NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Pregnancy – routine anti-D prophylaxis for rhesus negative women (review)

Final scope

Remit/appraisal objective

To review and update as necessary guidance to the NHS in England and Wales on the clinical and cost effectiveness of the use of routine antenatal anti-D prophylaxis for RhD-negative women[1], which was issued in May 2002.[2]

The current guidance will remain in place unless and until any new guidance has been issued. The review will consider whether any new evidence that has become available justifies a change in the original guidance.

Background

People who are RhD-positive have a protein on their red blood cells called D antigen, approximately 85% of the population are RhD-positive, although the percentage varies slightly across ethnic groups. Fetal blood type is jointly inherited from the parents and therefore may differ from the mother's blood type. RhD-negative women who carry an RhD-positive fetus may produce antibodies to the fetal RhD antigens after a fetomaternal haemorrhage (FMH). These antibodies may then cross the placenta in future pregnancies and cause haemolytic disease if the fetus is RhD-positive. No first child of an RhD-negative woman will be affected, unless the mother has been sensitised as a result of a prior miscarriage, abortion, prenatal diagnostic test, external cephalic version or, rarely, by a sensitising event earlier in the pregnancy.

Haemolytic disease of the newborn (HDN) can range in severity from being detectable only in laboratory tests, through to stillbirth, birth of infants with severe disabilities or death of newborn children from anaemia and jaundice.

Data from 2002 suggest that each year in England and Wales there are about 105,000 births to RhD-negative women, some 17% of all births. Of these babies, about 59%, or 62,000, are RhD-positive. This represents about 10% of all births each year in England and Wales. Before immunoprophylaxis became available, the frequency of HDN was 1% of all births and HDN was responsible for the death of one baby in every 2200 births. Anti-D prophylaxis (mostly administered postnatally) and advances in neonatal care have reduced the frequency of HDN to 1 in 21,000 births. In England and Wales, about 500 fetuses develop haemolytic disease each year, and must be closely

[1] Original remit: To advise on the clinical and cost-effectiveness and safety of the routine prophylactic use of anti-D immunoglobulin to prevent Rhesus isoimmunisation during pregnancy for all Rhesus negative primigravidae.

[2] Original guidance: NICE Technology Appraisal guidance No. 41 – Guidance on the use of routine antenatal anti-D prophylaxis for RhD-negative women. May 2002.

monitored. Each year around 25-30 babies die from HDN, 15 children will have major permanent developmental problems as a result of HDN, a further 30 will have minor developmental problems and it is believed that fetal loss due to haemolytic disease before 28 weeks' gestation accounts for about 20 spontaneous abortions each year.

Routine antenatal anti-D prophylaxis (RAADP) is currently a dose of anti-D immunoglobulin of at least 500 international units (IU) at 28 and 34 weeks' gestation or a single dose of at least 1500 IU at week 28 to 30 offered to RhD -negative women. If the woman has had, or is believed to have had, a sensitising event early in her pregnancy, antenatal anti-D prophylaxis (AADP) can be offered earlier, the dose depending on the gestation period.

The technology

Anti-D immunoglobulin is made from the plasma (liquid part of blood) of blood donors.

Anti-D Immunoglobulin (D-Gam; Bio Products Laboratory) available as 250, 500, 1500, 2500 IU vials, for intramuscular use (preferably into the deltoid muscle) only to rhesus-negative woman for prevention of Rh_0(D) sensitisation:

- Antenatal prophylaxis, 500 IU given at weeks 28 and 34 of pregnancy; a further dose is still needed immediately or within 72 hours of delivery.

Anti-D Immunoglobulin (Partobulin SDF; Baxter BioScience) available as a 1250 IU prefilled syringe, for intramuscular use only to rhesus-negative woman for prevention of Rh_0(D) sensitisation:

- Antenatal prophylaxis, 1000–1650 IU given at weeks 28 and 34 of pregnancy; if infant rhesus-positive, a further dose is still needed immediately or within 72 hours of delivery.

Anti-D Immunoglobulin (Rhophylac; CSL Behring) available as a 1500 IU prefilled syringe, for intramuscular or intravenous use to rhesus-negative woman for prevention of Rh_0(D) sensitisation:

- Antenatal prophylaxis, 1500 IU given between weeks 28–30 of pregnancy as a single dose; a further dose is still needed immediately or within 72 hours of delivery.

Anti-D Immunoglobulin (WinRho SDF; Baxter BioScience) available as 1500 and 5000 IU vials for intramuscular and intravenous use to rhesus-negative woman for prevention of Rh_0(D) sensitisation:

- Antenatal prophylaxis, by intramuscular or intravenous injection, 1500 IU given at week 28 of pregnancy; a further dose is still needed immediately or within 72 hours of delivery.

Intervention(s)	RAADP
Population(s)	Pregnant RhD-negative women
Standard comparators	• RAADP – different dosing regimens and different methods of administration • No RAADP
Outcomes	The outcome measures to be considered include: • Reduction in sensitisation (alloimmunisation) of RhD-negative women • Reduction of incidence of haemolytic disease of the newborn (HDN) • Survival of the child • Disability of the child • Health-related quality of life • Adverse effects of treatment
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. Time horizon for the economic evaluation should reflect the chronic nature of the condition. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	If the evidence allows, the appraisal will attempt to identify any subgroups of pregnant RhD-negative women that could be considered separately (e.g. RhD-negative women who will be sterilised after the birth, women who are certain they will have no more children and women who are in a stable relationship with the genetic father of their children and the father is known or found to be RhD-negative). If the evidence allows, the appraisal will attempt to assess the health-related quality of life of the mother, child and family, in keeping with the issues considered in technology appraisal no. 41, such as the impact of still births and disability on this outcome. Guidance will only be issued in accordance with relevant marketing authorisations.

Related NICE recommendations	Related Technology Appraisals: NICE Technology Appraisal guidance No. 41 – Guidance on the use of routine antenatal anti-D prophylaxis for RhD-negative women. May 2002. Related Guidelines: NICE clinical guideline No. 6 – Antenatal care: routine care for the healthy pregnant women. October 2003. This guideline is currently being reviewed, expected date of publication November 2007.
Current NICE guidance	NICE Technology Appraisal guidance No. 41 states: 1.1 It is recommended that routine antenatal anti-D prophylaxis (RAADP) is offered to all non-sensitised pregnant women who are RhD negative. 1.2 The clinician (obstetrician, midwife or general practitioner) responsible for the prenatal care of a non-sensitised RhD-negative woman should discuss with her RAADP and the options available so that the woman can make an informed choice about treatment. This discussion should include the circumstances where RAADP would be neither necessary nor cost effective. Such circumstances might include those where the woman: • has opted to be sterilised after the birth of the baby • is in a stable relationship with the father of the child, and the father is known or found to be RhD-negative • is certain that she will not have another child after her current pregnancy. The difference between RAADP (i.e. routine prophylaxis at 28 and 34 weeks) and prophylactic anti-D given because of likely sensitisation (see 1.3 below) should be clearly explained to the woman. 1.3 A woman's use of RAADP at 28 and 34 weeks should not be affected by whether she has already had antenatal anti-D prophylaxis (AADP) for a potentially sensitising event early in pregnancy. A woman's use of postpartum anti-D prophylaxis should similarly not be affected by whether she has had RAADP or AADP as the result of a sensitising event. Beyond this, AADP for a potentially sensitising event and postpartum anti-D prophylaxis are not the remit of this guidance. These matters are covered by the Royal College of Obstetricians and Gynaecologists' 'Green Top' 1999 guideline: Use of Anti-D Immunoglobulin for Rh

	Prophylaxis. 1.4 It is recommended that high-quality information, validated and produced at the national level, is made available to RhD-negative women and the relevant healthcare professionals.