

All you ever wanted to know about ANTI-D

By OMAR ALI, DIPCLINPHARM, MRPHARMS

This article looks at the issues surrounding the use of anti-D for the prevention of haemolytic disease of the newborn

Anti-D is the name given to a product whose main active constituent is immunoglobulin G. There are three products available in the United Kingdom (two of which, produced by BPL and Baxter Bioscience, are licensed for prophylaxis of haemolytic disease of the newborn, HDN), all of which are obtained from pooled human venous plasma. They consist of high concentrations of anti-D antibodies (IgG). Crucial to the situation as shown later, immunoglobulin G is the only maternal immunoglobulin which is transferred across the placenta to the unborn fetus.

WHAT IS ANTI-D USED FOR ?

Anti-D is used to prevent HDN. This is a potentially fatal complication caused by blood group incompatibilities between mother and baby. Situations where anti-D is used include abortion, miscarriages and maternal antenatal prophylaxis, or a situation where the mother's blood may mix and cause reaction with the fetal or newborn baby's blood. It is only Rhesus-negative women who will ever need anti-D.

The Rhesus factor is found within red blood cells. It is the presence or absence of D antigens on the surface of red blood cells that determines the Rhesus factor. The Rhesus factor is genetically determined, though, as will be seen later, it is liable to change. In people who are Rhesus positive [Rh(D)+ve], D antigen is present on red blood cells; in people who are Rhesus negative [Rh(D)-ve], no D antigen is present.

THE SIGNIFICANCE

Anti-D is only used when a Rh(D)-ve mother is pregnant with a Rh(D)+ve fetus. This can only happen when the father is Rh(D)+ve. However, a father who is Rh(D)+ve does not always father a baby who is Rh(D)+ve, since he may have both genes and may pass on either expression to his baby.

When the blood of a fetus who is

Rh(D)+ve mixes with the blood of a mother who is Rh(D)-ve, a number of interactions can occur which may have catastrophic consequences. Figure 1 shows the sequence.

WHAT IS HDN?

HDN presents in different ways and with varying levels of severity. Sometimes, it is only apparent from laboratory tests. Other forms of the disease are far more serious and can result in the baby being stillborn or severely disabled. Sometimes, the newborn baby dies soon after birth as a result of severe anaemia and jaundice. Intracranial haemorrhage also occurs. All this is due to the process of maternal antibodies attacking fetal red blood cells, which is easy to prevent.

All pregnant women are required to be screened for blood group typing. This consists of:

- ABO grouping of the mother to determine anti-A, anti-B or anti-O subtypes
- Rh(D) grouping of the mother to determine whether she is Rh(D)+ve or Rh(D)-ve)
- Antibody screening of the mother to determine other allo-antibodies apart from anti-A or anti-B

This allows evaluation of whether or not the mother's antibodies pose a risk to the baby *in utero* or during the birth process. If a mother who is Rh(D)-ve gives birth to a baby who is Rh(D)+ve, her antibodies will

cross the placenta and attack fetal RBC, causing haemolytic anaemia.

However, the mother's Rh(D) status may change during pregnancy or as a result of a previous pregnancy or breach/maternal trauma situation.

SENSITISING EVENTS

Sensitising events are those which result in the mother producing antibodies against the D antigen present in the fetal red blood cells. When blood from the fetus comes into contact with blood from the mother (fetomaternal haemorrhage), "transformation" or "sensitisation" occurs. It is known that in 50 per cent of cases, the mother's transformation is "silent", and will not be known overtly unless she is screened for the antibodies.

Potentially sensitising events are:

- Birth (the most common cause of sensitisation)
- Miscarriage
- Abortion
- Amniocentesis
- Vaginal bleeding
- External cephalic version (turning the baby's head down)

In fact, the size of fetomaternal haemorrhage increases as the pregnancy advances as does the risk (3 per cent in the first trimester, 45 per cent in the third trimester and 64 per cent at the time of delivery).

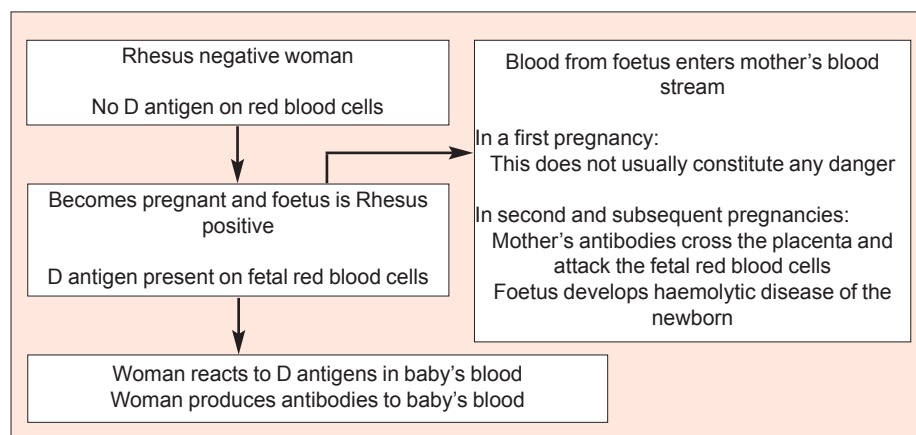


Figure 1: Outline of events when the mother is Rhesus negative and the foetus is Rhesus positive

Mr Ali is prescribing consultant, primary care and formulary development pharmacist, Surrey and Sussex Healthcare NHS Trust

Once a mother has been identified as Rh(D)-ve, it is recommended that she is tested for: ABO grouping, D-grouping, haemoglobin level and bilirubin level (all from the baby's cord blood), and ABO grouping (and repeated), D-grouping (and repeated) and antibody screening (in case she has become sensitised) from the maternal blood.

— HOW DOES ANTI-D WORK?

Anti-D immunoglobulins given to a mother who is Rh(D)-ve will prevent that mother from forming lethal antibodies against fetal Rh(D)+ve red blood cells. The ultimate objective is to prevent the baby suffering HDN. In essence, anti-D is protecting the baby from its mother's antibodies.¹ Anti-D is given most commonly in two situations — post-natally and antenatally.

— POSTNATAL ANTI-D

In the UK, it is conventional practice to give 500iu anti-D to every Rh(D)-ve mother within 72 hours following delivery of her baby (unless the baby's rhesus group is known to be Rh(D)-ve.)

This is to ensure that anti-D is not withheld in situations where the baby's D group is not known or where not enough blood has been collected to evaluate this successfully.

This postnatal dose serves primarily to prevent the mother from creating antibodies against further babies that she may deliver. A mother's first-born is never affected due to the delayed nature of the antibody synthesis and types of antibodies created — it will be further pregnancies that can cause problems.

Since this routine postpartum immunoprophylaxis using anti-D immunoglobulin (IgG) was introduced in 1969, the occurrence of HDN has been reduced drastically, with mortality rates decreasing from 18.4 per 100,000 live births in 1977 to 1.3 per 100,000 live births in 1992.

However, there are still significant numbers of cases despite this, as can be seen from the following:

- In England and Wales, there are 62,000 births of Rh(D)+ve babies to Rh(D)-ve mothers each year
- Of these, around 500 babies develop HDN each year
- Of these, around 25–30 babies die of HDN each year
- About 15 babies will have permanent developmental problems each year
- A further 30 babies will have minor developmental problems each year

Postnatal prophylaxis can prevent RhD sensitisation in approximately 90 per cent of cases. Despite this preventive programme however, approximately 1.5 per cent of Rh(D)-ve women continue to become sensitised as a result of a "silent" event, which is not detectable during a routine pregnancy.²

— WHY DO CASES STILL OCCUR?

Despite anti-D being given routinely cases of HDN still occur. There is evidence that the current Rh(D) sensitisation rate in the UK is, in part, attributed to failure to comply with postnatal prophylaxis guidelines, failure to recognise sensitising episodes and failure to assess the extent of fetomaternal haemorrhage.

— ANTENATAL PROPHYLAXIS

Studies have shown that a routine antenatal prophylaxis regimen of at least 500iu anti-D immunoglobulin at 28 and 34 weeks' gestation can reduce the RhD sensitisation rate from 1.5 per cent to 0.2 per cent or less;³ in other words, the number of Rh(D)-ive women who develop anti-D antibodies in association with the delivery of a Rh(D) +ive baby would be reduced from 1,000 per year to fewer than 140.

In England and Wales, there are 105,000 births to Rh(D)-ve women per year. This represents 17 per cent of all births and also represents the group of individuals who should receive routine prophylaxis. Of the 105,000 births, over half (62,000) are Rh(D)+ve. This represents 10 per cent of all births in England and Wales.

Based on an estimated population figure of 52,943,300 for England and Wales, approximately 992 Rh(D)-ive pregnant women could be sensitised each year, and as a result, 660 Rh(D)+ive babies would be at risk of developing HDN.

These national statistics make the case for national guidance, which is the reason why the National Institute for Clinical Excellence (NICE) has recommended routine prophylaxis.¹

The cost-effectiveness of routine antenatal prophylaxis compares favourably with other treatments, which are funded currently by the NHS.³

WHAT DOES NICE SAY?

In May 2002, NICE recommended routine antenatal anti-D prophylaxis and that at least 500iu should be offered to all non-sensitised Rh(D)-ive women at 28 and 34 weeks of pregnancy. Currently, there are two licensed regimens available in the UK:

- 500iu anti-D immunoglobulin (manufactured by Bio Products Laboratory) given intramuscularly at 28 and 34 weeks' gestation
- 1,250iu anti-immunoglobulin (manufactured by Baxter Bioscience) given intramuscularly at 28 and 34 weeks' gestation

The lower dose of 500iu is recommended by NICE and the Royal College of Obstetricians and Gynaecologists. The higher dose is used in some European countries.^{1,4}

IS ANTI-D SAFE?

There have been safety concerns surrounding anti-D, both for the mother and the unborn child.

Anti-D given during pregnancy is not harmful to the fetus. Loss of life should be unacceptable when effective, reliable, economic treatment exists. Although routine antenatal prophylaxis should reduce the RhD sensitisation rate significantly in Rh(D)-ive women, many midwives remain concerned about the safety of anti-D IgG, and about giving women an informed choice, and have therefore, eagerly awaited clear direction from NICE.^{3,4}

WHICH ANTI-D TO USE?

The more commonly used anti-D product in the UK is that from Bio Products Lab-

oratory (BPL) because it manufactures the recommended dose of 500iu (see above).

BPL is a not-for-profit organisation, reporting to and managed by the National Blood Authority (a Special Health Authority within the NHS). BPL manufactures a wide range of products from human plasma, and has been manufacturing intramuscular anti-D IgG since the late 1960s.

In view of the theoretical risk of variant Creutzfeldt-Jakob disease posed by UK plasma, BPL draws all its plasma from collection centres based in the United States. These centres are licensed by the US Food and Drug Administration and are members of the American Blood Resources Association (ABRA). To ensure UK and European standards are met, BPL and the UK Medicines Control Agency have undertaken a quality audit and approved the plasma for manufacture in the UK.

As plasma-derived products are susceptible to blood-borne viral contamination, product safety is an overriding concern for BPL.

The manufacturing method contains a specific virus inactivation step called solvent/detergent (S/D) treatment, which specifically inactivates lipid-enveloped viruses such as HIV, HBV and HVC. Approximately 35 million doses of S/D-treated products have been administered worldwide with no cases of reported transmission of enveloped viruses.⁵

PATIENT CHOICE

So that a woman can make an informed choice, the clinician responsible for her antenatal care should discuss routine antenatal prophylaxis. In some circumstances, routine antenatal prophylaxis may not be necessary, or cost-effective. An example of this would be where the woman has opted to be sterilised after the birth of the baby.

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