Routine antenatal anti-D prophylaxis

A review of the clinical effectiveness and cost-effectiveness of routine anti-D prophylaxis for pregnant women who are rhesus-negative

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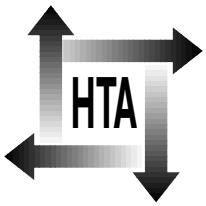
Executive summary

Health Technology Assessment 2003; Vol. 7: No. 4

Health Technology Assessment
NHS R&D HTA Programme



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Executive summary

Background

Haemolytic disease of the newborn affects the fetus or neonate, and results from the transplacental passage of maternal allo-antibodies directed against fetal red cell antigens inherited from the father. Over 90% of all cases of clinically significant haemolytic disease of the newborn affect rhesus D (RhD)-positive infants born to RhD-negative mothers. The mothers usually make the anti-D antibody following a small feto-maternal haemorrhage at delivery of the first RhD-positive infant. This does not harm that infant, but successive RhD-positive infants are then progressively more affected by haemolytic disease of the newborn.

Prophylactic anti-D, whether antenatal or post-partum, can only suppress primary RhD immunisation; it has no effect in women who have already developed anti-D, however weak. Some women currently become sensitised prior to delivery of the first pregnancy. It is estimated that between 55% and 80% of these develop 'silent' sensitisation – i.e. sensitisation in the absence of any identifiable risk event such as should prompt the administration of anti-D. It is such cases which the proposed intervention seeks to prevent.

Approximately 16% of women in the UK are RhD-negative, and in about 10% of all pregnancies the mother is RhD-negative and the fetus RhD-positive. During these pregnancies, the mother is at risk of becoming sensitised by transplacental haemorrhage. The severity of haemolytic disease of the newborn varies. In its mildest form, it is detectable only in laboratory tests. More commonly, the infant has a mild degree of jaundice which responds to phototherapy. More severe disease can cause physical disabilities and mental retardation. In its most severe form, the *in utero* anaemia causes cardiac failure, hydrops and intrauterine death. Prior to the introduction of any immunoprophylaxis, the frequency of haemolytic disease of the newborn was one per 100 births in second pregnancies, and higher in subsequent pregnancies. In the mid 1950s in England and Wales, haemolytic disease of the newborn was responsible for one death in every 2180 births. Since that time, anti-D prophylaxis and advances in neonatal care have had a major impact, and the current figure approximates to one death in every 20,800 births.

In 1999, the most recent year for which figures are available, there were 621,872 total births in England and Wales. Around 10% of these would have been RhD-positive infants delivered of RhD-negative women.

Current provision of routine antenatal anti-D prophylaxis (AADP) across England and Wales is very patchy. It has been estimated that approximately 12% of hospitals are currently operating a policy of offering this intervention to pregnant RhD-negative women.

Description of proposed service

The proposed service evaluated in this report is the routine offering of AADP either to all pregnant women who are RhD-negative or to RhD-negative primigravidae only. The intramuscular anti-D immunoglobulin would be given as two doses at 28 and 34 weeks. It would supplement, rather than replace, current standard practice of routinely offering anti-D within 72 hours of delivery to all RhD-negative women delivered of RhD-positive infants who are not already sensitised, and also offering anti-D within 72 hours to all unsensitised RhD-negative pregnant women who undergo a potential sensitising event. Otherwise such women would not be protected against large bleeds in the antenatal period or around the time of delivery.

Objectives

The overall aim of the report was to evaluate the clinical effectiveness of AADP for pregnant women who are RhD-negative, and the comparative cost-effectiveness of:

- offering routine AADP to all pregnant women who are RhD-negative
- offering routine AADP only to primigravidae who are RhD-negative
- not offering routine AADP.

In each case, it was assumed that the current programme of offering anti-D antenatally to ▶

all RhD-negative women who suffer a potential sensitising event, and post-partum to all RhD-negative women delivered of a RhD-positive infant, will continue.

Methods

A systematic review of the literature was performed to identify all studies that compared women receiving routine AADP with untreated controls or that evaluated the economic impact of routine AADP. A model-based economic evaluation of offering routine AADP to all pregnant women who are RhD-negative, and to RhD-negative primigravidae only, in addition to conventional AADP applicable to the NHS, was performed. This economic evaluation assessed the cost per fetal loss, stillbirth, neonatal or postneonatal death avoided, the cost per life-year gained (LYG) and the cost per quality-adjusted life-year (QALY) gained as a result of disabilities avoided.

Results

Number and quality of studies

Eleven studies met the inclusion criteria. They included seven non-randomised trials with historical or geographical controls, one randomised controlled trial (RCT), one quasi-RCT, one community intervention trial and one retrospective before-and-after study. A follow-up study to one of the non-randomised trials studied the safety and efficacy of antenatal prophylaxis by examining obstetric data relating to women in the trial in their first and subsequent pregnancies. Because of the paucity of RCT data (only one true RCT was found, and that used a dosage half that of the lowest dose currently considered appropriate), all these studies were retained for further consideration. However, most were methodologically poor.

Clinical effectiveness

In all studies, the proportion of women sensitised was lower in the intervention arm than in the control arm, although in some studies the difference was small and not statistically significant. Two doses of anti-D at 28 and 34 weeks' gestation appeared to be more effective than one dose at 34 weeks only. There appeared to be no significant difference between the effectiveness of two doses of 500 IU and two doses of 1500 IU. Although there was no evidence relating to the relative effectiveness of two doses of 1250 IU, it is unlikely that this will differ significantly from that of two doses of 1500 IU.

The best indication of the likely efficacy of a programme of routine AADP in England and Wales came from two non-randomised community-based studies. The pooled results of these studies suggested that such a programme may reduce the sensitisation rate from 0.95% to 0.35%. This gave an odds ratio for the risk of sensitisation of 0.37, and an absolute reduction in risk of sensitisation in RhD-negative mothers carrying a RhD-positive child of 0.6%. Although the number of such women needed to treat (NNT) to avoid one case of sensitisation was 166 (1/0.006), antenatally a RhD-negative woman will not know if she is carrying a RhD-positive child. Thus all RhD-negative pregnant women would require treatment, and not just the 60% who are carrying a RhD-positive child, making the overall NNT 278 (10/6 × 166).

It was estimated that currently 625 sensitisations of RhD-negative women per year lead to a total of at least 30 fetal deaths, stillbirths, neonatal and postneonatal deaths. Avoidance of sensitisation can thus be expected to avoid fetal/neonatal loss in 4.8% of cases. The NNT to avoid a fetal or neonatal loss in a subsequent pregnancy can therefore be estimated as approximately 5790.

Health economics

The drug costs of treating one pregnancy with two doses of 500 IU are £54.00, and with two doses of 1250 IU are £47.80, at NHS list prices. To this can be added an estimated cost of administration of £10.

The gross annual cost (including administration costs) of offering routine AADP to all RhD-negative pregnant women in England and Wales is estimated to be £6.1 million for the 2 × 1250 IU regimen, and £6.8 million for the 2 × 500 IU regimen. If cost savings from reductions in treating haemolytic disease of the newborn are considered, the total net cost to the NHS in England and Wales would be £5.7–6.4 million per year.

If routine AADP is only given to RhD-negative primiparae, the total gross cost of drugs would be approximately £2.4 million for the 2 × 500 IU regimen and £2.1 million for the 2 × 1250 IU regimen. The total cost of administration would be £450,000. The total net cost, including potential savings from reductions in haemolytic disease of the newborn, is estimated at approximately £2.3–2.6 million.

The cost per QALY gained from a policy of routine AADP given to primigravidae was calculated ▶

on the basis of the published literature relating to the quality of life impact of minor developmental problems and long-term neurodevelopmental problems in low birth weight infants. In these terms, routine AADP is economically attractive from the perspective of disability prevention alone, irrespective of attitudes to parental grief and valuation of stillbirths, neonatal and postneonatal deaths. Routine AADP given to all pregnant women who are RhD-negative is economically attractive, using a maximum acceptable cost-effectiveness ratio of £30,000 per QALY, if the lost child, associated parental grief and subsequent high intervention pregnancy are valued at more than 9 QALYs.

In addition, routine AADP given to primigravidae has a cost per LYG that is very low in comparison to other interventions routinely funded by the NHS. The incremental cost per LYG of giving routine AADP to **all** pregnant women who are RhD-negative is not as low, but there is still a chance of approximately 90% of the incremental cost-effectiveness being better than £30,000 per LYG compared to a primigravidae-only policy.

Conclusions

The evidence suggests that routine AADP is effective in reducing the number of RhD-negative pregnant women who are sensitised during pregnancy. However, it cannot prevent all instances of sensitisation, some of which occur either despite or before appropriate administration of anti-D.

Some cases of sensitisation in the UK are due to failure to adhere to the existing guidelines for the administration of anti-D either post-partum or in response to potential sensitising events. It should therefore be possible to reduce sensitisation rates by stricter adherence to current guidelines, and it could be argued that this should be pursued before initiating guidelines for the routine offering of AADP to pregnant women who are RhD-negative.

Issues relating to implementation of a policy of routine AADP

If a programme of routine AADP were to be adopted, watertight mechanisms would need to be developed to ensure that prophylaxis is offered at the appropriate time to all women at risk of sensitisation, in order to avoid additional cases of sensitisation attributable to failure to provide prophylaxis when appropriate. As with other blood products, mechanisms would also be required to ensure that individual women could be linked with specific batches of anti-D.

The widespread administration of an intervention that would benefit only a few (unidentifiable) individuals is well established in medical practice, and would not present new ethical issues. However, it would be imperative that women were encouraged to make an informed choice, based on adequate information. The prime responsibility for ensuring that women understand the implications of the intervention, and consent to it, would rest with midwives. In many cases these midwives would be based in the community and/or antenatal clinic, and would currently have varying levels of involvement with the administration of postnatal anti-D. The introduction of routine AADP would therefore have significant education and training implications.

Recommendations for further research

Further research is required to:

- attempt to identify any characteristics which might identify the 10% of RhD-negative women who are at risk of sensitisation, so that antenatal prophylaxis may be targeted specifically at these women
- confirm or disprove the preliminary findings that protection against sensitisation provided by AADP in primigravidae extends beyond the first pregnancy.

Publication

Chilcott J, Lloyd Jones M, Wight J, Forman K, Wray J, Beverley C, *et al.* A review of the clinical effectiveness and cost-effectiveness of routine anti-D prophylaxis for pregnant women who are rhesus-negative. *Health Technol Assess* 2003;**7**(4).

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The research reported in this monograph was funded as project number 00/23/01.

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ISSN 1366-5278