The outcome of babies of mothers with severe Rhesus incompatibility treated at Tygerberg Hospital, 1980 - 1993

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Objective. To determine the outcome of babies of mothers with severe rhesus (Rh) incompatibility treated by elective delivery when the amniotic optical density at 450 nm crossed Whitfield's action line (group 1), by plasmapheresis and immunotherapy (group 2) or by means of intra-uterine intravascular transfusions (group 3).

Study design. A retrospective study of 55 mothers and their 57 fetuses with severe Rh incompatibility at < 34 weeks' pregnancy duration.

Main outcome parameters. Number of mothers in each treatment group, prevalence of intra-uterine death, hydrops, intra-uterine intravascular transfusions, cord haematocrit, cord bilirubin, number of liveborn babies, birth weight, neonatal death, hyaline membrane disease (HMD) and exchange transfusions.

Study population and setting. All mothers and babies with severe Rh incompatibility (defined as an amniotic optical density of 450 nm in the upper and upper-mid zone on the Liley chart at < 34 weeks' pregnancy duration, previous fetal hydrops or Rh-related intra-uterine death (IUD), fetal hydrops on ultrasound or a fetal haematocrit < 30% at cordocentesis) treated at Tygerberg Hospital between January 1980 and January 1993. There were 20 fetuses each in groups 1 and 3, and 17 in group 2.

Results. A total of 48 babies (84%) were liveborn and of these 74% survived the neonatal period. There were 9

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IUDs of which 6 were due to hydrops fetalis and the remaining 3 to abruptio placentae and complications relating to intra-uterine intravascular transfusion. Of the 11 hydropic babies, 6 died *in utero*. The 6 neonatal deaths were due to hydrops fetalis (2), HMD, necrotising enterocolitis and triploidy. The majority of deaths occurred in group 1.

The mean birth weight of all 3 groups was 1 801 g (SD 519), the mean gestational age 31,83 weeks (SD 3,8), the mean cord haemoglobin level 10,23 g/dl (SD 2,8) and the mean cord bilirubin value 104,3 µmol/l.

Of the 23 mothers (all in groups 2 and 3) with a previous Rh-related IUD, 6 (26%) lost their babies again in the present pregnancy. All the babies in group 1 were liveborn, 76% of the babies in group 2 and 75% of the babies in group 3. Thirty-nine (95%) of the 41 intra-uterine intravascular attempted transfusions on fetuses in group 3 were successful. The 3 babies who received > 3 intra-uterine transfusions had a protracted anaemia after birth, requiring 3 - 4 transfusions.

Conclusions. The improved outcome of the fetuses is probably partly due to the plasmaphereses and intra-uterine intravascular transfusions as well as improved ante- and postnatal care. The fetuses who received > 3 intra-uterine intravascular transfusions had protracted anaemia after birth, requiring frequent blood transfusions.

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Rhesus (Rh) incompatibility is to a large extent a preventable problem.[1] Since the introduction of anti-D immunoglobin (Ig) prophylaxis to Rh-negative mothers, there has been a dramatic decrease in perinatal losses due to Rh iso-immune disease, but severely affected cases are still seen. It is estimated that only 44% of the Rh-negative patients in South Africa who should receive anti-D IgG according to accepted practices actually do receive it.[2] Severely affected pregnant women will therefore continue to require referral to tertiary centres as, without treatment, about 15% of all Rh-immunised pregnancies will result in stillbirth.[3]

The fall in perinatal mortality caused by Rh disease of the newborn is also related to an improvement in neonatal care, reduced family size and newer treatment modalities for the pregnant mother and fetus.[3]

The management of this disorder has changed progressively over the years from a more conservative approach where the baby is delivered if the amniotic bilirubin levels cross the action line on the Liley chart,[4] to plasmapheresis with immunotherapy[5] and more recently to intra-uterine intravascular red blood cell transfusions.[1,3,6] The last-mentioned form of therapy has improved survival of severely affected fetuses[6] to 70 - 80% and of non-hydropic fetuses to 80 - 90%, but is sometimes associated with specific neonatal complications such as a 'late' hyporegenerative anaemia.[7]

We report the outcome of babies of mothers with severe Rh disease treated at Tygerberg Hospital since 1980 by means of these three modalities.

Patients and methods

The files of all mothers and their babies with severe Rh incompatibility treated between January 1980 and January 1993 at Tygerberg Hospital, the teaching hospital of the University of Stellenbosch, were studied retrospectively.

Severe Rh incompatibility was defined as: (*i*) amniotic optical density of 450 nm in the upper-mid and upper zone on the Liley chart < 34 weeks' pregnancy duration (the mid zone of the Liley chart was subdivided into equal zones, the upper- and lower-mid zone); (*ii*) previous fetal hydrops or Rh-related intra-uterine death; (*iii*) fetal ascites or oedema on antenatal ultrasound; or (*iv*) a fetal haematocrit (Hct) < 30% at cordocentesis.

Before 1989, all patients with Rh incompatibility were managed according to a standard protocol using the Liley chart and Whitfield action line. In 1980 plasmapheresis with immunosuppression was commenced in mothers with a history of a previous severely affected fetus and when it was demonstrated beyond doubt in early pregnancy that the fetus was again severely affected. After 1989, ultrasound-guided cordocentesis was used to determine the degree of fetal haemolysis when the maternal anti-D titre rose above 64 in mid-trimester or hydropic changes were noted on antenatal ultrasound. Intra-uterine intravascular transfusions were started in 1989. An intra-uterine intravascular transfusion (IUIVT) was given when the umbilical venous haemoglobin concentration was < 10 g/dl or the Hct was < 30% at cordocentesis.

The mothers were divided into three groups according to the management they received for their Rh incompatibility: group 1 — those who underwent elective delivery if amniotic optical density at 450 nm exceeded Whitfield's action line or hydropic changes were detected on ultrasound; group 2 — those who received plasmapheresis and immunotherapy; group 3 — those who received intra-uterine intravascular transfusions.

Results

A total of 55 mothers and 57 fetuses (including 1 twin) were studied. The mean age of the mothers was 28,12 years (SD 4,65); median gravidity 4 (range 2 - 7); median parity 2 (range 1 - 6); 30 (54%) were of mixed descent, 24 (43%) were white and 1 (3%) black. Of the mothers 23 (41%) had had a previous Rh-related intra-uterine death (IUD) and 21 (38%) a previous hydropic fetus.

In the present study, there were 11 fetuses with hydrops fetalis of whom 6 died *in utero*. The other 3 IUDs were due to abruptio placentae, chorio-amnionitis and a cord haematoma respectively.

Forty-eight babies (84%) were liveborn and 74% survived the neonatal period. Their mean birth weight was 1 801,7 g (SD 519); mean gestational age 31,83 weeks (SD 3,8); mean cord haemoglobin concentration 10,23 g/dl (SD 2,8); mean cord bilirubin level 104,3 µmol/l and mean cord platelet count 177,5 x 10^9/l (SD 108,5). Eight babies (14%) required ventilation for hyaline membrane disease (HMD).

There were 6 neonatal deaths, of which 2 were due to severe HMD, 1 to necrotising enterocolitis (NEC) associated with severe perinatal asphyxia, 1 to triploidy and 2 to severe

hydrops fetalis. The death of one hydropic baby resulted from poor antenatal clinic attendance by the mother who returned for follow-up 6 weeks after a previous amniocentesis. The other hydropic baby died 1 week after an IUIVT followed by premature rupture of membranes and premature birth. In total 15 of the babies (26,5%) died ante- or postnatally.

There were 19 mothers and 20 fetuses in group 1, 16 mothers and 17 fetuses in group 2 and 20 mothers and fetuses each in group 3.

Seventeen of the mothers in group 1 had an indirect Coombs titre of > 64 and 2 had titres of 32 during the mid-trimester of pregnancy. Fifteen of the mothers in group 2 had an indirect Coombs titre > 256 and 1 a titre of 64. In group 3, 3 mothers had titres of 16, 2 had titres of 32 and the rest all had titres of > 64. Only 1 mother (5%) in group 1 had had a previous Rh-related IUD, as opposed to 9 (56%) in group 2 and 13 (65%) in group 3.

The causes of the IUDs in the present study according to the various treatment groups are shown in Table I.

Table I. Causes of IUDs in the various treatment groups

Group	1	2	3	All fetuses
No. of fetuses	20	17	20	57
No. of hydropic fetuses	1	4	6	11
No. of IUDs	0	4	5	9
Causes of IUD				
Hydrops fetalis	0	3*	3†	6
Cord haematoma	0	0	1	1
Chorio-amnionitis	0	0	1	1
Abruptio placentae	0	1	0	1

* Died at 23, 24 and 30 weeks.
† Died at 19, 23 and 26 weeks.

The neonatal characteristics and course of the babies in the three treatment groups are shown in Tables II and III respectively.

Table II. The neonatal characteristics of the various treatment groups

Group	1	2	3	All babies
Liveborn (%)	20 (100)	13 (76)	15 (75)	48 (84)
Mean weight (g)	1 921	1 773	1 699	1 801
Mean GA (wks)	33,4[a,b]	31,17[a]	30,85[b]	31,83
5 min Apgar score	8,1	8,2	7,9	8
Mean cord Hct (%)	38,4	32,8	31,6	34,69
Mean cord bilirubin (µmol/l)	104,4	96,15	112	104,3
Mean cord platelets x 10^9/l	192	194	154	177,5
With cord Hct < 30% (%)	7 (35)	7 (54)	7 (46)	21 (44)

GA = gestational age; Hct = haematocrit.
[a] Differed statistically at $P = 0,048$.
[b] Differed statistically at $P = 0,03$.

A total of 41 IUIVTs were attempted in the fetuses in group 3, of which 39 (95%) were successful. The mean gestational age at the first IUIVT was 28 weeks (range 18 - 33 weeks) and the mean number of IUIVTs was 1,5 (range 1 - 5). The 3 babies in group 3 who received > 3 IUIVTs, had a protracted anaemia requiring 3 - 4 blood transfusions each during the first 4 months of life, whereafter the anaemia resolved spontaneously.

Table III. Neonatal course of the babies in the various treatment groups

Group	1	2	3	All babies	*P*
Phototherapy (%)	95	100	80	94	NS
Exchange transfusions:					
< 2	9	8	4	21	NS
> 2	11	5	9	25	NS
HMD (%)	5 (25)	5 (38)	1 (7)	11 (23)	
HMD and ventilation (%)	5 (25)	1 (8)	2 (13)	8 (17)	
PPHN (%)	0	1 (8)	1 (7)	2 (4)	
Neonatal death (%)	4 (20)	1 (8)	1 (7)	6 (12,5)	
Cause of death:					
HMD	2	0	0	2	
Hydrops fetalis	1	1*	0	2	
Asphyxia	1	0	0	1	
Triploidy	0	0	1	1	

* Intraperitoneal transfusion 1 week before birth.

Discussion

Hydrops fetalis and/or intra-uterine and neonatal death commonly occur in the offspring of sensitised Rh-negative mothers with high antibody titres (> 64) early in pregnancy.[3] Allen *et al.*[8] reported on the outcome of 469 sensitised pregnancies managed conservatively and noted that 23% of fetuses were stillborn and 5% died of hydrops fetalis in the neonatal period. Walker[9] noted that a previous history of severe haemolytic disease is a valuable guide for predicting outcome. The risk of stillbirth is about 20% if the previous infant was severely affected and 63% if the previous baby was stillborn.[9] Without treatment the outcome for these fetuses remains dismal. It is often difficult to compare the outcomes of different treatment regimens for Rh iso-immunisation to each other or even to an untreated group of sensitised mothers, because of the unpredictability and variability of this disorder.[9]

In recent years, the management of Rh-sensitised mothers has improved dramatically with a marked reduction in the perinatal mortality.[3,10] This was also the trend in our study. Among the 23 mothers with a previous Rh-related IUD, 6 (26%) of their babies died. The improved outcome of the fetuses is probably partly due to the plasmapheresis and IUIVTs as well as to improved ante- and postnatal care.

Eighty-four per cent of the babies in the present study were liveborn; this correlates well with other reported series of severely sensitised mothers.[1,3,9] The severe degree of sensitisation of the mothers in this study is reflected by the low mean gestational age at which their babies had to be delivered.

In the 9 babies (15%) who died *in utero*, 6 deaths were due to hydrops fetalis. The 3 IUDs from hydrops fetalis in group 2 occurred before IUIVT became available at our institution. The other hydropic fetus in group 2 received an intra-uterine intraperitoneal transfusion but was nonetheless born hydropic after premature rupture of the membranes. This baby died soon after birth. Of the 6 hydropic fetuses in group 3, hydrops fetalis was reversed with IUIVT in 3 (50%) but not in the other 3 fetuses who subsequently died *in*

utero. All 3 of these were already severely hydropic at an early gestational age on referral to our unit. A recent report[1] indicates that hydrops fetalis can be reversed with IUIVT in about 60% of cases and that the survival rate is almost 90% in reversed cases, while survival is only 43% if the hydrops fetalis cannot be reversed with intra-uterine transfusions.

IUIVT is technically a more difficult procedure in the fetus < 24 weeks and is also hazardous.[6] The gestational ages of the 3 severely hydropic fetuses in group 3 who died in spite of IUIVTs, were 19, 23 and 26 weeks respectively. For this reason, plasmapheresis and immunotherapy should be reserved for the mother with severe sensitisation at a very early stage of pregnancy in order to prevent hydrops fetalis and to prolong pregnancy up to a point when IUIVTs can be performed with least risk to the fetus.[5]

The deaths of the other 2 fetuses in group 3 were due to procedure-related complications at 31 and 27 weeks, i.e. cord haematoma and chorio-amnionitis. Procedure-related complications do occur during and after IUIVTs, and include fetal bradycardia, cord haematoma, chorio-amnionitis, maternal sensitisation and chronic haemorrhage from the puncture site in the cord.[3,11] The fetal mortality rate for IUIVT has been reported to be 2% per transfusion.[3] A cord Hct of < 30% is regarded as an indication of severe Rh immunisation.[1] Seven of the babies (37%) in group 1 and 54% of the babies in group 2 had cord Hcts < 30% at birth and would have qualified for IUIVT had current criteria been applied.

Respiratory distress commonly occurs in babies of mothers with Rh sensitisation.[3,12] Eleven babies (23%) in the present study developed HMD, diagnosed on the basis of typical radiological changes on their chest radiographs. The majority of such cases occurred in groups 1 (25%) and 2 (38%). All 5 of the babies with HMD in group 1 required positive-pressure ventilation; 2 of these died. Many of the mothers in group 1 were managed in the early 1980s and some of them did not receive antenatal steroids for fetal surfactant induction. Of the 7 babies (38%) in the plasmapheresis group who developed HMD despite their mothers having received steroids for immunosuppression, only 1 required ventilation for a short period. Prednisone does not, however, cross the placenta as well as betamethasone.[13] All the mothers in group 3 received antenatal steroids and only 2 babies in this group developed HMD and required ventilation. They were born at 26 and 29 weeks respectively and were delivered for severe fetal distress caused by IUIVT-related complications (cord haematoma and fetal bradycardia). Surfactant production in these 2 babies could have been suppressed by the severe asphyxial episodes.

The highest neonatal mortality rate was evident in group 1 (20%) and this trend was due to severe HMD, NEC and hydrops. This could have been related to the facilities available in the ICU and non-availability of exogenous surfactant in the early 1980s.

There were 2 babies with persistent pulmonary hypertension (PPHN), 1 each in groups 2 and 3. Both required ventilation and survived. They were both relatively more mature at gestational ages of 33 and 35 weeks. No definite cause for the PPHN could be identified in either.

There were no differences in the total number of exchange transfusions or babies requiring more or fewer than two exchange transfusions between the 3 groups. There were 6 babies (30%) in group 1 and one set of twins (15%) in group 2 who did not require any exchange transfusions. One of the twin babies in group 2 was Rh-negative. All of their mothers had a history of a previous mildly affected baby not requiring exchange transfusions. This finding is in keeping with that of Walker *et al.*[9] that 34% of babies require exchange transfusions if the previous baby was only mildly affected. Walker *et al.*[9] however, found a stillbirth rate of 2% in this group of babies.

Three of the babies in group 3 required no exchange transfusions despite their mothers' previously having had severely affected babies. They all received > 3 IUIVTs. Many infants treated with IUIVT do not require exchange transfusions for hyperbilirubinaemia after delivery as most of their red blood cells at birth are transfused Rh-negative red cells.[7,14] The severity of neonatal hyperbilirubinaemia, as reflected in the number of exchange transfusions required in the babies receiving < 2 IUIVTs, was similar to that of the babies who did not receive IUIVTs.

A problem in babies who received IUIVTs is the presence of a 'late' hyporegenerative anaemia with a low reticulocyte count that develops 1 - 3 months after birth.[7,14] The exact reason for this anaemia is unclear, but may be related to ongoing haemolysis caused by circulating antibodies and reduced erythropoietin production.[14] Infants with this late anaemia of Rh incompatibility require top-up red blood cell transfusions until their anaemia resolves spontaneously, usually by the 3rd or 4th month of life.[7] The 3 babies in the present study who required > 3 IUIVTs all developed a prolonged anaemia requiring 3 - 4 top-up transfusions. The anaemia resolved spontaneously in all of them by the age of 4 months. Ohls *et al.*[7] recently reported 2 infants with late anaemia of Rh disease treated successfully with erythropoietin. Neither baby required red blood cell transfusions following the erythropoietin therapy. One baby, however, developed a transient neutropenia and the authors concluded that placebo-controlled trials need to be conducted before erythropoietin can be recommended as an alternative to erythrocyte transfusions for the late anaemia of Rh incompatibility.[7]

The management of mothers and their babies with severe Rh incompatibility is difficult, expensive and associated with maternal and neonatal morbidity and mortality. The first aim should be to ensure that all Rh-negative mothers are identified and treated prophylactically with anti-D IgG, as most cases of Rh incompatibility in South Africa are the result of the omission of prophylaxis.[2] If the Rh mother does become sensitised, she should be referred to a specialist early in pregnancy. A patient with severe Rh sensitisation before fetal maturity should be referred to a tertiary centre with the facilities for plasmapheresis and IUIVTs and the baby should be delivered at a unit experienced in the management of Rh incompatibility and its complications. The following criteria are used to diagnose severe Rh sensitisation: (*i*) a history of previous severe Rh sensitisation, i.e. Rh-related fetal loss, fetal hydrops, major morbidity or the necessity for intra-uterine transfusions; (*ii*) signs of fetal hydrops on ultrasound; (*iii*) amniotic fluid optical density in the upper-mid zone or in the upper zone of the Liley graph; (*iv*) an indirect Coombs titre of ≥1/16 at < 20 weeks' gestation.

Plasmapheresis combined with immunosuppressive therapy (although expensive, time-consuming and likely to cause maternal morbidity) or high-dose intravenous immunoglobulin,[15] are currently the only forms of therapy available to reduce very high antibody levels early in pregnancy at a stage when IUIVTs are technically very difficult to perform.

Babies who received IUIVTs should also be followed up for several months to monitor their haemoglobin levels and, if indicated, they should receive top-up transfusions. The place of erythropoietin in the management of this peculiar anaemia should be established to reduce the risk of transfusion-transmitted infections in the babies.

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