EFFECTIVENESS OF ANTENATAL DEXAMETHASONE IN REDUCING RESPIRATORY DISTRESS SYNDROME AND MORTALITY IN PRETERM NEONATES: A NESTED CASE CONTROL STUDY

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By

Wema Kibanga

A Dissertation Submitted in (partial) Fulfillment of the Requirements for the Degree of Master of Pharmacy (Hospital and Clinical Pharmacy) of

Muhimbili University of Health and Allied Sciences

October, 2021.

CERTIFICATION

The undersigned certifies that, they have read and hereby recommend for acceptance by Muhimbili University of Health and Allied Sciences, a dissertation entitled, *"**Effectiveness of antenatal dexamethasone in reducing respiratory distress syndrome and mortality in preterm neonates: a nested case control study."*** in partial fulfillment of the requirements for the degree of Master of Pharmacy (Hospital and Clinical Pharmacy) of Muhimbili University of Health and Allied Sciences.

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DECLARATION AND COPYRIGHT

I, **Wema Kibanga**, declare that this **dissertation** is my own original work and that it has not been presented and will not be presented to any other University for a similar or any other degree award.

Signature: _____ Date: _____

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I am thankful to God almighty for his protection and good health that led to the accomplishment of this work.

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Lastly, I would like to extend my heartfelt gratitude to my family (husband and parents) for their continued support throughout my academic career path.

DEDICATION

This work is dedicated to all preterm neonates.

ABSTRACT

Background: Respiratory distress syndrome (RDS) is a significant cause of preterm neonatal morbidity and mortality globally. Measures like the use of antenatal corticosteroids (ACS) and immediate resuscitation of the newborn after birth are taken to abate preterm related complications. Most studies that evidenced the benefit of ACS were done in high resource settings. However, some studies in low resource settings reported no benefit of ACS in improving neonatal outcomes. Such findings warrant for further studies in different settings.

Aim: To assess the effectiveness of antenatal dexamethasone in reducing RDS and mortality in preterm neonates in Dar es Salaam, Tanzania.

Methods: A three-month nested case-control study was conducted in Dar es Salaam at Muhimbili National Hospital and Amana Regional Referral Hospital. A total of 330 neonates delivered at 28 to 34 gestational weeks were enrolled consecutively and followed up through the study period. RDS was diagnosed within 48 h after birth. Cases were neonates with RDS and controls were those without. Maternal and neonatal socio-demographic and clinical data were recorded using a data abstraction forms. Proportions were used to summarize descriptive statistics. Overall mortality rate was calculated using incidence rate. Log ranking test and cox regression were used to graphically compare probability of death with time and measure association, respectively. Continuous variables were summarized using median and range then analyzed by Mann-Whitney U test. All tests were considered statistically significant at $p < 0.05$.

Results: Out of 330 preterm neonates enrolled, of which 110 were cases and 220 were controls. 71.8% of the participants were from MNH and 28.2% from Amana regional referral hospital. The median gestational age at delivery was 30 weeks and 6 days (28-34) among cases and 33 weeks (28-34) among controls ($p<0.001$). A one-minute APGAR score of less than seven was assigned to 38.2% of cases compared to 14.5% of controls ($p<0.001$).

ACS exposure was not associated with RDS occurrence (OR: 0.81; 95% CI 0.69-0.94), one-minute APGAR score of less than 7 (OR: 3.11; 95% CI 1.54-6.30), and neonatal birth weight

(OR: 0.998; 95% CI 0.997-0.999) were significantly associated with RDS. The overall mortality rate was 9 per 1000 neonates. Neonatal mortality occurred only among cases. A unit increase in gestational age was associated with a 30% reduction in neonatal mortality (Adjusted hazard ratio, AHR: 0.70, 95% CI: 0.5-0.92, p=0.011).

Conclusion: Antenatal dexamethasone is not associated with reduced RDS occurrence and neonatal mortality rates**.** Increase in gestational age is found to be an independent protective factor against RDS and neonatal mortality. One-minute APGAR score of < 7 and low neonatal birth weights are independent predictors of RDS in preterm neonates.

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LIST OF ABBREVIATIONS

ACS	Antenatal corticosteroids
AHR	Adjusted hazard ratio
AIP	Abnormally invasive placentation
APGAR	Appearance, Pulse, Grimace, Activity and Respiration
BMI	Body mass index
CHR	Crude hazard ratio
IVH	Intraventricular hemorrhage
LMICs	Low-and-middle-income countries
MNH	Muhimbili National Hospital
NEC	Necrotizing enterocolitis
NICU	Neonatal Intensive Care Unit
PROM	Premature Rupture of Membranes
RDS	Respiratory distress syndrome
SPSS	Statistical Package for Social Sciences

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Figure 3: Cumulative hazard curves showing the association between probability of death and time using Log-ranking test. 233

DEFINITION OF TERMS

TERM	DEFINITION
Antenatal corticosteroids	Medications administered to pregnant women at risk of preterm birth in order to accelerate the maturation of the fetus' lungs.
Respiratory distress syndrome	A syndrome of respiratory difficulty in newborn infants caused by a deficiency of a molecule called surfactant.
Surfactant	A fluid secreted by the cells of the alveoli (the tiny air sacs in the lungs) that serves to reduce the surface tension of pulmonary fluids
<1000g	Extremely low birth weight
1000-1499g	Very low birth weight
1500-2499g	Low birth weight
≥2500g	Normal birth weight

CHAPTER ONE

1.0 INTRODUCTION

1.1 Background

Preterm delivery is the leading cause of perinatal and neonatal morbidity and mortality (1). All countries share the problem of preterm birth; however, 81.1% of preterm births occur in Asia and sub-Saharan Africa (2). In Tanzania, prematurity and its complications is one of the leading causes of death among neonates (3). Preterm infants, due to their immaturity, are vulnerable to several complications such as impaired respiration also known as respiratory distress syndrome (RDS), difficulty in feeding, poor body temperature regulation, high risk of infection and neurological complications.

RDS is the leading cause of mortality among preterm infants. Factors like infections and smoking during pregnancy, gestational diabetes, mode of delivery and stress during delivery increase the likelihood of RDS in newborns (4). Several measures are in place to improve newborn outcomes in the settings of premature delivery, including administration of antenatal corticosteroids (ACS). ACS are administered to pregnant women at risk of preterm birth in order to accelerate the maturation of the fetus' lungs. They work by stimulating the production of surfactant-associated proteins and increase phospholipid synthesis by enhancing the activity of phosphatidylcholine, thus improve lung mechanics and gaseous exchange capacity (5). ACS have proven to reduce adverse neonatal outcomes associated with prematurity. The Cochrane meta-analysis demonstrated that, a single course of ACS in pregnant women at risk for preterm delivery was associated with a 38% reduction in RDS, 50% reduction in necrotizing enterocolitis (NEC), and a 48% reduction in intraventricular hemorrhage (IVH), hence an overall 25% reduction in neonatal deaths (6).

WHO recommends the use of either betamethasone or dexamethasone for women at risk of preterm birth from 24 weeks to 34 weeks of gestation when preterm birth is considered imminent, no clinical evidence of maternal infection and adequate childbirth care is available (7). An optimum time of delivery from corticosteroid administration is 2 to 7 days. A single repeat course of ACS is recommended if preterm birth does not occur within 7 days after the initial dose, and a subsequent clinical assessment demonstrates that there is a high risk of preterm birth in the next 7 days (7). However, in practice, most clinicians consider a single repeat course of ACS in women who are less than 34 weeks of gestation, who are at risk of preterm delivery within 7 days, and whose prior course of ACS was administered more than 14 days previously (8).

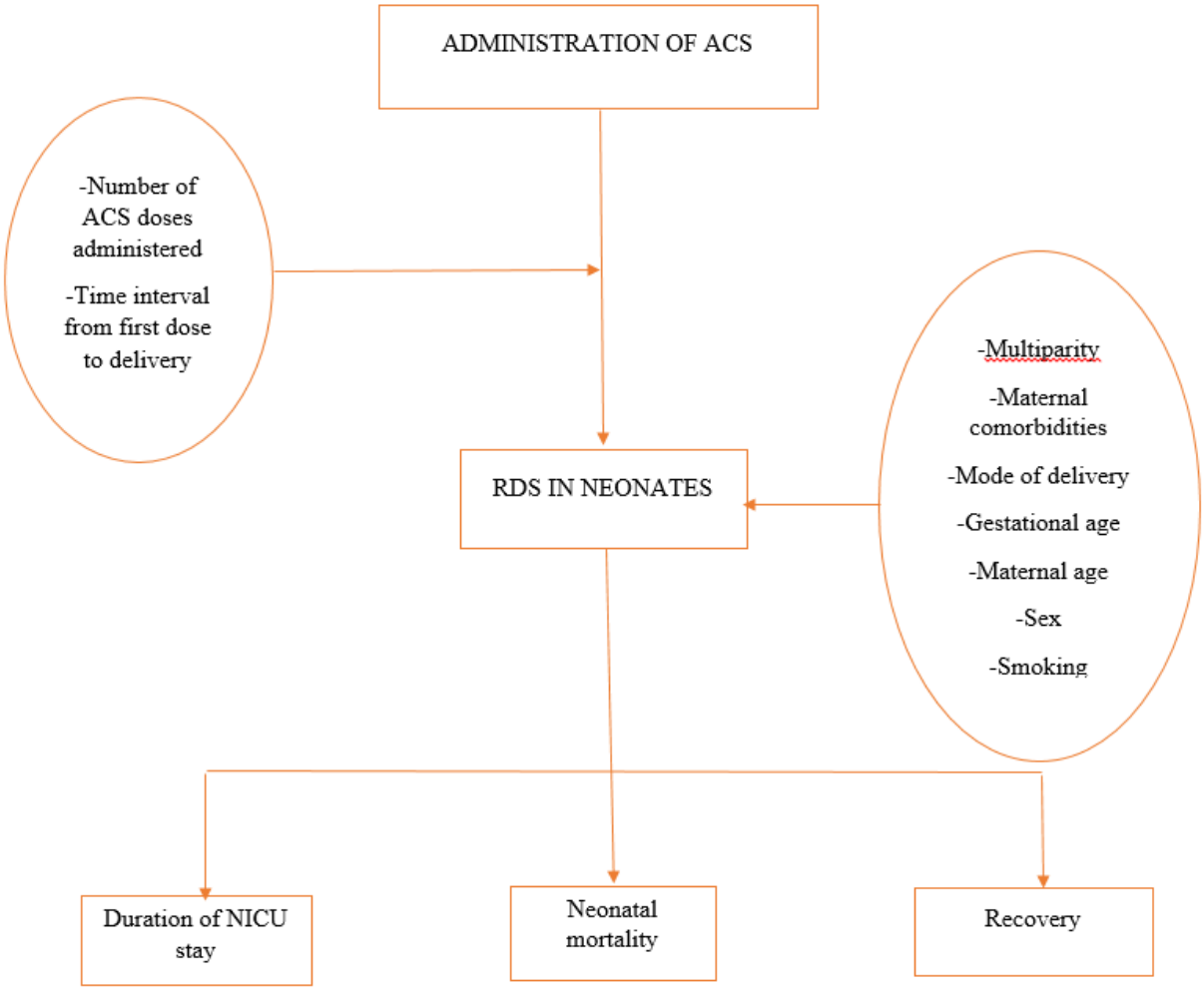
The use of ACS is however not without contention, because the treatment regimen remains largely un-optimized and vary considerably between countries. It is reported that, a significant proportion of women deliver outside the optimal 2- to 7-day therapeutic window after ACS initiation, and this delay can be associated with poor neonatal outcomes (9). The Cochrane meta-analysis of 2017 that formed the basis of WHO recommendations; included 29 trials that were conducted in high resource countries with standard neonatal care (6). Another review on the impact of ACS in low-and-middle-income countries (LMICs) had inconclusive findings because some studies in such settings reported no benefit of ACS in reducing neonatal mortality and RDS (10). Thus, there is lack of enough evidence on the benefit of ANC in low resource settings, where pregnant women start antenatal visits late together with inadequate number of neonatal care facilities.

Therefore, this study aimed at assessing the effectiveness of antenatal dexamethasone in reducing RDS and neonatal mortality in preterm neonates in resource-limited settings.

1.2 Problem statement

In Tanzania ACS are widely available to district hospital level since 2015, following the preparation of national guidelines for the use of ACS and their addition to the national essential medicine list. However, there have been a slow decline in neonatal mortality from 22.1 deaths per 1000 live birth in 2015 to 20.3 deaths per 1000 live births in 2019 (11). These findings are contrary to studies conducted in developing countries which reported that ACS are effective in reducing neonatal mortality (6). Because of differences in level of social-economic status, the conflicting findings necessitate studies in LMICs to assess the effectiveness of ACS. Therefore, this study assessed the effectiveness of antenatal dexamethasone in reducing RDS and mortality in preterm neonates in referral hospitals, Tanzania.

1.3 Conceptual framework



In the settings of imminent preterm delivery, administration of ACS results in reduced incidence and severity of neonatal RDS. This in turn results in reduced duration of NICU stay, neonatal mortality and quick recovery of the newborn. However, number of doses of ACS administered prior to delivery (usually four doses of 6 mg dexamethasone are required) and the time interval from first dose of ACS administration to delivery can affect the benefit of ACS to the neonate(12).

Multiparity, maternal comorbidities like hypertension and diabetes, mode of delivery, maternal age, gestational age and sex of the baby have been associated with the occurrence of RDS in the preterm neonate (13).

1.4 Rationale

Most studies that have evidenced the benefit of ACS in the settings of imminent preterm delivery have been conducted in high resource settings(6). However, there are studies in low resource settings that reported no benefit of ACS(14,15). Therefore, the rationale for conducting this study was the conflicting findings reported in the literature regarding the benefits of ACS. The findings of this study provide a basis for more research on the pre-conditions of ACS therapy in low resource settings.

Proposed Hypothesis

Null hypothesis: ACS is effective is in reducing RDS and mortality in preterm neonates.

1.5 Research questions

The following research questions were used in this study:

i. What is the differences in ACS exposure between cases and controls?
ii. What are the predictors of RDS among preterm neonates in the selected referral hospitals?
iii. What is the mortality rate of preterm neonates in the selected referral hospitals?
iv. What are the factors associated with neonatal mortality among preterm neonates in the referral hospitals?

1.6 Objectives

1.6.1 Broad objective

To assess the effectiveness of antenatal dexamethasone in reducing neonatal mortality and RDS in preterm neonates in referral hospitals, Tanzania.

1.6.2 Specific objectives

i. To determine the likelihood of developing RDS in controls and cases following exposure to ACS.
ii. To assess the predictors of RDS among preterm neonates in the selected referral hospitals.
iii. To determine mortality rate among preterm neonates in selected referral hospitals.
iv. To determine factors associated with neonatal mortality among preterm neonates.

1.7 LITERATURE REVIEW

1.7.1 Respiratory distress syndrome

Respiratory distress; characterized by cyanosis, tachypnea, chest retractions, grunting and nasal faring; is a major cause of neonatal morbidity and mortality throughout the globe (16). The neonatal mortality rate steadily declined linearly in the United States since the early 1900s to the early 2010s (17). RDS-specific mortality rate has also decreased over the past 60 years in the United States, however it remains difficult to quantify the effect of specific therapies on the decreased mortality rate (18).

In LMICs like Tanzania, RDS remains the most common cause of deaths among preterm infants, such that RDS-specific mortality is high (19). A study conducted in Brazil found that preterm infants with RDS were three times more likely to die compared to those without RDS (20). The true incidence of RDS in LMICs is difficult to determine due to limited and varying published data available (17).

A retrospective study done in Ethiopia found the proportion of neonates with RDS among those admitted was 42.9% (13)**.** Among infants born at eight hospitals in the Brazilian Network of Neonatal Research Centers, a diagnosis of RDS was the second highest risk factor for death after gestational age (20). In eight NICUs in Egypt, RDS was the most frequent cause of death (21). In a study conducted at Muhimbili National Hospital, Dar es Salaam (Tanzania), the rate of death from RDS was 52% (22). Limited and varying data available on RDS among preterm neonates in resource limited settings necessitates this study.

1.7. 2 Predictors of Respiratory Distress Syndrome

Several factors have been reported to predict the presence and severity of RDS among preterm neonates. Factors like maternal diabetes, caesarean section mode of delivery, male sex, home delivery and an APGAR score of less than seven have been reported to significantly predict the occurrence of RDS among preterm neonates in Ethiopia (13).

Advanced maternal age has been associated with increased risk of RDS based on increased levels of maternal diseases (hypertension, diabetes, placenta praevia and placental abruption) in older women. These conditions are related with preterm delivery and caesarean sections (31). Caesarean sections increase respiratory morbidity in neonates and this is likely to be due to a delayed removal of lung fluid and the lack of a stress response, which occurs during spontaneous labor (13).

Maternal diabetes has been associated with RDS occurrence because insulin has been shown to inhibit the accumulation of surfactant protein A (SP-A) and surfactant protein B (SP-B) messenger RNA (32). However, recent evidence has suggested that with modern antenatal care and good follow-up, diabetes mellitus, whether pre-gestational or gestational, does not seem to pose any additional risk of RDS to infants born with very low birth weight (33).

Other factors like foetal prematurity and premature rupture of membranes (PROM) have been reported as predictors of RDS occurrence in preterm neonates (34). PROM is the rupture of the fetal membranes before the onset of labor. In most cases, this occurs near term, but when membrane rupture occurs before 37 weeks of gestation, it is known as preterm PROM. Preterm PROM complicates approximately 3% of pregnancies and leads to a third of preterm births thus increasing the risk of prematurity and leading to a number of neonatal complications (35). Avoiding caesarean section following PROM is said to reduce the risk of respiratory morbidity of the neonate (36).

In a study conducted in Tanzania, RDS was significantly associated with lower birth weights, gestational age, birth asphyxia and male sex. However, maternal hypertension with or without albuminuria was inversely related to RDS. There was no significant association between RDS and mode of delivery, antepartum hemorrhage or premature prolonged rupture of membranes of more than 24 h (22). In addition, factors like abnormally invasive placentation (AIP) and female sex have been associated with increased RDS incidence (37,38). Such conflicting findings necessitate further studies on the predictors of RDS among preterm neonates in our settings.

1.7.3 Effectiveness of ANCs in reducing RDS and mortality

ACS accelerate development of pneumocytes, leading to structural and biochemical changes that improve surfactant production, thereby improving both lung mechanics and gas exchange (23). However, for these changes to occur, the lungs need to have reached a developmental stage biologically responsive to corticosteroids (24). Administration of ACS has also been associated with reduced risk of necrotizing enterocolitis (NEC) and intraventricular hemorrhage (IVH) (6).

Most of the studies that have reported benefits of ACS on preterm neonatal outcomes have been done in settings with adequate facilities to care for the newborns (6). An updated meta-analysis of randomized controlled trials (RCTs) that included evidence primarily from hospital settings in high-income countries found that treatment with ACS (compared with placebo or no treatment) was associated with a reduction in neonatal mortality and RDS (6). A 2011 prospective study reported a benefit of administering ACS to mothers at risk of preterm delivery before 26 weeks of gestation. In this study, exposed infants born at 22 to 25 weeks of gestation had significantly lower mortality and neurodevelopmental impairment at 18 to 22 months as compared to the unexposed ones (25). A large multicenter prospective cohort study among infants born from 23 to 34 weeks' gestation in the United States reported that exposure to ACS was associated with lower mortality and morbidity at most gestations compared with no exposure. The effect size of exposure to ACS on mortality seemed to be larger in infants born at the lowest gestations (26).

There are studies conducted in resource limited countries that report benefit of ACS in reducing RDS as well as neonatal mortality. For example, a study conducted in Pakistan reported 43.9% of RDS cases among preterm neonates unexposed to dexamethasone and 22.4% RDS cases among those exposed. Besides, mortality due to RDS occurred more in the unexposed group (27).

ACS have also been reported to be of little or no benefit in situations of intrauterine fetal growth restriction, late preterm to term pregnancies among others. A study conducted on live-born singleton infants with growth-restriction due to placental insufficiency, who were delivered by

caesarean section, reported no benefit in the use of ACS in growth restricted preterm fetuses with respect to short term neonatal outcome (28). A study on the benefit of ACS prior to elective caesarean section at 34–37 weeks of gestation reported no significant reduction in neonatal respiratory morbidity among those treated with corticosteroids (29). A cluster-randomized trial conducted in India, Pakistan, Zambia, Kenya, Guatemala and Argentina, to assess impact of a multi-faceted intervention including ACS to reduce neonatal mortality associated with preterm birth, found an overall increase in 28-day neonatal mortality and stillbirth associated with the intervention (30)

A retrospective analysis of medical records data in a small observational study that included 40 infants in a rural hospital in Tanzania born to women with eclampsia and severe pre-eclampsia reported higher rates of neonatal mortality among infants exposed to ACS (62% vs. 15%, exposed to unexposed) (15). Such conflicting findings necessitate further studies on the benefit of ACS in resource limited settings like Tanzania.

CHAPTER TWO

2.0 METHODOLOGY

2.1 Study design and settings

This was a three months hospital based unmatched nested case control study aimed at assessing the effectiveness of antenatal dexamethasone in reducing neonatal mortality and RDS in preterm neonates. This study was conducted in two referral hospitals in Dar es salaam including Muhimbili National Hospital (MNH) and Amana referral hospital. These hospitals are equipped with neonatal unit taking care of preterm neonates after delivery.

2.2 Study population

Neonates delivered at 28 to 34 weeks of gestation in Muhimbili National Hospital and Amana Referral Hospital. Based on differences in the neonatal unit capacities of the two facilities, a proportion of 70% of participants was targeted to be recruited from MNH and 30% from Amana Referral Hospital. Cases were neonates diagnosed with RDS whereas controls were those without RDS.

2.2.1 Inclusion criteria

All neonates admitted to NICU, whose mothers consented their inclusion in the study. Neonates were recruited within 24 hours after birth.

2.2.2 Exclusion criteria

Neonates delivered below 28 weeks of gestation and beyond 34 weeks of gestation, Neonates diagnosed with hypoxic ischemic encephalopathy or a primary neuromuscular condition and those with any congenital anomaly.

2.3 Sample size

A study conducted in Pakistan to assess the impact of ACS in preterm neonates reported 26% proportion of controls with exposure, 12.5% proportion of cases with exposure (39). Thus the two proportions were adopted in our sample size calculation using Kelsey's formula for unmatched case control studies sample size calculation (40);

$$N_1 = \frac{(Z_{\alpha/2} + Z_{\beta})^2 \, PQ \, (r+1)}{r(p_1 - p_2)^2} \; ; \; N_2 = rN_1 \; ; \; P = (p_1 + rp_2)/(r+1) \text{ and } Q = 1 - P$$

Where N1 is the number of cases, N_2 number of controls, $Z_{\alpha/2}$ is the standard deviation for a 95% confidence interval, Z_{β} is the desired statistical power (80%), r (2) is the ratio of controls to cases, p_1 and p_2 are proportions of cases and controls with exposure respectively. Therefore, sample size of (N=330) was used in this study including 110 cases and 220 controls.

2.4 Variables

Independent variables were parity, gravidity, smoking, antenatal dexamethasone (no of doses received), gestational age, maternal comorbidities like diabetes, mode of delivery, and time interval from antenatal dexamethasone initiation to delivery

Dependent variables; primary outcome was RDS and secondary outcome was neonatal mortality.

2.5 Data collection

Data was collected all through 24 hours as new admissions occurred. Neonates admitted in the neonatal unit, were recruited within 24 hours after birth.

2.5.1 Data collection tool

A data abstraction form consisting of three main sections namely neonatal birth history, maternal obstetrics history and neonatal clinical history including neonatal outcomes was pretested using 16 subjects prior to adoption for data collection. Pre testing was done by the principal investigator at MNH.

2.5.2 Data collection procedures

Data was collected by the principal investigator and three research assistants (nurses) who were trained prior to data collection. The maternal data including socio-demographics, delivery details, comorbidities and past medical history, antenatal history for current pregnancy, and details of ACS administration were documented. Neonatal characteristics including gender, birth weight, gestation age at birth, one- and five-minute APGAR scores among others were documented. Data was obtained from patient files, registries, pharmacy data base as well as antenatal clinic cards. Enrolled neonates were followed up until discharge while being monitored for oxygen saturation, medications used and mode and duration of oxygen supplementation.

2.5.3 Diagnosis of RDS

RDS was diagnosed by clinicians through observing the presence of respiratory rate (RR) >60/minute, subcostal or intercostal recessions, expiratory grunt or groaning, presence of nasal flaring, suprasternal retractions, decreased air entry on auscultation of the chest, gasping, choking and presence of cyanosis. Silverman Anderson Score was used in confirming and assessing severity of RDS (41)

2.5.4 Confirmation of gestational age

Gestational age determination was done by considering ultrasound measurement of the embryo in the first trimester, fundal height and details of last menstruation. Given the discrepancies associated with the above such as missing ultrasound results of the early pregnancy, Ballard's score assessed by clinicians was used to confirm the neonates gestation age within 24 hours of birth (42).

2.6 Data analysis

Data from the data abstraction forms were entered in excel sheets and then exported to and coded using Statistical Package for Social Sciences (SPSS) version 23.

Cohort data

Descriptive statistics such as socio-demographics and clinical baseline characteristics were summarized using proportions. The overall mortality rate was calculated using incidence rate. Furthermore, the log-ranking test was used to graphically compare the probability of death with time (in days). Factors which had p-value < 0.2 in log-ranking test qualified for cox regression analysis. Crude hazard ratio (CHR) and adjusted hazard ratios (AHR) were the effect measures for univariate and multivariate cox regression analysis, respectively. A p-value of < 0.05 was considered statistically significant at 95% confidence interval.

Case control data

Proportions were used to summarize descriptive information whereas Chi-square/Fisher's test and logistic regression were used to test the descriptive statistics and establish association between categorical variables, respectively. Continuous variables such as age were analyzed using Mann Whitney test where the descriptive part was summarized using median and range. Odds ratio was obtained by comparing the odds of exposure to dexamethasone among RDS cases to the odds of exposure to dexamethasone among controls. Univariate and multivariate binary logistic regression analysis was employed to determine the predictors of RDS among preterm neonates. All tests were considered statistically significant at $p< 0.05$.

2.7 Ethical consideration

The ethical clearance was sought from the MUHAS institutional review board ethical committee under director of research and publication (MUHAS-REC-03-2021-515). In addition to ethical clearance, permission to collect data was requested from the respective hospital management. Informed consent was obtained from mothers of the preterm neonates prior to data collection. Confidentiality was observed through the use of codes instead of the names of neonates during data collection and analysis.

CHAPTER THREE

3.0 RESULTS

3.1 Baseline neonatal and maternal characteristics of cases and controls

Out of 330 preterm neonates enrolled, of which 110 were cases and 220 were controls. 71.8% of the participants were from MNH and 28.2% from Amana regional referral hospital. The median gestational age at delivery was 30 weeks and 6 days (28-34) among cases and 33 weeks (28-34) among controls (p<0.001). A one-minute APGAR score of less than seven was assigned to 38.2% of cases compared to 14.5% of controls (p<0.001).

The median birth weight was 1400 (600-2400) among cases and 1800 (800-2700) among controls (p<0.001).

Table 1: Baseline neonatal characteristics

Variable	Case n = 110 (%)	Control n = 220 (%)	P-Value
Gender of baby			
Male	65 (59.1)	116 (52.7)	0.273
Female	45 (40.9)	104 (47.3)	
1 min APGAR score			
< 7	42 (38.2)	32 (14.5)	**< 0.001**
≥ 7	68 (61.8)	188 (85.5)	
5 min APGAR score			
< 7	13 (11.8)	4 (1.8)	**< 0.001**
≥ 7	97 (88.2)	216 (98.2)	
Birth weight			
Median	1400	1800	**< 0.001**
Range	(600-2400)	(800-2700)	

Table 2: Baseline maternal characteristics

Variable	Case n = 110 (%)	Control n = 220 (%)	P-Value
Maternal age at delivery (years)			
Median	28	27	0.520
Range	(17- 42)	(16 - 45)	
Marital status			
Married	91 (82.7)	160 (72.7)	**0.045**
Not married	19 (17.3)	60 (27.3)	
Level of education			
Informal	6 (5.5)	24 (10.9)	0.144
Primary	42 (38.2)	57 (25.9)	
Secondary	46 (41.8)	99 (45.0)	
College	4 (3.6)	11 (5.0)	
University	12 (10.9)	29 (13.2)	
Occupation			
Employed	11 (10.0)	21 (9.5)	
House wife	42 (38.2)	79 (35.9)	0.959
Self employed	46 (41.8)	99 (45.0)	
Unemployed	11 (10.0)	21 (9.5)	
Gestational age at delivery			
Median	30.8571	33	**< 0.001**
Range	(28-34)	(28-34)	
Mode of delivery			
SVD	72 (65.5)	126 (57.3)	0.153
Caesarean section	38 (34.5)	94 (42.7)	
Gravidity			
Primigravida	36 (32.7)	88 (40.0)	0.188
Multigravida	74 (67.3)	132 (60.0)	
Prenatal care			
Received	102 (92.7)	212 (96.4)	0.094
Not received	8 (7.3)	8 (3.6)	
Maternal NCDs			
Yes	50(45.5)	116 (52.7)	1.000
No	60(54.5)	104 (47.3)	
PPROM			
Yes	42 (38.2)	78 (35.5)	0.627
No	68 (61.8)	142 (64.5)	

3.2. Effect of Antenatal dexamethasone

RDS was found to occur more among preterm neonates whose mothers did not receive antenatal dexamethasone (61.8% with 95% CI (52.5% - 70.4%)) compared to those whose mothers received antenatal dexamethasone (38.2% with 95% CI (29.6% - 47.5%), X^2 (1, 330) = 5.838, *p = 0.016* (Figure 1).

Table 3 summarizes the time interval from first antenatal dexamethasone dose to delivery as well as the number of doses received. Most cases (51.2%) were delivered in less than two days from the time when the first dose was administered whereas most controls (49.6%) were delivered within two to seven days after the first dexamethasone dose.

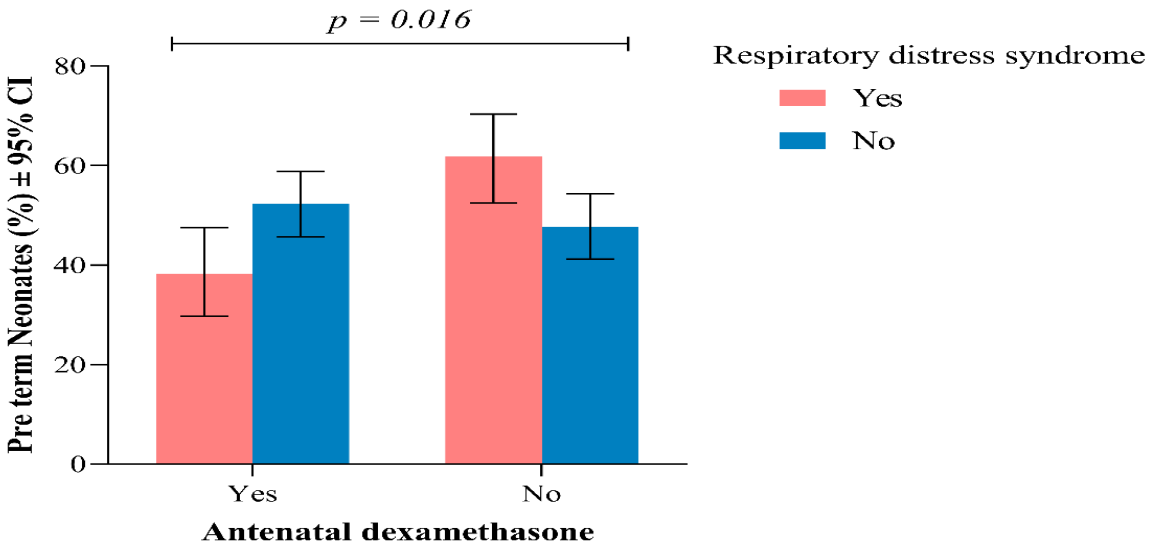


Figure 1 : Proportion of preterm neonates with respect to antenatal dexamethasone exposure and RDS.

3.2.1 Predictors of respiratory distress syndrome

Gestational age at delivery (AOR: 0.81; 95% CI 0.69-0.94), 1 minute APGAR score of less than 7 (AOR: 3.11; 95% CI 1.54-6.30), and neonatal birth weight (AOR: 0.998; 95% CI 0.997-0.999) were independently associated with RDS**.** Hereby, unit increase in gestational age at delivery is associated with a 19% decrease in the risk of developing RDS whereas a unit increase in neonatal birth weight is associated with a 0.2% reduction in RDS risk. Neonates who scored a one-minute APGAR score of less than seven were three times more likely to be diagnosed with RDS. In univariate analysis, the odds of developing RDS following exposure to antenatal dexamethasone among cases compared to controls was found to be 0.56; (95% CI 1.11-2.83) *p=0.016.* However, under multivariate analysis antenatal dexamethasone exposure was not associated with RDS (AOR: 0.61; 95% CI 0.86-3.15, *p=0.129)* as summarized in Table 3.

Table 3: Univariate and Multivariate analysis of factors associated with RDS

	Univariate analysis			**Multivariate analysis**		
Variable	**COR**	**95% CI**	**P - value**	**AOR**	**95% CI**	**P - value**
Gestational age (weeks)	0.65	0.57 – 0.74	< **0.001**	0.81	0.69 – 0.94	**0.007**
APGAR Score (1min)						
< 7	3.63	2.12 – 6.21	< **0.001**	3.11	1.54 – 6.30	**0.002**
≥ 7	Ref					
APGAR Score (5min)						
< 7	7.24	2.30 – 22.76	< **0.001**	2.19	0.52 – 9.28	0.287
≥ 7	Ref					
Mode of delivery						
Caesarean	0.71	0.44 – 1.14	0.153	1.23	0.63 – 2.36	0.562
NSVD	Ref					
Marital status						
Unmarried	0.56	0.31 – 0.99	**0.047**	0.54	0.5 – 1.19	0.125
Married	Ref					

Level of education						
Primary	2.95	1.11 – 7.85	**0.031**	2.87	0.87 – 9.54	0.085
Secondary	1.86	0.71 – 4.86	0.206	2.08	0.64 – 6.79	0.227
College	1.46	0.34 – 6.22	0.613	1.44	0.26 – 8.15	0.680
University	1.66	0.54 – 5.07	0.378	2.55	0.64 – 10.22	0.186
Informal	Ref					
Gravida						
Multigravida	1.38	0.85 – 2.23	0.189	0.94	0.49 – 1.78	0.844
Primigravida	Ref					
Prenatal care						
Yes	0.42	0.15 – 1.19	0.104	0.53	0.15 – 1.88	0.322
No	Ref					
ANC						
Yes	1.77	1.11 – 2.83	**0.016**	1.65	0.86 – 3.15	0.129
No	Ref					
Birth weight in (gm)	0.997	0.997 – 0.998	< **0.001**	0.998	0.997 – 0.999	< **0.001**

Key: COR: crude odds ratio, AOR: adjusted odds ratio, Ref: Reference group

3.3 Mortality

3.3.1 Incidence of mortality

The overall mortality rate was found to be 9 per 1000 neonates. Neonates delivered by mothers who did not receive antenatal dexamethasone had a high mortality rate (13 per 1000 neonates) compared to those whose mothers received antenatal dexamethasone (4 per 1000 neonates). The highest mortality rate was observed among cases (22 per 1000 neonates) than controls (0 deaths). Neonates with extremely low birth weight had a high mortality rate (31 per 1000 neonates) compared to other birth weight categories. Neonates with a one-minute and five-minute APGAR scores of less than seven had high mortality rates compared to scores greater than or equal to seven (14 per 1000 neonates and 18 per 1000 neonates respectively). Neonates delivered by mothers with non-communicable comorbidities had the lowest mortality rates (8 per 1000 neonates) compared to those whose mothers had no comorbidities. Neonates with gestational age of less than 32 weeks at delivery had a high mortality rate (15 per 1000 neonates) compared to those with 32 weeks and above. Primigravids and those delivered by spontaneous vaginal delivery had higher mortality rates compared to multigravidas and caesarean section (12 and 11 per 1000 neonates), respectively (Table 4).

Table 4: Mortality rate stratified by socio-demographic and clinical characteristics of the study participants

Characteristic	Category	Total N	Person time (Days)	Death N (%)	Incidence rate /1000 Neonates
RDS	Yes	110	1,052	23 (20.9)	22
	No	220	1,420	0 (0)	0
ANC	Yes	157	1,057	4 (2.5)	4
	No	173	1,415	19 (11)	13
Maternal NCDs	No	164	1,172	13 (7.9)	11
	Yes	166	1,300	10 (6.0)	8
Gravidity	Primigravida	124	815	10 (8.1)	12
	Multigravida	206	1,653	13 (6.3)	8
Birth weight	<1000g	17	192	6 (35.3)	31
	1000-1499g	86	800	10 (11.6)	13
	1500-2499g	221	1,458	7 (3.2)	5
	≥2500g	6	22	0 (0)	0
1 min APGAR score	< 7	74	643	9 (12.2)	14
	≥ 7	256	1,829	14 (5.5)	8
5 min APGAR score	< 7	17	164	3 (17.6)	18
	≥ 7	313	2,308	20 (6.4)	9
Mode of delivery	SVD	198	1,519	17 (8.6)	11
	Caesarean section	132	953	6 (4.5)	6
Gestational age at delivery	< 32	125	1,176	18 (14.4)	15
	32-34	205	1,296	5 (2.4)	4

*The overall mortality rate is 0.0093042 (9/1000 neonates per day)

3.3.2 Factors associated with mortality

Log rank test revealed that there is a significantly increased rate of death in neonates not exposed to antenatal dexamethasone (Figure 3a, p= 0.011), extremely low birth weight (Figure 3b, p= 0.001), a 5-minute APGAR score less than seven (Figure 3c, p= 0.222) and a 1-minute APGAR score of less than seven (Figure 3d, p=0.122).

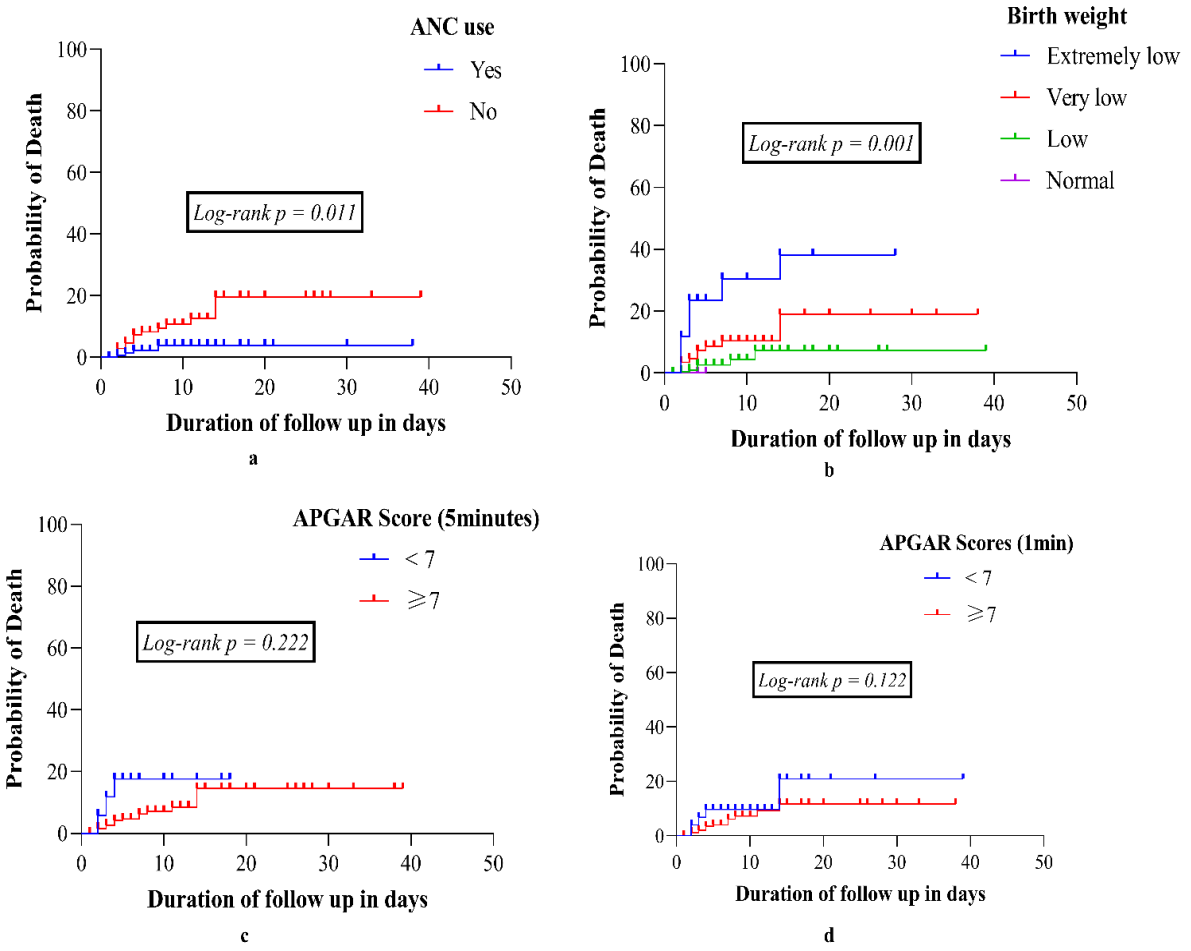


Figure 2: Cumulative hazard curves showing the association between probability of death and time using Log-ranking test.

A greater rate of death was observed in neonates with RDS (Figure 4b, P< 0.001), however no significant association was found with other factors including; primigravida, neonates whose mothers had no comorbidities and those delivered by spontaneous vaginal delivery.

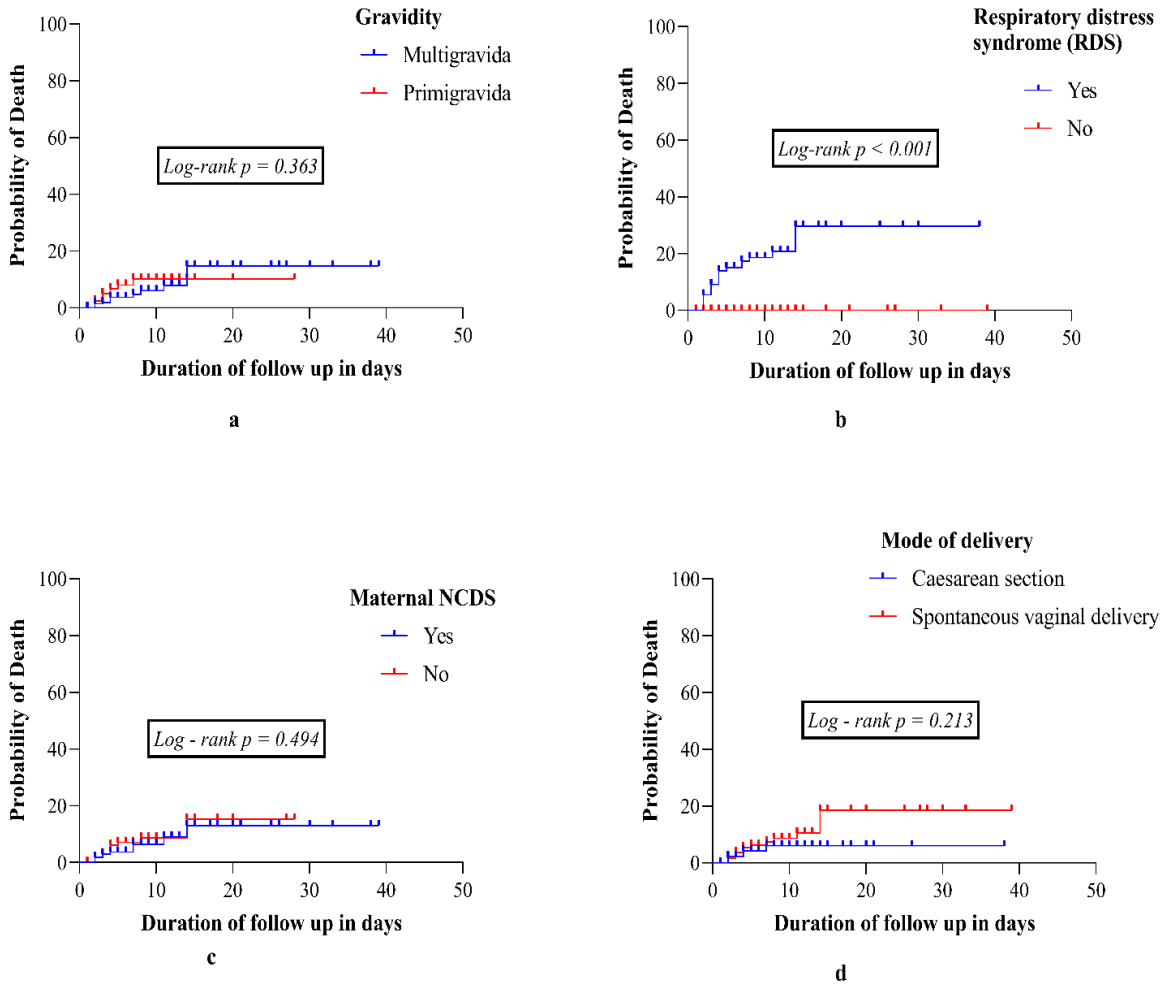


Figure 3: Cumulative hazard curves showing the association between probability of death and time using Log-ranking test.

Further analysis using Cox-regression demonstrated that only gestational age was significantly associated with mortality. A unit increase in gestational age had a 30% decrease in the risk of death (AHR: 0.70, 95% CI: 0.53-0.92, p=0.011) (Table 5). Although univariate analysis found an

Table 5: Univariate and multivariate Cox regression analysis for the risk factors for mortality among preterm neonates

	Univariate analysis			Multivariate analysis		
Variable	**CHR**	**95% CI**	**P - Value**	**AHR**	**95% CI**	**P - Value**
Use of ANC						
Yes	0.27	0.09 – 0.80	**0.018**	0.41	0.13 – 1.26	0.118
No	Ref					
Birth weight	0.99	0.997 – 0.999	< **0.001**	0.999	0.998 – 1.00	0.131
APGAR Score (1 min)						
< 7	1.91	0.82 – 4.42	**0.132**	1.46	0.61 – 3.47	0.397
≥ 7	Ref					
APGAR Score (5 min)						
< 7	2.09	0.62 – 7.11	0.236			
≥ 7	Ref					
Gravidity						
Primagravida	1.46	0.64 – 3.35	0.369			
Multigravida	Ref					
RDS*						
No	0.01	< 0.01 – 0.29	**0.008**			
Yes	Ref					
Maternal NCDs						
Yes	0.75	0.33 – 1.72	0.499			
No	Ref					
Mode of delivery						
Caesarean	0.56	0.22 – 1.42	0.223			
SVD	Ref					
Gestational age	0.59	0.47 – 0.76	< **0.001**	0.70	0.53 – 0.92	**0.011**

Keys: CHR: Crude Hazard Ratio, AHR: Adjusted Hazard ratio

association between mortality and antenatal dexamethasone exposure (CHR: 0.27, 95% CI: 0.09-0.80, p=0.018), birth weight (CHR: 0.99, 95% CI: 0.997-0.999, p<0.001) and RDS (CHR: 0.01, 95% CI: 0.01-0.29, p= 0.008); this was not replicated in multivariate analysis.

CHAPTER FOUR

4.0 DISCUSSION

This study aimed at assessing the effectiveness of antenatal dexamethasone in reducing RDS and mortality in preterm neonates in Dar es Salaam, Tanzania. In this study antenatal dexamethasone is not associated with reduced neonatal mortality rates and RDS occurrence in preterm neonates. Increase in gestational age is found to be protective against neonatal mortality and RDS. One minute APGAR score of < 7 and low neonatal birth weights are predictors of RDS in preterm neonates.

No association between antenatal dexamethasone use and RDS occurrence is contrary to other studies for example a study conducted in Brazil whereby RDS incidence was reduced with antenatal corticosteroid use (43). Differences in the epidemiology of preterm birth, exposure to infections, pharmacogenetical factors and quality of neonatal care could be the likely reasons for the observed differences.

This study also found gestational age at delivery (AOR: 0.81; 95% CI 0.69-0.94) and neonatal birth weight (AOR: 0.998; 95% CI 0.997-0.999), to be independent predictors of RDS in preterm neonates. Hereby, unit increase in gestational age at delivery is associated with a 19% decrease in the risk of developing RDS where as a unit increase in neonatal birth weight is associated with a 0.2% reduction in RDS risk. There is a direct relationship between gestational age at delivery and neonatal birth weight (44). These two are directly related to RDS occurrence because the latter happens as a result of immature lungs with inadequate surfactant. Surfactant production in the fetus mostly occurs after 30 weeks of gestation. Thus, neonates born prior to this age are likely to suffer from RDS (45)**.** These findings are similar to those done at a neonatal unit in Cameroon to assess the prevalence, predictors and outcomes of neonatal distress (46). Several other studies have shown similar findings on gestational age and neonatal birth weight as predictors of RDS in preterm neonates (47)(38). Also, in this study, 1 minute APGAR score of less than 7 was found to be an independent predictor of RDS in preterm neonates (AOR: 3.11; 95% CI 1.54-6.30). This finding is similar to the findings of a prospective study in Ethiopia that

showed an APGAR score less than 7 (AHR: 3.1 (95%CI: 1.8-5.0)) to be a significant predictor of RDS in preterm neonates (48).

This study found an overall mortality rate of 9 per 1000 preterm neonates. Death was reported in 23 (6.97%) of the preterm neonates. In this cohort, not receiving antenatal dexamethasone, low birth weights, RDS, low APGAR scores and prematurity have been associated with increased mortality rates. This could be due to the fact that preterm newborns are at greater risk of death, which could result from physical and physiologic immaturities (49). These findings are consistent with other studies and reports. A systematic review and meta-analysis of incidence density rate of neonatal mortality and predictors in sub-Saharan Africa found that low APGAR scores, respiratory distress syndrome and prematurity among other factors are associated with increased neonatal mortality rates (50). This can be because many countries in sub-Saharan Africa do not have enough facilities in terms of expertise and equipment that are capable of providing adequate care to neonates with respiratory problems and those who suffered from intrapartum hypoxia. However, contrary to our study, maternal comorbidities were associated with increased neonatal mortality rates (50). In our study neonates delivered by mothers with non-communicable comorbidities had the lowest mortality rates (8 per 1000 neonates) compared to those whose mothers had no comorbidities. This could be because mothers with comorbidities are more likely to receive preventive care such as ACS as the likelihood of preterm delivery is expected compared to those without.

Another study conducted at a neonatal unit in northern Tanzania on cause of specific neonatal mortality documented that prematurity was the second leading single cause of neonatal deaths especially in low birth weight neonates (94.7%), whereby case fatality declined with increasing birth weight (51). This is similar to our findings whereby more deaths occurred in the extremely low birth weight neonates and no deaths occurred in normal birth weight ones. Several other studies conducted in Tanzania report similar findings (52,53).

In our study fewer deaths occurred in the neonates exposed to antenatal dexamethasone (2.5%) compared to those unexposed to antenatal dexamethasone (11%). Although antenatal dexamethasone decreased incidence of neonatal mortality, there was no significant association upon multivariate analysis. These findings are consistent with several other studies that have shown fewer deaths with dexamethasone use (43,54,55). However, these findings are contrary to the antenatal corticosteroid trial (ACT trial) done in low resource settings, which found an overall increase in 28-day neonatal mortality and stillbirth associated with the intervention(14), and a study in a rural Tanzanian hospital, which found poor neonatal outcomes associated with antenatal corticosteroid use (15). This could be because our study was conducted in a tertiary and referral hospital which have the required facilities and expertise to care for preterm neonates.

In this study, majority of the deaths occurred in neonates delivered at 28 to 32 gestational weeks (14.4%). Similar to our findings, a multicenter hospital-based investigation of preterm neonatal mortality in China found most of the deaths (57.9%) occurred in neonates delivered at 28 to 32 weeks of gestation (56). A unit increase in gestational age was independently associated with a 30% reduction in neonatal mortality risk, according to our findings. Furthermore, in this study, spontaneous vaginal delivery had higher mortality rates compared to caesarean section. These findings are consistent to a study conducted in the US on very preterm infants, comparing the mortality rates between neonates delivered by primary spontaneous vaginal delivery and caesarean section. The study found that caesarean section significantly reduced the risk of neonatal death among the very preterm neonates (adjusted odds ratios of 0.58, 0.52, 0.72, and 0.81 for 22, 23, 24, and 25 weeks, respectively) (57). However, contrary to our findings, a review on trends in neonatal, post-neonatal, infant, child and under-five mortalities in Tanzania from 2004 to 2016 showed that neonates delivered by caesarean section had a higher risk of mortality compared to vaginal delivery (58). This can be because the study was conducted in referral hospitals with enough resources and well-trained personnel.

CHAPTER FIVE

5.0 LIMITATION, CONCLUSION AND RECOMMENDATIONS

5.1 Limitations

Standard diagnosis of RDS includes performing chest X-ray, however this was not routinely done to all neonates with RDS. Also, this study could be limited by the general limitation of nested case control studies; that is, reduced precision and power due to sampling of controls. However, the findings in this study are acceptable despite the limitations because of the mitigation measures employed like time censoring cases and controls as well as confirmation of RDS diagnosis by using Silverman Anderson Scores performed by well-trained clinicians.

5.2 Conclusion

Antenatal dexamethasone is not associated with reduced neonatal mortality rates and RDS occurrence in preterm neonates. Increase in gestational age is found to be protective against neonatal mortality and RDS. One minute APGAR score of < 7 and low neonatal birth weights are predictors of RDS in preterm neonates.

5.3 Recommendation

Larger prospective studies should be conducted to determine the exact preconditions of antenatal corticosteroid therapy in low-resource settings.

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APPENDICES

Data abstraction form

INCLUSION CRITERIA: Neonates delivered at 28 to 34 weeks of gestation

NEONATAL CHARACTERISTICS

Name: Baby of…….. DOB: ……

Gender ◯ Male ◯ Female

BIRTH HISTORY

Estimated Gestational Age: ……..weeks……days Birth weight: ……..grams

APGAR score: ……..

Ruptured membranes: …….hours before delivery.

Artificially ruptured? ◯ Yes ◯ No

Mode of Delivery: ◯ NSVD ◯ Elective caesarean ◯ Non elective caesarean

Assisted vaginal delivery: ◯ with forceps ◯ with vacuum

MATERNAL INFORMATION

Name: …….. File No: …….. Age: …….

Smoking ◯ Yes ◯ No

MATERNAL CLINICAL HISTORY

Gravida: ……. Para: …… PCMCT: ……

Prenatal care received? ◯ Yes ◯ No Antenatal dexamethasone received? ◯ Yes ◯ No

If Yes, date of first visit: …….. If Yes, Date of first dose: …….

Number of total visits: …… Number of total Doses: ……

MATERNAL COMORBIDITIES

Overt diabetes ◯ Yes ◯ No Gestational diabetes ◯ Yes ◯ No

Hypertension ◯ Yes ◯ No Pre eclampsia/ eclampsia ◯ Yes ◯ No

NEONATAL CLINICAL HISTORY

RDS ◯ Yes ◯ No

WEEK 1	CRITERIA	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
	Average daily PO_2							
	Average daily Duration of oxygen supplementation							
	Medications given							
WEEK 2	CRITERIA	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
	Average daily PO_2							
	Average daily Duration of oxygen supplementation							

	Medications given							

NEONATAL CLINICAL HISTORY WEEKLY SUMMARY

WEEK 1	**WEEK 2**
RDS ◯ Yes ◯ No	RDS ◯ Yes ◯ No
Management given:	Management given:
……	……
……	……
……	……
……	……
……	……
Secondary outcomes:	Secondary outcomes:
Died◯ Recovered◯ worsened◯	Died◯ Recovered◯ worsened◯
Others ;	Others ;
Duration of ventilation support:	Duration of ventilation support:
……	……
Duration of NICU stay:	Duration of NICU stay:
…….	…….
Comment/Any additional information:	Comment/Any additional information:
……	……
……	……
……	……
……	……...

Informed consent form

Informed Consent: English version

Patient Code:

Greetings,

My name is **Wema Kibanga**. I am a postgraduate student of Hospital and Clinical Pharmacy at Muhimbili University of Health and Allied Sciences. I am conducting a study titled: Effectiveness of antenatal dexamethasone in women at risk of preterm delivery in resource limited settings; a case control study

Study aim

This study intends to assess the effectiveness of antenatal dexamethasone in women at risk of preterm delivery in resource limited settings.

Study participants

It will involve neonates delivered at 28 to 34 weeks of gestational ages.

Confidentiality

Confidentiality and privacy of all the study participants will be a guiding principle during this study. Confidentiality will be respected during the research process because the information that will be collected will be used only for research purposes aimed at patients care improvement. Codes will be used to record participants' data and information that can identify a participant will not appear on the potential documents to p

Benefits and compensation

There will be no compensation to be provided to participants' family in relation to this study. The benefits from participating in the research will be to guide clinicians and researchers about antenatal corticosteroids optimization.

Risk

There will be no risk associated with participating in this study.

Rights to Withdraw and Alternatives

The participant has the rights to voluntary participate in the following study and refusal to participate or withdraw is not associated with any consequences. Refusal and withdrawal from the study will not be associated with the loss of health care benefits and rights from your health care provider.

Contact details

Wema Kibanga 0785637720

Director of research and publications MUHAS : +255-022-2152489

Have you understood the purpose of this study? YES ____ NO ____

Do you understand the risks and benefits of this study? YES ____ NO ____

Do you agree voluntarily to participate? YES ____NO ____

I have read the contents in this form and agree voluntarily to participate in the study.

Date: .....Participant Signature …….....

Date:.....Researcher/Research assistant signature.....

For research staff use only: tick accordingly

Note: Participant AGREED or DISAGREED to participate. Tick the option that apply

Informed Consent: Swahili version
RIDHAA YA KUSHIRIKI KATIKA UTAFITI

Namba ya utambulisho ya mgonjwa

Habari, Jina langu ni Wema Kibanga; nasoma masomo ya sayansi ya afya katika Chuo Kikuu cha Afya Muhimbili. Ikiwa ni sehemu ya masomo yangu, nimeanza utafiti kuhusu ufanisi wa dawa ya dexamethasone inayotolewa kwa wamama wenye hatari ya kupata watoto njiti.

MADHUMUNI YA UTAFITI

Kutambua ufanisi wa dawa ya dexamethasone inayotolewa kwa wamama wenye hatari ya kupata watoto njiti.

WASHIRIKI WA UTAFITI

Watoto njiti wote waliozaliwa kati ya wiki 28 mpaka 34 za ujauzito.

USIRI

Taarifa zote utakazotoa kwenye utafiti huu zitatunzwa kwa usiriwa hali ya juu sana. Taarifa zitakazokusanywa zitaingizwa kwenye kompyuta, zikiwa katika namba ya siri. Jina lako halitahitajika katika utafiti huu hii inaonyesha jinsi gani taarifa zako zitakavyotunzwa kwa usiri. Taarifa zote tutakazopata zitatumika kwa ajili ya utafiti huu tu na kwa ajili ya kuboresha huduma ya wagonjwa.

FAIDA

Hakuna faida yoyote ya moja kwa moja kwako au kwa familia yako katika kushiriki kwenye utafiti huu. Manufaa ya kushiriki kwako ni katika kuwawezesha madaktari na watafiti kuboresha matumizi ya dawa katika kukutibu wewe na wagonjwa wengine wenye tatizo kama lako.

ATHARI

Hakuna athari yoyote itakayotokea kwako kwa kushiriki utafiti huu.

HAKI YA KUJITOA KWENYE UTAFITI

Ushiriki wako katika utafiti huu ni hiari. Kama hautaridhia/ kuamua kusitisha mahojiano katika utafiti huu wakati tafiti inaendelea, hakuna adhabu yoyote itakayotolewa na utaendelea kupata huduma ya matibabu kama kawaida.

NANI WA KUWASILIANA NAE

Wema Kibanga 0785637720

Mkurugenzi wa tafiti chuo kikuu Muhimbili : +255-022-2152489

Una maswali?

Umeelewa yote juu ya utafiti huu? NDIYO_____/HAPANA_____

Umeelewa madhumuni ya utafiti huu? Ndiyo……..Hapana

Umeelewa faida na athari za utafiti huu? Ndiyo……..Hapana

Je unakubali kushiriki kwenye utafiti huu? Ndiyo…….Hapana

Nimesoma/nimeelezwa maelezo haya na nimeyaelewa. Nakubali kushiriki kwenye utafiti huu.

Sahii ya mshiriki……

Sahii ya mtafiti……

Tarehe…….

Kwa matumizi ya utafiti tu

Mushiriki AMEKUBALI ☐ au AMEKATAA ☐

Silverman Anderson Scoring

Score	**0**	**1**	**2**
Upper Chest Retractions	synchronized	lag on inspiration	see-saw movement
Lower Chest Retractions	none	just visible	marked
Xiphoid Retractions	none	just visible	marked
Nasal Flaring	none	minimal	marked
Expiratory Grunting	none	stethoscope only	naked eye and ear

From the above table, neonates with no retractions, flaring or grunting with synchronized respiratory movements will have a score of "0". Those with visible retractions of the lower chest and xiphoid, with the upper chest lagging compared to the lower on inspiration, will have a score of "1". Minimal nasal flaring and an expiratory grunt heard only with a stethoscope will also receive a "1". Marked retractions with a "see-saw" movement of the upper and lower chests will be scored "2". Thus normal babies will have a cumulative score close to "0". Severely depressed babies will have a score close to "10"