

Routine antenatal anti-D prophylaxis for RhD-negative women: a systematic review and economic evaluation

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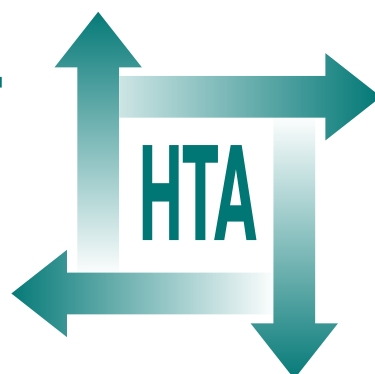
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Executive summary

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Executive summary

Background

Human blood is classified according to two main systems: the ABO system and the Rhesus (Rh) system. The Rh system consists of several related proteins, the most important of which is called the Rhesus D (RhD) antigen. People who have this antigen on their red blood cells are said to be RhD positive, whereas those who do not are said to be RhD negative. If the mother is RhD negative and the fetus RhD positive, the mother may react to fetal blood cells in her circulation by developing a template for producing anti-D antibodies, a process known as RhD sensitisation. Sensitisation is unlikely to affect the current fetus but may result in haemolytic disease of the newborn (HDN) during a second RhD-positive pregnancy. In its mildest form the infant has sensitised red cells, which are detectable only in laboratory tests; however, HDN may result in jaundice, anaemia, developmental problems or intrauterine death.

Routine antenatal anti-D prophylaxis (RAADP) can be given to RhD-negative women to prevent sensitisation and hence prevent HDN. A health technology appraisal of RAADP was carried out in 2002, which resulted in the national guidance that RAADP be offered to all non-sensitised pregnant women who are RhD negative. This assessment reviews the work carried out in the previous assessment report for the 2002 appraisal and considers additional RAADP regimens.

Objectives

The objective of this review is to consider whether there have been any advances in practice in the use of anti-D since the 2002 National Institute for Health and Clinical Excellence (NICE) appraisal, and to assess the current clinical effectiveness and cost-effectiveness of RAADP using D-Gam[®] (Bio Products Laboratory), Partobulin[®] (Baxter BioScience), Rhophylac[®] (CSL Behring) or WinRho[®] (Baxter BioScience) for RhD-negative women.

Methods

The scope of the assessment was to determine the clinical effectiveness and cost-effectiveness of any currently licensed regimen of RAADP in non-sensitised RhD-negative pregnant women, compared with either RAADP delivered using different dosing regimens or no RAADP. Relevant outcomes were a reduction in the incidence of sensitisation in RhD-negative women delivered of RhD-positive babies; a reduction in the incidence of HDN; survival of the child; disability of the child; health-related quality of life; and adverse effects of treatment.

Searches of systematic reviews, randomised controlled trials (RCTs) and non-RCTs relating to the clinical effectiveness or cost-effectiveness of RAADP were conducted in 10 bibliographic databases (MEDLINE, CINAHL, EMBASE, BIOSIS, Science Citation Index, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, NHS Health Technology Assessment database and NHS Economic Evaluations Database) from inception to July 2007. Additional searches were carried out around the outcomes of HDN and the costs and quality of life associated with the outcomes.

Inclusion criteria were as follows:

- Population: pregnant women who are RhD negative.
- Intervention: RAADP using either two doses of at least 500 IU at 28 and 34 weeks' gestation or a single dose of at least 1500 IU at 28 weeks' gestation, in either case followed, if the infant is RhD positive, by a further dose of anti-D given at, or within 72 hours of, delivery.
- Comparators: RAADP using different dosing regimens and/or methods of administration, or no RAADP.
- Outcomes: sensitisation (alloimmunisation) rates among RhD-negative women delivered of RhD-positive infants (the at-risk population); incidence of HDN; survival of the child;

disability of the child; health-related quality of life; or adverse effects of treatment.

- Study design: any of systematic reviews, RCTs or non-RCTs.

The exclusion criterion was studies considered methodologically unsound or not reporting results in the necessary detail.

Where appropriate, study results were combined in meta-analyses.

The health economic model developed for the 2002 NICE appraisal of RAADP was modified to assess the cost-effectiveness of different regimens of RAADP.

Results

The clinical effectiveness searches identified 670 potentially relevant articles. Of these, 12 papers were included in the review; they related to eight studies of clinical effectiveness.

With the exception of one RCT of the same anti-D preparation administered intravenously and intramuscularly, no additional studies were identified with regards to clinical effectiveness or cost-effectiveness from the previous assessment report, although some of the studies of clinical effectiveness included in the 2002 review were excluded because they did not use currently licensed doses of anti-D. Therefore, within the clinical effectiveness review eight studies were identified that compared licensed doses of RAADP with no prophylaxis; nine studies (including the 2001 assessment report itself) were identified within the cost-effectiveness review.

The clinical efficacy studies were generally of poor quality and do not provide a basis for differentiating between the regimens of RAADP. The best indication of the likely efficacy of a programme of RAADP in England and Wales comes from the two non-randomised community-based studies by MacKenzie and colleagues in 1999 and Mayne and colleagues in 1997. The pooled results of these two studies suggest that such a programme may reduce the sensitisation rate from 0.95% (95% CI 0.18–1.71) to 0.35% (95% CI 0.29–0.40). This gives an odds ratio for the risk of sensitisation of 0.37 (95% CI 0.21–0.65) and an absolute reduction in risk of sensitisation in RhD-negative mothers at risk (i.e. carrying a RhD-positive child) of 0.6%. The identified studies

suggest that RAADP is associated with minimal adverse events.

Of the nine studies identified within the cost-effectiveness review, only those by Vick (1996) and colleagues and Chilcott (2003) and colleagues describe a detailed modelling study that appears to be applicable to the UK NHS. Furthermore, no new mathematical models were provided within the manufacturers' submissions for the appraisal. The health economic model developed by the assessment group also incorporated two one-dose regimens as well as the two two-dose regimens included in the 2002 review. It suggests that the cost per quality-adjusted life-year (QALY) gained of RAADP given to RhD-negative primigravidae versus no RAADP is between £9000 and £15,000, and for RAADP given to all RhD-negative women rather than to RhD-negative primigravidae only is between £20,000 and £35,000 depending on the RAADP regimen (excluding WinRho). The one-dose regimen of 1500 IU of WinRho is estimated to have a cost per QALY gained above £60,000 for both indications. The sensitivity analysis suggests that the results are reasonably robust to changes in the assumptions within the model, the base-case sensitisation rate, the relative risk of sensitisation and the QALY valuation of a fetal loss having the biggest impact upon the results. The cost-effectiveness of RAADP improves slightly for ethnic minorities in England and Wales.

Discussion

Several arguments in addition to clinical effectiveness have been put forward to support the use of one or other regimen of RAADP; these relate to compliance, cost and safety. However, there is currently no published evidence comparing the different regimens of RAADP. The prices used in this assessment for anti-D itself are based upon *British National Formulary* drug prices but, as actual prices paid by hospitals vary according to supply and demand, the cost-effectiveness in practice may be better than that presented here. The formulation that is more expensive in terms of list price may in some cases be the cheaper drug because advantageous prices have been negotiated locally.

The health economic model does not explicitly take into account the quality of life of the parents as a result of the loss of a child or of having a disabled child because of the unquantifiable nature of these measures. However, the implication of this is that

the cost per QALY gained would be slightly lower than currently predicted.

Since the NICE guidance was issued in 2002, compliance rates with RAADP seem to have increased. However, although the implementation of a programme of RAADP should lead to a significant fall in the residual numbers of women becoming sensitised, some women continue to be affected. There are five possible reasons for continuing cases of sensitisation that require consideration:

- failure to recognise potential sensitising events in pregnancy as such and to treat them appropriately
- failure to assess the extent of fetomaternal haemorrhage (FMH) adequately
- failure to comply with postpartum prophylaxis guidelines
- refusal of RAADP by the mother
- failure to implement RAADP by some trusts, and incomplete adherence to advice (i.e. poor compliance with the second dose).

The key uncertainties associated with the assessment of RAADP are:

- the efficacy of different dosing regimens of routine anti-D prophylaxis
- the quality of life of children suffering from HDN and their parents (including parents of stillborn children)
- the incidence rate of outcomes as a result of HDN
- the costs associated with HDN in terms of the management of sensitisation and the management of developmental problems over a patient's lifetime.

Conclusions

All of the evidence indicates that RAADP reduces the incidence of sensitisation and hence of HDN. The economic model suggests that RAADP given to all RhD-negative pregnant women is likely to be considered cost-effective at a threshold of around £30,000 per QALY gained. The total cost of providing RAADP to RhD-negative primigravidae in England and Wales is estimated to be around £1.8–£3.1 million per year, depending upon the regimen of RAADP used (excluding WinRho). This takes into account the cost of RAADP and its administration, the cost of the management of sensitisation, and the cost savings associated with avoiding HDN. The additional cost of providing RAADP to all RhD-negative pregnant women in England and Wales is estimated to be around £2–£3.5 million.

Further research is recommended to:

- compare the efficacy of the different RAADP regimens; issues relating to compliance and safety may also influence the efficacy of the different regimens of RAADP and hence further research would also be useful in these areas
- confirm or disprove the preliminary findings that protection against sensitisation provided by RAADP in primigravidae extends beyond the first pregnancy
- aim to improve non-invasive genotyping of the fetus.

Publication

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