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CASE REPORT

Severe anti-D haemolytic disease of fetal and newborn in rhesus D negative primigravida

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Abstract

Introduction: Anti-D alloimmunisation may occur from the blood transfusion or fetomaternal haemorrhage which can lead to haemolytic disease of fetal and newborn (HDFN). The morbidity and mortality of HDFN related to anti-D is significantly reduced after introduction of anti-D prophylaxis and furthermore, anti-D HDFN in RhD negative primigravida is uncommonly seen. *Case Report:* A case of unusual severe HDFN due to anti-D alloimmunisation in undiagnosed RhD negative primigravida Malay woman is reported here. This case illustrates the possibility of an anamnestic response from previous unknown sensitisation event or the development of anti-D in mid trimester. The newborn expired due to hydrops fetalis and severe anaemia. Antenatally, the mother was identified as RhD positive and thus there was no antenatal antibody screening, antepartum anti-D prophylaxis or close fetal monitoring for HDFN. *Discussion:* The thorough antenatal ABO and RhD blood grouping with antibody screening is mandatory as part of prevention and early detection of HDFN especially due to anti-D alloimmunisation. Improper management of RhD negative women might lead to severe HDFN including in primigravida.

Keywords: Anti-D, HDFN, RhD negative, primigravida

INTRODUCTION

Anti-D alloimmunisation in Rhesus D (RhD) negative women can occur either due to blood transfusion or fetomaternal haemorrhage (FMH) which can lead to haemolytic disease of fetal and newborn (HDFN). The related morbidity and mortality of HDFN due to anti-D is significantly reduced after introduction of antepartum and postpartum anti-D prophylaxis. The correct application of the anti-D prophylaxis successfully reduced but not eliminated the anti-D alloimmunisation cases as evidence by previous study[1] and our local published data, which reported only 3 out of 20 RhD negative pregnant women were alloimmunised.[2]

Anti-D can cause very severe HDFN, where anti-D may develop a positive direct Coomb test (DCT) by 8th week of gestation and severe anaemia or death *in utero* may occur as early as in the 18th week of gestation.[3] However, with appropriate detection, monitoring and intervention, HDFN due to anti-D can be treated and managed successfully in almost all cases.[4]

The difference between anti-D and ABO HDFN is the latter can develop in any pregnancies including the first pregnancy, but it is restricted to group A or B babies born to group O mothers. However, it is different when HDFN is due to anti-D which is very rarely reported in primigravida.[5,6,7] The first baby is usually not affected unless there has been prior immunisation by abortion or transfusion or mildly affected if the first pregnancy is the immunising event and the woman does not have any prior sensitisation event. Furthermore, the primary response is usually weak and often produces IgM antibodies which is short-lived and rapidly converts to an IgG response but is insufficient to cause significant haemolysis.[1,8]

Here we reported a case of unusual severe HDFN due to anti-D in RhD negative primigravida without apparent previous sensitisation event and

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highlighted the importance of proper antenatal ABO and RhD blood grouping with antibody screening as a part of prevention and early detection of HDFN especially due to anti-D alloimmunisation.

CASE REPORT

A 24-year-old Malay primigravida, delivered a term baby boy through emergency lower segment caesarean section (LSCS) due to acute fetal distress. The baby was born flat (Apgar score of 1^1 and 2^5) with severe pallor and gross hydropic features but not jaundiced. The baby was immediately intubated for ventilation support. Severe HDFN had been suspected clinically.

Patient had uneventful antenatal follow up at health clinic and she was misidentified as blood group O RhD positive. However, blood grouping prior to LSCS was noted to be O RhD negative. Surprisingly, antibody screening and identification revealed presence of anti-D with a very high anti-D titre, 1:4096. There was no history of blood transfusion or any sensitisation event during pregnancy and she denied any previous history of miscarriage, ectopic pregnancy or extramarital conception.

The baby's haemoglobin was 3.3 g/dL with reticulocyte count of 16% and total white cells of $140x10^9$/L. Unfortunately, full blood picture was not done due to inadequate sample. His blood group was O RhD positive and the direct Coomb test (DCT) was positive for IgG (2+). Blood investigations (severe anaemia with reticulocytosis, positive DCT, mother with anti-D alloimmunisation and high titre of anti-D) supported the diagnosis of severe HDFN due to anti-D alloimmunisation. Two units of O RhD negative packed cells were successfully transfused and intravenous immunoglobulin (IVIg) infusion was given. However, the baby succumbed to death due to severe heart failure. The summary of the pregnancy event of this reported case is shown in Table 1.

DISCUSSION

As a prevention of RhD alloimmunisation, many countries including Malaysia practise to administer antenatal and postnatal anti-D

TABLE 1: Summary of pregnancy event

	Mother		Newborn (first child)
	Antenatal	**Intrapartum/postpartum**	
ABO and RhD grouping	O, RhD positive	O, RhD negative	O, RhD positive
Rh phenotype	Not done	rr (cde/cde)	Not done
Antibody screening and identification	Not done	Positive, anti-D	Not done
Anti-D titre	Not done	1:4096	Not done
DCT	Not done	Not done	Positive (2+)
Anti-D prophylaxis	Not given since was identified as RhD positive	Not indicated	–
Fetal outcome	No close fetal monitoring but initial ultrasound at first trimester revealed normal fetal growth	Fetal distress during delivery	Expired due to severe anaemia and hydrops
Risk of RhD alloimmunisation	Unknown Denied any extramarital conception, miscarriage, ectopic pregnancy, antenatal sensitisation events or history of blood transfusion		–

immunoglobulin (RhIg) prophylaxis in all non-immunised RhD negative women including primigravida.[1] However, RhD alloimmunisation still occurs due to the non-compliance of established guideline for RhIg prophylaxis and failure to detect fetomaternal haemorrhage (FMH) event or failure to identify RhD negative woman.[9] In this case report, patient was misidentified as RhD positive during antenatal follow up due to technical error in blood grouping. Hence, there was no antenatal antibody screening, close fetal monitoring and failure to administer routine antenatal anti-D prophylaxis which resulted in RhD alloimmunisation. ABO and RhD grouping errors can be due to clerical, technical and technician observation errors or mistakes in recording the result. Strict adherence to the standard procedure can further limit the error. Non-adherence to standard procedure and using of tile method despite recommended tube or microcolumn gel card for ABO and RhD grouping at antenatal clinic probably lead to misidentified RhD grouping in the reported case as it has high rate of error and inaccuracy.[10]

This case showed an unusual case of RhD alloimmunisation in RhD negative primigravida without apparent evidence of exposure to RhD antigen where she presented with severe HDFN with a very high anti-D titre. Based on our knowledge and literature review, there were only few reported cases of RhD alloimmunisation in primigravida especially without an apparent sensitisation event.[7,11,12,13]

There are a few possible explanations of alloimmunisation in this patient. The first explanation is due to an anamnestic response from unknown previous sensitisation event such as premarital conception, miscarriage, antepartum haemorrhage or blood transfusion which was all denied by the patient. It has been reported that some women became pregnant and spontaneously miscarried without being aware of either events.[14,15] Second exposure of RhD positive antigen from unrevealed FMH in the second or third trimester in this current pregnancy leads to a markedly increased of anti-D titre.

The second explanation is the new development of anti-D in the second trimester due to unrevealed FMH since there was no antenatal anti-D prophylaxis administration was given as patient was misidentified as RhD positive. The production of anti-D in RhD negative women is variable. Some women will become immunised after exposure to as little as 0.1-1.0 mL of RhD positive fetal red cells while some women will only become immunised after being exposed to as much as 200 mL of RhD positive red cells. As for some other women, they will never become immunised despite repeated exposure to RhD positive red cells.[16] Subsequent FMH in third trimester leads to a markedly increased of anti-D titre. Previous study reported that before the introduction of postnatal anti-D prophylaxis, 10 to 20% of RhD negative primigravidas became immunised during pregnancy and 8% of these women developed anti-D antibodies before 29 weeks of gestation.[17,18]

The third explanation is the theory of "Grandmother Syndrome" where probably the patient had been sensitised following FMH of RhD positive blood from her mother. Following exposure to the new load of RhD antigen from her RhD positive fetus through unrevealed FMH, the anamnestic response got awakened and led to this rare case of severe HDFN in the primigravida patient.[6,7,19] However, a group of researchers reported no evidence of anti-D production in RhD negative mother that was influenced by the RhD type of her mother.[20] Thus, the theory of "grandmother syndrome" is less likely to be the explanation of anti-D production in the case presented here.

CONCLUSION

This case showed an undiagnosed RhD negative in primigravida. Early detection is important for antenatal antibody screening, close fetal monitoring and routine antenatal anti-D prophylaxis to prevent fetal loss. This case illustrates the possibility of an anamnestic response of allo-antiD from previous sensitisation in a RhD negative mother, or the new development of anti-D in mid-trimester. Thus, it highlights the importance of investigations for the prevention or early detection of HDFN. This includes proper antenatal screening for blood grouping (ABO and RhD) and antibody screening and if neccessary regular monitoring of antibody screening and antibody titre.

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REFERENCES

1. Urbanik SJ, Greiss MA. RhD haemolytic disease of the fetus and the newborn. Blood Rev. 2000; 14: 44-61.

2. Hassan MN, Mohd Noor NH, Johan Noor SR, Sukri SA, Mustafa R. Red blood cell alloimmunisation among Malay pregnant women: A tertiary hospital experience. Int Med J. 2015; 22: 154-8.
3. Klein HG, Anstee DJ, editors. Mollison's blood transfusion in clinical medicine. 11th ed. Oxford:Blackwell Publishing. c2005. 865 p.
4. El Din SMN, Aramy ARM, Ali MS. Correlation between the RhD genotyping and RhD serotyping in isoimmunized pregnancies. Egypt J Med Hum Genet. 2011; 12: 127-33.
5. Kumar A, Patel MK, Chavda B, Ranjan A, Ahmad F. Hemolytic disease of the newborn: A study of 50 cases, Int J Sci Study. 2013; 1: 95-9.
6. Pushpa D, Umber A, Krishna S. An unusual case of immune hydrops occurring in a primigravida. J Obstet Gynecol Ind. 2004; 54: 501.
7. Biggins KR, Bowman JM. Rh(D) alloimmunisation in the absence of exposure to Rh(D) antigen. Vox Sang. 1986; 51: 228-30.
8. Moise KJ Jr. Management of rhesus alloimmunisation in pregnancy. Am Coll Obstet Gynecol. 2002; 100: 600-11.
9. Minon JM, Gerard CH, Chantraine F, Nisolle M. Anti-D prophylaxis reviewed in the era of foetal RHD genotyping. J Blood Disord Transfus. 2015; 6: 1-6.
10. Moghaddam ES, Khosravi S, Dorgalaleh A. Discrepancies in ABO and Rh grouping in Southeast Iran, an analysis of 3 years' experience. J Blood Disord Transfus. 2016; 7(4): 1-3.
11. Wong LK, Smith LH, Jensen HM. Hemolytic disease of the newborn following maternal self-injection of blood. Transfusion. 1983; 23: 348-9.
12. Badami KG, Vankecke C, Bingham J. Maternal IgM anti-D, borderline foetal Doppler middle cerebral artery velocities and absent neonatal haemolysis. Transfus Med. 2009; 19: 146-7.
13. Brunker PAR. Chimerism in transfusion medicine. The grandmother effect revisited. Chimerism. 2013; 4: 119-25.
14. Ellish NJ, Saboda K, Connor JO, Nasca PC, Stanek EJ, Boyle C. A prospective study of early pregnancy loss. Hum Reprod. 1996, 11; 406-12.
15. Wilcox AJ, Weinberg CR, O'Connor JF, Baird DD, Schlattere JP, Canfield RE *et al*. Incidence of early loss of pregnancy. N Engl J Med. 1988; 319: 189-94.
16. ACOG practice bulletin. Prevention of Rh D alloimmunisation. Number 4, May 1999 (replaces educational bulletin Number 147, October 1990). Clinical management guidelines for obstetrician-gynecologists. American College of Obstetrics and Gynaecology. Int J Gynaecol Obstet. 1999; 66: 69-70.
17. Bowman JM. Incidence of rh immunization. Can med Assoc J. 1969; 101: 112.
18. Bowman JM. Chown B, Lewis M, Pollock JM. Rh isoimmunization during pregnancy: Antenatal prophylaxis. Can Med Assoc J. 1978; 118: 623-7.
19. Kormozi GF, Mayr WR. Responder individuality in red blood cell alloimmunisation. Transfus Med Hemother. 2014; 41: 446-51.
20. Booth PB, Dunsford I, Grant J, Murray S. Haemolytic disease in first-born infants. BMJ. 1953; 2: 41-42.