ANTENATAL CORTICOSTEROID USE IN PRETERM DELIVERY AT KENYATTA NATIONAL HOSPITAL

A dissertation submitted in partial fulfillment for the award of degree of Master of Medicine in Obstetrics and Gynaecology of the University of Nairobi.

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DECLARATION

This is to declare that this research work and dissertation is my original work and that it was done with the guidance of my supervisors. It has not been submitted to any other university for the award of a degree.

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DEDICATION

This book is dedicated to my dear daughter Mitchelle, son Brian, wife Peninah for their unconditional love and support. To my parents for their sacrifice and support to give me the best education.

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OPERATIONAL DEFINITIONS

Labour: Intermittent uterine contractions that increase in frequency and intensity and result in effacement and dilatation of the cervix and spontaneous bearing down effort leading to expulsion of the products of conception. [1,4,45]

Preterm labour: labour occurring after 20weeks but before the completion of 37weeks' gestation. However in our setup, a gestation of 28 weeks is used due to poor neonatal survival rates.

Preterm birth is defined as delivery that occurs between 20 weeks and 37 weeks of gestation or a neonate born with a birth weight of 500grams or more[1-2] in our setup a gestation of 28weeks is used as the lower limit due to poor neonatal survival rates.

Late preterm birth: delivery occurring after 34 weeks but before completion of 37 weeks of gestation. **Late preterm infant:** an infant born at a gestational age between 34 and 37 weeks. Initially referred to as near term infants.

Expected Due Date (EDD): The calculated estimated date of delivery using Naegele's rule, i.e. by adding 7 days to the date of the first day of the last normal menstrual period and counting back 3 months. [1]

Symphysio-Fundal height: The distance between the upper border of the pubic symphysis and the upper border of the uterine fundus measured in centimeters. This corresponds to the gestation in weeks up to 36 weeks gestation. A variation of ± 2cm is accepted as normal.[16]

Last Menstrual Period (LMP): The first day of the last menstrual period. This precedes the conception day by approximately 14 days in a regular 28 day menstrual cycle. [4]

Quickening: The first perception of fetal movements by the pregnant woman. It is usually felt about the 18th week in primigravidae and about the 16th week in multiparae.[9]

Preterm pre-labour rupture of membranes: The spontaneous rupture of the amnion and chorion before the onset of labor before 37 weeks' gestation.

Pre-eclampsia: A syndrome characterized by the new onset of hypertension and proteinuria after 20 weeks of gestation in a previously normotensive woman[46].

One course of ACS: either 1)2 doses of betamethasone given as 24mg once daily for 24 hours or 2) 4 doses of dexamethasone given as 6mg 12 hourly for 24 hours.

LIST OF APPREVIATIONS

(i) ACOG American College of Obstetricians and Gynecologists

(ii) ACS – Antenatal Corticosteroids

(iii) ANC - Ante-Natal Care

(iv) CS- Caesarean section

(v) EDD - Estimated Due date

(vi) EGA- Estimated gestational age

(vii) FSB- Fresh Still Birth

(viii) KNH - Kenyatta National Hospital

(ix) LBW - Low Birth Weight

(x) LMP - Last Menstrual Period

(xi) MSB - Macerated Still-Birth

(xii) NBU - New Born Unit

(xiii) NICU – Neonatal Intensive Care Unit

(xiv) NRFS - Non-Reassuring Fetal Status

(xv) PROM Prelabour Rupture of Membranes

(xvi) PPROM- Preterm Prelabour Rupture of membranes

(xvii) PTL- Spontaneous preterm labour

(xviii) RCOG- Royal College of Obstetricians and Gynaecologists

(xix) RCT- Randomized Clinical Trial

(xx) RR- Relative risk

(xxi) SHO- Senior House Officer

(xxii) UON -University of Nairobi

ABSTRACT

Introduction

Preterm birth is the cause of at least 75% of neonatal deaths that are not attributable to congenital malformations. Antenatal corticosteroids given to mothers at risk of preterm birth between 24 and 34 weeks reduce the incidence and severity of respiratory distress syndrome, intraventricular haemmorhage, necrotizing enterocolitis and neonatal deaths. The World Health Organization recommends the use of one course of antenatal steroids for all pregnant women between 26 and 35 weeks of gestation who are at risk of preterm delivery within 7 days while both the American College of Obstetricians and Gynaecologists and the Royal College of Obstetricians and Gynaecologists recommend their use between 24 and 34 weeks of gestation. The use of ACS after 34 or 35 weeks of gestation is not recommended unless there is evidence of fetal pulmonary immaturity. Despite this, ACS are widely used locally across all gestational periods.

Objective

To determine the frequency of adminstration and impact of ACS in reducing the incidence and severity of RDS, NBU admissions and neonatal deaths in preterm neonates 28- 37 weeks gestation, born to women with PTL, PPROM or severe preeclampsia at KNH.

Methods

The study was conducted in Labour ward, NBU and the postnatal wards of Kenyatta National Hospital. It was a hospital-based cross sectional study with a descriptive and comparative design that compared the neonatal outcomes of mothers with preterm birth who received antenatal steroids and those who did not receive the steroids. The study population were mothers with preterm birth between 28-37 weeks gestation and

their neonates. The women who met the inclusion criteria and consented for the study were recruited sequentially immediately after delivery. The mothers were interviewed and the information obtained entered into a questionnaire. Maternal and neonatal medical records were scrutinized and information gathered filled in a structured questionnaire. The neonates were followed up until discharge/death or the 7th day, whichever came earlier. The outcome measures included occurrence of RDS, severity of RDS (use of and duration of oxygen therapy, admission to NICU and use of mechanical ventilation), neonatal NBU admissions and neonatal deaths. The outcomes were compared for gestational age.

Results

Two hundred and six (206) women who met the inclusion criteria were recruited: 114 had spontaneous preterm labour, 53 PPROM and 39 severe Pre- eclampsia. The overall frequency of antenatal steroid use at KNH was 35%. Forty six percent of those who delivered before 34weeks received ACS while 26% of those who delivered after 34 weeks received ACS. Dexamethasone was the only ACS used at KNH. Only 3 % (n=2) of the mothers received a complete course of ACS. ACS significantly reduced the occurrence and severity of RDS in preterm neonates up to 34 weeks gestation with 69% of neonates not exposed to ACS developing RDS compared to 38% of those who were exposed. ACS reduced neonatal mortality of preterm neonates across all gestational ages. However, the impact was more in those delivered before 34weeks (11.5% reduction in mortality) compared to those delivered > 34 weeks (5.8% reduction in mortality). ACS did not reduce the prevalence of NBU and NICU admissions.

Conclusions

ACS is effective in reducing the incidence and severity of neonatal RDS and mortality. The effect is significant in those born <34 weeks gestation.

Recommendations

There is urgent need to upscale the utilization of ACS at KNH. Measures should be put in place to ensure that patients get a complete course of ACS. There is need to standardize the dose of dexamethasone. The study provides local evidence to discourage the routine use of ACS after 34 weeks.

INTRODUCTION

The length of human pregnancy is variable. A normal pregnancy lasts between 38 and 42 weeks (260-294 days). This is referred to as a term pregnancy. Pregnancies that extend up to and beyond 42 weeks (294 days) are termed as post term pregnancies and those that end before 37 completed weeks are termed as preterm pregnancies.[1-4]

Pregnancies are expected to end in labour and delivery of a viable fetus at term.

Corticosteroids given to women at risk of preterm birth before 34weeks reduce neonatal deaths, respiratory distress syndrome, intraventricular haemorrhage and necrotizing enterocolitis[5, 6].

However, the use of antenatal steroids after 34 weeks gestation is controversial. After this gestation corticosteroids are still thought to be effective but the reduction in RDS, IVH and neonatal death is not significant. The number of women who will need to be treated to prevent one case of RDS would be much higher. The World Health Organization recommends the use of one course of antenatal steroids for all pregnant women between 26 and 35 weeks of gestation who are at risk of preterm delivery within 7 days while both ACOG and RCOG recommend considering the use of ACS after 34 weeks' gestation if there is evidence of pulmonary immaturity [5, 6, 7, 8,9,10]. Locally, ACS are routinely used after 34 weeks gestation but there are no local studies to support or refute their continued use at and beyond this gestation.

This study aimed at finding out the frequency of administration and the impact of ACS in preventing neonatal morbidity and mortality in obstetric subgroups with preterm birth in our set up.

LITERATURE REVIEW

Preterm labor is defined as labor occurring after 20 weeks but before the completion of 37 weeks gestation and preterm birth refers to the birth of a baby of less than 37 weeks gestational age[1, 3, 4].

Preterm birth is the leading cause of neonatal morbidity and mortality, accounting for 75% of neonatal deaths excluding those related to congenital malformations[1-4, 10]

The prevalence of preterm labour and delivery is 6% to 22 %, being lower in developed and highest in developing countries[1, 4]. In a cross-sectional study done in KNH in 2001, the prevalence of preterm labour was found to be 15.6%[11]. In the USA, the prevalence ranges between 12-13% and 5-9% in other developed countries[8]. By gestational age, 5% of preterm births occur at less than 28 weeks, 15% at 28–31 weeks, 20% at 32–33 weeks, and 60–70% at 34–36 weeks; this is in contrast to KNH where 28.5% of preterm births occur at 28-30 weeks, 30% at 31-33 weeks and 41.5% at 34-36 weeks.[11, 12]

Preterm birth is classified as either spontaneous or indicated. Spontaneous preterm births are caused by spontaneous preterm labor (40-45%) or following spontaneous premature rupture of the membranes (20-25%). Indicated preterm births account for 30-35% of preterm births and are induced for obstetrical reasons for example pre–eclampsia, eclampsia, hemorrhage and acute or chronic fetal compromise[12, 13]. A cross-sectional study done at KNH in 2001 found no associated factor in 52% of the preterm deliveries while 26.6% were due to preterm PROM and 8.5% due to pre-eclampsia, among other factors[11].

The causes of preterm labor and PROM are not fully understood. Three groups of women are at greatest risk for premature birth. These are: women who have had a previous premature birth, women who are pregnant with twins, triplets or more and women with certain uterine or cervical abnormalities[12].

Certain lifestyle factors may put a woman at greater risk for preterm labor. These include: Late or no prenatal care, smoking, drinking alcohol, substance abuse, exposure to the medication diethylstilboestrol, domestic violence (including physical, sexual or emotional abuse), lack of social support, extremely high levels of stress and long working hours with long periods of standing[1,4,6,12,14]. Maternal substance abuse increases the risk of preterm birth, but it is difficult to separate the risk attributable to the substance from other risk factors, which are common in these patients. Spence et al found that women with cocaine positive urine samples were at four-fold increased risk of developing preterm labor. Ney JA et al found positive urine toxicology 17 percent of women with preterm labor compared 2.8 percent controls with uncomplicated labor at term [6]. Cocaine was the most common substance identified and was detected in approximately 60 percent of women in preterm labor with positive toxicology tests [6, 14].

Certain medical conditions during pregnancy also may increase the likelihood that a woman will have preterm labor. These include: Infections (including urinary tract, genital tract, sexually transmitted and other infections), hypertension, diabetes, thrombophilia, being underweight before pregnancy, obesity, short inter-pregnancy intervals (One study found that an interval of less than 18 months between birth and the beginning of the next pregnancy increased the risk of preterm labor, though the greatest risk was with intervals

shorter than 6 months) , pregnancy following in vitro fertilization, birth defects in the baby and early pregnancy bleeding [1,4,12,15,16].

Certain demographic factors also increase the risk. These are: black race, extremes of age (below 17 or older than age 35 years of age) and low socioeconomic status.[1, 4, 12, 16]

Short-term morbidities associated with preterm birth include respiratory distress syndrome (RDS), hypothermia, hypoglycemia, jaundice, intraventricular hemorrhage, necrotizing enterocolitis, bronchopulmonary dysplasia, sepsis, and patent ductus arteriosus. Long-term morbidities include cerebral palsy, mental retardation, and retinopathy of prematurity.[1-3, 16]

Late preterm infants are usually healthier than babies born earlier. More than 99 percent of these babies survive, though they are 6 times more likely than full-term infants to die in the first week of life (2.8 per 1,000 vs. 0.5 per 1,000) and 3 times more likely to die in the first year of life (7.9 per 1,000 vs. 2.4 per 1,000) . These babies remain at higher risk than full-term babies for newborn health problems, including breathing and feeding problems, difficulties regulating body temperature, and jaundice. These problems are usually mild. Because their brain development is not complete, these babies may be at increased risk for learning and behavioral problems. Most do not develop serious disabilities resulting from premature birth.[17, 18]

Russell RB et al, however, found that late preterm infants are more than 3 times as likely to develop cerebral palsy and are slightly more likely to have developmental delays than babies born full term. Moster D found that adults who were born at 34 to 36 weeks

gestation may be more likely than those born full-term to have mild disabilities and to earn lower long-term wages[19, 20].

The diagnosis of preterm labour is not easy. Whereas the symptoms of imminent spontaneous preterm birth are four or more uterine contractions in one hour associated with cervical effacement and dilatation occurring before 37 weeks' gestation[1, 3], these may not be enough to define the risk of preterm labor. Oncofetal fibronectin in cervico-vaginal fluid and ultrasonography to determine cervical length may be considered to complement the clinical assessment. With the use of fetal fibronectin and sonographic evaluation of the cervix, it is possible to identify the majority of women who are not in preterm labor [1,3,16, 21, 22].

Generally, management of pre-term labour falls into 2 categories: expectant management (conservative) or intervention.[1, 3, 30]

In pregnancies between 24 and 34 weeks gestation or estimated fetal weight between 600 and 2500 g, intervention with corticosteroids has been shown to be of benefit in reducing fetal morbidity and mortality rates. Corticosteroids have been shown to decrease the incidence of neonatal respiratory distress, intraventricular hemorrhage, and neonatal mortality even when treatment lasts less than 24hours[1, 3, 5, 23].

For pregnancies between 35 and 37 weeks of gestation the fetal survival rate is within 1% of the survival rate at term. At this gestation fetal morbidity is less severe and is rarely a cause of long-term sequelae. Corticosteroids have not been shown to be of benefit in

fetuses of this age. Expectant management is usually the recommended course of action at this gestation; however antenatal steroids can be used if there is evidence of fetal lung immaturity[1, 5, and 23].

There are two most extensively studied steroid regimens: betamethasone 12 mg IM every 24 hours for a total of 2 doses; or dexamethasone 6 mg IM every 12 hours for a total of 4 doses.[1-3, 5, 13, 16, and 23] A metaanalysis concluded that betamethasone and dexamethasone are comparable in reducing the rate of most major neonatal morbidities and mortality in preterm neonates. While both ACOG and RCOG agree that either steroid can be used. RCOG Scientific Advisory Committee recommends that betamethasone is the steroid of choice to enhance lung maturity.[5,23,24, 25]

The optimal benefits of antenatal corticosteroids are seen 24 hours after administration, peak at 48 hours, and continue for at least 7 days. If therapy for preterm labor is successful and the pregnancy continues beyond 1 week, there appears to be no added benefit with repeated courses of corticosteroids.[1-3, 5, 13, 23, and 26]

The principles of managing the preterm PROM patient are similar to those for managing the preterm labor patient. The key difference is the much increased risk of developing chorioamnionitis associated with preterm PROM. Pregnancies beyond 34 weeks' EGA can be managed as a term pregnancy because there is no evidence that antibiotics, corticosteroids, or tocolytics improve outcome in these patients. These patients can be managed expectantly as long as they show no signs of chorioamnionitis.[1-3, 5, 13, and 23]

For pregnancies with PROM between 24 and 34 weeks estimated gestation, management with antibiotics alone and with antibiotics combined with corticosteroid therapy has shown improvements in neonatal outcomes.[1-3, 5, and 23.]

Respiratory distress syndrome (RDS) is one of the serious complications of preterm birth and the primary cause of early neonatal morbidity and mortality. Neonatal RDS affects approximately 1% of all live births, but affects 10% to 15% of all infants with a birth weight less than 2500g.[1-4 9, 27-30.] Accurate estimation of gestational age for example by use of early pregnancy obstetric ultrasonography and the routine use of antenatal corticosteroids to accelerate fetal lung maturity in women threatening to deliver before 34weeeks' gestation has resulted in a dramatic decrease in the incidence of RDS over the last 30 years.[27-33]. Respiratory distress syndrome occurs as a result of surfactant deficiency, poor lung anatomical development and immaturity in other organs. Respiratory distress can also result from a genetic problem with the production of surfactant associated proteins.[1-4, 9, 34, and 35.]

Respiratory distress syndrome begins at or shortly after birth. The clinical course for the acute disease lasts about 2 to 3 days. Despite huge advances in care, RDS remains the most common single cause of death in the first month of life in the developed world. Complications of RDS include metabolic disorders (acidosis, hypoglycaemia), patent ductus arteriosus, hypotension, chronic lung changes, and intracranial hemorrhage[36].

The diagnosis of RDS is made by the clinical picture of tachypnoea, tachycardia, chest wall retraction, expiratory grunting, flaring of the nostrils and cyanosis during breathing

efforts and the chest x-ray, which demonstrates decreased lung volumes, discrete, uniform infiltrate (sometimes described as a "ground glass" appearance) that involves all lobes of the lung, and air-bronchograms[36].

Management options of RDS include use of oxygen by mask for mild cases or via endotracheal tube in severe cases and use of exogenous surfactant[36].

Most cases of respiratory distress syndrome can be ameliorated or prevented if mothers who are about to deliver prematurely can be given antenatal steroids[1-3, 27, 28, 31-33, 36]

Despite being used for over 50 years to prevent respiratory distress syndrome, antenatal corticosteroid therapy is still controversial. Its use raises a number of questions which include: whether the use of antenatal corticosteroids are an effective therapy; who are the candidates for antenatal corticosteroid therapy; whether there benefit after 34 weeks' gestation; when is the optimal time to treat; which are the optimal steroids; what is the ideal dose and route of administration; are there any contraindications to the administration of ACS; are antenatal corticosteroids indicated in women with premature rupture of membranes; is the use of ACS recommended in pregnancies complicated by maternal diabetes mellitus; is the use of ACS effective in twin pregnancy and whether the treatment with corticosteroids can be repeated[9,23].

A number of studies have been done to try and answer some of the questions above. On the question of effectiveness and safety, a Cochrane review of twenty-one randomized controlled studies of antenatal steroid administration showed that treatment with antenatal corticosteroids was associated with an overall reduction in neonatal death in 18 studies,

RDS, cerebroventricular haemorrhage in 13 studies, necrotizing enterocolitis in 8 studies, respiratory support, intensive care admissions in 2 studies and systemic infections in the first 48 hours of life in 5 studies. The review did not find any increase risk to the mother of death, chorioamnionitis or puerperal sepsis[26].

The effectiveness, safety and long term effects of multiple courses of ACS has also been questioned. A Cochrane systematic review of 5 randomized controlled trials of women who had already received a single course of corticosteroids seven or more days previously and were still considered to be at risk of preterm birth, found that treatment with repeat courses of corticosteroid was associated with a reduction in occurrence and severity of any neonatal lung disease and serious infant morbidity. However, these benefits are associated with a reduction in some measures of weight and head circumference at birth[37].

Despite the reduction in infant morbidity and mortality associated with ACS, epidemiological and animal studies show that maternal corticosteroid administration delays myelination in the fetal brain and reduces the growth of all fetal brain areas, particularly the hippocampus. There may be long term effects on the setting of the hypothalamo-pituitary axis and glucose homeostasis. In preterm infants, antenatal corticosteroids have been associated with higher systolic and diastolic blood pressures in adolescence, possibly leading to clinical hypertension. The same studies however reveal no long term effects in cognitive functioning, working memory and attention, psychiatric morbidity, handedness, or health related quality of life [5, 38, 39]

JUSTIFICATION AND UTILITY

Despite the well documented evidence on the use and effectiveness of antenatal steroids and their lack of efficacy beyond 34 weeks gestation, these drugs are still widely used locally across all gestations. Their use especially after 34 weeks is largely because there are no local studies on ACS use. Clinicians also feel that most of the studies on ACS are done in high income countries that have better equipped NBUs/NICUs and access to affordable surfactant which is not the case locally.

This study aimed at finding out if antenatal steroids reduce the incidence and severity of RDS and neonatal mortality in preterm neonates at KNH.

RESEARCH QUESTION

Is the incidence and severity of RDS in infants born between 28-37 weeks due to PTL, PPROM or severe PET to mothers who received antenatal corticosteroids lower than those born to mothers who did not receive antenatal steroids?

NARRATIVE CONCEPTUAL FRAMEWORK

Spontaneous preterm labour, PPROM and severe PET are the leading causes of preterm birth at KNH. ACS are still widely administered to mothers at risk of preterm birth in an effort to reduce neonatal morbidity and mortality. Despite the proven benefits, there are mothers who are still not given this intervention despite obvious risks of preterm birth.

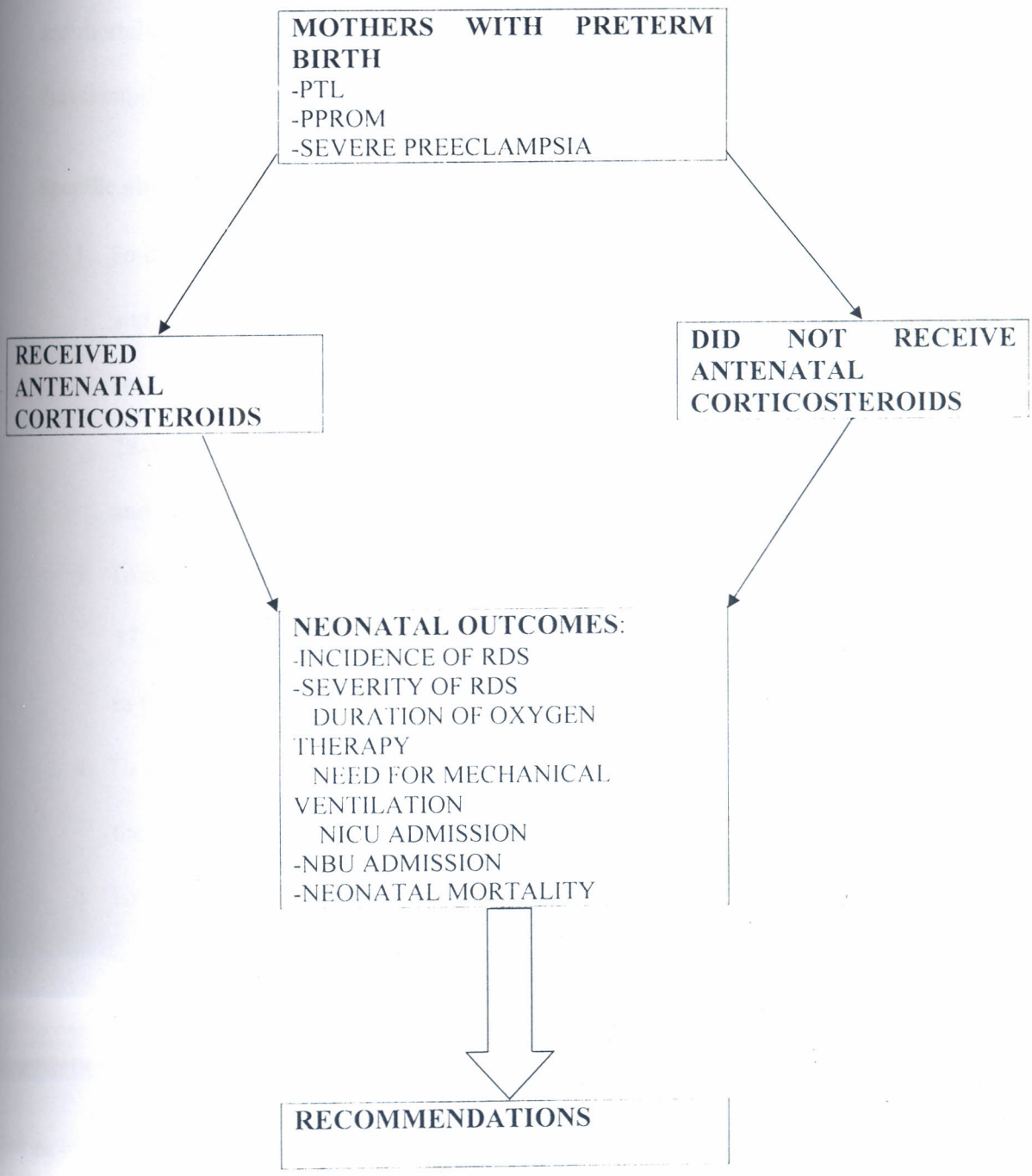
This was a comparative and descriptive research study that compared the neonatal outcomes of those exposed to antenatal steroids with those not exposed. The subgroups of mothers included were those with spontaneous preterm labour with intact membranes, PPROM and those undergoing elective delivery for severe pre eclampsia at 28-37 weeks of gestation (28weeks to 37^{+6} weeks). The outcomes were compared for gestational age among those exposed and those not exposed.

Study participants were recruited after delivery. Mothers were interviewed and the information obtained entered into a structured questionnaire. Labour and delivery records, treatment sheets, infant notes, admission and discharge records and operating theatre notes were scrutinized and information gathered entered in a structured questionnaire. Their neonates were followed up until discharge/death or 7 days after delivery, whichever came early.

The outcome variables measured were;

- Whether ACS was administered or not
- Occurrence of RDS
- Severity of RDS as determined by use and duration of oxygen therapy, NICU admission and use of mechanical ventilation.
- Prevalence of neonatal NBU admissions
- Neonatal deaths.

DIAGRAMMATIC REPRESENTATION OF THE CONCEPTUAL FRAMEWORK



OBJECTIVES

Broad objective:

To determine the impact of antenatal corticosteroids in reduction of neonatal morbidity and mortality in infants delivered between 28- 37 weeks due to PTL, PPROM or severe Preeclampsia at KNH.

Specific objectives

1. To determine the frequency of ACS use at KNH in mothers with PPROM, PTL, and severe preeclampsia at 28- 37 weeks.
2. To determine the incidence of RDS at KNH among neonates delivered between 28-37 weeks due to PTL, PPROM or severe PET whose mothers received ACS and in those whose mothers did not receive ACS.
3. To determine the severity of RDS at KNH among neonates delivered between 28-37 weeks due to PTL, PPROM or severe PET whose mothers received ACS and in those whose mothers did not receive ACS.
4. To determine the prevalence of neonatal admissions (NBU) among the ACS and the non ACS group.
5. To compare the neonatal mortality among neonates delivered between 28-37 weeks due to PTL, PPROM or severe PET whose mothers received ACS with those whose mothers did not receive ACS.

The diagnosis of RDS was made by a clinical presentation of tachypnoea, chest wall retraction, flaring of alae nasi, cyanosis during breathing efforts, expiratory grunting and tachycardia. A diagnosis of severe RDS was made if use of oxygen therapy lasted more

than 24 hours or if there was use of mechanical ventilation or if the neonate was admitted to NICU. Those who were put on oxygen therapy for <24hrs or did not require mechanical ventilation or were not admitted to NICU admission were categorized as having mild RDS.

METHODOLOGY

The study area:

The study area was Kenyatta National Hospital. The hospital is a national referral and teaching hospital. It is situated in Nairobi, 4 kilometers west of the central business district. It is also the main teaching hospital for the College of Health Sciences, University of Nairobi. The hospital caters to patients from Nairobi and its environs as well as referrals from other hospitals in the country and the greater Eastern Africa region.

KNH has one Labour ward, three antenatal/postnatal wards (GFA, GFB and 1A) as well as a NBU. Patients with a pregnancy above 20 weeks gestation and those who are in immediate puerperium are admitted in the antenatal/postnatal wards. Patients in labour or with conditions requiring close monitoring, such as preterm labour, are admitted in labour ward. There is a maternity theatre for caesarean sections and other obstetric procedures.

The NBU has a capacity of 50 beds. It is divided into seven key areas: the admission nursery which handles all new admissions for stabilization before they are redistributed to other nurseries; the isolation nursery for sick preterm neonates; nursery B which handles preterm neonates with a birth weight below 1600 grams; nursery C which handles neonates with a birth weight above 1600 grams and sick term neonates; nursery D which

handles stable neonates with a birth weight above 1750 grams and stable term neonates; NICU handles neonates who require ventilatory support and lastly the kangaroo room is for stable preterm neonates whose mothers are keen on kangaroo mother care.

The following groups of neonates are admitted to KNH NBU:

- All preterm neonates with a birth weight of less than 2000 grams
- Neonates with a birth weight of more than 2000 grams if they have RDS, birth asphyxia, jaundice, congenital anomalies
- Neonates of mothers with diabetes mellitus and rhesus negative blood group.
- Mother's condition for example if the mother is admitted to intensive care for any reason.

The low birth weight neonates are discharged once they attain a weight of 1800 grams or when stable for the other diagnoses.

The study design:

This was a hospital based cross sectional study. The subgroups of patients included were those with spontaneous preterm labour with intact membranes, *PPROM and those* undergoing elective delivery for severe pre eclampsia at 28-37 weeks of gestation (28weeks +0 days to 37 weeks +6 days). The outcomes were compared for gestational age.

The researcher and the data clerks had no influence in patient care. The diagnosis of PTL, PPROM and severe PET was made by resident(s) in obstetrics taking care of the mothers in labour ward. Similarly the diagnosis of RDS was made by the resident in neonatology who reviews the preterm neonates immediately after delivery. The decision to prescribe

or not to prescribe ACS; the ACS used and regime administered (single versus multiple courses) was left to the primary doctors managing the patient(s).

Randomization of patients into treatment and no treatment groups was not done.

The study population

Two hundred and six (206) mothers/neonate pairs at KNH labour ward with preterm birth between 28- 37 weeks consented for the study. These were distributed as follows PPROM 53 patients; spontaneous preterm labour 114 patients and severe pre-eclampsia 39 patients.

Gestation was confirmed by any three of the following criteria;

i) LMP

ii) Ultra-sound scan in early pregnancy

iii) Fundal height recording at admission

iv) Quickening

v) Positive pregnancy test after first missed period

vi) Serial ANC attendance fundal height recordings.

Exposure of interest

The exposure of interest was ACS use in the mothers before preterm birth between 28 and 37 week of gestation.

Sample size estimation

The Fischer's formula was used to calculate the sample size as below,

$n = (z^2pq)/d^2$

Where:

n= Sample size

Z $(1-\alpha)/2=1.96$ - is the value of the standard normal distribution corresponding to a significant level of α (alpha) for a 2-sided test at the 0.05 level

d=Absolute precision set at 5%

p = is the estimated proportion of preterm cases who have RDS

q = 1-p

The sample size computed for this study using an expected prevalence of RDS in preterm deliveries to be 15% [33-36] was:

$$n = \frac{(1.96)^2 \times 0.15 \times 0.85}{(0.05)^2}$$

n= 195.92. This was rounded off to 200 patients

Inclusion criteria:

- Mothers who gave informed consent.
- Mothers with spontaneous preterm labour between 28-37 weeks' gestation.
- Mothers with PPROM between 28-37 weeks' gestation
- Mothers with severe pre –eclampsia undergoing elective delivery between 28-37 weeks' gestation.

Exclusion criteria:

The following were excluded;

- Mothers who had medical conditions e.g. diabetes mellitus, thyrotoxicosis , cardiac disease, tuberculosis
- Mothers who had the following obstetric complications: IUFD, congenital fetal malformations and chorioamnionitis diagnosed on or before admission.
- Contraindications to steroid use.
- A mother with a combination of the conditions under investigation eg PPROM/PET /PTL; PET/PPROM or PET/PTL.

Data collection procedure

Data was collected by the principal researcher and three assistants. A pre-tested structured questionnaire was used to collect data. Consenting clients were recruited sequentially on a daily basis after delivery. The in-patient numbers were obtained from the admission and discharge registers in labour ward, maternity wards, maternity theatre and NBU. Mothers were interviewed and the information given entered into a structured questionnaire. Data from labour and delivery records, treatment sheets, infant notes, admission and discharge records and operating theatre notes was extracted and information entered in a structured questionnaire. Their neonates were followed up till discharge or 7 days after delivery, whichever was shorter.

Data collection instrument:

A structured questionnaire was used (Appendix II). It was administered by the interviewer(s). The questionnaire had both open-ended and closed-ended questions.

Quality control of data

The research assistants were trained on interviewing, information retrieval and filling the questionnaire. Recording of clinical findings in ante partum, intrapartum and postpartum period was entered after thorough scrutiny.

In order to avoid double participant recruitment, the participants' admission (in-patient) numbers were entered into a register upon recruitment for serialization. This register was counter-checked daily for any double entries and if discovered, one of the questionnaires was withdrawn and discarded and the serialization rectified before recruitment was continued.

Data Handling and analysis:

After data collection the completed forms were handed over to the biostatician for entry and analysis.

The extracted data was entered into Statistical Package of Social Science™ (SPSS) version 13.0 for Windows (SPSS, Chicago, IL, USA) statistical software to check for errors and the requisite statistical tests performed. Frequency distribution was used for part of the data cleaning. Data was analyzed using the same software. Descriptive analysis was performed to characterize the number and type of patient outcome. To obtain insight into the social demographics factors of the patients, frequency tables were used with accompanying percentages. Bivariate comparison of continuous symmetric characteristic was performed using t-test and using the Mann-Whitney test for non-symmetric characteristics. Fisher exact test and chi square test, as appropriate were used for comparison of categorical characteristics. Statistical significance was defined as a two tailed p-value of less than or equal to 0.05.

ETHICAL CONSIDERATIONS

Approval was sought from the KNH Ethics and Research Committee before the study was carried out. Informed consent of patients was obtained before participating in the study. Standard care was given to all mothers regardless of whether they consented or declined to participate in the study and subjects were not exposed to any risk by participating in the study. The records were coded and patients' names were not used. The information collected remained confidential and was not used for any other purposes apart from the study. No incentives were given to the study subjects.

STUDY LIMITATIONS

The following limitations were encountered:

- The quality of record keeping. A few cases were encountered where the exact time and number of doses administered could not be easily ascertained from the patient's records.

Mitigation of study limitations

The following was done to overcome the above limitation:

- The mothers were asked to recall when and the number of doses of ACS received. The primary nurses were also interviewed to corroborate this. in cases where this information was not available, the questionnaire was withdrawn and a new client recruited.

RESULTS

A total of 206 mother/neonate pairs were recruited into the study. This group was made up of 114(55.4%) mothers with spontaneous preterm labour, 53(25.1%) with PPROM and 39(18.9%) with severe pre-eclampsia. Seventy two (34.9%) mothers received antenatal steroids while 134(65.1%) did not. Neonates were grouped into those exposed to ACS and those not exposed. The neonatal outcomes were then compared for gestational age: overall (i.e 28-37 weeks); below 34 weeks (i.e 28-33^{+6}weeks) and above 34 weeks(i.e 34 -37^{+6} weeks).

Table 1: The socio-demographic characteristics of the mothers (n=206)

Characteristic	Exposed to ACS (n=72) No. (%)	Not exposed to ACS (n= 134) No. (%)	OR (95% CI)	P- value
Age(years)				
<20	6(8.3)	19(14.2)	Ref	
21-25	14(19.4)	60(44.8)	1.4(0.4-4.5)	0.584
26-30	26(36.1)	29(21.6)	0.4(0.1- 1.3)	0.0048
>31	26(36.1)	26(19.4)	0.3(0.1- 1.1)	0.0031
Marital status				
Single	4(5.6)	15(11.2)		
Married	68(94.4)	118(88.1)	0.5 (0.1 – 1.6)	0.196
Separated	0(0)	1(0.7)	-	
Education level				
None	1(1.4)	2(1.6)	Ref.	
Primary	18(25.7)	45(43.1)	1.3 (0.0 – 19.5)	
Secondary	30(41.4)	61(46.8)	1.0 (0.0 – 15.2)	0.185
Tertiary	22(31.4)	24(17.5)	0.6 (0.0 – 8.6)	
Occupation				
Unemployed	36(50.7)	74(55.6)	Ref.	
Self employed	16(22.5)	37(27.8)	1.1 (0.5 – 2.4)	
Salaried	17(22.5)	14(10.5)	1.1 (0.5 – 2.4)	0.193
Other	3(4.2)	5(3.8)	0.8 (0.2 – 4.6)	

Table 1 above shows that apart from age there was no statistical difference in the socio-demographic characteristics between those exposed to ACS and those not exposed. Those above 26 years formed the bulk of those who received ACS while those in the 21-25 year bracket formed the majority of those who did not receive ACS.

Table 2: Obstetric characteristics of the mothers (n= 206)

Characteristic	Exposed to ACS(n= 72) No. (%)	Not exposed to AC (n 134) No. (%)	Total	OR(95% CI)	P-value
Admission diagnosis					
PTL	17(23.3)	97(72.4)	114(55.4)		**<0.001**
PPROM	25(34.2)	28(20.9)	53(25.7)	0.2(0.1 – 0.4)	**0.056**
PET	30(41.1)	9(6.7)	39(18.9)	0.1(0.0 – 0.2)	**<0.001**
Gestation (weeks)					
Admission	32.62 (31.9-33.2)	33.88 (33.4-34.4)	------	-	**0.002**
Delivery	32.65	33.92	------	-	**0.003**
Mode of delivery					
SVD	33(45.8)	88(65.6)	121(58.7)	Ref.	**0.005**
C/S	35(48.6)	42(31.3)	77(37.4)	0.8(0.2 – 4.6)	
Breech	4(5.6)	4(3)	8(3.9)	0.4(0.1 – 1.9)	
Birth weight	1844.4g	2134.3g	------	-	**0.001**
Infant sex					
Male	40 (37.7)	66 (62.3)	106 (51.5)	1.3(0.7 – 2.4)	**0.389**
Female	32 (32)	68 (68)	100 (48.5)		

Table 2 above describes events at admission, labour and delivery. As shown in the table, spontaneous preterm labour was the leading cause of preterm birth accounting for 55.4% of preterm deliveries followed by PPROM (25.7%) and severe Pre-eclampsia (18.9%).

With regard to the primary event leading to preterm birth, the two study groups differed significantly. Spontaneous preterm labour accounted for 72.4% of those who didn't receive ACS, followed by PPROM (21 %) and severe Pre-eclampsia (6.7 %). Among those exposed to ACS, severe pre- eclampsia accounted for 41.1%, followed by PPROM 34.2% and spontaneous preterm labour 23.3% (p=< 0.001).

There was a statistical difference in gestation at delivery between the two groups.

The average gestational age at delivery for those who received ACS was 32.65 weeks compared to 33.91 for those not exposed to ACS(P=0.003).

Most deliveries were spontaneous vertex deliveries. There was a statistical difference in mode of delivery between the two groups. 48.6% of those who received ACS delivered through caesarean section compared to 31.3% of those who didn't receive ACS (p= 0.005).

There was a statistical difference in the birth- weight between the two groups. The neonates who were exposed to ACS had an average weight of 1844g compared to 2134g for those not exposed(p =0.001).

There was no statistical difference between the two study populations with regard to neonatal sex (37.7% male vs 32% of female neonates were exposed to ACS, P=0.389).

Table 3: Descriptive analysis of ACS use (n=206)

Variable	Category	Frequency	Percentage
Received steroid (n=206)	Yes	72	34.9%
	No	134	65.1%
Steroid received (n= 72)	Dexamethasone	72	100%
	Betamethasone	0	0%
Duration between first dose and delivery (n=72)	0-24hrs	34	47.2%
	24-48hrs	24	33.3%
	48-72hrs	3	4.2%
	>=72hrs	11	15.3%
Number of doses	1 dose	19	26.4%
	2 doses	45	62.5%
	3 doses	1	1.4%
	4 doses	2	2.8%
	Not known	5	6.9%

Table 3 above shows that 35% of the mothers received ACS. Out of these only 3 %(2 patients) received a complete course of 4 doses. 89% received either 1 or 2 doses. All the mothers received dexamethasone.

Eighty one (81) percent of mothers delivered before 48hours of adminstration of the first dose with only 19% delivering after 48 hours.

Table 4: Frequency of ACS use by gestational age (n=206)

Gestational age (weeks)	Steroid use		Total	Percentage
	Yes	No		
28	9	8	17	8.3%
29	5	10	15	7.3%
30	4	7	11	5.3%
31	5	4	9	4.4%
32	6	5	11	5.3%
33	13	13	26	12.6%
Subtotal 1	**42(47.2%)**	**47(52.8)**	**89**	**43.2%**
34	10	12	22	10.7%
35	8	20	28	13.6%
36	10	32	42	20.4%
37	2	23	25	12.1%
Subtotal 2	**30(25.6%)**	**87(74.4%)**	**117**	**56.8%**
Overall Total	**72**	**134**	**206**	**100.0%**

Table 4 above describes the trend of ACS use across the gestational ages under study. As shown, the frequency of ACS use diminished with increasing gestation. Fifty seven of all the preterm births occurred between 34-37 weeks gestation while 43.2% occurred between 28 -33(+6) weeks.

Forty seven percent (47%) of mothers with early preterm birth (28-33+6weks) received ACS compared to 26% of those with late preterm birth (34-37weeks).

Among those who received ACS 58.3% (42 out of 72) were in the early preterm birth group while 41.7% were in the late preterm group.

Table 5: Impact of ACS use on occurrence of RDS

Gestational age (Weeks)	Exposure to ACS	RDS		Relative risk (95 % CI)	P-value
		Yes (%)	No (%)		
Any number of ACS doses, any interval between first dose and delivery:					
28- 33 (n=89)	Yes	16(38.1)	26(61.9)	0.6 (0.4-0.9)	0.005
	No	32(68.1)	15(31.9)		
34- 37 (n=117)	Yes	12(40)	18(60)	1.1 (0.7 – 1.8)	0.755
	No	32(36.8)	55(63.2)		
Overall/ 28- 37 (n=206)	Yes	28(38.8)	44(61.2)	0.7 (0.6 – 1.1)	0.223
	No	64(47.8)	70(52.2)		
2 doses of ACS vs no ACS					
28-33 weeks (n=73)	2 doses	13(33.3)	23(66.7)	0.5 (0.3 – 0.8)	0.004
	No ACS	32(68.1)	15(31.9)		
34-37 weeks (n=97)	2doses	3(30)	7(70)	0.8 (0.3 – 2.2)	1.000
	No ACS	32(36.8)	55(63.2)		
Overall(n=180)	2doses	16(34.8)	30(65.2)	0.7 (0.5 – 1.1)	0.127
	No ACS	64(47.8)	70(52.2)		
48 hours of ACS exposure vs no ACS					
28-34 weeks	>48hours	3(30)	7(70)	0.4 (0.2–1.2)	0.0035
	no ACS	32(68.1)	15(31.9)		
34-37 weeks	>48hrs	0(0)	3(100)	--	0.550
	no ACs	32(36.8)	55(63.2)		
Overall (28-37)	>48hours	3(23.1)	10(76.9)	0.5 (0.2 -1.3)	0.157
	no ACS	64(47.8)	70(52.2)		

Table 5 above shows the effect of any ACS exposure, number of doses and duration of ACS exposure on occurrence of RDS. As shown, any exposure to ACS before 34 weeks gestation significantly reduces the incidence of RDS(38.1% among those who were exposed to ACS compared to 68.1% of those who were not exposed, RR 0.6, 95% CI 0.4 to 0.9 P=0.005). However there was no statistical difference between the two groups among neonates delivered after 34 weeks (40% among those exposed compared to 36.8% of those who were not exposed, RR 1.1, 95% CI 0.7- 1.8, P =0.223).

With regard to the impact of ACS dose on occurrence of RDS, table 5 shows that exposure to 2 doses of ACS before 34 weeks gestation significantly reduces the incidence of RDS. Thirty three percent (33%) of neonates born before 34 weeks and were exposed to 2 doses developed RDS compared to 68% of those who were not exposed to ACS (RR 0.5, 95% CI 0.3- 0.8, P= 0.004).

Exposure to ACS after 34 weeks gestation did not significantly reduce the incidence of RDS. Thirty percent (30%) of those exposed to 2 doses of ACS developed RDS compared to 37% of those not exposed to ACS (RR 0.8, 95 % CI 0.3- 2.2, P =1). This was not statistically significant.

Exposure to ACS for 48 hours before delivery significantly reduced the incidence of RDS among neonates delivered before 34 weeks gestation. Thirty percent (30%) of those exposed to ACS for 48 hours had RDS as compared to 68.1% of those not exposed to ACS (RR 0.4, P= 0.0035).

Among those born between 34- 37 weeks, none of those exposed to ACS for 48 hours developed RDS compared to 36.8% of those not exposed to ACS (RR 0.5, P 0.157, not statistically significant)

Table 6: Impact of ACS use on oxygen therapy

Gestational age (weeks)	Exposure to ACS	Oxygen use		Relative risk (95 % CI)	P-value
		Yes (%)	No (%)		
Need for oxygen therapy (n=201)					
28- 33	Yes	17(40.5)	25(59.5)	0.7 (0.4-1.0)	0.047
	No	29(61.7)	18(38.3)		
34- 37	Yes	11(36.7)	19(63.3)	1 (0.6 – 1.7)	0.994
	No	30(36.6)	52(63.4)		
Overall (28- 37)	Yes	28(38.9)	44(61.1)	0.9 (0.6–1.3)	0.429
	No	59(45.7)	70(54.3)		
Total		87(43.3)	114(56.7)		
Duration of oxygen Therapy n= 74					
		<24hours	>24hours		
28- 33 weeks	Yes	10(62.5)	6 (37.5)	0.5 (1.1 5.3)	0.025
	No	6 (25)	17(75.0)		
34- 37 weeks	Yes	9(100.0)	0 (0)	--	1.000
	No	23(95.8)	2(4.2)		
Overall (28-37 weeks)	Yes	19(76.0)	6 (24.0)	0.6 (0.9 -1.6)	0.284
	No	29(59.2)	20(40.8)		
Total		48(65)	26(35)		

Table 6 above shows the impact of exposure to ACS on need for and duration of oxygen therapy.

With regard to need for oxygen use, overall 43.3 % of neonates born between 28-37 weeks gestation required oxygen therapy; 38.9 % of those exposed to ACS required oxygen compared to 45.1 % of those not exposed. This was not statistically significant (RR 0.9, P= 0.429)

Exposure to ACS significantly reduced the need for oxygen therapy among neonates delivered before 34 weeks. About forty one percent (40.5%) of those exposed to ACS required oxygen therapy compared to 61.7% of those not exposed to ACS (RR 0.7,95 % CI 0.4- 1.0, P= 0.047). Exposure to ACS did not result in a reduction in oxygen therapy requirement in those neonates delivered between 34-37 weeks. An equal proportion of neonates (36.7% vs 36.6%) in both arms required oxygen therapy (RR 1, 95% CI 0.6-1.7, P= 0.994).

With regard to duration of oxygen therapy, exposure to ACS resulted in a reduction in need for oxygen therapy for more than 24 hours across all gestational ages. For neonates delivered between 28-33 weeks, there was a significant reduction in the need for oxygen therapy for more than 24 hours. Most (75.0 %) of those who were not exposed to ACS required oxygen therapy for more than 24 hours compared to 37.5% of those exposed to ACS (RR0.5, 95% CI 1.1-5.3, P= 0.025. For neonates born between 34-37 weeks, none of those exposed to ACS required oxygen for more than 24 hours compared to 4.2% of those who were not exposed(RR--, P=1).

Table 7: Impact of ACS use on need for mechanical ventilation

Gestation (Weeks)	Exposure to ACS	Mechanical ventilation		Relative risk	P-value
		Yes (%)	No (%)		
28- 33	Yes	1 (2.4)	41 (97.6)	0.3 (0.0 -2.4)	0.210
	No	4 (8.5)	43 (91.5)		
34- 37	Yes	0 (.0)	30(100.0)	--	0.180
	No	5(5.7)	82 (94.3)		
Overall (28-37)	Yes	1 (1.4)	71(98.6)	0.4 (0.0 -1.6)	0.427
	No	9(6.7)	125(93.3)		

Table 7 above shows that exposure to ACS reduces the need for mechanical ventilation across all gestational ages. This reduction however did not reach statistical significance. Overall 1.4% of neonates exposed to ACS required mechanical ventilation compared to 6.7% of those who were not exposed to ACS (RR 0.4, 95% CI 0.0-1.6, P= 0.427), about two percent of preterm neonates delivered before 34 weeks and exposed to ACS required mechanical ventilation compared to 8.5% of those not exposed (RR 0.3, 95% CI 0.0-2.4,P = 0.210). Among those delivered after 34 weeks, none of those exposed to ACS required mechanical ventilation compared to 5.7% of those not exposed (p = 0.180).

Table 8: Impact of ACS use on NBU and NICU admissions

Gestation (Weeks)	Exposure to ACS	Admission		Relative risk (95% CI)	P-value
		Yes (%)	No (%)		
NBU admission n=198					
28- 33+6	Yes	35 (85.4)	6 (14.6)	1.2(1.0-1.9)	0.113
	No	35 (71.4)	14(28.6)		
34- 37	Yes	15 (50.0)	15(50.0)	1.3 (0.9-2.1)	0.225
	No	29 (37.2)	49(62.8)		
28-37(overall)	Yes	50(70.4)	21(29.6)	1.4 (1.1-1.8)	0.242
	No	64(50.4)	63(49.6)		
NICU admission n= 206					
Overall (28-37)	Yes	6(9.1)	66(90.9)	1.9 (0.6-5.6)	0.349
	No	6(4.5)	128(95.5)		
28- 33	Yes	4(9.5)	38 (90.5)	4.5 (0.5-38.6)	0.130
	No	1 (2.1)	46 (97.9)		
34- 37 weeks	Yes	2 (6.7)	28 (92.3)	1.1 (0.2-5.7)	0.855
	No	5 (5.7)	82 (94.3)		

Table 8 above shows that there was no significant statistical difference in frequency of NBU and NICU admissions between ACS exposed neonates compared to those who were

not exposed. Contrary to expectation a greater proportion of those exposed to ACS were also admitted to either NBU or NICU.

With regard to NBU admissions, overall 70.4% of neonates exposed to ACS were admitted to NBU compared to 50.4% of those not exposed to ACS (RR 1.4, 95% CI 1.1-1.8, P = 0.242).For neonates delivered between 28- 34 weeks, 85.4% of those exposed to ACS were admitted to NBU compared to 71.4% of those not exposed (RR 1.2, 95% CI 1.0-2.1, P = 0.113). For neonates delivered after 34 gestational weeks, 50% of those exposed to ACS were admitted to NBU compared to 37.2% of those not exposed (RR 1.3, 95% CI 0.9- 2.1, P =0.225).

With regard to NICU admissions, 9.5% of those exposed to ACS before 34 weeks compared to 2.1% of those not exposed were admitted. (RR 4.5, 95% CI 0.5-38.6, P= 0.130). In the 34- 37 weeks group of neonates there was no difference with regard to NICU admission (6.7% vs 5.7% in the ACS and no ACS group respectively RR 1.1, 95% CI 0.2- 5.7, P= 0.855)

Table 9: Indications for NBU admission

Gestation (Weeks)	Exposure to ACS	Indication for NBU admission		Relative risk (95% CI)	P-value
		RDS (%)	Other (%)		
28- 33(n= 89)	Yes	17(38.1)	25(61.9)	0.6(0.4-0.9)	0.005
	No	32(68.1)	15(31.9)		
34- 37(n=127)	Yes	12(40.0)	18(60)	1.1(0.7-1.8)	0.755
	No	32(36.8)	55(63.2)		
28-37(n=206)	Yes	39(47.7)	43(52.3.)	1.1(0.8-1.3)	0.493
	No	64(47.8)	70(52.2)		

Table 9 above shows that there was a statistical difference between the two groups in terms of indications for NBU admission among neonates delivered before 34 weeks. In this group, "other" indications accounted for majority of the admissions to NBU among neonates exposed to ACS (61.9% vs 31.9% in the ACS and non-ACS groups respectively, RR 0.6, 95% CI 0.4-0.9, P 0.005). There was no statistical difference in indications for NBU admission for neonates delivered after 34 weeks (RR 1.1, 95% CI 0.7- 1.8, P= 0.755)

Table 10: The impact of ACS use on neonatal status by the time of discharge or 7th postnatal day (n=206)

Gestation (Weeks)	Exposure to ACS	Neonatal status		Relative risk (95% CI)	P-value
		Alive (%)	Dead (%)		
28- 33	Yes	31 (73.8)	11(26.2)	1.2 (0.9-1.6)	**0.224**
	No	29 (61.7)	18(38.3)		
34- 37					
	Yes	29(96.7)	1 (3.3)	1.1 (1.0-1.2)	**0.443**
	No	79 (90.8)	8 (9.2)		
28- 37					
	Yes	60(83.3)	12(16.7)	1 (0.9-1.8)	**0.631**
	No	108(80.6)	26(19.4)		

Table 10 above shows that exposure to ACS reduced neonatal mortality across all gestational ages. This reduction however was not statistically significant. Overall 16.7% of neonates exposed to ACS compared to 19.4% of those not exposed died.

Exposure to ACS before 34 weeks gestation led to a reduction in neonatal deaths within the first 7 days of life. Twenty six percent (26.2%) of neonates exposed to ACS before 34weeks died compared to 38.3% of those not exposed to ACS. this reduction was however not statistically significant(RR 1.2, CI 0.9-1.6, P = 0.224).

The above trend was also observed in those neonates delivered after 34 weeks gestation, mortality was 3.3% in neonates exposed to ACS compared to 9.2% of those not exposed (RR 1.1, 1.0- 1.2, P = 0.443). This study was however not powered to detect a significant reduction in neonatal mortality.

DISCUSSION

The study population consisted of mothers with preterm birth due to spontaneous preterm labour with intact membranes, Preterm Premature Rupture of Membranes or severe Preeclampsia. 206 clients were recruited over a three month period 19th March- 25th June 2011. During this period there were 2737 deliveries, therefore preterm birth due to the study conditions accounted for 7.5% of all deliveries. This is comparable to a study done at KNH in 2010 that found a prevalence of preterm birth at 8.7%[40]. However in our study mothers with APH, twin gestation, congenital anomalies and IUFD were excluded.

Besides age there was no significant difference in the socio-demographic characteristics of the two study groups. Most of those who received ACS were aged above 26 years while those who didn't receive were in the 21-25 year bracket. This study also revealed that majority of those who didn't receive ACS had PTL as the primary indication; therefore being younger could mean they were naïve and didn't recognize labour signs early enough to come to hospital in time.

There was a significant statistical difference in the gestational age at delivery of the two groups. The average gestational age at delivery was 33.5 weeks. Those who received ACS delivered at an earlier gestation compared to those who did not receive the ACS (32.7weeks vs 33.9 weeks respectively, p= 0.003. This is probably because clinicians are likely to administer ACS to mothers at risk of preterm birth before 34 weeks and not after as per the current ACOG/RCOG recommendations[23, 41].

Spontaneous preterm labour (PTL) was the leading cause of preterm birth, accounting for 55.4% of the deliveries, followed by PPROM 25.7% and severe PET 18.9%. This is comparable to the findings of a study at KNH on "the demographic and obstetric factors associated with delivery of preterm infants at KNH"[11]. In this study, spontaneous PTL accounted for 52% of the deliveries while PPROM accounted for 26.5% of the deliveries. However PET accounted for only 8.5% of the preterm deliveries then.

In those who received ACS severe PET was the leading cause of preterm birth at 41.4% followed by PPROM at 34.2% and PTL at 23.3%; this was significantly different from those who didn't receive ACS where PTL was the leading cause (72.4%) followed by PPROM at 20.9% and severe PET accounting for 9% of the deliveries ($p =<0.001$). This could be due to the fact that a number of patients with spontaneous preterm labour come in advanced labour hence the clinician has no adequate time to intervene with ACS. Contrary to this, delivery in severe PET is usually planned and a good number of patients with PET are admitted in time for investigations and stabilization before delivery. This gives ample time for them to receive ACS. Evidence accruing from two meta-analyses, did not show any difference in efficacy of ACS in patients with PET, PPROM or spontaneous preterm labour[24, 26].

The optimal mode of delivery for women at high risk of delivering a small baby is still controversial. In our study spontaneous vaginal delivery was the most frequent mode of delivery (58.7%). In an earlier study at Kenyatta National Hospital in 2001, 71.5% of preterm deliveries occurred vaginally[11]. There was a significant difference in mode of delivery between the two study groups. Forty nine percent of those who received ACS delivered via caesarean section compared to 31.3% of those who did not receive ACS.

The significant rise in caesarean deliveries could be partially attributed to the significant rise in the number of patients with severe preeclampsia delivering at this gestation (8.8% vs 18.9% in 2001[11] and 2011 respectively. A significant number of patients with PET are delivered via caesarean section since most will have a poor bishop score despite a need for urgent delivery. Most (65.6%) of those who did not receive ACS had spontaneous vaginal deliveries. This could be due to the fact that majority of those who did not receive ACS had PTL as the primary diagnosis and they might have presented in advanced labour hence obviating the need for caesarean delivery.

The overall frequency of ACS use at KNH was 35% with 47% of those with a gestational age of less than 34weeks receiving ACS compared to 26% of those with a gestational age more than 34 weeks. This is low compared to the findings of a study in the USA in 2003[42]. In this study the frequency of ACS use was found to have increased steadily over the years and stood at 75%. The low uptake of ACS could be due to several factors. These include late presentation of patients, drug stock outs; infrequent use of tocolytics and some clinicians not appreciating that even one dose of ACS can reduce neonatal morbidity and mortality. Additionally, a number of obstetricians rarely follow up neonates in NBU hence may not appreciate the impact the ACS have on both short and long term neonatal outcomes.

The steroid of choice at KNH is dexamethasone. Studies show that both betamethasone and dexamethasone are equally efficacious in reducing respiratory morbidity but the former is more expensive[25] hence dexamethasone is preffered in resource poor countries.

A full course of ACS is given intramuscularly as either 12mg of betamethasone given 24 hours apart for a total of 2 doses or 6mg of dexamethasone given 12 hourly to a total of 4 doses. The optimal benefits of antenatal corticosteroids are seen 24 hours after administration, peak at 48 hours, and continue for at least 7 days [5, 16, and 22]. In our study, majority of the mothers (89%) received either one or two doses of dexamethasone and only three percent (2 mothers) received a complete course.

Most mothers (81%) delivered before 48 hours of the first dose of dexamethasone with only 19 %(14 patients) delivering more than 48 hours after administration of the first dose. Despite the fact that most mothers received an incomplete course of ACS and delivered before 48 hours after its adminstration, the study revealed a significant impact in reduction of morbidity and mortality as discussed subsequently. It is not clear why most patients didn't receive full doses of ACS despite them being in the hospital long enough for the drugs to be administered. This could be due to the fact that some clinicians prescribe 2 doses of 12mg of dexamethasone given twice a day especially for those patients deemed to have an urgent indication for delivery. The other reason could be poor documentation

The impact of ACS in this study was assessed by determining the prevalence and severity of RDS, prevalence of NBU admissions and neonatal mortality. The diagnosis of RDS was made clinically by the picture of tachypnoea, chest wall retraction, flaring of alae nasi, expiratory grunting and tachycardia. A diagnosis of severe RDS was made if the neonate required oxygen therapy was more than 24 hours, was admitted to NICU or required mechanical ventilation.

The overall incidence of RDS among our study population was 44.7%; 53.9% among those delivered before 34 weeks and 37.6% among those delivered after 34 weeks. This is comparable to findings of others studies that found RDS to affect 40--50% of babies born before 32 weeks and 20.6% of those born at 34-36 weeks [23, 43]. There was a statistically significant reduction in the incidence of RDS in those neonates exposed to ACS and delivered before 34 weeks (38.1 % vs 68.1%, RR 0.6, 95% CI 0.4-0.9, P=0.005). For those neonates born after 34weeks exposure to ACS marginally reduced the incidence of RDS (30% vs 36.8% RR 0.8, 95% CI 0.3- 2.2, P=1). This trend is seen even when controlling for dose and duration of therapy. These findings are similar to those found [in] an RCT to assess the effectiveness of ACS in mothers at risk of preterm birth. In this study they found a significant reduction in occurrence of RDS in the treatment group (7/130) compared to the control group (16/132,) [37]. In this study, like in our study the largest difference was noted in those below 34 weeks gestation. This observation is due to the fact that ACS therapy is known to improve neonatal lung function via two mechanisms: by enhancing morphologic development in type 1 and type 2 pneumocytes, and by inducing lung enzymes in type 2 pneumocytes that stimulate phospholipid synthesis and subsequent release of surfactant (biochemical maturation). Both of these processes are thought to be in place by 34 weeks gestation.[44]

The adminstration of ACS reduced the severity of RDS. This reduction was however more significant in those neonates born before 34 weeks. With regard to use of oxygen therapy, overall 39% of neonates exposed to ACS required oxygen therapy compared to 46% of those not exposed (RR 0.9, p= 0.429). Among those delivered before 34 weeks 40.5% of those exposed to steroids compared to 62% of those not exposed to ACS

required oxygen therapy. This was statistically significant (RR 0.7, 95% CI 0.4- 1.0, P= 0.047). The impact was less remarkable in those born after 34 weeks where a similar proportion of neonates in both groups required oxygen therapy (36.6% of ACS group vs 36.7% of non –ACS group respectively RR=1, 95% CI 0.6-1.7, P= 0.994). The trend was similar with regards to duration of oxygen therapy where among those born before 34 weeks, 37% of those exposed to ACS required oxygen therapy for more 24 hours compared to 75% of those not exposed to ACS(RR 0.5, 95% CI 1.1- 5.3, P= 0.025). Similarly there was no statistical difference with regard to duration of oxygen therapy among the two groups of neonates delivered after 34 weeks (2 neonates in the non ACS group vs no neonate in the ACS group P=1).

With regard to mechanical ventilation ACS reduced the need for its use across all gestational ages. The reduction in need for mechanical ventilation was more significant in the 28-33 age bracket compared to the 34-37 weeks bracket, however this did not reach statistical significance. Overall 1.4 % of those exposed to ACS required mechanical ventilation compared to 6.7% of those not exposed (RR 0.4, P=0.427). In neonates delivered before 34 weeks 2.4 %(1 neonate) of those exposed to ACS required mechanical ventilation compared to 8.5 %(4 neonates) of those not exposed to antenatal steroids (RR 0.3, 95% CI 0.0-2.4, P= 0.210). None of the neonates exposed to ACS in the 34-37 week group required mechanical ventilation compared to 5.7 %(5 neonates) of those not exposed (P= 0.180).

ACS did not reduce the need for NICU admission. Contrary to expectation, the trend in this study was that those exposed to ACS were also likely to be admitted to NICU. This trend was observed more in those delivered before 34 weeks; however it did not reach

statistical significance. Among neonates delivered before 34 weeks 9.5% of those exposed to ACS compared to 2.1% of those not exposed were admitted to NICU (RR 4.5, 95% CI 0.5-5.7, P= 0.130). In neonates between 34-37gestational weeks an almost equal proportion (6.7% vs 5.7%) of those exposed to ACS compared to those not exposed were admitted to NICU (RR 1.1, 95% CI= 0.2- 5.7, P 0.855). This is probably due to the fact that some of the neonates were admitted to NICU for other reasons for example prematurity or neonatal sepsis. This assumption is supported by the fact that on average those who received ACS had a lower birth weight (1844g vs 2134g, p =0.001) and lower gestational age (32.6 weeks vs33.9weeks, p=0.003). These study findings are similar to those reported a Cochrane review of 21 RCTs to assess the effectiveness of ACS in mothers at risk of preterm birth. In this review, ACS were found to reduce both the need for respiratory support and intensive care admissions in 2 studies only[26].

In this study, ACS did not reduce the need for NBU admissions. For neonates delivered between 28- 34 weeks, most (85.4%) of those exposed to ACS were admitted to NBU compared to 71.4% of neonates who were not exposed (RR 1.2, 95% CI 1.0-1.9, P= 0.113). For neonates delivered between 34-37 gestational weeks, 50% of those exposed to ACS were admitted to NBU compared to 37.2% of neonates who were not exposed. The high number of NBU admission in neonates <34 weeks whose mothers received ACS could be due to other indications like prematurity, low birth weight, birth asphyxia, congenital anomalies, neonatal sepsis or maternal condition all of which are not affected by ACS use. This assumption is supported by the fact that overall those who were exposed to ACS had a lower gestational age (32.65 vs 33.91weeks, P =0.003), lower birth

weight (1844g vs 2134g, P =0.001), their mothers were likely to have preeclampsia and be delivered by caesarean section.

With regard to neonatal status at discharge or the 7th day of neonatal life, our study found out that ACS use reduces neonatal mortalities within the first 7 days of life. This benefit occurs across all gestational ages but did not reach statistical significance. This could be because our study was not powered to detect a significant statistical difference in neonatal mortality. Overall neonatal mortality was 16.7 %(12/72) among those exposed to ACS compared to 19.4 %(26/134) of those not exposed to ACS. With regard to gestational age, the effect is greater in neonates delivered before 34 weeks compared to those delivered after. Twenty six percent (11/42) of neonates delivered before 34 weeks gestation and exposed to ACS died compared to 38.3 %(18/47) of those not exposed to ACS (RR 1.2, 95% CI 0.9- 1.6, P =0.224). This is in contrast to those delivered after 34 weeks where the neonatal mortality was lower, 3.3 % (1/30) in the exposed group compared to 9.2 %(8/77) in those not exposed (RR 1.1, 95% CI 1.0- 1.2, P= 0.443). This trend is similar to the findings of an RCT to assess the effectiveness of ACS. This study found a significant reduction in neonatal deaths among the treatment group compared to the control group with the largest differences seen in those <34 weeks. A cochrane review of 21randomized controlled studies of antenatal steroid administration found that treatment with antenatal corticosteroids was associated with an overall reduction in neonatal death in 18 studies[26, 36]. This trend is due to the fact that a number of deaths in preterm neonates are due to respiratory morbidity, intraventricular haemmorhage and necrotizing enterocolitis all of which are reduced significantly by ACS exposure.

CONCLUSIONS:

Exposure to antenatal steroids reduces the incidence and severity of respiratory distress syndrome and neonatal mortality. This reduction is however more significant in those neonates delivered before 34 weeks of gestation.

RECOMMENDATIONS

This study shows that there is no extra benefit of ACS use after 34 weeks gestation; therefore clinicians should to be sensitized on need to avoid their unnecessary use after this gestation. During the course of the study it was noted there was no SOP at KNH on use of ACS in terms of which steroids to use, course to be used and dosage. It will be important for KNH to develop such a protocol.

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APPENDICES

APPENDIX I: CONSENT FORM

I, Dr. George Nyakundi Gwako am a post-graduate student in the department of Obstetrics and Gynaecology of the University of Nairobi carrying out a study on the **"Use and Impact of Antenatal Steroids in mothers with preterm birth between 28-37 weeks at KNH"**. My mobile phone contact is **0722992268**.

My supervisors are **Dr. Zahida Qureshi** Senior Lecturer in the Department of Obstetrics and Gynaecology, University of Nairobi and **Dr. Walter Kudoyi** of the Department of Obstetrics and Gynaecology, Kenyatta National Hospital.

This study has been reviewed and approved by the KNH/UON Ethics and Research Committee, and any questions or issues regarding the study could be addressed to:

The Chairman, KNH-ERC
P.O. Box 20723, Nairobi.
Tel. 2726300 ext 44102

This study entails comparing the neonatal outcomes of mothers with preterm birth who received antenatal steroids with those who did not receive the steroids. The study involves asking questions and looking at your medical records. This information will be used to improve the future management of patients.

Participation is voluntary and the information obtained will be confidential. Declining to give consent or withdraw from participation will not influence your management in any way. The procedures that will be carried out will not harm you or your baby.

Consent

I have been explained to about the study and I accept to participate. I have not been coerced or enticed in any way.

Participant's signature .....Date.....

Witness signature.....Date.....

APPENDIX II: QUESTIONNAIRE

THE USE AND IMPACT OF ANTENATAL STEROIDS IN MOTHERS WITH PRETERM BIRTH AT KNH

Date ____/____/____ Serial No.....

SOCIODEMOGRAPHIC DATA OF THE WOMAN

1. Mothers Age _____years
2. Marital status [ ]
    1. single
    2. married/ cohabiting
    3. separated
    4. divorced
    5. widowed
3. Educational level [ ]
    1. none
    2. primary
    3. secondary
    4. tertiary
4. Occupation
    1. unemployed /housewife
    2. self employed
    3. salaried employment
    4. other (specify)_____

OBSTETRICS

1. Number of pregnancies, including the current pregnancy. [ ]

2. When was the last menstrual period (LMP)?
    a. / /
    b. Not known

3. When was the expected due date (EDD)?

a. ____/____/____

b. Not known

4. What is the gestation in completed weeks?

5. Did the patient receive steroids? 1=Yes 2=No 3= not known.

6. If yes to (5) above, which steroid? 1= Dexamethasone. 2= Betamethasone. 3=Other

7. Duration between first dose and delivery.1 0-24hrs 2 24-48hrs 3 48-72hrs 4=>72hrs 5= Not known

8. Number of ACS doses received.

a) Dexamethasone 1=1dose 2=2doses 3=3doses 4=4doses 5= not known

b) Betamethasone 1 1dose 2 2doses 3 not known.

9. Number of ACS courses received. 1=1 2=2 or more 3= not known.

DELIVERY

1. Date of admission ___ / ____ / ____

2. Diagnosis on admission. 1=PTL 2=PPROM 3=PET

3. Date of delivery ___/____/____

4. Gestation at delivery in weeks.

5. Mode of delivery

1= SVD 2= Caesarean Section 3= Assisted vaginal delivery 4= Breech delivery

6. If C/S, what was the indication

NEONATAL OUTCOME

1. Infant sex 1=male 2=female.

2. What was the infant Apgar score at 5 minutes?

3. What was the infant birth weight in grammes?

4. Status at birth. 1 =Alive 2=FSB 3= MSB 9=Not documented

5. Was a diagnosis of RDS made? 1= yes 2= No

6. a) Was the baby put on oxygen? 1=Yes 2= No

b). If yes what was the duration of oxygen therapy? 1=<24hours 2= >24hours

7. a). Was the infant admitted to NBU? 1= Yes 2= No.

b). was the infant admitted to NICU? 1= Yes 2= No

c). If yes to 7(a) or (b) above, what was the indication? 1=RDS 2= Other

c). Was mechanical ventilation used? 1=Yes 2= No

d). What was the length of NBU/NICU admission. 1=1day. 2=2-3days. 3=3-7 days. 4=>7days

8. Status of infant on discharge or on the 7th day.1=Alive 2= Dead

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Ref: KNH-ERC/ A/42

9th March, 2011

Dr George Nyakundi Gwako
Dept. of Obs/Gynae
School of Medicine
University of Nairobi

Dear Dr Nyakundi

RESEARCH PROPOSAL: "THE USE AND EFFECTIVENESS OF ANTENATAL STEROIDS IN OBSTETRICS SUBGROUPS AT RISK OF PRETERM BIRTH : A CROSS SECTIONAL STUDY" (P355/10/2010)

This is to inform you that the KNH/UON-Ethics & Research Committee has reviewed and **approved** your above revised research proposal for the period 9th March 2011 – 8th March 2012.

You will be required to request for a renewal of the approval if you intend to continue with the study beyond the deadline given. Clearance for export of biological specimens must also be obtained from KNH/UON-Ethics & Research Committee for each batch.

On behalf of the Committee, I wish you a fruitful research and look forward to receiving a summary of the research findings upon completion of the study.

This information will form part of the data base that will be consulted in future when processing related research study so as to minimize chances of study duplication.

Yours sincerely,

PROF A N GUANTAI
SECRETARY, KNH/UON-ERC

c.c. The Deputy Director CS, KNH
The HOD, Records, KNH
The Chairman, Dept. of Obs/Gynae, UON
Supervisors: Dr. Zahida Qureshi, Dept of Obs/Gynae, UON
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