National Institute for Health and Clinical Excellence
Review of Technology Appraisal Guidance – No. 41
Guidance on the use of routine antenatal anti-D prophylaxis for RhD-negative women

Submission on behalf of the Royal College of Physicians and the Royal College of Pathologists

Consideration of new evidence that would justify a change in the original guidance

Introduction

The clinical management of the major complication of Rh-D sensitisation, haemolytic disease of the newborn, rests with obstetricians, midwives, and paediatricians. However, assessment of the potential for sensitisation and appropriate management to avoid such outcomes depends on the expertise of haematologists, the hospital blood transfusion laboratory and the national transfusion services. The establishment of anti-D prophylaxis to treat potentially sensitising episodes has been possible due to the combined expertise of these professional groups working together to develop a multidisciplinary approach to the care of pregnant women who are Rh-D negative. The evolution of clinical practice to encompass Routine Antenatal Anti-D Prophylaxis (RAADP) is also dependent on such multidisciplinary co-operation between clinical and laboratory domains. This report, provided on behalf of the Royal College of Pathologists, will focus on 3 key areas relating to Appraisal Guidance No. 41 particularly relevant to laboratory and transfusion services involvement in the multidisciplinary process.

1. Implementation issues
2. The impact of RAADP
3. The current position of relevant future technology.

1. Implementation issues

a) Level of implementation and laboratory considerations

In 2002 when guidance 41 was issued, it stated that about 30% of hospitals in England and Wales offered RAADP to women who were Rh-D negative. A recent postal survey of 233 hospital transfusion laboratories, has identified that of the 173/233 (75%) responding, 155/173 (90%) of centres have implemented RAADP fully, and of these, the transfusion laboratory is responsible for issue of anti-D immunoglobulin in 155/173 (90%)[1]. Information from transfusion laboratory personnel confirms that full involvement of the laboratory as part of a multidisciplinary approach is essential at all stages to ensure that RAADP is implemented. Key features of successful programmes are communication, information, documentation, appropriate resources, and audit.

Feedback from a wide range of laboratory managers has identified practical steps to address these key features to assist in the successful implementation of RAADP, or

improve an existing program. Inclusion of such advice as provided in Appendix 1[2], or similar, should be encouraged as part of the review of Guidance 41. It is hoped that compliance with these recommendations will improve the level and quality of implementation of RAADP throughout England and Wales; similar recommendations are likely to be included in the impending 2007 Health Service Circular on Better Blood Transfusion.

Differentiating passive from immune mediated anti-D can be difficult www.blood.org.uk/hospitals although this does not appear to be an increasing problem since the wider introduction of RAADP. However, 77 adverse events relating to administration of anti-D for all indications were reported to Serious Hazards of Transfusion for 2006 (SHOT)[3]. Lack of communication and poor documentation were common features for all incidents. A total of 13 women with immune anti-D received treatment with anti-D immunoglobulin. This demonstrates an ongoing need for improved education of both laboratory and clinical personnel. Misinterpretation can result in failure to monitor an immune antibody during the pregnancy and hence lead to HDN being missed. The data from SHOT do not specifically identify errors relating to the use of anti-D as part of RAADP. Recent BCSH guidelines[4] should be followed to avoid misinterpretation of results.

b) The technology

Product, dose and timing

Compliance and effectiveness

In 2002 when Guidance 41 was published, only two anti-D products were available with a UK license for use in antenatal prophylaxis, BPL 500 IU and Baxter BP Immuno 1250 IU, both given as two separate doses at 28 and 34 weeks gestation. The review undertaken at that time considered the available evidence for clinical effectiveness by meta-analysis of three separate groups of studies[14]. Two of the 3 groups included a total of 6 studies in which a two-dose regimen was used, involving 11,100 women, whilst the third group included 3 studies involving 11,400 women using a 1500 IU preparation given as a single dose at 28 weeks. The rates of postnatal anti-D sensitisation for each of the three groups were similar at 0.30%, 0.34% and 0.35% and all were significantly lower than sensitisation levels in control groups not given antenatal prophylaxis. The conclusion given in Guidance 41, 4.1.3 was “two doses of anti-D immunoglobulin 500 IU at 28 and 34 weeks into pregnancy appear to be as effective as one 1500 IU dose at 28 weeks” i.e no difference in effectiveness for preventing sensitisation was demonstrated between the single and two dose regimen. However, information and details of implementation given throughout the guidance referred to RAADP as being two doses of anti-D given at 28 and 34 weeks (Guidance document 1.2, 1.3, 3.3) and the data pertaining to Group 3 (two dose regimen) of the clinical effectiveness meta-analysis were considered to be most informative when considering the clinical and cost effectiveness of RAADP. As such the guidance implied that the preferred technology was the two-dose method, which was also in step with historical guidelines published by the Royal College of Obstetricians and Gynaecologists[5]. This ambiguity in the guidelines left them open to individual interpretation.

Since Guidance 41 was issued, there has been little information published regarding the implementation of RAADP, either in relation to the regimen used or to compliance with treatment. The effectiveness of a two-dose regimen is presumably dependent on receipt of the two doses at 28 and 34 weeks. However, a single dose regimen may offer a higher rate of compliance. A survey of 328 UK maternity units undertaken in 2005, of which 75% were offering RAADP, found that 81% of these used the two- dose regimen[6]. No information on compliance was collected in this study. Studies by MacKenzie[7,8] suggested that compliance with a two dose regimen is poor with rates of 76% for administration of both doses. However, a more recent study by Chaffe et al found compliance with the two-dose regimen to be as high as 86.5%[9]. Since 2002, several other products have acquired a license for the indication of prophylactic use, in particular two 1500 IU dose products. There continues to be no evidence to suggest that the single dose regimen at 28 weeks is less effective[10], and guidelines from several other countries, notably Canada, recommend the single dosing model[11]. However, the recent BCSH guidelines on prophylactic anti-D immunoglobulin[4] state "A single dose of 1500 IU anti-D, given i.m. at 28 weeks, may be an effective alternative RAADP regimen that potentially offers cost and logistic benefits. However, more evidence is required to establish its comparative efficacy."

This conclusion highlights the paucity of published studies addressing this area since Guidance 41 was issued.

The BCSH guidelines also recommend that "consideration should be given to limiting batch exposure" for situations where large or multiple doses of anti-D immunoglobulin may be required as treatment for sensitizing events. Limiting batch exposure limits donor exposure and as such this recommendation should apply to all women treated with any form of anti-D immunoglobulin. An important consideration when choosing an RAADP regimen will be what products are also available for treatment of ante-partum sensitizing events and post partum prophylaxis. Products from different manufacturers and of different doses are unlikely to have been generated from the same original donor plasma pools.

Which regimen to implement therefore remains open to individual departmental interpretation of the NICE guidance 41 and BCSH guidelines.

Anecdotal evidence suggests that many centres are changing to the single dose regimen for prophylaxis. Neither of the two manufacturers providing 1500 IU products licensed for this use also offer a 500 IU dose suitable for treating the majority of sensitising events. D-Gam is available in various doses, including 500 IU and 1500 IU, although the stated dose for antenatal prophylaxis is given as 500 IU at 28 and 34 weeks. Exposure of women to more than one manufacture's product during the entirety of their pregnancy is therefore unavoidable if a single dose regimen is used, unless higher doses than necessary are used for potentially sensitising events. The logistic and potential compliance benefits of a single dose regimen must therefore be balanced against the inevitable increased donor exposure. A limited survey of some London centres in November 2006 found 3 of 19 using a single 1500 IU dose at 28 weeks, with one other centre in the planning stage to switch[12], whilst information from the South West region recently shows that 6 out of 17 hospitals are now using the single dose[13]. A recent survey of 233 UK transfusion laboratories responsible for assessing antenatal samples found 53/173 (31%) of departments are now using the single 1500 IU dose at 28 weeks[1].

In summary:

The original guideline was somewhat ambiguous for dose and timing of administration. Although point 4.1.3 stated that the evidence suggests two doses of 500 IU at 28 and 34 weeks appear to be as effective as one 1500 IU dose at 28 weeks, all references to the implementation of RAADP, and in particular the patient information, consistently refer to RAADP as being a dose of anti-D at 28 and 34 weeks. Presumably this was because there was not a UK licensed product for single 1500 IU dose at the time of the original guidelines. The scoping document for the review states that RAADP is currently a dose of anti-D of at least 500 IU at 28 and 34 weeks, or a single dose of at least 1500 IU at week 28 to 30, which does reflect current practice across the UK. Recent information suggests that centres may be changing over to a single dose regimen, and presumably this is for logistic and perhaps compliance reasons. Although justified, such a change makes it more likely that women will be exposed to multiple anti- D immunoglobulin products, and hence experience greater donor exposure. Although the risk of infection with known pathogen, prion or virus, from anti-D is extremely low, and the estimated additional risk associated with RAADP over that of standard prophylaxis is minimal[14], the 4 cases of likely transfusion transmitted vCJD in the UK over the past 4 years highlight the need to ensure that all donor exposure is justified.

2. Impact of RAADP

a) Clinical effectiveness

There remains a paucity of UK data on the effectiveness of RAADP as measured by a relative reduction in frequency of anti-D sensitisation since the introduction of this treatment. However, a study by MacKenzie[8] reported in 2004 found that 248 of 261 (95%) RhD negative mothers treated with 1500 IU anti-D at 28 weeks and at delivery of RhD positive baby, had no anti-D detected at 6 or 11.5 months post delivery. Although this suggests that sensitisation was prevented and the prophylactic regimen is effective, the data should be interpreted with some caution. Measurable levels of anti-D may not be detectable in the serum post partum until repeat stimulation with a second sensitising event, such as a subsequent pregnancy. A more appropriate assessment of effective reduction in frequency of sensitisation would be the percentage of RhD negative women with anti-D immunoglobulin detected at early stages of a subsequent pregnancy. Such data are not currently available or easily identifiable on a UK basis, and will not be easily accessible without the establishment of a specific means of capture.

The assessment group involved in Guidance 41 constructed a model to assess the impact of RAADP on HDN-associated deaths in England and Wales. This anticipated a fall from 27 deaths per year to 15 per year if RAADP were given to all Rh-D negative primigravidae. To date, RAADP has not been implemented 100% across England and Wales, but data on the exact level of implementation are not available. Of reported studies, implementation within the UK appears to vary from 75%[6] to 89%[1]. Also, data on the percentage of eligible women taking up RAADP across England and Wales are not available, although the recent study by Chaffe et al (2007)[9] looking at the experience in two separate units in different regions, found

uptake to be 185/207 (89%). This lack of clarity in denominator data will make interpretation of the effectiveness of RAADP difficult to extrapolate from any fall in deaths from HDN.

b) Audit

Guidance 41 included information relating to the need for audit of the implementation process. It highlighted the importance of the following actions:

1. Making appropriate information available to pregnant, non-sensitised Rh-D negative women to allow them to make an informed choice about RAADP treatment

2. For those choosing RAADP, to ensure they receive it in a timely manner

Results of a recent survey of 233 UK laboratories issuing anti-D as part of an implemented RAADP program show that only 46/173 (27%) of respondents have audited the process[1]. Data from this small proportion of sites would be difficult to collate and would be unable to provide denominator data for the level of uptake of RAADP across England and Wales.

In order to critically assess the effectiveness of RAADP, an important addition to the revised guidance should include a requirement for the initiation of regular national audit, to which all antenatal units should contribute. This could be established either by the Royal College of Obstetricians and Gynaecologists or the Royal College of Pathologists. Ideally, this would address all aspects of RAADP, including the level of implementation, quality of information and support offered, percentage of eligible women receiving treatment and level of compliance with regimen for dose and timing.

c) Alternative outcomes as indicators of effectiveness

Assessment of the frequency of anti-D sensitisation as an outcome measure would require the establishment of a national study with appropriate ethical approval (this may not be necessary if conducted anonymously). This would allow the necessary non-routine blood testing to assess anti-D sensitisation during pregnancy and postpartum for primigravidae, and in addition to explore the level of sensitisation occurring in subsequent pregnancies.

Despite the difficulty in obtaining such information an important component of revised guidance should include consideration of the establishment of a robust method for the capture of such outcome data in addition to consideration of the incidence of HDN due to anti-D and other red cell antigens.

d) Traceability

The EU guide on good manufacturing practice recommends that records are kept to enable traceability of all blood products (including anti-D) from donors to recipients and vice versa[15]. The hospital transfusion laboratory is ideally placed to undertake this role as they are already used to issues relating to data capture and storage for other blood components. It is also vital that blood banks have accurate records of administration of anti-D to enable correct interpretation of pre-transfusion test results.

Many hospital transfusion laboratories have taken on responsibility for recording the administration of anti-D immunoglobulin as well as its issue, but other arrangements are in place in some units. These include pharmacy for issue, and midwifery for recording administration. The recent survey of 233 laboratories found 155/173 (90%) of those responding are responsible for the issue of RAADP, but only 119/173 (69%) are responsible for recording its administration. 19/173 (11%) of respondents were aware that anti-D was also supplied directly to antenatal clinics, GPs or community hospitals without any records being held in the transfusion department[1]. This variability of routes of issue and places of record of administration raises the potential for failures in traceability. The requirement for having robust mechanisms in place to ensure the sharing of appropriate information in a timely manner is also increased by these multiple pathways.

3. Future Technology

Guidance 41 6.2 acknowledged the existence of technology to provide antenatal fetal blood group analysis through the use of DNA in maternal plasma, and the potential impact of such analysis on the need for RAADP. Development of this technology has progressed significantly. Results of a study of 2046 blood samples from RhD negative pregnant women at 28 weeks gestation are shortly to be published[16]. They show that the fetal RhD phenotype was predicted correctly in 95.5% of cases. 3% of the results were unobtainable or inconclusive, and in 0.8% a false positive result was obtained. 0.5% of results were predicted to be pseudogenes or other gene variants and in only 0.12% was a false negative result obtained. Both these tests were performed on samples that were over a week old. This study shows that mass throughput genotyping of all RhD-negative women in a community setting is both feasible and potentially cost effective particularly in the context of expense, discomfort and blood product exposure that RhD negative women would otherwise undergo.

This study analysed blood samples taken at 28 weeks gestation. To enable the technology to be used to offer the current recommended prophylaxis at 28 weeks to RhD negative women identified as carrying a RhD positive fetus, results would have to be available by 28 weeks gestation. Testing must therefore be undertaken prior to 28 weeks and further work is required to confirm the reliability of such testing. An alternative approach such as that implemented by the Dutch could be used. In Holland RAADP is administered as a single dose (of 1000 IU) at 30 weeks gestation with similar figures for rates of prevention of sensitisation to those reported for 500 IU at 28 and 34 weeks and 1500 IU at 28 weeks[17].

A recent review of 9 published studies using maternal plasma derived DNA to determine fetal RhD status includes data in the largest study group of 1257 cases tested at 15 plus weeks of gestation, with an accuracy rate of 99%[18]. It is thus anticipated that such testing will be routinely available within the next 12-24 months and that the costs of implementation will not be prohibitive. In addition, when offset against the likely savings from reduced use of RAADP, and the benefit of avoiding additional donor exposure in Rh D negative women, the advantages of including this technology as part of future guidance will be significant.

Summary

Information to allow a full assessment of the level and quality of implementation of RAADP within the UK is not currently available. However, since Guidance 41 was issued several independent studies do indicate that the use of RAADP has increased although this information is not available as peer reviewed publications. Audit of the process is limited, and reasons for failure to implement remain anecdotal. Successful implementation is dependent on multidisciplinary involvement and does have resource implications. The technology used may be changing from a predominantly two dose to a single dose regimen.

It is not possible to define the true effectiveness of RAADP in reducing anti-D sensitisation in RhD negative pregnant women as there are no denominator data for level of uptake and no means of identifying the incidence of anti-D post first child or during a second pregnancy. Deaths from HDN only provide a surrogate marker.

There are no specific data to suggest that the introduction of RAADP per se has led to an increase in adverse events, although SHOT data on adverse events involving the administration of anti-D highlight the need for ongoing education for all involved with administration of anti-D, and the importance of maintaining full traceability records.

Definite progress has been made in the development of technology to allow targeted use of AADP, and this will impact on the nature of future guidance for the management of RhD negative women in pregnancy.

Recommendations

The revised guidance should:

Require all maternity units to take part in a national audit of RAADP to encompass its implementation, the technology used, level of uptake, adverse events, traceability and information available to pregnant women.

Make available the ‘practical guide to implementation’ (Appendix 1), or similar to support the wider and appropriate implementation of RAADP.

Consider the mechanism required for the establishment of a robust means of data capture to assess incidence of anti-D sensitisation and alloimmunisation to other red cell antigens.

Reinforce the need for anti-D immunoglobulin to be subject to the same rigorous process of patient identification, documentation, traceability requirements and adverse event reporting as for all blood products.

Support the need for ongoing and regularly updated education, training and competency assessment of all involved in the assessment of feto-maternal haemorrhage and the administration of anti-D immunoglobulin.

Support the continuing development of technology to allow the identification of fetal RhD status at a sufficiently early stage of gestation as to allow the targeted use of AADP.

References

1. Survey of current UK practice in relation to guidelines for Anti-D immunoglobulin on behalf of Royal College of Pathologists, Transfusion Subcommittee anti-D guidance working group, personal communication August 2007.
2. Opinions of transfusion laboratory personnel with experience of implementation of RAADP programs; S. Bates, personal communication 2007. Appendix 1 of this document.
3. Serious Hazards of Transfusion Report 2006, in press.
4. Parker, J., Wray, J., Gooch, A., Robson, S.& Qureshi, H. (2006) Guidelines for the use of prophylactic anti-D immunoglobulin. British Committee for Standards in Haematology.
5. Royal College of Obstetricians and Gynaecologists. (RCOG revised May 2002) Clinical green top guidelines:- use of anti-D immunoglobulin for Rh prophylaxis (22)
6. Harkness, M., (2005) Survey of implementation of NICE recommendation for routine antenatal anti-D prophylaxis in UK maternity units. Personal communication.
7. MacKenzie, I.Z., Bowell, P., Gregory, H., Pratt, G., Guest, C., & Entwistle, C.C. (1999) Routine antenatal Rhesus D immunoglobulin prophylaxis: the results of a prospective 10 year study. BJOG, 106, 492-497.
8. MacKenzie, I. (2004) Antenatal anti-D prophylaxis: one dose or two? Br J Mid, 12, 1-6.
9. Chaffe, B., Ford, J., Bills, V. (2007) Routine antenatal anti-D prophylaxis and patient compliance with the two-dose regimen. Transfusion (in press)
10. MacKenzie, I.Z., Findlay, J., Roseman, F., (2006) Compliance with routine antenatal rhesus D prophylaxis and the impact on sensitizations: observations over 14 years. BJOG
11. Fung Kee Fung, K., Eason, E. (2003) Prevention of Rh alloimmunisation. SOGC Clinical practice guidelines, JOGC, 133 1-9.
12. Audit of Anti-D clinics in London area Nov 2006. Personal communication
13. SW region RTC data for type and dose of Anti-D used in RAADP programs. Personal communication
14. National Institute for Clinical Excellence (NICE). (2002) Full guidance on the use of routine antenatal anti-D prophylaxis for RhD-negative women Technology Appraisal Guidance No.41
15. European Commission (2000), Manufacture of medicinal products derived from human blood or plasma – Revision of Annexe 14 to the EU Guide to Good Manufacturing Practice.
16. Daniels, G., et al Ann NY Acad Sci 2006; 1075: 88-95 and personal communication.
17. Koelewijn JM, de Haas M, Vrijkotte TGM, Bonsel GJ, van der Schoot E. Effect of a single gift of antenatal anti-D prophylaxis with 1000iu in week 30 on the incidence of Rhesus D immunisation in the first trimester of the next pregnancy. *Vox Sang* 2006;91
18. Denomme, G.A. & Fernandes, B.J.(2007) Fetal blood group genotyping. Transfusion, 47, sup 64S-68S.

Appendix 1

Requirement	Comments
Planning: An essential aspect of implementing the RAADP program.	Defining a project team and ensuring all relevant groups are represented aids implementation.
Education: Ensure that all staff involved with antenatal care are fully aware of the program and their responsibilities within that program	This requires the implementation of structured education sessions that explain the changes being made and how best to implement them to ensure success. These education sessions and regular updates must be given to all professional groups involved in the RAADP program.
Defining Responsibility: Clear definition of various professional roles.	Ensures that all areas are covered and there is no confusion regarding who is responsible for what.
Communication: Appropriate mechanisms must be in place to ensure timely and appropriate information transfer between all groups of staff involved in the care of with each woman.	Close cooperation between the blood transfusion department and the antenatal carers is essential. The audit trail, traceability and appropriate interpretation of laboratory investigations is dependent on information sharing.
Resources: Ensure that appropriate staffing levels are available to maintain full audit trail of the products used. Clerical support will often be required.	Maintaining a full audit trail requires time and resource. This may be done using paper or electronically or a combination of both.
Eligibility: All women that are at risk must be identified and offered RAADP.	It may be helpful to ensure that appropriate clinical comments are printed on the antenatal blood transfusion reports to highlight the fact that the woman is eligible to be offered anti D immunoglobulin.
Audit: A full audit trail of any product issued must be maintained and include the dose and batch number of the anti-D	This is required to be able to trace any woman receiving a specific batch. This information would be essential should a batch be recalled or batch traceability be

immunoglobulin given to the woman.	required.
Effective implementation: Ensure that effective audit takes place to measure the success of the programs implementation.	e.g. % of Rh-negative women that are offered RAADP. % that receive the full program of doses
Documentation: Evidence of process and receipt, or not, of anti-D must be included in the woman's notes (EU legislation).	It is also important to make sure that if a woman decides not to receive the RAADP that this is recorded for future reference.
Appropriate interpretation of investigations: Clear and appropriate clinical details must be supplied to the laboratory before investigations can be carried out.	Laboratory tests are often hindered by the lack of appropriate clinical details on requests for investigations. Appropriate clinical information is very important if the RAADP program is to be successful. Guidance 41 provided an information.
Information: All women should receive information about RAADP in a format that is understandable to all. This should include the benefits and risks.	Guidance 41 provided an information leaflet, but the survey by Harkness in 2005[6] identified 60 different information leaflets in use. The production of standard information should be considered through the use of a multidisciplinary group review of all current available leaflets.
Balance: Information and advice given to women must be free from bias as well as being factual.	Women often ask for advice on what they should do with regard to treatment. Any advice offered must be based on fact and not personal preference by the clinician looking after the patient.
Timing: Information on the RAADP should be given to women before booking or at an early stage in pregnancy, to allow opportunity to make informed choice.	Patient information leaflets should be made widely available in primary care so that RAADP is brought to the attention of women at a very early stage in their pregnancy.