Original Article

Prevalence of Clinically Significant Red Cell Alloantibodies in Pregnant Women

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ABSTRACT

Background

Hemolytic Disease of the Fetus and Newborn (HDFN) is the leading cause of anemia in fetuses and neonates, primarily due to maternal red blood cell alloantibodies that cross the placenta and attack fetal RBC with paternal antigens. The prevalence of these alloantibodies among pregnant women varies by country. This study aims to assess the local prevalence of clinically significant alloantibodies in pregnant women.

Methods

This retrospective study was conducted on total 6135 pretransfusion testing of pregnant women obtained from the hospital Laboratory Information System between 2020 and 2021 at the Blood Bank Unit of Hospital Canselor Tuanku Muhriz, University Kebangsaan Malaysia. Patients' age, parity, transfusion history, sensitizing events and antibody screening results were collected. A descriptive analysis was conducted on the prevalence, frequency, specificity of clinically significant antibodies, and associated risk factors. Association of age and clinically significant alloantibodies were assessed using the chi-square test ($p < 0.05$).

Results

The prevalence of clinically significant alloantibodies was 0.8%. Anti-Mi^a was the most common alloantibody, followed by anti-E and anti-M. No significant association was detected between maternal age and clinically significant alloantibodies. Six primigravida patients had clinically significant alloantibodies—anti-M, anti-Mi^a, and anti-E—without any sensitizing events, suggesting they may be naturally occurring. All pregnant women should ideally receive red cell antibody screening during routine antenatal check-ups to address the risk of HDFN. However, in resource-limited settings with low prevalence of significant alloantibodies and HDFN, this may not be cost-effective. Targeted screening for high-risk populations could be a better alternative.

Keywords

Maternal Red cell alloantibody; Hemolytic Disease of Fetus and Newborn (HDFN); Anemia

INTRODUCTION

The presence of red blood cell (RBC) alloantibodies of the IgG type in pregnant mothers is primarily responsible for causing Hemolytic Disease of Fetus and Newborn (HDFN), also known as alloimmune HDFN or erythroblastosis fetalis. The HDFN is caused by the maternal immunoglobulin G (IgG) antibodies that can cross the placenta and destroy the RBCs of the fetus carrying the corresponding antigen[1]. There are a few mechanisms by which these maternal alloantibodies can be acquired i.e. history of previous blood transfusion[2] and pregnancy with fetomaternal hemorrhage[3]. The risk factors for

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fetomaternal hemorrhage are a history of miscarriages, ectopic pregnancy, previous live birth or stillbirth, an invasive procedure such as cordocentesis and amniocentesis, etc[3]. Once the alloantibodies develop in pregnant mothers, the IgG alloantibodies can cross the placenta and enter the fetal circulation. If the fetal RBC express the cognate antigen, the antibodies will bind to the antigen and cause hemolysis of the fetal RBC, causing fetal/neonatal anaemia. Maternal immunoglobulin G (IgG) antibody is responsible for HDFN by crossing the placenta. The IgG antibody's fragment crystallizable (Fc) component enables it to cross the placenta. In contrast, immunoglobulin A (IgA) and immunoglobulin M (IgM) lack this Fc component, which prevents them from crossing the placental barrier[4]. More than 50 RBC alloantibodies are responsible for causing HDFN, with anti-D followed by anti-c and anti-K having the highest risk for severe cases[5]. Maternal alloimmunization can also lead to severe clinical consequences for mothers, such as miscarriages, early childbirth, etc[6].

The sign-symptoms of HDFN vary from mild and self-limited cases presenting with jaundice and varying degree of anemia to severe life-threatening hydrops characterized by severe anemia, hepatic and splenic hematopoiesis, heart failure, and edema[7]. HDFN encompasses ABO-HDFN, RhD-HDFN and HDFN due to alloantibodies other than anti-D such as anti-C, anti-c, anti-E, anti-K etc[8]. ABO HDFN typically tends to be less severe compared to those associated with the Rh and Kell blood group systems[9]. The frequency of Rh-HDFN cases has gradually declined after the implementation of routine immunoprophylaxis with Rh-D immunoglobulin in Rh-D-negative pregnant mothers over the last half-century[1]. The prevalence of RhD alloimmunization has been reduced from 16 to 0.3% in Western countries[3]. Anti-K can cause severe hemolysis and anemia in the intrauterine period by hemolyzing mature and precursor RBC as K antigen is present in the fetal immature erythroid cells[8].

In the context of the Malaysian population, two previous studies have shown the prevalence of clinically significant antibodies of about 0.99%[10] to 1.3%[11], where the majority of the antibodies detected were from the Rh group. The prevalence of red cell alloantibody among pregnant mothers varies in different countries and is reported to be 0.3% and 3.4%[1]. In most developed countries, screening for unexpected red cell antibodies in early pregnancy is part of the routine antenatal investigation[7,12]. In contrast, most developing countries, including Malaysia, where alloantibody screening for all pregnant women is still not practiced due to various limitations[10, 13,14]. The antibody screening during pregnancy is crucial for identifying clinically significant antibodies involved in HDFN and for guiding further management[12]. The antibody screening is also important for blood banks to ensure a prompt supply of antigen-negative blood when necessary, particularly for antenatal mothers with rare antibodies[15].

Managing alloimmunized pregnancy is challenging for obstetricians and immunohematologists[15]. Early detection enables the clinician to take early intervention by closely monitoring the fetus at risk for anaemia and minimizing the morbidity of the fetus by instituting early intervention and intrauterine transfusion where required[16]. The careful monitoring of maternal serial antibody titers, along with ultrasounds of the middle cerebral artery in the fetus, guides the need for intrauterine transfusions[17]. This study aims to determine the current prevalence of alloantibodies, specifically the clinically significant alloantibodies known to cause HDFN in all pregnant women and its association with the risk factors.

MATERIAL AND METHODS

This retrospective study was performed on patients who underwent pre-transfusion testing at the Blood Bank Unit of Hospital Canselor Tuanku Muhriz (HCTM), Universiti Kebangsaan Malaysia (UKM), between 2020 and 2021. Approval for this study was obtained from the Medical Research Council and Research Ethics Board of UKM (Research Ethics Number: UKM PPI/111/8 JEP-2022-447; Dated 15 July 2022). A total of 10549 pre-transfusion testing was retrieved from the hospital Laboratory Information System (LIS) between 1st January 2020 and 31st December 2021 for patients from the obstetrics ward, labour room and pregnancy assessment center. Among 10549 tests retrieved, a total of 4414 patients were found to have duplicate records, non-obstetrics history, patients with incomplete testing, and having positive anti-D with a history of documented Rh (Ig) administration were excluded from the study. The remaining 6135 pregnant women having a valid electronic medical record of ABO & RhD blood grouping, red cell antibody screening and identification were included in this study. Patients' age, parity, transfusion history, sensitizing events and

antibody screening results were collected. Patients with positive antibody screening with a clinically significant antibody were further investigated based on age as ≤ 34 years and ≥ 35 years, parity as ≤ 1 and ≥ 2, having a history of blood transfusion and presence of other sensitizing events. The sensitizing events include any history of miscarriages, ectopic pregnancy, previous live birth or stillbirth, invasive procedures such as cordocentesis and amniocentesis, etc.

ABO & RhD typing and antibody screening were performed using the gel card methodology with automated blood bank analyzer 'Biorad IH-1000'. Antibody screening was performed using commercial cell panel Bio-Rad ID-DiaCell I-II-III Asia. Samples that tested positive on the antibody screen were subjected to antibody identification manually to determine the specificity of the antibody by indirect antiglobulin testing using the manual gel card methodology in accordance with the American Association of Blood Banking guidelines, using commercial cell panel (11-cell panel, Bio-Rad ID DiaPanel, ID DiaPanel-P).

Data and statistical analysis were performed using SPSS Version 25. A descriptive analysis was conducted for the prevalence, frequency, and specificity of clinically significant antibodies and associated risk factors such as age, parity, history of packed cell transfusion, and sensitizing events. The association of age and clinically significant alloantibodies were determined using the chi-square test, where p was considered significant at $p < 0.05$.

RESULT

In this retrospective analysis, we determined the prevalence and specificity of clinically significant maternal red cell alloantibodies known to cause HDFN in a tertiary care facility and any significant association between advanced maternal age and development of red cell alloantibodies.

Table 1 shows the prevalence of clinically significant and insignificant alloantibodies and negative cases according to year. In total, out of 6135 pregnant women, 71 had a positive red cell antibody screen, with 51 of them having one or more clinically significant red cell alloantibodies, and 20 pregnant women had either clinically insignificant alloantibodies or antibodies not implicated in HDFN. The prevalence was 1.1% and 0.8% for overall maternal red cell alloantibodies and clinically significant red cell antibodies, respectively.

Table 1: Prevalence of maternal red cell alloantibodies by overall population and year.

Alloantibody	2020 (N = 2452)		2021(N = 3683)		Total(N = 6135)	
	n	%	n	%	n	%
Significant	26	1.1	25	0.7	51	0.8
Non-significant	9	0.4	11	0.3	20	0.3
Negative	2417	98.5	3647	99.0	6064	98.8

The distribution of age, parity, history of transfusion, and sensitizing events among the women who had clinically significant alloantibodies according to the year are summarized in Table 2. Among a total of 51 patients having clinically significant alloantibody, 15 (29.4%) were of advanced maternal age, 42(82.4%) were multigravida, 6 (11.8%) had transfusion history, and 20(39%) had sensitizing events.

Table 2: Characteristics of pregnant women with clinically significant red cell alloantibodies

Characteristic	2020	(n=26)	2021	(n=25)	Total (n=51)	
	N	%	n	%	n	%
Age group						
≤ 34 years	20	76.9	16	64.0	36	70.6
≥ 35 years	6	23.1	9	36.0	15	29.4
Parity						
≤ 1	5	19.2	4	16.0	9	17.6
≥ 2	21	80.8	21	84.0	42	82.4
History of transfusion						
Yes	4	15.4	2	8.0	6	11.8
No	22	84.6	23	92.0	45	88.2
Sensitizing events						
Yes	11	42.3	9	36.0	20	39.0
No	15	57.7	16	64.0	31	61.0

The association between alloantibody and age group are shown in Table 3. Out of 6135 pregnant women in our study, 4515 were aged ≤34 years, and the remaining 1620 were of advanced maternal age (≥35 years). Among the advanced maternal age group,15/1620(1%) women had clinically significant alloantibody, while, in the group of ≤34 years, 36/4515(0.8%) women had clinically significant red cell alloantibody. We found no significant association between maternal age and the development of clinically significant red cell alloantibodies (p value= 0.6248).

Table 3: Association between alloantibody and age group

Age group	Significant (n %)	*p*
≤ 34 years (n= 4515)	36 (0.8)	
≥ 35 years (n=1620)	15 (1.0)	0.6248
Total (n= 6135)	51	

The distribution of clinically significant red cell alloantibodies according to ABO grouping are shown in table 4. Among 51 patients, 13 belonged to blood group A, 17 to blood group B, 15 to blood group O and six to blood group AB. The most common clinically significant red cell alloantibodies detected were anti-Mi^a (n=22; 43%), followed by anti-E (n=11; 21%) and anti-M reactive at 37ºC (n=6; 12%). Other clinically significant alloantibodies detected were anti-Jka, anti-c, anti-C, anti-Jkb and anti-S. Five patients had more than one clinically significant red cell alloantibodies. The clinically insignificant alloantibodies or antibodies not implicated in HDFN were anti-Lea, anti-Leb, anti-P1, anti-Kpa, anti-M non-reactive at 37C and nonspecific auto IgG (Not shown in table).

Table 4: Distribution of red cell alloantibodies according to ABO blood group (n=51)

Antibodies	A	B	O	AB	Total n (%)
Anti Mi^a	7	7	7	1	22 (43)
Anti E	2	5	3	1	11 (21)
Anti-M reactive at 37ºC		2	3	1	6 (12)
Anti-Jka		1		1	2 (4)
Anti-c	1			1	2 (4)
Anti E + Anti c	1		1		2 (4)
Anti C + anti-e	1			1	2(4)
Anti E + Mi^a			1		1(2)
Anti-Jkb		1			1(2)
Anti-S		1			1(2)
Anti-C	1				1(2)
Total	13	17	15	6	51(100%)

DISCUSSION

HDFN is reported to be the most common cause of fetal anemia[18]. Despite advances in the prevention of pregnancy-related red cell immunization and management of pregnancies affected by HDFN over recent decades, the disease still poses a significant risk in affected pregnancies[19]. The introduction and administration of Rh (Ig) has dramatically reduced the incidence of anti-D-associated HDFN to as low as 0.1% since the 1970s, particularly in developed countries. However, red cell alloantibodies other than anti-D have emerged as a major cause of HDFN[1]. The overall prevalence of alloantibodies against non-Rh(D) antigens varies between 0.5-2.2%[15].

In our study, the prevalence of clinically significant red cell alloimmunization was 0.8% (800 per 100,000 pregnant females), and all of them were non-Rh(D) alloantibodies. In comparing the prevalence rate with the previous studies in Malaysia, we found the prevalence in our study population is slightly lower as compared to the study by Hassan et al. (0.99%) and Suria et al. (1.3%)[10,11]. The prevalence rate among different countries varies widely. In India, the prevalence is 1.02%-1.48%[13,20,21]; in Pakistan, 1.8%[22]; in Greece, 0.89%[23]; in Nigeria, 3.4%[24]; in Australia[25]. The variation in antibody prevalence could be due to variations in the homogeneity of different populations, study periods, sample sizes, study methods, etc. Our study did not

include patients with anti-D who had a documented history of Rh (Ig) administration. Therefore, anti-D alloantibodies were not detected here. Also, we have included a commercial screening cell panel with Mi^a antigen, thereby detecting the anti-Mi^a antibody, which may not have been added in other earlier studies.

A total of 51 clinically significant alloantibodies were identified in our study. The most common clinically significant red cell alloantibodies found were anti-Mi^a, followed by anti-E, anti-M and others. Anti-Mi^a antibody reacts with the Mi III phenotype of the Miltenberger subsystem. It is rarely reported in the West but is common in the Chinese and Southeast Asian populations[26]. In Malaysia, the prevalence of anti-Mi^a among the population was 0.2%-0.5%, and is the most frequently found alloantibody[27,28]. Anti-Mi^a has been reported to cause hemolytic transfusion reactions and HDFN. Thus, it is a clinically significant red cell alloantibody[29]. A case of neonatal isoimmune hemolytic disease caused by anti-Mi^a with significant fetomaternal hemorrhage was reported in Korea[30]. Severe HDFN cases of hydropic infants have also been reported recently[31].

The second most common red cell alloantibody found in our study was anti-E at 21%. It is reported that 14-20% of pregnant women are detected with anti-E specificity that causes HDFN[32]. A study done by Hassan et al. in Malaysia among pregnant women found anti-E to be the most common red cell antibody (13.73%) and the most common cause of HDFN[10]. In contrast to our study, in which anti-Mi^a was the most common red-cell antibody reported, no anti-Mi^a was reported in the study by Hassan et al. (2015)[10]. The probable reason for this difference could be the study population and method. The study population by Hassan et al. included only the Malays population, in whom the frequency of anti-Mi^a is low. It could also be that their screening panel did not include the Mi^a antigen. Therefore, no anti-Mi^a antibody was detected.

Anti-M (reactive at 37ºC) was our study's 3rd most common red cell alloantibody (n=6; 12%). The severity of HDFN caused by anti-M is widely variable, ranging from mild to fatal[33,34,35,36]. Severe HDFN causing hydrops fetalis and recurrent abortions has been reported due to alloanti-M, primarily in the Asian population[37].

The other clinically significant antibodies include anti-Jka, anti-Jkb, anti-C, anti-c, anti-e, and anti-S. We did not identify the allo anti-D in our study, possibly due to the proper immunization of RhD-negative mothers with antiD immunoglobulin in Malaysia. The low proportion of Rh(D) negative individuals in East Asia also contributes to the relatively higher frequency of non-Rh(D) HDFN in the population[38]. The most common non-RhD antibodies that cause HDFN are anti-K, anti-c, and anti-E. Notably, higher antibody titers are strongly indicative of severe fetal anaemia[39].

In this present study, B group patients had the highest alloimmunization, followed by O, A and AB blood group patients. A study by Hassan et al. found that alloimmunization rates were highest in blood group O patients, followed by A, B, and AB. There was no association between blood group and alloimmunization[10]. A study by Iqbal & Ahmed (2014)[40] on pediatric beta thalassemia major patients showed the highest frequency of antibody development was in blood group O. In Malaysia, blood group O is of the highest frequency, followed by B and A groups among the general Malay and Chinese populations, whereas in Indians, O and B were of the same frequency[41]. The diverse ethnic composition of Malaysia may influence the variation in blood group frequencies among the alloimmunized pregnant women in our study.

In our study, among the patients with clinically significant red cell alloantibodies, 82.4% were multigravida, 39% had experienced additional sensitizing events such as miscarriage or a history of early neonatal death, and 12% had a transfusion history. We investigated the association between maternal age and the development of clinically significant red cell alloantibodies, but no significant association was detected.

In our study, 9 (17.6%) primigravida patients were detected as having clinically significant red cell alloantibodies, where three patients had a sensitizing event after packed cell transfusion. However, six had no documented prior transfusion or other sensitizing events such as antepartum hemorrhage or invasive procedures. Among these six primigravida with no prior sensitizing events, three had anti-M, two had anti-Mi^a, and one had anti-E. The explanation of the presence of these three antibodies without prior sensitization is that these antibodies can be naturally occurring antibodies[26, 42,43].

In this present study, we did not follow up or investigate the newborn and infants of mothers with clinically significant red cell alloantibodies. However, Hassan et al. reported the incidence of HDFN among the Malay population to be about 0.2%[44]. A study conducted in

the Netherlands found that after implementing routine first-trimester antibody screening, the rate of hydrops declined from 39% to 15%[45]. In this era where medical science and technology are rapidly advancing, early detection of clinically significant maternal red cell alloantibodies enables the clinician to closely monitor the fetus at risk for anemia and institute intrauterine transfusion where required.

CONCLUSION

The prevalence of clinically significant maternal red cell alloantibodies was 0.8%. Anti Mi^a was the most common red cell antibody, followed by anti-E and anti-M. Ideally, all pregnant women should have a red cell antibody screening during routine antenatal check-up to anticipate and mitigate the risk of HDFN, including early referral to a fetomaternal specialist for high-risk pregnancies. However, this may not be cost-effective in a resource-limited setting with a very low prevalence of clinically significant red cell alloantibodies and a low incidence of HDFN. Alternatively, targeted screening of high-risk populations such as women with a bad obstetric history, multigravida, or history of any sensitizing events such as antepartum hemorrhage, invasive prenatal testing, and previous history of HDFN should be considered. A national, multi-center study on the latest prevalence and incidence of HDFN may be required to justify if routine maternal red cell alloantibody screening should be implemented as part of routine antenatal investigation and its cost-effectiveness.

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AUTHORS' CONTRIBUTION

Concept and design: Hussain ZM, Yousuf R, Suhemi NA, Abdul Aziz S

Manuscript writing: Hussain ZM, Abdul Aziz S

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All authors have approved the final version of the manuscript

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