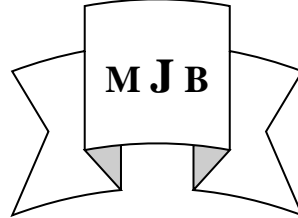


Factors Affecting Rh Isoimmunization and Suggested Protective Measures

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Abstract

Background: Hemolytic disease of newborn due Rh incompatibility is an important cause of hemolytic anemia and jaundice in newborn.

Objectives: To study the prevalence of Rh isoimmunization in our society and to define its risk factors and efficacy of protective measures.

Patients and methods: A prospective study was conducted on 120 Rh positive neonates whom their mothers are Rh negative delivered in AL-Zahra teaching Hospital in An Najaf city during the period from the first of May; 2010 till 31st of July; 2010. A full history was taken from their close family members. Thorough clinical examination and investigations were done .

Results: Seventy six of study group were males (63.3%) and 44 were females (36.7%), with male to female ratio 1.7:1 and full term were 109(90.8%) and preterm were 11(9.2%).

Development of jaundice due to Rh isoimmunization has significant association with the absence of maternal knowledge of her blood group and Rh and her husband blood group and Rh , increase maternal parity, and Siblings history of previous hospital admission due to neonatal indirect hyperbilirubinemia while previous blood transfusion to the mother didn't have that association.

Regular human anti-D immune globulin administration after each delivery of Rh positive neonate and abortion and ABO incompatibility associated with decreased risk of development of jaundice due to Rh isoimmunization.

Conclusion: Poor antenatal care regarding Rh negative pregnant women is still a major problem in our society and it's a significant risk factor for Rh isoimmunization , regular administration of human anti-D globulin is a protective measure.

العوامل المؤثرة على حدوث اليرقان في المواليد الحديثة بسبب اختلاف العامل الرئيسي بين الام ووليدها والوسائل المقترحة للحماية منه

الخلاصة

المقدمة: حالة تحلل الدم بسبب اختلاف العامل الرئيسي بين الطفل حديث الولادة وأمه هي حالة مرضية شائعة وهي سبب مهم لفقر الدم و لليرقان الولادي ومضاعفاته .

أهداف البحث: لأخذ فكرة عن هذه الحالة المرضية ومراجعة عوامل الخطورة ووسائل الوقاية من خلال الممارسة العملية اليومية .
الأدوات والوسائل: أجريت دراسة بحثية مستقبلية على مئة و عشرين طفلا يعانون من اختلاف عامل الرئيسي مع إلام تمت ولادتهم في صالة ولادة مستشفى الزهراء (ع) التعليمي للولادة والأطفال في محافظة النجف الأشرف خلال الفترة من الأول من شهر أيار وحتى الحادي والثلاثون من شهر تموز لعام ٢٠١٠، وتم أخذ المعلومات التاريخية من قبل أهل المرضى مع إجراء الفحص السريري والتحليل المختبرية اللازمة، واعتمادا على ما تقدم ذكره تم تقسيمهم إلى مجموعتين :

المجموعة الأولى تضم ٢٨ طفل الذين حدث فيهم اليرقان الولادي نتيجة تكسر الدم بسبب اختلاف العامل الرئيسي بين الطفل وأمه(١٩) طفل احتاجوا علاج ضوئي فقط و ٩ أطفال احتاجوا علاج ضوئي مع عمليات تبديل دم).

المجموعة الثانية تضم ٩٢ طفل لم يحدث اليرقان الولادي فيهم أو حدث لأسباب أخرى غير تكسر الدم بسبب اختلاف العامل الريسي بين الطفل وأمه.

النتائج: لقد وجد أن عدد الذكور ٧٦ طفلاً (٦٣,٣%) و عدد الإناث ٤٤ طفلاً (٣٦,٧%) وان عدد الاطفال مكتملين النمو ١٠٩ (٩٠,٨%) وعدد الاطفال الخديجين ١١ (٩,٢%).

وان حدوث اليرقان الولادي بسبب اختلاف العامل الريسي لديه ارتباط وثيق مع غياب معرفة إلام بزمرة الدم والعامل الريسي لديها ولدى زوجها ، زيادة حالات الولادة والإسقاط السابقة لدى إلام، وجود حالات يرقان ولادي سابقة والتي استدعت الدخول الى المستشفى لغرض العلاج لدى أخوة أو أخوات الأطفال المشمولين في هذه الدراسة، بينما عمليات نقل الدم السابقة لدى الأم ليس لديها ذلك الارتباط الوثيق.

إعطاء مضادات D إلى الأم خلال ٧٢ ساعة بعد كل ولادة وإسقاط، وعدم تطابق زمر الدم بين الطفل وأمه ترتبط مع انخفاض خطورة حدوث تكسر الدم بسبب اختلاف العامل الريسي.

الاستنتاج: انخفاض مستوى الرعاية الطبية للمرأة الحامل ذات العامل الريسي السالب وجنينها ما يزال مشكلة حقيقية في مجتمعنا ويعتبر عامل خطورة مهم لحدوث تكسر الدم بسبب اختلاف العامل الريسي، إعطاء مضادات D إلى الأم خلال ٧٢ ساعة بعد كل ولادة وإسقاط يعتبر وسيلة وقاية فعالة.

التوصيات: تحسين مستوى الرعاية الطبية للمرأة الحامل ذات العامل الريسي السالب ، والتوفير المستمر واعتماد نظام الجرعتين لمضادات D، وإدخال الوسائل المتقدمة لعلاج تكسر الدم بسبب اختلاف العامل الريسي.

Introduction

Hemolytic Disease Of The Newborn Due To Rh Incompatibility [Hdn-Rh]

Definition: [2]

Hemolytic disease of newborn is isoimmune hemolytic disease of newborn caused by the transplacental passage of maternal antibody active against RBC antigens of the infant and is characterized by an increased rate of RBC destruction. It is an important cause of anemia and jaundice and morbidity and mortality in newborn infants despite the development of a method of preventing maternal isoimmunization by Rh antigens.

Genetics: [1]

Individuals who are homozygous dominant (DD) or heterozygous (Dd) are Rh+. Those who are homozygous recessive (dd) are Rh- (i.e., they do not have the key Rh antigens).

Pathogenesis:

The Rh antigenic determinants are genetically transmitted from each parent, determine the Rh type, and direct the production of a number of blood group factors (C, c, D, d, E, and e), each factor can elicit a specific antibody response under suitable

conditions; 90% are due to D antigen and the remainder to C or E antigen [2].

Rh incompatibility can occur by 2 main mechanisms; The most common type occurs when an Rh-negative pregnant mother is exposed to Rh-positive fetal red blood cells secondary to fetomaternal hemorrhage during the course of pregnancy ; (usually more than 1 mL) , from spontaneous or induced abortion, trauma, invasive obstetric procedures, or normal delivery. Rh incompatibility can also occur when an Rh-negative female receives an Rh-positive blood transfusion [1,2].

Once sensitization has taken place, considerably smaller doses of antigen can stimulate an increase in antibody titer. Initially, a rise in IgM antibody occurs, which is later replaced by IgG antibody; the latter readily crosses the placenta and causes hemolytic manifestation, hemolytic disease rarely occurs during a first pregnancy because transfusion of Rh-positive fetal blood into an Rh-negative mother occurs near the time of delivery, too late for the mother to become sensitized and transmit antibody to her

infant before delivery, the fact that 55% of Rh-positive fathers are heterozygous (D/d) and may have Rh-negative offspring; [4]

And that fetal-to-maternal transfusion occurs in only 50% of pregnancies reduces the chance of sensitization. The overall incidence of isoimmunization of Rh-negative mothers at risk is low, with antibody to D detected in less than 10% of those studied, even after five or more pregnancies; only about 5% ever have babies with hemolytic disease, when the mother and fetus are also incompatible with respect to group A or B, the mother is partially protected against sensitization by the rapid removal of Rh-positive cells from her circulation by her preexisting anti-A or anti-B, which are IgM antibodies and do not cross the placenta[2].

Once a mother has been sensitized, her infant is likely to have hemolytic disease, the severity of Rh illness worsens with successive pregnancies, possibility that the first affected infant after sensitization may represent the end of the mother's childbearing potential for Rh-positive infants argues urgently for the prevention of sensitization, the injection of anti-D gamma globulin (RhoGAM) into the mother immediately after the delivery of each Rh-positive infant has been a successful strategy to reduce Rh hemolytic disease[2].

Significant sensitization in Rh negative mother can cause fetal anemia, heart failure, elevated venous pressure, portal vein obstruction, and hypoalbuminemia result in hydrops fetalis [clinical picture of excessive abnormal fluid in two or more fetal compartments (skin, pleura, pericardium, placenta, peritoneum, amniotic fluid)][2,6].

Clinical manifestation:

The severity of the disease may range from only laboratory evidence of

mild hemolysis (15% of cases) to severe anemia with compensatory hyperplasia of erythropoietic tissue leading to massive enlargement of the liver and spleen.

Diagnosis: [2]

Definitive diagnosis of erythroblastosis fetalis requires demonstration of blood group incompatibility and corresponding antibody bound to the infant's RBCs.

Postnatal Diagnosis:[2]

Immediately after the birth of any infant to an Rh-negative woman, blood from the umbilical cord or from the infant should be examined for ABO blood group, Rh type, Hct and hemoglobin, and reaction of the direct Coombs test. If the Coombs test is positive, a baseline serum bilirubin level should be measured, and a commercially available RBC panel should be used to identify RBC antibodies present in the mother's serum, both tests being performed not only to establish the diagnosis but also to ensure selection of the most compatible blood for exchange transfusion should it be necessary. The direct Coombs test is usually strongly positive in clinically affected infants and may remain so for a few days up to several months.

Treatment of a Liveborn Infant:

- 1- Stabilization of the baby
- 2- phototherapy
- 3- blood exchange transfusion
- 4- iv immunoglobulin

Prevention of Rh Sensitization:

Rh IgG, first released for general use in 1968, has been remarkably successful in the prevention of Rh incompatibility. The exact mechanism by which passive administration of Rh IgG prevents Rh immunization is unknown. The most likely hypothesis is that the Rh immune globulin coats the surface of fetal RBCs containing Rh antigens. These exogenous antibody-antigen complexes cross the

placenta before they can stimulate the maternal endogenous immune system B cells to produce IgG antibodies[39].

The risk of initial sensitization of Rh-negative mothers has been reduced to less than 1% by the intramuscular injection of 300 µg of human anti-D globulin (1 mL of RhoGAM) within 72 hr of delivery of an Rh-positive infant, ectopic pregnancy, abdominal trauma in pregnancy, amniocentesis, chorionic villus biopsy, or abortion. This quantity is sufficient to eliminate ≈ 10 mL of potentially antigenic fetal cells from the maternal circulation. Large fetal-to-maternal transfers of blood may require proportionately more RhoGAM. RhoGAM administered at 28–32 wk and again at birth (40 wk) is more effective than a single dose[2].

The RhD immunization-fetomaternal bleeding during last trimester would be largely eliminated by giving antiD-immunoglobulin antenatally in one of two possible doses; schedule: two doses of 500 IU given between 28 and 30 weeks[40].

Patients and Methods

A prospective study of 120 neonates delivered in AL-Zahra Teaching Hospital for Maternity and Children in Al-Najaf Al-Ashraf Governorate during the period from the first of May ; 2010 till 31st of July ;2010.

1223 pregnant women who admitted to labor room for delivery were examined for Rh typing.

One hundred fifty nine women were Rh negative,(28 of these women their delivered newborn infants were Rh negative so they were excluded) , the others 131 of these women their delivered newborn infants were Rh positive,11 of them were lost for follow up so the remaining 120 Rh positive neonates of Rh negative mothers were included in study group.

Data were collected regarding blood group and Rh of baby and mother, parity, history of abortion, anti -D immunoglobulin administration, family history of neonatal jaundice and type of treatment.

All the babies were examined thoroughly for the presence of jaundice, pallor and organomegally and any sign of kernicterus, in addition to determination of maturity and gestational age.

If neonates have any clinical finding suggestive hemolytic disease of newborn cord blood TSB more than 3mg/dL and/or cord blood Hb less than 14 gm/dl for full term and 12 gm/dl for preterm patients admitted and full investigations and treatment started.

If clinical examination completely normal and cord TSB 1-3mg/dl and cord Hb 14 gm/dl or more in full term and 12 gm/dl for preterm than neonate discharge and inform the family to bring him/her after 2-3 days for follow up or any time if he/her develop jaundice(with in first 10 days post-delivery).

Ninety two neonate, didn't develop jaundice or developed jaundice due to other causes.

The trace (28 neonate) their jaundice considered due to Rh incompatibility as show in figure (1).

Depending on clinical picture and laboratory data we decided the type of treatment (phototherapy alone or phototherapy with exchange transfusion).

Statistical analyses arranged in numbers, percentage and find relationships between different groups and calculate P value.

Investigations done for neonates:

- 1) Blood group and Rh typing(Slide technique
- 2) TSB
- 3) CBP and retics .
- 4) Direct coomb test.

Investigations done for mothers:

- 1) Blood group and Rh typing (Slide technique).
- 2) Rh antibody titer: using NISS IAT procedure if agglutination occur then titration done.

1);{ all of them developed jaundice within first 24 hours of life ,19 patients needed phototherapy alone and 9 patients needed phototherapy and blood exchange transfusions one of them developed hydrops fetalis and died }, and 92 didn't develop jaundice or developed jaundice that considered due to other causes than Rh incompatibility (group 2) as shown in figure(1).

Results

Study group were 120 neonates, 28 developed jaundice due to Rh incompatibility and required hospitalization and treatment (group

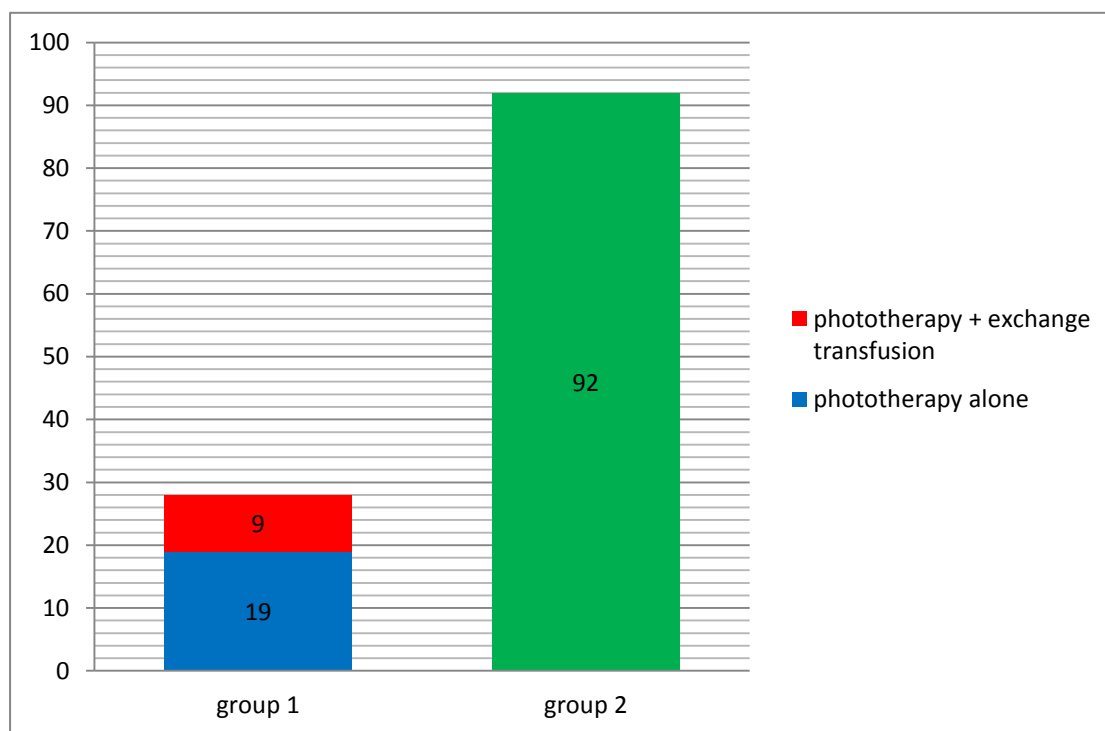


Figure 1 Show the distribution of our study group according to type

1. Gender and gestational age:

Seventy six of study group were males (63.3%) and 44 were females (36.7%),with male to female ratio

1.7:1 and full term were 109(90.8%) and preterm were 11(9.2%) as shown in figure (2) and (3) respectively.

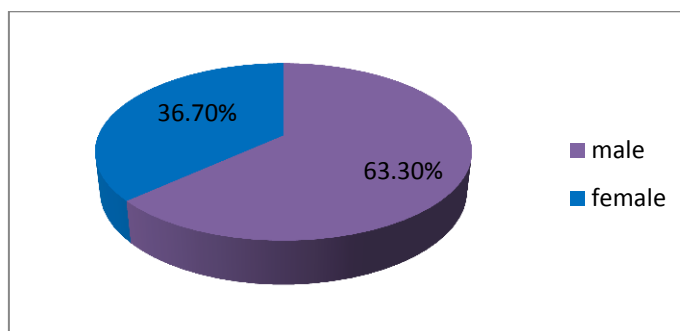


Figure 2 Distribution of patients according to gender

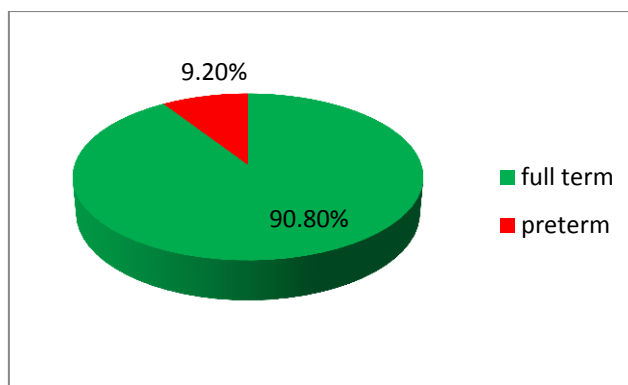


Figure 3 Distribution of patients according to maturity

2. Maternal knowledge of her blood group and Rh and her husband blood group and Rh:

we found that only 8 neonate(28.6%) in group(1) and 61 neonates(66.3%) in group(2) their mothers already know her blood group

and Rh and her husband blood group and Rh while

20 neonates (71.4%) in group (1) and 31 neonates(33.7%) in group (2) their mothers didn't know her blood group and Rh and her husband blood group and Rh. P value < 0.05 (significant) as shown in table (1).

Table 1 Relationship of knowledge of blood group Rh by mothers

Blood groups & Rh of mother and father	Group(1)		Group (2)		Total No.
	No.	%	No.	%	
Mothers already know	8	28.6	61	66.3	69
Mothers didn't know	20	71.4	31	33.7	51
Total No.	28		92		120

value < 0.05 (significant).

3. human anti-D globulin administration:

Only 6 neonates(21.4%) in group (1) and 58 neonates (63.1%) in group (2) their mothers had history of regular administration of human anti-D

immunoglobulin every delivery of Rh positive baby and abortion if present while 22 neonates(78.6%) in group (1) and 34 neonates (36.9%) in group (2) didn't have that history. P value < 0.05 significant as show in table (2).

Table 2 Show the distribution of maternal history of regular administration of human anti-D immunoglobulin following every delivery of Rh positive baby and abortion if present in group (1) and group (2).

maternal history of regular administration of human anti-D globulin	Group (1)		Group (2)		Total No.
	No.	%	No.	%	
Not present	22	78.6	34	36.9	56
Present	6	21.4	58	63.1	64
Total No.	28		92		120

P value < 0.05 (significant).

4. The Parity and jaundice management:

In group (1): no patients their mothers were primigravida and 19 patients their mothers were multigravida (2-5 delivery) 16 of them required phototherapy alone and 3 required phototherapy + exchange

transfusions and 9 patients their mothers were grand multigravida (> 5 delivery) 3 of them required phototherapy alone and 6 required phototherapy + exchange transfusion.

P value < 0.05 significant as show in table (3).

Table 3 The relationship of line of treatment according to parity

Line of treatment	Primigravida	Multi gravid (2-5 delivery)		Grand multi gravida (>5 delivery)		Total
		No.	%	No.	%	
Phototherapy alone	0	16	84.2	3	33.3	19
Phototherapy +Exchange transfusion	0	3	15.8	6	66.7	9
Total	0	19		9		28

P value < 0.05 (significant).

5. Siblings history of previous hospital admition due to neonatal jaundice :

Nine neonates (32.2%) in group (1) { 3 required phototherapy alone , 6 in whom required phototherapy + exchange transfusion } and 7neonates

(7.6%) in group (2) had Siblings history of previous hospital admission due to neonatal jaundice and 19 neonates(67.8%) in group (1) and 85

neonates(92.4%) in group (2) didn't have that history as shown in table (4) and table (5) respectively.

Table 4 Show the relationship of siblings history of previous hospital admission due to neonatal jaundice in group(1) and group(2).

Previous history	Group (1)		Group (2)		Total No.
	No.	%	No.	%	
Not present	19	67.8	85	92.4	104
Present	9	32.2	7	7.6	16
Total No.	28		92		120

P value < 0.05 (significant).

Table 5 Show the relationship of siblings history of previous hospital admission due to neonatal jaundice in phototherapy alone and phototherapy +exchange transfusion groups.

Previous history	Phototherapy alone group		Phototherapy+ Exchange transfusion group		Total No.
	No.	%	No.	%	
Not present	16	84.2	3	33.3	19
Present	3	15.8	6	66.7	9
Total No.	19		9		28

P value < 0.05 (significant).

6. History of previous blood transfusion to the mother:

Five neonates (17.9%)in group (1) and 31 neonates (33.7%)in group (2)their mothers had history of previous blood transfusion and 23

neonates(82.1%) in group (1) and 61 neonates(66.3%) in group (2) their mothers didn't have history of previous blood transfusion.

P value > 0.05 not significant as show in table (6).

Table 6 Show the distribution of previous blood transfusion to the mother in group (1) and group (2).

Maternal previous blood transfusion	Group (1)		Group (2)		Total
	No.	%	No.	%	
Not present	23	82.1	61	66.3	84
Present	5	17.9	31	33.7	36
Total	28		92		120

P value > 0.05 not significant.

Discussion

There are 5 mothers who already know her blood group and Rh and her husband blood group and Rh didn't have regular administration of human anti-D globulin following every delivery of Rh positive babe and abortion, 4 of them due to shortage of free of charge human anti-D globulin supply during certain periods and they cannot effort to buy it from private pharmacies, and 1 mother refused to receive that medication because some wrong social ideas.

When the mother and fetus are also incompatible with respect to group A or B, the mother is partially protected against sensitization by the rapid removal of Rh-positive cells from her circulation by her preexisting anti-A or anti-B, which are IgM antibodies and do not cross the placenta. Once a mother has been sensitized, her infant is likely to have hemolytic disease [2].

Although, we found that the presence of maternal history of regular administration of human anti-D immunoglobulin following every delivery of Rh positive baby and abortion will decrease development of

jaundice due to Rh incompatibility (p value < 0.05) and this results is compatible with that found by Dijk. B. V.[42] and Joseph K. S. et. al.[43], we found that 6 neonates (9.4%) from 64 neonates who their mothers have that history developed jaundice due to Rh incompatibility, this percent (9.4% in comparison to 1.4% found by Dijk. B. V.[42] and 2.1% found by Joseph K. S. et. al. [43] may be due to absence of two dose regime of human anti-D globulin once at 28-32 week and another one within 72 hours of delivery [2] in our hospital (only one dose of human anti-D globulin within 72 hours of delivery).

In this study we found as parity increases the severity of jaundice due to Rh incompatibility increases and the need for exchange transfusion will be high as we have shown that exchange transfusion was needed more in those whose mothers were grand multiparus (p value < 0.05), this finding was proved by Saleem S. Z. in 2000 [44] and Joseph K. S. et. al. [43], because fetomaternal transfusion occur with each pregnancy and the illness will be more worse with successive pregnancies [2].

Conclusion

- 1) Rhesus hemolytic disease of newborn is still a serious medical problem in our society.
- 2) Poor antenatal care regarding Rh negative pregnant women is still a major problem in our society and it's a significant risk factor for Rh isoimmunization.
- 3) Regular administration of human anti-D globulin is a protective measure against Rh isoimmunization.
- 4) Previous maternal transfusion is not a significant risk factor for Rh isoimmunization.

Recommendations

- 1) More efforts required to increase the knowledge of our society about the importance of antenatal care and explain the nature of Rhesus hemolytic disease of newborn.
- 2) Improve the quality of antenatal care regarding Rh incompatibility like regular measurement of maternal titer of IgG antibodies to D antigen at 12-16 , 28-32 and 36 weeks of pregnancy.
- 3) Provision a continuous supply of human anti-D globulin which should be at hand at any time and institution of 2 dose regime of human anti-D globulin once at 28-32 week and another one within 72 hours of delivery instead of one dose regime within 72 hours of delivery which in used in our hospital.
- 4) Introduction of more advance lines of management like intrauterine transfusion for those who are severely affected.

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