Deaths from Rh haemolytic disease of the fetus and newborn, 1977–87

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Rh haemolytic disease of the newborn (HDN) used to be a common disorder; in the 1950s the estimated incidence in the UK was 1 per 180 births [1].

The prophylaxis of HDN by giving a specific antibody (anti-D) to the mother shows how a simple procedure can control what is basically a genetic disease but one in which the environmental factors are known.

The process by which the disease arises is as follows. During pregnancy, and particularly during delivery, fetal red cells cross the placenta and enter the maternal circulation. When the mother is Rh-negative and the fetus Rh-positive, the fetal red cells may immunise the mother to Rh. (Unless stated otherwise, Rh implies D, the most important antigen of the Rh system.)

Primary immunisation to Rh occurs in about 17% of Rh-negative women as a result of a first pregnancy with an ABO-compatible, Rh-positive fetus [2]. Nevertheless, anti-Rh is only rarely detectable by the end of the first pregnancy; in about 50% of primarily immunised women it becomes detectable within the following 3 months, and in the remainder it becomes detectable only during a second pregnancy with an Rh-positive fetus [2], when the small number of fetal red cells which cross the placenta as early as the second trimester stimulate a secondary response. Potent anti-Rh may then develop; the antibody, which is predominantly IgG, crosses the placenta and sets up a haemolytic process in the fetus. This process may be so mild that the infant is virtually normal at birth and requires no treatment, or it may be so severe that the fetus dies in utero at any time from about the 20th week of pregnancy onwards.

During the period 1960–70 the incidence of Rh haemolytic disease declined steadily owing to numerous factors, such as better obstetric and neonatal care and the tendency to have smaller families [3]. However, it was the introduction of immunosuppressive prophylaxis, ie the injection of anti-Rh immunoglobulin (anti-Rh Ig) into Rh-negative women shortly after delivery, that introduced the hope of eliminating the disease altogether. Rh-positive red cells coated with anti-Rh do not induce Rh immunisation [4], and passively administered anti-Rh Ig can prevent Rh immunisation by injected Rh-positive cells [5,6]. If anti-Rh Ig is injected into Rh-negative women after delivery, Rh immunisation is almost always prevented [7,8].

The main objective of the enquiry reported here was to discover the circumstances in which mothers who had lost infants from Rh haemolytic disease had become immunised to Rh. From the beginning of 1977 to the end of 1987 death certificates were obtained every year from the Registrar General for all infants certified as having died from haemolytic disease of the newborn. In each case an approach was then made to the obstetrician who had been in clinical charge of the mother for permission to scrutinise the notes. An attempt was made to determine if the diagnosis was correct and, if so, the circumstances in which the mother had become immunised to Rh, an event that had sometimes occurred many years previously. Results for the years 1977–85 have been reported previously; for references to results for 1977–81 and for results for 1982–3, see [9]; for results for 1984–5, see [10].

It should be emphasised that the enquiry was concerned solely with deaths from haemolytic disease and not with the incidence of the disease as a whole.

Categorisation of cases

As a rule, sufficient evidence was available for cases to be categorised according to the scheme shown in Table 1. However, in a few cases there was uncertainty of one kind or another. We then had to decide what was most probable, and we dealt with those cases by applying certain rules, our chief aim being to try to decide whether anti-Rh Ig had been given when it was indicated. Four examples are given.

1. If a woman had been given anti-Rh Ig after a first pregnancy, and she made antibodies during the subsequent pregnancy, we categorised her as a failure (category 3), even though she might have only developed the antibody during the second pregnancy.

2. If a first pregnancy ended in a spontaneous abortion at 12 weeks and no anti-Rh Ig was given, and this was followed by second and third pregnancies resulting in the birth of healthy infants and anti-Rh Ig was

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given after each of them, and if in the fourth pregnancy the mother developed antibodies and the baby died of haemolytic disease, the failure to give anti-Rh Ig after the first pregnancy was held to be responsible (category 1) though in fact the mother might have been primarily immunised during the second or third pregnancy without forming detectable antibodies.

3. If a woman had experienced several previous pregnancies and had not been given anti-Rh Ig after every one of them, we placed her in category 1, even when it was quite possible that primary immunisation had occurred during the pregnancy under investigation.

4. If the mother of a stillborn infant had developed only a low concentration of antibodies and had some complication, such as eclampsia, and if the infant showed no definite signs of haemolytic disease, we categorised the death (in contradiction of the death certificate) as category 6 (death not due to haemolytic disease).

Results

Figure 1 shows the total numbers of deaths notified to the Registrar General as due to haemolytic disease of the fetus or newborn for each year from 1977 to 1983. The figure also shows the numbers in which, after perusal of the notes, we considered that there was adequate evidence that death was due to haemolytic disease as the result of immunisation to either anti-D or some other antibody. The figure shows that:

- the number of deaths from haemolytic disease due to anti-D fell progressively from 1977 to 1984 but then remained approximately constant;
- the number of deaths from haemolytic disease due to antibodies other than anti-D remained constant, being 3–4 for each of the years except 1984 (5) and 1987 (0);
- the number of cases registered as due to haemolytic disease but found by us to be due to some other cause, ie, the difference between the top line and the sum of the two lower lines in Fig. 1, fell progressively; the number was 45 in 1977 but only 8 in 1987.

Of the 38 deaths from haemolytic disease due to an antibody other than anti-D, the antibodies involved were as follows: anti-c with or without anti-E, 26; anti-K, 9; anti-c + anti-K, 2; anti-C, 1 (see Discussion).

Table 2 shows the numbers of cases in categories 1 to 4 for the years 1977 to 1987. The numbers in categories 1a and 1b (deaths in the offspring of mothers who had become immunised after not having been given anti-Rh Ig postnatally) fell rapidly in the first 5-6 years but thereafter fell only slowly. The number in category 1a (immunised prior to 1970) must fall to zero before long, and the number in category 1b should eventually become very small; failure to administer anti-Rh Ig after termination of pregnancy seems to account for some of the present cases [9].

Over the period 1977–87, total births in England and Wales rose from about $5.7 \times 10^6$ to about $6.8 \times 10^6$. Thus, whereas total deaths from haemolytic disease due to anti-D in 1987 were 25% (27/106) of the number in 1977, they were 21% if expressed in relation to birth rate (18.4 per 100,000 in 1977 and 3.9 per 100,000 in 1987).

As Table 2 shows, the numbers of the mothers immunised during their first pregnancy (category 2) and the numbers immunised despite postnatal anti-Rh Ig (category 3) remained approximately constant. Table 2

### Table 1. Classification of deaths registered as due to haemolytic disease of the fetus or newborn; in categories 1–4 it is due to anti-D

1. Mother believed to have been immunised by a pregnancy following which she was not given an injection of anti-Rh Ig; category divided into 1a and 1b:
   1a. Immunising pregnancy occurred before 1970 (when anti-Rh Ig not widely available)
   1b. Immunising pregnancy occurred from 1970 onwards
2. Immunised during first pregnancy (anti-D detected during, or within 7 days following, first pregnancy)
3. Immunised despite having been given anti-Rh Ig after one or more previous pregnancies (ie, failure of prophylaxis)
4. Immunised to D by blood transfusion
5. Haemolytic disease due to an antibody other than anti-D (anti-c, anti-K etc)
6. Death not due to haemolytic disease

### Table 2. Numbers of deaths in categories 1–4 (see Table 1) for 1977 to 1987

| Category | 1977 | 1978 | 1979 | 1980 | 1981 | 1982 | 1983 | 1984 | 1985 | 1986 | 1987 |
|----------|------|------|------|------|------|------|------|------|------|------|------|
| 1a.      | 53   | 40   | 40   | 31   | 14   | 17   | 4    | 1    | 5    | 8    | 1    |
| 1b.      | 32   | 28   | 24   | 23   | 12   | 16   | 12   | 11   | 11   | 9    | 9    |
| 2.       | 12   | 11   | 10   | 6    | 6    | 5    | 8    | 9    | 3    | 9    | 8    |
| 3.       | 9    | 7    | 12   | 11   | 9    | 6    | 9    | 9    | 8    | 5    | 10   |
| 4.       | 0    | 2    | 1    | 1    | 0    | 0    | 1    | 1    | 0    | 0    | 0    |
| Total    | 106  | 88   | 87   | 72   | 41   | 44   | 34   | 25   | 33   | 30   | 27   |

Deaths per 100,000 births

| Category | 1977 | 1978 | 1979 | 1980 | 1981 | 1982 | 1983 | 1984 | 1985 | 1986 | 1987 |
|----------|------|------|------|------|------|------|------|------|------|------|------|
| 1a.      | 18.4 | 14.6 | 13.5 | 10.9 | 6.4  | 7.0  | 5.4  | 3.9  | 5.0  | 4.5  | 3.9  |

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also shows that there were only six cases in the 11-year period in which the mother had been immunised to D by a blood transfusion.

Figure 2 shows the numbers of cases in which the infant was either stillborn or born alive. From 1977 to 1980 the numbers born dead were almost twice as great as the numbers born alive, but thereafter the numbers were approximately equal.

The fact that, in England and Wales, livebirths but not stillbirths occurring before the 28th week of pregnancy are registered leads to absurd anomalies: among the 1987 cases there was an infant born at 25 weeks

Fig. 1. Deaths from haemolytic disease of the fetus and newborn in England and Wales, 1977–87. Registered as due to haemolytic disease, ●. Probable true numbers: due to anti-D, □; due to anti-c etc, △.

Fig. 2. Numbers of deaths from Rh (D) haemolytic disease: stillbirths, ○; infants born alive, ■.
with hydrops and a cord Hb concentration of 59 g/litre; its twin was stillborn and therefore does not appear in the OPCS figures or in ours.

Discussion

Over the period 1977 to 1987 registered deaths from haemolytic disease of the fetus and newborn fell by more than 70%, but this fall occurred mainly between 1977 and 1983 and there has been little change since then (see Fig. 1).

Table 2 shows that the failure of the total mortality to decrease since 1983 is due mainly to the fact that deaths in categories 2 and 3 have remained constant. These categories include all cases in which postnatal administration could have been of no avail, either because the woman formed anti-D during her first pregnancy (category 2) or because she became immunised despite being given anti-Rh Ig postnatally (category 3); in most of these latter cases the woman presumably became primarily immunised during pregnancy, ie without forming detectable anti-D. Evidently, primary Rh immunisation which is initiated well before delivery can be prevented only by antenatal immunoprophylaxis. Administration of anti-Rh Ig at the 28th week of pregnancy, or at the 28th and 34th weeks, has been shown to reduce the frequency of Rh immunisation in pregnancy very substantially [11,12].

Figure 1 shows that over the period 1977–87 the numbers of deaths falsely registered as due to haemolytic disease fell substantially and progressively. This fall was due evidently to the dialogue with OPCS stimulated by this survey. The small number of deaths (8) falsely registered as due to Rh haemolytic disease in 1987 may be contrasted with the figure of 97 found in 1953 in an earlier survey [13].

Figure 2 shows that, whereas between 1977 and 1980 almost twice as many of the infants were born dead as were born alive, from then on the numbers were approximately equal. This change is undoubtedly due partly to the great advances in intrauterine treatment of haemolytic disease, so that fetuses who would previously have died in utero are now kept alive. The difference must also be due partly to advances in the management of premature infants so that pregnancies can be terminated earlier with a good chance of having a viable fetus.

In this connection it is of interest that the numbers in category 5 changed very little in the years 1977–86, whereas one might have expected that there would have been an increasing tendency for infants to be rescued by better obstetric care. However, the numbers are very small and the figure for 1987 may signal a downward trend. As described above, about two-thirds of the cases in category 5 were due to anti-c. It has been estimated that about one-third of women found to have anti-c during pregnancy have been immunised by an earlier transfusion, ie of c-positive blood [14]. These cases could be prevented by ensuring that c-negative (D-positive) women who had not reached the menopause were transfused only with c-negative blood. Such blood is readily available from blood transfusion centres.

As stressed previously [9,10], the fact that stillbirths occurring before the 28th week of pregnancy are not registered means that the OPCS figures and ours underestimate the true mortality rate from haemolytic disease of the fetus. We previously concluded that our figures might represent only two-thirds of the total fetal loss from haemolytic disease. However, the increasing success in treating severe cases in utero as early as the 20th week implies that the underestimate may be becoming smaller.

References

1. Walker, W. and Murray, S. (1954) The management of haemolytic diseases of the newborn. British Medical Journal, ii, 126.
2. Woodrow, J. C. (1970) Rh immunisation and its prevention. Seminars in Haematology, 3, 3.
3. Knox, E. G. (1976) Control of haemolytic disease of the newborn. British Journal of Preventive and Social Medicine, 30, 163.
4. Stern, K., Davidsohn, I. and Masaitis, L. (1956) Experimental studies on Rh immunisation. American Journal of Clinical Pathology, 26, 833.
5. Clarke, C. A., Donohoe, W. T. A., McConnell, R. B. et al. (1963) Further experimental studies on the prevention of Rh haemolytic disease. British Medical Journal, i, 979.
6. Freda, V. J., Gorman, J. G. and Pollack, W. (1964) Successful prevention of experimental Rh sensitisation in man with anti-Rh gamma 2 globulin antibody preparation: a preliminary report. Transfusion, 4, 26.
7. Combined Study (1966) Prevention of Rh-haemolytic disease: results of the clinical trial. A combined study from centres in England and Baltimore. British Medical Journal, 2, 907.
8. Pollack, W., Gorman, J. G., Freda, V. J. et al. (1968) Results of clinical trials of RhoGAM in women. Transfusion, 8, 151.
9. Clarke, C. A., Mollison, P. L. and Whitfield, A. G. W. (1985) Deaths from rhesus haemolytic disease in England and Wales in 1982 and 1983. British Medical Journal, 291, 17.
10. Clarke, C. A., Mollison, P. L. and Whitfield, A. G. W. (1987) Deaths from rhesus haemolytic disease in England and Wales in 1984 and 1985. British Medical Journal, 294, 1001.
11. Bowman, J. M., Chown, B., Lewis, M. and Pollock, J. M. (1978) Rh isoimmunisation during pregnancy: antenatal prophylaxis. Canadian Medical Association Journal, 118, 625.
12. Tovey, L. A. D., Townley, A., Stevenson, B. J. and Taverner, J. (1983) The Yorkshire antenatal anti-D immunoglobulin trial in primigravidae. Lancet, 2, 244.
13. Walker, W. and Mollison, P. L. (1957) Haemolytic disease of the newborn. Deaths in England and Wales during 1953 and 1955. Lancet, 1, 1309.
14. Fraser, I. D. and Tovey, G. H. (1976) Observations on Rh immunisation: past, present and future. Clinics in Haematology, 5, 149.