CASE REPORT

A Successful Delivery of an Extremely Immature Infant in Rh Incompatibility after Plasma Exchange

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Abstract

When Rh incompatible pregnancies occur, intrauterine fetal transfusion (IUT) and plasma exchange (PE) have made it possible to prolong the prenatal duration and to dramatically decrease the neonatal mortality. We administered a total of 10 PEs (from 20 weeks to 27 weeks of gestation) and one IUT (at 27 weeks and 1 day) for an Rh-isoimmunized gravida who already had a high maternal serum Rh antibody titer at the 14th gestational week, and delivered by Caesarian section (CS) an extremely immature infant of only 873 grams at 27 weeks and 4 days of gestation. The infant was hydropic with hyperbilirubinemia, therefore exchange transfusions were administered immediately after birth. The infant's weight reached the lowest point of 669 grams on the 13th day after birth, but began to increase thereafter. The baby weighed 3,052 grams on the 144th day and left the hospital without any complications.

Key words: Rh-isoimmunization, plasma exchange, intrauterine transfusion, extremely immature infant, exchange transfusion
Rh incompatible pregnancy which is predisposed to fetal hemolytic disease and fetal hydrops is extremely rare in Japan. This is attributed to the fact that Rh-negative persons account for only 0.5% of the total population and that the Rh antiserum injection (Immunoglobulin Anti-D KABI) is widely practiced to prevent Rh-isoimmunization.

When this disease does occur unfortunately, intrauterine fetal transfusion (IUT) and plasma exchange (PE) have made it possible to prolong the prenatal duration and dramatically decrease neonatal mortality.

We administered PEs and IUT for an Rh-isoimmunized gravida, and delivered by Caesarian section (CS) an extremely immature infant weighing only 873 grams. The infant was able to leave the hospital in good condition.

Case Report

The mother was 28 years old with group B, Rh factor ccdee blood. Her husband was with group B, Rh factor CcDEe blood. She experienced two induced abortions, and since then had an intrauterine fetal death at the 24th gestational week. Maternal serum Rh antibody titrations were high from the first trimester. Therefore, PE and IUT were administered.

Using the blood cell separator (CS-3000, Travenol Laboratories, Inc., Tokyo), a total of 10 PEs were administered to the Rh-isoimmunized gravida for from 20 weeks to 27 weeks of gestation, with each treatment duration varying from 3 to 7 days. On

![Fig. 1 Effect of plasma exchange.](image)

each PE, the replacement fluid amount consisted of 2,000 ml of fresh frozen plasma (FFP) and plasma protein fraction (PPF). Figure 1 shows levels of maternal serum Rh antibody titrations during PEs. Two amniotic fluid analyses were performed. At 19 weeks and 1 day of gestation, the total bilirubin was 0.9 mg/dl, JOD₄₅₀ was at 0.445, and the Rh antibody titer was 1:32. At 26 weeks and 6 days, the total bilirubin changed to 15 mg/dl, JOD₄₅₀ to 0.472, the Rh antibody titer was 1:64, and amylase was 238 su/dl, creatinine was 0.4 mg/dl, and the shake test was positive (when diluted, at a ratio of 1:2).

Other examinations included ultrasonography and a non-stress test (NST). At 23 weeks and 5 days of gestation, fetal ascites was not detected on the ultrasonography.
From the 25th week, fetal ascites began to appear. The amniotic cavity decreased at the 26th week, and completely disappeared at the 27th week. The fetal pleural effusion and the halo sign (double contour sign) on the fetal head were not observed. At the 26th week, deceleration due to mild uterine contraction was noticed, but at the 26 weeks and 5 days, reactive patterns were observed on the NST. However, these reactive patterns disappeared at 27 weeks and 1 day and the fetal quickening subsided (subjective symptom).
Betamethasone and digitalis administration was commenced. The IUT was performed under ultrasonographic guidance. The needle was inserted through the lower right abdominal wall into the peritoneal cavity of fetus. After spontaneous flow of approximately 30 ml of fetal ascites, 45 ml of fresh and tightly packed blood cells were injected (group O, Rh negative, WBC 7,500/mm³, RBC 738 × 10⁴/mm³, Hb 21.6 g/dl, Ht 66.1%). From the day after IUT, decrease in fetal ascites and increase in the amniotic cavity were observed on ultrasonography. Reactive patterns reappeared on the NST and fetal quickening resumed (subjective symptom). However, the deceleration due to uterine contraction continued. Therefore, at the 27 weeks and 4 days of gestation (after 2 days and 14 hours of IUT), we delivered by Caesarian section (CS) a female infant of 873 grams.

The infant was hydropic with abdominal distension, hypoproteinemia (total protein 2.7 g/dl), anemia (Hb 2.8 g/dl) and hyperbilirubinemia (total bilirubin 3.3 mg/dl (Fig. 2, Table 1). The enlarged edematous placenta weighed 540 grams. The infant received three exchange transfusions immediately after birth. Subsequently, the total bilirubin level decreased. The clinical course of the infant for two weeks after the birth at NICU is shown in Fig. 3. The hydrops disappeared on the 5th day after birth, and from the 7th day nasal feeding began. The infant's weight reached the lowest point of 669 grams on the 13th day, but began to increase satisfactorily thereafter.

The baby weighed 3,052 grams on the 144th day and left the hospital without complications such as respiratory distress syndrome (RDS) and intracranial hemorrhage, except for retrolental fibroplasia (type I, stage 2).

Discussion

Whenever maternal serum Rh antibody titrations show a titer of over 1:64 in the early stage, the rate of intrauterine fetal death is generally considered to be high. Rh incompatible levels must be determined by amniotic fluid analysis. For the prevention of such severe hemolytic diseases of the newborn (severe HDN) as those unable to survive the postnatal period, IUT is an extremely effective treatment. However, the effective application of IUT is limited to periods after the 25th gestational week. In case where hydrops develops prior to the 25th week, the survival rate is low, even with IUT.

New treatments, therefore, have long been needed for application from an early gestational stage in severe HDN. Plasma exchange (PE) using a continuous flow type cell separator has emerged as an effective treatment to prevent fetal hemolysis.

PE is commenced at around the 12th week of gestation and continues until around the 30th week. After the 30th gestational week, PE becomes less effective in controlling the maternal serum Rh antibody concentration. Therefore, it must be decided
whether to perform the initial IUT or to induce a delivery combined with postnatal treatment. The induced delivery is performed after ultrasonographic observation of either fetal ascites, double contour sign of the fetal head, or sinusoidal patterns on NST. These observations can also be useful in determining the severity of HDN.6

When the maternal serum Rh antibody titer is high, the indications of PE are determined by measuring \( \Delta \text{OD}_{450} \) and Rh antibody titration, or if possible Rh antibody concentration, in the amniotic fluid.8 The maternal serum Rh antibody titration does
Rh Incompatibility and Plasma Exchange

not serve as a mean of evaluating PE effectiveness. Since amniocentesis has a danger of causing fetomaternal transfusion, it should be avoided prior to the 28th gestational week. In clinical practice, the PE is administered when the maternal serum Rh anti-

**Table 2 Plasma Exchanges on Rh-isoimmunized Gravida in Japan (Ukita)**

<table>
<thead>
<tr>
<th>No.</th>
<th>Hospital</th>
<th>Highest anti-D titer</th>
<th>Anti-D titer &amp; Time at PE initiation</th>
<th>Plasma exchange</th>
<th>Mode &amp; Time of delivery</th>
<th>Weight at birth (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kurashiki central univ.</td>
<td>512</td>
<td>512 (33w)</td>
<td>FFP x 3</td>
<td>Ind (38w)</td>
<td>3,200</td>
</tr>
<tr>
<td>2</td>
<td>Hiroasaki univ.</td>
<td>2,048</td>
<td>2,048 (33w)</td>
<td>FFP x 2</td>
<td>CS (34w)</td>
<td>2,140</td>
</tr>
<tr>
<td>3</td>
<td>Hiroasaki univ.</td>
<td>16,384</td>
<td>8,129 (26w)</td>
<td>FFP x 3</td>
<td>IUFD (20w)</td>
<td>1,885</td>
</tr>
<tr>
<td>4</td>
<td>Kitasato univ.</td>
<td>4,096 (21w)</td>
<td>2,048 (17w)</td>
<td>FFP + PPF x 2</td>
<td>IUFD (22w)</td>
<td>660</td>
</tr>
<tr>
<td>5</td>
<td>Kitasato univ.</td>
<td>512 (26w)</td>
<td>512 (28w)</td>
<td>FFP + PPF x 2</td>
<td>CS (32w)</td>
<td>1,809</td>
</tr>
<tr>
<td>6</td>
<td>Kitasato univ.</td>
<td>1,024 (17w)</td>
<td>1,024 (17w)</td>
<td>FFP + PPF x 3</td>
<td>Ind (38w)</td>
<td>3,090</td>
</tr>
<tr>
<td>7</td>
<td>Kitasato univ.</td>
<td>1,024 (29w)</td>
<td>256 (12w)</td>
<td>FFP + PPF x 4</td>
<td>CS (35w)</td>
<td>2,440</td>
</tr>
<tr>
<td>8</td>
<td>Osaka univ.</td>
<td>2,048</td>
<td>1,024 (26w)</td>
<td>FFP x 1, PA-FFP x 7</td>
<td>Ind (37w)</td>
<td>2,660</td>
</tr>
<tr>
<td>9</td>
<td>Asahikawa univ.</td>
<td>512</td>
<td>256</td>
<td>FFP + PPF x 2</td>
<td>CS (32w)</td>
<td>1,495</td>
</tr>
<tr>
<td>10</td>
<td>Kurashiki central univ.</td>
<td>512</td>
<td>512 (14w)</td>
<td>PPF + FFP 3 unit x 8</td>
<td>CS (30w)</td>
<td>1,966</td>
</tr>
<tr>
<td>11</td>
<td>Kurashiki central univ.</td>
<td>512</td>
<td>512 (28w)</td>
<td>PPF + FFP 3 unit x 4</td>
<td>CS (31w)</td>
<td>1,684</td>
</tr>
<tr>
<td>12</td>
<td>Kitasato univ.</td>
<td>8,192 (29w)</td>
<td>8,192 (29w)</td>
<td>FFP + PPF x 2</td>
<td>CS (29w)</td>
<td>1,050</td>
</tr>
<tr>
<td>13</td>
<td>Osaka univ.</td>
<td>4,096</td>
<td>2,048 (22w)</td>
<td>PPF x 1, PA-FFP x 4</td>
<td>(27w)</td>
<td>800(ND)</td>
</tr>
<tr>
<td>14</td>
<td>Kurashiki central univ.</td>
<td>2,048</td>
<td>512 (29w)</td>
<td>PPF x 1, PA-FFP x 6</td>
<td>CS (33w)</td>
<td>2,150</td>
</tr>
<tr>
<td>15</td>
<td>Osaka univ.</td>
<td>4,096</td>
<td>2,048</td>
<td>PPF x 1, PA-FFP x 5</td>
<td>IUFD (20w)</td>
<td>385</td>
</tr>
<tr>
<td>16</td>
<td>Niigata city</td>
<td>4,096 (31w)</td>
<td>4,096 (31w)</td>
<td>FFP x 5</td>
<td>CS (34w)</td>
<td>2,210</td>
</tr>
<tr>
<td>17</td>
<td>Niigata univ.</td>
<td>1,024 (33w)</td>
<td>128 (24w)</td>
<td>FFP x 11</td>
<td>CS (33w)</td>
<td>1,710</td>
</tr>
<tr>
<td>18</td>
<td>Fukuoka univ.</td>
<td>4,096</td>
<td>512 (27w)</td>
<td>FFP x 2, PA-FFP x 3</td>
<td>CS (32w)</td>
<td>2,010</td>
</tr>
<tr>
<td>19</td>
<td>Kurashiki central univ.</td>
<td>4,096</td>
<td>1,024 (16w)</td>
<td>PPF x 1, PA-FFP x 33</td>
<td>CS (28w)</td>
<td>1,280</td>
</tr>
<tr>
<td>20</td>
<td>Gunma univ.</td>
<td>1,024</td>
<td>256 (11w)</td>
<td>FFP + PPF x 22</td>
<td>Ind (34w)</td>
<td>2,530</td>
</tr>
</tbody>
</table>

body titration is in the titer between 1:64 and 1:1,024 in the first trimester.

The maternal serum Rh antibody concentration is closely correlated with an Rh-
incompatible level, thus being useful for scheduling PE and in evaluating its effective-
ness.\textsuperscript{9,10} In Japan, measurement of Rh antibody concentration is not yet performed
on a routine basis.

Several hospitals in Japan have treated Rh-isoimmunized gravida with plasma
exchange but no case of successful delivery of an extremely premature infant prior
to 28 weeks of gestation has, yet, been reported (Table 2). Our report appears to be
the only report of a successful case in which an extremely premature infant arrived
alive with the lowest ever weight from an Rh-isoimmunized gravida. This report also
warns against induced abortion among nullipara, since the gravida in our report was
Rh-isoimmunized because of induced abortions on two previous occasions.

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