COLLEGE OF HEALTH SCIENCES, SCHOOL OF MEDICINE, DEPARTMENT OF OBSTETRICS AND GYNECOLOGY

POSTGRADUATE PROGRAM

PREGNANCY OUTCOME FOR RH-D ALLOIMMUNIZED PREGNANCIES AT TWO TEACHING HOSPITALS (TASH AND GMH), ADDIS ABABA, ETHIOPIA, 2023

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DECLARATION

I, Dr. Eyob Daniel, hereby declare that this thesis entitled **"Pregnancy outcome for Rh-D alloimmunized pregnancies at two teaching hospitals (TASH and GMH), Addis Ababa, Ethiopia, 2023"** was fully undertaken by me under the guidance of my advisor and that I have, to the best of my knowledge and effort, cited all various sources of information used in this thesis, and I am also declaring that this thesis has not been submitted to any other institution for the award of any certificate, diploma, degree or masters.

Dr. Eyob Daniel (MD)	_____	_____
Principal investigator	Signature	Date

I hereby certify that I have read and evaluated this research thesis relating to "**Pregnancy outcome for Rh-D alloimmunized pregnancies at two teaching hospitals (TASH and GMH), Addis Ababa, Ethiopia, 2023"** under my guidance from its inception up to its current format and that it can be submitted for final approval in partial fulfillment to the Degree of Specialty in Obstetrics and Gynecology. I also certify that the above declaration made by the investigator is correct to the best of my knowledge as an advisor.

Dr. Esayas Berhanu (MD)	_____	_____
Advisor	Signature	Date

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LIST OF ABBREVIATIONS

AAU- Addis Ababa University

Ab- Antibody

Ag- Antigen

CHS- College of health science

HDFN- Hemolytic Disease of the Fetus and Newborn

IgG- Immunoglobulin G

IgM- Immunoglobulin M

IUT- Intra uterine transfusion

MCA PSV- Middle cerebral artery peak systolic velocity

MoM- Multiples of medians

NICU- Neonatal Intensive Care Unit

PCV- Packed cell volume

Rh D- Rhesus D antigen

RBCs- Red blood cells

GMH- Gandi Memorial Hospital

TASH: - Tikur Anbesa Specialized Hospital

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ABSTRACT

Background: Rh alloimmunization refers to the process by which antibodies are produced against the Rh antigens that are found on the surface of red blood cells (RBCs). The disease burden is worse in developing countries, where universal anti D prophylaxis for Rh negative mothers is very suboptimal. The annual burden of still birth, neonatal death & severe hyperbilirubinemia is projected to be 41,000, 90,000, and 97,000 respectively. In a recent study at the three teaching hospitals of AAU the prevalence of Rh Alloimmunization is found to be 17.1%. This study provides measured pregnancy outcome for those mothers who are alloimmunized with Rh D antigen.

Objective: The aim of this study was to show the pregnancy outcome for RH-D alloimmunized pregnancies in the setup of two public hospitals (TASH and GMH) in Addis Ababa, Ethiopia.

Methodology: A hospital-based retrospective cross-sectional study was conducted on 52 pregnant women with Rh-D alloimmunization and managed at Tikur Anbesa Specialized Hospital (TASH) and Gandi Memorial Hospital (GMH) from January 2019 to January 2023. The data were collected by means of structured questionnaires. The data were entered, coded, and analyzed using Statistical Package for Social Science (SPSS) version 25. Descriptive statistics were used to assess the pregnancy outcome of pregnant women with RhD alloimmunization. Cross-tabulation was done to see the relation between variables.

Results: From the 52 pregnancies (4 with hydrops, 48 without hydrops), 44.2% had an intrauterine transfusion (IUT) during pregnancy, while 55.8% were not transfused. Among these, 42.3% of them didn't receive anti D prophylaxes in all pregnancies and 44% of them had unknown titer at booking. The median number of IUTs per fetus was two. Nearly twenty-eight (27.7%) had developed jaundice, 21% had developed anemia, and 8.5% had developed both jaundice and anemia. There were four perinatal deaths: two stillbirths and two early neonatal deaths. The general neonatal survival after alloimmunization was 90.4%; in the absence of hydrops 95.7% of the fetuses survived, whereas in the presence of hydrops, it dropped to 25%.

Conclusion and Recommendation: Rh D alloimmunization associated perinatal morbidity and mortality is a significant but less recognized problem. Neonatal jaundice is the major morbidity, whereas fetal hydrops is the major contributor for the perinatal mortality. Anti-D antibody coverage should be improved and antibody titers need to be determined for all Rh-alloimmunized pregnancies at booking. A prospective study with a large sample size is needed to identify factors affecting the survival of hydropic fetuses after IUT.

Key terms: RH-D alloimmunization, intrauterine transfusion, hydrops

1. INTRODUCTION

1.1 Background

Rh alloimmunization refers to the process by which antibodies are produced against the Rh antigens that are located on the surface of red blood cells (RBCs) [1]. The occurrence of this phenomenon depends on the successful entrance of a sufficient amount of erythrocytes from an Rh-positive fetus into the bloodstream of its Rh-negative mother [2].

The primary Rh antigen implicated in the majority of cases of severe Rh alloimmunization is the Rhesus D antigen (RhD). Additional examples of unusual Rh antigens encompass the c, E, and Kell antigens. The rarely occurring Rh antigens, namely Duffy, Kidd, M, and S, rarely give rise to substantial complications. Among all the blood group antigens, Rh D is considered to be the most potent. It has been observed that even a small quantity, ranging from 0.1 to 1 ml, of Rh D-positive blood is capable of inducing the development of antibodies [3].

In addition to the period of parturition, which is the most vulnerable time, other instances of fetomaternal hemorrhage include spontaneous or induced termination of pregnancy, ectopic pregnancy, invasive intrauterine procedures, blunt trauma to the abdomen, any antepartum hemorrhage, and external cephalic versions. The recipient's reticuloendothelial system (RES) identifies the antigens on red blood cells (RBCs) as exogenous and initiates an immune response by producing antibodies to eliminate these foreign RBCs. The anti-Rh antibodies are subsequently transferred to the fetus through the circulation of the placenta, resulting in the attack of fetal red blood cells and the development of fetal anemia. If left untreated, this can lead to severe consequences, such as hydrops and fetal death. During pregnancy, the medical term used to describe the condition is erythroblastosis fetalis, while after birth it is referred to as hemolytic disease of the newborn (HDN) [1].

The most severe feature of hemolytic disease of the fetus and newborn (HDFN) is attributed to maternal alloantibodies specifically targeting the D antigen within the Rh blood type system, which is known for its heightened immunogenicity [4–6].

1.2 Statement of the problem

In developed nations, there has been a notable decline in the prevalence of severe cases of Rh alloimmunization over the course of time. However, it is worth noting that in these countries, approximately 18% of women with Rh-negative blood types produce anti-D antibodies after receiving only post-partum anti-D prophylaxis within 72 hours. Whereas a smaller percentage of Rh-negative women, ranging from 0.1% to 0.3%, develop anti-D antibodies after receiving both post-partum and antepartum anti-D prophylaxis [7, 8].

The prevalence of disease is higher in underdeveloped nations, where the implementation of universal anti-D prophylaxis for Rh-negative women is suboptimal. In the absence of any postpartum or antepartum prophylaxis, approximately 14% of women will acquire anti-Rh antibodies within the ensuing 6 months, which affects future pregnancies. If there is no antenatal intervention, it results in stillbirth in about 14% of these pregnancies. Among those who have survived, it is estimated that 30% will experience severe disease, which has a fatal outcome in the absence of any therapy. Another 30% will exhibit moderate disease, presenting as hyperbilirubinemia, a condition that might potentially result in kernicterus if left untreated. The remaining proportion of survivors will remain asymptomatic. Therefore, it may be deduced that in the absence of any intervention, approximately half of Rh-immunized infants will either die or experience significant neurological impairment [9]. Based on the provided estimation, it is anticipated that the yearly incidence of stillbirth, neonatal death, severe hyperbilirubinemia, and kernicterus will reach 41,000, 90,000, 97,000, and 48,000 cases, respectively [1].

In modern prenatal care, it is common to give pregnant women with RhD-negative blood an injection of anti-RhD immunoglobulin IgG around the 28th week of pregnancy, followed by a booster injection around the 34th week of pregnancy [10]. However, the provision of anti-RhD immunoglobulin IgG in Ethiopia is hindered due to its unaffordability. Therefore, Rh alloimmunization continues to be a significant contributing factor to perinatal morbidity, compromising the quality of obstetric care for women in Ethiopia [11].

A recent study, which is a systematic review and meta-analysis conducted on the obstetric population in Ethiopia, revealed that the prevalence of Rh-negative blood groups is 10.8% [11]. In a cross-sectional study done in TASH, GMH, and ZMH hospitals, 17.1% of the Rh D-

negative obstetric population was found to have Rh D alloimmunization [12]. A five-year cross-sectional study done at a tertiary care hospital in Ethiopia, which was published recently, revealed that the overall neonatal survival of alloimmunization was 93.8%, 50% with hydrops fetalis, and 96.7% without hydrops [13].

1.3 Significance of the study

In countries where the neonatal mortality rate exceeds 5 per 1000 live births, there are estimated to be 26 million Rh-negative pregnancies and deliveries, according to a thorough meta-analysis by Bhutani et al. in 2013. Among this population, approximately 15% do not receive any form of prophylaxis. Without prenatal and postnatal interventions, the expected outcome of an Rh-immunized pregnancy would be a 14% rate of stillbirth, a 23.8% rate of neonatal death, and a 7.2% rate of kernicterus among infants who survive [14]. So far in our setup, there is no measured pregnancy outcome for those mothers who are alloimmunized with Rh D antigen. Hence, it is imperative to emphasize the significance of ongoing research pertaining to the pregnancy outcome of Rh D-alloimmunized pregnancies. The findings of the study will also provide policy makers, health practitioners, mothers and the community at large with useful insights regarding the perinatal outcome of Rh D alloimmunized pregnancies. By this it helps to deepen the current understanding about the significance of prevention of the condition.

2. LITERATURE REVIEW

Rh alloimmunization takes place only when a sufficient number of erythrocytes originating from an Rh-positive fetus enter the bloodstream of its Rh-negative mother. The amount needed to cause alloimmunization may be different for each patient. It may depend on how immunogenic Rh-positive red blood cells are and how sensitive the mother's immune system is [2].

Hemolytic disease of the fetus and newborn results from the active transportation of IgG-class antibodies across the placenta into the fetal circulation. Immunoglobulin M (IgM) antibodies are large enough to traverse the placental barrier; hence, they are not involved in hemolytic disease of the fetus and newborn (HDFN). When the fetus has an antigen against which the mother has alloimmunization, the IgG antibody binds to the fetal red blood cells (RBCs) and designates them for elimination through the endoreticulum of the spleen. Fetal anemia elicits higher rates of hematopoiesis; nonetheless, the degree of compensation may be inadequate to ameliorate the anemia [15]. The occurrence of severe uncompensated fetal anemia results in increased vascular flow rates, accompanied by cardiomegaly and congestive failure. Fetal hydrops follows, which manifests as the development of edematous tissue and skin, hepatosplenomegaly, heart failure, and the retention of serous fluid, which includes ascites, pleural effusion, and pericardial effusion. Hemolysis results in an increase in bilirubin levels, which are subsequently eliminated from the fetal circulation through the placenta. However, the bilirubin can be identified in the amniotic fluid. Severe fetal anemia and hydrops may result in fetal death, which subsequently leads to spontaneous abortion or stillbirth [16]. The process of hemolysis in newborns persists as long as there are passively transmitted maternal antibodies present in the serum following delivery. As the process of hemolysis persists, the neonate will suffer from a progressive worsening of anemia and hyperbilirubinemia. Subsequently, the neonate is put at risk of kernicterus and subsequent irreversible brain damage or death due to the immaturity of the blood-brain barrier, which allows bilirubin to enter the brain [15].

After the detection and identification of antibodies in the maternal serum, it is recommended to monitor the antibody titers over a period of time in order to identify any increase if the fetus is at risk of inheriting the antigen in question. Elevated anti-D titers beyond a threshold of 16 or 32 are commonly regarded as critical [15]. Typically, the management of these patients involves regular monitoring of ICT titers at intervals of two to four weeks, with the aim of ensuring that

the titers do not exceed the critical threshold. The term "critical titer" is typically used to refer to the titer level that poses a risk of developing fetal anemia and, subsequently, fetal hydrops [1].

If the levels of ICT titers don't reach the level of the critical threshold, most cases are managed conservatively. Once a critical titer is reached, the following management of both first alloimmunized pregnancies and future pregnancies is similar. Doppler velocimetry is employed in all of these instances to assess the degree of fetal anemia by measuring the MCA PSV. According to a recent meta-analysis of 12 studies conducted between 2008 and 2018, a MCA PSV value greater than 1.5 multiples of the median (MoM) is generally considered to have a high sensitivity (86%) and specificity (71%) in predicting moderate to severe fetal anemia [17]. Serial MCA PSV is initiated after the 20th week of gestation in the first pregnancy affected by alloimmunization. The frequency of these procedures, which are conducted at intervals of 1-2 weeks, is determined based on the severity of the clinical condition and the levels of indirect Coombs Test (ICT) titers [1]. In cases where the MCA PSV value exceeds 1.5 multiples of medians (MoM) based on gestational age, fetal cordocentesis is performed to determine fetal hemoglobin, specifically packed cell volume (PCV), as well as blood grouping. For the initial IUT, a fetal PCV that falls below two standard deviations for a given gestational age or is less than 30% is regarded as the established threshold [18].

Intrauterine transfusions (IUTs) are frequently carried out from 18 to 35 weeks of gestational age. This is because beyond 35 weeks, the procedure tends to carry a higher level of risk relative to the delivery of the fetus. Besides, the reliability of MCA PSV decreases as a result of an increase in false-positive results. Technical difficulties arise due to the small size of anatomical structures before 18 weeks. Intraperitoneal transfusion or intravenous immunoglobulin (IVIG) may occasionally be considered as a bridge therapy in pregnancies at less than 18 weeks of gestation with severe hydrops. The red blood cells (RBCs) utilized for intrauterine transfusion (IUT) are commonly obtained within seven days of donation, undergo irradiation to prevent the graft versus host reaction, and are leucodepleted to ensure that they are negative for CMV serology. They are of O-negative blood type, cross-matched to minimize the risk of minor antigen incompatibility, washed, and tightly packed to achieve a final packed cell volume (PCV) of 75% to 85% to avoid volume overload of the fetus. All pregnant women who are less than 35 weeks gestation get a complete course of corticosteroids at least 48 hours before the procedure, if

they have not already received it, in preparation for a potential emergency delivery. The various potential sites of access include the umbilical vein, peritoneal cavity, umbilical artery, and direct fetal heart. Among these, the umbilical vein is frequently chosen as the preferred route because of its ease of access and enhanced safety, particularly in cases with hydrops. In non-hydropic fetuses, the performance and safety of the intravenous (umbilical vein) and intraperitoneal routes are very similar and depend on the experience of the person performing the procedure. In certain cases, the intraperitoneal route may be favored for pregnancies at a lower gestational age (<22 weeks) [19].

The volume of blood to be transfused is calculated by Mandelbrot's formula as follows [20]:

Volume to be transfused= Vfetoplacental x (Hctfinal–Hctinitial)/ Hcttransfused blood

Fetoplacental volume (Vfetoplacental) = Fetal weight by USG x 0.14

Hematocrit (Hct) final (target) is assumed to be 40–50%

Hct of transfused blood varies from 75 to 85%

In cases of severe fetal anemia, an initial blood transfusion is administered, followed by a further transfusion after a two-day interval. In other circumstances, further transfusions are frequently given based on hematocrit levels, from every 2 to 4 weeks [1]. Following an IUT, a post-procedure fetal blood sample is taken to determine the fetal PCV, which provides a general guide for deciding the timing of a subsequent IUT. The next IUT usually takes place 10 days, 2 weeks, and 3 weeks after the first, second, and third IUTs, respectively. Another method is to estimate that the hemoglobin will drop by 0.4 g/dl/d (about 1% PCV per day), 0.3 g/dl/dl, and 0.2 g/dl/dl after the first, second, and third IUTs, respectively, and to do the IUT when the fetal PCV falls below 25% [1, 21]. Because adult red blood cells (RBCs) have replaced the fetal blood after the first and, at most, second IUT, the next MCV PSV measurements may not be as good at telling if more IUTs are needed. A recent meta-analysis found that MCA PSV >1.5 MoMs predicted moderate to severe anemia after the first, second, third, or more IUTs with a sensitivity of 78, 74, and 60%, respectively, compared to 86% before the first IUT [17]. Because of this, it is suggested that after the third procedure, more IUTs be scheduled, taking into account the expected drop in hemoglobin levels (0.3–0.4 g/dl/d) instead of relying on the values of MCA

PSV. Numerous publications advise IUTs up to 36 weeks of gestation. Delivery can be achieved within the gestational period, ranging from 37 to 38 weeks [1, 2, 22].

Rarely, after prior alloimmunization, severe anemia with or without fetal hydrops can develop before 20 weeks of gestation (particularly in multigravida). In such scenarios, options for management include plasma exchange, intravenous immunoglobulin (IVIg) injection, apheresis, and intraperitoneal transfusion [22, 23].

The delivery of the neonate of an alloimmunized patient is a controversial topic with limited literature. The conventional approach is to prolong the duration of the pregnancy until the fetus attains a gestational age that is considered sufficient for its survival. It is reasonable to continue with delivery by induction of labor at 37–38 weeks of gestation if the history and prenatal investigations show mild fetal hemolysis. If amniocentesis demonstrates fetal pulmonary maturity, early induction may be taken into account. In cases of pregnancies with severe sensitization, which necessitate several invasive operations, it is recommended to consider delivery at 32–34 weeks of gestation following the administration of maternal steroids to promote fetal pulmonary maturity [2]. Delayed cord clamping is used in babies who don't need any kind of resuscitation because recent research has indicated some advantages, including improved hematocrit, less need for exchange transfusions, and a subsequent top-up PRBC transfusion for late infancy anemia without any obvious risks [24, 25].

3. OBJECTIVES

3.1 General Objective

To show the pregnancy outcome for RH-D alloimmunized pregnancies managed in the setup of two public hospitals (TASH and GMH) in Addis Ababa, Ethiopia

3.2 Specific Objective

1. To describe perinatal morbidity associated with RH-D alloimmunized pregnancies
2. To assess perinatal mortality of newborns affected by RH-D alloimmunization

4. METHODS AND MATERIAL

4.1 Study area

The study was conducted at two purposely selected government hospitals in Addis Ababa, Ethiopia, i.e., Tikur Anbesa Specialized Hospital (TASH) and Gandi Memorial Hospital (GMH). TASH is a tertiary referral and teaching center of Addis Ababa University's College of Health Sciences. GMH is a tertiary referral hospital under the Addis Ababa Health Bureau, which is affiliated with Addis Ababa University, CHS.

4.2 Study design and period

A hospital-based retrospective cross-sectional study was used to assess the pregnancy outcome for Rh-D alloimmunized pregnancies at two teaching hospitals (TASH and GMH) from January 2019 to January 2023.

4.3 Source population

All Rh D negative women who were managed at TASH, and GMH during the study period.

4.4 Study population

All Rh D alloimmunized women who were managed at TASH, and GMH during the study period who fulfil the inclusion criteria.

4.5 Inclusion and Exclusion Criteria

Inclusion criteria: Rh D alloimmunized women for whom complete information is obtained on the medical chart.

Exclusion criteria: Incomplete documentation

4.6 Sample size & Sampling Technique

All cases who were managed for RhD alloimmunization from the two hospitals within the study period who fulfilled the inclusion criteria are included in the study. After all the chart numbers of babies of Rh negative pregnancies were obtained from NICU, the chart numbers of all Rh-ve

pregnant mothers were retrieved from the OR and labor ward delivery registry books and the chart numbers of those Rh negative pregnancies who took an intrauterine transfusions were obtained from the OR registry books. Then, each patient chart was retrieved from the archive rooms of the hospital. Accordingly, 52 case files were identified with RhD alloimmunization who fulfilled the inclusion criteria.

4.7 Study Variables

Dependent variable- Perinatal outcome

Independent variables- Socio demographic factors, parity, abortion, anti-D prophylaxis in previous pregnancies, ICT-Titer, Hydrops, Intrauterine transfusion

4.8 Operational definitions

Rh Alloimmunization: a process by which maternal immune system is sensitized to Rh D surface antigen of the erythrocytes of the fetus.

Indirect combs test: a test performed to find anti-D antibodies in the liquid part of blood which can attack the fetal RBCs.

Perinatal death: death of a fetus after 28 weeks of GA or a newborn within the first 7 days of life.

Rh D complication- is a perinatal death or neonatal jaundice that occur in a pregnant women who are known to be Rh D alloimmunized.

4.9 Data Collection and analysis

The completeness of each patient chart was checked before the data collection was started. Then the data was collected by a structured questionnaire from the charts of Rh D-alloimmunized women. Then the data was entered and analyzed using SPSS version 25. Descriptive statistics were used to describe the findings. Cross-tabulation was done to see the relationship between variables.

4.10 Ethical consideration

The proposal was approved by the Ethical Review Committee of the Department of Obstetrics and Gynecology Research and Publication Committee at Addis Ababa University. Permission was requested from each selected hospital to access the charts included in the study. Due to the retrospective nature of the study, there was no need to obtain consent from the patient. A letter of cooperation for the respective units, i.e., record office and NICU, was obtained from the department of obstetrics and gynecology.

4.11 Result Dissemination

Results will be presented to the Department of Obstetrics and Gynecology Research and Publication Committee, Addis Ababa University. A copy of the article will be submitted to the Addis Ababa University College of Health Sciences and other relevant bodies.

5. RESULT

5.1 Sociodemographic and previous delivery characteristics of study participants

During the study period, 52 Rh D-Allo-immunized pregnancies were identified. Among those women, 23 (44.2%) had an intrauterine transfusion during pregnancy, while 29 (55.8%) were not transfused. Majority (78.8%) of the study participants were from Addis Ababa. The mean age was 29.3 ± 4.3 years old and 40% of the study participants are primiparous. Most (59.6%) of the study participants had no history of previous pregnancy loss. (See Table 1 below)

Table 1 Sociodemographic and previous delivery characteristics of the study participants

Variable	**IUT in pregnancy**		**Total** (n=52) frequency (%)
	Yes (n=23) frequency (%)	No (n=29) frequency (%)	
Age Mean ± SD	29.6 ± 3.9	29.1± 4.7	29.3 ± 4.3
Residence			
Addis Ababa	17(73.9%)	24(82.8%)	41(78.8%)
Out of Addis Ababa	6(26.1%)	5(17.2%)	11(21.2%)
Previous delivery status			
nulliparous		2(6.9%)	2(3.8%)
One	8(34.8%)	13(44.8%)	21(40.4%)
Two	8(34.8%)	9(31%)	17(32.7%)
Three and above	7(30.4%)	5(17.2%)	12(23.1%)
Previous pregnancy loss(Abortion/ Ectopic or Molar pregnancy)			
None	15(65.2%)	16(55.2%)	31(59.6%)
One	4(17.4%)	11(37.9%)	15(28.8%)
Two	3(13%)	-	3(5.8%)
Three and above	1(4.3%)	2(6.9%)	3(5.8%)

5.2 Previous pregnancy experience on alloimmunization

The majority (42.3%, n=22) did not receive anti-D prophylaxes in all pregnancies, and 23.1% (n=12) of the participants had complications in previous deliveries due to RH alloimmunization. From the previous pregnancy complications (n=12), perinatal death accounts for 58.3% (n=7), and neonatal jaundice accounts for 41.7% (n=5). Twenty-five percent (n=3) of those with complications in previous deliveries had a history of IUT, and 41.7% (n = 5) of them had a history of hydrops. All of those with complications in previous deliveries who had history of IUT (n=3), had a history of hydrops in previous pregnancies and they all have received IUT in the current pregnancy. (See Table 2 below)

Table 2 Previous pregnancy experience on alloimmunization

Variable	**IUT in current pregnancy**		**Total** (n=52) frequency (%)
	Yes (n=23) frequency (%)	No (n=29) frequency (%)	
History of anti D prophylaxes in previous pregnancy			
Immunized in the first pregnancy	1(4.3)	1(3.4)	2(3.8)
Received in one or more Pregnancies	9(39.1)	9(31)	18(34.6)
Received in all pregnancies	3(13.1)	7(24.1)	10(19.2)
Not received at all	10(43.5)	12(41.4)	22(42.3)
Complication previous delivery Due to RH alloimmunization			
Yes	10(43.5)	2(6.9)	12(23.1)
No	13(56.5)	27(93.1)	40(76.9)
Types of complications			
Perinatal death	5(41.7)	2(16.6)	7(58.3)

Neonatal jaundice	5(41.7)	-	5(41.7)
IUT in Previous Pregnancy(n=12)			
Yes	3(25)	-	3(25.0)
No	7(58.3)	2(16.7)	9(75.0)
Hydrops in previous pregnancy(n=12)			
Yes	3(25)	2(16.7)	5(41.7)
No	7(58.3)	-	7(58.3)

5.3 IUT in current pregnancy

Majority (44.2%) of the study participants' titers were unknown at booking, while 36.5% had 1–8, 13.5% had 16–32, 3.8% had 64–128, and 1.9% had ≥ 256. Forty-four percent (n = 23) of them had IUT in the current pregnancy, and 17.4% (n = 4) of them had hydrops. Sixty-six intrauterine transfusions were performed on 23 fetuses. The median number of IUTs per fetus was two, and the number of IUTs ranged from 1 to 8. Thirty-nine percent of the transfusions were given via the cord vein, and 34.8% of the study participants had received their first IUT at a gestational age of >32 weeks.

All the abortions (n=3) and stillbirths (n=2) were from the IUT group. Among them, one of abortions and both of stillbirths were from the hydrops group. Most (n = 2) of the abortions were from the intraperitoneal route of transfusion, and all the stillbirths were from the cord vein route of transfusion. All the abortion complications occurred in those 20–24 gestational weeks at the first IUT, but there were no complications in those ≥ 32 weeks at the first intrauterine transfusion. (See Table 3 below)

Table 3 characteristics of intra uterine transfusion in the current pregnancy

variable	**Pregnancy outcome**			**Total** (n=52) frequency (%)
	Abortion (n=3) frequency (%)	Still birth (n=2) frequency (%)	Live birth (n=47) frequency (%)	
Indirect combs test titer				
≥256	1(33.3)	-	-	1(1.9)
64 – 128	-	-	2(4)	2(3.8)
16 – 32	-	-	7(24.1)	7(13.5)
1–8	-	1(50)	18(38.3)	19(36.5)
unknown	2(66.7)	1(50)	20(42.6)	23(44.2)
IUT in current pregnancy				
Yes	3(100)	2(100)	18(38.3)	23(44.2)
No	-	-	29(61.7)	29(55.8)
Hydrops In Current Pregnancy (n=23)				
Yes	1(4..3)	2(8.7)	1(4..3)	4(17.4)
No	2(8.7)	-	17(73.9)	19(82.6)
Number of transfusion Mean and median	2.33 2	1 1	3.17 2.5	2.87 2
Route of IUT (n=23)				
Cord vein	-	2(8.7)	7(30.4)	9(39.1)
Intra hepatic portion of umbilical vein	-	-	5(21.7)	5(21.7)
Intraperitoneal route	2(8.7)	-	1(4.3)	3(13.0)

intrahepatic UV & Intraperitoneal	1(4.3)	-	5(21.4)	6(26.1)
GA of first IUT(n=23)				
≤20	-	-	1(4.3)	1(4.3)
20+1-24	3(1.3)	-	4(17.4)	7(30.4)
24+1-27+6	-		1(4.3)	1(4.3)
28-32	-	2(8.7)	4(17.4)	6(26.1)
>32	-	-	8(34.8)	8(34.8)

5.4 Pregnancy Outcome

There were four perinatal deaths: two stillbirths and two early neonatal deaths. The majority (90.4%, n=47) were live births, and 85.7% (n = 42) were delivered at a gestational age of >36 weeks. Sixty-five percent of the participants delivered by caesarean section, and 95.7% had an Apgar score of >7 at the first minute of delivery. Nearly forty-three percent (42.9%) of the study participants had a birth weight of 3–3.49 kg. Nearly twenty-eight (27.7%) had developed jaundice, 2.1% had developed anemia, and 8.5% had developed both jaundice and anemia. Phototherapy alone was given for 87.2% (n = 41) of the neonates and exchange transfusion was given for three (6.4%) of the neonates (for one of them only exchange transfusion was given, and for the other two exchange transfusion was given with all other interventions), and 95.7% were discharged with satisfactory conditions.

Pregnancy outcomes in four hydropic fetuses demonstrated that there was only one (25%) live birth, two (50%) stillbirths, and one (25%) abortion. The two stillbirths were delivered vaginally, whereas the livebirth was delivered by cesarean delivery; had an Apgar score of ≥ 7 in the first minute with normal birth weight; had no complications; phototherapy was given and discharged with satisfactory condition. (See Table 4 below)

Table 4 Pregnancy outcome

Variable	**Hydrops**		**Total (n=52)** frequency (%)
	Yes (n=4) frequency (%)	No (n=48) frequency (%)	
Pregnancy outcome			
Abortion	1(25)	2(4.2)	3(5.8)
Stillbirth	2(50)	-	2(3.8)
Livebirth	1(25)	46(95.8)	47(90.4)
Gestational age at delivery (n=49)			
28-30	1(25)	-	1(2.0)
30+1 - 34	1(25)	1(2.1)	2(4.1)
34+1 - 36	-	4(8.3)	4(8.2)
>36	1(25)	41(85.4)	42(85.7)
Mode of delivery(n=47)			
Vaginal delivery	2	15(32.6)	17(34.7)
Cesarean delivery	1	31(67.3)	32(65.3)
First Min APGAR			
>7	1	44(95.65)	45(95.7)
<7	-	2(4.35)	2(4.3)
Birth Weight(kg)			
100–1.49	1	-	1(2.0)
1.5–1.99	1	-	1(2.0)
2.0–2.49	-	7(15.2)	7(14.3)

2.50–2.99	-	18(39.1)	18(36.7)
3.00–3.49	1	20(43.5)	21(42.9)
≥3.5	-	1(2.2)	1(2.0)
Neonatal complication			
Jaundice	-	13(28.3)	13(27.7)
Anemia	-	1(2.2)	1(2.1)
both	-	4(8.6)	4(8.5)
none	1	28(60.9)	29(61.7)
Type of Intervention			
Phototherapy	1	40(85.1)	41(87.2)
Phototherapy & Transfusion	-	3(6.4)	3(6.4)
phototherapy & exchange transfusion	-	1(2.1)	1(2.1)
All	-	2(4.3)	2(4.3)
Status of the neonate at NICU			
Early neonatal death	-	2(4.35)	2(4.3)
Discharged with satisfactory condition	1	44(95.65)	45(95.7)

6. DISCUSSION

Since the introduction of Rh D immunoprophylaxis, there has been a significant reduction in the incidence of hemolytic disease in the fetus and newborn [26]. Around 14% of Rh D-negative women will be alloimmunized if they are not given anti-D immunoprophylaxis. However, the risk of alloimmunization decreases to 1.8–2% with only postpartum prophylaxis and further decreases to 0.1–0.2% with the addition of antenatal prophylaxis [26]. In Ethiopia, there is no direct information from population-based studies regarding the extent of the problem of Rh D alloimmunization. A recent study done among the three teaching hospitals under Addis Ababa University found the prevalence of Rh D alloimmunization to be 17.1% in Rh D-negative pregnant mothers [12].

In our study, 52 women were identified who developed RH-D alloimmunization. From those women having RH-D alloimmunization, 44.2% (n = 23) received intrauterine blood transfusions. This result was comparable to studies conducted in India by Subhas et al., where 44.6% of the participants received IUT, and by Dadhwal et al., where 47.7% of the participants received IUT [27, 28]. Whereas in a recent study by Kureba et al. published in Addis Ababa, Ethiopia, the transfusion rate was found to be 21.42% [13].

The majority (42.3%) did not receive anti-D prophylaxis in all previous pregnancies, and 19.2% developed Rh alloimmunization despite receiving anti-D prophylaxis. This is different from what Subhas et al. found, where 22% of women did not get anti-D prophylaxis in any of their previous pregnancies and 31% developed Rh alloimmunization even though they got anti-D prophylaxis [27]. This might be due to the unaffordability of the prophylaxis, an undetermined blood group due to home delivery, and negligence about the importance of Rh D immunoprophylaxis. Other related factors might include inadequate dosing or antenatal sensitization [28].

Although Rh alloimmunization is a relatively rare condition in primigravid women, the grandmother theory or significant feto-maternal hemorrhage early in pregnancy could be possible explanations. In this study, 3.8% of all immunized women were immunized in their first pregnancies. It is relatively comparable to the findings of the studies done by Subhas C et al., who found 4.68% alloimmunized primigravidae women, and Al Joudi et al., who found 1.7% alloimmunized pregnant women [27, 29].

In our study, 3.8% had an antibody titer of 64–128 and 1.9% had a titer of ≥ 256, while the majority (44.2%) had their antibody unknown at the time of booking. In the study done by Subhas et al., the ICT titer was determined for all Rh D-alloimmunized pregnancies and found that 74% of women who received IUT, as compared to 38% who did not, had an anti-D titer of ≥ 1:64 at the time of booking [27]. The higher rate of unknown antibody titers at the time of booking could be due to most laboratory reports revealing only the qualitative results.

Rh D alloimmunization-related neonatal hyperbilirubinemia and related death and illness are still major problems in developing countries with a higher infant mortality rate [10]. In our study, neonatal jaundice occurred in 27.7% of the neonates and it is comparable to the study done in Nigeria, by Eleje et al. where 21.3% of the neonates developed neonatal jaundice [30]. Phototherapy alone was given for 87.2% of the neonates and 6.4% of the neonates received exchange transfusion. In the study by Kureba et al., 95.23% of neonates received phototherapy and supportive measures, and out of this, 71.4% required an exchange transfusion. Whereas, in the studies by Subhas et al. where 68% and 79% of neonates with or without hydrops and Sánchez-Durán et al. 63.2% required exchange transfusions [27], [31]. The lower rate of ET in our study may be due to the less severe degree of the jaundices, most of which were corrected by intensive phototherapy alone.

In our study, the general neonatal survival after alloimmunization was 90.4%, 95.7% in the absence of hydrops, and 25% in the presence of hydrops. All the stillbirths were from the hydrops group, and they had their first IUT later, after 28 weeks of gestation. Whereas a recently published study in Addis Ababa, Ethiopia, by Kureba et al. found that overall neonatal survival after alloimmunization was 93.8%, 50% with hydrops, and 96.7% without hydrops [13]. In their studies, Van Kamp IL et al. found that overall neonatal survival was 86%, 92% without hydrops and 78% with hydrops; Dadhwal et al. (88% without hydrops and 83% with hydrops); and Subhas C et al. (90% without hydrops and 59.5% with hydrops) [27, 28, 32]The relatively lower rate of survival in hydropic fetuses in our study was probably related to the severe degree of hydrops at presentation and other co-factors. The severity of hydrops has been related to a poorer outcome in other studies too [33]. Besides, in the absence of hydrops, perinatal survival steadily improved as gestation increases at first IUT, whereas hydropic fetuses had poorer survival when first IUT was given later in gestation.

7. LIMITATIONS AND STRENGTH OF THE STUDY

Due to the retrospective nature of the study, only 52 case files were available for analysis. Hence, it was difficult to make associations between various variables studied in Rh D-alloimmunized women due to the limited nature of the sample size. Despite these limitations, the findings of this study are expected to contribute a lot to the understanding of pregnancy outcomes in RhD-alloimmunized pregnancies, laying the foundation for further research in this area.

8. CONCLUSION

It was found that among the 52 case files of Rh D-alloimmunized pregnancies, 44.2% received intrauterine blood transfusions. Most of them didn't receive anti D prophylaxes in all pregnancies and majority had unknown antibody titer at booking. Neonatal jaundice is the major morbidity, whereas fetal hydrops is the major contributor for the perinatal mortality. All the stillbirths were from the hydrops group, and they had their first IUT later, after 28 weeks of gestation. In the absence of hydrops, perinatal survival steadily improved as gestation increased at first IUT, whereas hydropic fetuses had poorer survival when first IUT was given later in gestation. This suggests early detection and management of Rh D-alloimmunized pregnancies complicated by hydrops can significantly impact the outcome.

9. RECOMMENDATION

Anti-D antibody coverage should be improved and antibody titers need to be determined for all Rh-alloimmunized pregnancies at booking. A prospective study with a large sample size is needed to identify factors affecting the survival of hydropic fetuses after IUT.

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11. ANNEXES

Questionnaire

Maternal socio-demographic characteristics & previous delivery experience

1. Maternal age…
2. Address: A)Addis Ababa B) Outside Addis Ababa
3. Previous delivery? A)0 B) 1 C) 2 D) 3 or more
4. Previous pregnancy loss (abortion/Ectopic or Molar pregnancy) A) 0 B) 1 C) 2 D) 3 or more
5. Anti-D prophylaxis in previous pregnancies
   A. Received in one or more pregnancies
   B. Received in all pregnancies
   C. Not received in any pregnancy
   D. Immunized in first pregnancy
6. Was there any complication due to an Rh D alloimmunization? A) Yes B) No
7. If yes, what was the complication?
   A. Termination of pregnancy
   B. Perinatal death
   C. Neonatal jaundice
8. Was there requirement of intrauterine transfusion? A) Yes B) No
9. If yes, was there hydrops? A) Yes B) No

Intrauterine transfusion

10. ICT Titre at booking
    A. ≥256
    B. 64 – 128
    C. 16 – 32
    D. 1–8
    E. Unknown
11. Was there an intrauterine transfusion? A) Yes B) No
12. If the answer for the above question is yes, was there hydrops? A) Yes B) No
13. Number of intrauterine transfusion ……
14. What was the route for the intra uterine transfusion?
    A. Cord vein
    B. Intra hepatic portion of umbilical vein
    C. Intraperitoneal route

15. Gestational age at first transfusion (weeks)
    A. <20
    B. 21-24
    C. 25-28
    D. 28-32
    E. >32

Pregnancy outcome

16. What was the outcome of the pregnancy
    A. Abortion
    B. Stillbirth
    C. livebirth
17. Gestation at delivery (weeks)
    A. 28–30
    B. 30+1–34
    C. 34+1–36
    D. >36

18. What was the mode of delivery
    A. Vaginal delivery
    B. Cesarean delivery

Neonatal outcome

19. 1st minute APGAR SCORE A) ≥7 B) <7
20. Birth weight (Kg)
    A. ≤1
    B. 101–149
    C. 15–199
    D. 20–249
    E. 250–299
    F. 300–349
    G. ≥35
21. Was there neonatal complication A) yes B) No
22. If yes, what was the complication
    A. Neonatal jaundice
    B. Anemia
    C. Others specify…
23. Was there any intervention done for the neonate?
    A. Yes
    B. No

24. If yes, what was the intervention
    A. Phototherapy
    B. Immunoglobulin therapy
    C. Transfusion
    D. Exchange transfusion
    E. Others Specify……
25. What was the neonatal outcome after admission to NICU
    A. Early neonatal death
    B. Discharged with satisfactory condition