Case Report

INTRA-UTERINE FOETAL BLOOD TRANSFUSION

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Since the first report by Liley[1] of a successful intra-uterine foetal blood transfusion in a case of Rhesus incompatibility, further reports have come from other units throughout the world.[2-5] Since the technique for the procedure is constantly being modified and since full data on the infants so delivered should be available for study, we are presenting a further case report.

Patient

Mrs. J. P., a White female aged 26, first attended the antenatal clinic at Groote Schuur Hospital on 17 February 1965. She had had no illnesses of note and had not undergone any operation previously. She had never received a blood transfusion.

Previous Obstetric History

15 July 1958. A full-term pregnancy was complicated by pre-eclamptic toxaemia. Spontaneous onset of labour was followed by spontaneous vertex delivery of a living male infant weighing 7 lb. 5 oz. (3·29 kg.): The mother's blood group was known to be A Rhesus-negative. No postdelivery blood specimen was made available for examination for anti-D antibodies. Husband O Rhesus-positive (CDe/cDE).

17 September 1959. A pregnancy was complicated at 37 weeks by pre-eclamptic toxaemia. Spontaneous onset of labour was followed by spontaneous vertex delivery of a living male infant weighing 5 lb. 11 oz. (2·58 kg.). The infant developed haemolytic jaundice owing to Rhesus incompatibility and soon after birth underwent an exchange transfusion, but thereafter progressed satisfactorily.

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2 November 1961. A pregnancy was complicated at 37 weeks by pre-eclamptic toxaemia and a rising titre of Rhesus anti-D antibodies (Table I).

TABLE I. HISTORY OF BLOOD GROUPS, ANTIBODY TITRES, BIRTHS AND RELATED PROCEDURES

Date				
1958	*Patient* A Rh-negative (cde/cde) *Husband* O Rh-positive (CDe/cDE)			
15.7.58	Delivery of male infant 3·29 kg.—Healthy			
17.9.59	Delivery of male infant 2·58 kg.—Haemolytic disease of newborn. Exchange transfusion (no details available).			
	Rhesus Anti-D Antibodies			
	Saline	*Albumin*	*Trypsin*	*Coomb's*
12.10.61	0	1 : 2	1 : 2	1 : 4
28.10.61	1 : 8	1 : 16	1 : 32	1 : 64
1.11.61	1 : 4	1 : 16	1 : 128	1 : 128
1.11.61	Induction of labour (EDD 23.11.61)			
2.11.61	Delivery of female infant 4 lb. 1 oz. Coomb's positive, Hb.13·4G/100 ml. Total bilirubin 6·5 mg./100 ml. Exchange transfusion—Infant died 4.11.61			
1.10.64	1 : 2	1 : 4	1 : 8	1 : 16
4.11.64	1 : 2	1 : 4	1 : 8	1 : 16
9.12.64	1 : 2	1 : 4	1 : 8	1 : 16
20.1.65	1 : 8	1 : 8	1 : 32	1 : 32
3.2.65	1 : 8	1 : 8	1 : 16	1 : 32
18.2.65	1 : 4	1 : 8	1 : 32	1 : 32
18.2.65	(30 weeks) Amniocentesis-bilirubin 0·45 mg./100 ml.			
25.2.65	(31 weeks) Amniocentesis-bilirubin 0·37 mg./100 ml.			
26.2.65	1 : 4	1 : 8	1 : 8	1 : 32
3.3.65	(31 weeks 6 days) Intra-uterine foetal blood transfusion—134 ml.			
15.3.65	1 : 16	1 : 32	1 : 32	1 : 64
15.3.65	(33 weeks 4 days) Intra-uterine foetal blood transfusion—162 ml.			
26.3.65	(35 weeks 1 day) Intra-uterine foetal blood transfusion—175 ml.			
1.4.65	Spontaneous vertex delivery—Living female 5 lb.			
1.4.65	Immediate post-delivery			
	1 : 32	—	—	1 : 128
22.4.65	1 : 64	—	—	1 : 256

Surgical induction of labour was followed by spontaneous vertex delivery of a living female infant weighing 4 lb. 1 oz. (1·814 kg.). This infant underwent an immediate exchange transfusion but died within 48 hours from suspected hyaline membrane disease. Autopsy was not performed.

Examination of cord blood gave the following results: O Rhesus-positive, direct Coomb's positive; haemoglobin 13·4 G/100 ml.; serum bilirubin—direct 0·4 mg./100 ml., total 6·5 mg./100 ml.

Present Obstetric History

The last menstrual period was on 22 July 1964. The estimated date of delivery was 29 April 1965. The patient first attended an antenatal clinic on 28 September 1964 and was transferred to Groote Schuur Hospital on 17 February 1965.

At all examinations the blood pressure was within normal limits, the weight gain was average and the urine contained no abnormal constituents. The Papanicolaou smear was grade 1 normal. The haemoglobin level was maintained between 11·5 and 12·5 G/100 ml.

It was considered from the past history and the laboratory findings (Table I) that the foetus had an extremely poor prognosis. Therefore on 18 February 1965 an amniocentesis was performed so that a more accurate intra-uterine foetal prognosis could be obtained from an examination of the liquor amnii. About 20 ml. of a rather viscid yellowish fluid was withdrawn. Amniocentesis was repeated on 25 February 1965. The results for bilirubin content according to the spectrophotometric method of White *et al.*[6] were respectively 0·45 mg./100 ml. and 0·37 mg./100 ml. The prognostic interpretation of values for bilirubin estimation was made according to Mackay and Watson.[7]

On the strength of the past history, rising anti-D titre in the maternal blood and the bilirubin content of the liquor amnii, intra-uterine foetal blood transfusion was considered necessary.

Immediately before the intra-uterine transfusion on 3 March 1965, liquor amnii samples of 18 February and 25 February, which had been stored at 2°C under protection from light, were further investigated spectrophotometrically by Liley's method. Both specimens indicated that the foetus fell into the group with a very bad intra-uterine prognosis.

THE RADIOLOGICAL TECHNIQUE OF INTRA-UTERINE FOETAL BLOOD TRANSFUSION

Under a premedication of Pethidine, 100 mg., and Promazine, 25 mg., an intra-uterine foetal blood transfusion was performed on 3 March, when the foetus was 31 weeks 6 days mature.

Modern radiographic equipment, incorporating image intensification and TV monitoring, greatly simplifies this procedure compared with previously described methods when plain radiography was used.[1,2,4] The method of Holman and Karnicki[4] was followed in broad outline for the first transfusion of this foetus and thereafter the procedure was modified in the light of experience, in order to utilize the image intensifier and TV monitor to their full advantage.

1. Immediately before the transfusion, a plain radiograph was taken of the mother's abdomen in the supine position with a metal marker on the umbilicus. This provided a visual record of the lie of the foetus, particularly the position of the limbs, the costal margins and the vertebral column. The target area of the foetal abdomen could then be visualized, making allowance for the thighs and liver. The umbilical marker provided a maternal landmark for correlation with the foetal target area in selecting a line of approach for the needle.
2. A 16-cm. Tuohy needle was introduced under local anaesthesia. As soon as it made contact with the foetus, this became obvious by the foetal movement that was imparted to it. Slight resistance was then overcome as the needle passed through the foetal abdominal wall.
3. Approximately 5 ml. of a water soluble radio-opaque medium were then injected through the Tuohy needle under TV control. The foetal peritoneal cavity was immediately outlined by the opaque medium in a most convincing manner. The transfusion was then carried out, no further radiographic control being required. Previous authors[1,3-5] describe the introduction of an epidural catheter into the peritoneal cavity through the Tuohy needle, which is then withdrawn. This refinement was discarded after the first transfusion, since direct injection of opaque medium through the needle gave immediate and more convincing confirmation of its position in the foetal peritoneal cavity, and the transfusion of packed cells proceeded far more expeditiously through the Tuohy needle than through the necessarily fine-bore polythene catheter.
4. The radiographic factors were 60kv and 2mA, with a positive screen and a stationary grid. The TV camera is of the vidicon type. The screening current of 2mA is rather higher than is customary with image intensification, but is justified by the improved contrast which these factors provide in the pregnant patient. Foetal irradiation is minimal since the screening period with this technique is of only a few seconds' duration.

The first procedure took a total of 1 hour 20 minutes to perform, although the actual transfusion of 134 ml. of packed very fresh group O Rhesus-negative blood taken in acid-citrate-dextrose needed only 20 minutes. The blood was warmed to 37°C in a waterbath immediately before transfusion. It was found that frequent rinsing in heparin solution of the syringes used for injection allowed easier flow of the packed cells into and out of the syringes.

The procedure was repeated (*a*) on 15 March 1965 (33 weeks 4 days mature) when the total procedure time was 22 minutes and 162 ml. of blood was transfused, and (*b*) on 26 March (35 weeks 1 day mature) when the total procedure time was 15 minutes and 175 ml. of blood was transfused.

Postoperatively on each occasion the patient was confined to bed for 24 hours, was given 250 mg. of ampicillin 6-hourly for 4 days (no antibiotics were administered during the procedure) and was discharged home on the

4th postoperative day. Four days after each transfusion the patient noted a marked increase in foetal movement.

On 31 March 1965 the patient re-attended the antenatal clinic and was found to have a blood pressure of 140/100 mm.Hg. She was immediately readmitted for absolute bed rest.

The Labour

Contractions commenced at 9 p.m. on 31 March. The membranes ruptured at 4.10 a.m. on 1 April. The liquor amnii was a pale brown colour.

At 4.57 a.m. on 1 April 1965 spontaneous vertex delivery of a living female infant occurred. The third stage was uncomplicated. The placenta, which was not weighed, was disproportionately large for the size of the baby.

The puerperium was uncomplicated. Lactation was successfully established. The mother was discharged home on 26 April 1965.

The Infant

The delivery of the female infant weighing 2·27 kg. was uneventful and the Apgar rating at birth was 9/10.

Her condition appeared to be satisfactory, though the liver and spleen were both enlarged and a faint icteric conjunctival tinge was noticeable. There were 2 healing puncture marks on the abdomen approximately 2 cm. above each side of the umbilicus. The mucous membranes were well coloured. Examination of the group O Rhesus-negative cord blood (Table II) showed a haemoglobin of 14·1 G/100 ml.; total bilirubin of 7·6 mg./100 ml. with a direct bilirubin of 2·1 mg./100 ml.; reticulocyte count of 0·5%; a direct negative Coomb's test and foetal haemoglobin of 8 G/100 ml. by spectrophotometry. A cord blood smear showed 90% adult red blood cells and 10% foetal red blood cells, employing the technique of Kleihauer and Betke.[9] Gastric aspiration produced 5 ml. of altered blood. Examination of the infant at one hour showed all the systems to be normal.

An uneventful exchange transfusion of 183 ml./kg. body weight using O Rhesus-negative salt-free albumin-enriched blood[10] in acid-citrate-dextrose was carried out at the age of 2½ hours.

Over the next 24 hours the baby became more jaundiced and the pulse rate and respiratory rate fluctuated between 90 - 120 and 40 - 65 respectively. No abnormality was detected on ECG examination. There was no sign of the respiratory distress syndrome and the baby's general condition was good throughout. Frequent melaena stools containing adult haemoglobin were passed.

TABLE IV. UMBILICAL ARTERIAL ACID-BASE STUDIES

Age	*pH mm.Hg*	*PCO_2 mm.Hg*	*PO_2 mm.Hg*	*BE mEq./l.*	*Buffer base mEq./l.*	*St. Bic. mEq./l.*	*Act. Bic. mEq./l.*
2½ hours pre-exchange	7·38	38·5	72	−2·0	45	22·3	22·0
4½ hours post-exchange	7·32	41·0	55	−4·7	42	20·3	20·5
17 hours	7·39	47·0	60	+2·9	50	26·1	27·5
31½ hours pre-exchange	7·23	53	70	−5·4	40	19·6	22·0
33 hours post-exchange	7·29	57	65	−0·2	46	23·8	26·0
Donor blood	6·48			−16·0	30	12·4	

At 29 hours the baby appeared hyper-irritable, and suckled less well, though no abnormality was detected on neurological examination. The total bilirubin was 24·8 mg./100 ml.

TABLE II. RESULTS OF HAEMATOLOGICAL INVESTIGATIONS AND SERUM BILIRUBIN LEVELS—INFANT

Age in hours	*Bilirubin*			*Hb. G/100 ml.*	*PCV %*	*Retics./ 100+bc*	*Platelets/ cu.mm.*	*WBC/ cu.mm.*
	Total mg./100 ml.	*Direct mg./100 ml.*	*Indir. mg./100 ml.*					
Birth	7·6	2·1	5·5	14·1		0·5		
2½ Pre-exchange	10·0	2·9	7·1	14·4				
4½ Post-exchange	3·2	1·2	2·0	11·9				
16	16·4	4·3	12·1	12·5				
29	24·8	8·2	16·6	14·1				
31½ Pre-exchange	24·9	8·7	16·2	13·9	40	0·5	107,000	6,500
33 Post-exchange	10·8	2·6	8·2	10·7	31		61,000	
53	18·3	5·5	12·8	11·0				
62½	16·3	9·0	7·3	11·5				
77	13·2	8·9	4·3	12·5				
Days								
5	—	—	—	11·5				
11	3·9	3·2	0·7	11·3	30	0·0	250,000	11,400
22	1·3	0·8	0·5	9·0	20	0·1	169,000	6,600
26	—	—	—	7·0		0·0		
33	—	—	—	6·0	17	0·0	143,000	8,000

TABLE III. RESULTS OF BIOCHEMICAL INVESTIGATIONS—INFANT

Age	*Urea mg/ 100 ml.*	*Na mEq./l.*	*Cl mEq./l.*	*K mEq./l.*	*Ca mg./ 100 ml.*	*Glucose mg./ 100 ml.*	*Albumin G/ 100 ml.*	*Globulin G/ 100 ml.*	*SGOT karmen units*	*Alk. phos. KA units*	*TT*	*ZT*
4½ hours post-exchange		146	98	5·3	8·5	31			54	8·7	0	4
31½ hours post-exchange		142	93	3·9	10·9		4·6	2·5				
Donor blood		150	65	3·4	9·0		4·8	1·5				
33 hours post-exchange		142	94	3·2	10·9	130	4·5	1·2				
11 days	28	140	105	6·1	10·1	40	3·7	1·4	40		0	4
22 days	18	120	100	5·2		30					0	6

with a direct bilirubin of 8·2 mg./100 ml. The haemoglobin was 14·1 G/100 ml. with evidence of haemo-concentration of the blood. A second exchange transfusion of 200 ml./kg. body weight using O Rhesus-negative albumin-enriched blood in acid-citrate-dextrose was carried out at the age of 31½ hours. Transient twitchings of the left leg lasting 1 - 2 minutes were observed during the exchange. Serum electrolyte, blood sugar and umbilical arterial acid-base studies showed no abnormality (Tables III and IV). No further twitchings were observed. An antibiotic cover of cloxacillin and ampicillin was given for 9 days.

After day 14 all clinical evidence of jaundice had disappeared; the infant thrived, the liver appeared normal, though the spleen was still enlarged. The total bilirubin was 3·9 mg./100 ml. with a direct bilirubin of 3·2 mg./100 ml., Hb. 11·3 G/100 ml., platelet count 250,000, WBC 11,400 and the reticulocyte count 0·0%. Dr. P. Lanzkowsky reported on a bone-marrow examination as follows: 'Bone marrow aspirated from the tibia showed a moderately cellular marrow with moderate erythroid hyperplasia giving a myeloid:erythroid ratio of 2:1. The differential marrow count and normal range for each cell type is shown in Table V.'

TABLE V. DIFFERENTIALS

Cell type	*Bone marrow*		
	Range	*Counted*	*% Total*
Myeloblast or leucoblast	0·3–5·0	0	0
Promyelocyte	0·5–8·0	2	0·3
Myelocyte—neutrophilic	5·0–25·0	69	11·0
Myelocyte—eosinophilic	0·5–3·0	3	0·5
Metamyelocyte—neutrophilic	14·0–35·0	98	16·0
Metamyelocyte—eosinophilic	0ccas.	7	1·0
PMN—basophilic	0·0–0·8	0	0
PMN—eosinophilic	0·5–6·0	26	4·3
PMN—neutrophilic	4·0–35·0	44	7·7
Lymphoblast	None	0	0
Lymphocyte	4·0–35·0	201	34·0
Monoblast	None	0	0
Monocyte	0·0–5·0	0	0
Plasma cell	0·0–1·5	0	0
Reticulum cell	0·0–2·0	6	1·0
Megakaryocyte	0·03–3·0	2	0·3
Mitoses (R & W series)		3	0·5
Unclassified cells		–	–
Pronormoblast	0·0–3·0	1	0·2
Basophilic normoblast	0·0–5·0	31	5·0
Polychromatophilic NB	5·0–34·0	91	15·2
Orthochromic normal	0·0–8·0	16	3·0
Megaloblast	None	0	0
Total nucl. cells		600	100·0
M : E ratio (varies with age)	3 : 1 to 20 : 1	2 : 1	

The results of all the biochemical and haematological investigations carried out on the infant are tabulated in Tables II - IV. No abnormality was detected on X-ray of the chest and abdomen at 8 hours of life. A negative blood-culture examination was obtained after the second exchange transfusion.

From the 14th to the 26th day of life the haemoglobin of the blood showed a progressive drop from 11·3 G/100 ml. to 7 G/100 ml. A transfusion of 30 ml. of fresh O Rhesus-negative blood raised the haemoglobin to 11·5 G/100 ml. The haemoglobin fell again over the following 7 days to 6·0 G/100 ml. so that a further transfusion of 100 ml. of O Rhesus-negative blood had to be given. The baby thrived throughout this period and there was no evidence of infection or blood loss. Despite the marked erythroid hyperplasia confirmed by a second bone-marrow examination and a falling haemoglobin, repeated reticulocyte counts showed the absence of reticulocytes. No factual explanation is apparent at the present time.

DISCUSSION

The preliminary investigations necessary before deciding on the need for an intra-uterine foetal blood transfusion have been well stated by Liley[1] who also described the technique used in the first successful case reported in October 1963.

The present case report varies in that the image intensifier and TV monitor were used to great advantage in determining when the Tuohy needle had entered the foetal peritoneal cavity. An epidural catheter was not used because of reasons already stated and because the introduction of a catheter would, with the technique described, reduce hardly at all the time that the needle is present in the foetus. The technique would appear from the number of puncture marks on the foetal abdomen to have failed on one occasion—possibly the third.

Despite the risks attached to the procedure, we favour repeated transfusions at approximately 12-day intervals until the foetus is at least 36 weeks mature. The absorption of the donor cells from the foetal peritoneal cavity results in a significant increase in foetal movement by the fourth post-transfusion day and this movement starts decreasing about the tenth post-transfusion day. Infants delivered when 36 weeks mature or more, have a very much better prognosis than those delivered between 34 and 36 weeks.

The use of progesterone in the uterine muscle at the point of passage of the transfusion needle might possibly reduce the risk of a premature onset of labour.

Detailed results of infant differential marrow counts, umbilical arterial and acid-base studies, biochemical investigations and haematological investigations have been given. The discrepancy between the marked erythroid hyperplasia in the bone marrow in association with a falling haemoglobin and the absence of reticulocytes in the peripheral blood is under investigation.

The presence of adult haemoglobin in the melaena stools does not mean that some of the transfused blood was injected into the foetal intestinal tract. As the foetus had mainly donor blood circulating, melaena stools from any cause would contain adult haemoglobin.

SUMMARY

A case of successful intra-uterine foetal blood transfusion is presented. Success depends on correct and early assessment of suitable patients, accurate localization of the foetal peritoneal cavity and intensive postnatal paediatric care. It is essentially a team effort.

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