Regular Review

Rh(D) haemolytic disease of the newborn: the changing scene

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Haemolytic disease of the newborn due to anti-D used to be a major cause of perinatal mortality in Britain. In the 1950s, before the development of exchange transfusion, amniocentesis, intrauterine transfusion, and early induction of labour, mortality from stillbirths and neonatal deaths was about 1.5 per 1000 births, equivalent to well over 1000 deaths a year. After the introduction of the above technical improvements there was a gradual reduction in mortality such that by 1969, 708 deaths due to Rh(D) haemolytic disease of the newborn were recorded in Britain (13 per million population a year).^{1,2} This achievement was not dramatic and represented a considerable workload for obstetricians and paediatricians. The breakthrough which accelerated the improvement in fetal mortality came in the 1970s with the introduction of anti-D immunoglobulin prophylaxis, and by 1979 mortality had been reduced to 105 stillbirths and postnatal deaths. The latest statistics (1983) have been analysed in detail at p 17 by Clarke, Mollison, and Whitfield and they identify 34 deaths (stillbirths and postnatal deaths) due to Rh(D) haemolytic disease of the newborn (5.4 per 100 000 births). Thus deaths from this disease now contribute 0.33% to the combined stillbirth and perinatal mortality rates (1614 per 100 000 births). Even given the inaccuracy of official statistics it would seem that Rh(D) haemolytic disease is no longer a frequent cause of death.

Nevertheless, the continued appearance of new cases of immunisation of women is disturbing.³ The mortality statistics obscure the fact that there are still appreciable numbers of affected babies being saved by medical intervention and who would have died 10 years ago. Furthermore, deaths from haemolytic disease of the newborn occurring before 28 weeks would be recorded as abortions and not included in the above statistics.

Over the past five to 10 years new cases of immunisation have appeared at the rate of some 600-800 a year, and analysis of the reasons why the present prophylaxis programme has failed to eliminate haemolytic disease of the newborn shows that in the year of study (1978) some 800 new cases (14.6 per million population a year) of Rh(D) sensitisation appeared in Britain as a whole.^{4,5} About 140 of these mothers had become immunised before the anti-D immunoglobulin era; this cohort will decrease and be beyond reproductive age by the year 2000. The current prophylaxis programme, therefore, still fails to prevent some 600-700 Rh(D) negative women (12 per million population a year) being immunised each year. There are three main reasons for this: failure to give anti-D immunoglobulin when indicated, failure of protection by passive anti-D immunoglobulin, and intrapartum immunisation.

The administration of anti-D immunoglobulin is based on the concept that immunisation occurs as a result of transplacental haemorrhage of Rh(D) positive fetal cells into the susceptible Rh(D) negative mother. Since this occurs most frequently at delivery the standard British practice is to give 100 µg (500 IU) anti-D immunoglobulin within 72 hours (preferably within 24 hours) of delivery. It is important, but not always appreciated, that there are other potentially sensitising episodes that are indications for intrapartum anti-D immunoglobulin, including abortion (spontaneous, threatened, or therapeutic), antepartum haemorrhage, amniocentesis, and external version. Before 20 weeks' gestation 50 µg (250 IU) should be given, after 20 weeks 100 µg (500 IU).

Failure to give anti-D immunoglobulin when indicated is the result of human error—for example, if there is a delay in determining the baby's blood group (or the mother is discharged from hospital early). Anti-D immunoglobulin should be given without waiting for the laboratory results in cases where waiting for results would delay administration beyond 72 hours, but this should be the exception rather than the rule because if this policy were to be adopted widely, apart from being unscientific, it would increase the usage of anti-D immunoglobulin by 70%. About half to one third (200-300) of the new cases of immunisation in Britain are the result of failure to give anti-D immunoglobulin,⁴ and some 36% of deaths due to haemolytic disease of the newborn occur in women who are immunised as a result of such failure (p 17). Even in a region where there is high awareness of the problem, some 20% of new cases are the result of administrative failures.^{3,5} Half of the failures of administration (100-200 cases a year) occur after abortion, therapeutic and spontaneous abortion contributing equally.³ Failure to give anti-D immunoglobulin after termination can be due only to ignorance or indolence, but spontaneous abortion presents a more difficult problem because if this occurs in early pregnancy the event may not be reported to a doctor. In an attempt to increase general awareness the Department of Health and Social Security has produced a blood group card for issue (by testing laboratories) to every Rh(D) negative woman as soon as pregnancy is confirmed and the blood group determined. The effectiveness of this approach is doubtful since many regional transfusion centres have issued similar blood group cards for years without noticeable impact on the failure rate. Encouragingly, however, National Health Service anti-D immunoglobulin will continue to be made freely available to the private sector, thus avoiding the possibility of an "artificial" shortage and failures of administration. Giving anti-D immunoglobulin when indicated in all

cases would therefore reduce the number of new cases in Britain by some 200-300 a year and reduce deaths to 10-20 a year at 1983 rates. But what of the remainder?

Some 300-400 new cases a year may be attributed to failure of passive anti-D immunoglobulin to prevent maternal immunisation, either because insufficient immunoglobulin was given or because intrapartum sensitisation has occurred before postpartum anti-D immunoglobulin is indicated. The failure rate with the 100 µg dose is not significantly higher than with the 300 µg dose used in North America,⁶ but it is British practice to estimate the size of any transplacental haemorrhage by the Kleihauer test (fetal cell count) and give "additional anti-D immunoglobulin as required (20 µg anti-D "neutralises" 1 ml fetal red blood cells). This is particularly important in obstetric complications which are associated with large transplacental haemorrhages such as placental abruption, manual removal of placenta, and fulminant eclampsia. Failure to give sufficient anti-D immunoglobulin undoubtedly causes some cases of immunisation, but many, if not most, of the "failures of protection" are the result of occult intrapartum transplacental haemorrhage, particularly in the third trimester. Intrapartum immunisation in Britain, as shown by the failure rate in Rh(D) negative primigravidas with Rh(D) positive babies, is about 0.7-0.9% of those at risk.^{7 8}

Failures of protection may be reduced substantially by giving anti-D immunoglobulin antenatally at 28 and 34 weeks,⁶ but it has been argued that in Britain such a regimen applied to all Rh(D) negative women would not be cost effective since only six to eight deaths from haemolytic disease of the newborn a year would be prevented at a cost of some £1.8m (1980 prices) for the additional anti-D immunoglobulin.⁴ Four times as much anti-D immunoglobulin would be required (33 million µg) compared with the present postpartum programme. This would entail expanding the programme of immunising and boosting Rh(D) negative volunteers for the additional anti-D plasma together with the inherent risks. On the basis of the Yorkshire regional data Tovey and Taverner concluded that the five to 10 mothers each year who develop anti-D during their first pregnancy seem to be hyperresponders.⁵ Although they constituted only 18% of the new cases, half of the deaths from haemolytic disease of the newborn occurred in this group. Antenatal prophylaxis limited to Rh(D) negative primigravidas was proposed as being potentially cost effective since only twice as much anti-D immunoglobulin would be required, compared with the present regimen, and it would save two deaths a year in the Yorkshire region at a rough cost of £25 000 a child. (This would extrapolate to some 30 deaths from haemolytic disease of the newborn in Britain—a higher figure than that estimated for primigravidas on the wider population survey of Tovey.⁴) The results of the Yorkshire antenatal trial show that the failure rate in Rh(D) negative primigravidas with the present postpartum protocol was 0.9% (18/2000).⁷ The cohort given 100 µg anti-D immunoglobulin at 28 and 34 weeks had a failure rate of 0.16% (2/1238) in those mothers delivered of a Rh(D) positive baby. Undoubtedly antenatal anti-D immunoglobulin is effective in lowering the incidence of immunisation, but will this have any effect in reducing mortality from haemolytic disease of the newborn?

To examine the data for first pregnancies, some nine expected sensitisations were prevented at a cost of about £4500 each. In Britain as a whole this would prevent some 140 new cases (about 20% of the total). Unfortunately, it is not possible to assess the benefits on mortality from haemolytic

disease of the newborn from this trial because there were no deaths related to haemolytic disease of the newborn in the control group—which seems at variance with Tovey's original observation of a high fetal mortality in the "presensitised primigravidas." The probable reason for this disparity is the historical nature of the original data,⁵ together with the considerable improvement in the management of haemolytic disease of the newborn in recent years. The actual benefit of introducing antepartum anti-D immunoglobulin in Britain is, therefore, questionable. Most of the women who become immunised have heterozygous consorts, so an affected baby is by no means certain. Even then, the risk of fetal death during the first pregnancy seems to be very small.

Two factors have played a major part in the improved survival of babies affected by Rh(D) haemolytic disease of the newborn: better surveillance of the immunised mother during pregnancy, and the greatly improved management of very low birthweight babies in neonatal intensive care units. If the immunised mother carries a Rh(D) positive fetus the risks of continued intrauterine haemolysis leading to hydrops fetalis have to be balanced against the risks of premature delivery or intrauterine transfusion. Fetal haemolysis is assessed by spectrophotometric bilirubin concentrations (Δ OD 450) in liquor taken at serial amniocentesis. The timing of amniocentesis is determined on the basis of the obstetric history and the maternal anti-D concentration, but not before 20 weeks' gestation since intrauterine transfusion is not normally feasible before 23 weeks. A serum anti-D concentration of less than 4 IU/ml is rarely associated with severe disease, whereas a concentration greater than 20 IU/ml is almost always a bad prognostic sign.⁹ That these values need to be interpreted in relation to the gestational age and the trend in antibody concentration is equally important. Some anti-Ds behave atypically, and amniocentesis may be unnecessary in some cases even with a high anti-D concentration.¹⁰ No additional information is gained from analysis of the anti-D concentration in amniotic fluid. With the use of ultrasound it is possible to assess the fetus in utero and recognise the prehydropic state (characterised by rapid accumulation of ascitic fluid). This should be taken as an indication for intrauterine transfusion even if the Δ OD 450 is not in the danger zone, or immediate delivery if the fetus is sufficiently mature to survive. Intrauterine transfusion is technically difficult before 23 weeks, and the survival of hydropic babies before 23 weeks is poor (90% mortality)—a reflection of the severity of the disease and the risks of intraperitoneal transfusion in the small fetus. An appreciable mortality is associated with the procedure itself, which should, therefore, be restricted to fetuses which are at risk of becoming hydropic yet too immature to deliver. Nevertheless, technical advances in monitoring and performing intrauterine transfusions have increased perinatal survival to 80-90% in some centres.¹¹⁻¹³

A few immunised women with high anti-D concentrations develop hydrops before 23 weeks, resulting in intrauterine death before standard intrauterine transfusion into the fetal peritoneal cavity can be attempted. In these cases direct intravenous fetal blood sampling and transfusion through the umbilical vessels may be undertaken as early as 18 weeks' gestation using fetoscopy.¹⁴ Repeated intravascular fetal transfusions may be undertaken and hydrops may be reversed in utero with considerably improved survival rates (up to 85%) in expert hands. Determination of the fetal Rh(D) type is also possible in immunised women with a previous intrauterine death and a Rh(D) heterozygous consort.¹⁴ Mortality associated with fetoscopy is 3-5%.

Intensive plasma exchange to remove maternal anti-D immunoglobulin should also be considered in this group of highly immunised women. Plasma exchange of 3-4 litres may be required up to three or more times a week for the duration of the pregnancy if the level of anti-D is to be reduced.^{15 16} In the absence of immunosuppression there may be a rapid rebound of antibody concentrations which cannot be controlled even with daily plasma exchange, and fetal death ensues. The effects of plasma exchange on amniocentesis are less convincing, showing that there is sufficient residual circulating maternal antibody to cross the placenta and affect the fetus. Evaluation of reported success in using plasma exchange is difficult because results are compared with historical controls, and, as noted above, other important advances have contributed to the improved fetal mortality from haemolytic disease of the newborn. Selection criteria may not be particularly stringent and in many cases it is apparent that the babies already had an excellent chance of survival with conventional management. Plasma exchange is not to be undertaken lightly because the mother is being put at risk as well as the baby, and maternal deaths attributable to exchange with fresh frozen plasma have been reported.¹⁷ Plasma exchange should not be considered unless there is a history of previous fetal loss or severe haemolytic disease of the newborn requiring multiple exchange transfusions and there is a strong possibility that the father is Rh(D) homozygous. In suitable cases exchange should be undertaken early, as soon as the pregnancy has been evaluated. Provided that the fetus is monitored for developing hydrops by ultrasound, amniocentesis may be delayed until intrauterine transfusion can be undertaken at 23-24 weeks if required. If there is doubt about the fetal Rh(D) group, and there is a very high presenting anti-D concentration from a previous pregnancy, plasma exchange may be undertaken until fetoscopy and fetal sampling are carried out at 18-20 weeks, further management depending on the Rh group.

In the older fetus early delivery without prior transfusion may be the better choice, since mortality attributable to exchange transfusion (1%) is much smaller than that with intrauterine transfusion. The mortality and morbidity of very low birthweight babies have decreased steadily with the introduction of advanced life support systems, some centres

achieving greater than 80% survival after 28 weeks' gestation. With the decreasing incidence of severely affected babies requiring intrauterine transfusion, experience of the technique has declined in Britain to the extent that only a few regional centres specialising in the management of haemolytic disease of the newborn can claim to be expert. There is, therefore, a tendency to deliver early, even as early as 29-30 weeks, rather than risk intrauterine transfusion.

Rh(D) haemolytic disease of the newborn is likely to remain with us for some time yet. No matter what prophylactic programme is adopted human errors will continue and new cases will appear. The number of affected cases is now at a stage where management must be undertaken at a regional level, where the appropriate obstetric, paediatric, and blood transfusion skills are available. To look to the future there is the possibility of unlimited quantities of anti-D immunoglobulin being produced in vitro by biotechnological methods. For treatment a safe effective human immunoglobulin product will be required. Some progress has been made in producing monoclonal anti-D with Epstein-Barr virus transformed cell lines,¹⁸ but the problem of clinical acceptability of such material for prophylaxis in otherwise healthy people has to be resolved. The clinical efficacy of monoclonal anti-D immunoglobulin has also to be established. Preliminary in vitro studies show that, though the currently available monoclonal anti-D immunoglobulins will agglutinate Rh(D) positive red cells, they are poor at mediating Fc receptor functions as expressed by ADCC red cell lysis and macrophage immune adherence and phagocytosis (S S Armstrong *et al*, paper given to the British Blood Transfusion Society scientific symposium, Manchester, 1984). This suggests that clearance of Rh(D) positive red cells in vivo might be defective and therefore provide insufficient prophylaxis against Rh(D) haemolytic disease of the newborn. For the foreseeable future, therefore, polyclonal anti-D immunoglobulin from volunteer blood donors will continue to be the mainstay of the British Rh(D) haemolytic disease of the newborn prophylaxis programme.

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