

PREVENTION OF RHESUS (D) IMMUNISATION— Some Causes of Failure in Northern Ireland

by

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INTRODUCTION

DURING the past decade there has been a dramatic fall in the incidence and mortality from Rh haemolytic disease (Tovey 1976; Magee, Harley, Campbell and McClure, 1969-78). This is due to two factors, firstly the appreciable fall in the number of Rh (D) negative women having babies, particularly if they had developed Rh antibodies previously; and secondly the routine administration of anti-D immunoglobulin to Rh (D) negative women delivered of Rh (D) positive infants. This prophylactic programme is aimed at prevention of Rh (D) immunisation, because once this occurs, there is a serious risk of haemolytic disease in any Rh (D) positive baby and this tends to become progressively more severe with increasing mortality in subsequent pregnancies (Walker, Murray and Russell, 1957). Recently it has become apparent that the decline in the incidence of Rh (D) immunisation has halted, and that a significant number of Rh (D) negative women still develop anti-D as a result of pregnancy. We present the results of an investigation into the causes of the problem in Northern Ireland and discuss the measures required to solve it.

PATIENTS AND METHODS

The routine prophylactic programme in Northern Ireland as in the rest of the United Kingdom is to administer 100 μ g anti-D immunoglobulin to all Rh (D) negative women who have given birth to a Rh (D) positive baby within three days of delivery. A larger dose is given to the small number of women who have a transplacental fetal haemorrhage of greater than 4 ml as determined by the Kleihauer technique. It is also recommended in the United Kingdom that all Rh (D) negative women should receive anti-D immunoglobulin following an abortion, (Standing Medical Advisory Committee, 1976). All ante-natal patients in the province are tested for the presence of irregular antibodies by the Northern Ireland Blood Transfusion Service and Rh (D) negative cases are tested at least three times during each pregnancy. All samples are tested manually using saline, albumen, enzyme and indirect Coomb's techniques.

During 1978-1979 anti-D was detected in 117 ante-natal patients. Of these there were 50 patients in whom anti-D was detectable for the first time and it was decided to analyse these patients for possible causes of sensitisation. The obstetric history was obtained and details of all previous pregnancies, including those ending in abortion, taken from the original notes. The following information was particularly noted; the baby's Rh (D) group (where appropriate), result of Kleihauer test, record of anti-D administration (including the dose) and history of blood transfusion. If any of the information was not recorded in the case notes it was obtained from the laboratory responsible for performing the tests and issuing anti-D immunoglobulin.

RESULTS

No cases had a history of transfusion with Rh (D) positive blood. Nineteen patients had been pregnant before 1969 (when anti-D prophylaxis first became available) and were excluded from the analysis. In one patient, who had a previous pregnancy in a different country, the cause of sensitisation remains uncertain, but the remaining cases were divided into three categories:-

1. *Failure of Administration*

There were 11 patients in this category, which included those patients who failed to receive anti-D immunoglobulin, following a previous normal delivery of a Rh (D) positive baby (two cases) or following an abortion (nine cases). Of the latter, the previous abortion had almost certainly been the cause of sensitisation in six cases, but this was less certain in the remaining three.

2. *Failure of Treatment*

There were 17 patients in this category, all of whom had a record of having received anti-D immunoglobulin where appropriate. The result of the Kleihauer test was recorded in each of these cases and in three patients this indicated the presence of a large transplacental haemorrhage. In none of these cases was anti-D given in a dose pro-rata with the calculated volume of fetal cells which is the method recommended (Wagstaff, 1978). Instead an arbitrary number of extra doses of anti-D were given daily until fetal cells could no longer be demonstrated in the maternal blood. In at least two of these cases this inadequate treatment was clearly the cause of sensitisation.

3. *Primigravidae*

In only two cases were antibodies detected during a first pregnancy.

In category 1 all patients produced antibodies early in pregnancy with the exception of two cases. The antibody detected was usually of high potency. Five of the babies in this category required an exchange transfusion and there were no deaths. In categories 2 and 3 (with one exception) the antibody only became detectable in the last trimester of pregnancy. The antibody was invariably weak, often being detectable by an enzyme method only, and none of the babies had an exchange transfusion. There was one neonatal death, but this was unrelated to haemolytic disease.

DISCUSSION

It is well established that small transplacental haemorrhages can occur during pregnancy sufficient in amount to cause sensitisation to blood group antigens, especially in the last trimester (Bowman, Chown, Lewis and Pollock, 1978; Cook, 1979). This is clearly the case in primigravidae though only two cases were detected during the two year period under examination. The antibodies found in primigravidae are always very weak and the number detected tends to be higher if the more recently developed auto-analysis techniques are used for antibody detection. Those patients who received adequate prophylaxis for all previous

pregnancies are also likely to have been sensitised during the current pregnancy. In these cases the antibody is not likely to be detected until the last trimester (this was the case in all but one patient). It was occasionally difficult to be sure that patients who failed to receive anti-D immunoglobulin when indicated were sensitised as a result, especially following abortions which are less likely to cause sensitisation than a normal delivery. However, in all except two cases who had failed to receive anti-D prophylaxis when indicated, antibody was detected early in the current pregnancy, indicating that sensitisation must have occurred as a result of a preceding pregnancy. It can be seen that the stage in pregnancy when antibody first appears provides a clue to the cause of sensitisation.

Only two cases were sensitised as a result of failing to receive anti-D immunoglobulin following a previous normal delivery. Both of these patients had been delivered at home, a factor in favour of hospital delivery. Attention has been drawn to the fact that some failures of administration following normal delivery are due to the baby being grouped wrongly as Rh (D) negative (Tovey, Murray, Stephenson and Taverner, 1978). This problem, which did not apply in our two cases, could be solved by administering anti-D immunoglobulin to every Rh (D) negative mother at delivery irrespective of the baby's Rh (D) group.

It is well recognised that spontaneous abortion in Rh (D) negative women causes sensitisation in about 3-4 per cent of cases (Freda, Gorman, Galen and Treacy, 1970; Tovey, 1979) and this can be prevented by the administration of 50 μ g anti-D immunoglobulin (Simonovits, 1979). Our findings confirm the importance of anti-D prophylaxis following abortion, but at the time of writing this is not routine practice in Northern Ireland (with the exception of a few units). It is essential to obtain the blood group from all women who are aborting, and if this is Rh (D) negative, to administer 50 μ g anti-D immunoglobulin if the abortion is at 20 weeks gestation or less, and 100 μ g if over 20 weeks. It will obviously be difficult to cover all these cases as the mother (or her doctor) may sometimes be unaware she is aborting. We are planning to issue a special card to all Rh (D) negative expectant mothers drawing attention to the need for anti-D immunoglobulin administration following normal delivery and abortion.

In no case had there been a failure to carry out a Kleihauer test following a previous normal delivery, but it does appear that some patients with large transplacental haemorrhages are not managed in the recommended way (Wagstaff, 1978) and that this led to sensitisation in at least two cases.

The majority of cases represent failures of treatment and could not have been prevented by the currently recommended regime. These cases were presumably due to ante-natal sensitisation and there is evidence that this can be almost entirely prevented by ante-natal administration of anti-D immunoglobulin (McMaster Conference, 1979). This programme would involve the administration of 100 μ g anti-D immunoglobulin to all Rh (D) negative women on two separate occasions during the last trimester and would be in addition to the existing post-natal prophylaxis. Clearly this practice would involve a massive increase in requirements for anti-D and place a considerable strain on transfusion centres. The cost benefit in the United Kingdom as a whole has been questioned although a pilot study is in progress. It has been stated that there is a stronger case for ante-natal prophylaxis in countries with a high birth rate and where effective birth control is not practised by

those already immunised (McMaster Conference, 1979). This suggests that Northern Ireland might obtain greater cost benefit than the rest of the United Kingdom. In contrast to our findings a survey of first-affected cases in Yorkshire showed a slight majority were due to "failure of administration" (Tovey, 1978). This difference appears to be mainly due to their higher incidence of failure to cover appropriate normal deliveries.

As would be expected in first-affected cases, few of the babies in the group under analysis were severely affected by haemolytic disease. There were no deaths attributable to the presence of Rh (D) antibodies and only 5 out of 31 babies required exchange transfusions. The latter all occurred in the "failure of administration" category which is not surprising in view of the much more potent antibodies found therein. The absence of any severely affected cases in the "failure of treatment" category or in primigravidae is in agreement with other workers (Tovey, 1979). This observation has been used as an argument against the introduction of ante-natal prophylaxis, but once Rh (D) immunisation occurs there remains the much greater risk to the baby in subsequent pregnancies.

SUMMARY

It is gratifying that very few Rh (D) negative mothers fail to receive anti-D immunoglobulin following the normal delivery of a Rh (D) positive baby, but it does seem that this could be reduced even further by discouraging home delivery. The incidence of sensitisation could also be reduced by the routine use of prophylactic anti-D for abortions in all Rh (D) negative women, and possibly by the better management of large transplacental haemorrhages following normal delivery. Further improvement will only be obtained by the introduction of anti-D prophylaxis during the ante-natal period.

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