BURDEN OF RHESUS ISO IMMUNIZATION AND PREGNANCY OUTCOMES AT THE KENYATTA NATIONAL HOSPITAL, 2013-2019

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DECLARATION

This research was undertaken in part fulfillment of the Masters of Medicine in Obstetrics and Gynecology from the University of Nairobi and was my original work and has not been undertaken and or presented for a degree in any other University.

29th May 2020

…… ……

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CERTIFICATE OF AUTHENTICITY

CERTIFICATE OF AUTHENTICITY

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DEDICATION

I dedicate this work to my parents: Joackim Abayo Rakuom and Mary Awino Abayo for their prayers, financial support and inspiration.

To my siblings Janet Atieno and James Omondi for their prayers and encouragement.

LIST OF ABBREVIATIONS

ANC	Ante-natal care
ASCP	American Society of Clinical Pathology
EDD	Expected Due Date
GBD	Gestation by Dates
HBSAg	Hepatitis B surface antigen
HDFN	Haemolytic Disease of the Fetus and New born
HDN	Hemolytic Disease of the Newborn
HIV	Human immunodeficiency virus
IUT	Intra Uterine Transfusion
KNH	Kenyatta National Hospital
LNMP	Last Normal Menstrual Period
MOH	Ministry of Health
NICE	National Institute for Clinical Excellence
NICU	Neonatal Intensive Care Unit
RAADP	Routine Antenatal Anti-D Prophylaxis
RBC	Red Blood Cell
RBS	Random blood sugar
RhD-ve	Rhesus D negative
RhD+ve	Rhesus D positive
SOP	Standard Operating Procedures
SPSS	Statistical Package for Social Scientists Software
SSA	Sub-Saharan Africa
VDRL	Venereal disease research laboratory
WHO	World Health Organization

OPERATIONAL DEFINITIONS

Hemolytic Disease of the Foetus and Newborn: Hemolytic Disease of the Newborn (HDN), occurs when fetal red blood cells (RBCs), which possess an antigen that the mother lacks, cross the placenta into the maternal circulation, where they stimulate antibody production. The antibodies return to the fetal circulation and result in RBC destruction. This can occur in utero and soon after birth. It occurs in mothers with Rhesus Isoimmunization and also in ABO incompatibility.

Hydrops Fetalis: is a serious fetal condition defined as abnormal accumulation of fluid in two or more fetal compartments, including ascites, pleural effusion, pericardial effusion, and skin edema, anasarca.

Rhesus Iso Immunization: The process by which fetal Rh+ erythrocytes enter the circulation of an Rh- mother, causing her to produce Immunoglobulin G antibodies, which cross the placenta and destroy the erythrocytes of Rh+ fetuses. Rh iso-immunization can also be caused by Blood Transfusion with mismatched blood.

Adverse Maternal Outcomes: These include anemia, miscarriages and premature labor

Fetal Outcomes: These include hydrops fetalis, prematurity, poor APGAR score, Intra uterine fetal demise, Neonatal Mortality, NBU/NICU admission, Birth Weight, Neonatal Jaundice

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ABSTRACT

Introduction: The ABO and the Rh systems remain the most clinically significant blood group antigens on the red cell membranes. The pathology of rhesus isoimmunisation entails an antigen antibody reaction between the maternal Rh antibodies in a RhD-ve woman and the red blood cell membrane in a RhD+ve foetus with resultant effect on the foetus and neonate. Isoimmunization is the process of immunizing an individual with antigen derived from a similar subject, provided that the said antigen was initially absent. Though knowledge about immunity in pregnancy is ever increasing daily, there is paucity of data about the maternal and foetal outcomes of iso immunized women locally. Continued update will result in better management of pregnant women who develop Rh Iso immunization.

Objective: To determine the prevalence and outcomes of rhesus iso immunization among Rh –ve pregnant women at the Kenyatta National Hospital between January 2013 and December 2019.

Methodology: This was a cross sectional study conducted at the Kenyatta National Hospital among women with Rhesus negative blood group as seen between January 2013 and December 2019. Following ethical approval from the KNH-UoN ERC, a sample survey for all the records of the 216 eligible women was done and data on the sociodemographic, isoimmunization status and clinical and maternal – fetal outcomes collected. The collected data was uploaded to the SPSS version 23 software for cleaning. A total of 194 were analysed using SPSS version 24 software. Univariate analysis was done for the sociodemographic and clinical characteristics. The prevalence of iso-immunization was calculated and presented as proportions. Fishers test statistic was used to calculate the association of rhesus iso immunization with maternal (anemia, mode of delivery and miscarriage), foetal and neonatal outcomes (Hydrops Foetalis, IUFD, poor APGAR Score and admission to NICU). A p value of 0.05 was taken to be significant statistically.

Results: The mean gestation (SD) at delivery was 38.94 (3.0). Among the women with rhesus negative blood group, a majority (81, 41.8%) had blood group O-ve, 65 (33.5%) had blood group A-ve, 38 (19.6%) had blood group B –ve while only 4 (2.1%) had blood group AB –ve. The prevalence of rhesus Isoimmunization was 4.0%. Four of the iso-immunized participants (50%) had a caesarian delivery compared to 129 (69.4%) of the non iso immunized participants (p, 0.226). Three (37.5%) of the participants with iso-immunization had their fetus diagnosed with hydrops fetalis compared to only 1 (0.5% in the non iso immunized group ($p<0.001$). Iso immunized women were more likely to deliver earlier than 38 weeks, have children with IUFD, poor APGAR score, or admitted to the NICU ($p <0.001$).

Conclusion: Rh negative pregnancies constitute a vital facet of our obstetrics population at the KNH. The uptake of anti-D at 34 weeks is suboptimal, in line with the guidelines. There are significantly higher rates of maternal and fetal complications among women with rhesus iso immunization.

Recommendations: We recommend further studies, preferably case control studies, with larger numbers of iso immunized women to better demonstrate the strength of the association between iso immunization and maternal – fetal outcomes.

CHAPTER ONE: INTRODUCTION

1.1 Background

The red blood cell (RBC) membrane comprises of surface markers which include the ABO system and the Rhesus (Rh) system (1). The "Rhesus antigen" blood group of monkeys has around 85% similarity with human beings (2). The Rh system consists of two related proteins, RhD and RhCE, which express the D and CE antigens, respectively.

The ABO system and the Rh system remain the most important antigens on the red blood cell membrane (3). RhD positive (RhD+ve) people's red blood cells contain the D antigen while those that do not have are Rhesus D negative (RhD-ve) (1). The pathology of rhesus isoimmunisation entails an antigen antibody reaction between the maternal Rh antibodies in a RhD-ve woman and the red blood cell membrane in a RhD+ve foetus with resultant effect on the foetus and neonate.

1.2 Prevalence of Rhesus Negative Blood Group

The prevalence of RhD-ve blood group varies widely in different populations. The prevalence is highest among Basques of spain with an estimated 35% (phenotypically) and 60% (genotypically); the Caucasians were found to have a prevalence of more than 14% (4) with the prevalence among the different ethnic groups of the Sub Saharan Africa ranging between 2.4 to 4.5% (staffan). In a study done by Worlledge and colleagues (5) the prevalence of RhD-ve status of the Nigerian population was at 5%; 2.4% in Cameroon as reported by Tagny et al (6); and 3.9% in Kenya in a study by Mwangi J (7).

1.3 Pathophysiology and Prevalence of Rhesus Iso – Immunization in Pregnancy

Iso-immunization is the process of immunizing an individual with antigen derived from a similar subject, provided that the said antigen was initially absent (3). Therefore, if the mother is RhD-ve and the foetus RhD+ve (inherited from the father), she has the potential to form antibodies if exposed to the foetal antigens, a process known as RhD sensitization (8,9).

Rhesus iso-immunization occurs in a RhD-ve mother by one of two mechanisms either from feto-maternal haemorrhage through escape of the foetal cells through the placenta or from incompatible blood transfusion (10). Predisposing factors for feto-maternal haemorrhage include delivery, spontaneous or induced abortion, ectopic pregnancy, miscarriage, intrauterine foetal death, abdominal trauma, antepartum haemorrhage, amniocentesis, chorionic villous sampling, foetal blood sampling, embryo reduction, shunt insertion, external cephalic version, manual removal of the placenta and caesarean section (10).

Even without an apparent predisposing factor, there has been a notable presence of red cells in maternal blood for pregnant women in the first trimester (6.7%), second trimester (15.9%), and third trimester (28.9%) (10). The risk of sensitization can occur before or during the process of delivery; it is notably however that about 30% of RhD-ve individuals never become sensitized even when given RhD+ve blood (non-responders) (10).

Most sensitization cases take place at birth (10). This rarely affects the first pregnancy but has adverse effects on subsequent pregnancies if no medical intervention is taken. As a result, Rh+ve first borns do not get affected as they are exposed to Rh +ve fetal erythrocytes for a short duration with minimal exposure for the development of anti-D antibodies.

The Rh iso – immunization is more prevalent in Sub-Saharan Africa (11). This observation can be attributed to: poor antenatal practices with failure to identify Rh-ve women, unaffordability of drugs to help neutralize RhD +ve antigens that may have entered the mother's blood during pregnancy, inability of healthcare personnel to access all Rh-ve pregnant women, late response to sensitizing event and unavailability of quality facilities to treat the Iso immunized pregnant women (9).

1.4 Antenatal Antibody Screening for Rhesus D Antigen

The World Health Organization (WHO) recommends that all women to undergo blood group and antibody screening to establish the risk of haemolytic disease of the newborn during their first appointment to the clinic when they have a positive pregnancy test (12). A small percentage of below 2% of women test positive for blood group sensitization (12). Whether or not to conduct repeat screening at 28weeks has been controversial, with those in support arguing that there is a likelihood of finding out a small portion of RhD-ve pregnant women who had undergone the first blood screen developing an immune response to foreign antigens from RhD+ve (13).

The American Society of Clinical Pathology (ASCP) recommends that anti-D should only be administered to a Rhesus negative pregnant woman after testing for unexpected antibody.

The benefits of this testing is that it reduces the need for anti D immunoglobulin which is costly and relieves the women off the discomfort that comes with the administration of the drug and lowers their likelihood of encountering side effects (14). Paternal testing is necessary for all RhD-ve expectant women. If paternal tests prove that he is RhD-ve, anti D should not be administered.

Tests such as the indirect coombs test that are used to establish the presence of antibodies in the Rh factor in the maternal blood even though they are rarely done. Other sources have put forward the use of molecular genetics to determine the individual blood group especially in RhD –ve pregnant women (15).

The Rosette test can detect alloimmunization caused by very small amounts of feto-maternal hemorrhage. When a high clinical suspicion of large feto-maternal hemorrhage is present (>30 mL blood), the Kleihauer-Betke acid elution test can be performed. The amount of Rh IgG required for treatment after sensitization is at least 20 mcg/mL of fetal RBCs (1).

Nevertheless, there are no National guidelines that should guide its implementation. Therefore, high-throughput modifications of this foetal D-typing would be useful for testing the foetuses of all Rhesus –ve pregnant women in order to avoid unnecessary administration of anti D (16)

The presence of maternal red cell antibodies during pregnancy is a relatively common finding and requires close collaboration between the blood transfusion laboratory, obstetric and neonatal care providers (17).

In the event that Rh –ve pregnant mother gives birth before she arrives at the hospital or in the emergency section without prior appointment with the doctor, those handling her should ensure they take blood samples from the umbilical cord of the infant and take it to the laboratory to test for ABO blood groups and Rh type. The Laboratory additional tests like direct coombs test. (1) This is aimed at assessing the possibility of occurrence of iso immunization during pregnancy and at birth.

CHAPTER TWO: LITERATURE REVIEW

2.1 Introduction

Rh D iso-immunization, a disease of genetic predisposition, has been a focus of concern for obstetricians and haematologists for centuries (18). With the discovery of Rh immune type of antibody by Race and Weiner (1944) which can cross placental barrier, it became evident that it is responsible for erythroblastosis fetalis (2).

2.1 Management of Rhesus Iso – Immunization in Pregnancy

Before 1970, HDFN caused by anti D had a weighty impact on the death rate and likelihood of sickness; by 1990, prevention of HDFN by using anti D immunoglobulin were developed which reduced mortality by1.18 per 1000 births (1). This led NICE to put forward that any Rh –ve pregnant woman be administered anti D at 28weeks with or without a booster dose at 34weeks (19) with subsequent reduction in the incidences of Iso immunization.

Anti D is administered to non-sensitized Rh-negative women immediately after delivery. It is advisable that ABO and Rh blood group tests are part of the evaluation that pregnant women should undergo during their ante natal clinic visit. Unless the father to the unborn child is found to be Rh –ve after blood grouping, all Rh –ve pregnant women will be subjected to human anti D immunoglobulin injection after delivery or miscarriage in order to avoid risks of incompatibility in future pregnancies (20).

Development of Intra Uterine transfusion in some regions of SSA has had a huge impact in improving the treatment of HDFN and as a result the mortality rate of foetuses has reduced (23). Intra-Uterine transfusion is necessary for foetuses suffering from HDN. Some of the complications of survivors of intra-uterine transfusion include growth restrictions and impairment of the nervous system resulting in cerebral palsy and deafness (24).

2.2 Fetal and Neonatal Outcomes in Women with Rhesus Iso – Immunization

Hypertension Disease of the Newborn (HDN) occurs when the foetus red blood cells releases an antigen that is strange to the mother's body into maternal circulation prompting the mother to produce antibodies to destroy that antigen (25). Mild jaundice, anaemia and hydrops foetalis are the main signs of HDN. As a result of the bilirubin being cleared by the placenta, the main risk to the fetus is the development of anaemia. Extra medullary hematopoiesis (due to anaemia) may result in hepatosplenomegaly with resultant risks during labor and delivery such as asphyxia and splenic rupture.

In the post-natal period, the newborn may experience problems as a result of the mother being Iso immunized. The neonate may develop yellowness of skin and eyes, anaemia, have low sugar level and develop difficulty in breathing (25). The laboratory findings vary with the severity of HDN and may include: anemia hyperbilirubinemia, reticulocytosis (6 to 40%), elevated nucleated RBC count (>10/100 WBCs), thrombocytopenia, leucopenia, hypoalbuminemia and RhD-ve blood type. A blood smear may show polychromasia and anisocytosis (20).

Following Intra-uterine Transfusion (IUT) the Direct Antiglobulin test will be negative, but the Indirect Antiglobulin Test will be positive (25). Ninety Seven percent (97%) of HDFN cases are as a result of Rh disease while the remaining 3% is due to other Iso immunization (2). Although sensitization is unlikely to affect the current fetus during the first pregnancy, it can lead to HDFN during a subsequent RhD +ve gestation. Handlers of unexplained child birth of a Hydrops foetalis newborn should ensure that it is non-traumatic and a neonatologist should be on standby to attend to the infant (17).

Hemolytic Disease of the Newborn can be avoided by preventing the fetal blood from entering the maternal circulation before or during delivery in Rh –ve pregnancy and before and after birth immune prophylaxis by administering anti D prophylaxis at 28 weeks of gestation and within 72 hours after delivery. The frequency of Rh sensitization during gestation ranges from 1-9% (2) and perinatal loss due to Rh allo immunization has been reported to be between 1% and 2.5% in India (2). Risk of Iso immunization decreased 1.5% by post-natal anti D prophylaxis and to 0.18% by additional routine antenatal anti D prophylaxis (RAADP) (2).

Additionally, children born with mothers who develop Rhesus Iso immunization may develop complications with subsequent fetal demise. In a study by Khatun J (26), the possible and expected foetus health condition in informed parents signified a 14% fetal mortality as a result of Rh allo-immunization. The frequency was higher due to unavailability of necessary facilities for caring for the newborns.

2.3 Maternal Obstetric Outcomes among Mothers Rhesus Iso Immunization

In a study conducted by Sreelatha et al in India, where the maternal outcomes among pregnant women with rhesus negative blood group was evaluated, 298 (56.4%) of the women delivered vaginally and 230 (43.5%) by section the common indication for which was fetal distress (27). Nine (1.70%) of the women had a positive indirect Coombs test. They were further investigated and followed with regular Doppler of the MCV (27). In another study conducted by Gorle et al., 37(7%) cases developed preeclampsia, 26(4.9%) cases developed fetal growth restriction, 2(0.3%) cases associated with abruption (28).

Similarly, in another study conducted by Neelam Singh et al, where maternal and fetal outcomes among Rh negative mothers were assessed, 15 mothers had adverse maternal outcomes: 8 mothers had preeclampsia/pregnancy induced hypertension, 3 had abruption placentae, 2 had oligohydramnios, 1 had still birth while another 1 had polyhydramnios (29).

2.4 Conceptual Framework

The RhD –ve antigenicity on the RBC membrane has over time been studied and the effects on the fetal and neonatal growth documented in literature. The pathophysiology of this genetically predetermined condition entails the destruction of the fetal RBCs by antibodies of an already sensitized RhD-ve mother. Some of the known predisposing factors to iso immunization include miscarriage, intra uterine instrumentation, trauma in pregnancy and parity. This dose dependent iso immunization may lead to the development of anemia, with resultant development of hydrops

foetalis. Post natally, this can lead to jaundice, kernicterus and anemia with resultant heart failure.

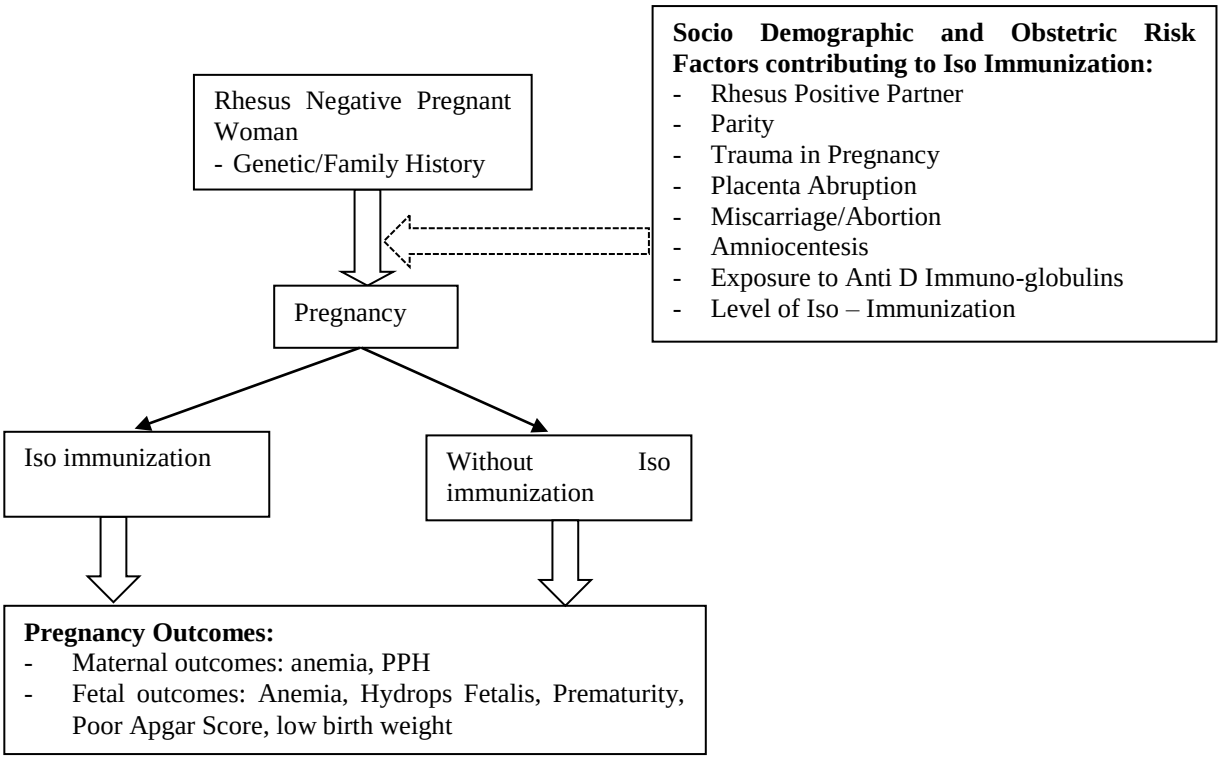

Figure 1: Conceptual Framework

The development of the anti D antibody administered to the already iso immunized mother has however led to a significant reduction in the adverse foetal outcomes experienced among mothers with RhD-ve blood group. Additionally, routine screening of the blood group during the ANC period has resulted into early identification and management of women with RhD-ve blood group. With advancement in medical care, intra utero management of the affected foetus can be through IUT of blood to correct the anemia.

2.5 Study Justification

Determining the prevalence of Rh negativity among pregnant women is an essential step in recognizing the magnitude of Rh alloimmunization complications in pregnant women, hence the development of nationwide screening, prevention and management programs based on the calculated prevalence and complications. Rhesus alloimmunization is a serious preventable disease that develops in RhD-ve pregnant women and carries major impact in the prenatal outcome including major morbidity and mortality.

A preliminary study of 89 Rh D-negative women over a 2-year period in Nigeria showed that Isoimmunization due to Rh incompatibility has been poorly studied in the SSA region with many questions unanswered such as the optimal time for delivery of these women and proportion of them that constitute non-responders. Currently, little is known about the status of Rh Iso-immunization and the management outcome in Kenya.

The objective of this study was therefore to determine the prevalence, socio- demographic characteristics and pregnancy outcomes of Rh Iso immunized pregnant women managed at the Kenyatta National Hospital. The results of the study will help in further understanding the disease burden and in the development of standard operating procedures (SOPs) to aid the management of complications among women with Rhesus Iso immunization.

2.6 Research Question

What is the prevalence of rhesus iso immunization and pregnancy outcomes among women who are rhesus negative who presented at the Kenyatta National Hospital between January 2013 and December 2019?

2.7 Study Objectives

2.7.1 Broad Objective

To determine the prevalence of rhesus iso immunization and pregnancy outcomes among women who are rhesus negative who presented at the Kenyatta National Hospital between January 2013 and December 2019.

2.7.2 Specific Objectives

Among Rhesus Negative women who attended antenatal and delivery Services at the Kenyatta National Hospital between January 2013 and December 2019:

1. To determine the prevalence of Rhesus Iso Immunization
2. To determine the adverse maternal outcomes
3. To determine the adverse fetal outcomes

CHAPTER THREE: METHODOLOGY

3.1 Study Design

The study was a cross sectional study in which files for 194 women with blood group 'Rhesus Negative' as documented at the first ANC visit were retrieved and the rhesus isoimmunization status, the perinatal and maternal outcomes determined and a documentation of the Iso Immunization state, maternal and fetal outcomes at delivery done. The exposure status was women who had documented evidence of rhesus isoimmunization.

3.2 Study Site

The study was conducted at the Kenyatta National Hospital (KNH). The KNH is one of the largest referral facilities in East and Central Africa. It also serves as a teaching facility housing the University of Nairobi's School of Medicine. The Department of Obstetrics and Gynecology handles on average 1200 mothers in the ANC and 2000 deliveries per month, serving the wider Nairobi metropolitan population and referrals from surrounding counties. The department is managed concurrently by the KNH Obstetricians, midwives and the University of Nairobi lecturers and registrars in Obstetrics and Gynecology.

Routinely, pregnant women are booked for review at the ANC. At the initial encounter, all the pregnant women undergo the basic ANC profile tests that includes testing for the ABO and Rhesus blood groups. The KNH being a referral hospital admits both patients who attended ANC services at the hospital and referrals from other facilities for delivery. For those who are admitted as referral from other facilities, the ANC profile is documented from the mother baby booklet or

any other laboratory reports that the patient would have carried along. The records for all the patients reviewed in the hospital are kept in the registry department at the hospital.

The KNH being one of the National referral facilities handles mainly high-risk patients across various departments. More than half of the high-risk patients come in as referrals from surrounding health facilities and might often have, among others, blood group and rhesus type results. A minority of the patients are regular low risk obstetric patients requiring routine management of pregnancy. These patients are often without a previous ante natal profile results hence the need to perform the ante natal profile tests. On average, 216 patients with Blood Group Rhesus Negative were reviewed at the KNH ANC clinic for the period January 2013 to December 2019. This translates to an average of 31 patients per year.

The management of patients with Rh-ve blood group entails administration of anti D, 300mcg between 28 and 34 weeks. Upon delivery, cord blood from the neonate is taken for conducting the direct coombs test. The anti D is further administered to the mother whose child tests positive for the direct coombs test within 72 hours of delivery.

3.3 Study Population

Records of women who were rhesus negative and attended antenatal clinic or delivery services at the KNH

3.3.1 Inclusion Criteria

1) Records of women with blood group ‘rhesus negative’ (with or without isoimmunization) who attended ANC and delivered at the KNH between January 2013 and December 2019 and with complete records at the registry

3.3.2 Exclusion Criteria

1. Records with missing files or incomplete data

3.4 Sample Size Calculation

Sample size calculation for the records to be reviewed was done using the formula of proportions as follows:

$$n = \frac{Z^2_{1-\alpha/2} \times p(1-p)}{d^2}$$

The assumptions for this study were derived from a similar study by Khatun J et al (3), where they described the outcomes of deliveries among mothers with blood group ‘rhesus negative’ as follows:

- n= sample size
- Z= level of statistical difference = 1.96
- P = proportion of neonates born of mothers with rhesus iso – immunization (14%)
- d= Estimated error, taken as 0.05

Substituting this in the formula gave a sample size of **186** as shown below:

$$n = \frac{1.96^2 \times 0.86\ (1-0.86)}{}$$

0.05 x 0.05

= 186

Applying a 4% mark up for possible lost to follow up and poor documentation, the recalculated sample size was 104/100*186=**194**

3.5 Sampling Procedure

A sample survey of all the 216 records for patients with rhesus negative blood group and who were seen at the KNH antenatal clinic and maternity units was done. Records that satisfied the inclusion criteria were separated for data abstraction.

3.6 Data Variables

A detailed data entry form was filled in for each record for the patients with blood group rhesus negative for the following data variables:

Study Variables

Objective	**Variable**	**Variable Classification**
Prevalence of blood group rhesus negative	Number of patients with rhesus negative blood group/total number of patients with blood group results	Exposure variable
Socio-demographic characteristics	Age of the mother Level of education Family history of blood group rhesus negative Marital Status Parity Partner's blood group	
Antenatal and Intrapartum Maternal Outcomes	Anemia	Outcome Variables
	Miscarriage	
	Premature labor	
Antenatal and Intrapartum Foetal and Neonatal Outcomes	Hydrops Fetalis IUFD	Outcome Variables

	Pre maturity Fetal Anemia Jaundice Neonatal mortality	

3.7 Data Collection and Management

Three research assistants trained in data collection procedures were engaged to retrieve all the patient files with a diagnosis of blood group RhD-ve at the KNH registry for the period of the study, checked their completeness and separated the files with complete documentation across the ANC attendance, delivery and the immediate post-natal period. As shown in figure 3, a total of 216 records for patients with documented rhesus blood group negative were separated for review. Of these 9 files were missing (could not be traced) while 10 files did not have complete data relevant for the study.

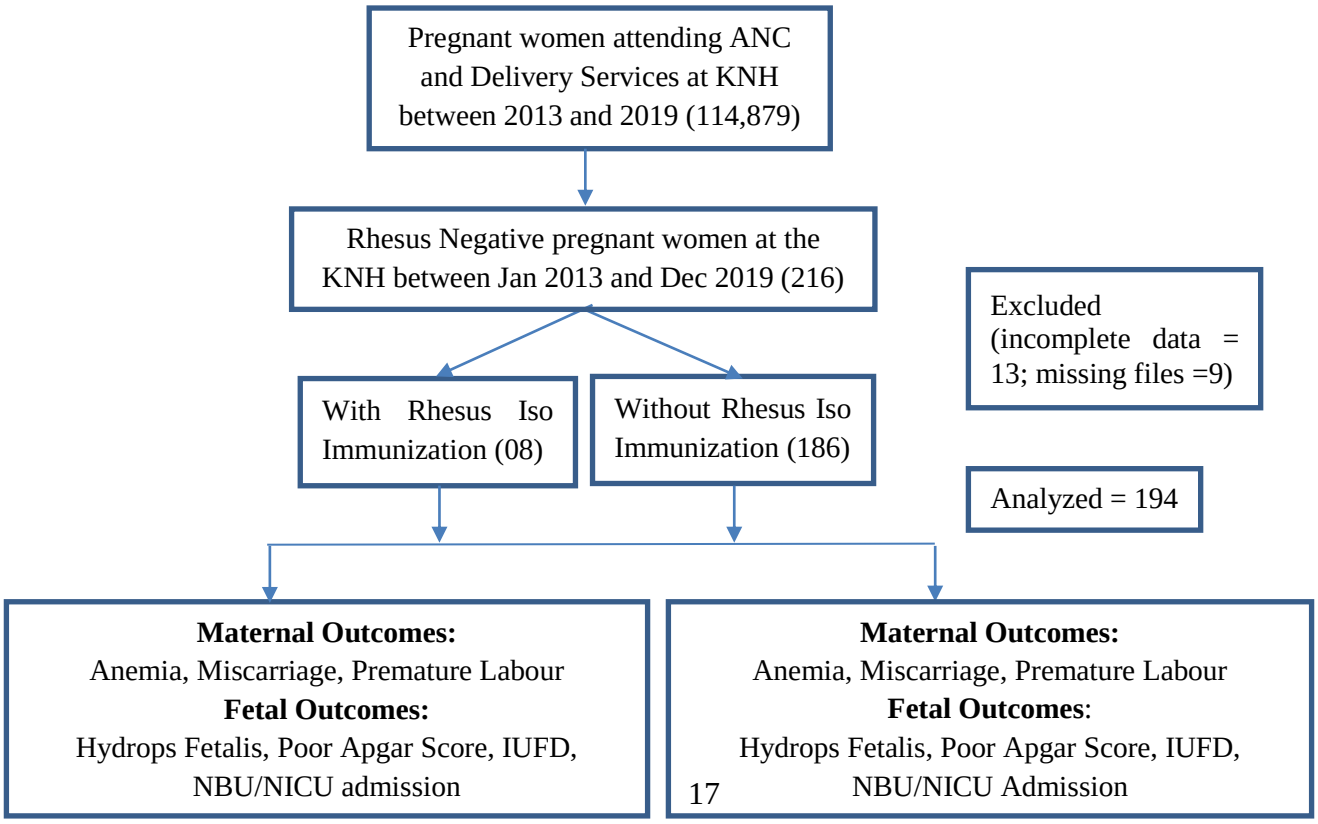

Figure 3: Study Flow Diagram for the study on the burden of rhesus iso immunization and the maternal and fetal outcomes at the Kenyatta National Hospital

3.7.1 Data Capture Tool

A detailed data entry form was filled in for each of the patients with rhesus negative blood group. Data on maternal socio demographics, medical history, obstetric history, ante natal management, antenatal and intrapartum maternal and foetal outcomes, gestation age at delivery and mode of delivery was captured. Neonatal outcomes included birth weight, APGAR scores and neonatal intensive care unit (NICU) admission.

3.7.2 Reliability and Validity

The data capture tools for patients at KNH are globally accepted standardised instruments that capture accurate data. Because data was collected retrospectively, our data collection tool was not pretested to ascertain its reliability. However, the face validity technique was used to ascertain the validity of our data capture tool. Printed copies were shared with colleagues and lecturers in the department of obstetrics and gynaecology to gauge its suitability for data collection. Their suggestions were factored into the final copy of the tool.

3.7.3 Data Quality Assurance Procedures

Two measures to make sure the data that was collected was of high integrity and acceptable scientifically were put in place. First, only research assistants with a medical background

(clinical officers or nurses with background training in basic research) were engaged during the data collection process. They also underwent a rigorous half a day training on data collection practices such as confidentiality and the techniques for extracting retrospective data accurately. Data capture tools were checked for accuracy by the data manager and data cleaned before analysis.

3.8 Data Analysis

The collected data was uploaded in a spreadsheet for cleaning before analysis using the Statistical Package for Social Scientists Software (SPSS version 23). The sociodemographic and clinical characteristics of the study participants were analyzed and presented in frequency tables. Univariate analysis for the sociodemographic and clinical characteristics was done and presented in frequency tables. The prevalence of rhesus iso-immunization over the 7-year period was calculated as the number of iso-immunized women as the numerator and the number of study participants (rhesus negative women) as the denominator and presented as a percentage. The maternal, fetal and neonatal outcomes were documented and the association of iso immunization with maternal, foetal and neonatal outcomes analysed using the Fishers exact test. The findings were visualized in tables, taking a p value of 0.05 to be significant statistically.

3.9 Ethical Considerations

Ethical approval was sought and obtained from KNH-UON ERC on (9^{TH} April 2020) (P52/02/2020). Throughout the cycle of this project, patient confidentiality was maintained at all times. Personal information such as names were not captured on our data collection tools.

Moreover, only the principal investigator and the statistician had access to the collected data and the data was stored in a password protected database. Since it is a retrospective study, consent form was not a requirement.

CHAPTER FOUR: RESULTS

This chapter presents the results for the study of the study in which records for 194 mothers with rhesus negative blood group that were followed up at the KNH between 2013 and 2019 were assessed; out of these, 8 had rhesus isoimmunization while 186 did not have documentation of isoimmunization. The socio-demographic characteristics, maternal and fetal characteristics of the participants was documented and analysed.

As shown in table 1, a majority of the study participants (53.6%) were aged between 25 to 35 years, 27.8% were aged between 19 to 24 years while 18.6% were aged between 36 to 49 years. About half of the participants, 49% had attained secondary level of education, 75 (38.7%) had attained tertiary level while 12.3% had attained primary level of education. Of the 194 records that were analysed, 177 (91.2%) were documented as married, while the rest were single. Out of the 194 documented responses about the parity, 134 (69.1%) were multigravidae while 60 (30.9%) were primigravidae.

Table 1: Characteristics of the Rhesus Negative Women who attended Antenatal Clinic at the Kenyatta National Hospital between January 2013 to December 2019

Characteristic	**N=194**	**Proportion (%)**
Age; Mean (SD)	28.64 (5.49)	
Age		
19 – 24	54	27.8
25 – 35	104	53.6
36 – 49	36	18.6
Level of Education		
Primary	24	12.3
Secondary	95	49.0
Tertiary	75	38.7
Marital Status		
Single	17	8.8
Married	177	91.2
Missing		
Parity		
Primi-gravidae	60	30.9
Multi-gravidae	134	69.1

Among the women with rhesus negative blood group, a majority (81, 41.8%) had blood group O-ve, 65 (33.5%) had blood group A-ve, 38 (19.6%) had blood group B –ve while only 4 (2.1%) had blood group AB –ve. Only 30 records had the partners' blood group documented; out of these, 23 (73%) had blood group B+ve, 6 (20%) had blood group A+ve while 2 (7%) had blood group O+ve.

Table 2: Blood Group types for the Rhesus Negative and the partners who attended the ante natal clinic at the Kenyatta National Hospital

Variable	Frequency (n=194)	Proportion (%)
Patient's Blood Group		
A-ve	65	33.5
AB-ve	04	02.1
B-ve	38	19.6
O-ve	81	41.8
Partner's Blood Group (n=30)		
A+ve	06	03
B+ve	22	11
O+ve	02	01
Missing	164	85

The prevalence of rhesus iso-immunization among rhesus negative women who attended the ANC and delivery services between January 2013 to December 2019 was 4.1%; this was determining by calculating the denominator as number of non iso-immunized rhesus negative women as the denominator (194) and the number who developed iso-immunization during the ANC period as the numerator (8).

As shown in table 7, Fishers test was use to calculate the association of maternal and fetal factors with the iso-immunization. Out of the 10 women with a diagnosis of anemia, 1 (20%) was from the iso immunized group, while 9 (4.9%) of the non-immunized women. This finding was not significant statistically, p, 0.239. Out of the 36 participants who had miscarriages, 5 (62.5% of the iso immunized) had a miscarriage compared to 31 (16.7% of the non iso immunized); being iso immunized therefore was associated with a higher chance of having a miscarriage, and this was significant statistically (p, 0.006). Four of the iso immunized participants (50%) had a Cesarean delivery compared to 129 (69.4%) of the non iso immunized participants; this

difference was however not significant statistically (p, 0.263). Only 1 out of the 8 iso immunized participants (12.5%), had Antepartum hemorrhage while 5 (2.7%) of the non iso immunized participants had antepartum hemorrhage; this was however not significant statiscally (p, 0.226).

The fetal and neonatal outcomes that were assessed included presence of hydrops fetalis, intra uterine fetal demise (IUFD), fetal weight less than 2500g, APGAR score less than 7 and admission to the Neonatal Intensive Care Unit (NICU). Three (37.5%) of the participants with iso immunization had their fetus diagnosed with hydrops fetalis compared to only 1 (0.5% in the non iso immunized group. This finding was significant statiscally (p, <0.001).

A higher proportion of participants in the iso immunized group, 5 (62.5%) reported having had an IUFD compared to those in the non iso immunized group (3, 1.6%). This difference was statiscally significant (p, <0.001). Participants who were iso immunized were more likely to deliver at less than 38 weeks' gestation and have children with a birth weight of less than 2500g (8, 85.5%) compared to those in the non iso immunized group (10, 5.5% and 8, 4.3% respectively). These findings were statistically significant (p, < 0.001). Children born of mothers in the iso immunized group were more likely to be have poor APGAR score 96, 75% compared to those in the non iso immunized group (4, 2.2%); this was significant statistically, p, <0.001. These children were also more likely to be admitted into the NICU 3, 37.5% compared to 5, 2.7%, p, 0.002.

Table 3: Adverse maternal and fetal outcomes among rhesus negative women at the Kenyatta National Hospital, between January 2013 to December 2019.

Variable	Iso-Immunized	Not Iso-Immunized	P value
Maternal Outcomes			
Anemia (n=9)	01 (20)	9 (4.9)	0.239
Miscarriage (n=36)	05 (62.5)	31 (16.7)	**0.006**
Mode of Delivery (CS) (n=133)	04 (50.0)	129 (69.4)	0.263
Antepartum hemorrhage (n=6)	01 (12.5)	5 (2.7)	0.226
Fetal and Neonatal Outcomes			
Hydrops Fetalis	3 (37.5)	1 (0.5)	**<0.001**
IUFD	5 (62.5)	3 (1.6)	**<0.001**
Gestation at birth	6 (85.7)	10 (5.5)	**<0.001**
Fetal weight (<2500)	6 (85.7)	8 (4.3)	**<0.001**
Apgar Score	6 (75.0)	4 (2.2)	**<0.001**
Admission to NICU	3 (37.5)	5(2.7)	**0.002**

Out of the 8 iso immunized women, 6 (75%) had experienced a pregnancy loss before; none of the 6 patients had documented evidence of having received anti D after the pregnancy loss. Seven (87.5%) of the iso immunized women had the ICT titres done with positive titers.

CHAPTER FIVE: DISCUSSION

Among the women with rhesus negative blood group, the prevalence of rhesus iso-immunization was 4.0%. The prevalence of rhesus iso-immunization compares with the findings by Adeyemi et al. in Ogbomosho, where it was 5.5% and lower than the 9.1% reported by Onwuhafua and Adze in Kaduna, Nigeria (12). Although none of the women had documentation of repeated antibody test in the pregnancy, there have been reports of development of Rh antibodies in the course of the pregnancy.

Routine antenatal prophylaxis has been reported to reduce the rate of sensitization during pregnancy to 0.2% (5). The NICE recommends that a non-sensitized Rh-negative woman should receive 3 vials of anti-D immunoglobulin in an uncomplicated pregnancy (at 28, 34 weeks gestation and postnatally after delivery of a Rhesus positive baby) (19) . Repeat doses are given at 6 weekly intervals from 28 weeks because the half-life of immunoglobulin is only 24 days and it persists for only 6 weeks (13). As revealed in our study, 176 (93%) of the women received anti D at 28 weeks.

Women with iso immunization are more likely to develop complications both in the antenatal period and in the immediate post-partum period (13). Out of the 36 participants who had miscarriages, 5 (62.5% of the iso immunized) had a miscarriage compared to 31 (16.7% of the non iso immunized) (p, 0.006). Four of the iso immunized participants (50%) had a Ceserian delivery compared to 129 (69.4%) of the non iso immunized participants (p, 0.263). Only 1 out of the 8 iso immunized participants (12.5%), had Antepartum hemorrhage while 5 (2.7%) of the

non iso immunized participants had antepartum hemorrhage (p=0.226). Mild anemia was found in only 1 woman (20%) compared to 9 (4.9%) among the non-immunized women (p=0.239).

In a study conducted by Sreelatha et al in India, where the maternal outcomes among pregnant women with rhesus negative blood group was evaluated, 298 (56.4%) of the women delivered vaginally and 230 (43.5%) by section the common indication for which was fetal distress (27). Similarly, in another conducted by Neelam Singh et al, where maternal and fetal outcomes among Rh negative mothers were assessed, where 15 mothers had adverse maternal outcomes: 3 had abruption placentae, (29).

Hydrops fetalis is one of the foetal complications that arise among women with rhesus iso immunization. In our study, 3 (37.5%) of the participants with iso immunization had their fetuses diagnosed with hydrops fetalis compared to only 1 (0.5%) in the non iso immunized group. Of all infants with hydrops fetalis, 10-20% dies in utero or in the early neonatal period before effective therapy possible. 50% of affected infants need treatment during neonatal period (5).

Additionally, children born with mothers who develop Rhesus Iso immunization may develop complications with subsequent fetal demise. In our study, a higher proportion of participants in the iso immunized group, 5 (62.5%) reported having had an IUFD compared to those in the non iso immunized group (3, 1.6%) (P=<0.001). In a study by Khatun J in Bangladesh, (26), the fetal outcome in sensitized patients showed that overall fetal loss due to Rh immunization was 14%.

The higher rate of complications in our study could be due to a lack of early fetal surveillance and intra uterine management of potentially complicated cases of iso-immunization.

Participants who were iso immunized were more likely to deliver children with a birth weight less than 2500g (8, 85.5%) compared to those in the non iso immunized group (10, 5.5%) (p, < 0.001). Additionally, children born of mothers in the iso immunized group were more likely to be have poor APGAR score (96, 75%) compared to those in the non iso immunized group (4, 2.2%) (p, <0.001). These children were also more likely to be admitted into the NICU (3, 37.5%) compared to 5, 2.7% (p, 0.002). Similar to those by Eleje et al in Nigeria where 31.4% of the newborns in the iso immunized group had a poor APGAR score at 5 minutes and got admitted to the NICU (7). Similarly, out of 366 live born babies, 41 (11.2%) babies were admitted in SNCU. The higher proportions in our study could be due to the fact the numbers for the iso immunized women was low compared to Nigeria where we have a documented higher proportion of women with rhesus negative blood group (3).

The study is limited by its retrospective design hence amenable to gaps in documentation. Additionally, due to the low numbers of women with rhesus iso-immunization, the Fischers exact test as used may be a bit conservative, i.e. its actual rejection rate is below the nominal significance level for most other robust tests. In this regard, we could not therefore perform more robust correlation tests for the relationship between the outcomes studied in Rh negative iso-immunized pregnant women and Rh negative non iso-immunized women.

Conclusion

Rh negative pregnancies constitute a vital facet of our obstetrics population at the KNH and the prevalence of iso immunization is 4.0% among women with blood group rhesus negative at the KNH. Though the number of women with iso immunization was low, a there was a significantly higher rate of miscarriages, hydrops fetalis, IUFD and poor APGAR score at birth in this population.

Recommendations

We recommend closer monitoring and management of patients with rhesus iso-immunization to avert adverse pregnancy outcomes.

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ANNEXES

Annex 1: Study Timelines/Timeframe

Activity	2019/2020								
	Oct	**Jan**	**Feb**	**March**	**April**	**Apr**	**May**	**Jun**	**Jul**
Proposal Development									
Proposal Presentation									
Ethics Committee Review									
Data Collection									
Data Analysis									
Results Presentation									
Publication									

Annex 2: Study Budget

ACTIVITY	ITEM	KSHS
Proposal Development	Printing of data capture tools	5,000
	Printing copies of proposal	2,000
Data Collection	Five research assistants @1000 per day for 5 days	25,000
	Stationery such as pens and pencils and rubbers	500
Data Analysis	Statistician	40,000
Thesis Development	Printing of draft theses	2,000
	Printing of final theses	4,000
	TOTAL	**76,500**

Annex 3: Data Abstraction Tool

Title: The Burden of rhesus iso immunization and maternal and perinatal outcomes at the Kenyatta National Hospital

Serial No.

Demographics

1. What is the patient's age? .....
2. What is the patient's marital status? .....
   - Single
   - Married
   - Divorced
   - Separated
3. What is the patient's level of education?
   - None
   - Primary
   - Secondary
   - College/university
4. What is the patient's employment status?
   - None
   - Casual
   - Business
   - Permanent
5. Religion
   - Catholic
   - Protestant
   - Muslim
   - Other
6. What is the patient's blood group

7. What is the partner's blood group

   A

   B

   O

   Not indicated

Obstetrics History

When was the patients Last Normal Menstrual Period (LNMP)……

When was the expected due date (EDD)……

What was the Gestation by Dates (GBD) at delivery……

What is the patient's Parity……

Mode of Delivery

- SVD
- Ceserian Section

History of the following during the pregnancy:

Ante partum hemorrhage

- Yes
- No

Previous history of miscarriage

- Yes
- No

Gestation at Delivery in weeks

……..

Was the mother given anti D

- Yes
- No

If yes, under what gestation (in weeks)?

……

Neonatal Outcomes

Gestation at Delivery

- Pre term
- Term

Hydrops fetalis

- Yes
- No

IUFD

- Yes
- No

APGAR Score at 5 minutes

……

Birth Weight

……

Admission to NICU

- Yes
- No

Antenatal Profiles

Did the patient have ANC profiles? YES…… NO…….. if yes please indicate the results of the tests done:

1. Hemoglobin levels
2. Blood group at booking
3. Human immunodeficiency virus (HIV) status: POSITIVE…….. NEGATIVE……
4. Venereal disease research lab status (VDRL) POSITIVE…… NEGATIVE……
5. Random blood sugar (RBS) value…….
6. Hepatitis b surface antigen (Hep HBSAg Positive…….. Negative……
7. Urinalysis
8. OGTT

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Ref: KNH-ERC/A/124

9th April 2020

Dr. John Abayo Otieno
Reg. No.H58/6758/2017
Dept. of Obstetrics and Gynaecology
School of Medicine
College of Health Sciences
University of Nairobi

Dear Dr. Otieno

RESEARCH PROPOSAL – BURDEN OF RHESUS ISO IMMUNIZATION AND MATERNAL AND PERINATAL OUTCOMES AT THE KENYATTA NATIONAL HOSPITAL(A retrospective Cohort Study for the Period January 2013 to December 2019) (P52/02/2020)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and approved your above research proposal. The approval period is 9th April 2020 – 8th April 2021.

This approval is subject to compliance with the following requirements:

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

Protect to discover

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

Yours sincerely,

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

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