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Summary of guideline recommendations
for the use of Rh D immunoglobulin
(Anti-D) in obstetrics



NHMRC

National Health and Medical Research Council

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recommendations
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INTRODUCTION

The discovery, introduction and utilisation of Rh D immunoglobulin (anti-D) for prophylaxis against haemolytic disease of the newborn has been one of the major medical achievements of the past half century. This condition is caused by Rh blood group incompatibility between a woman and her baby, leading to the isoimmunisation of a woman with Rh D negative blood against Rh D positive blood. It was previously a major cause of perinatal mortality, morbidity, long-term disability and mental handicap, and the associated emotional and health costs were high.

Rh D immunoglobulin can be used to prevent isoimmunisation and the possibility of haemolytic disease of the newborn occurring in a subsequent pregnancy through administration:

- to Rh D negative women with no preformed antibodies soon after delivery of an Rh D positive infant;
- during pregnancy, for a potentially sensitising event such as miscarriage, ectopic pregnancy, amniocentesis or abdominal trauma; and
- routinely during pregnancy, usually at 28 and 34 weeks gestation, to Rh D negative women with no preformed antibodies.

However, because Rh D immunoglobulin can only be derived from human plasma, there are a number of issues associated with its supply and availability that must be considered along with gold standard usage identified through the scientific literature.

After demonstration in the 1960s that administration of Rh immunoglobulin to Rh D negative mothers soon after the delivery of Rh D positive babies dramatically reduced the incidence of immunisation, a mechanism for producing Rh D immunoglobulin in Australia was sought. In 1968, Australia became the first country in the world to be self-sufficient in Rh D immunoglobulin.

However, for a variety of reasons both within Australia and worldwide, antibody levels have declined, and in recent years there has been insufficient anti-D to meet Australian requirements. There are continuing difficulties in rectifying the shortfall, despite an intensive effort by the blood banks and CSL¹ to increase local supply so that Australia can again be self-sufficient in anti-D within two years.

Until self-sufficiency is reached, issues concerning the most effective use of limited anti-D supplies must be considered carefully.

1 Formerly known as the Commonwealth Serum Laboratories

In 1997 the NHMRC appointed a Working Party to review the evidence on the effectiveness and cost effectiveness of anti-D in obstetrics, to establish the availability of anti-D over the next two to five years, and to develop guidelines advocating the most effective use of the available supply.

The guideline recommendations and a brief discussion of the reasoning behind them are given below. The full report contains additional information about anti-D use and supply in Australia, the full literature review and cost-effectiveness analysis, and a number of strategies to increase domestic production of anti-D to a self-sufficient level.

GUIDELINE RECOMMENDATIONS

General

- *For successful immunoprophylaxis, Rh D immunoglobulin should be administered as soon as possible after the sensitising event, but always within 72 hours. If Rh D immunoglobulin has not been offered within 72 hours, a dose offered within up to 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.*

Postpartum administration

- *A dose of 125 µg (625 IU) Rh D immunoglobulin should be offered to every Rh D negative woman following 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 ≥ 6 ml of fetal red cells (12 ml of whole blood). Further doses should be administered sufficient to prevent maternal immunisation.*

There is evidence from a systematic review of randomised controlled trials that prophylaxis with postpartum anti-D immunoglobulin is effective in reducing the risk of sensitisation after pregnancy and in a subsequent pregnancy, irrespective of the ABO blood group status of mother and baby. The reviewed trials found that prophylaxis is effective when anti-D is given within 72 hours of birth.

The evidence on the optimal dose of anti-D to recommend for prophylaxis is limited. Standard doses vary between countries, depending on the relative availability and costs of anti-D and the costs of laboratory assessments of the volume of fetomaternal haemorrhage.

It is reasonably well established that 20 µg of anti-D will protect against a fetomaternal haemorrhage of 1 ml of fetal Rh D positive red cells (2 ml of whole blood). The standard Australian dose of 125 µg should protect against a fetomaternal haemorrhage of up to 6 ml of fetal Rh D positive red cells (12 ml of whole blood). A fetomaternal haemorrhage greater than this amount is uncommon but if it does occur, the woman will be at risk of sensitisation if she receives only the standard dose. For this reason, it is recommended that at the time the baby's blood is sent for grouping, a maternal sample is also sent for assessment of the fetomaternal haemorrhage, and further doses of anti-D administered sufficient to prevent maternal immunisation.

Antenatal administration for indications

First trimester

- *A dose of 50 µg (250 IU) Rh D immunoglobulin should be offered to every Rh D negative woman with no preformed anti-D to ensure adequate protection against immunisation for the following indications up to and including 12 weeks gestation:*
 - *miscarriage;*
 - *termination of pregnancy;*
 - *ectopic pregnancy; and*
 - *chorionic villus sampling.*
- *A dose of 50 µg Rh D immunoglobulin is sufficient to prevent immunisation by a fetomaternal haemorrhage of 2.5 ml of fetal red cells (5 ml whole blood).*
- *Until a 50 µg Rh D immunoglobulin vial becomes available in Australia, 125 µg Rh D immunoglobulin should be used.*
- *The Working Party strongly recommends that women undergoing termination of pregnancy be tested to determine their Rh D type, to avoid unnecessary use of Rh D immunoglobulin.*

There is no level I evidence available to support the use of anti-D for indications during pregnancy. Despite limitations with many of the studies, the available lower level evidence indicates that transplacental haemorrhage can occur after six weeks gestation and can be associated with medical, surgical and spontaneous abortion, ruptured ectopic pregnancy, and probably chorionic villus sampling.

There is evidence of an increased risk of immunisation following surgical abortion and ruptured ectopic pregnancy, supporting the use of anti-D for these indications.

There is insufficient and conflicting evidence about whether Rh D negative women experiencing threatened miscarriage or spontaneous miscarriage without curettage should receive anti-D.

The Working Party considers that the recommended dose of anti-D for all potentially sensitising first trimester events should be 50 µg. It is acknowledged that this recommendation will have no impact on the amount of anti-D used because of the current packaging into doses at 125 µg. However, in the long term, if a 50 µg dose becomes available, its use should lead to a halving of the amount of anti-D used in the first trimester.

Beyond the first trimester

- *A dose of 125 µg Rh D immunoglobulin should be offered to every Rh D negative woman with no preformed anti-D to ensure adequate protection against immunisation for the following indications 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); and*
 - *external cephalic version (performed or attempted).*
- *As evidence for the efficacy of this dose for these indications is not available, it is recommended that the magnitude of fetomaternal haemorrhage be assessed and further doses administered, especially where transplacental access or puncture of fetal blood vessels occurs.*

Genetic studies

The available evidence on genetic studies indicates that amniocentesis is associated with an increased rate of immunisation, and that anti-D is successful in reducing the rate of sensitisation following amniocentesis. A standard dose (125 µg) of anti-D should be offered, except where it is known that the father is Rh D negative, or where the fetal blood group is Rh D negative.

An estimation of the fetomaternal haemorrhage should be performed after all invasive tests, particularly fetal blood sampling, chorionic villus sampling, transplacental amniocentesis and insertion of fetal amniotic shunts.

Trauma, antepartum haemorrhage and external cephalic versions

The available evidence supports the prophylactic use of anti-D following external cephalic version, although dosage levels have not been considered.

No evidence on the prophylactic use of anti-D for trauma or antepartum haemorrhage was found. The incidence of such haemorrhages large enough to cause immunisation does not appear to be known.

However, it is recommended that all women with abdominal trauma considered sufficient to cause a degree of placental separation, revealed or concealed antepartum haemorrhage and performed or attempted external cephalic version should receive the standard dose (125 µg) of anti-D, with estimation of the fetomaternal haemorrhage as outlined above. Where such situations arise in association with immediate delivery, the standard procedures associated with the postpartum administration of anti-D should be implemented.

Compared with the usage of anti-D post delivery and in the first trimester, the continued administration of anti-D in such cases would not significantly affect the overall volume of use. Failure to prevent an immunisation occurring in these circumstances would be unacceptable from both a health care cost and human point of view.

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 administered until further notice.***

There is no level I evidence to support the routine administration of Rh D immunoglobulin antenatally to unsensitised Rh D negative women at any gestation. However, there is considerable lower level evidence supporting the efficacy of this practice.

Although the public health significance of antenatal Rh D isoimmunisation occurring in the absence of obvious precipitating factors is not large in terms of numbers of events, there is an effective and cost effective strategy to avoid them. In a climate of limited supply of Rh D immunoglobulin, most events could still be avoided through the practice of routine antenatal prophylaxis of primigravidae only. While there is not scientific evidence available to support the efficacy of this practice, it would seem to be reasonable on clinical grounds, because it is in second and subsequent pregnancies that serious morbidity or mortality occur.

The view of the 1997 Edinburgh Consensus Conference Panel was that there is no ethical or economic justification for limiting antenatal prophylaxis to Rh D negative primigravidae and administration of Rh D immunoglobulin to all Rh D negative women antenatally as routine prophylaxis should be regarded as the ideal or 'gold standard'.

However, this 'gold standard' cannot be achieved at this time as Rh D immunoglobulin is not available in sufficient quantities to meet the demand generated by antenatal prophylaxis, universal or otherwise. The results of the cost-effectiveness study indicate that postpartum administration should have first call on the available supplies of Rh D immunoglobulin. Administration to women with potentially sensitising antenatal events ranks second on economic grounds, followed by routine antenatal prophylaxis to primigravidae only.

It is noted that current constraints on supply may alter in the foreseeable future. The above recommendation should be reviewed on a regular basis and amended according to the availability of supplies of Rh D immunoglobulin existing at the time.

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