CASE REPORT

Rare and Multiple Alloimmunization in Antenatal Women: A Case Report

Swati Garg[1], Vidisha Payal[2], Urvashi Sharma[3], Ram Mohan Jaiswal[4]

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Abstract

Maternal alloimmunization is uncommon and highly variable, and general obstetricians are not familiar with, non-ABO, non-D alloimmunization. Therefore, when a woman with anti-D alloimmunization, who has received antibody prophylaxis, still develops fetal anemia in a subsequent pregnancy, it is commonly labeled as inadequate prophylaxis or a coincidental non-immune cause of fetal anemia. We report a similar case of unusual and multiple alloimmunization, where anti-D, anti-C, and anti-U antibodies were present resulting in hemolytic disease of the fetus and newborn (HDFN). The case emphasizes the need for routine and periodic antibody screening in all pregnant women, irrespective of their ABO and Rh status, which will allow monitoring from early pregnancy and timely intervention to avoid poor fetal and neonatal outcomes.

Keywords: Alloimmunization, Anti-U antibody, Antibody prophylaxis, Antibody screening, Foetal anemia.

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Aim and Background

Alloimmunization during pregnancy is not common and most obstetricians are unaware of the presence of more than 50 non-AB blood groups involved in HDFN.[1] There is a common misconception that only anti-D is associated with HDFN, and screening is required only for Rh-D-negative women.

We are reporting a similar case of unexpected multiple alloimmunization during pregnancy, where because of a delay in reporting, evaluation, and timely intervention with appropriate antigen-negative blood, we could not save the fetus. Though a thorough evaluation of present pregnancy has given us a chance to prepare us better for her future pregnancy.

Case Description

A 28-year-old woman of lower middle socioeconomics class came to antenatal OPD of MGMC & Hospital, Jaipur with 7 months pregnancy and a history of weakness and easy fatigability for 15 days. She was 4th gravida, with 1st full-term vaginal delivery 4 years back and 2nd and 3rd spontaneous abortions, each of 1.5 months, followed by evacuation, 2.5 and 1 year back. The first pregnancy was uncomplicated; the baby is healthy, without a history of neonatal anemia or jaundice. She was not sure about receiving anti-D prophylaxis during or after childbirth and abortions. Her period of gestation came out to be 26^{+2} weeks and she did not have any antenatal check-ups in this pregnancy.

Her past medical, surgical, and family history was not significant and there was no history of blood transfusion or drug abuse in the past. Her examination revealed mild anemia with about 28 weeks of pregnancy and a regular fetal heart sound. On initial workup, she was found to have moderate anemia with O negative blood group (Fig. 1). Her husband's blood group was O positive and her indirect Coombs test was positive, with a titer of 1:16. Doppler scan showed a single live Fetus of 25^{+5} weeks, with middle cerebral artery peak systolic velocity (MCA-PSV) of 47 cm/sec, indicating mild anemia and no signs of fetal hydrops. The high-performance liquid chromatography (HPLC) revealed a β thalassemia trait which explains the comparatively high red blood cell count in a complete blood count report otherwise indicating iron deficiency anemia.

The patient was advised to have a nutritious diet, iron, calcium, and protein supplement and was advised to come for follow-up after one week. On follow up MCA PSV rose to 54 cm/sec and Rh antibody titers to 1:64.

Considering her rising titers and increasing levels of fetal anemia, counseling of the patient and her attendants was done regarding the need for intrauterine transfusion (IUT) in the coming days and the blood center was informed. For the future need of IUT, the blood sample was sent for a cross match, but in spite of a trial with around 100 units of O-negative leuko-reduced packed RBCs, not even a single unit of blood was found to be compatible for transfusion. On the extended cell panel, the patient was found to have anti-D, anti-C, and anti-U antibodies (Fig. 2). As the patient herself was anemic with thalassemia trait, transfusion with the mothers' blood could not be used for IUT.

[1–3]Department of Obstetrics & Gynecology, Mahatma Gandhi Medical College & Hospital, Jaipur, Rajasthan, India

[4]Department of Immuno Haematology Blood Transfusion, Mahatma Gandhi University of Medical Sciences and Technology, Jaipur, Rajasthan, India

Corresponding Author: Swati Garg, Department of Obstetrics & Gynecology, Mahatma Gandhi Medical College & Hospital, Jaipur, Rajasthan, India, Phone: +91 9414048000, e-mail: drswati_garg@hotmail.com

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Patient consent statement: The author(s) have obtained written informed consent from the patient for publication of the case report details and related images.

CBC (COMPLETE BLOOD COUNT)

Parameter		Result Values	Biol.Ref. Interval	Method
WBC		8.5 10^3/µL	4.0 - 10.00 10^3/µL	DC detection & flowcytometry
RBC		3.86 10^6/µL	Adult: : 3.8 - 4.8 10^6/µL	DC detection
Haemoglobin (HB)	L	7.2 g/dL	12.0 - 15.0 g/dL	Photometric Principle
HCT	L	26.4 %	36.0 - 46.0 %	Calculated/by RBC histogram
MCV	L	68.5 fL	83.0 - 101 fL	Calculated/ by RBC Histogram
MCH	L	21.3 pg	27.0 - 32.0 pg	Calculated
MCHC	L	31.1 g/dl	31.5 - 34.5 g/dl	Calculated
Platelets Count	L	130 10^3/µL	150 - 410 10^3/µL	DC detection
RDW-CV	H	18.0 %	11.6 - 14.0 %	Calculated
MPV	H	13.4 fL	6.0 - 11.0 fL	By Platelet Histogram
Neutrophil		68.9 %	40.0 - 80.0 %	Flowcytometry/VCS technology
Lymphocyte		22.0 %	20.0 - 40.0 %	Flowcytometry/VCS technology
Monocyte		4.9 %	2.0 - 10.0 %	Flowcytometry/VCS technology
Eosinophil		3.7 %	1.0 - 6.0 %	Flowcytometry/VCS technology
Basophil		0.5 %	0.0 - 2.0 %	Flowcytometry/VCS technology/microscopy

Fig. 1: Complete blood count

Antibody Identification — Specimen Serum

Blood Group & Rh Typing — O Rh(D) Negative

Antibody Screen — Positive

Antibody Identified — Anti-U Anti-D Anti-C

Antigen Typing

	S	s	M	N	K	Fyb
Results	NEG	NEG	NEG	POS	NEG	NEG

Technical Note:

Antibody identification done using a 11 cell/ extented cell panel of reagent red cells coated with Rh , Kell, Duffy, Kidd,Lewis,P, MNS, Lutheran and Xg antigens using gel card by microtyping techniques.

We have confirmed the presence of anti-U in the patient's plasma, reacting moderate strength by LISS IAT with untreated cells and marginally stronger with papain treated cells.
We also confirmed the presence of anti-D in her plasma, reacting strongly by LISS IAT with untreated and papain treated cells.
In addition, we found anti-C present, reacting weakly by LISS IAT with untreated cells and stronger with papain treated cells.
No additional antibodies were detected (the presence of anti-E, -K, -Fyb were excluded).
Results were confirmed from International red cell reference laboratory.

Fig. 2: Antibody panel report

On follow-up scan after 1 week at 28^{+2} weeks gestation, it was found that intrauterine fetal death had already occurred. With due consent and counseling, induction of labor was done and a mildly hydropic male child of 1.57 kg was born.

Conclusion

The case report highlights the need for routine and periodic antibody screening of all antenatal women and a message that non-ABO, the non-D antibodies should be considered in all alloimmunized women who give a suggestive history but no beneficial effect of anti-D prophylaxis.

Clinical Significance

Maternal alloimmunization occurring because of non-AB red blood cells antibodies during pregnancy results in a high-risk clinical consequence to both mother and fetus. More than 60 red blood cell antigens can initiate antibody response but D is the most common and most immunogenic, followed by K, E, c, e, Jka, Fya, C, S, Jkb, Fyb, s.[2] These antibodies, especially IgG can cross the placenta and cause fetal red cell hemolysis, anemia, and subsequent hydrops in fetus, and kernictus with neurodevelopment delay in the newborn, comprising the HDFN. In severe cases, this may lead to fetal demise, which occurred in our case. There are maternal complications also, like the presence of non-specific antibodies in maternal serum can confound blood bank testing, and such mothers are at risk of hemolytic transfusion reaction, and also has an impact on future childbearing.

The incidence of maternal alloimmunization is highly variable depending on the type of antigen involved, the population in question due to differing rates of antigen frequency, and the route of exposure, i.e., via pregnancy, transfusion, transplant, or intravascular drug abuse. For example, in India, 93% population is D positive, whereas, blacks are 92% positive, and Asian and Native Americans are 99% Rh D positive.[3] More than 330 blood group antigens are known, with more than 50 documented to cause HDFN.[2] Rhesus D blood antigen is the most immunogenic, and its association with HDFN was first described by Levin and Stetson in 1939.[2] The alloimmunization incidence in 1960 was 14% before the initiation of Rh immunoglobulin therapy and associated HDFN was 1%. This decreased to 0.2% in developed countries (2.9–6.5% in developing countries) after the standardization of Rh Ig administration during pregnancy.[4] The rate of alloimmunization among Rh. D negative pregnancy range from 6.9 to 12.8% and the frequency of unexpected antibodies in India is found to be 1.3%–1.5% in some of the study.[5] The rate of non-D, non-ABO alloimmunization is low, 0.15–1.1%, but is becoming a greater percentage of maternal alloimmunization and HDFN.[2]

Alloimmunization in women from multiple antibodies increases the risk of HDFN (5.6 times) especially when anti-D is compounded with additional antibodies. Patients with thalassemia, sickle cell, and myelodysplasia syndromes are especially prone to alloimmunization with incidence up to 37, 47, and 58.6% respectively. The presence of multiple antibodies and an associated presence of the thalassemia trait has caused a sudden and unexpected rise in fetal anemia in our case.

Thorough evaluation of this pregnancy has given us an opportunity for a preparedness and a hope for better outcome in her next pregnancy. We plan a therapeutic plasma exchange and use of intravenous immunoglobin according to the antibody titers in the next pregnancy. The appropriate donor will be timely identified in case of need for IUT. Another option will be to offer assisted reproductive technology with an Rh D negative donor.

In India, routine ABORH grouping and anti-D prophylaxis are done at all the health centers but antibody screening is done only at tertiary care centers with transfusion facilities. In developing countries, universal antibody screening for all antenatal women may not be justified looking at the cost and infrastructure required, but protocols can be made for pregnant women with adverse obstetric history, in order to decrease the occurrence of preventable perinatal morbidity and mortality due to HDFN. Also, as there is the possibility of the development of antibodies in the later gestational period, the antibody screening should be periodic, helping in diagnosis at an early stage and referral of antenatal mothers with irregular antibodies to a tertiary care center for appropriate management.

Patient Consent

Written informed consent was obtain from the patient for publication of this case report and accompanying reports and figures.

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