Wanted: Rh D negative donors

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SYNOPSIS

Rhesus (Rh) D immunoglobulin is given to Rh negative women who have certain antenatal indications or give birth to an Rh positive baby. This prevents the development of maternal antibodies which could cause haemolytic disease of the newborn in future pregnancies.

The Australian Red Cross Blood Service (ARCBS) collects high titre anti-D plasma from donors to produce Rh D immunoglobulin. The supply is insufficient to meet all the indications and revised guidelines restricting the use of Rh D immunoglobulin have recently been released. These highlight the need to recruit more blood donors. Doctors are encouraged to refer donors with anti-D antibodies, or Rh negative donors who may be interested in being immunised, to the ARCBS.

Index words: blood donation, rhesus, antenatal care.

(Aust Prescr 2000;23:36–8)

Introduction

Women with a Rhesus (Rh D) negative blood group carrying a Rhesus positive fetus can develop antibodies against the fetus. Isoimmunisation may occur if fetal red blood cells enter the maternal circulation either during pregnancy or following birth. The antibodies, once formed, can cross the placenta and bind to the fetal Rh D positive cells and destroy them. This causes haemolytic disease of the newborn. These antibodies may also affect future pregnancies. To prevent isoimmunisation Rh D immunoglobulin (anti-D) is given to Rh D negative women who have Rh D positive babies.

An anti-D antibody can only develop if the mother is negative for the Rh D antigen. There are ethnic variations in the frequency of Rh D negative individuals with approximately 17% of women in Australia being negative for the Rh D antigen. They are, therefore, at risk of developing anti-D if they give birth to an Rh D positive baby. There will not be a problem if the father is also Rh D negative, as the fetus will be Rh D negative.

Rh project in Australia

In the 1960s it was discovered that it was possible to prevent the body's immune response to the D antigen by giving anti-D post partum.[1] A joint project was established in 1966 by the Australian Red Cross Blood Service (ARCBS) and Commonwealth Serum Laboratories to provide high titre anti-D plasma. This became known as the Rh Project. The first donors had been either immunised by previous exposure, e.g. by transfusion or pregnancy, or were deliberately immunised by being given Rh D positive cells intravenously by the Blood Transfusion Service.

In order to maintain the donors' anti-D titres it was necessary to boost their antibody production by giving them further injections of D positive cells. They were injected with 1 mL of red cells when the titre of anti-D fell (about every six months). Each donor was fully informed about the risks of boosting and advised to discuss it with their own doctor.

Boosting however was electively ceased in November 1991 as it was believed there were sufficient stockpiles of Rh D immunoglobulin and an adequate input of high titre anti-D plasma for processing. Following the cessation of boosting, the titres of anti-D in the plasma received for processing progressively declined. Boosting had to recommence in late 1994 as it became evident that the country was in fact facing a supply crisis. At first, boosting involved only those donors who had previously been boosted, however in December 1995 boosting was extended to donors with preformed anti-D who had not previously been boosted. Boosting in women was limited to those who were postmenopausal or who had had a hysterectomy. This decision was made because Australia was still unable to meet its requirements. These boosted donors now provide 95% of the plasma available for processing.

Despite these efforts and the Royal Australian College of Obstetricians and Gynaecologists Interim Guidelines to reduce usage of Rh D immunoglobulin, Australia ran out of immunoglobulin in 1995. A worldwide shortage of plasma for Rh D immunoglobulin production currently exists.

Donor recruitment

The Rh Project donors are now an elderly group. Many of them are retiring from the boosting program, some are forced to cease donating due to health reasons and others will have to leave because of their age. The success of the project means it is becoming increasingly difficult to find new donors with anti-D because there is a much smaller number of women developing anti-D in the community.

The ARCBS is currently boosting donors across Australia. Despite the maximisation of anti-D collection over the last two years by recruiting and boosting all possible acceptable donors, the Australian supply is only just sufficient to meet the current indications. We would need to increase the supply three times to be able to provide routine antenatal prophylaxis at 28 and 34 weeks of pregnancy.

Guidelines

The National Health and Medical Research Council (NHMRC) has recently released new guidelines for using the limited supply of Rh D immunoglobulin in obstetrics.[2] The main document and a summary as well as a consumer leaflet are available on the NHMRC internet web site http://www.nhmrc.health.gov.au (under Publications, Women's Health).

General

For successful immunoprophylaxis, Rh D immunoglobulin should be given as soon as possible after the sensitising event, but always within 72 hours. If Rh D immunoglobulin has not been given within 72 hours, a dose offered within 9–10 days may provide protection. Blood should be taken from the mother, before administration of the Rh D immunoglobulin, to assess the magnitude of fetomaternal haemorrhage. The blood group of the father is not taken into consideration when determining immunoprophylaxis. This is because the important end point is whether the baby is Rh D positive and the mother is Rh D negative. It is not possible to know the baby's group exactly by knowing the mother's and father's blood groups. In this situation there may also be uncertainty about who the father is.

Postpartum administration

A dose of 125 microgram (625 IU) Rh D immunoglobulin should be offered to every Rh D negative woman following the delivery of an Rh D positive baby.

Rh D immunoglobulin should not be given to women with pre-formed anti-D antibodies, except where the preformed anti-D is due to the antenatal administration of Rh D immunoglobulin.

The magnitude of the fetomaternal haemorrhage should be assessed by a method capable of quantifying a haemorrhage of at least 6 mL of fetal red cells (12 mL of whole blood). The traditional method was the Kleihauer test although several centres are now using flow cytometric assays. The choice of test does not matter significantly as long as the laboratory can accurately quantify the amount of fetomaternal haemorrhage. One dose of 125 microgram Rh D immunoglobulin will protect against a haemorrhage of 6 mL of fetal red cells. If the fetomaternal haemorrhage is assessed as being greater than 6 mL of fetal red cells then additional doses of Rh D immunoglobulin should be given, i.e. another 125 microgram of Rh D immunoglobulin for every extra 6 mL of fetal red cells.

Antenatal administration for potentially sensitising events

First trimester

Rh D immunoglobulin should be offered to every Rh D negative woman with no preformed anti-D antibodies to ensure adequate protection against immunisation for the following indications up to and including 12 weeks gestation:

- miscarriage
- termination of pregnancy
- ectopic pregnancy
- chorionic villus sampling

A dose of 50 microgram Rh D immunoglobulin is sufficient. However, until this dosage size becomes available in Australia, 125 microgram should be used.

There is insufficient and conflicting evidence about whether or not women having a threatened miscarriage should receive Rh D immunoglobulin. Until further evidence is available it would seem prudent to give Rh D immunoglobulin if the clinician was aware of the threatened miscarriage.

After the first trimester

A dose of 125 microgram Rh D immunoglobulin should be offered to every Rh D negative woman with no preformed anti-D antibodies to ensure adequate protection in the following situations after 12 weeks gestation:

- genetic studies (chorionic villus sampling, amniocentesis and cordocentesis)
- abdominal trauma considered sufficient to cause fetomaternal haemorrhage
- each occasion of revealed or concealed antepartum haemorrhage (where the patient suffers unexplained uterine pain the possibility of concealed antepartum haemorrhage should be considered, with a view to immunoprophylaxis)
- external cephalic version (performed or attempted)

It is recommended that the magnitude of the fetomaternal haemorrhage be assessed after the event and following any further procedures or trauma.

Antenatal prophylaxis

Universal prophylaxis with Rh D immunoglobulin to Rh D negative women with no preformed anti-D antibodies at 28 and 34 weeks gestation is generally regarded as best practice. However, due to supply constraints, routine antenatal prophylaxis should not be given until further notice.

Future supply

To secure future supply of anti-D, the NHMRC recommends recruiting more donors to the Rh Project and in the interim, registering and importing anti-D from overseas.

There is no prospect in the medium term of the availability of a monoclonal anti-D and hence we will continue to need volunteer blood donors. Anyone with anti-D is potentially valuable as a blood donor. The ARCBS is currently re-introducing primary immunisation. Rh D negative male donors and postmenopausal Rh D negative females who may be interested in being immunised should be referred to the ARCBS. For further information please contact your local ARCBS Collection Centre or call 131495.

REFERENCES

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2. National Health and Medical Research Council. Guidelines on the prophylactic use of Rh D immunoglobulin (Anti-D) in obstetrics. 1999. http://www.nhmrc.health.gov.au/publicat/wh-home.htm

Self-test questions

The following statements are either true or false (answers on page 47)

5. First trimester abortion is no longer an indication for giving anti-D to a Rhesus negative woman.
6. Rhesus immunoglobulin should be given within 72 hours of a sensitising event.

Prescribing by numbers

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The results of clinical studies are often presented in terms of the relative risk reduction achieved with an active treatment over a control. The relative risk reduction is usually expressed as a percentage and can appear impressive but, as it is isolated from the underlying incidence of the event being prevented, it has little value in the clinical situation.

Absolute risk reduction is the difference in event rates between active and control groups, but it can be difficult to visualise its clinical relevance. The reciprocal of the absolute risk reduction gives the number of patients who need to be treated to prevent one event. This is the **number needed to treat** and is a more useful measure which can be used to compare a range of interventions.[1]

Calculations

$$\text{Event rate} = \frac{\text{events in group}}{\text{number of subjects in group}}$$

$$\text{Relative risk reduction \%} = \left(\frac{\text{event rate control} - \text{event rate active}}{\text{event rate control}}\right) \times 100$$

$$\text{Absolute risk reduction} = \text{event rate control} - \text{event rate active}$$

$$\text{Number needed to treat to prevent one event} = \frac{1}{\text{absolute risk reduction}}$$

The results of the Helsinki heart study[2] (see box) were generally presented as a reduction of 34% in the incidence of coronary heart disease with gemfibrozil treatment.

Expressing results as the number of patients who need to be treated to prevent one event (or for one patient to benefit) is much more meaningful. It can be useful when discussing treatment options with patients.

Example

Helsinki heart study

Subjects: 4081 asymptomatic men aged 40–55 with dyslipidaemia (total cholesterol minus HDL ≥5.2 mmol/L).

Treatment: gemfibrozil 600 mg twice daily (2051 men) or matched placebo (2030 men) in a five year randomised double-blind study.

Results: number of events (fatal, non-fatal myocardial infarction or cardiac death)
gemfibrozil – 56 events, placebo – 84 events.

Calculations

Event rate placebo = $\frac{84}{2030}$ = 0.041 (4.1%)

Event rate active = $\frac{56}{2051}$ = 0.027 (2.7%)

Relative risk reduction % = $\frac{0.014}{0.041} \times 100$ = 34%

Absolute risk reduction = 0.041 – 0.027 = 0.014 (1.4%)

Number needed to treat for five years to prevent one event = $\frac{1}{0.014}$ = 71 men

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1. Cook RJ, Sackett DL. The number needed to treat: a clinically useful measure of treatment effect [published erratum appears in Br Med J 1995;310:1056]. Br Med J 1995;310:452-4.
2. Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P, et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. N Engl J Med 1987;317:1237-45.