WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 5, Issue 2, 1130-1140. Research Article ISSN 2277– 7105

MATERNAL ALLOANTIBODIES AND FOETAL COMPLICATIONS IN JIMMA SPECIALIZED HOSPITAL, SOUTH-WESTERN ETHIOPIA

Dr. Sureshkumar P. Nair[*1], Dr. Hailemariam Segni[2] and Mehidi Kassim[1]

[1*]Dept of Biomedical Sciences, College of Health Sciences, Jimma University.

[2]Dept. of Gynaecology & Obstetrics, College of Health Sciences, Jimma University.

Article Received on
04 Dec 2015,

Revised on 25 Dec 2015,
Accepted on 14 Jan 2016

***Correspondence for Author**
Dr. Sureshkumar P. Nair
Dept of Biomedical Sciences, College of Health Sciences, Jimma University.

ABSTRACT

Alloimmunization of RhD negative mothers may lead to haemolytic disease of the foetus and new born. This is one of the reasons behind foetal loss and death. Even though this problem is well studied, well explained in medical literature and well known to the medical professionals, it remains as a serious problem in many developing countries either due to the lack of infrastructure or due to the poor socio-economic conditions of the population all over the world. However, in Ethiopia, the prevalence of haemolytic disease of the foetus and newborn and risk factors behind this problem has not been studied yet. This is a prospective longitudinal hospital based study focused on 3679 maternity patients who visited the Jimma University Specialized Hospital, Ethiopia, during the time November 2013 to November 2014. Response rate was 100%. Out of this 231 were RhD negative mothers. This RhD negative subgroup population and their new born babies were studied to reveal the foetal outcome, alloimmunization status and the contributing factors for haemolytic disease of foetus and new born. The prevalence of RhD negativity was 6.3% and weak-D was 1.3% of RhD negative mothers. RhD alloimmunization prevalence was 4.5% in urban and 9.8% in rural RhD negative population. Still birth among the study population was 12.0%. Among RhD alloimmunized mothers, still birth rate was 46.2%. Pearsons Chi-square test shows a significant association between alloimmunization and haemolytic disease of foetus and new born (p-value<0.0001). Immunoglobulin prophylaxis status was 68.7% in urban and 40.1% out of Jimma. This study reveals the low health care facility of the population inhabiting out of Jimma. The prevalence of RhD alloimmunization was very high compared to developed

countries. This was mainly due to the failure of immunoglobulin prophylaxis and due to various socio-economic conditions of the population.

KEYWORDS: RhD alloimmunization, Haemolytic disease of the foetus and Newborn, Immunoglobulin prophylaxis.

INTRODUCTION

Alloantibodies are antibodies produced against specific antigens which are introduced in to the body due to many reasons. Of these most important one is antibodies produced against different blood groups. This antibody production may be due to blood transfusion or because of pregnancy. The alloantibody produced at the reproductive age of a female may cause haemolytic disease of the foetus and new born during subsequent pregnancies. Haemolytic disease of the new born is one of the leading causes of foetal loss and neonatal jaundice among infants.[1,4] Haemolytic disease of the new born usually occurs when an RhD negative mother has an RhD positive baby. In first pregnancy usually, there is no complication occur. However, if first child birth is a complicated one with foeto-maternal bleeding, there is a chance of RhD sensitization. This sensitization may produce immunological memory in the mother and for future pregnancies, if baby is again RhD+ve then this may results in the boosting of Rh antibodies and can result in erythroblastosis foetalis or haemolytic disease of foetus and new born.

The alloantibodies associated complications varies in range. The leading cause of haemolytic disease of the new born is usually RhD antigen.[1] ABO incompatibility also can cause HDN. When O group mother bears a foetus of A, B or AB blood group, there is chance of HDN but severity will be comparatively less. Kell, Kidd, Duffy, M, N, S and s blood group also rarely cause HDN. The chance of HDN due to multiple alleles of Rh gene like E, C, e and c also cannot be excluded.[1]

In developed nations with high quality of health care, there is a decline in the foetal loss and death due to HDN.[2] The introduction of advanced perinatal care with proper immunoglobulin prophylaxis, a high percentage of hospital delivery, advanced high quality obstetric care, advanced neonatal care like intrauterine transfusion, change in the abortion law, proper immunization status of the population all these minimise the chance of HDN globally.[3] The associated complications of HDN are hyperbilirubinemia, kernicterus and anemia. Post natal care mainly consists of intensive phototherapy, regular monitoring of total

bilirubin and direct bilirubin, direct antihuman globulin test and exchange transfusion. The risk of HDN increases with complicated pregnancies like placental abruption, spontaneous abortion, ectopic pregnancies and caesarean delivery.[14,15] This risk can be minimised by giving proper immunoglobulin prophylaxis.[13]

MATERIAL AND METHODS

This is a cross sectional study carried out in Jimma specialized hospital from November 2013 to November 2014. Jimma is the largest city in the south-west of Ethiopia, located in the Jimma Zone of the Oromia region. The city of Jimma has a latitude and longitude of 704'N 36^0 50' E. It is 356 kms far from Addis Ababa and has an altitude of 1760 meters above the sea level with mean annual rain fall of 17 mm throughout the year and the annual temperature range is between 10^0c-30^0c. In Jimma there is one specialized hospital, two health centres, three health stations and sixteen private clinics.

The study group consists of all antenatal patients visiting the hospital for delivery and the neonates born in the hospital, those ready to cooperate with the study were included. RhD positive antenatal cases with normal live births and still birth due to other reasons were excluded. Data were collected using a standard questionnaire. The incomplete antibody status of all RhD negative patients visiting the maternity ward and labour room of the speciality hospital were analyzed using indirect antihuman globulin test. Data were collected using a standard questionnaire which contains socio-economic characteristics, place of previous delivery, history of pregnancy, history of blood transfusion, history of abortion, still birth, miscarriage, history of immunoglobulin prophylaxis, indirect antihuman globulin result and foetal outcome. The standard questionnaire was developed based on the questionnaire developed by Hellen Keller International[5] and was verified and consented by Jimma University College of Public Health and Medical Science Research and Postgraduate studies Department. New born baby's blood group, total bilirubin and direct bilirubin, reticulocyte count, haemoglobin and direct antihuman globulin test were conducted routinely for suspected cases. The alloantibodies were tested using antihuman globulin reagent of Ortho diagnostics and of Tulip diagnostics.[7,8] The total serum bilirubin and serum direct bilirubin was estimated by using the method of Van Den Bergh.[11] Reticulocyte was counted using Brilliant cresyl blue technique.[12]

Ethical clearance was obtained from the Jimma University Ethical Committee. The participants were informed on the purpose of the study. Written information sheets were

prepared in English and translated to local language Oromifa and Amharic and given to the subjects selected for the study. Written consent was obtained from each patient before starting the study. Privacy and confidentiality were maintained. The results were given to respective clinicians for the proper care of the patients. The collected data were entered in to computer daily, cleaned and data were analyzed by Pearson chi square, Fisher's exact test and Spearman correlation using SPSS version-20.

RESULT

This study covered a total population of 3679 maternity patients admitted in the Jimma university specialized hospital for a period from November 2013 to November 2014 representing both urban and rural Jimma population. Of this 231 subjects were RhD negative. The alloimmunization status concerning Rh-D was studied. All ABO group patients with still birth and neonatal jaundice were followed to elucidate the haemolytic disease of the newborn and foetus.

Among the study population, 39.1% were found to be O positive. Next highest group was A +ve with 36.0%, B+ve represents 16.7% and AB +ves were 4.0%. It was noticed that 6.3% of the study population comprises RhD negative subjects. 1.3% of RhD negative mothers were weak D positive.[6] This study reveals that literacy rate was far below ie., 42.7% of the sub group population were illiterate. Among the subgroup population, 40.3% of the urban and 60.4% of rural were far below the poverty line. Among the maternity patients, those visited Jimma specialised hospital 37.2% of the rural and 17.9% of the urban had previous history of home delivery. 59.1% of the rural and 31.3% of the urban patients was not received immunoglobulin prophylaxis. Among the subgroup population 4.5% of the urban and 9.8% of the rural were developed alloantibody because of improper management of RhD negative mothers. This study indicates that there exists a significant association between literacy and income with immunoglobuliin prophylaxis (p value 0.0001). The result shows that there is significant association (p value 0.0001) between parity and place of labour with that of alloantibody formation. There was a significant association between a positive indirect antihuman globulin test with foetal out come and HDN (p value (<0.0001).

Table 1 – Blood group profile of the study population.

Blood group and Rh-D	Total antenatal cases studied n=3679	Percentage %
A- Positive	1245	36.0
A – Negative	61	1.6
B – Positive	617	16.7
B – Negative	31	0.8
O – Positive	1439	39.1
O – Negative	125	3.4
AB – Positive	147	4.0
AB – Negative	14	0.4
Rh D Negative	231	6.3
Du^{+v} (Weak D) Among Rh D negatives	3	1.3

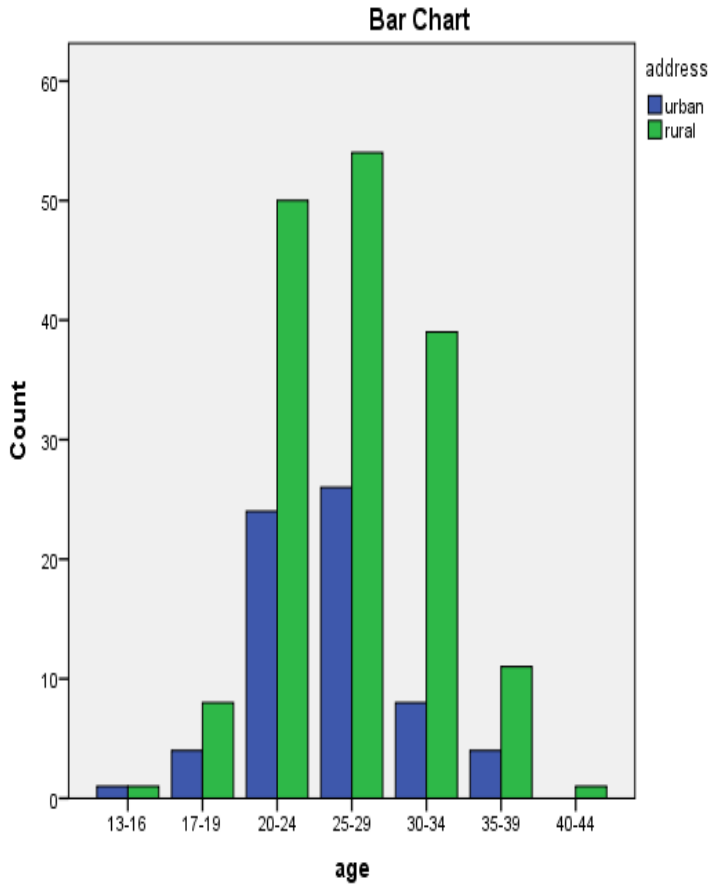

Fig 1 – Age group of the study population.

Table 2: Socio-demographic variables of the subgroup population.

Variables	urban n=67		rural n=164		Total n=231	
	n	%	n	%	n	%
Literacy						
Illiterate	13	19.4	70	42.7	83	35.9
Read write	4	6.0	8	4.9	12	5.2
1-6 grade	11	16.4	26	15.9	37	16.0
7-12 grade	21	31.3	39	23.8	60	26.0
>12 grade	18	26.9	21	12.8	39	16.9
Annual income in dollars						
<200	27	40.3	99	60.4	126	54.5
201-300	20	29.9	30	18.3	50	21.6
301-500	8	11.9	16	9.8	24	10.4
>501	12	27.9	19	11.6	30	13.4
Previous Place of labour						
Home	12	17.9	61	37.2	73	31.6
Health centre	10	14.9	24	14.6	34	14.7
Other hospitals	1	1.5	2	1.2	3	1.3
JU hospital	43	64.2	69	42.1	112	48.5
Both home and hospital	13	15.0	8	4.9	9	3.9
History of Immunoglobulin prophylaxis						
Given full course	46	68.7	67	40.9	113	48.9
Not given	21	31.3	96	59.1	118	51.1
Indirect antihuman globulin Test						
Positive	3	4.5	16	9.8	19	8.2
Negative	64	95.5	148	90.2	212	91.8

Table 3: Association of socio-demographic variables and immunoglobulin prophylaxis.

Variables	History of immunoglobulin prophylaxis				Chi square	P value
	Given n=212		Not given n=19			
	n	%	n	%		
Literacy						
Illiterate	20	24.1	63	75.9	47.516	0.0001*
Read write	4	33.3	8	66.7		
1-6 grade	19	51.4	18	48.6		
7-12 grade	36	60.0	24	40.0		
>12 grade	34	87.2	5	12.8		
Income						
<200	40	31.5	87	68.5	38.584	0.0001*
201-300	31	62.0	19	38.0		
301-500	21	87.5	3	12.5		
>501	21	70.0	9	30.0		

Table 4: Association between different factors which cause alloimmunization.

Variables	Indirect antihumanglobulin Test				Chi square	P value
	Negative n=212		Positive n=19			
	n	%	n	%		
Previous history of Still birth						
Yes	14	6.6	5	26.3	8.976	0.012*
No	198	93.4	14	73.7		
Previous history of abortion						
Yes	58	27.4	6	31.6	0.273	0.872
No	154	72.6	13	68.4		
History of pregnancy						
Primi	81	38.2	0	0	29.161	0.0001*
2	52	24.5	0	0		
3	32	15.1	6	31.6		
4 and > 4	47	22.2	13	68.4		
History of immunoglobulin prophylaxis and alloimmunization.						
Given	113	53.3	0	0	19.826	0.0001*
Not given	99	46.7	19	100		
Place of labour						
Home	59	79.7	15	20.3	25.811	0.0001*
Health centre	30	88.2	4	11.8		
Hospital	123	100.0	0	0		

Table 5: Association of alloimmunization status and foetal outcome.

Variables	Indirect antihuman globulin test				Chi square	P value
	Negative n=212		Positive n=19			
	n	%	n	%		
Normal live birth	199	93.9	0	0	147.679	0.0001*
Still birth(IUFD)	7	3.3	6	31.6		
With neonatal jaundice	4	1.9	13	68.4		
Preterm	2	0.9	0	0		
Association of alloimmunization and the prevalence of HDFN among the studied population						
Normal live birth	211	99.9	6	31.6	141.411	0.0001*
Live birth with HDN	1	0.5	13	68.4		

Table 6: Foetal outcome of the subgroup population.

Foetal outcome	urban		rural		total	
	n=67	%	n=164	%	n=231	%
Live birth	62	92.5	137	83.5	199	86.1
Still birth	1	1.5	12	7.3	13	5.6
With neonatal jaundice	3	4.5	4	8.5	17	7.4
Preterm	1	1.5	1	0.6	2	0.9
HDN						
Normal	64	95.5	153	93.3	217	93.9
With HDN	3	4.5	11	6.7	14	6.1

Early neonatal death						
1st week	1	1.5	12	7.3	13	5.6
2nd week	0	0	2	1.2	2	0.9
3rd week	0	0	1	0.6	1	0.4
Normal	66	98.5	149	90.9	215	93.1

DISCUSSION

Effective management of antenatal cases and the introduction of RhD immunoglobulin and timely administration of immunoglobulin, in turn, reduced the prevalence of haemolytic disease of the foetus and new born in developed countries from 14% to 1-2%. In many European countries and in US, it is less than 0.1%.[2,4] In many developing countries still HDFN persists as a serious contributing factor for perinatal and neonatal mortality. This may be due the lack of properly trained Medical or paramedical professionals, blood grouping mistakes, failure in the detection of weak RhD positive antigens, or due to the failure of immunoglobulin prophylaxis. The rate of perinatal mortality is globally accepted as an indicator of the health and socio-economic development of the country. In many developing countries the perinatal mortality is as high as 15-200/1000 live birth.[9] In Ethiopia various data indicate that the perinatal mortality is unacceptably high 37 to 52/1000 live birth.[20,21] compared to <0.3/1000 child birth in developed countries.

The Immunoglobulin prophylaxis has a crucial role in the prevention of HDFN and it has a critical socio-economic back ground. The Immunoglobulin prophylaxis given to Rh D negative mothers as per WHO criteria is two times during pregnancy, ie., at 28 weeks of gestation and 72 hours after delivery if the foetus is RhD positive.[13] Due to many socio-economic reasons, there is a chance of dropout of regular hospital visits. In such dropout cases, there is always 10% chance of alloimmunization due to lack of immunoglobulin prophylaxis.[1] Home deliveries may result in the lapses of timely blood grouping and administration of immunoglobulin within 72 hours of delivery. The socio-economic back ground of many developing countries may play an important role in the increased perinatal mortality due to improper perinatal care.[1]

This prospective study depicts the differences in the delivery of health care between the urban and rural population of Jimma. This study covered a population of 3679 mothers who visited Jimma specialized hospital. From this population, a subgroup population of 231 RhD negative mothers was derived and factors associated with RhD alloimmunization and immunoglobulin prophylaxis were studied. The prevalence of RhD negativity was 6.3% and

weak D (D^u) were 1.3% of RhD negative mothers. This study could not reveal the relation between alloimmunization and Weak D. The data shows that the study population was from low economic group and many of the mothers could not afford the high cost of immunoglobulin prophylaxis. This study shows that there exists a significant association between income status and immunoglobulin prophylaxis (p value <0.0001). The data indicates that the prevalence of still birth was 8.2% among the RhD negative mothers. This prevalence might have been due to the high prevalence of the home delivery there exists in the population.[20,21] The prevalence of Haemolytic disease of the new born was 4.5% in urban and 6.7% in rural Jimma population compared to 0.3/1000 live birth in European and North American population.[22] Among the urban population home delivery was 17.9% and that of rural it was 37.2%. This might be different from the original situation prevalent in the community. Many community based studies as a part of the community-wide education programme of the Jimma University revealed that the actual status of the home delivery was around or more than 85% in rural population of Jimma. Prevalence of home delivery was directly associated with immunoglobulin prophylaxis given to the RhD negative mothers. Immunoglobulin prophylaxis failure rate was 31.3% in urban and 51.9% in rural population. This might be due to low socioeconomic status of the population. The RhD negative subgroup shows a high prevalence of alloimmunization rate (8.2%), ie., urban 4.5% and that of rural 9.8%. Anti D is the most common cause of haemolytic disease of the new born and foetus.[17,18] Screening RBC alloantibodies in the first trimester antenatal visits are well-established practise in many of the developed parts of the world. This is done to detect possible HDFN case by anti D.[19] This study reveals the association between the prevalence of anti D and still birth (p value <0.0001). Illiteracy also act as a contributing factor in the failure of immunoglobulin prophylaxis (p value <0.0001). This study indicates that there is a significant association between parity and alloimmunization (p value <0.0001). It is noticed that foetal outcome and immunoglobulin prophylaxis were significantly associated (p value <0.0001). Babies of 68.4% of alloimmunized mothers developed HDFN.

CONCLUSION

This study reveals that there is a high prevalence of alloimmunization of RhD negative mothers (9.8% in rural). Moreover, there is a high prevalence of haemolytic disease of the foetus and newborn in the studied population. Many community studies revealed that surrounding rural area of the Jimma, the home delivery rate was around 85%. The high rate of home delivery, low socio-economic conditions of the population, occurrence of weak-

RhD, failure in blood grouping of the newborn and low rate of immunoglobulin prophylaxis were some of the contributing factors behind high alloimmunization rate. The total rate of alloimmunization was 8.2% in RhD negative mothers compared to 0.56% in Greek RhD negative mothers, 5.76 in Greek[22] and 0.06 to 0.3% European and North America [18,22]. So immunoglobulin prophylaxis should be taken as a compulsory program all over Ethiopia with strict follow-up and providing immunoglobulin and the associated laboratory investigation of the mothers and newborn should be of free of cost, in order to reduce foetal complications.

ACKNOWLEDGEMENT

We are expressing our sincere gratitude and indebtedness to Jimma University, Ethiopia for the providing the fund and ethical sanction for the project. Moreover, we place on record our whole hearted thanks to the Heads and staffs of Obstetrics and Gynaecology, Neonatal Care Unit and Clinical Laboratory, Jimma University Hospital and those who have consented for the study.

REFERENCE

1. Mollison PL, Engelfreit CP, Contreras M. Blood Transfusion in Clinical Medicine. 10th ed., Oxford, UK; Blackwell Science, 1997.
2. Chavez GF, Mulinare J, Edmonds LD. Epidemiology of Rh haemolytic disease of the new born in the United States. JAMA, 1991; 265: 3270-4.
3. Knox EG. Control of the heamolytic diserase of the new born. Brit J Prev Soc Med, 1976; 30: 163-169.
4. Geifman-Holtzman O, Wojtowycz M, Kosmas E, Artal R. Female allo-immunization with antibodies known to cause haemolytic disease. Obstetrics and Gynecology, 1997; 89(2): 272-75.
5. Helen Keller International. XXII IVACG meeting vitamin A and common agenda for micronutrients. November 2004, Lima Peru.
6. Agre PC, Davies DM, Issitt PD, Lamy BM, Schmidt PJ, Treacy M, Vengelen-Tyler VA. Proposal to standardize terminology for weak D antigen. Transfusion, 1992; 32: 86–87.
7. Coombs RRA, Mourant AE, Race RR. A new test for the detection of weak incomplete Rh agglutinins. Brit J Exp Path, 1945; 26: 255-66.
8. Walker RH. Relevance in the selection of serologic tests for the obstetric patient. In: Garratty G. Editor. Hemolytic disease of the new born, Arlington VA; Americal Association of Blood Banks, 1984; 173-174.

9. Neonatal and Perinatal Mortality. Country, Regional and Global Estimation, WHO, 2004.
10. Richardus JH, Graafmans WC, Verloove-Vanhorick SP, Mackenbach. The perinatal mortality rate as an indicator of quality of care in international comparisons. Medcare, 36(1): 54-66.
11. Harold Varley. Practical Clinical Biochemisry. 4th ed., London; Heinemann Professional Publishing Ltd, 2005; 349-394.
12. Kanai L Mukherjee. Medical Laboratory Technology: A procedure Manual for Routine Diagnostic Tests. New Delhi; Tata McGraw-Hill Publishing Company Limited, 1996; I: 287-88.
13. Moise KJ Jr. Management of rhesus alloimmunization in pregnancy. Obstet Gynecol, 2008; 112(1): 164-76.
14. Moise KJ. Hemolytic disease of the fetus and new born. In: Creasy RK, Resnik R. Maternal-fetal Mediine: Principles and Practise. 6th ed., Philadelphia; WB Saunders, 2008; 477-503.
15. Moise KJ Jr. Red blood cell alloimmunization in Pregnancy. Seminars in Hematology., 2005; 42: 169-178.
16. Harkness UF, Spinnato JA. Prevention and management of RhD isoimmunization. Clin Perinatol, 2004; 31(4): 721-42.
17. Giblett E. Blood group antibodies causing hemolytic disease of the new born, Clinical Obstetrics and Gynecology, 2008; 7: 1044-1055.
18. Davies J, Chant R, Simpson S, Powell R. Routine antenatal anti D prophylaxis- is the protection adequate ? Transfusion Medicine, 2011; 21: 421-426.
19. Engelfriet CP, Reesink HW, Judd WJ, et al. Current status of immunoprophylaxis with anti D immunoglobin. Vox Sanguinis, 2003; 85: 328-337.
20. FMOH/WHO. Child Health in Ethiopia-Background Document for the National Child Survival Conference, April 24-26, 2004, Addis Ababa.
21. Govt. of Ethiopia. Report on Progress in implementing the world fit for Children Plan of Action in Ethiopia. Addis Ababa, 2007.
22. Foudoulaki Paparizos L, Valsami S, Bournas N, Tsantes A et al. Alloimmunisation during pregnancy in Greece: need for nationwide HDFN prevention programme. Transfusion Medicine, Official journal of British Blood Transfusion Society, 2013.