
Addis Ababa University

PREVALENCE OF RHESUS NEGATIVE GENE AMONG PREGNANT WOMEN AND ASSESSMENT OF EFFECTIVE MANAGEMENT OF RH NEGATIVE PREGNANCY IN GANDHI MEMORIAL HOSPITAL, ADDIS ABABA, ETHIOPIA

BY: BETHLEHEM TSEGAW (BSC)

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SUBMISSION FROM

Prevalence of Rhesus Negative Gene among pregnant women and Assessment of Effective Management of RH Negative pregnancy in Gandhi Memorial Hospital, Addis Ababa, Ethiopia

By

Bethlehem Tsegaw Tilaye

Approved by the examining board

Prof. Mesganaw Fantahun _____

(Advisor) signature

Dr. Nigussie Deyess _____

(Internal Examiner) signature

Dr. Alemayehu Mekonnen _____

(External Examiner) signature

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First of all I would like to praise God for making it all possible for me. And I am grateful for my family for their encouragement.

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ACRONYMS/ ABBREVIATIONS

HDFN	Hemolytic disease of the fetus/newborn
FMH	Feto–maternal hemorrhage
Rh D	Rhesus D
RAADP	Routine antenatal anti-D prophylaxis
NICE	National Institute for Health and Clinical Excellence
Ig G	Immunoglobulin G
IgM	Immunoglobulin M

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ABSTRACT

Introduction: Despite the introduction and widespread use of Rhesus (Rh) D immunoglobulin for prevention of hemolytic disease of the fetus/newborn (HDFN), Rh alloimmunization remains a significant problem in perinatology. Care management with anti-D prophylaxis in patients presenting with severe alloimmunization is difficult to access in Sub-Saharan Africa.

Objective: This study aims to determine the prevalence and assess the existing mechanism for management of Rh negative pregnant women in Gandhi Memorial hospital.

Methods: A cross sectional study using quantitative and qualitative methods was used in the study. A total of 497 women case files were included in the study from September, 2012 to August, 2014 to determine the prevalence by using systematic random sampling. Then another 384 case files of Rh negative women was included by simple random sampling for assessment of the management of Rh negative pregnancy. SPSS was used for data entry and analysis .Tables were used to show the results, percents and frequencies to describe the variables. Univariate and Bivariate analysis using Chi square was conducted and p value was determined. In the qualitative method in-depth interview with 7 key informants by using purposive sampling, to assess the availability and affordability issues of medication was done. Data was analyzed as per the procedure i.e. recording, transcribing, translation and organizing and content analysis was conducted using open code software.

Result

The prevalence of Rh negative was 7.2% with 95%CI (6.9, 7.5). The utilization rate of Anti D was 14.3%. There was 4.7% offer of RAADP at 28 weeks. Regarding Anti D administration all socio demographic factors included in the study were not statistically significant with anti D administration. Qualitative data suggest that special consideration is necessary on this issue

Conclusion and Recommendation

The prevalence of Rh negative women is of a high magnitude keeping in view the prevalence rate of the other African countries estimate. There is lack of proper management of Rh negative pregnant women. Special attention should be given to Rh negative pregnancy to be included in maternal health programs by Ministry of health, donors and other collaborators.

1. INTRODUCTION

1.1 Background

Despite the introduction and widespread use of Rhesus (Rh)D immunoglobulin for prevention of hemolytic disease of the fetus/newborn(HDFN), Rh alloimmunization remain a clinical challenge(1). The associated disease in the pregnant patient's offspring—hemolytic disease of the fetus or newborn—was once a major contributor to perinatal morbidity and mortality (2). However, the widespread adoption of guidelines for the antenatal and postpartum use of Rh immune globulin in industrialized countries has resulted in a major decrease in the frequency of this disease(2). It is still contributing to the neonatal morbidity and mortality in the world due to non-immunization, under-immunization, and false Rh typing in rare cases (3).

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1.2 Statement of the problem

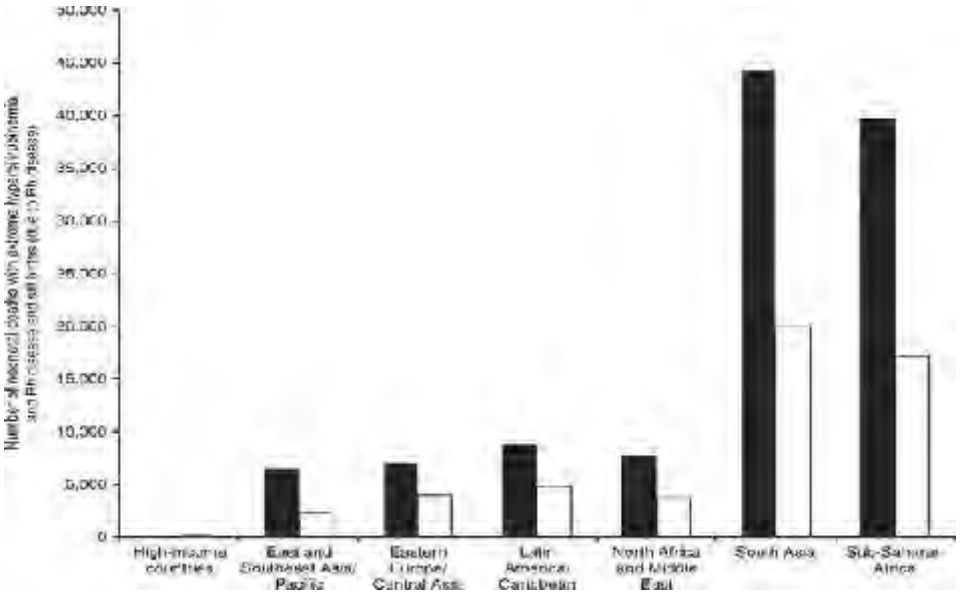
Despite the fact that the prevalence of Rh-negative phenotype is significantly lower among Africans than Caucasians, Rh alloimmunization remains a major factor responsible for perinatal morbidity in Sub-Saharan Africa and may result in the compromise of the woman's obstetric care due to the unaffordability of anti-D immunoglobulin (4). Care management with anti-D prophylaxis in patients presenting with severe alloimmunization is difficult to access in Sub-Saharan Africa. In addition to poor access to anti-D prophylaxis, there is lack of alloimmunization in prevention during illegal abortions and poor documentation of adequate information in patients' medical notes. These factors are highly responsible for the difficult management of Rh-negative patients (4, 5). Although Rh negative blood groups are generally lower in Africa, it is still important to understand the prevalence and management of Rh-negative women in sub-Saharan Africa (6).

1.3 Significance of the study

Erhabor Osaro et al has indicated that cost constraints have remained a limiting factor preventing people from access to best possible treatment and care in Sub-Saharan African countries. There is also the urgent need for African leaders to take up the bold challenge to provide universal access to anti-D prophylaxis for Rh-negative women. Per capita income in most settings in Sub-Saharan Africa is low and continues to affect affordability to prophylactic anti-D treatment (5). In Ethiopia, the prevalence and utilization rate of Anti D prophylaxis for Rh-negative pregnant women was not investigated**.**

African leadership for child survival: A Promised Renewed- on January 16-18, 2013, the government of Ethiopia convened a meeting of Africa ministers of health and global experts aimed at celebrating reduction in preventable child death through sharper national plans and improved monitoring and evaluation. The African continent shares a significant global burden of newborn, child and maternal deaths. Of the 3.5million such death per year in Africa, more than 1 million are newborns.

A research by Vinod B. et al showed Global estimate of still birth and neonatal death due to kernicterus associated with Rh disease is illustrated among different countries Eastern Europe/Central Asia, Latin America, sub-Saharan Africa, and South Asia. Three-quarters of mortality occurred in sub-Saharan Africa and South Asia. Kernicterus with Rh disease ranged from 38, 28, 28, and 25/100,000 live births for Eastern Europe/Central Asian, sub-Saharan African, South Asian, and Latin American regions, respectively (29).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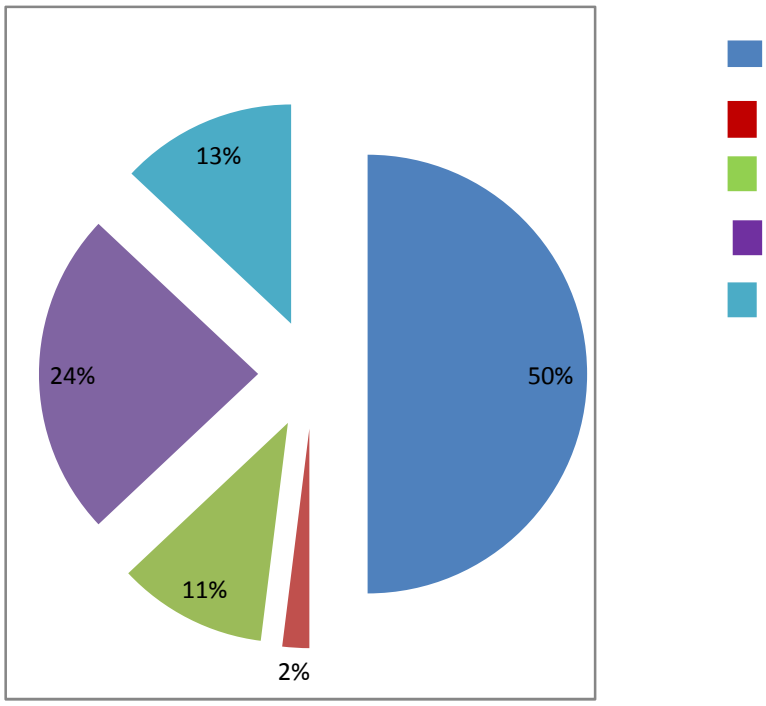
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2. LITERATURE REVIEW

2.1 Overview of RhD Negative pregnancy

The first case of HDFN was probably described in 1609 in the French literature by a midwife (7). The modern era of Rhesus disease probably began in 1939 when Levine and Stetson described an antibody in a woman who gave birth to a stillborn fetus. One year later, Levine and associates were able to demonstrate a causal relationship between RhD antibodies in RhD-negative women and HDFN in their offspring (7,8).Levine and Stetson demonstrated that erythroblastosis fetalis was due to a fetal blood group antigen, inherited from the father, entering the maternal circulation and causing maternal isoimmunization (9). Since then, there have been rapid developments in techniques for diagnosis, treatment, and prevention of this disease. The effectiveness of the administration of anti-D immunglobulin for preventing Rh-immunization in pregnancies of Rh negative women, and also in cases of Rh mismatched transfusions, is now recognized and has been in use since 1966, but only on a wide scale since 1971(10). However, we have reached the 21st century and the burden of alloimmunisation in pregnancy is still on our backs (11).

Women who are Rh negative require particular antenatal care and monitoring during pregnancy. If the fetus carried is Rhesus positive, there is a risk that mixing of fetal and maternal blood cells will lead to the woman becoming sensitized, which may cause fetuses in any subsequent pregnancies to suffer from HDFN (12, 13). HDFN may result in jaundice, anemia, developmental problems, or intrauterine death (5). Prior to 1970, HDFN due to anti-D was a significant cause of morbidity and mortality. By 1990, a reduction in mortality from 1.2 per 1000 births to 0.02 per 1000 births had been achieved in response to the introduction of immunoprophylaxis with anti-D immunoglobulin (14). A further reduction to between 0.17% and 0.28% was achieved by introducing prophylaxis during the third trimester of pregnancy. These findings contributed to the NICE (National Institute for Health and Clinical Excellence) recommendation that all D-negative pregnant women who do not have immune anti-D should be offered anti-D immunoglobulin routinely during the third trimester of pregnancy**.** The frequency of Rh-negative phenotype in previous studies is Nigeria 4.44%, 3.9% in Kenya, 4.06% in

Guinea, and 2.4% in Cameroon. These findings are much lower than the 14% prevalence of Rh-negative phenotype observed in studies among Caucasians (4, 5). However, care management with anti-D prophylaxis in patients presenting with severe alloimmunization is difficult to access in Sub-Saharan Africa (5).

2.2 Alloimmunization

Rh alloimmunization (Sensitization) occurs when maternal immune system is sensitised to D(Rh) erythrocyte surface antigens (15,16). If the mother is RhD-negative and the fetus RhD-positive, during pregnancy small amounts of fetal blood can enter the maternal circulation (an event called feto–maternal haemorrhage or FMH). “The presence of fetal RhD-positive cells in her circulation can cause a mother who is RhD negative to mount an immune response, producing a template for the production of antibodies as well as small amounts of antibodies against the RhD antigen (anti-D antibodies).This process is called sensitization or alloimmunisation (4, 5, 10, 17)’’. “Alloimmunization in pregnant women has been found to range from 0.4% to 2.7% worldwide” (4, 11).

Sensitisation can happen at any time during pregnancy, but is most common in the third trimester and during childbirth. Sensitisation can follow events in pregnancy known to be associated with FMH, such as medical interventions (chorionic villus sampling, amniocentesis or external cephalic version), terminations, late miscarriages, ante partum haemorrhage and abdominal trauma, ectopic pregnancy, intrauterine death and stillbirth (5,17,18). It can also occur in the absence of an observed potentially sensitizing event. The risk of sensitisation is affected by the ABO blood type of the fetus, with a lower risk if it is incompatible with the mother's ABO type (17). The risk of alloimmunization is affected by several factors, including the degree of FMH and maternal immune response (16).

When a large volume of fetal blood enters the mother’s circulation, her immune system is stimulated and B lymphocyte clones that recognize the RhD antigen are established. The initial IgM anti-D immunoglobulin response is short lived, with a rapid switch to IgG production. Unlike IgM, IgG anti-D crosses the placenta and bind to RhD antigen on the surface of fetal red blood cells (18, 19). These antibody-coated fetal red blood cells are removed from the fetal circulation. Fetal anemia results if the red blood cells are removed faster than they are produced.

Severe anemia can lead to fetal heart failure, fluid retention and swelling (hydrops), and intrauterine death. Before birth, anemia and hydrops can be managed with intrauterine transfusions, but this carries a 2% risk of fetal loss. When red blood cells are broken down, bilirubin is released. In utero this is cleared by the placenta and is not harmful. However, after birth the neonatal liver cannot cope with the excess production of bilirubin, and this leads to jaundice or HDFN. Low levels of jaundice are not harmful but, if left untreated, higher levels can result in damage to specific areas of the neonatal brain, causing permanent brain damage (kernicterus). This can lead to a range of neurodevelopmental problems, such as cerebral palsy, deafness, and motor and speech delay. Postnatal jaundice can be treated with phototherapy and exchange transfusion (4, 17, 18).The risk of sensitisation is greatest in the first pregnancy and decreases with each subsequent pregnancy. Once sensitisation has occurred it is irreversible (17). A report to determine the frequency of occurrence of alloantibodies among pregnant women in Port Harcourt, Nigeria identified alloantibodies in the serum of (3.4%) of pregnant women studied (4). Non-invasive determination of fetal Rh status is now possible through the analysis of cell-free circulating fetal DNA in maternal plasma as early as the 10th week of pregnancy; that is, before the alloimmunization process is triggered. Therefore, it one of the major factor in perinatal morbidity and may result in the compromise of the woman's obstetric career (15, 20).

2.3 Immunoprophlaxis

Antenatal and postnatal administration of anti-D immunoglobulin is now clearly recognized to prevent RhD alloimmunisation. However, for it to work it must be given in sufficient dose and before immunisation has occurred (18).Current recommendations for immunoprophylaxis from the Royal College of Obstetricians and Gynaecologists and NICE are as follows: (18)

- ✓ “After delivery, irrespective of the dose of antenatally administered anti-D, postnatal prophylaxis must be given and include a screening test to identify women with a large FMH”
- ✓ “After sensitising events before delivery and after abortion”
- ✓ “Anti-D is no longer necessary in women with threatened miscarriage with a viable fetus and cessation of bleeding before 12 weeks’ gestation”

- ✓ “should be given to non-sensitised RhD negative women at 28 weeks and 34 weeks of pregnancy”(21)

2.4 Anti-D immunoglobulin

“Anti-D immunoglobulin is produced by the pooling and fractionation of plasma from large numbers of donors who themselves are RhD-negative and have been exposed to RhD-positive RBCs to stimulate the production of RhD antibodies (19, 22).” It consists of pooled polyclonal anti-D IgG from plasma donors (23).Therefore exists in limited supply (4). The mechanism of anti-D has not been fully elucidated**.** Anti-D should be available in cases of potentially sensitizing events (5). Following birth of a D positive infant at least 500 iu anti-D, i.m. must be administered to the woman if the FMH is ≤ 4 mL. Additional dose of anti-D immunoglobulin is necessary for larger FMH and the dose to be administered by intramuscular route should be calculated as 125 i.u for each additional mL of FMH. In cases of very large FMH i.e., in excess of 80 mLs, intravenous anti-D should be considered. A 500 iu, i.m. dose is sufficient for 4mL of fetal cells (24).

“Anti-D prophylaxis has significantly reduced the incidence of erythroblastosis fetalis caused by sensitization to the D-antigen and perinatal deaths from alloimmunization have fallen 100-fold in the developed world”. In the absence of anti-D prophylaxis to prevent incidence of HDFN, options such as exchange blood transfusion and intrauterine transfusion (IUT) can significantly reduce mortality and prevent stillbirths (5). Hence, Rh testing of the baby's father may be offered to all Rh-negative pregnant women to eliminate unnecessary blood product administration (25).

In most health facilities in Ethiopia, quantification of FMH which could have been significant to ensure a sufficient dose of Anti D given for Rh negative mother is not common. The common clinical practice is to administer 300 μg doses (the only available dose in Ethiopia) to every affording un sensitised woman (26). Anti-D Ig should only be given to women who are not already sensitised or have immune anti-D in their serum. It cannot reverse the immune response once sensitization has occurred (28).

A previous report on the utilization rate of anti-Rh antiserum in South African population groups for the years 1983–1985 indicated the effectiveness of anti-D prophylaxis in the prevention of HDN. The crude utilization rate of anti-Rh antiserum was 41%–44% for all population groups

combined. The rate for Blacks, Whites, Indians, and Coloreds was 14%–20%, 89%–94%, 59%–64%, and 45%–51%, respectively (4, 5).

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2.5 Routine antenatal anti-D prophylaxis

The UK NICE evaluated, first in 2003 and subsequently updated in 2009, the potential benefits from offering RAADP to all non-sensitized Rh negative pregnant women. In both evaluations, it was concluded that RAADP was cost-effective and should be delivered to all non-sensitized Rh negative pregnant women (12). “RAADP should be offered to all D negative non-sensitised pregnant women at 28 and 34 weeks gestation at routine antenatal visits (21).”A dose of at least 500 iu, i.m. is recommended on each occasion. It is important that the 28-week antibody screening sample is taken prior to the first routine prophylactic injection being given (24). Therefore, there is strong evidence for the effectiveness of RAADP for prevention of sensitisation, in support of the policy of offering routine prophylaxis to all non-sensitised pregnant Rh negative women (12, 17, 22). “Although the implementation of a program RAADP has led to a significant decline in the residual numbers of women becoming sensitized in most developed countries, a significant number of women are not fortunate enough to have access in Sub-Saharan Africa and thus continue to be affected (5).” Therefore, there is a need for adequate counseling of pregnant women on the importance of Rh D negative factor during the antenatal period in order to prevent HDFN (27).

3. OBJECTIVE

3.1 General Objective

- ✓ To determine the prevalence of Rh negative pregnancy and assess the existing mechanism for management of Rh negative pregnant women in Gandhi Memorial hospital.

3.2 Specific objectives

- ✓ To determine the prevalence of Rh negative pregnant women visiting Gandhi Memorial Hospital.
- ✓ To determine the utilization rate of Anti D immunoglobulin among Rh negative pregnant women in Gandhi Memorial Hospital.
- ✓ To explore the offer of RAADP in prevention of sensitization in antenatal visits.
- ✓ To assess issues related to the availability and affordability of the Anti D medication.

4. METHODS AND MATERIALS

4.1 Study design and period

A cross sectional study using quantitative and qualitative methods was used in the study. The study was conducted in two major phases. First, a two year retrospective study of women who booked for delivery care at Gandhi Hospital1 September, 2012 to August, 2014, was carried out used to determine the prevalence of Rh negative pregnancy. Then assessment of the management of Rh negative women was conducted on women who booked for delivery care at Gandhi Hospital. Qualitative study was conducted to assess availability and affordability of Anti D medication. The study was conducted from August 2014 to April 2015.

4.2 Study Area

The study was conducted at Gandhi hospital. The hospital is situated in Addis Ababa. It was established during the period of Emperor Haile Selassie with the collaboration of Indian donors in 1959.At the beginning, it was established to give delivery service only through time the activities has increased. The hospital has a total of more than 110 beds and delivers 25 neonates each day. ANC visit is over 4000 annually.

4.3. Population

4.3.1 Source population

All pregnant women who attended at Gandhi hospital for delivery care from September, 2012 to August, 2014, (for the last two years) were the source population.

4.3.2 Study population

All Rh negative pregnant women who attended at Gandhi hospital for delivery care from September, 2012 to August, 2014, (for the last two years) were the study population.

4.4 Sample size determination

A pregnant women who visited the hospital from September 2012 to August 2014(for the last two years) was taken from delivery register log books. The total number of pregnant women who visited Gandhi hospital in the study period for delivery is 16898 form delivery register books.

The frequency of RhD-negative phenotype from previous studies ranges from 4.44% in Nigeria, 4.06% in Guinea, 3.9% in Kenya to 2.4% in Cameroon(5). Therefore, using a formula for sample size determination for single proportion and assuming p=0.03, d=0.015, n is calculated as follows

Sample size to estimate prevalence of the Rh negative pregnancy

$$n = \frac{\mathbf{Z}^2 p(1-p)}{d^2}$$

Where n = number of sample

$\mathbf{Z}^2$= (1.96)2for 95% confidence

P = “best guess” for prevalence

d = maximum tolerable error for the prevalence estimate

$$=\underline{1.96^2 * 0.03*(1-0.03)}/(0.015)^2$$

=497(this sample size will be used to determine the prevalence)

In order to estimate the number for the assessment of the management of Rh Negative pregnancy, using a formula for sample size determination for single proportion and assuming p=0.5, d=0.05, n is calculated as follows

$$n = \frac{\mathbf{Z}^2 p(1-p)}{d^2}$$

p =is the estimated proportion of an attribute that is present in the population.

d =is the desired level of precision

$\mathbf{Z}^2$= (1.96)2for 95% confidence

$$= (1.96)^2(0.5)(1-0.5)/(0.05)^2$$

=384 (this sample size will be used for the assessment part)

4. 5 Sampling technique

Gandhi hospital is selected because it is well known institution in giving delivery service in the country and the patient attending there are coming from different parts of the country. For the first part of quantitative study records of pregnant women who attended delivery care at the hospital in two years preceding the survey was selected by using systematic random sampling to determine the prevalence.

The sampling interval (K) was determined by dividing the number of units in the population (i.e total delivery within the two year) by the desired sample size. Then a number between one and **K** at random was selected. This number is called *the random start* and would be the first number included in the sample. Every K^{th} unit after that first number was selected until the desired sample size was reached.

K=total population in the study period/sample size

K=16898/497=34

For second part of the quantitative study records of Rh negative pregnant women who attended delivery care at the hospital was selected by using Simple random sampling to assess the management of Rh negative pregnancy.

But for qualitative study purposive sampling was be used to select health professionals(Doctors and Pharmacists) that are key in giving the information to assess the availability and affordability issues by the investigator and the sample size was determined until the information was saturated.

4.6 Data Collection Methods

Quantitative data was collected to describe the prevalence of Rh negative pregnant and data extraction format was used to assess the management of Rh negative pregnancy. Data extraction format was developed using questions which include current knowledge of blood group, anti-D and its administration, current sources of information regarding complications of Rh incompatibility during and after pregnancy, its risk to new born including demographics and characteristics of the participants.

First to determine the prevalence data was collected from three delivery registration book. Then experienced data collectors received half day training on the study design and data collection methods to facilitate the data collection procedure .Two data collectors were used (pharmacists). Out of 497 cards 12 were replaced by the consecutive number since the card were lost. The problem encountered during data collection were in the delivery register book there was misinterpretation of numbers while they write consecutive number therefore in order to avoid this problem counting was done to make the predetermined interval.

For the assessment part five Registration book samples for hematology were used to randomly select pregnant women who are Rh negative and then the card numbers were taken from the log books. 384 cards numbers were selected. Two data collectors were used (pharmacists).

Qualitative data was collected by In-depth interview of key informants in the study area. Open-ended questions were used to enable the participants to express their viewpoint comprehensively (in-depth). The in-depth interview was conducted by the principal investigator. Interviews were audio recorded, with participant permission, and lasted between 15-20 minutes. The interview was conducted on May 4-8, 2015.

4.7 Study variables

4.7.1. Dependent variables

- ✓ Administration of Anti D

4.7.2. Independent variables

- ✓ Employment status
- ✓ Indirect combs test
- ✓ Direct combs test
- ✓ Marital status
- ✓ Educational status
- ✓ Age

4.9 Data management and analysis

In this study general demographic data, immunization type, history of prophylactic and therapeutic administration of the anti D immunoglobulin, current diagnostic and therapeutic management, and finally pregnancy outcome was analyzed by using data extraction format from the case files of Rh negative women with or without Anti D administration. Including threatened and actual miscarriage, ectopic pregnancy, stillbirths, and early neonatal deaths was noted.

In the quantitative data coded variables was entered into Statistical Package for the Social Sciences (SPSS) soft ware program for analysis. Then analysis was carried out by using descriptive statistics such us frequency, crosstabs and explore.

Univariate analysis was conducted to summarize the distribution of each individual variable. Descriptive statistics was employed to determine frequency distribution. Tables are used to show the results, percents and frequencies to describe the variables. Then bivariate analysis was carried out in order to see the relationship of between dependent and independent variables. In this study both variables are categorical variables so crosstabs was used to determine Chi square test and p-value.

While in the qualitative study data was analyzed as per the procedure i.e. recording, transcribing, translation and organizing and content analysis was conducted using open code software. In-depth interviews (IDIs) were conducted with 7 health care providers. Sampling was purposive. All providers delivering services were invited to interview and none refused. Interviews were recorded, transcribed, and translated into English .Data were analyzed through an iterative process, including stages of (i) data familiarization, through transcript review; (ii) development of coding , from words derived deductively from the research questions and inductively from the data, (iii) abstraction of coded data into thematic matrices (iv) interpretation, methodological synthesis and report writing.

4.10 Data Quality Assurance

During data collection experienced data collectors were used after being trained. Data extraction format was checked for completeness every day at the time of data collection. Prior to any analysis being performed, all data were checked for errors in entry i.e. the soft copy was cross checked with its hard copy. The principal investigator checked the completeness of the information

4.11 Ethical Consideration

In order to precede the data collection permission was obtained from Collage of health science, School of Public Health, to grant official letter to Gandhi Hospital, Addis Ababa, and then final permission from Gandhi Hospital administrators was obtained. After ethical clearance was obtained, the study was conducted. To ensure confidentiality of the participants, all data was treated in a manner that protects the confidentiality and anonymity of the participants in the study. The information obtained and collected from the research was coded, and at all times remain the property of the researcher to maintain the privacy of the participants.

Written consent was obtained from each study participant during data collection for the qualitative study. Full right was given to the study participants to refuse or to take- part in the study as well to withdraw at any time even during the interview. Privacy and confidentiality was maintained throughout the study by interviewing the patient alone and by using a code instead of their names. There was no benefit the study participants can get in terms of money or other item.

4.12 Dissemination of the Result

After completing the study, the final research paper with findings and recommendations is submitted to Collage of Health Science, School of Public Health, Gandhi Hospital and Federal Ministry of Health (FMOH). In addition the result will be disseminated as required and where the finding can be supportive in decision making.

5. RESULT

Four hundred and ninety seven women who booked for delivery care at Gandhi Hospital from September, 2012 to August, 2014, (for the last two years) were selected randomly by systematic random sampling to determine the prevalence. Out of these 417 were found to Rh positive while 44 (8.8%) the Rh status was not documented. The prevalence of Rh negative was 36(7.2%) with 95%CI (6.9, 7.5).Then three hundred eighty four case files of Rh negative women were included and the results are as follows

5.1. Socio-Demographic Characteristics

Among the total of the participants of 384, age groups between 25 and 34 are the highest in number which account 214(55.7%) and relative to other groups,women between 35>= have smaller portion 43 (10.7%). In terms of marital status, women who are married take the highest number accounting 292(76%) concerning educational status, women are literate are 82(21.4%) , while 281 (73.2%) the educational status was not documented. Looking at their employment status 60(15.6%) are employed and 150(39.1%) are unemployed.

Regarding Anti D administration all socio demographic factors included in the study were not statistically significant with anti D administration and have chi square ranging between 4.4-12.6 and p value >0.2

Table 1: Socio-demographic Characteristics of the participants Gandhi Memorial Hospital A.A. May, 2015(n=384)

Variables(n=384)	Frequency	Percentage(%)
Age group		
15-24	127	33.1
25-34	214	55.7
>35	43	10.7
Marital status		
Single	23	6
Married	292	76
Married but not living together	2	0.5
Divorced	2	0.5
Widowed	2	0.5
Not documented	63	16.4
Educational status		
Illiterate	21	5.5
literate	82	21.4
missing	281	73.2
Employment status		
Employed	60	15.6
Unemployed	150	39.1
missing	174	45.3

5.2. Obstetric history

The result birth order, pregnancy outcome, indirect comb's test, direct coomb's test is as follows on the following table.

Table 2: Obstetric history women visiting Gandhi Memorial Hospital A.A, May, 2015(n=384)

Variables(n=384)	frequency	Percentage (%)
PREGNANCY OUTCOME		
Live birth	236	61.5
Still birth	26	6.8
Abortion	86	22.4
Not documented	36	9.4
BIRTH ORDER		
1st pregnancy	138	35.9
2nd pregnancy	142	37.0
3rd pregnancy	58	15.1
other	46	12.0
INDIRECT COMB'S TEST		
Yes	101	26.3
No	270	70.3
No need	13	3.4
DIRECT COMB'S TEST		
Yes	163	42.4
No	217	56.5
No need	4	1.0

5.3. Anti D drug management

Anti D administration was documented on 14.3% and 69.5% lack documentation and 16.1% of the participants do not need administration since the partner was Rh negative.

Out of the 14.3% of the administration of the Anti D, consent was not obtained and documented in none of them. Regarding the dose of medication all of the administered Anti D was documented and 8.3% is 300 µg while 5.5% is 250 µg. All of them have received Anti D within 72 hours i.e. 14.3%.The offer of RAADP at 28 weeks was seen in the 4.7% case file of all the participants.

Table 3: Anti D drug management Gandhi Memorial Hospital A.A, May, 2015(n=384)

Variables(n=384)	Frequency	Percentage (%)
ADMINISTRATION OF ANTI D (with in 72 hours)		
Yes	55	14.3
No	265	69.5
No need	62	16.1
CONSENT OBTAINED		
No	322	83.9
No need	62	16.1
DOSE OF ANTI D		
300	32	8.3
250	21	5.5
Not documented	269	70.1
No need	62	16.1
RAADP 28 wks		
yes	18	4.7
No	348	94.0
No need	18	4.7
RAADP 34 Wks		
Yes	4	1
No	362	94.3
No need	18	4.7

5.4 Clinical and social variables

When we see the distribution of blood group among RH negative mothers blood type O was the highest 38.8%.

Table 4: Clinical and social variables, Gandhi Memorial Hospital A.A, May, 2015(n=384)

BLOOD GROUP		
A	105	27.3
AB	29	7.6
B	101	26.3
O	149	38.8
SERVICE GIVEN		
free	17	4.4
charged	367	95.6
RH of the FATHER		
Yes	72	18.8
No	312	81.3

5.5 Relationship between dependent and independent variables

5.5.1 The relationship between socio demographic characteristics and Anti D administration

Age, marital status, educational status and employment status were not significantly associated with Anti D administration.

Table 5: Socio demographic characteristics associated with Anti D administration at Gandhi Memorial hospital, A.A MAY, 2015(n=384)

	Anti D administered				
	Yes	No	OR (95%CI)	Chi-Square	P value
Age group					
15-24	16(15.5)	87(84.5)	1.00	0.53	P>0.05
25-34	33(18.4)	146 (81.6)	1.23(0.61, 2.49)		
35 and above	6 (15.0)	34 (85.0)	0.96 (0.31,2.91		
Educational status					
Illiterate	2(10%)	18(90)	0.43(0.09, 2.06)	1.17	P>0.05
Literate	15(20.5)	58(79.5)	1.00		
Employment status					
Employed	11(19.6)	45 (80.4)	1.32 (0.58, 3.01)	0.45	P>0.05
Unemployed	19(15.6)	103(84.4)	1.00		
Marital status					
Married	42(17.4)	199 (82.6)	1.21(0.40,3.69)	0.12	P>0.05
Others	4(14.8)	23(85.2)	1.00		

5.5.2 The relationship between administration of Anti D with indirect and direct combs test

Administration of AntiD was significantly associated with indirect and direct Coomb's test.

Tables 6 : Indirect and direct coombs test associated with anti D administration at Gandhi Memorial hospital, A.A MAY, 2015(n=384)

	Anti D administered				
	Yes	No	OR (95%CI)	Chi-Square	P value
Indirect Coomb's test					
Yes	26 (31.0)	58 (69.0)	3.23(1.77,5.91)	15.4	P<0.001
No	29 ()12.2)	209 (87.8)	1.00		
Direct Coomb's test					
Yes	40 (37.4)	67(62.6)	7.96(4.14, 15.32)	46.6	P<0.001
No	15 (7.0)	200 (93.0)	1.00		

5.6 The relationship between indirect and direct comb's test

Bivariate analysis was conducted by using cross tabs, Chi square test =146.65 and the p value is<0.01.

Table 7: Direct coombs test associated with indirect coombs test at Gandhi Memorial hospital, A.A MAY, 2015(n=384)

Variable(n=384)		**Direct coombs test**			Chi square	p value	95%CI
Indirect cooombs		Yes	No	No need	146.65	<0.001	0.000-0.000
	Yes	62	39	0			
	No	92	178	0			
	No need	9	0	4			

5.7. Key findings of the In depth interview

Regarding the availability and affordability of Anti D medication, qualitative study was conducted with key informants. All of the respondents surveyed were employed. Out of the 7 respondents, 6 were men and 1 was female. Participants were health professionals but were not asked to specify race, job position and so on since it is sensitive issue.

All of the respondents agreed that the medication is charged and it is expensive. And the proposed solution for the price is, majority agreed there should be funding. As two respondents noted:

"Like TB & HIV drugs it should be given emphasis and also the policy should make improvement on this issue." Respondent 3

"Ok, my recommendation first there should be special concern given by partners or the government itself shall be given special concern. The other is it could also have its own fund, reporting system, monitoring and evaluation and also enrollment and fund is recommended. Especially there are program that work on maternal and child health so they should include this case." Respondent 5

Concerning availability issues majority has established that they have seen shortage of medication on occasions. As two respondents explained:

"With the information at my hand I know the drug will be stock out most of the time at PFSA." Respondent 5

"This drug is brought from governmental institution but it is still expensive, it is above 3000.00 Birr. You could imagine how the price will be in private institution. In addition to this there is shortage sometimes."
Respondent 2

As regards to management of the condition majority agreed there is a need of special Attention. As one respondent remarked:

"The basic thing is a concern issue but I don't see concern, the government should also work towards this, special concern is necessary. The other thing is also concerning medical coverage of health workers awareness is also an issue. For example during this interview I feel there is something I should do for this anti D medication." Respondent 5

Furthermore, many highlighted there is increase in consumption of medication for the past years which would be attributed either increase number of case or increase in delivery to health facilities. As two respondents stated:

"But I can see the consumption is increasing for example 5 vials was used for 1 month but now 10 vials which was available yesterday today only 5 vials are left. Therefore it is increasing "Respondent 2

"I can't tell the exact number but the consumption of this medication is increasing. And it could be due to 2 reasons, one the actual case is increasing or the number of women delivering in hospitals is increasing. The consumption of medication is increasing. Therefore I think the case is increasing either of the two reasons. "Respondent 6

The emerging ideas in this study was creating awareness of health professionals, the assumption of the condition in rural areas that it is cursed by supernatural force and is called "Shotelaye" ,illegal distribution of the drug, policy improvement and social factor :

"First not having a child is one problem & also it has a problem on health. The other thing it is has social factor. The woman will fight with family and her husband since the community is not aware on this issue because they think it is super natural force that bring this & believe she is cursed. Therefore I think there is a lot to be done on this issue."Respondent 4"

The existing policy should support this case & also funding should be there." Respondent 3

Table 8: Summary of the key findings of the In depth interview

Themes: 1. Anti D medication is expensive and needs fund. 2. Rh negative pregnancy needs special attention. 3. There is shortage of Anti D medication 4. There is increase in consumption of Anti D.		
Categories		Response given
Distribution of medication	All of them	Charged, expensive
Proposed solution for the price	Majority	Funding should be there to make it free
Management of the condition	Majority	Needs special concern, needs attention
Consumption	majority	increase in demand ,good consumption record keeping
Availability of medication	Majority	Shortage of medication

6. DISCUSSION

This study is the first of its kind in Ethiopia that has lined the significance to give special emphasis to Rh negative pregnancy. The prevalence of Rh negative pregnant women visiting Gandhi Memorial Hospital in the study period is found to be 7.2%.This finding is higher than the frequency of RhD-negative phenotype in previous studies in Nigeria 4.44%, 3.9% in Kenya, 4.06% in Guinea, and 2.4% in Cameroon(5). Since it is a pioneer study this figure shows emphasis should be given to this condition and other research should be conducted at a national level to overcome the problem associated with this condition.

A research in Pakistan by Sadia N. et al indicates when maternal sensitization to the D antigen is present, it is important to establish the paternal zygosity. In the white population, the incidence of heterozygosity for the D antigen is 56%. In such cases of paternal heterozygosity, only 50% of the fetuses will be potentially at risk for isoimmunization. Therefore, by establishing the paternal zygosity, improved counseling of couples concerning risks and treatment options must be provided (3). A research in Nigeria by Okeke found 42.6% of the husbands the Rh negative women had their Rh blood groups documented(27).But in this study Rh type of the father documented is 18.8%which is much smaller than the analogous study.

A study in USA reveled the crude utilization rate of anti-Rh antiserum was 41%–44% for all population groups combined. The rate for Blacks, Whites, Indians, and Coloreds was 14%–20%, 89%–94%, 59%–64%, and 45%–51%, respectively (4). In this study the crude utilization rate is 14.3% which is on the range for Blacks in the above study but there is still much work to be done when we compare to other countries because utilization rate is one of the basic indicator to guarantee of the nonoccurrence of sensitization.

A study conducted by Francesco et al found the newborn's blood group was determined in a sample of cord blood in 85%(14) ,but this study finds only 42.4% of the new born ’s had their cord blood tested for blood type and Rh status which is much lower than above study. Since this test is very important to determine the Rh type of the new born so that the Anti D administration is confirmed.

In 2005, a survey of obstetric units reported that 75% offered RAADP, and of these 81% used one of the two-dose regimens (17). And in Northern Ireland, all 12 maternity units offer RAADP, in England and Wales this figure was 180 of 243 (74%) and in Scotland 28 of 39 (72%) (21). But in this study there was the offer of RAADP at 28 weeks is 4.7% is much smaller , this may be due to poor documentation or lack of awareness on the importance of offering RAADP. Therefore this indicates a lot of work to be done regarding the importance of RAADP.

This study finds among the Rh negative pregnant women (86) 22.4% had abortion due to incomplete abortion, therapeutic abortion and ectopic pregnancy but only 5.8% had Anti D administration documented. But the Royal College of Obstetricians and Gynaecologists and NICE recommends anti D administration "After sensitising events before delivery and after abortion" (18).

A research done Vinod K. B. et al. estimated the global burden of Rh disease among different countries, the finding for the poorest countries indicate 11% for stillbirths(29), but this study finds 6.8% still birth which is better but emphasizing the need for special attention.

Regarding Anti D administration all socio demographic factors(age, marital status and educational level, employment status) included in the study were not statistically significant with anti D administration and have chi square ranging between 0.1-0.6 and p value >0.05, this may be due to administration of Anti D medication mainly depends on high cost of the currently available immunoprophylaxis and dissemination of effective Rh disease prevention. And also the lack of association may be due to missing values due to poor documentation of information.

Bivariate analysis was conducted, Chi square =0.454 and the p value=0.53, this indicates there is no association between employment status of anti D administration. This may be due to since the price of the drug is expensive it may not be affordable for majority of the population and also there was lack proper documentation of the employment status on the case files therefore the comparison was not all inclusive.

A Chi square of 15.44 and the p value<0.001,and the multi variante analysis shows that women who took indirect coombs test are more likely to get administration of Anti D (0R=3.23, 95%C.I 1.77-5.91) compared to women who did not get the test ,this result indicates before administration of Anti D the pregnant women were checked whether she was sensitized or not by using indirect combs test..

When we see the direct combs test, Chi square of 140.534 and p value <0.001, the multi variante analysis shows that women who took direct coombs test are more likely to get administration of Anti D (0R=7.96, 95%C.I 4.14-15.32) compared to women who did not get the test which indicates cord blood was taken to check the Rh status of the newborn before administration of Anti D

Bivariate analysis of Chi square test of 46.63 and the p value is<0.01, result shows relationship between the tests i.e. a practitioner which request indirect test will also allow the direct test to be performed

This study is limited by the fact that it is a pioneer study on Rh negative pregnant women in Ethiopia with poor (inadequate) documentation of vital information.There is need for proper continuing education about this preventable disease for Obstetricians, Hematologists, and also need to put in place a proper protocol for the management of Rh D negative pregnant women to prevent Rh D iso-immunization.

Qualitative methods included in-depth interviews with key informants to assess the access and affordability issues of medication; content analysis was done, combining deductive and inductive approaches. Results demonstrated that effective management of the Rh negative was not as integrated in practice as had been expected. The lack of proper supervision were often viewed as including the high price of the medication, the increase in consumption, lack of concern and shortage of medication. Qualitative data suggest that special consideration is necessary on this issue.

Therefore by combining quantitative and qualitative methods, it has been possible to both measure whether Rh negative pregnant women were actually had received effective management, through the accounts of case files or health records and insight of health professionals, purported were not always realized in practice.

7. STRENGTHS AND LIMITATIONS OF THE STUDY

7.1Strengths

Data collectors were trained and experienced.

Is a pioneer study.

Both quantitative and qualitative research.

7.2 Limitations

Case files of selected participants lack documentation of vital information.

8. CONCLUSION AND RECOMMENDATION

8.1 Conclusion

The prevalence of Rh negative women is 7.2%, which is of a high magnitude keeping in view the prevalence rate of the other African countries estimate. There is lack proper management of Rh Negative pregnant women in terms of affordability issues, shortage of medication and special concern.

8.2 Recommendation

- An Rh negative woman requires special supervision including proper documentation of case files, training of staff.
- Improvement of access and affordability of Anti D medication.
- Special attention should be given to Rh negative pregnancy to be included in maternal health programs by Ministry of health.
- Guidelines should be developed for people who engage in the area.
- Rhesus Negative Registration format is recommended for health facilities, Annex 8(page 45)
- Other research should pursue this study to improve management of the condition by including other parts of the country particularly in rural areas and also assessment of the knowledge, attitude and practice of health professionals is also important.

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10. ANNEXES

10.1 Annex 1 Check list used to assess the management of RhD negative pregnancy

Section 1: Socio demographic information

No.	Questions	Coding Categories
101	Age in years	_____
102	What is the marital status?	1. Single 2. Married 3. Married but not living together 4. Divorced 5. Widowed 6. Not documented
103	Where does the patient live?	1. Addis Ababa 2. Regional state
104	What is the level of education?	1. Illiterate 2. Primary 3. Secondary 4. Diploma 5. Higher level 6. Not documented
105	What is the employment status?	1. Employed 2. Unemployed 3. Not documented

Section 2: Questions regarding previous obstetric history

	History of previous obstetric		
201	Miscarriage	1.Yes	2. No
202	Therapeutic abortion	1.Yes	2. No
203	C-section	1.Yes	2. No
204	Ectopic pregnancy	1.Yes	2. No
205	External cephalic version	1.Yes	2. No
206	Fall / abdominal trauma	1.Yes	2. No
207	Intrauterine death	1.Yes	2. No

Section3: Questions regarding on the current obstetric history

No.	Questions	
301	Does the Rh type of the father tested and documented?	1. Yes 2. No
302	What is the birth order?	1. First pregnancy 2. Second pregnancy 3. Third pregnancy 4. Other
303	The service was given to the patient	1. Free of charge 2. Charged for fee
304	What is the pregnancy outcome?	1. Live birth 2. Stillbirth 3. Abortion 4. not documented
305	What is the blood group of the patient?	1. A 2. B 3. O 4. AB
306	Dose Indirect Coomb's test performed	1. Yes 2. No 3. No need

307	Dose direct Coomb's test performed	1. Yes 2. No 3. No need
308	How many times does indirect coomb's test performed?	1. One times 2. Two times 3. Three times

Section 4: Question regarding the Anti D drug management

401	Was patient's informed consent was obtained and recorded in the maternal and hospital case notes for the administration of anti-D?	1. Yes 2. No 3. No need
402	Was administration of anti D documented?	1. Yes 2. No 3. No need
403	What was the dose of Anti D?	1. 300 2. 250 3. Not documented 4. No need
404	Was it given within 72 hours of delivery?	1. Yes 2. No 3. No need

Section 5: Questions regarding RAADP

No.	Questions about the use of prophylaxis at	
501	28 weeks	1. Yes 2. No 3. No need
502	34weeks	1. Yes 2. No 3. No need

10.2 Annex 2: Question for the Qualitative study: English

1. Do you think RH negative pregnancies are commonly occurring now days?
   - Can you estimate from how many pregnant women Rh negative can occur

2. How does the consumption of Anti D medication being determined?
   - Are there special measures for this condition?

3. Is Anti D medication is being distributed to patient for free or charged for fee?
   -if it is charged, do you think it is affordable when we compare it to other medication.
   -what do you suggest to be done.

4. What kinds of tests are available to adjust the dose Anti D medication?

5. Do you think RH negative pregnant women are being effectively managed?
   -regarding affordability of medication.
   - training professionals.

6. What will be the consequence if Rh negative mother did not receive Anti D medication?

10.3 Annex 3: Information sheet

My name is Bethlehem Tsegaw I am conducting a study for Master in Public health. My research title is Prevalence of Rhesus negative gene among pregnant women and assessment of effective management of D negative pregnancies in Gandhi Memorial Hospital, Addis Ababa.

You are randomly selected to participate in this study as an individual who has knowledge and background in the desired field.

Participation in this study will require approximately 15 minutes of your time. The survey consists of questions regarding the management of Rh negative pregnant women. Participation will take place in the privacy of your office. There are no known risks or discomforts associated with this research. Any information obtained during this study which could identify you will be kept strictly confidential. The data will be stored and will be coded by the investigator .There will no personally identifiable information in the study report.

Participation in this study is voluntary. You can refuse to participate or withdraw at any time during the research.

Sincerely,

10.4 Annex 4: Consent form

The research objective, importance has been clearly explained by the investigator. There are no known risks or discomforts associated with this research In addition full right has been given to me to refuse or to take- part in the study as well to withdraw at any time even during the interview.

Based on the information addressed to me, I have accepted to participate in the study.

.

Signature_____

Date_____

10.5 Annex 5: Question for Qualitative study: Amharic version

1. **አር ኤች የደም አይነት በአሁኑ ወቅት በብዛት እየታየ ይመስልዎታል**?

2. **የአንቲዲ መድሐኒት ጥቅም ላይ የሚውለው መጠን በምን ይታወቃል**?

- ለዚህ መድሐኒት የተለየአሰራር አለው

3. **የአንቲዲ መድሐኒት ለታካሚዎች የሚሰጠው በነጻ ወይስ በገንዘብ ክፍያ ነው**?

- ገንዘብ የሚከፈልበት ከሆነ ዋጋው ለታካሚዎች ተመጣጣኝ ይመስልዎታል

- ለዚህም ሲባል ምን እነዲደረግ ይመክራሉ

4. **የመድሐኒቱን መጠን ለእያንዳዱ ታካሚዎች ለማስተካከል ምን አይነት ምርመራ አለ**?

5. **አር ኤች ኔጌቲቭ የሆኑ እናቶች በአሁኑ ሰአት በቂ ክትትል እየተደረገ መሆኑን ያምናሉ**?

ለምሳሌ ከመግዛት አቅም ከባለሙያም አንጻር

6. **አንድ አር ኤች ኔጌቲቭ የሆነች እናት የአንቲዲ መድሐኒት ባትወጋ የሚደርስባት ጉዳት**

ምንድን ነው ?

10.6 Annex 6: Information sheet: Amharic version

የመረጃ መስጫ ቅጽ

ጤና ይስጥልኝ

ይህን ጥናት የማከናውነው ቤተልሄም ፀጋው ስሆን በአዲስ አበባ ዩኒቨርሲቲ ፣ የጤና የሳይንስ የህብረተሰብ ጤና ትምህርት ቤት ፣ የማስተርስ ተማሪ ስሆን በዚሁ ትምህርት ለመመረቅ አንዱና ዋናው ተግባር ይህን የመመረቂያ ፅሁፍ ነው።

የዚህ ጥናት ርዕስ አር ኤች ኔጋቲቭ እርግዝና ምን ያህል እንደሚከሰት እና ውጤታማ የህክምና ክትትል ግምገማ ነው።

ይህ ደብዳቤ በዚህ ምርምር ላይ ተሳታፊ እንዲሆኑ ለመጋበዝ የተዘጋጀ ሲሆን የዚህ ጥናት ዋና ዓላማ የእናቶች የጤና አገልግሎት በተለየ የአርኤች ኔጌቲቭ የደም አይነት በአሁኑ ሰዓት እየተሰጡ ያሉትን የተለያዩ አገልግሎቶች ያላቸውን ውጤታማነት ለማየት ነው።

እርሶዎ በዚህ ጥናት በመሳተትፎዎ ሊደርስብዎ የሚችል የጤና ወይም አካላዊ ጉዳት የለም።ለዚህ ጥናት ሲባል ከእርስዎ የተወሰደና እርስዎን ሊገልጽ የሚችል ማንኛውም መረጃ ሚስጥርነቱ የተጠበቀ ይሆናል። መረጃውም በአጥኚው ኮምፒተር በፓስወርድ ተቆልፎ የሚቀመጥ ይሆናል። የዚህ ጥናት ሪፖርት ሲዘጋጅ በግለሰብ ስም ወይም ደረጃ የሚጠቀስ ሪፖርት አይኖርም፡

የጥናቱም ውጤት የእናቶች የጤና አገልግሎት አሰጣጥ ለማሻሻል ይውላል።

በማንኛውም ጊዜ በጥናቱ ያለመሳተፍ ወይም የማቋረጥ መብትዎ የተጠበቀ ነው።

በጥናቱ ላይ ለመሳተፍ ፍቃደኛ ኖት ?

1. አዎን ፈቃደኛ ነኝ 2. ፈቃደኛ አይደለሁም

ፈቃደኛ ከሆኑ የስምምነቱን ቅፅ አንብበው የስምምነቱን ማረጋገጫ ፊርማ ይፈርሙ ::

10.7 Annex 7: Consent form: Amharic version

የስምምነት ማረጋገጫ ቅፅ

የዚህ ጥናት አላማ ፣ ጥቅምና ምቾትን ሊያጋድሉ የሚችሉ ሁኔታዎችን ተነግሮኛል :: በተጨማሪም በማንኛውም ጊዜ በጥናቱ ያለመሳተፍ ወይም የማቋረጥ መብቱ የተጠበቀ እንደሆነ ፣ ይህ ውሳኔ ምንም አይነት ተፅህኖ እንደማያስከትልብኝ ተነግሮኛል :: ጥያቄም ለመጠየቅ እድልም ተሰቶኛል ::

ከላይ በተሰጠኝ መረጃ መሰረት በጥናቱ ለመሳተፍ ተስማምቻለሁ ::

ፊርማ _____

ቀን: _____

Rhesus Negative Register		
Surname	Forenames	Date of birth
Address		Telephone number

10.8 Annex 8 Rhesus Negative Registration format

Patient's blood group and genotype Date of birth					Husband's blood group and genotype			
Obstetric history								
	Antibodies							
Gravida	Booking	28	36	Delivery	Six month post partum	Baby's group	Anti-D given	Complication
Blood transfusions								

NOTE: This format is adopted *from Journal of the Royal College of General Practitioners, 1980, 30, 35-39.*