INFLUENCE OF SELECTIVE INDUCTION OF LABOUR ON MORTALITY IN HAEMOLYTIC DISEASE OF THE NEWBORN

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In the past few years the mortality in haemolytic disease of the newborn has fallen considerably, but obstetricians and paediatricians still differ in the management of the expectant mother with rhesus antibodies.

The Medical Research Council in 1949 initiated controlled trials of treatment: firstly, between exchange and simple transfusions; and, secondly, between routine induction of labour and spontaneous delivery. The preliminary results of the trials were published in 1952 by Mollison and Walker and showed that exchange transfusion resulted in a lower mortality (13%) than simple transfusion (37%), while the incidence of kernicterus was also lower after exchange transfusion than after simple transfusion. They concluded that routine premature induction of labour three to five weeks before the estimated date of delivery resulted in a higher mortality (36.4%) than when labour ended spontaneously (24.1%). A later review by Armitage and Mollison (1953) of the children born during these Medical Research Council trials showed that infants born prematurely were more liable to kernicterus and to mental and motor defects than those born spontaneously.

Since the official recommendations by the Medical Research Council in 1952 regarding exchange transfusion and premature induction of labour, other workers have also emphasized that premature induction of labour has no place in the routine treatment of haemolytic disease of the newborn—for example, Walker and Murray (1954). These expressed views have probably resulted in the virtual cessation of premature induction of labour for this disease in most obstetrical hospitals and units in the United Kingdom.

However, at the Royal Maternity Hospital, Belfast, these views have never been fully accepted in Professor Macafee's department, where induction of labour has been carried out when indicated. This approach has received support from Watson, Crosse, and Hatchuel (1954), who showed the strikingly beneficial results obtained by premature induction of labour on two occasions in one particular patient. Kelsall and Vos (1955) also reported a series of 246 consecutive cases of haemolytic disease of the newborn and suggested that the overall mortality could be lowered by the premature induction of labour at the optimal time after 35 weeks of gestation followed, where necessary, by exchange transfusion. The mortality rate of infants spontaneously delivered was 23.4%, compared with 10.7% in infants born after premature induction of labour. These figures show a statistically significant preference for controlled induction. Kelsall and Vos claimed to show that controlled induction of labour and subsequent exchange transfusion had virtually eliminated stillbirths after 35 weeks' gestation and had not been associated with an un-

due increase in neonatal deaths. They also stated that kernicterus had become so rare in their induced cases as to be practically never seen.

Present Investigation

Following these reports the results of 143 pregnancies complicated by rhesus incompatibility have been reviewed from January, 1951, to December 31, 1955, at the Royal Maternity Hospital, Belfast. Since the patients were admitted either to one unit in which, as a general rule, selective induction of labour was undertaken or to another unit in which spontaneous delivery was preferred, two roughly comparable series are available.

All the mothers were rhesus-negative and had rhesus antibodies in their serum. Each live-born infant had a positive Coombs test except in two cases. One was born with a cord haemoglobin level of 12.3 g. per 100 ml. (90%) and a negative Coombs test, but exchange transfusion was undertaken. The other infant was born with a cord haemoglobin level of 16 g. per 100 ml. (108%) and a serum bilirubin level of 3 mg. per 100 ml.; the Coombs test was not recorded but exchange transfusion was done, the mother having rhesus antibodies and a history of previous infants affected by haemolytic disease of the newborn. All stillbirths and neonatal deaths were assumed to be the result of haemolytic disease of the newborn. Only those patients delivered at or after the 36th week are considered, the period of gestation being calculated by Naegele's method from the date of the first day of the last menstrual period.

As a general rule, exchange transfusion was undertaken if the haemoglobin of the cord blood, estimated by the Medical Research Council photometer, was below 14.8 g. (100%) but not if it was above 17.7 g. (120%). When the haemoglobin was between 17.7 g. and 14.8 g. exchange transfusion was usually done if the serum bilirubin was greater than 2.7 mg. per 100 ml. (normal range, 1.5–2.5 mg. per 100 ml.: King, 1951), especially when associated with enlargement of the spleen, a previous family history of severe haemolytic disease of the newborn, prematurity, or if the umbilical cord was jaundiced. Warm rhesus-negative group O citrated blood was used, giving at least 50 ml. of packed cells per lb. (110 mg. per kg.) of body weight of the infant.

The obstetrician was responsible for the selection of patients for premature induction of labour, which was based on a clinical assessment of each case. The indications have been, to a certain extent, arbitrary, but a previous seriously affected or stillborn child with haemolytic disease, a rising rhesus antibody titre, and a homozygous rhesus-positive husband have had an important influence on the selection of cases for induction. During the last few weeks of a rhesus-incompatible pregnancy, alteration in the foetal heart or diminution of foetal movements may also indicate urgent delivery by caesarean section, and in some of the infants so born the cord haemoglobin has been found to be as low as 7.4 g. per 100 ml. (50%). In this series labour was usually induced in the 37th or 38th week, but the need for a more accurate method of determining when termination of pregnancy is indicated is discussed below.

Findings

If death *in utero* occurred before 36 weeks of gestation the possibility of induction of labour would have been excluded, and this might weight the total mortality unfavourably against the spontaneously delivered group. For this reason the mortality rate in the spontaneous group is shown in Table I, corrected by excluding any known deaths *in utero* before the 36th week of gestation (four in number). In the remainder, the foetal heart was heard after the 35th week; or the infant, if stillborn, was fresh and unmacrated. Table I also shows that the total mortality rate in the spontaneous group is notably higher (29%) than in the induced group (16%). Nevertheless, the severity of the haemolytic disease was probably greater in the induced cases, as the incidence of

exchange transfusion was higher (68 transfusions in 76 cases) in the induced group than in the spontaneous group (29 transfusions in 63 cases). The average haemoglobin level in the cord blood was slightly lower (87%) in the induced group than in the spontaneous group (93%). By conventional standards, however, the statistical analysis is not significant in such a small series.

Table II shows the duration of pregnancy at which delivery occurred after induction was carried out, compared with that at which spontaneous delivery occurred.

TABLE I.—*Mortality At or After 36 Weeks in 139 Cases of Rhesus Incompatibility Known to be Viable After 35 Weeks (Royal Maternity Hospital, Belfast)*

Labour	No. of Cases	Survival	Neo-natal Deaths	Still-births	Total Mortality	% Mortality
Induced ..	76	64	11	1	12	16
Spontaneous ..	63	45	6	12	18	29

$$\chi^2 = 2.6128. \text{ D.F.} = 1. \quad 0.20 > P > 0.10.$$

TABLE II.—*Number of Deliveries, Duration of Pregnancy, Stillbirths, and Neonatal Deaths Each Week Between 36 Weeks and Term, with Average Haemoglobin Values (Royal Maternity Hospital, Belfast)*

	Week of Gestation						Total
	36	37	38	39	40	41 +	
<i>Induced Group</i>							
Neonatal deaths ..	2	0	5	4	0	0	11
Stillbirths ..	1	0	0	0	0	0	1
Total deaths ..	3	0	5	4	0	0	12
.. deliveries ..	7	6	35	20	7	1	76
Average Hb level (%) ..	81	80	84	93	85	96	87
<i>Spontaneously Delivered Group</i>							
Neonatal deaths ..	2	1	0	1	1	1	6
Stillbirths ..	1	0	6	4	1	0	12
Total deaths ..	3	1	6	5	2	1	18
.. deliveries ..	3	5	14	13	16	12	63
Average Hb level (%) ..	61	101	91	82	94	99	93

The beneficial effect of selective premature induction of labour in haemolytic disease of the newborn can also be illustrated by individual case records.

Case 1.—A patient aged 29 had the following history. Her first infant was born at term weighing 9 lb. (4 kg.) and is alive and well; her second was also born at term weighing 9 lb. (4 kg.) but died at 3 days of age with jaundice; her third and fourth infants were stillborn at 38 weeks. In her fifth pregnancy she was found to be rhesus-negative and to have a rhesus antibody titre of 1/16. An elective caesarean section was undertaken at 37 weeks; the infant was born suffering from haemolytic disease of the newborn with a haemoglobin level of 12 g. per 100 ml. (82%). Exchange transfusion was performed, and the infant's subsequent progress has been excellent.

Case 2.—A patient, aged 35 and rhesus-negative, had the following history. Her first two infants, born at term, are alive and well; her third infant was stillborn at 39 weeks; her fourth infant, born at term, died on the fifth day with jaundice; her fifth infant was stillborn at term; her sixth infant, born at term, died 12 hours later with jaundice; her seventh infant was born at term, became slightly jaundiced later, did not require a transfusion, and is alive and well; her eighth and ninth infants were each born at term; both had exchange transfusions, but died 12 hours later with severe jaundice. In her tenth pregnancy rhesus antibodies were present. She was induced and delivered at the 38th week; the infant was born suffering from haemolytic disease, with haemoglobin of 9.6 g. per 100 ml. (65%). Exchange transfusion was performed and the child is alive and well.

Discussion

These individual family histories and the comparison of results in 139 infants with haemolytic disease of the newborn

TABLE III.—*Comparison of Mollison and Walker (1952), Kelsall and Vos (1955), and Royal Maternity Hospital, Belfast, Mortality Rates in Haemolytic Disease of Newborn*

	Mollison and Walker (1952)		Kelsall and Vos (1955)		Present Series	
	Induced	Spont.	Induced	Spont.	Induced	Spont.
No. ..	77	108	112	111	76	63
Survived ..	39	82	100	85	64	45
Neonatal deaths ..	22	12	11	1	11	6
Stillbirths ..	6	14	1	19	1	12
Deaths { No. ..	28	26	12	26	12	18
% ..	36.4	24.1	10.7	23.4	16.0	29.0

suggest that the mortality from this disease can be lowered by selective premature induction of labour rather than by awaiting spontaneous delivery. The reduction of the total mortality from 29% in the spontaneously delivered group to 16% in the induced group in this series is similar to that from 23.4% to 10.7% in Kelsall and Vos's series (Table III), but the reverse of the findings of the Medical Research Council trials.

Such results, however, cannot be compared with the findings in the Medical Research Council trials, where routine induction of labour was undertaken three to five weeks before term and the form of treatment was dictated by selection of random numbers. The difference in the mortality rates in the induced cases in the present series and in the Medical Research Council trials may have resulted partly because the random selection of patients for routine induction fails to distinguish between mildly and severely affected cases and therefore needlessly exposes to the hazards of prematurity a number of infants unaffected or only mildly affected. Likewise, the selected period for induction, about the 36th week, in the Medical Research Council trial, may not have been the optimal time to terminate a particular pregnancy.

It cannot be too strongly emphasized that each rhesus-incompatible pregnancy should be treated on its merits.

The mortality rates reported by Kelsall and Vos (1955) for the induced group and the group delivered spontaneously are much lower than those in the present series and may be due to several factors. An important difference in their technique of exchange transfusion is in the use of freshly collected heparinized blood in place of stored citrated blood. Campbell (1955) has drawn attention to the high plasma potassium content of stored blood and noted that toxic levels of potassium occur in infants undergoing exchange transfusion, which might be a factor in causing death during transfusion. Possibly of equal importance is an alteration of the ratio of diffusible to non-diffusible calcium in stored citrated blood, and work is proceeding on this problem.

Kelsall and Vos also exchanged larger quantities of blood, 150–250 ml. per lb. (330–550 ml. per kg.) body weight of the infant during transfusion, but this is not necessarily an advantage, as in the present series exchange transfusion has been repeated on a second or even a third occasion if indicated subsequently by a high serum bilirubin level.

It is obviously necessary to have a method of determining the severity of haemolytic disease of the newborn during the course of pregnancy so that the optimal time for induction of labour can be more accurately selected. In 1952 Kelsall and Vos published a method of carefully standardized and repeated antenatal titrations of maternal serum by the anti-globulin method of Coombs and found it to be an accurate guide to treatment. They tested the serum of pregnant rhesus-negative women at monthly intervals and, if antibodies were detected, at weekly intervals after the 32nd week. They claimed that a titre of 1/64 or higher was an indication for induction at 36 weeks or onwards. If the father was homozygous and the maternal antibodies were high but stationary, induction was carried out at 38 weeks. If the titre was lower and stationary, the pregnancy was allowed to continue, the antibody level being checked at weekly intervals.

On clinical grounds some guidance can be gained from the previous family history. Walker and Murray (1956) have shown that in their series of infants with haemolytic disease of the newborn there was a general trend to more severe disease in succeeding pregnancies. They also showed that the stillbirth rate was about 10% when there had been no previously affected baby but that it was nearly 30% in subsequently affected babies. Moreover, in families where a previous infant was stillborn as a result of haemolytic disease there was an 80% chance that the next baby, if allowed to go on to spontaneous delivery, would also be stillborn. This in itself justifies the need for premature induction of labour in these patients, for this procedure will increase the likelihood of the infant being born alive and give it a chance of survival with treatment in spite of the hazards of prematurity. It is, however, essential to know in such a rhesus-incompatible pregnancy that the husband is homozygous rhesus-positive, as this will influence the choice of treatment.

The rhesus antibody titres in saline and albumin media of the maternal blood in this series have not necessarily corresponded with the severity of the disease in the infant. The need for a reliable method of assessment such as the antibody titration method described by Kelsall and Vos (1952) and the importance of weekly estimations of antibody levels are well illustrated by the following case record.

A patient aged 30 had the following history. Her first infant, born weighing 4 lb. (1.8 kg.), suffers from cerebral palsy; her second infant is alive and well; her third child died at 9 days of age with jaundice; her fourth pregnancy terminated at 36 weeks and the infant was stillborn. In her fifth pregnancy she was found at 10 weeks to be rhesus-negative with an antibody titre of 1/2. At 34 weeks the foetal heart was heard. Arrangements were made for her to be admitted at 38 weeks for possible induction of labour. Spontaneous onset of labour at 37 weeks resulted in delivery of a macerated stillborn foetus which showed at post-mortem examination all the features of haemolytic disease of the newborn.

Allowing for the clinical difficulties and possible statistical variables inherent in comparing different series of such cases, selective induction of labour based on the family history and clinical assessment of each rhesus-incompatible pregnancy would seem to have reduced the total mortality in haemolytic disease of the newborn.

Summary and Conclusions

The results of 143 pregnancies of rhesus incompatibility delivered spontaneously or by selective premature induction of labour are reviewed.

There is a notable lowering in the total mortality in haemolytic disease of the newborn in the induced group (16%) compared with that of the group delivered spontaneously (29%).

The severity of the disease was probably greater in the induced group, as twice as many exchange transfusions were performed and the average haemoglobin level was lower than in the group spontaneously delivered.

The beneficial results of selective premature induction of labour are also illustrated by the individual case histories.

The time of induction was based on the previous maternal history and by clinical assessment of the individual patient.

Selective premature induction of labour is thought to reduce the total mortality from haemolytic disease of the newborn.

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ADDENDUM.—Since this article has been accepted for publication a further paper on the subject has been published by W. Walker, S. Murray, and G. K. Russell in the *Lancet* on February 16, 1957.

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BRUCellosis in Children

BY

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Brucellosis is a disease of mistakes. If we do not think of it we miss it; or we may think of it and test for it, yet find nothing. It eludes us. Nevertheless, as a cause of pyrexia of undetermined origin it is important; and obscure headaches, lassitude, abdominal pain, or arthritis may be due to its smouldering activity.

Case 1.—A girl of 6 was referred to me because of abdominal pain, lassitude, and irritability. I could find no abnormality, and investigations proved negative. Her family had moved house a few months earlier and she had been sent to a new school. I assumed that her symptoms were due to psychological upset and hoped that they would settle down in the course of time. Three months later I was asked to see her again because she was no better. She then had some enlarged glands in the neck, axillae, and groins, and her liver was palpable. A white cell count showed a leucopenia, with a diminished number of neutrophil polymorphs. Serum agglutinations against *Brucella abortus* were positive at 1 in 320 dilution. Chlortetracycline and streptomycin were given for seven days. Her temperature fell rapidly and she felt better within a week. Her recovery was complete and permanent.

I was able to learn by my mistake in this case. From that time I was more keenly aware of the possibility that brucellosis might be the cause of vague or unexplained symptoms. In the course of time I met with a number of children who were undoubtedly suffering from brucella infection. I scrutinized the notes of 2,000 children I had seen in hospital during the previous four years and made a retrospective diagnosis in several others. It is important to record my findings in order that others may learn from my mistakes as I have done. I hope thereby to reduce the number of cases in which pain, fever, and arthritis remain unexplained, and also to shield children from unjustified accusations of neurosis and malingering.

Dalrymple-Champneys (1950) has given an excellent review of the history, ecology, and symptomatology of this disease, which he calls "a neglected problem." Full reference to the previous work has been made by Huddleson (1939) and Harris (1941, 1950) in their exhaustive monographs, and it is evident that any system of the body may be affected.

Sander (1933) said that the disease in children did not differ at all from that in adults; but Huddleson wrote that in Malta, where it is commonest in children, it is relatively mild and often passes unnoticed. Williamson