optimal window (44).

Documented studies on the efficacy of single or incomplete dose of antenatal corticosteroids are few and even fewer studies on single dose dexamethasone administration exist. Most of these studies were carried out in developed countries and the results are conflicting. In two large studies conducted by Elimian et al in New York and one by Chien et al in Canada showed that a single dose of betamethasone and partial steroid treatment on neonates born at 23 to 34 weeks

gestation had reduced mortality but no difference were shown in RDS, NEC, neonatal sepsis or length of hospital stay (15,45). However, there was reduced rate of NEC and mortality in a study carried out in Australia in very premature infants who were born more than 48 hours after steroid exposure compared to those who were born in less than 12 hours after exposure to steroids (17). A different study by Costa did not find any positive neonatal outcome with a single dose of betamethasone at 25 to 34 weeks gestation (16).

There are no studies in low income countries looking at the efficacy of single dose compared to multiple doses of antenatal corticosteroids in reducing rates of RDS, necrotizing enterocolitis, neonatal septicemia and neonatal death.

Therefore does incomplete dosing of dexamethasone confer any benefit to premature neonates? The study by Gwako et al, showed reduced rate of RDS and neonatal mortality among neonates who received dexamethasone, but only 3% had complete dose of dexamethasone. With this observation, could it be that a single 12-mg dose is equally efficacious as 24-mg dose of dexamethasone? (12).

2.2 Problem statement

In a randomized controlled study, only 25% of women delivered within the optimal window of steroid administration: 12 hours to 7 days after the second dose (37). Makhija et al discovered that only 26.5 to 28.5% of women delivered within the optimal window defined as 48 hours to 7 days after the first dose or third dose and only 32.1% of women with preterm PROM delivered within the optimal window (44).

Documented studies on the efficacy of single or incomplete dose of antenatal corticosteroids are few and even fewer studies on single dose dexamethasone administration exist. Most of these studies were carried out in developed countries and the results are conflicting. In two large studies conducted by Elimian et al in New York and one by Chien et al in Canada showed that a single dose of betamethasone and partial steroid treatment on neonates born at 23 to 34 weeks gestation had reduced mortality but no difference were shown in RDS, NEC, neonatal sepsis or length of hospital stay (15,45). However, there was reduced rate of NEC and mortality in a study carried out in Australia in very premature infants who were born more than 48 hours after steroid exposure compared to those who were born in less than 12 hours after exposure to steroids (17). A different study by Costa did not find any positive neonatal outcome with a single dose of betamethasone at 25 to 34 weeks gestation (16).

In the Elimian et al study, low APGAR score was defined as a score of less than 7 at 5 minutes, diagnosis of RDS was diagnosed clinically by the need for mechanical ventilation and oxygen therapy for at least 48 hours in the presence of characteristic chest finding, and. diagnosis of NEC was made clinically (feeding intolerance, no passage of stools, abdominal distension and absent or reduced bowel sounds) and confirmed by a plain abdominal x-rays. Neonatal septicemia was also diagnosed by positive blood cultures (15)

There are no studies in low income countries looking at the efficacy of single dose compared to multiple doses of antenatal corticosteroids in reducing rates of RDS, necrotizing enterocolitis, neonatal septicemia and neonatal death. Therefore does incomplete dosing of dexamethasone confer any benefit to premature neonates? The study by Gwako et al, showed reduced rate of RDS and neonatal mortality among neonates who received dexamethasone, but only 3% had

complete dose of dexamethasone. With this observation, could it be that a single 12-mg dose is equally efficacious as 24-mg dose of dexamethasone? (12).

2.3 Conceptual Frame Work

2.3.1 Narrative

Preterm birth is a leading cause of neonatal mortality and morbidity (>15%) with a projection of rising in the coming years. It has extensive ramifications to the neonate and the society in general. The consequences of preterm birth in the early neonatal period include development of respiratory distress syndrome, necrotizing enterocolitis, neonatal septicemia and neonatal deaths. Preterm PROM accounts for up to a third of the causes of preterm birth. Luckily, we have antenatal corticosteroids (either dexamethasone or betamethasone) to reduce the preterm birth complications.

However, as we gear towards increasing the utilization of dexamethasone, we are encountered with the reality that administration of a complete dose of this commodity may not be possible. This may be accidentally discovered or be due to unavoidable onset of labour among women with preterm PROM at 28 to 34 weeks gestation. In this study, neonatal case notes of neonates born to those mothers were checked to establish whether they were at increased risk of developing respiratory distress syndrome, necrotizing enterocolitis, neonatal septicemia and dying simply because of receiving a single 12-mg dose of dexamethasone. We also looked at whether exposure to single 12-mg dose of dexamethasone was associated with longer duration of stay in NICU/NBU. Data was collected retrospectively.

2.3.2 **Schematic conceptual framework**

The schematic conceptual framework was as shown below.

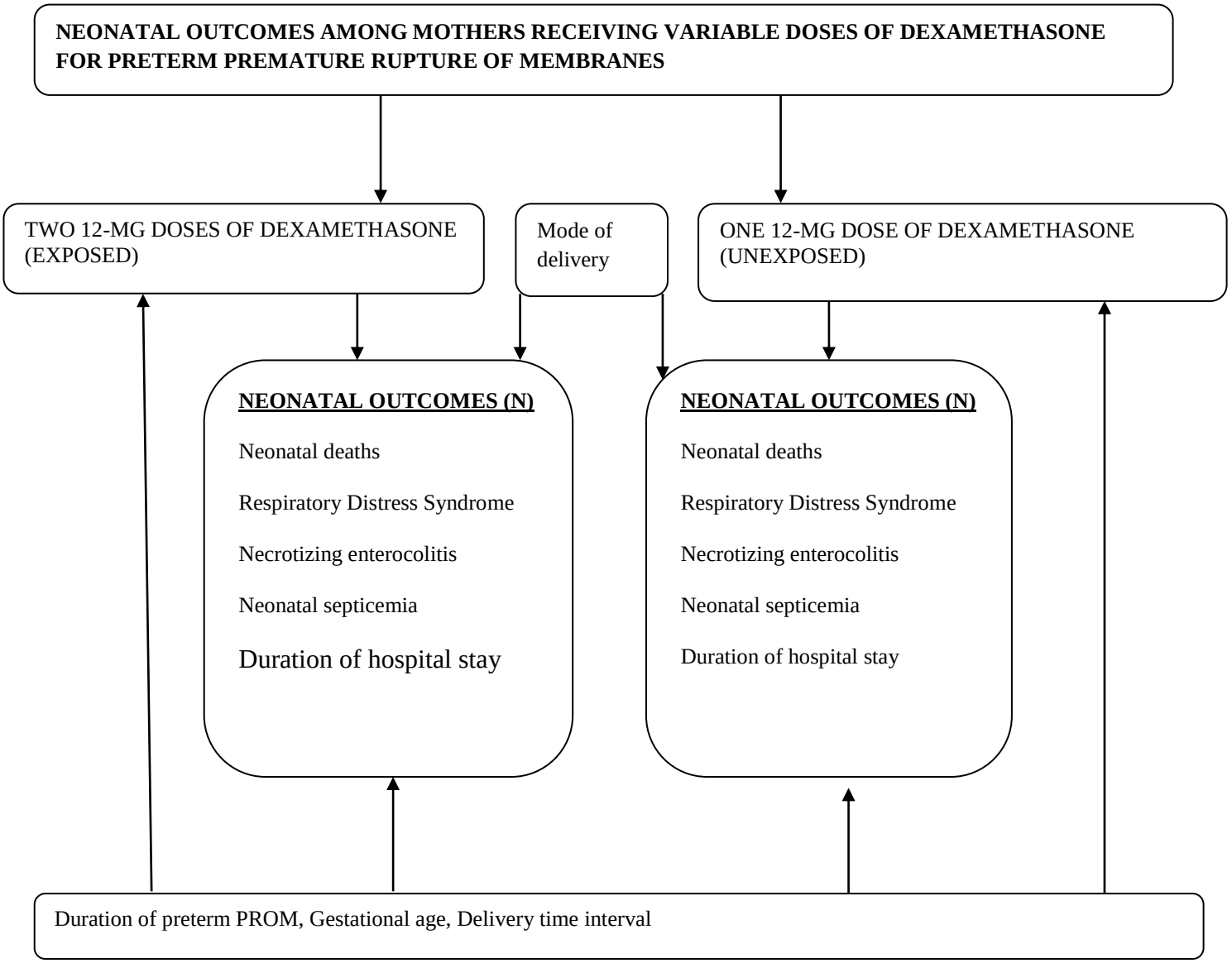

Figure 1: Schematic Framework

2.4 Justification

While the practice of administering antenatal corticosteroids among pregnant women at risk of preterm delivery is widespread, the preterm birth rates are shown to be on the rise necessitating even more emphasis on their need and increased usage (4). Many studies have shown there is a benefit in steroid use in pregnant women at risk of preterm birth (5). The benefits accrued are neonatal lung maturity, reduced necrotizing enterocolitis, intraventricular hemorrhage, neonatal mortality among others.

Most of the studies conducted have been on administration of a complete dose of steroids (total of 24 mg) described as single course of either dexamethasone or betamethasone. Only a few pragmatic studies have been carried out on benefits of antenatal corticosteroids on incomplete dose or single dose of antenatal corticosteroids in developed world. However, the results from these studies have been conflicting (15–17). In the literature, no studies evaluating the beneficial effects on the use of a single dose of antenatal corticosteroids have been done in our region and Kenya. Yet from the same literature review we found out that completion of a single course of antenatal corticosteroids may not be possible in some circumstances, such as preterm PROM, and is aimed at but never achieved in 30 % of cases even in developed countries. The rates are even lower in resource-constrained countries (3-10%) (12).

In such cases where a complete 12-mg course of dexamethasone may not be administered, ‘are the newborns at an increased risk of RDS, NEC, neonatal mortality and neonatal septicemia?’ How does this affect the length of stay of the neonates in hospital? Kenyatta National Hospital is in a developing country and if the question on efficacy of administering a single 12-mg dose of

dexamethasone to neonates born prematurely can be answered then we can ‘alter’ practice, save many neonatal lives and reduce cost. To this end, my study compared the early neonatal outcomes among neonates whose mothers had preterm PROM and received two 12-mg doses of dexamethasone and those who received one 12-mg dose of dexamethasone between 28 to 34 weeks gestation at KNH

3 RESEARCH QUESTION

Is there a difference in early neonatal outcomes among neonates whose mothers had preterm PROM at 28 to 34 weeks gestation and received two 12 mg doses of dexamethasone and those whose mothers received one 12-mg dose of dexamethasone at KNH?

3.1 Null hypothesis

There is no difference in early neonatal outcomes among neonates whose mothers had preterm PROM at 28 to 34 weeks gestation at KNH and received two 12 mg doses of dexamethasone and those whose mothers received one 12-mg dose of dexamethasone.

4 OBJECTIVES

4.1 Broad objective

To compare the early neonatal outcomes among neonates admitted to NBU whose mothers had preterm PROM and received two doses of 12 mg dexamethasone and those who received one 12-mg dose of dexamethasone between 28 to 34 weeks gestation at KNH.

4.2 Specific objectives

- To compare the maternal socio-demographic and reproductive characteristics of the mothers of the neonates exposed antenatally to either two 12-mg or one 12-mg dose of dexamethasone between 28 to 34 weeks gestation
- To describe the patterns of administration of dexamethasone; the duration between admission and administration of the first dose, the lengths of time from the first and last doses to delivery, personnel instructing administration of dexamethasone and the impact on early neonatal outcomes
- To compare the early neonatal outcomes; APGAR score <7 at 5 minutes, respiratory distress syndrome, necrotizing enterocolitis, neonatal septicaemia, neonatal mortality and duration of hospital stay for the two groups.

5 METHODOLOGY

5.1 Study Design

This was a retrospective cohort study. We studied 328 neonates born at 28 to 34 weeks gestation between January 1, 2011, and December 31, 2015, at KNH and whose mothers received either two 12-mg doses of dexamethasone or one 12-mg dose dexamethasone, and who were subsequently admitted to the new born unit up to day seven of life after PPROM. Early neonatal outcomes between 164 neonates of mothers who received two 12-mg doses of dexamethasone (exposed) were compared with 164 neonates of mothers who received single 12-mg dose of dexamethasone (unexposed). In both groups the mothers were between 28 to 34 weeks gestation and had preterm PROM.

5.2 Study site and setting

The study was carried out in Kenyatta National Hospital (KNH); the largest referral and teaching hospital in Kenya situated in the capital city, Nairobi. The hospital caters for patients from Nairobi and its environs as well as referrals from different parts of Kenya and East and Central Africa. The maternity unit takes care of high risk pregnancies as well as low risk pregnancies. It is also serves as a teaching hospital for the University of Nairobi, school of medicine and Kenya Medical Training College.

Study context: KNH has one labour ward on ground floor, three antenatal/postnatal wards (GFA, GFB and 1A) as well as a newborn unit. It provides delivery care to 1300 women per month. Patients in labour or those who need close monitoring are admitted in labour ward. It is in labour ward that pregnant patients at 20 weeks gestation or more who attend antenatal clinic at KNH as well as walk- in- clients and referrals are triaged for admission to either labour ward or the antenatal wards depending on their diagnoses.

There is a nurse assigned to triage room that works in consultation with the registrar in labour ward; checks maternal vital signs and fetal well-being. Initial patient management may start here including administration of the first dose of dexamethasone if need be depending on the gestational age which is determined by the last normal period and confirmed by first or early second trimester ultrasound. The practice in KNH is to administer two doses of 12-mg given intramuscularly 12 hours apart at 28 weeks to 34 weeks gestation (19)**.** Patients are then assigned a nurse. One nurse can be assigned 5-7 patients per shift. Management is further based on the standard practice of management of preterm PROM at KNH and upon delivery. The neonates are assessed by the paediatric resident in consultation with neonatologist on call if they develop respiratory distress or have any other condition that warrants NBU admission.

The NBU has more than 1000 admissions per month with a 50-bed capacity. It is divided into seven key areas: the admission nursery handles all new admissions for stabilization before they are redistributed to other nurseries; the isolation nursery for sick preterm neonates; nurseries B2 and B3 have incubators and handles preterm neonates with a birth weight below 1600g, each incubator may have 3-4 neonates depending on the workload; nursery B4 has cots and handles neonates with a birth weight above 1600g as they wait to gain weight and complete antibiotic cover as well as sick term neonates weighing between 2000-3000g; nursery B1 handles neonates above 3000g who are sick; nursery D handles stable neonates with a birth weight above 1750g and stable term neonates; NICU handles neonates who require ventilatory support and the kangaroo room stable preterm neonates for kangaroo mother care. All preterm neonates with a birth weight of less than 2000g and other neonates with RDS, NEC, and neonatal septicemia are admitted to the NBU. Diagnoses and management of the conditions is as shown in Box 2 below

5.3 Study population

Records of 328 neonates who were admitted in the new born unit in the 5 year period between January 1, 2011, and December 31, 2015 whose mothers had preterm PROM and delivered at the maternity unit (met eligibility criteria) at 28 to 34 weeks gestation and were exposed to antenatal corticosteroids were used for data collection. The records of the mothers were also searched for data collection

The study population was divided into two cohorts where early neonatal outcomes between 164 neonates of mothers who received two doses of 12-mg dexamethasone (exposed) were compared with 164 neonates whose mothers received single doses of 12-mg dexamethasone (unexposed)

5.3.1 Inclusion criteria

For a record to be eligible for inclusion;

- A neonate admitted in NBU whose mother had preterm PROM between 28 to 34 weeks gestation
- Antenatal exposure to either two 12-mg doses of dexamethasone or single 12-mg dexamethasone dose

5.3.2 **Exclusion criteria**

We excluded records of neonates whose mothers had preterm PROM at 28 to 34 weeks gestation with;

- Chorioamnionitis (uterine tenderness, foul smelling lochia, fetal tachycardia) or existing infection
- Active phase of labour which will be confirmed by any two of the following criteria; palpable uterine contractions –at least three in ten minutes or cervical dilatation equal to or greater than 4cm
- Pregnancies complicated by co-morbidities such as preterm labour, preeclampsia, antepartum hemorrhage, diabetes, perinatal haemolytic disease
- Intrauterine fetal death
- Congenital malformations
- Previously treated with corticosteroids
- Contraindication to corticosteroids
- Indication for immediate delivery
- Anticipated delivery > 7 day

5.4 Sample size determination

Sample size was calculated using Fleiss formula (Chow S, Shao J, Wang H. 2008. *Sample Size Calculations in Clinical Research*. 2nd Ed. Chapman & Hall/CRC Biostatistics Series. page 100):

$n= \{pA(1-pA) + pB(1-pB)\} * 2\{(Z_{1-\alpha/2} + Z_{1-\beta})^2\}/ (pA - pB)^2$

Where:

n = required minimum sample size in each exposure group

$Z_{1-\alpha/2}$ = percentage of the normal distribution corresponding to the required (two-sided) significance level i.e for significance level of 5%, $Z_{1-\alpha/2} = 1.96$

$Z_{1-\beta}$= area under the normal distribution curve corresponding to 100%-power i.e. if power = 80% (100%-power) = 20% and $Z_{1-\beta}= 0.84$

pA = incidence of poor early neonatal outcomes in neonates whose mothers had preterm PROM, and received two 12-mg of dexamethasone between 28 to 34 weeks gestation at KNH=0.3

pB = incidence of early neonatal outcomes in neonates whose mothers had preterm PROM, and received one 12-mg of dexamethasone between 28 to 34 weeks gestation at KNH=0.45

pA and pB are the expected sample proportions of the two groups (0.3 and 0.45/0.5 respectively)(5,12)

$n= \{0.3(1-0.3) + 0.45(1-0.5)\} * 2\{(1.96+ 0.84)^2\}/ (0.3 - 0.45)^2$

n = 164 per group

2n = 328

5.5 Sampling procedure

Purposeful sampling method was used to get records of neonates whose mothers had preterm PROM between 28 to 34 weeks gestation**.** Simple random stratified sampling based on exposure (two 12 mg dosing) or non-exposure (single 12 mg dosing) status was used to select two groups of 164 mothers each. A sampling frame was obtained containing inpatient numbers of all mothers admitted to the hospital with preterm PROM during the period of the retrospective cohort and treated using dexamethasone.

These subjects were stratified into two groups – two 12-mg and one 12-mg dexamethasone dose- and simple random selection was conducted within each group using computer generated random numbers to obtain the minimum required sample size. The sample to be obtained was an unmatched random sample and any potential confounding based on gestational age, among other factors was adjusted for in the analysis.

5.6 Recruitment of participants

The study recruited a total of 328 participants out of a total of 589 mothers who were initially screened for eligibility, figure 3. There were 525 mothers who met the inclusion criteria of whom 453 had complete records. The sample of 328 participants selected from the 453 mothers meeting eligibility criteria and having complete data included 164 mothers receiving single 12 mg dose of dexamethasone and 164 mothers receiving two 12-mg dose of dexamethasone.

Participants were recruited as per the flow chart shown below

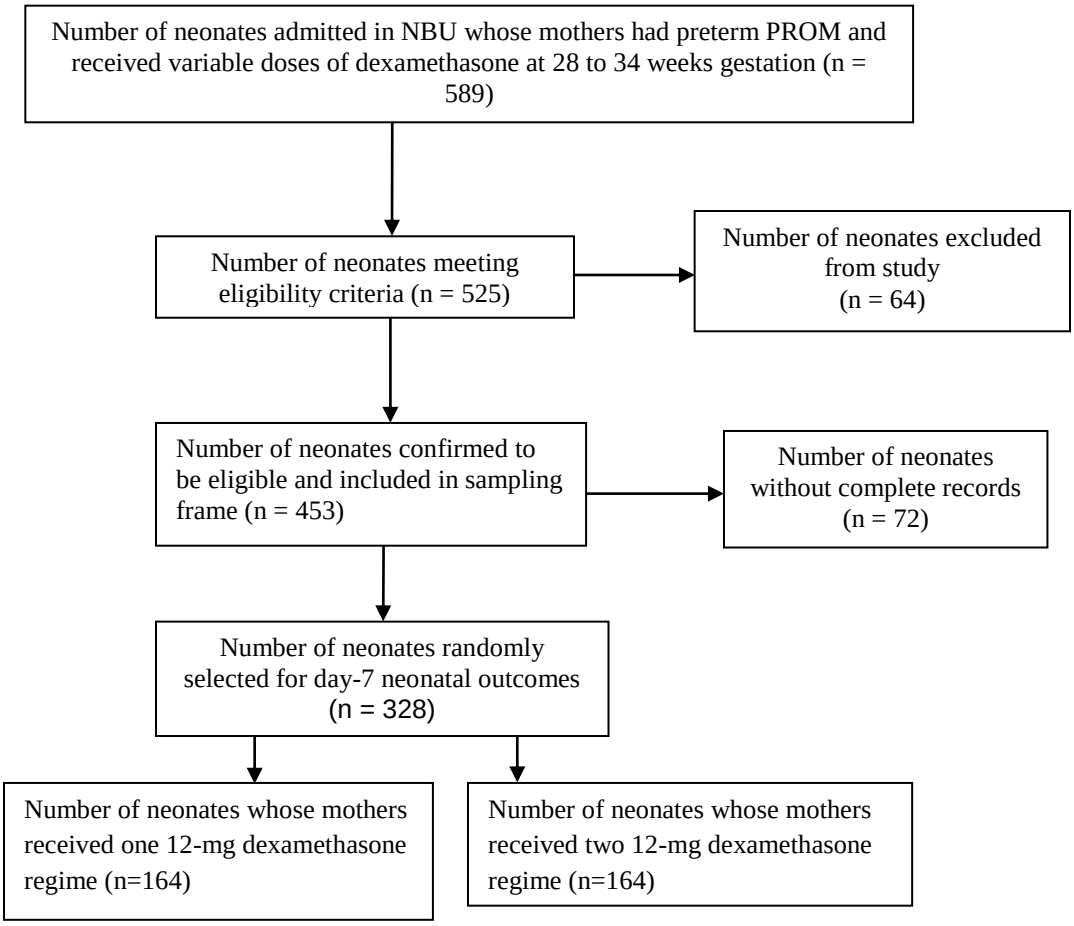

Figure 2: Study Flow chart showing recruitment of participants

5.7 Data Variables

Cohort studies confer the benefit of studying the association between one exposure and multiple outcomes. This cohort examined five outcomes (dependent variables) presented in Box 1, with four measured as cumulative incidences and a single outcome presented as a mean. The primary exposure (independent variable) in the study was dosages of dexamethasone administered. A complete course was defined as two 12 mg doses of dexamethasone administered twice over 24 hours prior to delivery (exposed) while incomplete dose was defined as one 12 mg dexamethasone dose prior to delivery (unexposed)

Cumulative incidences for each early neonatal outcome: respiratory distress syndrome, necrotizing enterocolitis, neonatal septicemia, neonatal mortality and the mean duration of hospital stay for the two12-mg and single 12-mg dexamethasone groups was calculated and compared. Secondary exposures included potential confounding variables of the association between outcomes and dexamethasone dose namely: gestational age, duration of preterm PROM, birth weight and type of delivery. Outcome and exposure variables and the sources of data according to each objective are shown in Box 1 below.

Objective	**Outcome variable**	**Exposure variable**	**Sources of data**
Incidence of respiratory distress syndrome	Incidence of respiratory distress syndrome	Number of neonates with RDS Dexamethasone dose	Delivery register Antenatal admission book Maternal case notes Nursing cardex Neonatal case notes
Incidence of necrotizing enterocolitis	Incidence of necrotizing enterocolitis	Number of neonates with NEC Dexamethasone dose	Neonatal case notes in NBU or NICU Laboratory investigations
Incidence of neonatal septicemia	Incidence of neonatal septicemia	Number of neonates with neonatal septicemia Dexamethasone dose	Laboratory investigations Neonatal case notes
Incidence of neonatal mortality	Incidence of neonatal mortality	Number of neonatal deaths Dexamethasone dose	Neonatal case notes
Duration of hospital stay	Number of days of admission in NBU/NICU	Number of days of admission Dexamethasone dose	Neonatal case notes

Figure 3: Box 1 showing outcome and exposure variables

5.8 Data collection instruments

Data on all the exposure variables and the outcome of interest was extracted from the health records of patients; patient case notes-maternal and neonatal case notes, nursing cardexes and laboratory investigations were checked to obtain additional information; antenatal admission books and delivery registers were also sought to obtain useful information as indicated in Box 2. All the patients' case notes were in the custody of the health information department and once approval was obtained from Ethics and Review Committee, a copy of the same was submitted to the head of health information department who allowed the health record officers to retrieve the case notes for the principal investigator and the research assistants.

Data was collected using standardized data retrieval/abstraction form for every patient case note retrieved (see appendix 1 and 2). The principal investigator together with the research assistants filled in the data retrieval forms based on information obtained from the patient case notes (health records).

5.9 Data management / Quality assurance

Four research assistants, medical students who had rotated in Obstetrics and Gynaecology unit, were recruited. The principal investigator trained the research assistants on the study protocol and procedures before commencement of data collection, to assist with data management exercise including data collection and entry. This was done in the week preceding the start of data collection and went on till the principal investigator was confident that the assistants were well trained on data collection.

The principal investigator obtained patient case notes and all other sources of data from the Health information department. The research assistants assisted the principal investigator in collection of information from patient case notes including, information on neonatal outcomes

and exposure to dexamethasone, filling of the data retrieval forms (data entry) and ensuring the health records were not accessible to other people and only used for the purpose of research. The research assistants did not need authorization to access the patients' records once the principal investigator had permission from head of health information department in KNH.

Quality assurance was ensured during data collection through training of research assistants on the study tool and data abstraction process, providing SOP manuals to guide data collection, and close supervision of the data collection by the principal investigator until the data collectors (research assistants) were familiar with the process. The principal investigator filled out twenty questionnaires/data retrieval forms with the research assistants and used this opportunity to verify the clarity of the questions in the data retrieval forms. The patient and neonatal records/case notes used for training were obtained outside the study period.

5.10 Data Quality and Security

The principal investigator inspected all the questionnaires for completeness prior to data entry. Any missing data was completed by referring back to the medical records. If it was established that medical records were also incomplete a code was assigned for these missing data and they were reported during analysis to gauge the potential for bias.

All the collected data was de-identified and anonymized. Data was then entered into a Microsoft excel spread sheet with inbuilt consistency and validation checks. It was cleaned using statistical software to inspect each variable in the database for completeness, validity and cross validation of entries in related variables.

5.11 Data Storage

The filled abstraction forms were stored in a lockable safe. Data was stored in a password protected external storage device and only the statistician, the principal investigator and her

supervisors were privy to the data. The data will be stored and will be accessed for a period of 3 years from the time of collection. This will be discarded after the three year period has elapsed.

5.12 Data Sharing and Access

This data was shared with utmost confidentiality. Once processed, the principal investigator plans to publish the trial findings and this will be accessed from medical journal sites

5.13 Data Analysis

Data was analyzed using IBM SPSS software (version 21). Univariate comparison of the socio-demographic and reproductive characteristics of the two 12-mg versus single 12-mg dose dexamethasone treatment was done using proportions. Cumulative incidences for each early neonatal outcome: respiratory distress syndrome, necrotizing enterocolitis, neonatal septicemia, neonatal mortality and the mean duration of hospital stay for the two12-mg and single 12-mg dexamethasone groups was calculated and compared.

The cumulative incidences were calculated using all cases with each outcome known to have occurred during the duration of the retrospective cohort study, divided by the number of neonates in the study at baseline, per unit time. Bivariate analysis of relative risk for the different early neonatal outcomes (RDS, NEC, neonatal sepsis and neonatal mortality) was calculated to obtain measures of association according to the different socio- demographic and reproductive characteristics. Multivariate analysis was then done. Level of significance was set at $p<0.05$ and precision at the 95% confidence intervals.

5.14 Ethical Considerations

No consent was sought from patients as only their case notes were reviewed and data collected from these records. The study commenced after ethics approval was granted by the University of Nairobi and KNH Research and Ethics Review Committee (ERC).

Permission to undertake this study was sought from KNH-reproductive health department and health information department once ERC approval was granted.

Health records were in the safe custody of health information department and only the principal investigator and research assistants were allowed access to the health records; data collection took place within the health information department premise. No one was allowed to leave with patient case note/s out of the premise. Health information obtained was stored securely; filled data abstraction forms were stored in a lockable safe by the principal investigator to prevent loss. All computer entries which were password protected and only accessible to the Principal Investigator and statistician, was used for research purpose only without modification or disclosure. The filled data abstraction forms will be stored for not more than three years after which it will be disposed of by shredding.

Confidentiality was maintained at all times with anonymity to patient details and the abstraction forms allocated study numbers. Only the investigators accessed data for the purpose of the study. There were no major risks anticipated during the study period and after. Important findings were made available to Kenyatta National Hospital Management, Department of Obstetrics and Gynaecology- University of Nairobi and policy makers at the MoH Division of Reproductive Health.

5.15 Study Limitations and Mitigation

The limitation of this study was missing data which can lead to an over or under estimation of the effect estimate data secondary to its retrospective nature and the presence of many confounding factors. This challenge was overcome by increasing the sample size. Case notes with complete data were analyzed prospectively until adequate sample size was achieved. Use of antibiotic prophylaxis in the mothers was not determined and this could have been a confounder that was not adequately addressed in this study. Other confounders were taken care of at analysis stage with multi-variate regression models.

The gestational age could not be accurately determined as data was collected retrospectively. However, gestational age was determined based only on the last normal menstrual period as recorded and confirmed with first trimester ultrasound (if available) to reduce the confounding effect of this on the immediate neonatal outcomes.

6 RESULTS

The study included a total of 328 neonates delivered at 28 to 34 weeks gestation and admitted to NBU at KNH between January 1, 2011 and December 30, 2015 to mothers who had preterm PROM. Of these, 164 neonates were exposed antenatally to two doses of 12 mg dexamethasone and another 164 neonates were exposed to single dose of 12 mg dexamethasone (unexposed).

Maternal socio-demographic and reproductive characteristics

As shown in table 1 below: There were no differences in the socio-demographic characteristics between the two groups with the mean maternal age being 27.3 years in the two-dose group and 27.2 years in the single dose group; most of the mothers were married 133 (81%) in the exposed versus 139 (85%) in the unexposed group, p=0.379; majority of the participants had secondary education 63(38%) and 84(51%) in the two 12mg dexamethasone dose group and single 12 mg dexamethasone group respectively. Unemployment was high with 78(48%) in the two-dose dexamethasone population and 71(43%) in single –dose dexamethasone population respectively, p=0.169. table 1.

However, statistically significant differences were in some reproductive characteristics; about 97(59%) were multiparous in the two dose 12-mg dexamethasone group, p= 0.002 while 88(54%) were primigravida in the single dexamethasone cohort, p=0.006; majority of the neonates in the two-dose group were born at 32-34 weeks gestation 100 (61%), p<0.001 compared to 30-31 weeks gestational age at birth of most neonates in the single 12 mg dexamethasone dose group 66(40%, p=0.002); the two-12 mg dexamethasone dose group had a shorter duration of preterm PROM before onset of labour, less than 12 hours 54 (33%) compared to 25(15%)in the single dexamethasone group, p < 0.001. Most of mothers of neonates in the single 12 mg dexamethasone group had longer duration of preterm PROM before onset of labour

ranging from 12 to 48 hours 86 (52%), $p<0.001$, table 1. The mean birth weight was comparable, 1737.3±314.9g and 1745.8±380.8g, for the single 12-mg and two 12-mg dexamethasone doses respectively, table 1.

Table 1: Socio-demographic and reproductive characteristics of mothers who had preterm PROM and received variable doses of dexamethasone between 2011 and 2015 at KNH

Variable	Two 12-mg doses dexamethasone (N = 164) n (%)	One 12-mg dose dexamethasone (N = 164) n (%)	P value
Maternal age (years)			
Less than 18	5(3)	5(3)	1.0
18-24	50(30)	66(40)	0.065
25-29	60(37)	38(23)	0.008
30-34	30(18)	28(17)	0.772
More than 35	19(12)	27(16)	0.203
Marital status			
Single	23(14)	18(11)	0.404
Married	133(81)	139(85)	0.379
Divorced	8(5)	7(4)	0.792
Education level			
None	5(3)	3(2)	0.474
Primary	40(24)	32(20)	0.286
Secondary	63(38)	78(48)	0.094
Tertiary	56(34)	51(31)	0.556
Occupation			
Unemployed	84(51)	71(43)	0.15
Employed	54(33)	66(40)	0.169
Other	26(16)	27(16)	0.881
Parity			
Primigravida	63(38)	88(54)	0.006
Multipara	97(59)	69(42)	0.002
Grand-multipara	4(2)	7(4)	0.358
Gestational age			
28-29 weeks	24(15)	37(23)	0.065
30-31 weeks	40(24)	66(40)	0.002
32-34 weeks	100(61)	61(37)	<0.001
Birth weight (g)	1745.8±380.8	1737.3±314.9	0.825
Rupture of membranes before labor onset			
Less than 12 hours	54(33)	25(15)	<0.001
12-48 hours	54(33)	86(52)	<0.001
More than 48 hours	56(34)	53(32)	0.725
Mode of delivery			
Spontaneous vertex delivery	82(50)	122(74)	<0.001
Caesarean delivery	82(50)	42(26)	<0.001

Patterns of administration of dexamethasone

As shown in table 2 below: Up to 67 (41%) ($p = 0.01$) of mothers received the first dose of the two-dose dexamethasone regimen in less than an hour after admission while only 45 (27%) mothers received the single-dose less than an hour after admission, $p = 0.01$, table 2. There was significant difference in the duration between administration of the first dose and delivery among mothers receiving two-dose dexamethasone: 142 (87%) delivered more than 24 hours after the first dose compared to 65 (40%) deliveries within a similar period in the single dose non-exposed group ($p < 0.001$). Most mothers who received two doses of dexamethasone had a significantly longer duration of time from when they received the last dose till delivery, more than 24 hours in 134 (82%) ($p <0.001$) compared to the ones who received single dose dexamethasone. Up to 104 (61%) of the mothers who received single 12-mg dexamethasone stayed for 12-24 hours and more than 24 hours in hospital before delivery, $p<0.001$, table 2.

Table 2: Pattern of dexamethasone administration among mothers who had preterm PROM and received variable doses of dexamethasone between 2011 and 2015 at KNH

Variable	Two 12-mg dexamethasone doses (N=164) n (%)	One 12-mg dexamethasone dose (N=164) n (%)	P value
Lengths of time from admission to administration of the first dose			
Less than 1 hour	67(41)	45(27)	0.01
1-4 hours	44(27)	66(40)	0.01
More than 4 hours	53(32)	53(32)	1
Duration between first dose and delivery			
Less than 12 hours	2(1)	64(39)	<0.001
12-24 hours	20(12)	39(21)	0.027
More than 24 hours	142(87)	65(40)	<0.001
Length of time from the last dose to delivery			
Less than 12 hours	18(11)	64(39)	<0.001
12-24 hours	12(7)	39(21)	<0.001
More than 24 hours	134(82)	65(40)	<0.001
Personnel instructing administration of dexamethasone			
Consultant	19(12)	5(3)	0.003
Registrar	145(88)	159(97)	0.003

Early neonatal outcomes following dexamethasone administration

Immediate delivery outcomes

Our results showed no difference in the incidence of APGAR <7 at 5 minutes scores with 18(11%) of neonates delivered after two-dose dexamethasone administration relative to 11 (16.7%) neonates delivered to mothers receiving single-dose having APGAR scores below 7, table

4.

RDS, NEC and neonatal mortality

On univariate analysis, there were no significant differences in the occurrences of RDS, NEC and neonatal mortality between the two groups. A total of 112 (68.3%) and 124 (75.6%) of neonates who had two doses of 12-mg dexamethasone and single dose 12-mg antenatal dexamethasone respectively, had a diagnosis of RDS (p = 0.127). The incidence of NEC was 4 (2.4%) among neonates whose mothers received two-dose dexamethasone and 2 (1.2%) (p = 0.318) in the single dose dexamethasone group, table 3. Forty neonatal deaths (24.4%) occurred in the two 12-mg dexamethasone dosed group compared to 50 deaths (30.5%) in the single 12-mg dexamethasone dose group, (RR = 0.86, 95% CI 0.66-1.11, p = 0.234), table 3

Neonatal sepsis

Complete course of two 12-mg dexamethasone was associated with increased risk of clinically diagnosed neonatal septicemia 78 (47.6%) compared to single 12-mg dose dexamethasone 59 (36%). The group receiving single 12-mg dose had 22% lower odds of neonatal sepsis (OR = 0.78, 95%CI 0.62 to 0.99, p = 0.039) compared to the two 12-mg dexamethasone dose group, table 3.

Length of hospital stay

The number of neonates who stayed in hospital for more than 7 days was slightly higher 77 (54.9%) among neonates who were exposed to two doses of dexamethasone (complete course) compared to those who received single dose of dexamethasone 90 (47%), p =0.23. However, the length of hospital stay did not show any statistical significance, table 3.

Table 3: Early neonatal outcomes of mothers receiving variable doses of dexamethasone for preterm PROM at 28 to 34 weeks gestation between 2011 and 2015 at KNH

Variable	Single 12-mg dexamethasone dose N=164 (n %)	Two 12-mg dexamethasone dose N=164 (n %)	RR (95% CI)	P Value
APGAR <7 at 5 min				
Yes	18(11.0)	11(6.7)	1.00	
No	146(89.0)	153(93.3)	0.79(0.58-1.07)	0.127
RDS				
Absent	52(31.7)	40(24.4)	1.00	
RDS diagnosed	112(68.3)	124(75.6)	0.84(0.67-1.05)	0.127
NEC				
Absent	160(97.6)	162(98.8)	1.00	
NEC diagnosed	4(2.4)	2(1.2)	1.34(0.75-2.39)	0.318
Neonatal sepsis				
No sepsis diagnosis	105(64.0)	86(52.4)	1.00	
Sepsis	59(36.0)	78(47.6)	0.78(0.62-0.99)	0.039
Length of stay				
Less than 3 days	31(18.9)	38(23.2)	1.00	
Less than 7 days	43(26.2)	49(29.9)	1.04(0.74-1.46)	0.82
More than 7 days	90(54.9)	77(47.0)	1.20(0.89-1.61)	0.23
Neonatal outcome				
Alive	124(75.6)	114(69.5)	1.00	
Dead	40(24.4)	50(30.5)	0.85(0.66-1.11)	0.234

We did subgroup analysis by gestational age into 3 groups defined as 28-29 weeks, 30-31 weeks and 32-34 weeks gestation categories to determine if association was modified by gestational age. Single dose dexamethasone was associated with increased mortality at 28-29 weeks gestation (RR 2.52 95%CI 1.27 to 5.01; p=0.008) but at 30-31 weeks gestation, mortality was decreased (RR 0.48 95%CI 0.25 to 0.90; p=0.023) with single dose dexamethasone.

There was 34% lower risk of RDS in the single 12-mg dose dexamethasone group at 32-34 weeks gestational age (RR 0.66 95%CI 0.53 to 0.83; p=0.0) compared to the two 12-mg dexamethasone group, table 4.

Table 4: Early neonatal outcomes of mothers receiving variable doses of dexamethasone for preterm PROM at different gestational ages between 2011 and 2015 at KNH

Variable		Single 12-mg dose	Two 12-mg dose	RR (95% CI)	P value
Age 28-29 weeks					
RDS	Absent	5(20.8)	10(27.0)	1.00	
	RDS diagnosed	19(79.2)	27(73.0)	1.24(0.56-2.76)	0.6
Neonatal sepsis	Absent	10(41.7)	11(29.7)	1.00	
	Sepsis diagnosed	14(58.3)	26(70.3)	0.73(0.39-1.37)	0.331
Neonatal outcome	Alive	8(33.3)	26(70.3)	1.00	
	Dead	16(66.7)	11(29.7)	2.52(1.27-5.01)	0.008
Age 30-31 weeks					
RDS	Absent	8(20.0)	21(31.8)	1.00	
	RDS diagnosed	32(80.0)	45(68.2)	1.51(0.79-2.88)	0.216
Neonatal sepsis	Absent	24(60.0)	37(56.1)	1.00	
	Sepsis diagnosed	16(40.0)	29(43.9)	0.90(0.55-1.50)	0.694
Neonatal outcome	Alive	31(77.5)	35(53.0)	1.00	
	Dead	9(22.5)	31(47.0)	0.48(0.25-0.90)	0.023
Age 32-34 weeks					
RDS	Absent	39(39.0)	9(14.8)	1.00	
	RDS diagnosed	61(61.0)	52(85.2)	0.66(0.53-0.83)	0
Neonatal sepsis	Absent	71(71.0)	38(62.3)	1.00	
	Sepsis diagnosed	29(29.0)	23(37.7)	0.86(0.65-1.13)	0.276
Neonatal outcome	Alive	85(85.0)	53(86.9)	1.00	
	Dead	15(15.0)	8(13.1)	1.06(0.76-1.47)	0.732

On adjusting for various confounders, women aged >30 yrs had 3 fold higher risk of early neonatal mortality (RR 3.34, 95%CI 1.74 to 6.41; p<0.001) as shown in table 5 below.

Table 5: Multivariable regression to adjust for confounders for early neonatal mortality for neonates of mothers with preterm PROM at 28 to 34 weeks gestation in the period between 2011 and 2015, KNH

Variable	RR	95% CI		P value
Dexamethasone dose				
Two 12-mg dose	1.0			
Single 12-mg dose	1.03	0.70	1.52	0.879
Maternal age				
18-24	1.0			
25-29	0.98	0.50	1.88	0.94
30-34	3.50	2.00	6.11	<0.001
More than 35	3.34	1.74	6.41	<0.001
Parity				
Primigravida	1.0			
Multipara	0.63	0.36	1.09	0.098
Gestation age				
28-29 weeks	1.0			
30-31 weeks	0.95	0.63	1.43	0.81
32-34 weeks	0.59	0.33	1.07	0.082
Duration of PROM				
Less than 12 hours	1.0			
12-48 hours	0.65	0.38	1.11	0.119
More than 48 hours	0.97	0.64	1.47	0.895
Birth weight				
<1500 g	1.0			
1500 g and above	0.65	0.41	1.03	0.067

Adjustment for confounding factors by multivariate logistic regression analysis revealed the risk of neonatal sepsis was higher with longer duration of preterm PROM: the risk of neonatal sepsis was doubled significantly with 12-48 hours of preterm PROM (RR 2.0, CI 95% 1.26-3.19, p=0.004), table 6.

Table 6: Multivariable regression to adjust for confounders for early neonatal sepsis for neonates of mothers with preterm PROM at 28 to 34 weeks gestation in the period between 2011 and 2015, KNH

Variable	RR	95% CI		P value
Dexamethasone dose				
Two 12-mg dose	1.0			
Single 12-mg dose	1.13	0.85	1.51	0.393
Maternal age				
Less than 18	1.0			
18-24	0.77	0.41	1.43	0.406
25-29	0.63	0.33	1.18	0.15
30-34	1.28	0.68	2.41	0.438
More than 35	0.48	0.20	1.13	0.094
Parity				
Primigravida	1.0			
Multipara	0.96	0.70	1.34	0.83
Gestation age				
28-29 weeks	1.0			
30-31 weeks	0.72	0.46	1.12	0.145
32-34 weeks	0.67	0.38	1.17	0.162
Duration of PROM				
Less than 12 hours	1.0			
12-48 hours	2.00	1.26	3.19	0.004
More than 48 hours	1.57	0.98	2.53	0.061
Birth weight				
<1500 g	1.0			
1500 g and above	0.64	0.40	1.00	0.052

On adjusting for confounders for RDS, the risk of RDS was reduced by 21% following Caesarean delivery (RR 0.79 95%CI 0.68 to 0.92; p=0.002) while longer duration of time from administration of last dose of dexamethasone to delivery significantly increased the risk of RDS (RR 1.49 95%CI 1.22 to 1.83; p<0.01) for 12-24 hours and (RR 1.26 95%CI 1.01 to 1.57; p=0.043) for more than 24 hours respectively, table 7.

Table 7: Multivariable regression to adjust for confounders for RDS for neonates of mothers with preterm PROM at 28 to 34 weeks gestation in the period between 2011 and 2015, KNH

Variable	RR	95% CI		P value
Dexamethasone dose				
Two 12-mg dose	1.0			
Single 12-mg dose	1.08	0.93	1.26	0.296
Gestation age				
28-29 weeks	1.0			
30-31 weeks	1.03	0.83	1.27	0.814
32-34 weeks	1.14	0.89	1.47	0.295
Birth weight				
<1500 g	1.0			
1500 g and above	0.85	0.71	1.03	0.097
Mode of delivery				
Spontaneous vertex delivery	1.0			
Caesarian delivery	0.79	0.68	0.92	0.002
Duration from last dose to delivery				
Less than 12 hours	1.0			
12-24 hours	1.49	1.22	1.83	<0.001
More than 24 hours	1.26	1.01	1.57	0.043
Personnel instructing administering of dexamethasone				
Consultant	1.0			
Registrar	1.64	1.01	2.67	0.044

7 DISCUSSION

The maternal-socio demographic and reproductive characteristics were comparable for the exposed and the unexposed groups in the study: mean ages of the mothers; marital status; level of education; occupation; parity and birth weight. This implies the comparability of the early neonatal outcomes. The differences in the gestational age at the time of delivery between the cohorts was taken into account by performing stratified analysis by gestational ages and adjustment for confounders such as mode of delivery, duration of preterm PROM and gestational age by multivariate logistic regression.

One of the key findings of the study on pattern of dexamethasone administration demonstrated inadequate initiation of antenatal dexamethasone immediately at the time of admission; this could have led to the incomplete administration of just a single 12-mg dexamethasone dose. Again, up to 61% of the mothers in the cohort stayed in the hospital for even longer than 12 hours before delivery; this should have allowed completion of the total dexamethasone. There was no explanation for this finding and therefore another study in future may look into it. The neonates whose mothers received two 12-mg doses of dexamethasone had a longer time interval between the last dose and delivery, possibly increasing the optimal time for dexamethasone to act but at a greater risk of neonatal sepsis secondary to prolonged preterm PROM. A previous study showed similar finding of low administration of dexamethasone with up to 26% of the mothers getting a single 6 mg dexamethasone dose despite 47% having interval to delivery lasting up to 24 hours (12). A different study showed that increased time interval to delivery was associated with better outcomes (46)

The study showed no differences in the incidences of APGAR scores< 7 at 5 minutes, RDS, NEC and mortality in the early neonatal period among mothers who had preterm premature rupture of membranes and received single 12-mg dose dexamethasone compared to those who received two 12-mg doses of dexamethasone. Our findings are similar to two previous studies: comparing neonatal outcomes among women who received incomplete dose of betamethasone versus those who did not, showed no significant differences in low APGAR scores, rates of RDS and NEC; Another, found no difference in neonatal morbidities but had increased RDS with the steroid exposed (betamethasone) group (15,16). This was contrary to findings in a study of very preterm neonates which demonstrated decreased mortality and NEC only with complete course of betamethasone (17).

There was increased neonatal sepsis in the cohort that received two 12-mg doses of dexamethasone. This probably is due to the immunosuppressive effect of corticosteroids and the longer time to delivery interval in this cohort. Two other studies showed increased risk of sepsis with steroid exposure (7)(17).

On adjusting for various confounders, there were no differences in RDS, neonatal septicemia and mortality between the exposed and the unexposed groups based on the dose of dexamethasone administered. Increased maternal age was significantly predictive of neonatal mortality. A different study showed decreased neonatal mortality with steroid exposure but no differences in low Apgar scores, NEC and neonatal sepsis on adjusting for gestational age (15).

Subgroup analysis by gestational age showed increased mortality in the single 12 mg dexamethasone dose group at 30-31 weeks but decreased mortality at 28-29 weeks and no difference at 32-34 weeks. This may have been caused by the low number of neonates in the sub-

groups during sub-group analysis. Another study showed conflicting findings in the different gestational age groups (16)

There was no significant difference in the duration of hospital stay in the study, with more than half of the neonates staying longer than seven days in the NBU. However, other studies on the total duration of hospital stay showed that steroid exposure was associated with a longer duration of hospital stay (16,17).

The limitation of this study was missing data secondary to its retrospective nature and the presence of confounding factors. This study adds to the little pool of studies on dexamethasone and particularly the ones comparing single 12-mg dexamethasone dose to two 12-mg doses of dexamethasone in Kenya, in the region and in the world. It also encompasses a large diverse population from a referral facility and teaching hospital and the results may be generalizable in these areas.

Our results imply that incomplete single 12 mg dexamethasone dose confers similar benefits as complete course of two 12 mg doses of dexamethasone in preventing early neonatal outcomes and clinicians should not hesitate to administer it in patients with imminent preterm birth.

8 CONCLUSIONS

The incidence of early neonatal outcomes of mothers with preterm PROM at 28 to 24 weeks gestation at KNH in 2011 to 2015 were similar for mothers who received two doses of 12 mg dexamethasone and those who received single dose dexamethasone dose apart from early neonatal septicemia which was increased in the two 12 mg dexamethasone group

9 RECOMMENDATIONS

A single dose of dexamethasone reduces some adverse early neonatal outcomes in mothers with preterm PROM at 28 to 34 weeks gestation and it should be given at the earliest opportunity even when the standard two 12 mg doses of dexamethasone may not be completed

Further larger studies need to be conducted to evaluate the association of two 12mg dexamethasone dose and duration to delivery with septicemia in neonates of mothers with preterm PROM at 28 to 34 weeks gestation

There is need to address the third delay in timely administration of essential medication as well as completing the prescribed dose by health workers

TIME FRAME

Project months	September 2016	October 2016	November 2016- April 2017	May 2017	June 2017- October 2017	January- April 2018	May 2018
Proposal development							
Proposal presentation							
Ethical approval							
Training of assistants							
Data collection							
Data analysis							
Final presentation							

BUDGET

CATEGORY	REMARKS	UNITS	UNIT COST (KSHS)	TOTAL (KSHS)
Proposal Development	Printing and binding drafts	10	2,000	20,000
	Proposal Copies	12	1,500	18,000
Data Collection	Stationery Packs (Pens, questionnaire papers and Study Definitions)	LS	20,000	20,000
	Training research assistants	LS	25,000	25,000
	Research assistants (2)	2	30,000	60,000
Data Analysis	Statistician	1	50,000	50,000
Thesis Write Up	Computer Services	1	20,000	20,000
	Printing drafts	5	2,000	10,000
	Printing and binding Thesis	4	2,500	10,000
Miscellaneous expenses	Transport, communication and logistics	LS	30,000	30,000
Total budget(Kshs)				263,000

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10 APPENDICES

10.1 Appendix 1: Female Data Retrieval Forms for early neonatal outcome variables of neonates born at 28 to 34 weeks gestation to mothers who had preterm PROM at risk of preterm birth

- The data retrieval forms were filled by ticking appropriately according to the patient case notes/patient files

Date ____/_____/____ Serial No…….

- Maternal socio-demographic characteristics

1. Age (years)
   - *(a) <18*
   - *(b) 18-24*
   - *(c) 25-29*
   - *(d) 30-34*
   - *(e) >35*
2. Marital status
   - *(a) Single*
   - *(b) Married*
   - *(c) Divorced*
   - *(d) separated*
3. Education level
   - *(a) None*
   - *(b) Primary*
   - *(c) Secondary*
   - *(d) Tertiary*
4. Occupation
   - *(a) Unemployed*
   - *(b) Employed*
   - *(c) Other*
5. Obstetric history
   - *(a) Parity*
   - *(b) Primigravida*
   - *(c) Multipara*
   - *(d) Grand-multipara*
6. Gestational age
   - *(a) 28-29 weeks*
   - *(b) 30-31 weeks*
   - *(c) 32-34 weeks*
7. Birth weight in grams
8. Duration of preterm PROM

(a)<12 hours
(b) 12-48 hours
(c) >48 hours

9. Mode of delivery
   (a) Spontaneous vertex delivery
   (b) Caesarean delivery

- Patterns of dexamethasone administration

10. Total dose of dexamethasone administered

(a) two 12-mg dose

(b) single 12-mg dose

11. Lengths of time from admission to administration of the first dose

(a) <1 hour

(b) 1-4 hours

(c) >4 hours

12. Duration from the first dose to delivery

(a)<12 hours

(b) 12-24 hours

(c) >24 hours

13. Duration from the last dose to delivery

(a) <12 hours

(b) 12-24 hours

(c) >24 hours

10.2 Appendix 2: Neonatal outcome data retrieval form for early neonatal outcome variables of neonates born at 28 to 34 weeks gestation to mothers who had preterm PROM at risk of preterm birth

14. APGAR Score at 5 mins <7
15. Reason for NBU/NICU admission
    (a) Diagnosis of RDS
    (b) Diagnosis of NEC
    (c) Diagnosis of neonatal septicemia

16. Duration of stay in NBU/NICU (days)
    (a) <3 days
    (b) <7 days
    (c) >7 days
17. Neonatal outcome
    (a) Alive
    (b) Dead

10.3 Appendix 3: KNH protocol on preterm labour and preterm PROM (SOP/KNH/OBS/GYN/059)

	PREMATURE RUPTURE OF MEMBRANES(PROM)	**SOP/KNH/OBS&GYN/059**

1.0 Scope: women presenting to labour ward with premature rupture of membranes

3.0 Purpose:

4.0 Term & Definitions

- Preterm PROM – Rupture of fetal membrane before term (37 completed weeks)
- Prolonged PROM – if 24hrs elapse between rupture of the membrane and onset of labour in a term pregnancy.

5.0 Responsibility

6.0 Method

Risk above:
- Preterm labour
- Prolapse of the cord
- Placental abruption

(Amniotic – important cause of endomyometritis and puerperal sepsis) Preterm PROM – prolonged – potter's syndrome like features – extra ordinary flexion's wrinkling of the skins. Risk of pulmonary hypoplasia and limbs positioning defect in the newborn.

Symptoms/signs:
- Report of sudden gush of fluid or continued leakage
- Colour and consistency of the fluid
- Presence of flecks of vernix or meconium
- Decrease in size of the uterus.
- Increase prominence of the fetal to palpation.

DDX – Hydrorrhea gavidrum
Vaginitis
Increase vaginal secretions
Urinary incontinence.

Sterile speculum examination

- pooling – the collection of amniotic fluid in the posterior fornix.

- Nitrazine test – sterile cotton tipped swab used to collect fluids form the posterior fornix and apply it to nitrazine paper. In presence of amniotic fluid the paper turn blue (Alkaline Ph.7.0 -7.25)
- Ferning – a drop of fluid from the posterior fornix should be placed on a slide and allowed to air dry. Amniotic fluid will form a fern like pattern of crystallization.

The above three confirm ROM. Absence of one of the above – indication for further testing because other factors can produce false positive results:-

Alkaline PH on nitrazine test
- Vaginal infections
- Presence of blood or semen
- Ferning – cervical mucus

During speculum examination
- Inspect cervix to determine degree of dilation, effacement and for cord prolapsed.
- Patient can cough or perform a valsalva maneuver and check loss of fluid through os.

If there is a significant vaginal pool
- collect for fetal lung maturation
- Collect for gram stain and culture and sensitivity and wet mount preparation.

NB: If no fluids take cervical secretion for gram stain and culture and sensitivity.

If no fluid is found, a dry pad should be placed under the patient's perineum and observed for leakage.

Ultrasound – dating/oligohydramnios – if still no confirmation and patient's history is highly suspicion for PROM, may perform amniocentesis and insert a dilute solution of Evans blue or indigo carmine dye. Remove some amniotic fluid first for physiologic maturity testing; analysis for white blood cells or bacteria and possible culture and sensitivity testing. After 15-20 minutes, insertion of sterile vaginal speculum will reveal blue dye in the vagina if the membrane are ruptured.

Laboratory tests

- complete blood count with differential count
- Urinalysis and culture and sensitivity

Amniocentesis – Determine fetal maturity check presence of infection.

Amniotics – safer to deliver than keep the fetus in utero. (organism – streptococcus B/D; anaerobes

- fever – temperature chart 4 hourly
- Maternal leukocytosis - >16,000/ml considered alarming
- Uterine tenderness – checked 4 hourly
- Tachycardia – maternal pulse >100/min
    - Fetal heart rate>160/min
- Foul smelling amniotic fluid

NB: Frequent fundal examination may cause uterine tenderness. Use of steroids may cause mild luecocytosis. Also labour cause leucocytosis (20 – 25% increase) Amniotic fluid – if numerous leucocytes bacteria on gram stain or aerobic or anaerobic culture. Amniotics present – deliver irrespective of gestation and cover with broad spectrum antibiotics.

Continuous fetal monitoring if possible. Term pregnancy without amnionits (>37 wks) Observe next 6-12 hours – if not yet in labour – induce labour if no contraindication. If term with indication for caesarian section – deliver immediately.

Preterm pregnancy without amnionitis

34 – 37 weeks – manage as term pregnancy because no evidence that antibiotics, corticosteroids or tocolytic improve outcome hence deliver.
NB: must be sure of dates if not do carry lung maturity testing before delivery.

<24weeks – very low rates of fetal salvage with considerable maternal risk. Use of steroids/tocolytics/antibiotics to prolong the pregnancy – no proven benefit. Hence expectant management or actively terminate pregnancy.

24 – 34 wks – interventions to prolong pregnancy and improve outcome. Rule out amniotics.

Amniotic fluid – pool in the vaginal
Or amniocentesis – culture and sensitivity Gram
Gram stain
Check for lung maturity

Antibiotic

7.0 Reference

10.4 Appendix 4: KNH-UON Ethics Review Committee approval

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06 APR 2017
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6th April 2017

Dr. Scholastica Akinyi Odhiambo
Reg. No.H58/76608/14
Dept.of Obs/Gynae
School of Medicine
College of Health Sciences
University of Nairobi

Dear Dr.Odhiambo

REVISED RESEARCH PROPOSAL – NEONATAL OUTCOMES AMONG MOTHERS RECEIVING VARIABLE DOSES OF DEXAMETHASONE FOR PRETERM PREMATURE RUPTURE OF MEMBRANES AT KENYATTA NATIONAL HOSPITAL: A COHORT STUDY (P906/11/2016)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and **approved** your above revised proposal. The approval period is from 6th April 2017 – 5th April 2018.

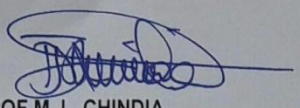
This approval is subject to compliance with the following requirements:

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) 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*).
f) Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
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.

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

"Protect to Discover"

Yours sincerely,



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