Efficacy and long term effects of antenatal prophylaxis with anti-D immunoglobulin

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Abstract

***Objective*—To measure the safety and efficacy of antenatal treatment with anti-D immunoglobulin.**

***Design*—Open study with historical controls.**

***Setting*—Multicentre study in 17 hospitals in West Yorkshire.**

***Patients*—1238 Rh negative women who delivered Rh positive infants after 34 weeks in their first pregnancy in 1980-1 (group 1) and 2000 similar primigravidas from 1978-9 (group 2). Obstetric data were collected for 616 women in group 1 who had a subsequent pregnancy, 536 similar women in group 2, and 410 Rh positive but otherwise similar primigravidas who delivered in the same hospitals in 1978-81 (group C).**

***Interventions*—Anti-D immunoglobulin 100 μg intramuscularly was given at 28 and 34 weeks to the mothers in their first pregnancy who delivered in 1980-1.**

***End points*—Detection of anti-D antibody in the first or any subsequent pregnancy in groups 1 and 2. For all three groups having subsequent pregnancies gestation at delivery, birth weight, fetal survival at one month, pre-eclampsia defined as blood pressure >140/90 on two occasions more than 12 hours apart, and proteinuria >0·25 g/l.**

***Measurements and main results*—Antenatal immunisation to Rh(D) occurred in six mothers in group 1 and 32 group 2. Most immunisations occurred in the first or second pregnancy. The rates of abortion, gestation at delivery, birth weight, and fetal survival were not significantly different among the three groups. The incidence of pre-eclampsia was lower in mothers given antenatal anti-D immunoglobulin, but the difference was not significant.**

***Conclusions*—Antenatal prophylaxis with anti-D immunoglobulin is effective, and the effect of giving it in the first pregnancy persists into at least the second pregnancy. It seems to be safe for the fetus in the index and subsequent pregnancies.**

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Introduction

Routine administration of anti-D immunoglobulin after delivery or abortion will prevent only 90-95% of cases of Rh sensitisation even if there are no failures of organisation.[1,2] New cases continue to occur mainly because of sensitisation during pregnancy, which renders prophylaxis after delivery impotent.[3,4] Several workers have shown that giving anti-D immunoglobulin antenatally will prevent many of these cases.[3,5,6] Antenatal prophylaxis, however, has been criticised on the grounds that it is not cost effective[7-9]; that the risk to donors providing the extra plasma for anti-D immunoglobulin, who require immunisation and boosting by the injection of foreign cells positive for Rh(D), is unacceptably high in the light of the possible benefits[7,8]; and that its safety to the mother and the fetus has not been adequately shown.[10]

The economic argument has been answered by a study in Canada,[11] and, although the risk to donors, particularly of infection with transmitted viruses, remains, careful selection of red cells for injection and modern techniques of testing have reduced the chances of complications to almost nil. There remains the risk to the mother and fetus. Hensleigh has persistently criticised antenatal prophylaxis on this ground[10,12] and commented that although Bowman stated that there is abundant evidence that a dose of 300 μg is harmless,[2] no references or data were provided to substantiate this claim. He continued, "it is essential to know of adverse effects, even infrequent ones, which could only be detected in properly designed and controlled studies."[12] Although Bowman vigorously defended his data,[13] no detailed studies of long term effects of antenatal prophylaxis seem to have been done.

We therefore reviewed the obstetric outcome in a large sample of patients who received antenatal anti-D immunoglobulin in the Yorkshire antenatal prophylaxis trial.[6] These patients were compared with a sample of patients who received only postnatal prophylaxis and were in the control group of the Yorkshire trial. A further control group, women positive for Rh(D), who of course did not receive anti-D immunoglobulin, was added.

Patients and methods

We studied three groups of patients. The criteria for selection for the original 2069 mothers enrolled in the Yorkshire trial in 1980-1 who received antenatal anti-D immunoglobulin and the 2000 enrolled in 1978-9 who did not have been described in detail elsewhere.[6] All were primigravidas.

Group 1 comprised 1238 of the 2069 mothers who received 100 μg (500 IU) of anti-D immunoglobulin at 28 and 34 weeks and were delivered of an infant positive for Rh(D). A total of 889 had had at least one subsequent pregnancy, and detailed obstetric follow up data were available for 616.

Group 2 comprised 2000 mothers who received anti-D immunoglobulin only after delivery of an Rh(D) positive infant. Of these, 751 had had at least one subsequent baby, and detailed obstetric follow up data were available for 536.

Group 3 comprised 410 Rh(D) positive mothers whose first pregnancy had proceeded beyond 34 weeks in 1978-81 and who had not received anti-D immunoglobulin.

The following data were collected for each patient: maternal age, date and hospital of delivery, baby's sex, birth weight, length of gestation, perinatal outcome (recorded as live birth, stillbirth, or perinatal death), any other perinatal complications, any obstetric complications (particularly the maximum blood pressure), whether a diastolic pressure exceeded 90 mm Hg on

two or more occasions 12 hours apart, and whether the patient had proteinuria >0·25 g/l. When we reviewed the data the criteria for perinatal and obstetric complications, apart from hypertensive complications, varied so much that we included in the analysis only the objective outcomes of survival, birth weight, gestational age at delivery, maternal blood pressure, and proteinuria.

Standard serological techniques were used for grouping and antibody testing as detailed elsewhere.[6]

Results

Table I shows the serological outcome. The number of mothers sensitised was significantly reduced if they had received antenatal prophylaxis rather than postnatal prophylaxis. This was particularly so in the second pregnancy.

The groups were well matched for hospital of delivery and maternal age at first delivery. There was a comparable spread of cases from 17 hospitals. The maximum proportion of cases from any one hospital was 13·8% and the minimum 0·6%; in each group the mean age was comparable. There were minor differences in the years in which the women were first delivered (table II).

The number (and percentage of valid cases) of first pregnancies delivered before 37 weeks was 26 (4·3%) in group 1, 19 (3·6%) in group 2, and 13 (3·2%) in group 3. In the second pregnancy the numbers of abortions before 12 weeks were 37 (6·3%), 10 (2·0%), and 29 (7·5%), respectively: of abortions from 12 to 28 weeks six (1·0%), 13 (2·6%), and 13 (3·3%), respectively; and of deliveries before 37 weeks 24 (4·1%), 23 (4·6%), and 22 (5·7%), respectively. The mean birth weights in the first pregnancy were 3270 g, 3265 g, and 3190 g and in the second pregnancy 3365 g, 3335 g, and 3305 g. The numbers of babies weighing under 2500 g in the first pregnancy were 22 (3·7%), 28 (5·3%), and 35 (8·6%) and in the second 20 (3·8%), 21 (4·7%), and 23 (6·8%). The numbers of perinatal deaths in the first pregnancy were two, six, and two and in the second three, five, and one. None of the differences between the groups were significant, and, although there were too few deaths for meaningful analysis, no excess was seen in the study group.

The incidences of hypertension and proteinuria were lower in the group given antenatal anti-D, but again the differences did not reach significance (table III).

TABLE II—*Mean ages of women in each group and year in which first delivery occurred. Figures are numbers (percentages)*

	Group 1 (antenatal anti-D) (n=616)	Group 2 (postnatal anti-D) (n=536)	Group 3 (Rh-positive) (n=410)
Median age (years)	22·5	23	22
Year of first delivery:			
1977		37 (6·9)	10 (2·4)
1978		200 (37·3)	19 (4·6)
1979	20 (3·2)	288 (53·8)	311 (75·9)
1980	506 (82·1)	3 (0·6)	35 (8·5)
1981	89 (14·4)	7 (1·3)	32 (7·8)

TABLE III—*Incidence of hypertension* and proteinuria† in three groups of women studied. Figures are numbers of women affected among valid cases (percentages)*

	Group 1 (antenatal anti-D)	Group 2 (postnatal anti-D)	Group 3 (Rh positive)
First pregnancy	14/585 (2·4)	17/515 (3·3)	11/379 (2·9)
Second pregnancy	7/525 (1·3)	8/458 (1·7)	6/324 (1·9)
Third pregnancy	5/120 (4·2)	3/113 (2·7)	4/129 (3·1)

*Diastolic blood pressure >90 mm Hg on two occasions 12 hours apart.
†Urinary protein concentration >0·25 g/l on result of dipstick testing 1+.

Discussion

The data in table I confirm that antenatal prophylaxis decreased the incidence of maternal sensitisation in mothers entered into the Yorkshire trial.[6] In the original report[6] antenatal prophylaxis was reported to have failed in two mothers in their first pregnancy. At delivery they had antibody concentrations of 2 and 4 IU respectively. A further 282 mothers had antibody concentrations below 0·5 IU; the antibodies were detectable only by enzymes and were judged to be passive antibodies from the previous injection at 34 weeks. Two of these mothers had persistent unchanged concentrations of antibody in at least one subsequent pregnancy and were delivered of Rh(D) negative infants. Although these cases were labelled as failures of protection, the possibility that the mothers had the rare "naturally occurring" anti-D[16] antibody cannot be ruled out.

Most advocates of antenatal prophylaxis advise giving anti-D immunoglobulin to unsensitised Rh(D) negative mothers in every pregnancy, but our experience suggests that this may not be necessary. Many of the patients in the Yorkshire trial had four or more pregnancies, and, as table I shows, only one produced anti-D antibody in her second pregnancy, none in the third, and only one in the fourth even though antenatal prophylaxis was given only in the first pregnancy. This emphasises the importance of the mother's immunological response to the first Rh(D) positive stimulus and the advantage of modifying it by giving anti-D immunoglobulin.

We tried to explore further the safety of antenatal prophylaxis. Among the 1640 mothers who had at least one further pregnancy (889 plus 751, table I) we were able to follow up clinically 1152 (616 in group 1 and 536 group 2, 70%). All the information suggested that the cases were representative, and there was no evidence of different obstetric care. Our results showed no evidence that antenatal prophylaxis was detrimental to either mother or infant. In particular, we cannot support the findings of Tabsch *et al* of a trend towards increased perinatal mortality and morbidity in infants whose mothers received anti-D immunoglobulin in the second trimester after amniocentesis.[1-4] This discrepancy may well be due to our antenatal prophylaxis being given later in pregnancy or the selection of mothers requiring amniocentesis. Bowman pointed out that only a small amount of foreign immunoglobulin crosses the placenta into the fetus's circulation after antenatal prophylaxis[2]; this was even less in our series as the dose of anti-D immunoglobulin was 100 μg

TABLE I—*Follow up of antibody state in first and subsequent pregnancies. Antenatal anti-D immunoglobulin was given only in first pregnancies of trial group*

	First pregnancy		Second pregnancy		Third pregnancy		Fourth pregnancy	
	Antenatal regimen	Postnatal regimen	Antenatal regimen	Postnatal regimen	Antenatal regimen	Postnatal regimen	Antenatal regimen	Postnatal regimen
Pregnancies	2069	2000	889	751	256	189	52	45
Delivered of Rh(D) positive infants (no antibodies)	1234	1881	604	582	167	121	32	18
Delivered of Rh(D) negative infants (no antibodies)	831		159	125	29	33	6	11
Anti-D detected	4	19	1	9		3	1	1

(500 IU) compared with 300 μg used in the Canadian work.[3]

Widespread administration of anti-D immunoglobulin antenatally in this regimen would not be possible at present because of limited supply from a decreasing pool of immunised donors. Immunoglobulin produced by genetic engineering, however, may be available soon, and trials are planned to study the effectiveness of even lower doses.

When studying a treatment regimen for any side effects it is important to avoid the bias created by considering only untoward consequences. Unexpected benefits are also possible, and we paid particular attention to any effects anti-D immunoglobulin may have had on the incidence of hypertensive disease such as pre-eclampsia. Some evidence suggests that previous blood transfusions may reduce the incidence,[15] and possibly some blood products also do so. The data collected, however, though not contradicting this hypothesis, showed no significant difference.

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Damp housing, mould growth, and symptomatic health state

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Abstract

***Objective*—To examine the relation between damp and mould growth and symptomatic ill health.**

***Design*—Cross-sectional study of random sample of households containing children; separate and independent assessments of housing conditions (by surveyor) and health (structured interview by trained researcher).**

***Setting*—Subjects' homes (in selected areas of public housing in Glasgow, Edinburgh, and London).**

***Subjects*—Adult respondents (94% women) and 1169 children living in 597 households.**

***End points*—Specific health symptoms and general evaluation of health among respondents and children over two weeks before interview; and score on general health questionnaire (only respondents).**

***Measurements and main results*—Damp was found in 184 (30·8%) dwellings and actual mould growth in 274 (45·9%). Adult respondents living in damp and mouldy dwellings were likely to report more symptoms overall, including nausea and vomiting, blocked nose, breathlessness, backache, fainting, and bad nerves, than respondents in dry dwellings. Children living in damp and mouldy dwellings had a greater prevalence of respiratory symptoms (wheeze, sore throat, runny nose) and headaches and fever compared with those living in dry dwellings. The mean number of symptoms was higher in damp and mouldy houses and positively associated with increasing severity of dampness and mould (dose response relation). All these differences persisted after controlling for possible confounding factors such as household income, cigarette smoking, unemployment, and overcrowding. Other possible sources of bias that might invalidate the assumption of a causal link between housing conditions and ill health—namely, investigator bias, respondent bias, and selection bias—were also considered and ruled out.**

***Conclusion*—Damp and mouldy living conditions have an adverse effect on symptomatic health, particularly among children.**

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Introduction

Showing a direct relation between damp housing and ill health is by no means straightforward. Firstly, those living in the worst housing conditions are likely to be experiencing other forms of adversity, such as low income and unemployment. Secondly, personal behaviour may also play a part in the causation of ill health. An equally important methodological concern is the process of the data collection itself. If information about health and housing conditions is elicited in the same interview respondents may exaggerate the prevalence of problems, leading to a spurious association between the two phenomena. Moreover, the researchers themselves may influence reporting.

In 1986 we carried out a preliminary study in Edinburgh, which attempted to overcome these methodological difficulties by using a double blind research design.[1] Children living in damp houses, particularly where there was also mould growth, were reported to have higher rates of respiratory and gastrointestinal symptoms, aches and pains, and fever than children in dry dwellings. These differences could not be attributed to smoking or differences between damp and dry households regarding unemployment, income, overcrowding, or duration of tenancy. The numbers of households that included a child was not large enough (n=101), however, to permit a full analysis of the role of other possible confounding variables. Accordingly, we carried out a larger scale, more detailed investigation.

Subjects and methods

The study was conducted in three major cities: Edinburgh, Glasgow, and London. Within each city discrete geographical areas of public housing were