

# Administration of RhD immunoglobulin to prevent maternal Rhesus alloimmunisation



## Dr Bev Quested

Transfusion Nurse

Educator

Australian Red Cross  
Blood Service

**The discovery and implementation of RhD immunoglobulin prophylaxis against haemolytic disease of the newborn (HDN) was one of the major medical achievements of the late 20th century.**

HDN can have devastating effects for the fetus and newborn baby as well as implications for subsequent pregnancies leading to further morbidity and mortality. RhD immunoglobulin used for prophylaxis is obtained from human plasma.

## The past

The 1960s saw strong emerging evidence that administering RhD immunoglobulin to RhD negative mothers who had given birth to an RhD

positive baby soon after delivery dramatically reduced the incidence of RhD immunisation and HDN. Haemolytic disease of the newborn due to RhD incompatibility remained a major cause of fetal death and neonatal morbidity into the 1970s, with 80 deaths recorded in the 1974 Australian census.<sup>1</sup>

In 1967, the Rh Project was established as a joint project by the Red Cross National Blood Transfusion Committee and Commonwealth Serum Laboratories (CSL). The Rh Project involved the Red Cross collecting high titre anti-D plasma from donors and CSL processing it into RhD immunoglobulin. In 1968, Australia became the first country in the world to be self-sufficient in RhD immunoglobulin.

The first Rh Project donors were RhD negative women who had produced anti-D and RhD negative men who had become immunised during blood transfusion. These groups were unable to supply sufficient anti-D to meet Australia's needs, so the Australian Red Cross Blood Service (ARCBS) enrolled RhD negative donors who were deliberately transfused with RhD positive blood so that they would produce anti-D. Such a process is undertaken under stringent safety standards and ethical oversight.

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Over the years, there were decreasing numbers of sensitised Rh negative women suitable to become donors and many of the original donors, after 30 years of donating, could no longer participate. Enrolment of new donors was slow. Coupled with reduced donors was an increasing recognition of the role of prophylaxis during pregnancy in the 1990s. Importation of RhD immunoglobulin was needed to supplement local supplies.

The aim in the late 1990s was to provide prophylaxis for all RhD negative pregnancies and regain self-sufficiency. To achieve this a staged program was implemented. Clinical guidelines which balanced best practices with available supply were implemented until self-sufficiency was established.<sup>1</sup> A new group of volunteer donors were sensitised to produce anti-D. Also, a smaller 250iu vial of RhD immunoglobulin was introduced for first trimester sensitising events, allowing available product to be used judiciously. Australia has been self-sufficient for RhD immunoglobulin since February 2006 and it is now available for all women who require it.

## The present

CSL produces Australia's RhD immunoglobulin from plasma donated by Australian volunteers and collected by ARCBS. The donations are routinely screened and the manufacturing process includes pasteurisation and nanofiltration to reduce the risk of viral transmission.<sup>2</sup> *Guidelines for the Prophylactic Use of RhD Immunoglobulin (anti-D) in Obstetrics*<sup>3</sup> were released in 2003 by the National Blood Authority and approved by the NHMRC, updating the 1999 review. RhD immunoglobulin is available in two doses (250iu and 625iu) enabling an effective dose to be used throughout pregnancy.

## Postpartum administration

A systematic review undertaken by Crowther and Middleton<sup>4,5</sup> found anti-D given to Rh negative women within 72 hours after they had given birth to a Rh positive infant reduces the risk of RhD alloimmunisation of the mother, however, evidence on the optimal dose is limited. Current National Blood Authority guidelines recommend 625iu (125µg) of RhD immunoglobulin be given within 72 hours of the birth to RhD negative women with no preformed anti-D. This dose will cover fetomaternal bleeds of up to 6ml of fetal red cells or 12ml of whole blood. A blood sample from the mother should be taken prior to administering RhD immunoglobulin to determine if further doses are required to cover a larger bleed. Fetomaternal bleeds of more than 30ml occur in approximately 0.6 per cent of births.<sup>6</sup> CSL RhD immunoglobulin can only be given intramuscularly. An imported preparation (WinRho® SDF, Baxter) is for IV use and can be used to treat large fetomaternal haemorrhages.

## During pregnancy

Despite the postpartum administration of RhD immunoglobulin, there were still one to 1.5 per cent of RhD negative women with a RhD positive baby who became immunised during the pregnancy.<sup>7,8,9</sup> Silent sensitising events such as transplacental haemorrhages are thought to constitute the major means of immunisation.<sup>7</sup> However, transplacental haemorrhages large enough to cause sensitisation do not normally occur until the third trimester.<sup>10</sup> Administration of 500iu (100µg) RhD immunoglobulin at 28 weeks and 34 weeks gestation to women in their first pregnancy

can reduce this risk to about 0.2 per cent or less.<sup>11</sup> Furthermore, the incidence of immunisation at two to 12 months after giving birth was less in the group who received the 500iu dose than with women who received a lower dose of 250iu at 28 and 34 weeks, indicating that the larger dose was more effective.<sup>7</sup> While the studies are not level one evidence, Crowther<sup>7</sup> concluded that 'antenatal prophylaxis is also likely to decrease the number of sensitisations without adverse effects and should be considered to be complementary to postpartum prophylaxis'. Furthermore, Crowther<sup>7</sup> calculated that 213 women will need to be treated with antenatal RhD immunoglobulin prophylaxis to avoid one case of sensitisation. In Australia, for antenatal prophylaxis the recommended dose contains 625iu (125µg) of RhD immunoglobulin to be given at 28 and 34 weeks.

### Sensitising events

RhD immunoglobulin is administered to women with no preformed anti-D antibodies, who experience a sensitising event during pregnancy. Sensitising events are those in which the risk of fetal blood crosses into the maternal circulation. These events can include miscarriage, termination of pregnancy, ectopic pregnancy, invasive prenatal procedures, external cephalic version, abdominal trauma and antepartum haemorrhage. The National Blood Authority guidelines<sup>3</sup> ([www.nba.gov.au/guidelines](http://www.nba.gov.au/guidelines)) recommend minimum doses depending on the time of gestation and the particular clinical situation. In pregnancies before 20 weeks, a dose of 250iu is usually sufficient to cover sensitising events for a single pregnancy, however, in some cases estimation of foeto-maternal haemorrhage should be undertaken to ensure adequate prophylaxis.

### Issues surrounding current practice

One of the difficulties with RhD immunoglobulin involves interpretation of laboratory blood results, as there is no mechanism to distinguish between RhD immunoglobulin administered prophylactically or the anti-D made by the women. This means it is imperative that the routine blood test is taken before the RhD immunoglobulin is given at 28 weeks. Detection of a high RhD titre may be misinterpreted as a result of passive immunisation and a failure to detect a fetus at risk of HDN. 2007 *Guidelines for Blood Grouping and Antibody Screening in the Antenatal and Perinatal Setting*<sup>12</sup> help manage testing and reporting throughout the pregnancy and investigation of sensitising events.

The UK Systematic Hazards of Transfusion (SHOT) program reports on adverse events related to RhD immunoglobulin. In 2008, 137 errors related to RhD immunoglobulin were reported to SHOT<sup>13</sup>, including the omission or late administration of doses (58/138) that placed women following potentially sensitising events at risk of developing anti-D. The other major category was inappropriate administration of RhD immunoglobulin (63/138). These included 38 RhD positive women being given RhD immunoglobulin; 14 women receiving RhD immunoglobulin when they already had RhD antibodies; and six women who received RhD immunoglobulin despite giving birth to an RhD negative infant. To address some of these issues which relate to information and knowledge deficits, an e-learning package is currently being collaboratively developed by ARCBS and the Scottish National Blood Transfusion Service.

### The future

The prevalence of RhD negative grouping varies in ethnic groups; one in six (17 per cent) of Australian men and women are RhD negative.<sup>14</sup> Furthermore, one in six RhD negative women will have a partner who is also RhD negative. If both parents are RhD negative their baby will always be RhD negative. Therefore, approximately five out of six RhD negative women will have a partner who is RhD positive. If the RhD father is homozygous (which 45 per cent of the

men will be), the fetus will always be RhD positive. If the RhD father is heterozygous (which 55 per cent of the men will be), there is a 50 per cent chance the fetus will be RhD positive.<sup>9</sup> Putting all this together, a group of 600 RhD negative women will have 237 (40 per cent) RhD negative babies. This means that 40 per cent of RhD negative women will receive RhD immunoglobulin unnecessarily. Testing the RhD status of the father relies on a certainty of paternity. Tests from prenatal diagnostic laboratories performing genetic testing indicate non-paternity rates up to 20 to 30 per cent.<sup>9</sup>

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Groundbreaking work by Hyland *et al*<sup>15</sup> enabling non-invasive analysis of fetal DNA by analysis of maternal blood samples to determine fetal RhD status provides a new tool in detecting and managing Rhesus sensitisation. In the near future, it may well become routine practice to establish fetal Rh status and administer RhD immunoglobulin prophylactically to only those RhD negative women who are carrying an RhD positive fetus.

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