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


CRD summary
This review assessed routine antenatal anti-D prophylaxis (AADP) for pregnant women who are Rhesus-negative. Routine AADP reduced the number of Rhesus-negative women who were sensitised during pregnancy. Some instances of sensitisation could still occur before or despite administration of AADP. The conclusions appear supported by the evidence presented, though the variable quality of included studies should be noted.

Authors' objectives
To investigate the clinical and cost-effectiveness of routine antenatal anti-D prophylaxis (AADP) for pregnant Rhesus D (RhD)-negative women.

Searching
Twelve electronic databases (listed in the review) were searched; the search terms and dates were reported. In addition, several sources (listed in the review) were searched to identify current and grey literature. There were no date or language restrictions.

Study selection
Study designs of evaluations included in the review
Systematic reviews, randomised controlled trials (RCTs), non-randomised controlled trials, or economic evaluations were eligible. Studies considered methodologically unsound were excluded from the meta-analyses.

Specific interventions included in the review
Comparisons of routine AADP with no treatment were eligible. Studies that did not use appropriate dosage regimens were excluded from the meta-analyses. The dose of anti-D used in the included studies varied between two doses of 1,500 international units (IU) to two doses of 250 IU. Where stated, anti-D was administered intramuscularly or intravenously.

Participants included in the review
Studies of pregnant women who were RhD-negative were eligible. Where stated, the women in the included studies were primigravidae, primigravidae and unsensitised multigravidae, or primiparae.

Outcomes assessed in the review
Studies reporting sensitisation rates of women at risk, adverse events, or cost were eligible. The former included: the number of RhD-negative women found to be sensitised in a subsequent pregnancy due to a prior RhD-positive pregnancy; the number of RhD-negative women found to be sensitised during the current pregnancy, or within 3 days of delivery; the number of RhD-negative women found to be sensitised at postnatal follow-up; and the total number of RhD-negative women sensitised or sensibilised. Studies that did not report the results in sufficient detail were excluded from the meta-analyses.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
RCTs and observational studies were rated as good, fair or poor according to the similarity of the groups at baseline in terms of prognostic factors. This quality criterion was taken from the quality criteria proposed by the NHS Centre for
Reviews and Dissemination. The authors did not state how many reviewers performed the quality assessment, or whether the assessment was independent or how any discrepancies were resolved (if more than one reviewer). The reviewers were not blinded to the author, institution, or journal.

Data extraction
One reviewer extracted the data and a second checked them. Any disagreements were resolved by discussion.

Methods of synthesis
How were the studies combined?
A narrative synthesis of the studies was undertaken. Studies considered to be comparable in terms of their design and the dose of anti-D were combined in a binary logistic regression using a fixed-effect model. The odd ratios (ORs) were reported along with 95% confidence intervals (CIs).

How were differences between studies investigated?
Heterogeneity was assessed using a statistical test, although it was not specifically stated what this test was. In addition, the results were tabulated separately for sensitisation during pregnancy (or within 3 days of delivery) and sensitisation at post-natal follow-up.

Results of the review
Eleven studies (reported in 10 articles) were included. There was one RCT, one quasi-RCT, four prospective studies with historic controls, one prospective study with historic/geographic controls, one controlled before-and-after study, one retrospective study with historic controls, one retrospective survey with geographical controls, and one retrospective survey (before-and-after). A total of 29,288 women were given, or were available to receive AADP in the 11 studies; a total of 12,153 women comprised the control groups in the 10 studies where it was reported.

Six studies were rated as poor quality, three as good, and two as fair.

Clinical effectiveness (10 studies): the proportion of sensitised women was lower in the intervention arm than in the control arm for all studies. In some studies this 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, although none of the studies directly compared the two regimens. There appeared to be no significant difference between the effectiveness of two doses of 500 IU and one dose of 1,500 IU.

Dose regimen 500 IU at 28 and 34 weeks - primigravidae results: one quasi-RCT, one prospective study (historic controls), one controlled before-and-after study, and one retrospective study (before-and-after); (n=13,490). The OR of sensitisation with AADP was 0.33 (95% CI: 0.20, 0.55). The point estimates of the sensitisation rates were 0.30% (95% CI: 0.22, 0.38) and 0.89% (95% CI: 0.21, 1.56) for the AADP and control groups, respectively.

Dose regimen 1,500 IU at 28 weeks - primigravidae and multigravidae results: two prospective studies (historic controls) and one retrospective study (historic controls); (n=18,867). The OR of sensitisation with AADP was 0.20 (95% CI: 0.13, 0.29). The point estimates of the sensitisation rate were 0.34 (95% CI: 0.28, 0.40) and 1.60 (95% CI: 0.37, 2.83) for the AADP and control groups, respectively.

Dose regimen 500 IU at 28 and 34 weeks - primigravidae results: one controlled before-and-after study and one retrospective survey (before-and-after); (n=9,317). The OR of sensitisation with AADP was 0.37 (95% CI: 0.21, 0.65). The point estimates of the sensitisation rate were 0.35 (95% CI: 0.29, 0.40) and 0.95 (95% CI: 0.18, 1.71) for the AADP and control groups, respectively. Further results relating to failure of protection, longer-term outcomes, and ABO blood group compatibility were reported in the review.

Cost information
Yes. At NHS list prices, the drug costs for treating one pregnancy were £54.00 for two doses of 500 IU, and £47.80 for two doses of 1,250 IU. The administration cost was estimated to be £10. Further results relating to the cost or cost-
effectiveness were reported in the review.

**Authors’ conclusions**
Routine AADP was effective in reducing the number of RhD-negative pregnant women who are sensitised during pregnancy. However, some instances of sensitisation can still occur before or despite administration of AADP.

**CRD commentary**
The objective of the review was clear and the predetermined inclusion criteria were appropriate. The authors did not state how the papers were assessed for inclusion, thus it is unclear whether steps were taken to minimise bias in this process. The literature search was thorough. The quality of the included studies was assessed according to only one criterion, and details relating to how judgements of validity were made were not provided. However, various aspects of quality were discussed in the narrative. The authors’ conclusions appear to reflect the findings, but should be viewed in light of the limitations of the review.

**Implications of the review for practice and research**
Practice: The authors stated that, in the case of adopting a programme of routine AADP, it would have to be ensured that prophylaxis was offered at the appropriate time to all women at risk of sensitisation. They also stated that women would have to be encouraged to make an informed choice based on adequate information, and this would have implications on education and training.

Research: The authors stated that research is needed to determine characteristics that may identify the 10% of RhD-negative women at risk of sensitisation, and to confirm or disprove preliminary results that the role of AADP in protecting against sensitisation in primigravidae extends further than the first pregnancy.

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