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Original Research Article

Maternal and perinatal outcome in Rh negative mothers

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ABSTRACT

Background: The objective of this study is to find out the incidence and foetomaternal outcome of Rh negative women during pregnancy.
Methods: In the study group, the labor was monitored carefully and the mode of delivery and the outcome of labor was studied in detail. Baby was thoroughly examined for any obvious congenital anomaly, weight, sex and condition was also noted particularly for hydrops. If neonate was Rh positive, then the mother was given postpartum immunoprophylaxis within 24 hours of delivery. The new born were followed for 3 days and were watched for the development of Jaundice. Mothers were advised to attend postnatal clinic for check-up after 6 weeks of delivery.
Results: Blood group distribution of newborn: 37 were Rh positive and 18 were Rh negative. Raised Rh antibody titre was not found in any of the 55 cases. Maximum cases 47 delivered at 38-40 weeks, 2 cases delivered after 40 weeks and 6 patients delivered between 30-38 weeks. Maximum cases 37 delivered normally, 12 required cesarean section and 2 had forceps delivery. The babies who developed NNHB were managed either by sunrays exposure only or by phototherapy. The babies who had anemia immediately after birth were carefully monitored and considered for exchange transfusion.
Conclusions: Tremendous advances in the medical services and technology during the last few decades have revolutionized the treatment of Rh disease. Various studies have been conducted and several are going on the in this field to achieve zero incidence of this disease.

Keywords: Hydrops foetalis, Isoimmunization, Immuunoprophylaxis

INTRODUCTION

With the discovery of the Rh factor by Landsteiner and Weiner 1941, the recognition of its clinical importance and the practical application of this knowledge in therapy constitute one of the great advances of modern research where theory, observation and practice, in the space of a very few years, pieced themselves together to form a coherent picture.

Rhesus (Rh) incompatibility refers to the discordant pairing of maternal and fetal Rh type. It is associated with the development of maternal Rh sensitization and hemolytic disease of the neonate (HDN). An individual can be classified as Rh-positive if their erythrocytes express the Rh D antigen; otherwise, an individual is Rh-negative if they do not.

This phenomenon becomes clinically significant if a mother is Rh-negative becomes sensitized to the D antigen and subsequently, produces anti-D antibodies (i.e., alloimmunization) that can bind to and potentially lead to the destruction of Rh-positive erythrocytes. This is of particular concern if a Rh-negative mother is

carrying a Rh-positive fetus, which can result in consequences along the spectrum of HDN ranging from self-limited hemolytic anemia to severe hydrops fetalis.[1]

The incidence of the disease however is now on decline worldwide from 1.3-1.7% in 1980s to 0.17% in 1990s. The proportion of people who are Rh negative also varies according to race. For example, in China and Japan it is most uncommon, and it might be suggested that the elder civilization of the Chinese has, by a process of natural selection, bred out an undesirable gene. In India previously, it was thought that it is present only in Parsis, but afterwards it was detected in others also.[2]

One of most dreadful implication of ABO incompatibility or Rh incompatible pregnancy is Erythroblastosis foetalis. It is a treacherous hemolytic disease of foetuses and new born which affect less than 1% of all pregnancies, the excessively rapid destruction of erythrocyte which is characteristic of this disease, produces profound anasarca.

Red cell destruction by hemolysis is caused by specific antibodies entering the foetal circulation during pregnancy. These antibodies are produced by mother in response to antigenic stimulation of foetal red cell entering the maternal circulation by the way of placenta. These erythrocytes possess antigenic factor not present normally in the mother and therefore are capable of initiating antibody production.[1,2]

The incidence of Rh incompatibility in Rh negative women carrying a Rh-positive foetus is about 10% of all Rh-negative pregnancies. Sensitization however occurs only in about 5% of these cases giving an incidence of 6-7/1000 of all the pregnancies and 1-15 Rh negative pregnancies.

First pregnancy is rarely affected, and as a rule the degree of sensitization increase with subsequent pregnancies. Once sensitization has occurred, the clinical and laboratory approach to evaluate and treat the disorder is difficult.[3,4]

Various studies have been conducted and several are going on to achieve zero incidence of this disease. With the introduction of techniques of Amniocentesis and spectrophotometric analysis of Amniotic fluid, the pregnancy can well be followed up and timely terminated to have best perinatal outcome. The early detection of the disease with raised antibody titre is of utmost importance.

The newer treatment modalities like intra uterine transfusion and Intra venous immunoglobin helps further to reduce the overall mortality and morbidity. When the above techniques are combined with antepartum and postpartum immunoprophylaxis there is a further decline in the incidence foetal complications and perinatal mortality.[5,6]

METHODS

The present study was carried out in 55 patients who were attending antenatal clinic and were admitted in obstetric unit of Department of Obstetrics and Gynaecology in J. K. Hospital and L. N. Medical College, Bhopal. They were investigated from March 2016 to February 2018.

On admission, history of the patients was taken regarding her age, address and occupation, Menstrual history and detailed obstetrical history was taken regarding gravidity, parity, abortion, D&C following abortion and number of living term and preterm issues. Any history of neonatal Jaundice in previous children and if present type of treatment if required and outcome of such a neonate: number of still births and history of hydrops foetalis in previous pregnancies. Inquiry is made regarding any history of bleeding per vaginumin the present pregnancy which included threatened abortion and APH. Any history of blood transfusion was taken into consideration. It was a randomized control prospective type of study.

Inclusion criteria

- Women between 30 to 36 weeks gestational age based on menstrual dates or earliest USG.
- Singleton pregnancy.
- Case with intact membranes.
- Presence of live foetus.

Exclusion criteria

- Any maternal (e.g. significant APH) or foetal (non-reassuring heart rate pattern) condition necessitating immediate delivery.
- Severed anemia.
- Multiple gestation (twins, triples etc.)
- Hydramnios.
- Premature rupture of membranes.
- Failure to give consent.

Complete general examination of the patients was done which included degree of anemia, pulse, BP, and pedal edema. Systemic examination was done to exclude other medical disorders viz. respiratory disease, CVS disorders, chronic hypertension, chronic nephritis and any other chronic illness.

Obstetrical examination Complete examination including fundal height, lie and position of the foetus, presentation, AFI assessment was done and FHS was noted. Internal examination was done in patients who presented with labor pains.

Investigation Routine examination of the blood which included blood grouping and typing, Hb%, total and differential blood count, platelets, blood sugar, and urine for the presence of albumin was done by standard

method. Husband blood grouping and typing of all the Rh-negative patients was done.

Rh antibody titre of the patients was done at first visit and were repeated accordingly at 28 weeks and 32 weeks. Patients whose husbands were Rh positive and having negative antibody titre were offered antepartum Rh lG immunoprophylaxis. Ultrasonography was done to know the gestational age, foetal wellbeing, amount of liquor, placental grading, maturation and to rule out any congenital malformations. The USG was repeated at regular intervals as per need.

The labor was monitored carefully, and the mode of delivery and the outcome of labor was studied in detail. Inj. methergine was not given after delivery and the placenta was examined for hyperplacentosis. Cord blood was collected and was sent for ABO/Rh typing, Hb% serum bilirubin (total, direct and indirect) and direct Coomb's test to know the neonatal status. Baby was thoroughly examined for any obvious congenital anomaly and weight, sex and condition was noted particularly for hydrops foetalis. If neonate was Rh positive, then the mother was given postpartum immunoprophylaxis within 24 hours of delivery.

The new born were followed for 3 days and were watched for the development of Jaundice. The babies who development NNHB were managed either by sunrays exposure only or by phototherapy. The babies who had anemia immediately after birth carefully monitored and considered for exchange transfusion. They were advised to attend postnatal clinic for check-up after 6 weeks of delivery.

Statistical analysis

Data was analyzed using SPSS 20 statistical package. A descriptive analysis was done on all variables to obtain a frequency distribution. The mean±SD and ranges were calculated for quantitative variables. Continuous variables were compared by the Student's t-test. Proportions were analyzed with the chi-square test. A P value of 0.05 or less was considered statistically significant.

RESULTS

Raised Rh antibody titre was not found in any of the 55 cases. Of the total 55 cases, maximum cases 50 delivered at 37-40 weeks, 1cases delivered after 40 weeks and 4 patients delivered between 30-37 weeks. Maximum cases [41] delivered normally, 12 required caesarean section and 2 had forceps delivery.

The Table 1 reveals that there was no stillbirth or ENND due to sensitization. There 1 ENND due to other causes. 14 new-borns had anaemia (mild to severe) and 7 had NNHB (Neonatal hyperbilirubemia) which was mild to severe. None developed hydrops.

Table 1: Overall foetal outcome.

	No. of patients	Percentage
Premature delivery	4	8
Mature delivery	50	92
Post mature delivery	1	2
SB due to sensitizers	-	-
SB due to other causes	1	2
Early neonatal delivery due to Rh haemolytic disease	-	-
ENND (Early Neonatal Death) due to other causes	1	2
Neonatal anaemia	14	25
Neonatal jaundice	7	12.72
Hydrops foetalis	-	-

The Table 2 shows that maximum babies had Hb% between 14-16 gm% (40%), 35% had Hb% between 16.1-18% gm%. Only 2 babies had severe anemia and 12 (21%) had Hb% between 10-14 gm%.

Table 2: Distribution according to Hb% level in new born Rh negative.

Hb%	No. of patients	Percentage
<10	2	4
10-14	12	21
14-16	22	40
16-18	19	35

The Table 3 shows that serum Bilirubin in 48 babies was <2.8 mg%; 1 had level between 2.8-4.0mg% and 6 babies had level >4.0 mg%.

Table 3: Distribution of cases according to serum bilirubin level.

Serum Bilirubin 109/128 in gm% of Bilirubin 109/128 (indirect)	No. of patients	%
<2.8	48	87
2.8-4.0	1	2
>4.0	6	11

The Table 4 shows that 8 cases were associated with PIH/preeclampsia and only 1 was associated with polyhydramnios. 3 cases were associated with abruption placentae.

Table 4: Maternal outcome in Rh negative patients.

Associating factors	No. of patients	Percentage
PIH/preeclampsia	8	15
Abruption placentae	3	5
Oligohydramnios	2	4
Polyhydramnios	1	2

Majority of the patients delivered a term baby by vaginal route 37 (66%), 2 patients were delivered by forceps

(4%) and 12 delivered by cesarean section 22 %. Only (8%) patients had preterm delivery.

Overall foetal outcome

A. Maturity: 50 were full term newborn, 4 preterm and only 1 was post term baby.
B. Anaemia: The incidence of anaemia was 25% in newborn, of which 2 had severe anaemia and 12 had mild to moderate anemia.
C. Neonatal hyperbilirubinemia: The incidence of NNHB was 13%, 7 newborns had NNHB of which 1 had mild and 6 had moderate to severe NNHB. Out of 7 NNHB 6 were born full term and 1 was pre-term delivery.

Overall maternal outcome

15 cases had one or more high risk factors.

A. 8 Rh negative mothers had preeclampsia /PIH, 3 had abruption placentae, 2 had oligohydramnios and 1 had polyhydramnios.
B. 4 had preterm delivery.
C. 1 had still birth.
D. 1 baby had NNHB whose mother had oligohydramnios.
E. There was no incidence of Isoimmunisation found in present study.

Birth weight of newborn was average between 2-3 kg: Overall perinatal death in babies born to Rh negative mothers (55) were 2 out of which 1 was SB. None of the patients received antepartum immunoprophylaxis. Of the 37 patients who delivered Rh positive foetuses, 35 received postpartum Anti-D Rh IgG immunoprophylaxis.

DISCUSSION

Immunoprophylaxis via Rh Ig is of value when alloimmunization has not yet occurred. If a Rh-negative mother has been found to have positive anti-D antibody titers, then Rh Ig treatment will not be effective, and those mothers should not be given Rh Ig. Accordingly, American College of Obstetricians and Gynecologists advises routine antibody testing before giving Rh Ig.

Even with the availability of Rh Ig for the management of potential Rh incompatibility, the risks of alloimmunization have not been completely eliminated. Contributing factors include inappropriate Rh Ig administration (i.e. dosing, timeline according to recommendations) and occult fetomaternal bleeding that occurs before the advised Rh Ig dosing at 28 weeks. Often, the potential source of bleeding cannot be determined.

Most of the discussion of the antibodies involved have been non-specific thus far; however, it is important to make some distinction between the different types of antibodies. If a Rh-negative mother is antibody positive for IgG, this is of clinical concern because IgG antibodies can cross the placenta and cause HDN. However, it is possible that an antibody screen can be positive for IgM antibodies (i.e. Lewis antibodies); however, these are not of clinical consequence since they do not cross the placenta.[1]

Freda VJ did work on prevention of Rh isoimmunization, it was a progress report of the clinical trial in mothers. Many workers have shown conclusively that passive antibody is capable of specific immunosuppression of the active immunity that follows injection of an antigen. Our specific hope that the method might work for Rh was supported by the implications of Levine's observations and by actual experimental data of Stern et al, that circulating anti-A and anti-B antibodies actually do prevent Rh-negative mothers from being sensitized to the antigen from the baby.[2]

Levine P also published their study on serological factors as possible causes in spontaneous abortions. Shortly after the pathogenesis of erythroblastosis fetalis was established, the writer had an opportunity to study the bloods of women having history of abortions and stillbirths not attributable to erythroblastosis fetalis. However, a difference was observed in the blood group of the mother on the one hand and of the father and of the fetus on the other, which could be interpreted as isoimmunition by the blood factors A and B. In these instances, the mother's blood was lacking the blood factors A and B, one of which was present in the father and in the affected fetus. This sort of mating is defined as incompatible in contrast to those compatible matings in which the blood factors of the father and of the mother either are identical or in which the mother carries the dominant blood factor.[3]

Izetbegovic S in a similar study, studied occurrence of ABO and Rh D incompatibility with Rh negative mothers These antibodies are directed against antigens of father's origin, which are present in the fetal/ children's erythrocytes and that the mother's immune system recognizes them as foreign antigens. Most of immune antibodies appear in mothers with O Rh D: negative blood type. The emergence of immune antibodies in the Rh D negative mothers was 1%, the appearance of ABO incompatibilities amounted to 2.3% of present sample. In order to reduce the occurrence of alloimmunization of the mother to erythrocyte antigens of the newborn that can lead to major complications in subsequent pregnancies of Rh D: negative mothers and HDN constant monitoring in order to prevent them is necessary. Prevention is essential because once immunized mother will remain immunized for life.[4]

Bujandrić N, Milanović MK et al studied the importance of immunohematology testing in the neonatal period. In order to diagnose hemolytic disease of the newborn it is necessary to determine ABO/ Rh blood group, direct

antiglobulin test and indirect antiglobulin test in newborns as well as ABO/ Rh and indirect antiglobulin test in their mothers due to a possible incompatibility between the blood types of the mother and her baby. The study was aimed at reviewing and analyzing the results of screening of the newborns and pregnant women on the territory of South Backa. Testing neonates and pregnant women contributes to the detection of blood type incompatibility between the mother and her child; it provides an opportunity for clinicians to implement the adequate prevention of Rh D alloimmunization as well as to make timely diagnosis and to introduce treatment of hemolytic disease in newborns. Taylor JF et al in similar studies found Sensitization of Rh-negative daughters by their Rh-positive mothers.[5,6]

Wiener AS. Worked on a new test (blocking test) for Rh sensitization. In Rhesus haemolytic disease sensitization of Rh-negative individuals against the Rh factor can often be detected by in vitro tests for anti-Rh agglutinins in the individual's plasma. However, it was soon found that there are many Rh-negative patients who are strongly sensitized to the Rh factor, as proved by the occurrence of an intragroup hemolytic transfusion reaction or a baby with erythroblastosis (hemolytic disease of the fetus and newborn), yet the plasma does not contain demonstrable anti-Rh agglutinins. The purpose of this paper is to describe a new in vitro test, the "blocking test," with the aid of which Rh sensitization can be detected in many of these problem case.[7]

In almost similar studies Owen RD, Wood H et al found evidence for actively acquired tolerance to Rh antigens. Clarke CA et al did work on prevention of Rh-haemolytic disease and Renkonen KO, Timonen S et al studied factors influencing the immunization of Rh-negative mothers.[8-10]

The risk assessment study for hemolytic disease of the fetus and newborn in a University Hospital in Turkey was done by Altuntas N, YenicesuIet al. The aim of the study was to provide data on the frequency and nature of maternal RBC alloimmunization in pregnant women in a tertiary care hospital. In this study, the authors retrospectively evaluated the indirect antiglobulin test results of Rh-negative pregnant women performed in present Blood Bank between 2006 and 2012. Indirect antiglobulin test positive women also underwent confirmatory antibody screening and identification. During the study period, 4840 women admitted to antenatal clinics. With regards to the major blood group systems (ABO and Rh), the most common phenotype was O positive (38.67%). There were 4097 D-antigen-positive women (84.65%) and 743 women with D-antigen-negative phenotype (15.35%). The prevalence of alloimmunization was found to be 8.74% in D-antigen negative group. However, large-scale studies on pregnant women need to be done in order to collect sufficient evidence to formulate guidelines and to define indications for alloantibody screening and identification.[11]

Alvey JP in their study on Rh Incompatibility, which was an investigation in 200 cases, found that spectrophotometric analysis of a single specimen of liquor amnii, preferably taken at 32 weeks, affords a means of accurately determining the extent of the hemolytic process, especially when regard is given to both the type of curve produced and to a quantitative assessment of bilirubin in the liquor. By this method, it is possible to segregate all cases of Rh isoimmunization into three groups, designated A, B, and C. It is suggested that induction of labor is unnecessary in Group A (26.5 per cent of cases), that induction of labor at 38 weeks suffices in Group B (41 per cent of cases), and that, between 34 and 36 weeks, it is indicated in Group C (32.5 per cent of cases).5. The method of amniocentesis has been shown to be free from any immediate risk to mother or to infant.[12]

In a study regarding prevention of Rh alloimmunization. Fung Kee Fung K et al, they provided guidelines on use of anti-D prophylaxis to optimize prevention of rhesus (Rh) alloimmunization. Decreased incidence of Rh alloimmunization and minimized practice variation with regards to immunoprophylaxis strategies. Anti-D Ig 300 microg IM or IV should be given within 72 hours of delivery to a postpartum non-sensitized Rh-negative woman delivering a Rh-positive infant. These guidelines have been reviewed by the Maternal-Fetal Medicine Committee and the Genetics Committee, with input from the Rh Program of Nova Scotia. Final approval has been given by the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.[13]

Kristinsdottir T et al worked on positive Coomb's test in newborns. They made a summary of cases diagnosed in the Blood Bank in the years 2005 to 2012. Hemolytic disease of the fetus and newborn (HDFN) is caused by the destruction of fetal red blood cells due to red cell antibodies produced by the mother. HDFN can cause fetal hydrops during pregnancy or neonatal jaundice after birth. Direct Antiglobulin Test (DAT) detects antibodies bound to red cells and is a valuable test aiding in the diagnosis of HDFN. ABO blood group mismatch between mother and child was the most common cause for a positive DAT in neonates in Iceland in the years 2005-2012. Almost half of the neonates required treatment but usually phototherapy was sufficient. Rarely, blood transfusion or exchange transfusion was necessary in severe cases of ABO blood group mismatch or non-A/B red cell alloantibodies.[14]

CONCLUSION

Tremendous advances in the medical services and technology during the last few decades have revolutionized the treatment of Rh disease. Various studies have been conducted and several are going on the in this field to achieve zero incidence of this disease. With the introduction of techniques of Amniocentesis and spectrophotometric analysis of Amniotic fluid, the pregnancy can well be followed up and timely terminated

to have best perinatal outcome. The early detection of the disease with raised antibody titre is of utmost importance.

The newer treatment modalities like intra uterine transfusion and Intra venous immunoglobin helps further to reduce the overall mortality and morbidity. Further it is expected that the above techniques combined with antepartum and postpartum immunoprophylaxis a further decline in the incidence of Rh negative and so the Perinatal mortality can be lowered down.

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