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A Study of Maternal and Fetal Outcome in Rhesus Negative Pregnancy in A Tertiary Care Institute

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Abstract

Introduction: Rh incompatibility is a major cause neonatal hyperbilirubinemia, hydrops fetalis and stillbirth.

Objectives: To study maternal and fetal outcomes in Rh-negative pregnancy in terms of antenatal interventions of intrauterine blood transfusions, Gestational age at the time of delivery, birth weight, APGAR score, Stillbirth, Hydrops, neonatal anemia, neonatal jaundice, kernicterus, need for phototherapy or exchange transfusions.

Methodology: A prospective, observational study was conducted on 114 pregnant women with Rh negative blood group irrespective of their age, parity, gestational age and administration of Rh Anti-D Ig in previous or present pregnancy.

Results: 42.1% were in the age group of 26-30 years. 73.7% patients delivered at term. 89.5% patients were registered with 10.5% being unregistered, who did not receive antenatal Anti D prophylaxis. 81.6% babies were found to be Rh positive after birth hence their mothers received postnatal Anti D prophylaxis. Only one case of isoimmunization resulting in an intrauterine fetal demise was noted in the study in an unregistered patient. (p value=0.003) Neonatal jaundice was found in 91.6% cases where mother did not receive Antenatal Anti D prophylaxis. (p value=0.0005)

Conclusion: Rhesus isoimmunization is one of the preventable causes of neonatal morbidity and mortality. The incidence of the ill effects of the disease can be curbed with timely antenatal registration of a pregnant woman with blood grouping and Rh typing. Timely

administration of antenatal and postnatal prophylaxis should be done.

Keywords: Hemolytic Disease of Newborn, Rhesus alloimmunization, Anti D immunoglobulin.

Introduction

Rhesus antigen, encoded on chromosome 1, was first discovered in the Macacus Rhesus monkey by Karl Landsteiner and Weiner in 1941, with whom 85% humans share this antigen[1,2,3]. Individuals are classified as Rh-positive or Rh-negative based on the presence or absence of this antigen. The inheritance of Rh antigen follows an autosomal dominant pattern, meaning an Rh-positive father is likely to pass the antigen to the fetus, causing incompatibility with an Rh-negative mother.[1] Rh incompatibility primarily occurs through Rh-positive blood transfusions to Rh-negative individuals or fetomaternal hemorrhage during pregnancy, such as in cases of abortion, trauma, or delivery. The maternal immune system responds in two phases: initial production of IgM antibodies (which cannot cross the placenta) followed by IgG antibodies that can, leading to severe hemolysis in the fetus. Complications range from mild anemia to hemolytic disease of the fetus and newborn (HDFN)[2]. In India, the incidence of Rh-negative pregnancy is 3%-5.7%, affecting 276 per 100,000 live births[2,5]. Without treatment, 50% of HDFN cases result in death or brain damage[6]. Rh disease accounts for 97% of cases, with 3% due to minor antigens like Kell and Duffy[1]. The first pregnancy is rarely affected due to slow antibody production, but sensitization risks increase with subsequent pregnancies[7].

In Rh-negative mothers carrying Rh-positive fetuses, the incompatibility rate is approximately 10%[8]. Advances in modern obstetrics, including timely administration of anti-D immunoglobulin, have reduced the incidence of is immunization by 1.5%[9,10]. However, cases persist, primarily due to a lack of awareness and inadequate screening, particularly in rural areas of developing countries like India[9]. Since complications arising from this isoimmunization can be prevented with prior and timely testing of patients, it is of utmost importance that we screen patients in time.

Materials and Methods

Aim and Objectives

To study maternal and fetal outcomes in Rh-negative pregnancy in terms of antenatal interventions of intrauterine blood transfusions, Gestational age at the time of delivery, birth weight, APGAR score, Stillbirth, Hydrops, neonatal anemia, neonatal jaundice, kernicterus, need for phototherapy or exchange transfusions.

Methodology

This institution-based prospective observational study was conducted over 18 months (August 2021–January 2023) at a tertiary care institute, involving 114 Rh-negative pregnant women. Participants were selected irrespective of age, parity, gestational age, or Rh Anti-D immunoglobulin (Ig) administration in previous or current pregnancies. Women with co-morbidities such as diabetes, preeclampsia, thyroid disorders, and epilepsy were excluded. Informed consent was obtained from all participants. Detailed histories of current and past pregnancies, including abortion, neonatal jaundice, stillbirths, hydrops fetalis, and use of antenatal prophylaxis, were recorded. Participants underwent general and obstetric examinations, routine antenatal investigations, and an indirect Coombs' test. Ultrasonography was performed to assess gestational age, fetal wellbeing, amniotic fluid levels, placental condition, and congenital anomalies. Labor was closely monitored, and outcomes were studied. Cord blood was tested for ABO/Rh typing, hemoglobin levels, serum bilirubin, and

direct Coombs' test. Neonates were examined for their sex and birth weight, anomalies, hydrops fetalis. Rh-positive neonates prompted postpartum immunoprophylaxis for mothers within 72 hours. Neonates were followed for three days for jaundice and anemia, with phototherapy provided for jaundice and exchange transfusion considered for anemia. Maternal outcomes (gravidity, delivery mode) and perinatal outcomes (gestational age, NICU admissions, fetal demise, neonatal death) were evaluated.

Data analysis utilized SPSS version 22.0, with descriptive statistics for continuous variables and frequencies for categorical variables. Associations were assessed using Chi-square and Fisher's exact tests, with significance at $p < 0.05$.

Results and Observations

During the study, 11,533 deliveries occurred, with 171 Rhesus-negative pregnancies, yielding an incidence of 1.48%. Of these, 114 cases met inclusion criteria. Most patients were aged 26–30 years (42.1%; mean age: 26.59 ± 4.4 years). Multigravida cases predominated (74.6%), while 25.4% were primigravida. (Table No. 1)

Table 1: Maternal Characteristics

Characteristics		Frequency	Percentage	
	19-25	44	38.6	Mean (SD)- 26.59± 4.40 Range 19-37
	26-30	48	42.1	
	>30	22	19.3	
Gravida	1	29	25.4	
	2	42	36.8	
	3	33	28.9	
	4	9	7.9	
	5	1	0.9	
Gestational age (weeks)	< 37	17	14.9	Mean (SD)- 38.15± 1.64 Range31.2-41.0
	37-40	84	73.7	
	≥ 40.0	13	11.4	
Mode of Delivery	LSCS	43	37.7	
	Vaginal	69	60.5	
	Forceps	1	0.9	
	Vaccum	1	0.9	
Postpartum Prophylaxis in Previous Pregnancy	Anti D Received	26	30.58	
	Anti D not Received	59	69.41	
Antepartum Prophylaxis in Present Pregnancy	Anti D Received	102	89.5	
	Anti D Not Received	12	10.5	

Most patients (73.7%) delivered at term (37–40 weeks), while 14.9% had preterm deliveries. Unregistered patients (10.5%) lacked antenatal visits and did not receive antenatal immunoprophylaxis, while 61.4% had

5–8 visits and 17.54% patients had 0-4 visits. Antenatal prophylaxis was administered to 102 registered patients between 28–32 weeks. Only 30.58% received Anti-D in previous pregnancies. B-negative was the most common maternal blood group (32.5%), and A-positive was the most frequent paternal blood group (30.7%).

Amongst mothers, majority (32.5%) were had a B negative blood group whereas most fathers (30.7%) fathers were A positive. (Table no. 2)

Table 2: Maternal and Paternal Blood Group Distribution

Blood Group	Mother Rh Negative n (%)	Father Rh Positive n (%)
A	29 (25.4)	35 (30.7)
AB	17 (14.9)	18 (15.8)
B	37 (32.5)	33 (28.9)
O	31 (27.2)	28 (24.6)

Majority (99.12% patients) had negative Indirect Coombs' test. The one patient who had a positive Indirect Coombs' test was unregistered and had a titre of 1:32 at the time of presentation at delivery.

Most patients (60.5%) delivered vaginally whereas 37.7% patients were delivered by caesarean section. 0.9% patients were each delivered by forceps and vacuum delivery. As per Table no. 3, maximum i.e. 32.5% cases were done in view of previous cesarean section followed by Oligohydramnios (16.3%) and meconium-stained amniotic fluid (16.3%)

Table 3: Indication for Cesarean Section

Indication for Caesarean Section	N=43	Percentage
Breech	3	7.0
Contracted Pelvis	3	7.0
Failed Induction	2	4.7
Fetal Distress	4	9.3
Meconium-Stained Liquor	7	16.3
Oligohydramnios	7	16.3
Previous LSCS	14	32.5
PROM	3	7.0
Scar Tenderness	1	2.3
Abruption Placenta	2	4.7

In the study, 18.4% of babies were Rh-negative, while 81.6% were Rh-positive, necessitating postpartum prophylaxis for their mothers. Among the Rh-positive babies, 29.8% were B positive, 24.6% O positive, 17.5% A positive, and 8.8% AB positive. Direct Coombs' test was negative in 93% of babies, with 7% testing positive. Male babies accounted for 55.3% of deliveries, while females were 44.7%. APGAR scores were favorable, with 84.2% scoring above 7 at one minute and 96.5% above 7 at five minutes; however, 0.9% had scores below

3 at both intervals. Most babies (97.3%) were born alive, with one case of intrauterine fetal demise in an unregistered Rh isoimmunized patient. Two neonatal deaths (1.8%) occurred due to prematurity and low birth weight. Healthy babies constituted 65.7% of the cohort, while 44.7% developed neonatal jaundice requiring phototherapy; 22.8% needed nursery admission, and 21.9% required NICU care. Neonatal anemia affected 8.77% of babies, necessitating blood transfusions, and one case required exchange transfusion. Prematurity and low birth weight were additional reasons for NICU admission.

Adverse perinatal outcomes, including fetal demise and neonatal deaths, were significantly associated with unregistered pregnancies ($p<0.003$ and $p<0.002$, respectively). Registration and antenatal care significantly improved neonatal outcomes, with 65.7% of babies in registered cases showing no adverse perinatal outcomes ($p<0.001$). (Table no.4)

Table 4: Association between ANC Registration and Neonatal Outcome

Outcome	Registered (n=102) n (%)	Not Registered (n=12) n (%)	P Value
Healthy	67 (65.7)	-	<0.001*
Nursery	19 (18.6)	7 (58.3)	0.002*
NICU Admission	21 (20.6)	4 (33.3)	0.313
Neonatal Anemia	9 (8.82%)	1 (8.33%)	0.954
Phototherapy	40 (39.2)	11 (91.7)	0.001*
Exchange Transfusion	-	1 (8.3)	0.003*
IUFD	-	1 (8.3)	0.003*
Neonatal Death	1 (1.0)	1 (8.3)	0.002*

In the study, 67% of term babies were healthy compared to 2% of preterm babies ($p<0.001$). Most preterm babies (88.2%) required NICU admission, and 94.1% needed phototherapy ($p<0.001$). Neonatal anemia requiring blood transfusion occurred in 29.41% of preterm and 5.15% of term babies ($p=0.001$). One preterm baby needed an exchange transfusion ($p=0.016$), and two preterm babies (11.8%) died due to prematurity and low birth weight ($p<0.001$). (Table No. 5)

Table 5: Association between Time of Delivery and Neonatal Outcome

Outcome	Preterm (n=17) n (%)	Term (n=97) n (%)	P Value
Healthy	2 (11.8)	65 (67.0)	<0.001*
Nursery	1 (5.9)	25 (25.9)	0.071
NICU Admission	15 (88.2)	10 (10.3)	<0.001*
Phototherapy	16 (94.1)	35 (36.1)	<0.001*
Neonatal Anemia	5 (29.41)	5 (5.15%)	0.001*
Exchange Transfusion	1 (5.9)	-	0.016*

IUFD	-	1 (1.0)	0.674
Neonatal Death	2 (11.8)	-	<0.001*
LBW	16 (94.1)	3 (3.1)	<0.001*

The Antenatal Anti-D immunoglobulin prophylaxis (AADP) was statistically significant in reducing neonatal jaundice (p value= 0.0005) Neonatal jaundice was found in 91.6% neonates whose mother did not receive Anti D prophylaxis. (Table no. 6)

Table 6: Association between Antenatal Anti-D Immunoprophylaxis and Incidence of Neonatal Jaundice

	Jaundice	No Jaundice	
Anti D Received (102)	40 (39.21%)	62 (60.78%)	P value= 0.0005
Anti D Not Received (12)	11 (91.66%)	1 (8.3%)	

Discussion

Red blood cells express millions of antigens of which the ABO group and Rh group of antigens are of utmost importance[11]. The discovery of these groups of antigens has a proven significance in the field of transfusion medicine and obstetrics, especially in concern to Hemolytic Disease of Fetus and Newborn (HDFN). The Rh blood group, is highly antigenic and this can be attributed to polymorphic genes encoding them[12]. In absence of Rh antigen, RBC is found to have an abnormal shape and increased osmotic fragility leading to shorter lifespan of the cell. This eventually leads to hemolysis which is a significant cause of hyperbilirubinemia and Hemolytic disease of newborn[5]. The incidence of Rhesus negative pregnancy in India is around 3-5.7% in India whereas in our study, incidence was found to be 1.48% which was similar to the study done by Yadav et al (1.68%)[4]. Our study revealed maximum number of cases of Rhesus negative pregnancy in age group of 21-30 years (70.19%) followed by more than 30 years (19.29%) and least number of cases in the age group less than 20 years (10.52%). This is consistent with other studies done by Sreelatha et al[5]., Khatun J. et al[8]. and Eleje at al[10]. with maximum number of cases belonging to age group 21-30 years. 36.8% cases in the present study were second gravida which is consistent with other studies done by Eleje at al.[10], and Rajvathi et al[13]. i.e. (38.2% and 39.5% respectively). Highest number of cases (73.7%) cases delivered at term in our study which is consistent with other studies done by Tripathi et al[3]., Yadav et al[4]. and Chintada et al[14]. with incidence of 90.9%, 89.5% and 86% respectively. Most number of cases in our study had B negative blood group (32.5%) which is consistent with studies done by Agarwal et al[1]., Khatun et al[8]. with 48% and 36% cases. 60.5% patients in our study delivered vaginally (which is consistent with other studies done by Agarwal et al[1]., Tripathi et al[3]., Sreelatha et al[5]. with 52.8%, 66%. 56.4% cases respectively. In our study, 37.7% cases were delivered by caesarean section. Incidence of forceps and vacuum delivery in our study (0.9% each) was comparable to study done by Sreelatha et al. with 1.1% and 1.7% cases respectively[5]. Highest number of neonates in our study had B positive blood group (29.8%), followed by O positive blood group in 24.6% cases with similar incidence of 30.62% and 24.49% respectively in study done by Khatun et al[8].. In our study, 58.77% babies were healthy after delivery which is comparable to findings in studies done by Tripathi et al[3]. and Shradha et al[9]. with 58.18% and 58.34% cases respectively. There was one case of isoimmunization in our case with hydrops fetalis in our study (0.9%) which was similar to study done by

Yadav et al[4]. Our study had 1.8% cases of neonatal deaths which is similar to 2% cases as seen in the study by Tripathi et al[3]. Our study had 44.73% cases of neonatal jaundice requiring phototherapy. This is comparable to 58.84% cases of neonatal jaundice in study by Chintada et al[14]. In our study, neonatal anemia was found in 8.77% cases requiring blood transfusion which is similar to 7.3% cases in study by Yadav et al[3]. However, 21.92% cases in our study needed NICU admission which was highest among all the studies. The probable reason for this is high proportion of preterm babies. Maximum number of patients (89.47%) in our study were given antenatal prophylaxis in comparison to all other studies with least number, 25.26% patients in study done by Yadav et al[4]. The probable reason for the same might include ANC registration with frequent antenatal visits at a tertiary care hospital. A total of 93 patients (81.57%) patients who delivered babies with their blood group as Rh positive were given postpartum prophylaxis with Anti D given within 72 hours of delivery since it is freely available by local municipal supply and none of the patients refused the injection. This figure is comparable to studies done by Tripathi et al[3]., Yadav et al[4]. and Chintada et al[14].

Rhesus isoimmunization, a preventable cause of fetal complications, necessitates early blood group and Rh typing in pregnancy. Anti-D prophylaxis, administered antenatally and postnatally, has significantly reduced the incidence of hemolytic disease of the newborn (HDN), though it is not entirely eradicated due to factors like lack of awareness and cost. A study done in 2000s by Joshep, highlighted underutilization of anti-D prophylaxis in India, while Deka et al. found that failure to administer anti-D after medical termination of pregnancy (MTP) accounted for over 50% of Rh D alloimmunization cases. The Federation of Obstetric and Gynaecological Societies of India (FOGSI) recommends documenting the blood group of both partners, administering 100 mcg of anti-D after first-trimester sensitizing events, routine antenatal prophylaxis (300 mcg at 28 weeks), and postnatal prophylaxis if the newborn is Rh-positive. Promoting family planning is crucial, as the risk of isoimmunization rises with increasing parity[2,9].

Conclusion

Rhesus alloimmunization, a significant cause of neonatal morbidity and mortality, has been extensively studied, leading to advancements such as anti-D immunoglobulin, which has reduced perinatal risks. Despite these developments, challenges persist, particularly in developing countries where neonatal morbidity, including hyperbilirubinemia and anemia, places a burden on intensive care units. In a recent study, 21% of affected neonates required NICU care for jaundice, anemia, phototherapy, and blood transfusions, with a perinatal mortality rate of 2.63%. Severe neonatal anemia can impair growth and increase the risk of sepsis.

Contributing factors include the high cost of anti-D immunoglobulin and limited awareness, especially in rural areas with poor access to antenatal care. Preventive measures, such as early antenatal registration, blood grouping, Rh typing, and timely prophylaxis administration, are essential. Emerging treatments like intrauterine transfusion and intravenous immunoglobulin further reduce risks. Family planning services should be encouraged. alongside, it is imperative to ensure Anti-D prophylaxis use after abortions and deliveries which can help curb the incidence of complications of Rhesus alloimmunization.

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