Rh haemolytic disease: continuing problem of management

D J Swinhoe, D H Gilmore, M B McNay, M J Whittle

Abstract

Eighteen patients with severe Rh haemolytic disease, all of whom underwent fetal blood sampling and intrauterine transfusion, were studied. Twelve babies survived (67%) all of whom were delivered by lower segment caesarean section. There were three intra-uterine deaths resulting in late abortion, one stillbirth with trisomy 21, and two neonatal deaths (both from severe prematurity). The traditional prognostic indicators were all inaccurate, and fetal blood sampling and measurement of the fetal packed cell volume were the most direct methods of assessing haemolysis. The progression of severe Rh disease is unpredictable, and we believe that all cases should be referred to specialist centres for advice or treatment.

Severe Rh haemolytic disease has become rare since the introduction of anti-D prophylaxis in the late 1960s.¹ New cases still occur, however, because of failure to administer anti-D, because a 'silent' immunising event occurs, or because the immunising event overwhelms the effect of the anti-D prophylaxis.²

Several authors have outlined the current approach to the management of Rh disease, including the use of intravascular transfusion.³⁻⁵ Numbers are necessarily small and the reports of individual groups provide useful information. We report our experience from a single regional unit that receives referrals from Scotland and the north west of England.

Patients and methods

Eighteen patients with fetuses severely affected by Rh haemolytic disease were treated from 1986 until the end of July 1988. They had a total of 50 previous pregnancies, five of which had ended before 28 weeks' gestation because of Rh disease; 45 were delivered after 28 weeks of which eight were stillbirths and one died in the neonatal period (20%).

Indications for treatment during their current pregnancies were: (i) an obstetric history of a previously affected baby with a cord haemoglobin concentration of less than 100 g/l, a baby requiring exchange or top up transfusions, a fetus requiring intrauterine transfusion, or a previous pregnancy resulting in a late abortion, stillbirth or neonatal death from Rh disease; (ii) a change in the optical density 450 of the amniotic fluid, indicating the need for intervention using 'Whitfield's action line'⁶; and (iii) ultrasonographic evidence of hydrops—for

example, ascites, skin oedema, and pericardial or pleural effusions.

Fetal blood samples were all taken with a 20 gauge needle and a needle guide attached to a 5 mHz sector transducer (Diasonics, DRF 400). Samples were immediately checked to make sure that they were fetal in origin, and the packed cell volume was used to calculate the amount of donor blood required to raise the fetal packed cell volume to 0.40.⁷ Coombs's test, karyotype, blood grouping, infection screen, and biochemical analysis were also carried out on this first sample.

Patients were given oral lorazepam 4 mg and cephadrine 500 mg two hours before the procedure, intramuscular papaveretum 10 mg and perphenazine 5 mg one hour before the procedure for pain relief, prophylaxis of infection, and to reduce fetal activity. Diuretics, inotropic or chronotropic drugs, and muscle relaxants were not used. No patient underwent plasmapheresis,⁸ and by the time of referral all had raised antibody concentrations (mean=40 IU/ml, range=11-256 IU/ml). The initial fetal blood samplings were carried out at a mean gestational age of 25 weeks (range=18-31), the mean packed cell volume being 0.20 (range 0.08-0.32).

They underwent a total of 72 transfusions: intravascular alone (n=39), intraperitoneal alone (n=14), intravascular (n=8) with additional elective intraperitoneal transfusions (n=8), which were counted as separate procedures. Three intracardiac transfusions were done because of technical problems with cordocentesis. The mean number of transfusions per patient was four (range 0-9). We failed to cannulate the cord 19 times, nine times because the fetus moved.

The data have been divided into groups based on the baby's condition at delivery in the last pregnancy, as this was thought to be the most important prognostic indicator: mild—Coombs's test positive, baby possibly needing phototherapy but no transfusion; moderate—exchange or top up transfusion needed after delivery, and severe—previous late abortion, stillbirths, or neonatal death, cord haemoglobin <100 g/l at delivery or previous intrauterine transfusion.

Results

The timing of the 'sensitising event', the Liley zone of the first sample of amniotic fluid taken, the change in antibody content, the ultrasound appearances at presentation, the packed cell volume at the time of first fetal blood sampling, and the mean gestational age at

Queen Mother's
Hospital, Glasgow,
Department of Obstetrics
and Gynaecology
D J Swinhoe

Department of
Midwifery
D H Gilmore

Department of
Ultrasonography
M B McNay

Department of Fetal
Medicine
M J Whittle

Correspondence to:
Dr M J Whittle,
Department of
Fetal Medicine,
Queen Mother's
Hospital, Yorkhill,
Glasgow G3 8SJ.

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Table 1 Predicted severity of Rh disease based on outcome of previous pregnancies and investigation and outcome of present pregnancy

	Mild (n=6)	Moderate (n=3)	Severe (n=9)
Time of sensitising event:			
Unknown	0	0	1
Silent, antenatal	2	1	5
Despite anti-D	2	1	2
Anti-D not given	2	1	1
Optical density (Liley zone) of amniotic fluid:			
IIB	0	2	1
IIA	4	0	2
IB	0	0	1
Amniocentesis not done	2	1	5
Serum anti-D concentration (IU/ml):			
At time of booking	8	26	53
Mean value by time of first fetal blood sample	40	24	33
Maximum increase	×25	×4	×7
Single: multiple antibody ratio	2:4	0:3	2:7
Appearance on ultrasound scan:			
Normal	3	0	5
Ascites alone	0	2	2
'Hydrops'	3	1	2
Packed cell volume at time of first fetal blood sample:			
>0.30	1	0	1
0.20 to 0.30	3	1	7
<0.20	2	2	1
Mean gestational age at time of first fetal blood sample (weeks)	25	27	24
Mean No of transfusions	3.6	2.8	5.2
Outcome:			
Normal	5	1	6
Abortion	0	1	2
Stillbirth	0	0	1
Early neonatal death	0	1	0
Late neonatal death	1	0	0

the time that the first sample was taken were arranged in the three prognostic groups. There were six patients in the mild group, three in the moderate group, and nine in the severe group (table 1).

SENSITISING EVENT

Only one of the 18 patients had an inadequate explanation for sensitisation (seven had silent antenatal events, and five had overwhelming sensitising events). Silent antenatal sensitisation was more common in the severe group but there were no other important correlations. Anti-D prophylaxis had not been given to five patients.

AMNIOTIC FLUID

Of the 10 patients in whom an initial amniocentesis was carried out, one had optical density 450 in Liley zone IB, six in zone IIA, and three

in zone IIB. There were no patients with measurements in zone IA or III.

There was no correlation between the results of amniocentesis at presentation and the prognostic group; eight patients did not have amniocentesis.

ANTIBODY CONCENTRATION AT THE TIME OF BOOKING

The mean antibody concentration in the blood at the time of booking varied with the severity of the past obstetric history, and patients in the severe group were more likely to have higher mean antibody concentrations in early pregnancy than those in the mild group. By the time of the first fetal blood sample, however, the difference between the mild and severe groups had disappeared. There was a noticeable difference between groups when the 'increase to maximum antibody concentration' was considered. There

Table 2 Details of birth, neonatal requirements, and outcome related to severity of Rh disease predicted by obstetric history

Case No	No of intrauterine transfusions	Gestational age at delivery (weeks)	Mode of delivery	Birth weight (g)	Apgar score		Cord blood concentrations	
					1 min	5 mins	Haemoglobin (g/l)	Bilirubin (μmol/l)
Mild disease								
1	3	34	Caesarean section	1940	6	8	122	95
2	7	29	Caesarean section*	1520	1	4†	120	79
3	5	33	Caesarean section	1790	7	7	120	30
4	7	32	Caesarean section	1790	7	8	115	30
5	3	33	Caesarean section	2350	9	9	137	50
6	3	33	Caesarean section	1190	9	9	128	70
Moderate disease								
7	0	32	Caesarean section*	1780	6	9	50	120
8	1	27	Vaginal	1260	Not recorded		48	Not applicable
9	5	27	Caesarean section*	1250	1	3	100	Not applicable
Severe disease								
10	3	32	Caesarean section	2060	9	10	110	100
11	9	33	Caesarean section	2230	9	10	73	144
12	6	32	Caesarean section	2720	7	9	161	89
13	4	32	Vaginal	3060	0	0	Not applicable	
14	6	31	Caesarean section*	2040	8	9		
15	3	22	Vaginal	630	Not recorded		12	Not applicable
16	4	33	Caesarean section	1900	9	10	95	Not recorded
17	2	33	Caesarean section	2700	6	8	146	121
18	2	25	Vaginal	1150	Not recorded		60	Not applicable

*Emergency operation; †Apgar score at 10 mins=7.

was a 25 fold increase in the mild group compared with a sevenfold increase in the severe group. Patients in the moderate and severe groups were more likely to have multiple and rare antibodies.

APPEARANCES ON ULTRASONOGRAPHY

Ten of the 18 fetuses had ultrasonographic evidence of ascites, but of these, six had definite evidence of hydrops (defined as scalp oedema and ascites); one of the fetuses developed these signs during treatment. Patients in the mild group were more likely to have a normal ultrasound scan at the time of fetal blood sampling.

INITIAL PACKED CELL VOLUME

In 16 of the 18 cases the packed cell volume of the fetus was less than 0.3, and there were no differences among the groups. The mean gestational age at which the first fetal blood sample had to be taken and the number of transfusions necessary to treat the fetus adequately were similar in the three groups, except that case 7 in the moderate group did not have an intrauterine transfusion (table 2).

OUTCOME OF PREGNANCY

Twelve babies survived (67%) (table 2). All the babies who had a normal outcome were delivered by elective lower segment caesarean section. Half the babies who were delivered by emergency caesarean section died including two neonatal deaths of babies who were delivered because of acute complications during intrauterine transfusions. There were three intrauterine deaths (chromosomally normal, late abortions), occurring because of sudden deterioration together with technical difficulties during transfusion. The stillborn fetus had trisomy 21 that was detected at the time of the first fetal blood sample (case 13), and intrauterine treatment was abandoned after full discussion with the parents.

NEONATAL OUTCOME

There was no significant difference in birth

weight, Apgar scores, cord haemoglobin, serum bilirubin concentration, peak serum bilirubin concentration, number of days of artificial ventilation, number of days receiving oxygen, the need for exchange or top up transfusions, and grouping according to obstetric history. Six of the 10 fetuses with ascites alone or evidence of hydrops at the time of the first fetal blood sample had a normal outcome. The hydrops resolved, after intrauterine transfusion in all cases, apart from the chromosomally abnormal fetus. Five patients of the eight who had normal ultrasonographic appearances at the time of the first fetal blood sample had normal outcomes.

Discussion

Severe Rh haemolytic disease requiring treatment is now uncommon (occurring in roughly one in 6000 pregnancies) and outcome should be optimal if supervision is restricted to a few specialist centres. Not only is the problem rare but the traditional methods of assessing prognosis are inaccurate; there seems to be little correlation between obstetric history and any of the previously used predictors of outcome (table 1).

PAST HISTORY

Rh haemolytic disease increases in severity with each subsequent pregnancy. This effect can, however, be unexpectedly aggressive, so that even patients predicted to be in the mild category can have pregnancies affected by devastating disease.

MATERNAL ANTIBODIES

Both the serum antibody concentration at the time of booking, and its change early in pregnancy, are poor predictors of fetal outcome. The rise in antibody content was not always associated with a rapid fall in fetal haemoglobin concentration as might be expected during haemolysis. Indeed, a rise in antibody concentration occurred after the fall in fetal haemoglobin concentration in five cases. The rise in antibody concentration has been considered, at

Peak serum bilirubin concentration ($\mu\text{mol/l}$)	No of exchange transfusions	No of top up transfusions	No of days artificially ventilated	Respiratory distress syndrome	Cranial ultrasound scan	Outcome
339	4	0	6	Yes	Normal	Alive
280	2	0	11	Yes	Intraventricular haemorrhage	Late neonatal death
Not recorded	0	0	Not recorded	No	Normal	Alive
61	1	1	0	No	Normal	Alive
150	0	1	0	No	Normal	Alive
130	0	1	0	No	Normal	Alive
320	3	0	4	No	Normal	Alive
						Late abortion
						Early neonatal death
320	2	0	0	No	Normal	Alive
219	3	0	1	No	Normal	Alive
245	3	0	0	No	Normal	Alive
						Stillbirth
Not recorded	0	0	0	No	Normal	Alive
						Late abortion
Not recorded	2	0	0	No	Normal	Alive
157	0	1	0	No	Normal	Alive
						Late abortion

Change in fetal packed cell volume and gestational age in case 4. IVT=intravenous transfusion, IPT=intraperitoneal transfusion, and ICT=intracardiac transfusion.

least in part, to be related to cordocentesis itself,⁹ but we could find no evidence to support this view and think that it is more likely to be a reflection of the disease.

The antibody concentration, and its rise, have been used in the past to judge the extent of Rh disease, but serious disease may be present in patients with comparatively low antibody concentrations. An increasing proportion of patients with severe disease, however, have multiple and rarer antibodies. More information is required about the transfer of maternal antibodies, antibody avidity, and the fetal factors concerned in acute haemolysis before we can understand the importance of these observations.

AMNIOTIC FLUID OPTICAL DENSITY 450

All our patients showed signs of severe Rh disease quite early in pregnancy, and consequently most of the values obtained indicated the need for urgent intervention. Amniotic fluid analysis has a part to play in mild to moderate disease,¹⁰ but probably not when events dictate intervention before 24 weeks' gestation at which time repeated fetal blood sampling may be a more appropriate investigation.

ULTRASONOGRAPHY

This seems to be of limited value in the assessment of Rh disease,¹¹ as deterioration may be so rapid that an apparently normal fetus one day may have become hydropic the next. It did prove useful, however, in monitoring treatment and the resolution of hydropic features after transfusion.

FETAL BLOOD SAMPLING

Direct measurement of the packed cell volume of the fetus gives precise information about the progress of the disease and permits accurate calculation of the volume of blood required for transfusion. Other 'causes' of fetal hydrops may

also be excluded, and the fetal karyotype assessed.

The figure shows the changes in the fetal packed cell volume with repeated intrauterine transfusions in one patient, and shows the typical peaks after transfusion and troughs beforehand. As treatment proceeds, fetal red cells disappear as a result of destruction and marrow suppression. The packed cell volume stabilises, so that the interval between treatments may be lengthened; these may be further extended by combining intraperitoneal and intravenous transfusion.

SENSITISING EVENTS

A good case can be made for the introduction of routine antenatal prophylaxis with anti-D, which appears to reduce the incidence of 'silent' antenatal sensitisation; seven of the 17 patients in whom the method of sensitisation was known became sensitised in this way. Of concern is the large proportion of patients who never received any anti-D at the time of a sensitising event or at delivery.

CONCLUSION

Rh haemolytic disease is still a serious problem for those few affected pregnancies and it is unlikely to disappear. Although it is a rare condition it necessitates intensive management from both obstetric and paediatric units. All potentially affected cases, possibly with the exception of patients with only traces of antibodies, should be referred as early as possible to a regional unit for either advice or treatment. This need is emphasised by the rather unpredictable course that Rh disease now seems to follow.

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