ovular, which reduced the likelihood of complications such as hydramnios; and there were no signs of pre-eclampsia until labour had started.

We should like to thank Dr. J. G. Steyn, Medical Superintendent of Frere Hospital, for permission to publish this paper and for his cooperation throughout, and Dr. E. L. F. McConnachie, Head of the Dept. of Obstetrics and Gynaecology, for his help in organizing the facilities for the premature babies.

We would also never have managed without the help of the matron, Miss C. L. Meghun, and Sisters M. E. Otte, G. Mytuka, L. Gallant, D. Lumko, E. Nomkweso and I. Pfeifer. Thanks are due also to Dr. J. B. Naude for assistance with the delivery of the quintuplets; Dr. E. L. F. McConnachie, Mr. Marius Garb, Mr. R. J. Bomford and the Tukutese Quintuplets Trust (Pty) Ltd. for the photographs; Mrs. R. Rauber for the Spanish translation; Johnson & Johnson (Pty) Ltd. for obtaining reprints of all the relevant literature. Finally, we should like to make special mention of Dr. G. F. Harris of Butterworth, who first saw the patient and diagnosed the quintuplet pregnancy before transferring the patient to the Frere Hospital.

ADDENDUM

On 25 October 1967 Ngesi Tukutese delivered twin girls weighing 6 lb. 8 oz. and 7 lb. 11 oz. at the Frere Hospital. The twins, who are binovular, are progressing well.

INTRA-UTERINE TRANSFUSION IN THE MANAGEMENT OF SEVERE RHESUS ISO-IMMUNIZATION*


The first successful intra-uterine transfusion was reported by Liley in November 1963. This was followed by a further 2 successful cases reported by McCrostie in 1964. The procedure represents a realistic approach to the prevention of intra-uterine death in selected instances, allowing additional time for foetal maturation to occur in utero. Subsequent experience1-11 has confirmed the value of the technique and it has become accepted in many centres throughout the world.

Our experience, summarized in Table I, dates from March 1965, and our first successful case was reported in July 1965. This paper, which involves 13 infants on whom a total of 26 intra-uterine transfusions were performed, describes how we select our cases for the procedure, the technique employed, the complications encountered and the results obtained.

SELECTION OF PATIENTS

It has been shown that 40-45% of all stillbirths and hydropic live births due to haemolytic disease occur before the 34th week of pregnancy12,13 and it is our aim to salvage these infants, in whom the hazards of prematurity are overwhelming when induction is carried out before 34 weeks. In common with other workers in this field, we find that antibody titres are totally unreliable in the assessment of the individual case, their value being limited to the selection of cases for amniocentesis. Selection of cases for transfusion is based upon analysis of liquor amnii by spectrophotometry and, to a lesser extent, the past history. The first amniocentesis is performed between 24 and 32 weeks' gestation, and in those cases with a poor past history, the liquor is analyzed by spectrophotometry and, to a lesser extent, the past history.

Following spectrophotometric analysis of the liquor, the optical density difference value (ODD) at the 450-mu peak is plotted on a modification of Liley's chart14 (see Fig. 1).

Our indications for transfusion may be summarized as follows:

1. An initial or subsequent result falling in the upper zone.
2. A rise, on subsequent amniocentesis, within mid-zone C.
3. A rise, on subsequent amniocentesis, from a lower zone into mid-zone C.

Should these results be obtained at or after the 34th week of pregnancy, the case would be managed by immediate termination of pregnancy rather than intra-uterine transfusion.

REFERENCES

Indications for the procedure in the patients in this series are summarized in Table II, and amniocentesis results in this series are graphically represented in Fig. 2.

![Fig. 1. Prediction chart (modification of Liley's chart).](image1)

![Fig. 2. Amniocentesis results in this series.](image2)

The indications for transfusion in 2 of the cases merit more detailed discussion. It will be noted that there is no amniocentesis result for case 10. This patient had had 2 previous pregnancies, the first of which terminated in the delivery of an unaffected infant. The second pregnancy was terminated at 36 weeks, on the basis of amniocentesis findings, and the very severely affected infant died 3 days after birth. The patient was seen for the first time in her third pregnancy at 28 weeks, with an anti-D titre of 1:256, gross oedema and raised blood pressure. Amniocentesis was unsuccessful and X-ray showed signs of hydrops foetalis. Three days after apparently successful intra-uterine transfusion, she delivered a stillborn, grossly hydropic infant. In the second instance, case 11, the amniocentesis result did not fulfil our usual criteria for transfusion as based on liquor amnii spectrophotometry alone. This patient had had 4 live births, followed by 3

**TABLE II. INDICATIONS FOR TRANSFUSION**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Index No.</th>
<th>Affected infants</th>
<th>Previous losses</th>
<th>Antibody titres</th>
<th>( \text{ODD}^* \text{ at 450 m\text{	extmu}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A1</td>
<td>2</td>
<td>1</td>
<td>1:32</td>
<td>0.220 (30-5 w)</td>
</tr>
<tr>
<td>2</td>
<td>A16</td>
<td>5</td>
<td>3</td>
<td>1:124</td>
<td>0.200 (30.5 w)</td>
</tr>
<tr>
<td>3</td>
<td>A64</td>
<td>1</td>
<td>0</td>
<td>1:16</td>
<td>0.100 (29.0 w)</td>
</tr>
<tr>
<td>4</td>
<td>A71</td>
<td>1</td>
<td>0</td>
<td>1:16</td>
<td>0.125 (32-0 w)</td>
</tr>
<tr>
<td>5</td>
<td>A128</td>
<td>2</td>
<td>1</td>
<td>1:16</td>
<td>0.120 (30-0 w)</td>
</tr>
<tr>
<td>6</td>
<td>A146</td>
<td>2</td>
<td>1</td>
<td>1:16</td>
<td>0.185 (32-0 w)</td>
</tr>
<tr>
<td>7</td>
<td>A158</td>
<td>2</td>
<td>0</td>
<td>1:32</td>
<td>0.460 (27-4 w)</td>
</tr>
<tr>
<td>8</td>
<td>A180</td>
<td>2</td>
<td>0</td>
<td>1:32</td>
<td>0.170 (30-0 w)</td>
</tr>
<tr>
<td>9</td>
<td>A222</td>
<td>3</td>
<td>3</td>
<td>1:256</td>
<td>0.424 (32-0 w)</td>
</tr>
<tr>
<td>10</td>
<td>A223</td>
<td>1</td>
<td>1</td>
<td>1:256</td>
<td>0.140 (30-2 w)</td>
</tr>
<tr>
<td>11</td>
<td>A245</td>
<td>5</td>
<td>4</td>
<td>1:256</td>
<td>0.270 (32-2 w)</td>
</tr>
<tr>
<td>12</td>
<td>A215</td>
<td>3</td>
<td>0</td>
<td>1:256</td>
<td>0.483 (27-3 w)</td>
</tr>
<tr>
<td>13</td>
<td>A229</td>
<td>3</td>
<td>1</td>
<td>1:256</td>
<td>0.506 (24-0 w)</td>
</tr>
</tbody>
</table>

*\( \text{ODD}^* = \text{optical density difference.} \)
neonatal deaths at 40 weeks, 36 weeks and 34 weeks, followed by an intra-uterine death at 32 weeks. Transfusion was performed at 28\(\frac{1}{2}\) weeks, and 4 days later she delivered a stillborn hydropic infant.

**TECHNIQUE**

Modern radiographic equipment, incorporating image intensification and television monitoring, greatly simplifies this procedure compared with the earlier descriptions when plain radiography was used.\(^{2,5,10}\) Initially, the method described by Holman and Karnaiki\(^{11}\) was followed in broad outline, but thereafter the technique was modified in the light of experience, in order to utilize the image intensifier and television monitor to their full advantage.

The procedure is performed in the X-ray department, the patient having been sedated with 100 mg. of pethidine and 25 mg. of promazine. It is desirable that the patient should be placed on the table a \(\frac{1}{2}\) hr. before commencing the transfusion, so that the foetus may assume a stable position.

Immediately before the transfusion, anteroposterior and lateral radiographs are taken, in the supine position, and with a metal marker on the umbilicus. This provides a visual record of the lie of the foetus, the position of the limbs, the costal margins and the vertebral column. The target area of the foetal abdomen can then be visualized, making allowance for the thighs and the liver. The umbilical marker provides a maternal landmark for correlation with the foetal target area in selecting the line of approach for the needle. At this stage the foetal lie is corrected by external manipulation, if necessary, to give access to the foetal anterior abdominal wall.

After surgical cleansing and draping, the puncture site is infiltrated with local anaesthetic. A tiny skin incision is made and a 16-gauge Tuohy needle is introduced through the maternal abdominal and uterine walls into the amniotic cavity. It is then advanced towards the foetal abdomen under television control, and as soon as it makes contact with the foetal anterior abdominal wall.

Confirmation of its presence in the foetal peritoneal cavity, and as soon as it makes contact with the foetus this becomes obvious by the foetal movement imparted to it. Slight resistance is then overcome as the needle passes through the foetal abdominal wall. Approximately 5 ml. of 45% Hypaque is then injected through the needle under television control. The flow of dye in characteristic pattern around the loops of bowel and under the diaphragm confirms the proper position.

Fresh group O Rhesus-negative packed red cells in acid-citrate-dextrose, compatible by cross-match with the mother's serum, are transfused directly through the Tuohy needle. The blood is warmed to 37°C in a waterbath immediately before transfusion.

The volume of packed cells transfused has varied greatly, the minimum being 50 ml. at 28 weeks and maximum 175 ml. at 34 weeks. Until recently there has been little agreement concerning the optimum amount to be transfused. Charles et al.\(^{12}\) and Gordon et al.\(^{13}\) have pointed out that the amount given should be determined by the estimated foetal and placental blood volume, i.e. up to 15% of the estimated foetal weight. On this basis it is calculated that the amount transfused should be approximately 75% of the estimated total blood volume. This would indicate amounts of 80 ml. at 28 weeks and up to 180 ml. at 32 weeks.

Postoperatively the patient is kept in bed for 24 hours and we have administered a routine 4-day course of ampicillin. The patients are usually allowed home on the 4th day. The procedure is repeated fortnightly until such time as it is considered that the foetus is of sufficient maturity and weight to be safely delivered, usually the 38th week.

Our technique differs in 2 respects from that described by most other workers. In common with Little et al.\(^{14}\) and Charles et al.\(^{12}\) we do not introduce a catheter through the Tuohy needle. This refinement was discarded after the first transfusion, since direct injection of opaque medium through the needle gives immediate and more convincing confirmation of its presence in the foetal peritoneal cavity.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Transfusions</th>
<th>Delivery</th>
<th>Haemoglobin</th>
<th>No. exchange transfusions</th>
<th>Foetal outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>5</td>
<td>CS</td>
<td>32-4</td>
<td>14-0 99-4</td>
<td>Alive</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>CS</td>
<td>30-0</td>
<td>11-5 94-4</td>
<td>Alive</td>
</tr>
<tr>
<td>11</td>
<td>1</td>
<td>CS</td>
<td>32-3</td>
<td>11-5 95</td>
<td>Alive</td>
</tr>
<tr>
<td>12</td>
<td>3</td>
<td>CS</td>
<td>30-0</td>
<td>11-5 94</td>
<td>Alive</td>
</tr>
<tr>
<td>13</td>
<td>3</td>
<td>CS</td>
<td>33-0</td>
<td>11-5 95</td>
<td>Alive</td>
</tr>
</tbody>
</table>

NND = Neonatal death; CS = caesarean section; SB = stillbirth; RDS = respiratory distress syndrome.
and the transfusion of packed cells proceeds more expeditiously through the needle than through the necessarily fine-bore catheter.

Nor do we perform amniography, in order to outline the foetal gut, as a matter of routine before the transfusion. Its use involves additional uterine trauma and we have restricted it to those early cases in whom the foetal skeleton is difficult to visualize on the television screen. We would recommend its use in cases of under 30 weeks' gestation.

COMPLICATIONS

In our experience, intra-uterine transfusion has proved to be a relatively simple procedure, although it is not without risk, particularly to the foetus. There were 2 technical failures in this series. In one of these (case 5, Table III) transfusion was successful when attempted on 2 subsequent occasions. In the other (case 12, Table III) 3 previously successful transfusions had been performed. Pregnancy was immediately terminated, with a successful outcome.

As the procedure is performed in the X-ray department, where it is virtually impossible to maintain operating theatre standards of asepsis, our constant fear has been that of infection. That this fear was justified was unfortunately demonstrated in case 9 (Table III). This patient developed severe pyrexia and obvious signs of intra-uterine infection 48 hours after the second transfusion, in spite of prophylactic ampicillin. Spontaneous labour ensued and she delivered a macerated, grossly infected foetus.

We have constantly been aware of the possibility of trauma to some vital foetal organ. We have needled and injected dye into soft tissues, the pleural space, bowel and bladder, without ill-effect. The greatest danger seems to be trauma to the foetal liver. This has occurred once, to our knowledge (case 8, Table III). This patient developed severe pyrexia and obvious signs of intra-uterine infection 48 hours after the second transfusion, in spite of prophylactic ampicillin. Spontaneous labour ensued and she delivered a macerated, grossly infected foetus.

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least 5 of the infants seemed to be surviving entirely upon the donor cells in their circulation. These figures have convinced us of the efficacy of this method of treatment of haemolytic disease.

Delivery at about 35 weeks has been our goal, the earliest delivery among survivors being 32 weeks and 4 days (case 5). This patient commenced labour spontaneously 8 days after the last transfusion. The remaining 7 live-born infants were delivered between 34 weeks 4 days and 36 weeks 3 days, 5 of them by caesarean section. We prefer delivery by this means, purely from the point of view of convenience as the team of obstetrician, paediatrician and serologist can be assembled at a given time.

The condition of the babies at birth has been good and none has been sufficiently distressed to require immediate exchange transfusion. The first transfusion has usually been carried out at about 3 hours under optimal conditions.

Six of the live-born infants required 2 exchange transfusions, and one case required 3 exchange transfusions. Case 6 was unusual in that the infant required 5 exchange transfusions. This infant, who was delivered 3 days after the second intra-uterine transfusion, had a cord haemoglobin level of only 10·7 G/100 ml., only 50% of this being donor in origin. The exchange transfusions were dictated by rapidly rising bilirubin levels, which were not a feature of those infants born with higher percentage of donor cells.

The respiratory distress syndrome (RDS) has been a problem in this series, cases 2, 3 and 12 being affected and the last being the only survivor. Unlike Gordon et al., we have not encountered a high incidence of neonatal infections.

It is still too early to make any accurate long-term assessment of the condition and state of development of surviving infants.

<table>
<thead>
<tr>
<th>TABLE VII. RISK OF FOETAL DEATH FROM TRANSFUSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foetal deaths after 26 transfusions</td>
</tr>
<tr>
<td>(exclude 3 hydrops foetalis and 4 transfusions)</td>
</tr>
<tr>
<td>Foetal deaths after 22 transfusions</td>
</tr>
</tbody>
</table>

attributed to the procedure itself. Friesen et al., in their series of 96 intra-uterine transfusions, estimated the operative mortality as 14·5%. This emphasizes the necessity for establishing stringent indications before intra-uterine transfusions are done.

The universal failure to save hydropic infants would appear to establish hydrops foetalis as a contraindication to intra-uterine transfusion. We have not as yet attempted to reduce oedema fluid by either intraperitoneal dialysis or administration of diuretics to the foetus at the time of transfusion. These methods may offer some hope of success.

In retrospect we feel that our selection of cases has been reasonably satisfactory, and we propose in future to maintain our present criteria for intra-uterine transfusion. We feel strongly that enlightened management can lead to an enormous reduction in foetal loss in Rhesus disease. By means of spectrophotometric analysis of liquor amnii, selective premature termination of pregnancy and limited intra-uterine transfusion, in the type of patients described here, the perinatal mortality due to Rhesus iso-immunization in the Obstetric Units of the University of Cape Town was reduced to 6% during 1966.

**SUMMARY**

This paper describes our experiences with the procedure of intra-uterine transfusion of the foetus, the indications, technique employed, complications encountered and results obtained. Thirteen infants were treated, 8 were born alive and 6 survived. The procedure carries a definite risk to the foetus and the indications must therefore be stringent. The results obtained suggest that this technique represents a realistic means of salvaging infants severely affected by Rhesus iso-immunization.

We wish to thank Prof. D. A. Davie for his constant advice and encouragement; Dr. M. C. Botha, Pathologist-in-Charge of the Cape Provincial Blood Grouping Laboratory, for placing the facilities of his laboratory at our disposal; Mr. J. Rees and Mrs. I. du Toit for their expert technical assistance; and Dr. J. G. Burger, Medical Superintendent of Groote Schuur Hospital, and Dr. J. A. Hendriksz, Director of Hospital Services, Cape Province, for permission to publish. This work was made possible by grants from the University of Cape Town Staff Research Fund, the C. L. Herman Bequest and the Council for Scientific and Industrial Research.

**REFERENCES**