Rhesus incompatibility and a survey of the care of rhesus negative pregnant women in one general practice

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SUMMARY. I review some of the literature and developments in research concerning rhesus immunization and report on a small survey, carried out in a group practice with a list size of about 12,000, of women who were delivered during the first 10 months of 1977. There were 106 deliveries (including one set of twins), and 16 rhesus negative mothers (one of whom had the twins). Of 17 infants delivered to these mothers, eight were rhesus negative, seven rhesus positive, and two were not grouped. None of the mothers developed antibodies and all the rhesus negative mothers at risk received anti-D. However, the survey shows discrepancies between hospital and practice records and recommendations to improve this are suggested.

Introduction

IT is 40 years since Levine and Stetson (1939) demonstrated that erythroblastosis fetalis was due to a fetal blood group antigen, inherited from the father, entering the maternal circulation and causing maternal isoimmunization. Since then, there have been rapid developments in techniques for diagnosis, treatment, and prevention of this disease. The effectiveness of the administration of anti-D immunglobulin for preventing Rh-immunization in pregnancies of rhesus negative women, and also in cases of rhesus mismatched transfusions, is now recognized and has been in use since 1966, but only on a wide scale since 1971. However, there is still a failure rate of one to two per cent following prophylaxis.

The rhesus blood group

There are six main rhesus genes, three carried on each of one pair of chromosomes. Three, C, D, and E, are dominant and their alleles c, d, and e are recessive. The most important gene in rhesus incompatibility is the dominant D gene and it accounts for 95 per cent of cases. In the United Kingdom population, 17 per cent of individuals are rhesus negative and 83 per cent rhesus positive.

Development of rhesus immunization

The rhesus antigens in the lipoprotein of the red cell membrane are well developed as early as 38 days' gestation (Queenan *et al.*, 1973) and are a potential stimulus to maternal antibody production in rhesus negative women any time during pregnancy. Fetal cells do cross the placenta into the maternal circulation and this has been detected as early as the eighth week of gestation, but the exact conditions facilitating their entry are still not known. Most fetal cells enter the maternal circulation at delivery and it is known that sensitization can occur due to placental leaks during pregnancy, although there is a decreased response to antigens due to high oestrogen levels inhibiting the normal immune response.

Larger transplacental haemorrhages may occur in pre-eclamptic toxaemia, antepartum haemorrhage, uterine manipulation, Caesarean section, manual removal of placenta, abdominal injury, amniocentesis, and also following abortion, especially a surgical termination.

The other factor concerned in the process of rhesus immunization is the ABO blood group of mother and fetus. If the fetal cells are ABO compatible with those of the mother, they will persist in her circulation and stimulate antibody formation (Figure 1).

Types of antibody

IgM (saline antibody) develops first in response to a primary stimulus by antigens. It disappears rapidly and does not cross the placenta.

IgG (albumin antibody) develops some days later, remains longer, and crosses the placenta possibly by an active transport mechanism.

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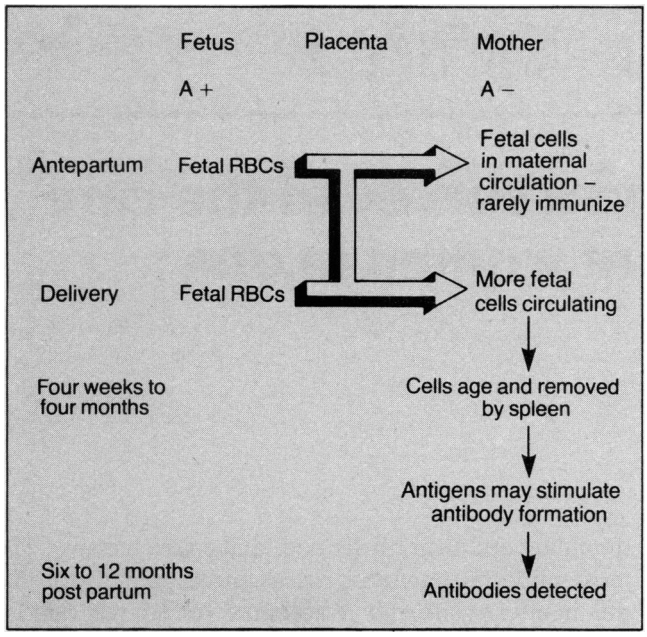

Figure 1. *Scheme of antibody formation. Source: Robinson, J. G. (1969). Modern Trends in Obstetrics. London: Butterworths.*

The antibody titre is measured by serial dilutions of maternal serum.

Despite well controlled trials where anti-D has been given to all mothers at risk there is still a failure rate of one to two per cent in preventing rhesus immunization (Medical Research Council, 1974; Simonovits *et al.*, 1974); however, one survey showed that even though protection had failed, the infants were less severely affected than would have been expected (Tovey and Robinson, 1975).

Rhesus immunization occurring during a first pregnancy with no preceding abortion or transfusion may result from:

1. Rhesus incompatible fetal to maternal transfusion early in pregnancy initiating a maternal immune response.

2. Maternal to fetal transfer of rhesus incompatible red cells while the patient was herself in utero, or at her delivery (Bowen and Renfield, 1976).

These cases show that knowledge is incomplete regarding the underlying aetiological factors in the immunizing process.

Reports have been made of a high male:female ratio among the sensitizing first-born children. This raises the question of whether the immunological relation between the mother and her male fetus results in a placenta more predisposed to cellular exchange or whether there is a Y-linked factor that renders the male red cell more antigenic than its female counterpart. One reported series showed that rhesus negative women with blood group A, B, or AB who carried an ABO-compatible rhesus positive male were at highest risk. The antepartum use of anti-D has potential prophylactic value in this instance (Scott *et al.*, 1977).

Antenatal diagnosis

Routine blood tests on every pregnant woman are essential (Figure 2). Antibodies may appear at any time during pregnancy.

In Britain 10 per cent of all pregnant women will be rhesus negative bearing a rhesus positive fetus. Any rhesus negative woman pregnant for the first time with a rhesus positive fetus and not treated after an abortion or delivery with anti-D has a one in six chance of developing anti-D antibodies.

If the mother has had one affected infant and her partner is homozygous 'D' the chance of producing a second affected child is one in 12 and each succeeding pregnancy will be affected. If he is heterozygous 'D' the chance of producing a second affected child is one in 15 and probably every other child will be affected.

The risk of stillbirth is eight per cent in a first affected pregnancy and 70 per cent if the mother has had a previous stillbirth or infant suffering from hydrops.

Prevention of rhesus immunization

The following is based on a publication by the Central Health Services Council (1976):

1. At delivery venous blood is taken from the mother and from the cord. The mother's ABO and rhesus group should be known and the antibodies checked. The baby's ABO and rhesus group are determined, also the serum bilirubin and haemoglobin, and the direct Coombs test is carried out.

2. If the baby is rhesus positive, the Kleihauer test should be performed, the size of transplacental haemorrhage estimated and the appropriate dose of anti-D given as soon as possible after delivery, and certainly within 60 hours—although it is still worth giving up to six weeks post partum as long as the direct Coombs test is negative. The standard dose is 100 micrograms unless the Kleihauer count shows more than two fetal cells per high power field, when the required dose is calculated. Following a large transplacental haemorrhage daily

Table 1. Mortality figures for haemolytic disease of the newborn (HDN) in England and Wales.

	Infant mortality from HDN (all types)	Stillbirths from HDN (rates per 1,000 births)	Stillbirths due to rhesus incompatibility
1951	505	—	—
1968	254	496	430
1974	75	171	134

Source: Central Health Services Council (1976). *Haemolytic Disease of the Newborn.* London: HMSO.

samples should be taken to check that fetal cells are eliminated.

3. Following induced or spontaneous abortions, including ectopic pregnancies, 50 micrograms of anti-D should be given if the pregnancy is at 20 weeks or less, or 100 micrograms after the 20th week. The risk of immunization in spontaneous abortion with curettage is about three to four per cent but rises to 5·5 per cent after induced abortion (Queenan, 1973).

4. Any woman subjected to sensitizing episodes in pregnancy caused by trauma to the placenta should be given 50 to 100 micrograms anti-D without delay.

5. Confirmation of the success of prophylactic treatment is obtained by sampling the mother's blood six

Figure 2. *Suggested plan of management. Source: Garrey, M. M., Govan, A. D. T., Hodge, C. H. & Callander, R. (1969). Obstetrics illustrated. Edinburgh: Churchill Livingstone.*

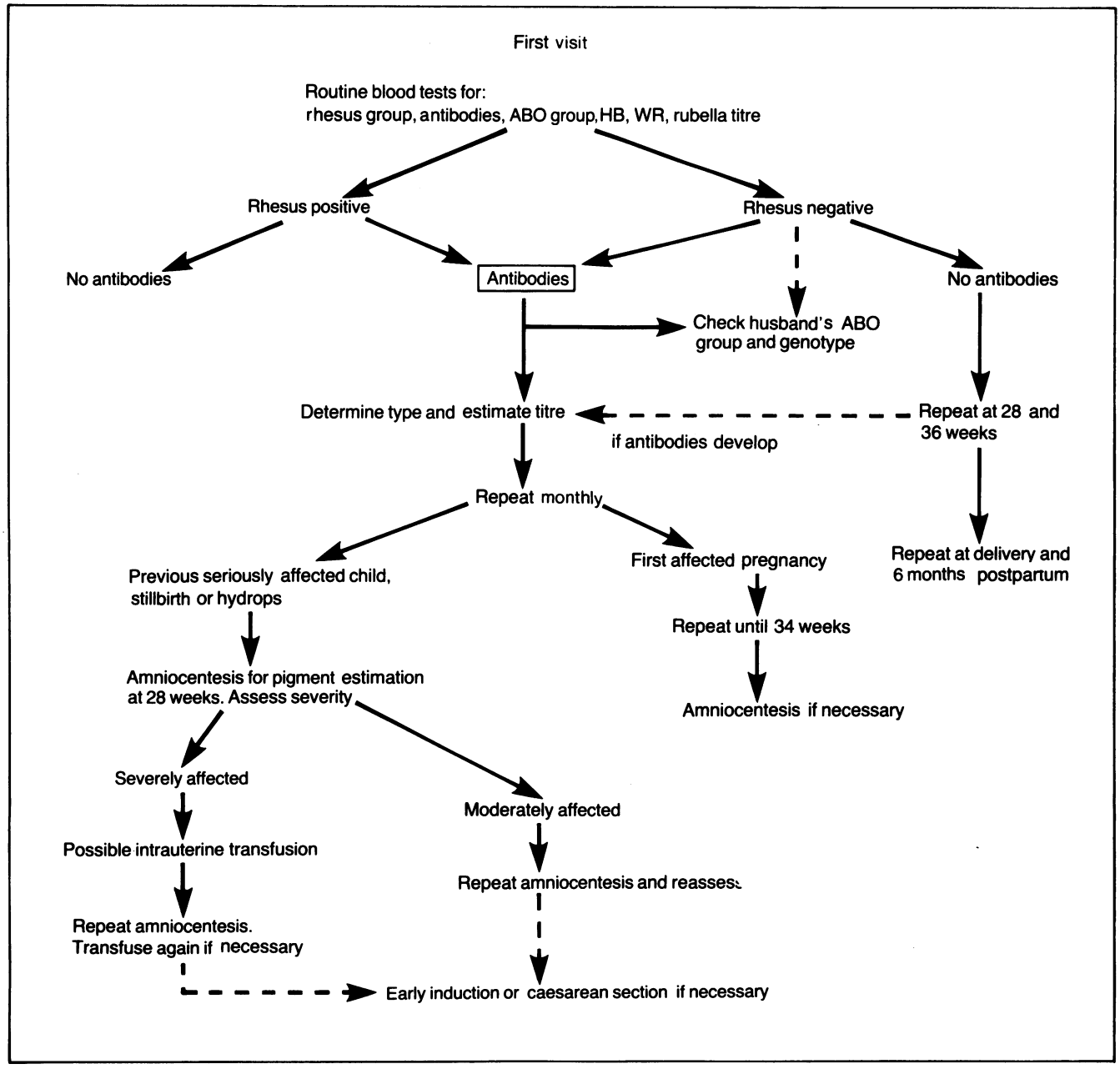

Table 2. Comparison of information between practice and hospital records.

	Total 16 pregnancies		Complete record of antenatal Rh antibodies	Maternal blood for antibodies and fetal cells after delivery	Cord blood for Hb grouping, direct Coombs, and bilirubin	Baby's rhesus group		Baby's ABO group		Anti-D given and recorded	Husband's blood group
	Gravida	Patients				Negative	Positive	Compatible	Incompatible		
Practice records	1 2 3	4 5 7	8	0	1	2	3	1 1*	0 2	6	3
Local general practitioner hospital	5		5	5	5	2	3	1 2*	1 1	not required 3	0
Consultant hospital	11 (including twins)		11	9	10	6	4	5 2*	1 2	not required 5	3

*Mothers most at risk of immunization from transfusion of fetal cells.

Rhesus Negative Register								
Surname	Forenames				Date of birth			
Address					Telephone number			
Patient's blood group and genotype				Husband's blood group and genotype				
Obstetric history								
	Antibodies							
Gravida	Booking	28	36	Delivery	Six months postpartum	Baby's group	Anti-D given	Complications
Blood transfusions								
The reverse of the card may be used for additional information								

Figure 3. *Suggestion for rhesus negative card.*

months after delivery and early in succeeding pregnancies. Treatment is judged to have been successful if there are no antibodies.

6. A consideration in the future would be to give rhesus negative newborn females of rhesus positive mothers anti-D so that a first immunization by materno-fetal transfusion can be prevented.

Complications of anti-D immunoglobulin

These are extremely rare, but may include unexplained febrile reactions and allergic reactions. Antepartum administration has no effect on the fetus except for an occasional positive direct Coombs test.

Mortality figures for haemolytic disease of the newborn

Mortality figures for haemolytic disease of the newborn in England and Wales for the years 1951, 1968 and 1974 are shown in Table 1.

In this country from 1969 anti-D was available to all unsensitized rhesus negative mothers delivered of a rhesus positive ABO compatible infant. In 1971 anti-D became available to all unsensitized rhesus negative women delivered of rhesus positive infants after 20 weeks, and for all rhesus negative women after an induced abortion.

Survey

Aim

I wished to study the care of all rhesus negative women delivered in one general practice between 1 January 1977 and 31 October 1977 and compare their practice and hospital notes.

Method

I examined the practice records to identify the rhesus negative women who were pregnant and then checked their hospital records after delivery.

Results

There were 106 deliveries in the practice during the study period; 16 rhesus negative mothers were identified, one of whom had twins. One patient refused venepuncture, so no blood group was available.

According to the practice records, these women had a total of 35 pregnancies, including one miscarriage and one termination. Anti-D had been given and recorded on 10 occasions, a further three had rhesus negative infants, but of the remainder there is no record. The baby's group was recorded in the notes on only eight occasions, three being rhesus negative. Recording of maternal antibodies was incomplete in the practice records in over half of the pregnancies. There were very

few records of blood taken at delivery or of the cord blood. Of the eligible patients there were no records of antibodies being checked six months after delivery.

A summary of the records of the 1977 deliveries of the patients is shown in Table 2.

Of deliveries to rhesus negative women, five were at the local general practitioner maternity unit and 11 at the nearest consultant hospital. One of these was a stillbirth at 37 weeks after antepartum haemorrhage. Cord blood was taken and the baby was O rhesus negative, compatible with mother; direct Coombs test was negative.

There were two cases from the hospital notes where there was no record of maternal or cord blood having been taken after delivery. In one case both husband and wife were rhesus negative, so it was probably felt to be unnecessary; in the second case anti-D was given. The mother who delivered twins was O rhesus negative, and the twins O and A positive; fetal cells persisted in the maternal circulation and four doses of anti-D were given. Of the 17 deliveries, the four starred in Table 2 are the ones most likely to put the mother at risk of immunization from transfusion of fetal cells. It is therefore particularly important to follow up these women by ensuring they receive anti-D and checking for antibodies six months after delivery.

Discussion

This small survey shows a discrepancy between hospital and practice records, and a need for better communication between hospital and general practice. The notes show that all hospital deliveries are carefully monitored and rhesus negative women bearing rhesus positive infants receive anti-D. However, there is a loophole where women, especially primigravidas where the blood group may be unknown, miscarry early in pregnancy, particularly if treated at home. Thus it is important to educate patients about rhesus immunization. Perhaps all teenage girls should have their blood group recorded.

Recommendations

I make the following recommendations for better record keeping in the pregnancies of rhesus negative women:

1. Ensure that blood is taken for blood group and antibodies, in addition to other routine specimens, from all pregnant women at booking (around 12 weeks).

2. Ensure that any woman who has a miscarriage, especially those treated at home, has her blood group checked and anti-D given if required. Perhaps the midwife could be asked to do this. The same applies to any woman having a termination.

3. A coloured sticker indicating a rhesus negative group should be put on the main record envelope and on the antenatal card, for easy recognition. In addition, RH.NEG should be written in red on the notes and antenatal card, as stickers sometimes peel off.

4. For rhesus negative women, the husband's group and genotype should be recorded. This is relevant if the mother develops antibodies, but if the father is rhesus negative there will be no need for anti-D to be given.

5. Maternal antibodies should be checked at 12, 28, and 36 weeks during the antenatal period—if antibodies appear, more frequent assessment is required. Maternal blood should be taken after delivery for antibodies and screening for fetal cells. The results must be recorded on the postnatal discharge form and antenatal record card.

6. Cord blood should be taken for the baby's group, haemoglobin, direct Coombs test, and serum bilirubin. If infant is jaundiced any treatment should be recorded.

7. Ensure that anti-D is given to all rhesus negative women who give birth to a rhesus positive infant. This is particularly important after early hospital discharge.

8. If the baby is stillborn or a neonatal death, cord blood should be taken if possible for the usual tests, and these recorded with the infant's weight, condition, presence or absence of jaundice, congenital abnormalities, and condition and weight of the placenta.

Points five to eight all require better hospital liaison; laboratory report copies should be sent to practices.

9. Follow up for antibodies six months after delivery. At present the onus is on the mother to remember to have this done, if she was told in the first place. A register at the practice would allow the mothers to be recalled at the appropriate time. A suggested layout for a rhesus negative card is shown in Figure 3.

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