

RHESUS IMMUNIZATION IN PREGNANCY

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An analysis of 66 cases of Rhesus immunization seen at Addington Hospital, Durban, during a 2-year period (1 August 1951 to 31 July 1953) is presented. During this period, 4,064 deliveries took place, of which 2,282 were of Europeans.

The percentage of women who were found to be immunized to Rhesus is 1.62. This figure is much lower than that given by most hospitals, probably because 43.8% of the cases confined at this hospital and by its district maternity service are Coloured and Indian women, in whom the incidence of Rhesus-negative individuals is much less than in Europeans (see below).

The Rhesus Clinic of the hospital has referred to it cases of Rhesus immunization from the whole of the province of Natal.

Two of the 66 Rh-immunized cases ended in abortion before the fifth month.

TABLE I. BABIES BORN TO 64 RH-IMMUNIZED WOMEN

A. <i>Rh-positive babies:</i>	
1. Coombs-test positive and affected clinically	.. 47
2. Coombs-test positive and unaffected clinically	.. 6
3. Coombs-test negative	.. 1
B. <i>Rh negative babies</i> 10	
	<hr/> 64

TABLE II. FATE OF THE 54 RH-POSITIVE BABIES

Lived	44
Died	5
Stillborn	5
		<hr/> 54

Causes of Death (prenatal and postnatal)

Hydrops foetalis	3
Macerated foetus	2
Kernicterus	2
Icterus gravis	2
Unknown (stillbirth, no P.M.)	1
		<hr/> 10

TABLE III. TYPES OF DELIVERY IN RH-POSITIVE BABIES UNAFFECTED CLINICALLY

Vaginal Delivery, not induced	6*
Induction of Labour	0
Caesarean Section (at 37 weeks)	1
		<hr/> 7*

* Including 1 Coombs-test negative (the rest were Coombs-test positive).

TABLE IV. TYPES OF DELIVERY, TREATMENT AND FATE OF THE 47 RH-POSITIVE, CLINICALLY AFFECTED BABIES

	Vaginal Delivery, not Induced	Premature Induction by Rupture of Membranes	Caesarean Section	Totals	Died after Birth
Exchange Transfusion	19	1	7	27	3
Direct Transfusion	5	0	0	5	0
No Transfusion	9	0	1	10	2
Stillborn	4	1	0	5	—
	<hr/> 37	<hr/> 2	<hr/> 8	<hr/> 47	<hr/> 5

TYPES OF DELIVERY OF THE 5 BABIES WHICH DIED AFTER BIRTH

Vaginal Delivery, not Induced	4
Induction of Labour	0
Caesarean Section	1

Expected date of Delivery. Of the 37 Rhesus-positive babies which were purposely allowed to proceed to term, only 7 went beyond their expected date, of which 6 passed the expected date by 2-8 days, whilst the 7th case (kernicterus) passed the expected date by 28 days. Of the other 30 which were born before the expected date, 10 were born approximately at term, and the other 20 before the expected dates by the following periods:

Length of Time before Expected Date (Days)	No. of Cases
9	2
10	2
14	6
18	1
24	1
30	3
35	1
36	1
38	1
48	1
53	1
	<hr/> 20

Of the above 20 cases, 18 were affected clinically, of which 9 received exchange transfusions. Not one baby of the 20 weighed less than 5½ lb.

According to this small number of cases, it seems that there is a natural tendency for Rhesus-positive cases to be delivered before the expected date.

Of the 37 Rhesus-positive babies in which vaginal delivery was allowed without induction, 4 were stillborn and 4 died after birth. The date of birth (in relation to the expected date) in the 8 dead babies was as follows:

Died after birth (4):

Case 1. Born 14 days before the expected date of delivery (hydrops—lived 20 minutes).

Case 2. Born 28 days after the expected date of delivery (kernicterus).

Case 3. Born 5 days before expected date of delivery (icterus gravis).

Case 4. Born 18 days before the expected date of delivery (kernicterus).

Stillborn (4):

Case 1. 6 days before expected date (Stillborn, no post-mortem).

Case 2. 30 days before expected date (macerated foetus).

Case 3. 14 days before expected date (macerated foetus).

Case 4. 14 days before expected date (hydrops foetalis).

TABLE V. RELATIONSHIP BETWEEN PREVIOUS HISTORY AND THE FATE OF THE RH-POSITIVE CHILD

Previous History		Lived	Died	Stillborn
None (36)	No treatment	10	2	3
	Treatment	21	0	0
Definite (15)	No treatment	3	0	2
	Treatment	7	3	0
Uncertain (3)	No treatment	2	0	0
	Treatment	1	0	0

A 'previous history' includes cases in which one or more previous babies had haemolytic disease, or where the mother had been blood-transfused. It can be seen that out of 15 cases with a definite history only 10 lived, whereas out of 36 cases with no history 31 survived.

THE ANTIBODY TITRE

(A) *Rh-positive infants with Coombs test positive, unaffected clinically*

There were 6 cases in this group and 3 were primigravidae. Study of the antibody titre revealed that in not one case was the mother's albumin agglutinin titre higher than 256. The series is too small to draw definite conclusions, however.

(B) *Rh-negative infants born of Rh-negative mothers who showed evidence of Rh-immunization*

There were 10 cases in this group and not one was a primigravida. Only one gave a history of having had a blood transfusion previous to the present pregnancy. The highest albumin agglutinin titre present was 512 in this group. One must assume that in 9 of the cases the antibodies were provoked by a previous pregnancy.

(C) *Rh-positive infant, Coombs test negative*

One case only (para 1, gravida 2). Highest albumin agglutinin titre during the pregnancy was 8.

(D) *Rh-positive infants, Coombs test positive, affected clinically, received exchange transfusion*

1. Sub-group treated by Caesarean section. (excluding neonatal deaths, *q.v.*): This sub-group comprised

6 cases treated by Caesarean section at between 36 and 38 weeks' gestation. Lowest birth-weight recorded was 5 lb. 12½ oz. The highest albumin agglutinin titre recorded in the mothers' blood antenatally was 1,024 and in not one case was there a synchronous drop of the saline agglutinin titre with a rise in the albumin agglutinin titre—said to indicate a severe degree of immunization by some authorities.¹

2. Sub-Group treated by Spontaneous Delivery (excluding Neonatal Deaths, *q.v.*): This sub-group comprised 16 cases. Study of the saline and albumin agglutinin titre revealed that no inference could be drawn about the prognosis of the child. The saline agglutinin titre in one case (para 1, gravida 2) rose to 16,384, with albumin agglutinin titre rising to 2,048, the day before delivery. The earliest titre during the pregnancy was at the 26th week (by her dates) (complete 512, incomplete 32). The infant was severely affected, being jaundiced at birth, with hepatomegaly and splenomegaly, and a haemoglobin of 82%; 10 normoblasts/100 white cells; serum bilirubin 3.7 mg.%; Coombs test strongly positive. It received 730 c.c. of female Rh-negative blood while 670 c.c. of its own blood was removed. The baby survived.

(E) *Rh-positive infants, Coombs test positive, affected clinically, either direct transfusions or no transfusion used (excluding neonatal deaths)*

Comprises 13 cases. Five received small direct transfusions, the remainder no transfusions at all. These cases were regarded clinically as of mild degree only. No inference may be drawn from the study of the agglutinin titres. In 11 of the cases the highest albumin agglutinin titre in the mother's blood, antenatally, was 512, while in the remaining 2 cases one showed an albumin agglutinin titre of 1,024 as its highest level, 2 weeks before delivery, whilst the other showed a titre of 2,048 in both the saline and albumin agglutinin estimations just before delivery.

(F) *Rh-positive infants, Coombs test positive, stillborn or died within 24 hours of birth*

Ten cases—5 stillborn and 5 died. In 3 of these cases only could the agglutinin titre be said (by present-day standards) to be prognostically helpful. Two of these were shown at post-mortem to be cases of kernicterus. Case 1 kernicterus showed a rise of albumin agglutinin titre from 512 to 2048, with a synchronous fall of saline agglutinin titre from 128 to 64, 6 days before delivery. Case 2 kernicterus showed a saline agglutinin titre of 128 with an albumin agglutinin titre of 8192 3 weeks before delivery. This titre fell to 32 and 1024 respectively 6 days before delivery. Case 3 (macerated foetus) showed an albumin agglutinin titre of 32,768 10 days before delivery.

In the other 7 cases, definitely no help could be gained by knowledge of their agglutinin titres. The 3 cases of hydrops foetalis showed surprisingly low agglutinin titres, the highest readings of albumin agglutinin titres being 1024, 512, 32. In all 3, there was no synchronous lessening of the saline agglutinin titre associated with a rise in the albumin agglutinin titre. Thus it can be

readily seen that the agglutinin titre is not very helpful from a prognostic point of view.

1. ANTENATAL ROUTINE

At Addington Hospital, blood is taken for Rh grouping from all patients at their first antenatal visit, and if Rh-negative, the blood is tested for antibodies; it is tested again at 30, 34, 36 and 38 weeks for antibodies. The cord blood of all infants is sent to the Rhesus laboratory, regardless of whether the mother was Rh-negative or positive, and the following tests are made: (1) Wassermann reaction, (2) haemoglobin estimation, (3) Coombs test. In cases where, during the pregnancy, the mother showed evidence of immunization the same tests are made on the cord blood, and also the following investigations: (4) Rhesus type of the blood, (5) Megaloblasts per 100 white blood-corpules, (6) Serum-bilirubin level.

2. PROGNOSIS

(a) Before Delivery

As can be seen from the previous paragraphs, the mothers' antibody-titre level during pregnancy has been a disappointing guide in prognosis. The finding of agglutinins before the fifth month, usually indicates that the woman has been immunized before she became pregnant. A titre of agglutinins, particularly the albumin variety, which increases considerably during the pregnancy, may indicate that the foetus is Rh-positive, but more than this one cannot say.

The antenatal elicitation of pitting oedema of the foetal scalp is a sign I have found to be extremely valuable in diagnosing hydrops foetalis in cases where the X-ray appearances are doubtful. J. C. M. Browne (1950) has pointed out that the radiological signs of this condition are not reliable and may be present when the foetus is normal and healthy. Most cases of Rh immunization occur in multiparae, and in them, with vertex presentation, one can usually palpate, the foetal head vaginally through the multiparous os, aided by pushing the vertex into the pelvis, and decide whether pitting oedema is present, which it is suggested, is diagnostic of hydrops foetalis. This sign can be used in the later weeks of pregnancy. During labour one can, with experience, differentiate the oedema caused by a caput succedaneum from that felt in a case of hydrops foetalis. The latter is less rubbery and more diffuse, and more easily 'pitted into' with the fingers, and if one can gain access beyond the periphery of the caput succedaneum, one can easily decide if it is a case of hydrops or not.

(b) After Delivery

The affected infant's condition at birth is placed into one of 3 categories, namely severely affected, moderately affected, or mildly affected. The serological tests together with the infant's clinical condition at birth, (namely, whether jaundiced or cyanosed, and the presence of splenomegaly) are taken into account in placing the infants in these categories.

The presence of jaundice at birth, or its onset within a few hours, has been stated by Mollison *et al.*² to be

the most reliable clinical sign of severity. This has been our experience also, as has been the finding of these authors that the degree of anaemia in the cord blood is the most valuable laboratory index of severity.

The normal megaloblast count is taken as 5 or less per 100 white cells, and normally they disappear from the blood within a day or two of birth. When the megaloblast count is pronounced it is highly suggestive evidence of erythroblastosis foetalis.

It has been shown that erythroblastemia is a very common feature in infants born to diabetic or prediabetic mothers.^{3, 4}

The normal serum-bilirubin level is taken as approximately 1.7 mg. per 100 ml. at birth.⁵ A raised serum bilirubin is a valuable corroborative finding, provided it is not an isolated serological item.

The percentage of kernicterus in the present survey is 3.8% out of 53 Coombs-test positive infants. Stiller⁶ found that 14% out of 29 patients with haemolytic disease failed to develop normally and were obviously backward at the age of one year. Mollison² has stated that the incidence of kernicterus when all degrees of haemolytic disease are included may well prove to be lower than 14% because Stiller's series included mainly moderate or severe degrees of the disease.

The two cases of kernicterus in this survey showed a cord haemoglobin concentration at birth of 4.4 g. and 16.9 g. per 100 ml. respectively. Armitage and Mollison⁷ suggest that a cord haemoglobin of 17.5g. per 100 ml., or higher, is a strong indication that the infant will not develop kernicterus if left untreated.

3. TREATMENT

(a) Obstetric Management

Our present method of management at Addington Hospital is one of conservative treatment of the mother. We allow the mothers to have a vaginal delivery at term unless other obstetric reasons are present which may indicate premature induction of labour or Caesarean section. We found that this method gives as good results as premature induction of labour, if not better, largely by eliminating the premature infant, which in addition may occasionally be Rh-negative. From this small series, it seems that there is a tendency for these immunized mothers to go into spontaneous labour somewhat before the expected date, but our birth weights do not indicate any infants that can be classed as premature, taking 5½ lb. or below as the standard of prematurity. We now regard Caesarean section as having no place in the management of an immunized mother.

(b) Indications for Transfusion

The infants are grouped as stated in the section on 'Prognosis after Delivery'. The severely and moderately affected ones are, as a rule, immediately treated by exchange transfusion. The mildly affected ones are not usually given any immediate treatment; they are often found to be the first affected infants in a family. They are closely observed and are given direct transfusions should their haemoglobin levels, which are estimated daily, drop.

We follow the advice given by Mollison and Cutbush⁸ that a haemoglobin value of below 15.5 g. %, if supported by other evidence of the disease, should be taken as an indication for treatment. The degree of sensitization of the infant's erythrocytes and the degree of erythroblastæmia are unreliable guides, usually. Occasionally in mild cases erythroblastæmia is absent even on the first day of life.

(c) *Technique of Exchange Transfusion*

Apparatus Drip stand, Rh-negative Group-0 blood, normal saline (2 vacolites), blood set with filter, 2 three-way cocks in series, small, medium and large plastic catheters,⁹ 2 10-c.c. glass syringes with finger controls, cord scissors, dissecting forceps (toothed and plain), artery forceps (medium), metal probe. Heparin (for intravenous use). Sp. vini rect., gauze swabs, cord dressings, cord ligatures.

The Polyethylene catheter is not autoclaved but kept in 1% Cetavlon; it tends to float in this solution and so must be kept down by a weight. The lumen of the catheter must be syringed with Cetavlon, for the Cetavlon does not enter the lumen readily.¹⁰

Technique (time allowed 1½-3 hours). The blood set and filter, three-way cocks, catheters and syringes are rinsed through with normal saline. The contents of the second vacolite of normal saline are poured into a bowl and heparin is added (1 c.c. per 200 c.c. of normal saline) for use during the procedure, e.g. for rinsing syringes to prevent sticking.

The infant is placed with its feet at the end of the bed or table, and the legs are immobilized in a blanket. The arms may be adequately immobilized by folding the vest or jacket upwards over the arms.

The abdomen and cord are cleaned with Sp. vini rect. and draped with sterile towels. The cord is held vertically by the artery forceps with which it is clamped (an assistant does this) and is cut through, 1 to 1½ inches from the umbilicus.

The cut surface is carefully examined for bleeding sites. The umbilical arteries usually go into spasm more readily than the vein, though not invariably, and will therefore ooze less. The presence of a patent urachus is looked for.

The medium catheter is rinsed in heparinized saline, and passed into the lumen of the vessel which oozes most. If the vessel is very tortuous it may be necessary to straighten out the spiral twists in the cord by passing a metal probe first. Resistance is felt at the umbilicus and spasm of the vessel may be felt gripping the tip of the catheter. Gentle, steady pressure will usually overcome these. The catheter may be passed to a depth of 3-4 inches, until greater resistance is felt.

When the tip of the catheter reaches the mouth of the ductus venosus, or the portal vein, blood may well out of the open end of the catheter, but more probably it will have to be withdrawn to prevent the vessel wall collapsing against the opening in the tip of the catheter. Spasm of the vessel may persist up to half an hour, but will suddenly relax, allowing free withdrawal of the blood.

All 3 vessels may have to be catheterized before the vein is found and blood withdrawn.

The three-way cocks are now affixed to the catheter, and the syringe applied to their free end. 10 c.c. of blood are withdrawn and ejected *via* the waste cock into a receiver. From the bottle of donor blood on the drip stand, 10 c.c. are allowed to run into the syringe by opening the appropriate cock. This blood is slowly injected into the umbilical vein.

This procedure is continued, 10 c.c. out and 10 c.c. in, until the required amount of blood has been replaced. It is convenient to have someone recording the figures on paper. The total volume given is calculated on the basis of 100 c.c. per lb. body-weight. If the donor blood has been slightly packed, i.e. about 15% plasma decanted, then 100 c.c. is withdrawn for every 100 given. Otherwise, for every 100 c.c. withdrawn, an extra 10 c.c. is given. This is done to try and get the maximum final haemoglobin level.

When the syringe becomes sticky it may be rinsed in the heparinized saline. Delay over rinsing may give the blood time to clot in the catheter. The second syringe can be used while the first is being rinsed. Changing catheters during the procedure is a messy business.

The infant's condition is watched constantly, particularly for signs of respiratory or circulatory collapse. The infant should be kept at a consistently warm temperature. Sedation has not been found necessary. Lethargy appears to be proportional to the amount of haemolysis that has taken place *in utero*.

Finally the catheter is slowly withdrawn and the cord stump clamped with artery forceps as close to the umbilicus as possible. The stump has usually become oedematous from handling and may be friable. A cord ligature is then necessary in addition to the clamp. Cord dressing and binder are applied. The infant is left in the crib for 8-12 hours, after which time it may be treated as a normal child, nursed and breast fed if the mother's condition is satisfactory.

Daily haemoglobin estimations on capillary blood from the heel are done for a week, and then weekly until spontaneous erythropoiesis is established—usually by the 6th week.

(d) *Value of Blood from Female Donors*

In reviewing 208 cases of erythroblastosis treated by exchange transfusion, Allen *et al.*¹¹ noted that although the mortality was 15.1% in the whole group, no deaths occurred in the 42 babies who received blood from females. Analysis of other factors, such as sex of the infant, severity of illness, the mother's anti-Rh titre and length of gestation failed to reveal any other factor that could be held responsible.

At Addington Hospital the statistics of the Paediatric Department do not confirm this superiority of blood from female donors. (Dr. H. L. Wallace).

(e) *Treatment of Erythroblastosis by Transfusion with sedimented Red Cells*

Pennell¹² treated 33 patients with erythroblastosis foetalis by transfusion of compatible sedimented red-cells from bank blood; 3 died (10.7%)—a mortality which compares favourably with that in other reports on exchange transfusion. He argues that incomplete or blocking or albumin Rh antibodies require an 'activator', which is supplied by both human and bovine albumin, to effect agglutination of red cells. This 'activator' is diminished to an ineffectual level in the plasma of the newborn. He says the adult plasma or serum causes pronounced agglutination of red cells, which are coated with the blocking (or albumin) antibody. It is thought, therefore, that transfusion of erythroblastotic children with adult whole-blood may be contra-indicated because the infused adult plasma may activate the incomplete antibody present in the baby. Pennell holds that there are other advantages in transfusing with sedimented red-cells, viz.

1. Severe anaemia is overcome by a comparatively small volume (50-60 c.c.) which cannot overburden the infant's circulatory system.

2. The procedure is simple, and can be carried out *via* a scalp vein in 15-20 minutes.

3. Does not require special equipment or specially-trained transfusion teams.

4. Eliminates administration to the infant of a large amount of extraneous substances such as sodium citrate, heparin and calcium gluconate, which are employed in exchange transfusions.

The amount of adult plasma which sedimented cells contain is about 5%. The fact that the infant's coated cells are allowed to remain seems to be of no consequence.

At Addington Hospital, about 80-100 c.c. of visible

plasma is withdrawn from each 500 c.c. bottle of donor blood for both exchange and direct blood-transfusions.

(f) Breast Feeding

It is our practice to allow all infants, once their general condition allows of it, to be taken to the breast. The subject seems to be *sub judice*.

It is not possible, according to Marrack,¹³ to say whether the small amounts of antibodies in the mother's milk are absorbed by the baby. Many authors have advised that infants affected with haemolytic disease of the newborn should not be breast-fed. Cathie¹⁴ has published the results of some experimental work on this subject. He found that 12 Rh positive infants who received high-titre anti-Rh serum by mouth for a whole day in place of their normal feeds failed to show any evidence of antibody absorption; that is to say, their red cells did not give a positive direct anti-human-globulin test, nor did their serum appear to contain any free antibody. He also found that an Rh-positive infant with haemolytic disease, whose erythrocytes had first ceased to show a direct positive anti-human-globulin test, did not subsequently develop a positive test when fed for 24 hours with breast milk with a titre of 32.

4. MORTALITY RATE

(a) *Exchange Transfusion.* There were 6 deaths in 38 cases which received exchange transfusions (15·8%)—computed up to November 1953.

(b) *Rh-positive, Coombs-test positive.* Ten infants died out of 53 Rh-positive Coombs-test positive infants (18·9%).

(c) *Infants by Total Number of Immunized Mothers.* Ten infants died out of 64 Rh-immunized mothers (15·6%).

5. CONCLUSION

The writer has come to the following conclusions:

1. That the antibody titre in the pregnant immunized woman does not serve as a reliable guide to the severity of haemolytic disease in the infant.

2. That spontaneous vaginal delivery gives as good results as prematurely induced labour, if not better.*

3. That Caesarean section has no place in the management of the Rh-immunized woman.

4. That radiological evidence in the antenatal diagnosis of hydrops disease is often misleading.

5. That the elicitation in the later weeks of pregnancy of pitting oedema of the foetal scalp, by vaginal examination in the Rh-immunized woman, is often an

invaluable aid in diagnosing the presence of hydrops foetalis, particularly where the radiological evidence is lacking or confusing.

6. That a large percentage of these Rh-immunized women go into spontaneous labour before their expected date.

7. That Indian women resident in Natal are virtually all Rhesus-positive. Not a single case of Rh-immunization was seen in 784 Indian antenatal patients over a 2-year period.

8. That amongst the Coloured population (people of mixed European and non-European extraction) in Durban, the incidence of Rh-immunization is extremely low. Five cases of Rh-immunization out of a total of 834 deliveries over a 2-year period were seen, a percentage of 0·59.

9. That the foetal mortality rate is higher in those cases in which the mother has given birth to one or more infants with haemolytic disease, or in which the mother had been blood-transfused previously.

* Armitage and Mollison⁷ (1953) have come to the conclusion that routine premature induction of labour probably increases mortality.

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