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


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

- Rapid, soothing relief from the itching and burning caused by thrush
- 6 day course effective in mixed infections
- A range of treatment options to suit personal preferences
- Dedicated to women for over 20 years
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; (ii) 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 Whittlefield 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 (IUVT) 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 fluid 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 a previous Rh-related intra-uterine death (IUFD) and 21 (38%) a previous hydropic fetus.

Forty-eight babies (84%) were liveborn and 74% survived the neonatal period. Their mean birth weight was 3.017 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 value 104.3 µmol/L. 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 hydptic baby died 1 week after an IUlVT followed by premature rupture of membranes and premature birth. In total 15 of the babies (26.5%) died anten- 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 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

<table>
<thead>
<tr>
<th>Group</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>All fetuses</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of fetuses</td>
<td>20</td>
<td>17</td>
<td>20</td>
<td>57</td>
</tr>
<tr>
<td>No. of hydptic fetuses</td>
<td>1</td>
<td>4</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>No. of IUDs</td>
<td>0</td>
<td>4</td>
<td>5</td>
<td>9</td>
</tr>
</tbody>
</table>

Causes of IUD

- Hydrops fetalis
- Cord haematois
- Chorio-amnionitis
- Abrupplio placenta

Stage at diagnosis:

- Died at 23, 24 and 30 weeks.
- Died at 19, 23 and 25 weeks.

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

Table II. Neonatal characteristics of the various treatment groups

<table>
<thead>
<tr>
<th>Group</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>All babies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liveborn (%)</td>
<td>20 (100)</td>
<td>15 (75)</td>
<td>21 (77)</td>
<td>66 (84)</td>
</tr>
<tr>
<td>Mean weight (g)</td>
<td>1921</td>
<td>1773</td>
<td>1699</td>
<td>1801</td>
</tr>
<tr>
<td>Mean GA (wks)</td>
<td>33.4*</td>
<td>31.7*</td>
<td>30.85*</td>
<td>31.83</td>
</tr>
<tr>
<td>5 min Apgar score</td>
<td>8.1</td>
<td>8.2</td>
<td>7.9</td>
<td>8</td>
</tr>
<tr>
<td>Mean cord Hct (%)</td>
<td>38.4</td>
<td>32.8</td>
<td>31.6</td>
<td>34.68</td>
</tr>
<tr>
<td>Mean cord bilirubin (umol/l)</td>
<td>104.4</td>
<td>96.15</td>
<td>112</td>
<td>104.3</td>
</tr>
<tr>
<td>Mean cord platelets x 10^9/l</td>
<td>192</td>
<td>194</td>
<td>154</td>
<td>177.5</td>
</tr>
<tr>
<td>With cord Hct &lt; 30% (%)</td>
<td>7 (35)</td>
<td>7 (34)</td>
<td>7 (46)</td>
<td>21 (44)</td>
</tr>
</tbody>
</table>

Practice: gestational age; Hct = haematocrit.

* Differed statistically at P = 0.048.
** Differed statistically at P = 0.03.

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

<table>
<thead>
<tr>
<th>Group</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>All babies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phototherapy (%)</td>
<td>95</td>
<td>100</td>
<td>80</td>
<td>94</td>
</tr>
<tr>
<td>Exchange transfusions:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 2</td>
<td>9</td>
<td>8</td>
<td>4</td>
<td>21</td>
</tr>
<tr>
<td>&gt; 2</td>
<td>11</td>
<td>5</td>
<td>9</td>
<td>25</td>
</tr>
<tr>
<td>HMD (%)</td>
<td>5 (25)</td>
<td>5 (28)</td>
<td>1 (7)</td>
<td>11 (63)</td>
</tr>
<tr>
<td>HMD and ventilation (%)</td>
<td>5 (25)</td>
<td>1 (6)</td>
<td>2 (13)</td>
<td>8 (17)</td>
</tr>
<tr>
<td>PPHN (%)</td>
<td>0</td>
<td>1 (6)</td>
<td>1 (7)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Neonatal death (%)</td>
<td>4 (20)</td>
<td>1 (6)</td>
<td>1 (7)</td>
<td>6 (12.5)</td>
</tr>
<tr>
<td>Cause of death:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HMD</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Hydrops fetalis</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Asphyxia</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Triplody</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

* Intraparitional 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. Allen et al. 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 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. 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.

In recent years, the management of Rh-sensitised mothers has improved dramatically with a marked reduction in the perinatal mortality. 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 IUlVTs 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. 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 IUl VTs from hydrops fetalis in group 2 occurred before IUlVT became available at our institution. The other hydptic fetus in group 2 received an intra-uterine peritoneal transfusion but was nonetheless born hydptic after premature rupture of the membranes. This baby died soon after birth. Of the 6 hydptic fetuses in group 3, hydrops fetalis was reversed with IUlVT in 3 (50%) but not in the other 3 fetuses who subsequently died in...
uterine. All 3 of these were already severely hydropic at an early gestational age on referral to our unit. A recent report indicates that hydrops fetalis can be reversed with IUlVt 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 intrauterine transfusions.

IUlVt is technically a more difficult procedure in the fetus < 24 weeks and is also hazardous. The gestational ages of the 3 severely hydropic fetuses in group 3 who died in spite of IUlVts, were 29, 26 and 28 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 IUlVts can be performed with least risk to the fetus.

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 IUlVts, and include fetal bradycardia, cord haematoma, chorio-amnionitis, maternal sensitisation and chronic haemorrhage from the puncture site in the cord. The fetal mortality rate for IUlVt has been reported to be 2% per transfusion. A cord Hct of < 30% is regarded as an indication of severe Rh immunisation. 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 IUlVt had current criteria been applied.

Respiratory distress commonly occurs in babies of mothers with Rh sensitisation. 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. Predisposition does not, however, cross the placenta as well as betamethasone. 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 IUlVt-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. that 34% of babies require exchange transfusions if the previous baby was only mildly affected. Walker et al. 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 IUlVts. Many infants treated with IUlVt do not require exchange transfusions for hyperbilirubinaemia after delivery as most of their red blood cells at birth are transfused Rh-negative red cells. The severity of neonatal hyperbilirubinaemia, as reflected in the number of exchange transfusions required in the babies receiving < 2 IUlVts, was similar to that of the babies who did not receive IUlVts.

A problem in babies who received IUlVts is the presence of a 'late' hyporegenerative anaemia with a low reticulocyte count that develops 1 - 3 months after birth. The exact reason for this anaemia is unclear, but may be related to ongoing haemolysis caused by circulating antibodies and reduced erythropoietin production. 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. The 3 babies in the present study who required > 3 IUlVts 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. 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.

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. If the Rh mother does become sensitised, she should be referred to a specialist as 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 IUlVts 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 intrauterine 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, are currently the only forms of therapy available to reduce very high antibody levels early in pregnancy at a stage when IUlVls are technically very difficult to perform.

Babies who received IUlVls 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 erythropoetin 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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REFERENCES


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HPV typing of vulvovaginal condylomata in children

C. A. Wright, L. Taylor, K. Cooper

Objective. To determine the human papillomavirus (HPV) subtypes in vulvovaginal warts in prepubescent children.

Design. Histopathology case series.

Setting. Outpatient and gynaecology clinics of hospitals in the greater Johannesburg area.

Patients. All cases of vulvovaginal warts diagnosed in children under the age of 12 years received at the South African Institute for Medical Research, Johannesburg, during the period 1 January 1991 to 31 December 1993.

Main outcome measures. Positivity for 'genital' HPV types 6, 11, 16, 18, 31, 33 and 35 using non-isotopic in situ hybridisation (NISH) and polymerase chain reaction (PCR). Results. Eight of the 8 vulvovaginal warts contained HPV 11 when assessed by means of NISH (89%). PCR amplified HPV DNA in all 9 (100%) of the biopsies.

Conclusion. Detection of genital subtypes of HPV in childhood condylomata acuminata points strongly to sexual abuse, but should only be used as a guide to further investigation by a multidisciplinary team.

C. A. Wright, M.B.CH.B., F.F.PATH., M.R.C. PATH.

Condylomata acuminata (CA) are anogenital warts caused by human papillomaviruses (HPVs) and are usually sexually transmitted. Although more than 70 HPV types have been identified, they are to a large extent body-site specific. The subtypes most commonly associated with CA are 6, 11, 16 and 18. Respiratory papillomatosis in young children is also associated with HPV 6 and 11. HPV type 1 causes most plantar warts while HPV 2 is responsible for most common warts.

This retrospective study was undertaken to: (i) determine the incidence of 'genital' HPV types in vulvovaginal warts in prepubescent children; (ii) identify those children in whom possible sexual transmission had occurred; (iii) identify anogenital lesions with 'oncogenic' potential in childhood. The latter is significant as the incidence of genital cancer in South African women is high.

Subjects and methods

Vulvovaginal warts diagnosed in this department in children under the age of 12 years between January 1991 and December 1993 were reviewed.