TRANSFUSION MEDICINE
Official Journal of the British Blood Transfusion Society
British Blood Transfusion Society
Transfusion Medicine | LETTER TO THE EDITOR

Clinical disparity of haemolytic disease of the fetus and newborn in twin pregnancy

Dear Sir,

A 32-year-old Caucasian woman, blood group O RhD-negative (cde/cde, rr), gravida 4 para 2, presented to our institution for management of a spontaneously conceived dichorionic twin pregnancy. Her previous pregnancy was affected by Haemolytic Disease of the Fetus and Newborn (HDFN), necessitating induction at 38 weeks gestation for elevated and rising levels of anti-D and the baby required phototherapy after delivery.

This current pregnancy was a dichorionic twin pregnancy. Both anti-D and anti-G antibodies were detected through indirect antiglobulin testing in a maternal sample at 13 weeks gestation. Anti-D antibody levels were quantified using the Astoria Pacific International 300 (API 300) continuous flow analyser (CFA) using group O R_1R_1 (CCDDee) reagent cells (Marsh *et al.*, 1968) and are measured in IU mL^{-1}. The following levels of anti-D were used to guide management; <4 (HDFN unlikely), 4–15 (moderate risk of HDFN), >15 (risk of severe HDFN) (Gooch *et al.*, 2007). Anti-D quantitation levels are provided in Table 1.

The patient underwent surveillance for fetal anaemia with middle cerebral artery (MCA) Doppler studies once and subsequently twice weekly from 24 weeks gestation. Owing to increasing MCA Doppler Peak systolic velocity values (PSVs) as shown in Table 1, twin A required three intrauterine transfusions (IUTs) by cordocentesis of packed red blood cells (PRCs) of 100, 60 and 160 mL at 27, 29 and 34 weeks gestation, respectively. Anti-D antibody levels rose dramatically to 330 IU/mL following the first IUT. While twin B had evidence of mild intrauterine fetal anaemia (PSV 1·5 MoMs), this did not persist and an IUT was not required. There was no evidence of hydrops or fetal compromise in either twin throughout the pregnancy.

The twins were delivered via caesarean section at 34 weeks and 3 days of gestation for the indication of suspected chorioamnionitis. Twin A was 2·4 kg with Apgar scores of nine at 1 and 5 min. Twin A was blood group O RhD-positive (R_2r phenotype) cDE/cde, with a strongly positive direct antiglobulin test (DAT) (4+, IgG), haemoglobin of 16·9 g/dL, reticulocytes 222×10^9 L^{-1} (4·2%) and bilirubin of 132 μmol L^{-1}. On the first day of life this infant received intravenous immunoglobulin, phototherapy and a subsequent double volume exchange transfusion using irradiated whole O RhD-negative blood at 8 hours of life in addition to two transfusions of PRCs at 20 mL kg^{-1} per bolus for treatment of HDFN. Twin B was noted to be 2·2 kg and the same Apgar scores as her sister. Twin B was A RhD-positive (R_0r phenotype), cDe/cde with a strongly positive DAT (4+, IgG), haemoglobin of 7·7 g dL^{-1}, reticulocytes 335×10^9 L^{-1} (18·2%) and bilirubin 114 μmol L^{-1}. This infant required five transfusions of PRCs from day 1 to day 20 of life at 20 mL kg^{-1} per bolus.

Table 1. Current pregnancy – antibody levels and corresponding gestation (weeks) in addition to correlating right middle cerebral artery (MCA) peak systolic velocity (PSV) values form twin A (cm s^{-1}).

Gestation (weeks)	Anti-D quantitation (IU mL^{-1})	MCA PSV twin A (cm s^{-1})
13	21·76	–
17	45·56	–
22	75·76	–
25	65·12	34
27	66·53	68[1]
29	330·03	55
34	214·67	86[1]
Gestation (weeks)	Anti-G titration	
Throughout	1/4	

[1]MCA PSV above 1·5 multiples of the median for gestational age.

Pathologic examination confirmed the presence of dichorionic placentation. Both placental discs appeared similar with no pallor, colour difference, oedema or evidence of chorioamnionitis. The placenta from twin A weighed 479 g and showed no gross pathological findings with an unremarkable umbilical cord. Microscopically, there was evidence of laminar decidual necrosis, villous oedema and increased fetal nucleated red blood cells. These findings correlate with the presence of fetal haemolytic anaemia resulting in the release of immature erythroid precursors (erythroblasts) into the circulation of twin A. The placenta from twin B weighed 490 g and also showed no gross pathology with an unremarkable umbilical cord. Microscopically there was mild acceleration with chorangiosis. Placental weights were in keeping with gestational age with findings consistent with that of HDFN.

Supplemental investigations included a screen of maternal plasma for immune anti-A (IgG), which was detectable at a titre of 1/512, and a negative screen for class II human leukocyte antigen (HLA) antibodies. There was insufficient neonatal blood to analyze anti-D levels or perform elution studies at the time of delivery, however at 10 weeks of infancy anti-D quantitations measured for investigative/academic purposes in twin A and twin B were 2·2 and 1·4 IU mL^{-1}, respectively.

This report describes a case of dichorionic twins both of which were RhD-positive, with equally strongly positive

Correspondence: Dr Fionnuala Mone, UCD Obstetrics and Gynaecology, School of Medicine and Medical Science, National Maternity Hospital, Holles St, Dublin 2, Dublin, Ireland.
Tel.: +353 1 637 3100; fax: +353 1 637 3436; e-mail: fmone@nmh.ie

First published online 13 August 2015
doi: 10.1111/tme.12230

result on DAT (4+, IgG) but differentially affected by RhD allo-isoimmunization antenatally and HDFN postnatally. It is interesting to note that despite relatively normal MCA PSV values below 1·5 multiples of the median in twin B, this infant had a notable anaemia at birth. While it would seem counter-intuitive that there would be discordant involvement by the twins by HDFN, it has been described a number of times before (Beischer *et al.*, 1969 Knuppel *et al.*, 1984 and Bowman, 1985). The former papers suggested a protective effect of fetal maternal ABO incompatibility as recognized to occur in RhD alloimmunization. However the effect of ABO incompatibility on differing severity of disease in twins was disputed in the paper by Bowman (1985) who suggested other possible mechanisms, including differences in placental perfusion, fetal erythropoiesis fetal hepatocellular function.

A second explanation for the discrepancy in severity of HFDN between twins may be because of the fact they had different Rh haplotypes (R_2r and R_or), which may result in different RhD antigen density on red cells (Issitt & Anstee, 1998).

A third possible mechanism is the presence of Fc-receptor blocking antibodies; cases have been described in the literature whereby the presence of monocyte IgG alloantibodies which are HLA-DR specific prevent HDFN, despite a strongly positive DAT result through blocking FcR-mediated haemolysis (Dooren *et al.*, 1992; Dooren *et al.*, 1993). In this case the maternal plasma did not contain antibodies to HLA class II antigens.

Fourthly, there may have been diminished placental transport of IgG to the less severely affected twin. Twin B was noted to have a lower residual anti-D level than twin A when tested at 10 weeks of age despite having not received a whole-blood exchange (Dooren & Engelfriet, 1993).

In conclusion we report a case of a dichorionic diamniotic twin pregnancy with both infants displaying a discrepancy for the severity of RhD isoimmunisation antenatally and HDFN postnatally, despite the twins being RhD positive. We postulate that this is because of ABO incompatibility or impaired placental transport of IgG causing the more severely affected twin (A) to confer a protective effect to the less severely affected twin (B).

ACKNOWLEDGMENTS

All authors contributed to and approved the final manuscript. FM, SC, SH, RM, FMcA and PMcP contributed to essential intra-uterine transfusion and fetal medicine antenatal investigation and management of this case. JQ, BD, ML, MW, PD and JF performed relevant haematological and pathological investigations relevant to this case study and were also pivotal in clinical management antenatally and postnatally.

CONFLICT OF INTEREST

The authors have no competing interests.

F. Mone[1,2], J. Quigley[3], B. Doyle[4], M. Lambert[4], M. Woolfson[4], P. Downey[3], S. Carroll[1], S. Higgins[1,2], R. Mahony[1], F. M. Mcauliffe[1,2], J. Fitzgerald[3] & P. Mcparland[1] *[1]Department of Fetal Medicine, National Maternity Hospital, Dublin, [2]UCD Obstetrics and Gynaecology, School of Medicine and Medical Science University College Dublin, [3]Department of Pathology and Laboratory Medicine, National Maternity Hospital, Dublin, [4]Irish Blood Transfusion Service, National Blood Centre, Dublin*

REFERENCES

Beischer, N.A., Pepperell, R.J. & Barrie, J.U. (1969) Twin pregnancy and erythroblastosis. *Obstetrics & Gynecology*, **34**, 22–29.

Bowman, J.M. (1985) Alloimmunization in twin pregnancies. *American Journal of Obstetrics and Gynecology*, **153**, 7–13.

Dooren, M.C. & Engelfriet, C.P. (1993) Protection against Rh D-haemolytic disease of the newborn by a diminished transport of maternal IgG to the fetus. *Vox Sanguinis*, **65**, 59–61.

Dooren, M.C., Kuijers, R.W.A.M., Joekes, E.C. *et al.* (1992) Protection against immune haemolytic disease of newborn infants by maternal monocyte-reactive IgG alloantibodies (anti-HLA-DR). *Lancet*, **339**, 1067–1070.

Dooren, M.C., van, Kamp, I.L., Kanhai, H.H.H., Bennebroek Gravenhorst, J., von, dem Borne, A.E.G.K.R. & Engelfriet, C.P. (1993) Evidence for the protective effect of FcR-blocking IgG alloantibodies HLA-DR in Rh D-haemolytic disease of the newborn. *Vox Sanguinis*, **65**, 55–58.

Gooch, A., Parker, J., Wray, J. & Qureshi, H. (2007) Guideline for blood group and antibody testing in pregnancy. British Committee for Standards in Haematology Blood Transfusion Task Force. *Transfusion Medicine*, **17**, 252–262.

Issitt, P.D. & Anstee, D.J. (1998) *Applied Blood Group Serology* (4th edn). Miami, Florida, Montgomery Scientific Publications.

Knuppel, R.A., Shah, D.M., Rattan, P.K., O'Brien, W.F. & Lerner, A. (1984) Rhesus isoimmunization in twin gestation. *American Journal of Obstetrics and Gynecology*, **150**, 136–142.

Marsh, W.L., Nichols, M. & Jenkins, W.J. (1968) Automated detection of blood group antibodies. *The Journal of Medical Laboratory Technology*, **25**, 335–342.