INTRAUTERINE TRANSFUSION

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The treatment of haemolytic disease of the newborn has advanced dramatically in recent years. The analysis of the liquor amnii, (Bevis, 1956; Liley, 1961, 1963; Walker, 1962), has permitted more precise assessment of the state of the foetus in utero. For very severely affected babies an early induction of labour at 32 to 34 weeks of pregnancy was practised but with poor results. The survival rate of such premature infants, badly affected by haemolytic disease, was extremely small.

In order to prolong intrauterine life of the affected foetus, Liley (1963) introduced intraperitoneal foetal transfusion. Blood introduced into the peritoneal cavity becomes absorbed into the foetal circulation and helps the foetus to survive until reasonable maturity is reached.

Intrauterine Transfusion

In 1964 we reported our first attempts at intraperitoneal transfusion of the foetus (Holman and Karnicki, 1964). Since then we have treated 54 infants and have met a number of complications. The purpose of this communication is to report on our further experience and the changes in our views and techniques.

We commence by assessing the past history of the patient and her pregnancies, which should be as complete as possible. It is not sufficient to know that there was a stillbirth delivered at 36 weeks; what one needs to know is as precisely as possible at what maturity the infant was seriously affected and when it actually died. Sometimes it is possible to know when intra-uterine death had occurred, or that the foetus had become less active, some weeks earlier. Since complications in pregnancy often lead to iso-immunization the influence of these in relation to the fate of previous pregnancies must also be considered. What we are seeking to forecast is whether an intra-uterine transfusion is likely to be needed, at what stage hydrops foetalis is likely to appear, when delivery will be possible and whether any other problem, such as placental insufficiency or a tendency to premature delivery, may be present.

The antibodies are titrated in saline and in albumin and by the indirect Coomb's technique and most regard is paid to the latter. Antibody titres are a very rough guide and whenever possible we seek to correlate the titre in the previous pregnancy with its effects on the infant.

The present pregnancy will offer little information of value until after quickening. Loss of the foetus before 20 weeks is very rare but from that time the patient should be watched with extra care and the antibody titre checked regularly.

We believe that spectrophotometric examination of the liquor amnii is a necessary preliminary to intra-uterine transfusion but we cannot agree that amniocentesis should be practised routinely on ante-natal patients with iso-immunization. Since our first report (Holman and Karnicki, 1964), in which we referred to the danger of foetal exsanguination, about 500 amniocenteses have been performed here and two foetuses have been lost by puncture of a vessel on the foetal aspect of the placenta. We have no doubt that amniocentesis should be restricted to those patients in whom the history or the antibody titre indicates a risk of stillbirth. In practice this means all patients with an anti-D titre of 1 in 32 or more by the indirect Coomb's test plus those with a lower titre who have had a previous stillbirth or severely affected liveborn infant. In many cases the need for amniocentesis is clear at the beginning of the pregnancy and the real problem is not whether, but when, to do it. When we have the history of a previous stillbirth as a guide we usually commence amniocentesis at least a month before the maturity at which intra-uterine death occurred and not later than 26 weeks. If the previous affected infant was liveborn we defer amniocentesis until 28 - 30 weeks unless the antibody titre is exceptionally high. In the case of a first affected pregnancy the antibody titre is the only guide available and one can only judge on the degree of affection seen in other foetuses at the same titre.

Our anxiety in regard to amniocentesis rests largely on the risks of puncturing the placenta. After about 30 weeks of pregnancy it is often possible to exclude anterior placenta by palpation and to find a safe puncture site. Between 20 and 30 weeks clinical assessment of the placental site is difficult or impossible. We have been dissatisfied...
with the results of radio-isotope localisation and cannot always afford to wait several days for an answer. We therefore attempt amniocentesis with a 1½" hypodermic needle which, in general, would be expected either to enter the amniotic cavity or to enter, but not pass through the placenta. Believing, as we do, that women with anterior placentas have an appreciably greater risk of a foetomaternal blood leak from ante-natal palpations, we do not think that the chance of entering it with a needle adds greatly to that risk. If the amniocenteses have been performed without drawing blood it will be possible to proceed to intra-uterine transfusion whenever indicated but if blood has been drawn the placenta must be localised and we now submit our patients to arterial placentography and find that this is most helpful.

Although the method described by Liley (1961) for estimating the absorption peak at 450 m\(\mu\) (see Fig. 1) is usually reliable we have found that the presence of haemoglobin and associated pigments in amniotic fluid may make an accurate assessment impossible at a time when it is essential. Knox, Fairweather and Walker (1964) showed that the part of the curve between 490 and 520 m\(\mu\) is related to the height of the 450 m\(\mu\) peak above the baseline and that it is unaffected by the presence of haemoglobin (see Fig. 2). Dr. D. N. Whitmore has analysed our curves and has shown that the difference between the optical density readings at 490 and 520 m\(\mu\) multiplied by a factor of 1.49 normally yields the same figure as does Liley's method. Because
there are occasional discrepancies we calculate both figures and accept the answer if they agree.

In the interpretation of the results we have been guided by Liley's analysis and plot the calculated peak at 450 μ against the maturity in weeks on semilogarithmic graph paper. Fig. 3 shows Liley's chart extrapolated backwards from 27 to 20 weeks. Although our results correlate fairly well with Liley's we have found that there is a significant overlap in the lower middle zone between unaffected and moderately severely affected infants, and that hydropic infants can yield peaks below the upper zone.

Once amniocentesis has been performed it should usually be repeated at weekly intervals. In the course of two weeks an infant can pass from the normal to the severely affected group.

The decision to perform an intra-uterine transfusion is fairly easy to make if it rests on a sudden increase in the 450 μ peak into the area of the chart associated with hydropic and stillborn foetuses. Since hydrops foetalis is generally irreversible and is the chief cause of death in this group of foetuses, intra-uterine transfusion is only likely to be successful if given before the foetus becomes too anaemic. To determine the latest time at which transfusion will succeed is quite difficult and requires consideration of the course of the present and previous pregnancies and of the antibody titres. We think that, where there has been a previous stillbirth, it is better to start before the period at which the previous infant's movements became weak. Where there has been no previous stillbirth the problem usually affects foetuses of about 30-34 weeks' maturity in which the risks of intra-uterine transfusion are not great and we are tending to the view that, in a doubtful case, there may be less risk to the foetus in transfusing than in waiting.

The major deterrent to intra-uterine transfusion is the position of the placenta. In pregnancies between 20 and 30 weeks it may be impossible to reach the foetal abdomen without penetrating the placenta and we regard this as an unacceptable risk. In pregnancies over 30 weeks the anterior placenta does not occupy the whole of the anterior aspect of the uterus and it is usually possible by arterial placentography to discover an area through which the transfusion can be done with safety.

In our first report we were considering foetuses of about 32-34 weeks and were able to place a Tuohy needle in the foetal abdomen without using
Urografin as a marker for the foetal gut. When less mature foetuses were presented for this treatment it became clear that swallowed Urografin was of great value as a marker when foetal bones were barely visible: it also permitted more accurate puncture of the lower abdomen, thus avoiding damage to liver and spleen. In those early days we did not have the use of an image intensifier and television set linked to the X-ray unit. Once this became available we found that we could use it as Liley now did and usually manage without ordinary X-ray pictures providing that the foetus had swallowed the Urografin. The foetal gut is clearly visible on the television screen and the puncture is much easier.

**Technique**

Our present technique starts with the injection of 15 - 20 ml. of Urografin into the amniotic cavity on the day before the transfusion. The foetus swallows this and concentrates it at first in its small intestine and later in the large bowel. Even a foetus as small as 21 weeks will do this successfully. If the Urografin is not apparent in the gut it is probable that the foetus is hydropic, the alternatives being that it is anencephalic or has duodenal atresia. On one occasion, however, we found that the Urografin could not be seen in the foetal gut until about three days after injection; the foetus had haemolytic disease but was not hydropic and was otherwise normal.

It is usually easier to aspirate liquor than to inject fluid into the amniotic cavity. As the foetus has a tendency to block the needle with its limbs, which a sharp needle could easily penetrate, the Urografin might be injected into foetal tissue instead of the amniotic cavity. We therefore use an arteriography trocar and cannula for the injection of the Urografin. The trocar is removed as soon as the amniotic cavity is entered and the contrast medium can then be injected safely.

For the actual transfusion it is best for the foetus to be in a lateral position. On the day of the transfusion the patient is asked to lie quietly on her back in the hope that the foetus will settle into the lateral position in the hollow beside the maternal spine. In this position the needle can pierce the mother’s abdomen directly above the foetal abdomen and pass easily into the foetal peritoneal cavity. When the foetus is in the posterior position the needle has to pass between the limbs which makes the operation rather difficult. Furthermore, the placenta is likely to be in the anterior position and limit access. Obviously it is equally difficult to transfuse if the foetus is completely anterior. The relation of the foetal position to the area of the anterior surface free from placenta is of great importance in the successful performance of the transfusion. For example, one patient had an anterior placenta which covered everything except the left side of the fundus; the foetus was in the left sacro-lateral position and the foetal head was directly under the only possible site for puncture. We postponed the operation until the next day by which time the foetus had turned to the left occipito-lateral position and its abdomen was easily accessible. Whenever the foetal abdomen is difficult of access it is better to postpone the operation than to persevere.

Premedication consists of pethidine 100 mg. and promazine 50 mg. intramuscularly one hour before transfusion. Antibiotic cover is provided by four mega-units of penicillin and one gram of streptomycin divided into four doses over 24 hours.

The operation takes place in the X-ray department with strict aseptic precautions. A local anaesthetic is given through a 1½” needle at the site chosen for puncture. This is determined by the position of the foetus and placenta, aiming at the lower quadrant of the foetal abdomen in order to avoid the liver and spleen which are usually enlarged. The foetal bladder occupies a large part of the lower abdomen but there appears to be no risk attached to puncturing this organ.

The skin is nicked with a knife before the Tuohy needle is introduced. A 6” Tuohy needle has proved satisfactory providing that the sharp edges on all aspects of the orifice have been blunted. The Tuohy needle is introduced into the uterine cavity and under television screening the needle is directed towards the foetal abdomen. Small babies are very mobile and may have to be transfixed through the buttock with a separate needle to reduce movement. It is possible to feel the various structures through which the Tuohy needle passes; the foetal abdomen offers little resistance and one is aware when the needle enters the abdominal cavity. In some cases ascitic fluid can be aspirated and is easily recognised as it is more deeply pigmented and more viscous than the liquor. When the needle is in the right position the catheter will pass through it easily. We use a 24” “Pink Portex” nylon catheter, O.D. 1.02 mm. If the needle is in a tissue the catheter cannot be pushed in at all and if it is in the bladder it does not pass very easily. Once the whole catheter has been introduced, 2 ml. of Urografin are injected through it and a characteristic picture of contrast medium between the coils of gut, under the diaphragm and outlining the foetal abdomen, is seen on the television screen. The blood is now injected and is followed by 2 - 3 ml. of Myodil, an inert oily radio-opaque solution which will remain in the peritoneal cavity indefinitely and will help to guide the Tuohy needle during the next intra-
Table 1 shows the results of intra-uterine transfusion from November 1963 to March 1966. We performed 84 intra-uterine transfusions on 54 babies and saved 27 of them.

Table 2 shows the rate of survival as we went on with the operation. Until September 1965 we had a survival rate of nearly 60%. From about that time we accepted more severe cases and attempted much earlier transfusions. The earliest we did was 21 weeks. One of the patients had five transfusions, the first one at 25 weeks, but we failed to save this hydropic baby which was born at 36 weeks. This attempt to save babies early in pregnancy has lowered the survival rate to 50%.

Table 3 shows the result of intrauterine transfusion in relation to previous obstetric history. Two-thirds of our cases had bad obstetric histories. They had previously lost babies or had had very badly affected infants requiring exchange transfusion. One-third of the patients were in the first affected pregnancy. The results of each group are approximately the same; namely about 50% perinatal mortality; the proportion of hydropic babies is even higher among the first affected babies. These results are in line with Liley's (Liley, 1961) observation that one-third of stillbirths due to rhesus immunisation occur amongst the first affected pregnancies.

Table 4 shows the results of intrauterine transfusions in relation to the duration of pregnancy. When intrauterine transfusion was given after 30 weeks of pregnancy we saved two-thirds of the babies. Below 30 weeks we only saved three out of 19.

The next two Figures 4 and 5 show the peak optical density in relation to duration of pregnancy of successful and unsuccessful cases respectively. In the successful group most of the patients are in the upper zone and the duration of pregnancy is over 30 weeks, a few cases are at 27, 29 and 30 weeks of pregnancy and a few in the upper middle zone. In the unsuccessful group most are in the upper zone and are under 31 weeks of pregnancy.

Looking at the proportion of foetal haemoglobin...
TABLE 2
RESULTS OF INTRA-UTERINE TRANSFUSIONS FROM NOVEMBER 1963

<table>
<thead>
<tr>
<th>No. of I.U.T.</th>
<th>No. of Patients</th>
<th>Babies Alive</th>
<th>Foetal Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total</td>
</tr>
<tr>
<td>September 1965</td>
<td>46</td>
<td>34</td>
<td>20 (59.9%) 14 (40.1%)</td>
</tr>
<tr>
<td>March 1966</td>
<td>84</td>
<td>54</td>
<td>27 (50.0%) 27 (50%)</td>
</tr>
</tbody>
</table>

TABLE 3
RESULTS OF I.U.T. IN RELATION TO OBSTETRIC HISTORY

<table>
<thead>
<tr>
<th>No. of Cases</th>
<th>Alive</th>
<th>Foetal loss Hydrops</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bad Obstetric History</td>
<td>35</td>
<td>18</td>
</tr>
<tr>
<td>First Affected Baby</td>
<td>19</td>
<td>9</td>
</tr>
</tbody>
</table>

TABLE 4
RESULTS OF INTRA-UTERINE TRANSFUSION IN RELATION TO DURATION OF PREGNANCY

<table>
<thead>
<tr>
<th>Weeks of pregnancy—</th>
<th>21</th>
<th>22</th>
<th>23</th>
<th>24</th>
<th>25</th>
<th>26</th>
<th>27</th>
<th>28</th>
<th>29</th>
<th>30</th>
<th>31</th>
<th>32</th>
<th>33</th>
<th>34</th>
<th>35</th>
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</thead>
<tbody>
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<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
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<td>M</td>
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<td>SB</td>
<td>SB</td>
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<td>SB</td>
<td>SB</td>
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<td>SB</td>
<td>SB</td>
<td>SB</td>
<td>SB</td>
<td>SB</td>
<td>ND</td>
</tr>
<tr>
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<td>M</td>
<td>SB</td>
<td>ND</td>
<td>SB</td>
<td>ND</td>
<td>SB</td>
<td>ND</td>
<td>SB</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>M</td>
<td>M</td>
<td>SB</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>SB</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

A = Alive birth
M = Miscarriage
SB = Stillbirth
ND = Neonatal Death
to total cord haemoglobin, Figure 6, we can say that the transfusion was justified in almost every case. Case No. 4 shows 40% of foetal haemoglobin. The first recording of the optical density peak was 0.33 but at the time of transfusion the optical density was 0.081: This error was due to plasma in the liquor. The haemoglobin level of 40% shows that it was as well we did the transfusion because the chance of survival when the haemoglobin is under 50% is poor.

Case 9 is a mystery. The husband is heterozygous. The second child was rhesus-negative but deeply jaundiced at birth. She had lost her third child which was rhesus-positive. The optical density level was rising steadily and entered the upper middle zone; the antibody titre was also rising. The foetus had an intrauterine transfusion at 34 weeks and a deeply jaundiced rhesus-negative baby was born and required three exchange transfusions. There was no ABO incompatibility nor any other recognisable abnormality.

Table 5 shows the analysis of foetal loss. Three children died from prematurity. Intrauterine transfusion had been difficult and had required prolonged manipulation. This may have caused premature labour.

We lost one child as a result of cardiac arrest during exchange transfusion. Cardiac massage was too vigorous. Severe bruising of the heart occurred and the child died from cardiac failure.

The other child was lost because of haemorrhage from the umbilical artery, which had been catheterised in the development of a new technique for exchange transfusion.

All the stillbirths and 3 of the neonatal deaths were due to hydrops foetalis. This is the largest single factor responsible for failures. Once hydropic changes have taken place intrauterine transfusion has little chance of saving the baby.

Complications
Maternal complications have been surprisingly few and have been largely due to anterior placenta. One patient had an intraperitoneal haemorrhage as a result of the puncture of the uterine wall directly over the placental site with a Tuohy needle. The uterine musculature at the site of placental attachment is more vascular and can contract less well than that elsewhere.

Two patients became shocked when the Tuohy needle pierced the placenta but responded to blood transfusion. We believe that it is necessary to
know the location of the placenta before operation and to avoid puncturing it.

We have sought for evidence of other complications such as infection and amniotic fluid embolism but have found no evidence of them.

Table 6 shows the number of patients who had premature onset of labour. Two of these started labour before the infant was transfused and two others had had previous spontaneous premature deliveries. Three infants were hydropic and this, in our experience, predisposes to premature labour. Prolonged manipulation during the operation was probably responsible for the premature onset of labour in two cases. In four cases we could find no cause other than the intrauterine transfusion, which could be held responsible for the premature onset of labour.

In one case a new antibody (anti Jk\(^a\)) appeared in the mother after an intrauterine transfusion with Jk\(^a\) positive blood and made the selection of a further donor difficult. (Kelly and Kenwright, 1966).

Foetal complications were more numerous. On four occasions the autopsy showed previous puncture or laceration of the liver which had healed. In three stillborn macerated foetuses there were adhesions between the small intestines and clotted,
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TABLE 5

CAUSES OF FOETAL LOSS WITH I.U.T.

<table>
<thead>
<tr>
<th>Causes</th>
<th>No. of Cases</th>
<th>SB</th>
<th>ND</th>
<th>Ab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prematurity</td>
<td>3</td>
<td></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Hydrops</td>
<td>20</td>
<td>15</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Death due to cardiac arrest during exchange</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>transfusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death due to ruptured umbilical artery</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>exchange transfusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abortion, macerated</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number</td>
<td>27</td>
<td>15</td>
<td>8</td>
<td>4</td>
</tr>
</tbody>
</table>

TABLE 6

DAYS OF ONSET OF LABOUR AFTER I.U.T.
NUMBER OF TRANSFUSIONS 84

<table>
<thead>
<tr>
<th>Days after I.U.T.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perinatal Loss</td>
<td></td>
<td>2</td>
<td></td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Alive</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

unabsorbed blood. This latter may make punctures on the television screen difficult to interpret.

On many occasions the needle and catheter entered the foetal bladder but no infant suffered as a result of this. In one case the pleural cavity was punctured and outlined with urografin without evidence of subsequent ill-effects. We also managed, in a particularly difficult case with anterior placenta, to put a Tuohy needle into the foetal skull, presumably through a suture, and injected urografin. This infant showed no neurological abnormalities at birth and is now four months old and appears to be developing normally.

About 10 inches of nylon catheter snapped off and was left inside one foetal abdomen. The child is now 18 months old and shows no sign of any abnormality. It is to avoid this that we advise blunting the inner aspect of the tip of the Tuohy needle. Animal experiments were performed by the courtesy of the Institute of Child Health and have suggested that the nylon catheter will be quite harmless.

Further Management

We have endeavoured to deliver these infants by the vaginal route after surgical induction and have not performed Caesarean sections unless indicated for obstetric reasons. Delivery has usually been effected at about 36 weeks except in one case where the infant was small and induction was delayed an extra week.

After birth these infants still require exchange transfusions to clear the bilirubin and a few of them have been poorly for some time but have eventually done well. One has required operation for bilateral inguinal hernia and also had a persistent jaundice for about two months.

When these infants are born they are usually anaemic but not seriously so. The bilirubin level is high and sometimes higher than one sees in severe haemolytic disease. The direct Coomb's test may be negative or show a mixture of positive and negative cells. The clinical condition of the infants is often less satisfactory than would be expected by the haemoglobin level. Despite this and the degree of
jaundice we have usually succeeded in rescuing these infants with two one-pint exchange transfusions. These infants may have very high levels of free antibody and several of them have destroyed all their newly formed red cells so that at about six weeks of age we have been obliged to give a top-up transfusion. This has been given by the intraperitoneal route and the absorption has been quite satisfactory.

Most of the surviving infants have been watched and so far none have shown any evidence of deafness or spasticity and are all making normal progress. One required operation for bilateral herniae and also had persistent jaundice for about two months but now has no detectable sequelae.

Summary

Between November, 1963 and March, 1966, 54 foetuses were given intrauterine transfusions and 27 of them survived. The technique used is described and the indications and complications are discussed.

Our thanks are due to the many obstetricians who have referred their patients to us. The work entailed has put extra burdens on many of our colleagues and the staff of the maternity, paediatric, pathology and radiology departments, to all of whom we are greatly indebted; above all we must acknowledge the great help given by Miss A. Austin and our radiologists Dr. N. A. W. Morrison and Dr. J. D. Irving.

REFERENCES


KELLY, J., and MARGARET KENWRIGHT (1966): Personal communication.


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J. Karnicki and C. A. Holman

doi: 10.1136/pgmj.42.494.755

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