NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Overview

Routine antenatal anti-D prophylaxis for RhD-negative women (review of technology appraisal guidance 41)

The overview is written by members of the Institute's team of technical analysts. It forms part of the information received by the Appraisal Committee members before the first committee meeting. The overview summarises the evidence and views that have been submitted by consultees and evaluated by the Assessment Group, and highlights key issues and uncertainties. To allow sufficient time for the overview to be circulated to Appraisal Committee members before the meeting, it is prepared before the Institute receives consultees' comments on the assessment report. These comments are therefore not addressed in the overview.

A list of the sources of evidence used in the preparation of this document is given in appendix A.

1 NICE guidance

This technology appraisal is a review of 'Guidance on the use of routine antenatal anti-D prophylaxis for RhD-negative women' (NICE technology appraisal guidance 41 [2002]; available from www.nice.org.uk/TA041). That guidance is as follows.

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.

2 Background

2.1 The condition

Human red blood cells carry many antigens on their surface. These antigens determine a person’s blood type. The most important are the ABO antigens and the RhD antigen. People with the RhD antigen are RhD positive and those without are RhD negative. A baby inherits its blood type from both parents. Therefore a RhD-negative mother can carry a RhD-positive baby.

During such a pregnancy small amounts of foetal blood can enter the maternal circulation (an event called feto-maternal haemorrhage or FMH). This can happen at any time, but is most common in the third trimester and during childbirth. The presence of foetal RhD-positive cells can cause the RhD-negative mother to mount an immune response, producing a template for the production of antibodies and small amounts of antibodies against RhD antigen (anti-D antibodies). This process is called sensitisation or alloimmunisation.

Sensitisation has no adverse health effects for mother or baby. However, if the mother is exposed to the RhD antigen during a subsequent pregnancy, the immune response is quicker and much greater. The anti-D antibodies produced by the mother can cross the placenta and bind to RhD antigen on the surface of foetal red blood cells. These antibody-coated foetal red blood cells are removed from the circulation. If the rate of destruction of red cells is greater than their rate of manufacture, this results in foetal anaemia. Severe anaemia can lead to foetal heart failure, fluid retention and swelling (hydrops), and intrauterine death. When red blood cells are broken down bilirubin is released. In utero this is cleared by the placenta and is not harmful. However, after birth the neonatal liver cannot cope with the excess production of bilirubin, and this leads to jaundice (haemolytic disease of the newborn or HDN). Low levels of jaundice are not harmful, but, if left untreated, higher levels can damage specific areas of the neonatal brain causing permanent brain damage (kernicterus).

Not all occurrences of FMH lead to sensitisation. The risk of sensitisation is affected by the ABO blood type of the foetus, with a lower risk if it is incompatible with the mother's ABO type. Sensitisation depends on the volume of foetal blood entering the mother's circulation and the mother's immune response. The risk of sensitisation is greatest in the first pregnancy and decreases with each subsequent pregnancy. Sensitisation can be prevented by administering passive immunisation with anti-D immunoglobulin to women in situations where FMH is likely (after delivery, miscarriage, abortion, invasive procedures or abdominal trauma). Administration of anti-D

immunoglobulin has no beneficial effect once sensitisation has already occurred. Parents who have lost babies because of HDN will find it difficult to achieve their intended family size because sensitisation will affect subsequent pregnancies with RhD-positive babies.

The severity of HDN varies depending on the properties of the maternal antibody, the level of antibody in maternal blood and duration of exposure of the foetus to the antibody. Postnatal jaundice can be treated with phototherapy and exchange transfusion. Before birth, anaemia and hydrops can be managed with intrauterine transfusions, but this carries a 2% risk of foetal loss. Moreover, babies who have HDN or have undergone intrauterine transfusions can go on to manifest a range of neurodevelopmental problems, such as deafness, motor and speech delay, and cerebral palsy.

The incidence of HDN depends on the proportion of the population who are RhD negative; this figure is approximately 16% in the white population in the UK, but is lower in other ethnic groups. For the year 2005, it was estimated that 65,000 RhD-positive infants were born to RhD-negative women in the UK (10% of all births). Without routine antenatal anti-D prophylaxis (RAADP), but with the use of anti-D following other sensitising events, 1% of these women (approximately 650) would have become sensitised. Of these, approximately 550 would go on to have a further pregnancy. Taking into account subsequent pregnancies, it is estimated that about 520 affected pregnancies in England and Wales per year will require close monitoring because the mother is RhD negative and has been sensitised. Between 10% and 12% of these babies will require intrauterine transfusions. It is estimated that foetal anaemia and HDN will lead to approximately 37 foetal or neonatal deaths, 21 children with minor developmental problems and 8 children with major developmental problems.

2.2 Current management

NICE guidance (see section 1) recommends that RAADP should be offered to all non-sensitised pregnant women who are RhD negative. RAADP can be given as two doses of anti-D immunoglobulin of 500 IU at 28 and 34 weeks' gestation or a single dose of 1500 IU at 28 weeks' gestation (only two dose

regimens were included in TA 41, as single dose regimens were not licensed at the time of publication). The current uptake of RAADP is not universal and both single-dose and two-dose regimens are in use. In 2005, a survey of obstetric units reported that 75% offered RAADP, and of these 82% used the two-dose regimen. However, recent survey evidence suggests that the single-dose regimen is increasingly preferred for logistical reasons. RAADP is usually administered by community midwives or at antenatal clinics.

It is also standard practice to give anti-D immunoglobulin within 72 hours to all RhD-negative women who give birth to RhD-positive babies and to all RhD-negative women following potential sensitising events. These events include medical interventions (chorion villus sampling, amniocentesis, external cephalic version), terminations, late miscarriages, antepartum haemorrhage and abdominal trauma. RAADP is given in addition to the anti-D given in the situations described above. Moreover, its use is not affected by the administration of anti-D for other indications earlier in the pregnancy. Women who may not require prophylaxis include those planning to have no more children and those in a stable relationship with a father known to be RhD negative. However, there can be confidentiality issues in establishing paternity, and a woman can change her mind about having further children.

A test is currently being developed that would allow the determination of foetal RhD type. This test uses the polymerase chain reaction (PCR) to detect foetal DNA in maternal blood. Use of this test would allow anti-D prophylaxis to be targeted at women who are known to be carrying a RhD-positive foetus. However, the accuracy and cost of this test are currently unknown.

3 The technologies

Table 1 Summary description of technologies

Non-proprietary name	Anti-D immunoglobulin	Anti-D immunoglobulin	Anti-D immunoglobulin	Anti-D immunoglobulin
Proprietary name	D-Gam	Partobulin SDF	Rhophylac	WinRho SDF
Manufacturer	Bio Products Laboratory	Baxter Bioscience	CSL Behring	Baxter Bioscience
Dose	2 × 500 IU	2 × 1000–1650 IU	1 × 1500 IU	1 × 1500 IU
Acquisition cost (BNF edition 53)	£54	£70	£46.50	£313.50
NHS price	£39	[redacted]		

Anti-D immunoglobulin is a human blood product extracted from the plasma of blood donors with high-titre circulating anti-D antibodies. Anti-D is extracted by two methods: fractionation and ion-exchange chromatography. Fractionation gives a lower yield of anti-D than chromatography (50-60% of that in the original plasma compared with 90%). Therefore chromatography needs less donor plasma for the extraction of the same amount of anti-D. Moreover, the anti-D prepared by fractionation can only be given intramuscularly, whereas that prepared by chromatography can be given intravenously or intramuscularly. Intravenous administration is more effective, weight for weight, than intramuscular administration. Until recently the anti-D produced by chromatography was unstable in solution and had to be made up before administration, but a newer product, which is stable in solution (Rhophylac, Table 1), is now available in the UK. Chromatography also produces a purer product that is less likely to provoke allergic reactions.

All preparations of anti-D carry a small risk of localised or generalised allergic reactions. Moreover, although blood donors are carefully screened for transmissible infections, there is always a small risk of the transmission of blood-borne infections. Anti-D produced by the fractionation method has an excellent safety record, but anti-D produced by ion-exchange chromatography

has been associated with outbreaks of hepatitis C. Production now involves further steps to minimise the risk of virus transmission, but there are still concerns that these may not be effective against all types of viruses. Because of the theoretical risk of the transmission of Creutzfeldt-Jakob disease (vCJD), all anti-D is prepared from plasma from the USA, where vCJD has not been reported.

The anti-D preparations available for use in the UK are shown in Table 1.

D-Gam is produced by a not-for-profit, government-owned plasma fractionation unit. It is available in vials containing 250, 500, 1500 or 2500 IU. The 500 IU dose has UK marketing authorisation for RAADP in non-sensitised RhD-negative women at 28 and 34 weeks' gestation and for use following the birth of a RhD-positive baby. The 250 IU dose has UK marketing authorisation for the treatment of potentially sensitising events up to 20 weeks' gestation and the 1500 and 2500 IU doses for the treatment of large FMHs. Because it is extracted by fractionation, D-Gam is suitable for intramuscular use only.

Partobulin SDF is prepared by a modified fractionation process. For RAADP two intramuscular doses of 1000–1650 IU are given at 28 and 34 weeks' gestation. It also has UK marketing authorisation for use post partum and following potentially sensitising events.

Rhophylac is extracted by adsorption chromatography. The recommended dose for RAADP is 1500 IU given between 28 and 30 weeks' gestation. Rhophylac can be given intramuscularly or intravenously. It can be used post partum, following potentially sensitising events and for the treatment of RhD-negative people following transfusions of RhD-positive blood or blood products.

WinRho SDF has UK marketing authorisation for RAADP at a single dose of 1500 IU given intravenously or intramuscularly at 28 weeks' gestation. However, in the UK it is marketed and used solely for the treatment of immune thrombocytopenic purpura.

4 The evidence

4.1 Clinical effectiveness

The Assessment Group identified eight studies from the previous review (TA 41) that compared RAADP using one of the currently licensed regimens with a control group, which were suitable for inclusion in the current review. Four studies used two doses of 500 IU at 28 and 32 weeks' gestation, one study used two doses of 1500 IU at 28 and 34 weeks' gestation, and three studies used a single dose of 1500 IU at 28 weeks' gestation. Five new papers were identified for the current review. One of these presented follow-up data from a trial included in the original review, relating to women in subsequent pregnancies. A further three related to two previously included trials included in the original review but did not present new data. One was a randomized controlled trial (RCT) comparing intravenous with intramuscular Rhophylac.

Only one study was a RCT (the new study that compared intramuscular and intravenous Rhophylac), but this was not powered to detect differences between the two treatment arms. One study was a quasi-RCT with year of birth used to allocate participants to treatment groups. One of the other studies was a community intervention trial (controlled before-and-after study), one was a retrospective before-and-after trial, and five were non-randomised studies with historical or geographical controls. Five studies recruited only primigravidae (women with a first pregnancy) and four recruited primigravidae and non-sensitised multigravidae (women with a second or subsequent pregnancy). Three studies used contemporary controls. The remaining studies used historical controls that may overestimate the effectiveness of RAADP because changes in obstetric care may have led to a decrease in sensitisation. Alternatively the use of historical controls may underestimate the effectiveness of RAADP because newer assays for maternal anti-D are more sensitive. Most studies reported the rate of sensitisation according to the presence of maternal anti-D antibody at the time of delivery and 6 months after delivery. However, the true rate of sensitisation is higher due to the phenomenon of silent sensitisation. Such women have no detectable antibody

but have developed the template for antibody production and will mount an augmented immune response following FMH in any future pregnancy with an RhD positive baby. Only two studies included data on the rate of sensitisation in subsequent pregnancies, – but these necessarily excluded women who did not undertake further pregnancies. As some proportion of women who do not go on to a further pregnancy are sensitised, the true rate of sensitisation cannot be known.

In the control groups (women who did not receive RAADP but may have received anti-D for other indications), the proportion sensitised ranged from 1.2 to 1.8% (0.8–1.6% in primigravidae and 1.4–2.2% in multigravidae). In all studies the rate of sensitisation was lower in the intervention arm. Because the new trial was not applicable to be included in the meta-analysis, the results of the meta-analysis from the original review are reproduced in Table 2. This meta-analysis divided the trials into three groups: group 1 comprised four studies that used two doses of 500 IU at 28 and 34 weeks' gestation in primigravidae; group 2 comprised three studies that used a dose of 1500 IU at 28 weeks' gestation and included primigravidae and multigravidae; and group 3 comprised two community-based trials in the UK that used two doses of 500 IU at 28 and 34 weeks' gestation in primigravidae. Group 3 was considered the most representative for the cost-effectiveness analysis. This group consisted of trials that took as their primary endpoint the number of RhD-negative women who had a RhD-positive baby and were found to be sensitised in a subsequent RhD-positive pregnancy.

Analysis of the intervention groups of all trials showed that 65 women were reported to have been sensitised. In 29 of these women there was possible or probable treatment failure (sensitisation occurred despite appropriate administration of anti-D), in 19 there was possible or probable logistical failure (prophylaxis not administered despite intention to do so according to protocol), and 12 of the women were sensitised in a previous pregnancy when RAADP was certainly or probably not given. The best estimates were judged to be those from two UK community-based studies. These showed that compared with no RAADP, the risk of sensitisation decreased from 0.95% to 0.35% with

RAADP (giving an odds ratio for the risk of sensitisation of 0.37 and an absolute reduction in risk of sensitization in RhD-negative mothers at risk [i.e. carrying a RhD-positive baby] of 0.6%).

Table 2 Results of meta-analysis

	Group 1 2 × 500 IU anti-D primigravidae	**Group 2 1 × 1500 IU anti-D**	**Group 3[a]**
Test for heterogeneity, p-value	0.812	0.940	0.976
Odds ratio of sensitisation with antenatal prophylaxis	0.33 (0.20, 0.55)[b]	0.20 (0.13, 0.29)	0.37 (0.21,0.65)
Rate of sensitisation of control group (%)	0.89 (0.21, 1.56)	1.60 (0.37, 2.83)	0.95 (0.18, 1.71)
Rate of sensitisation of group with antenatal prophylaxis (%)	0.30 (0.22, 0.38)	0.34 (0.28, 0.40)	0.35 (0.29, 0.40)

[a]Mayne (1997) and MacKenzie (1999).
[b]Figures in parentheses are 95% confidence intervals.

The results do not allow comparison of different regimens because no studies compared them directly. There are concerns that a single dose of anti-D at 30 weeks' gestation will not protect against FMH at 28 or 39 weeks' gestation. Moreover, neither single or two-dose regimens provide protection against a large FMH. Use of a single-dose regimen may improve compliance by avoiding logistical failures associated with a second dose, but will have no effect if the reason for non-compliance is a mother's refusal of treatment. Single-dose regimens entail lower administration costs and the total cost of the anti-D immunoglobulin at current prices quoted by the manufacturers, is lower. However, because none of the manufacturers of the 1500 IU dose (used in single-dose regimens) also produce a 500 IU product suitable for treating potential sensitising events, a single-dose regimen could expose women to products from a larger number of blood donors, with increased risk of blood-borne infections. The amount of donor plasma needed to extract two

doses of 500 IU is obviously less than that needed for a single dose of 1500 IU, although the extraction process used to retrieve the immunoglobulin also has an impact.

No serious adverse events related to the administration of RAADP were reported by any of the studies included in the meta-analysis.

4.2 Cost effectiveness

A systematic review of the cost effectiveness of RAADP identified 11 papers relating to nine studies. Eight had been identified by the previous review (TA 41) and the ninth was the cost-effectiveness analysis for that review. Five studies used UK costs, but only two evaluations were applicable to the NHS. One study from Scotland calculated incremental costs per case of HDN and foetal loss prevented. The results suggested that for most anti-D regimens the use of RAADP in primigravidae would be cost saving in terms of prevention of sensitisation and foetal loss. When RAADP for all RhD-negative women was compared with that for primigravidae, the additional cost per incident of sensitisation prevented ranged from £2900 to £8200 depending on the regimen used. The cost per HDN-associated foetal loss avoided was £42,000–120,000. A study from Oxford suggested that a programme of routine prophylaxis would be cost saving if HDN were eradicated. Similar cost savings were predicted in a study of prophylaxis in England and Wales. The independent economic evaluation for the previous review calculated that the incremental cost-effectiveness ratio (ICER) was £11,000–13,000 per quality-adjusted life year (QALY) for primigravidae compared with no prophylaxis. For multigravidae compared with primigravidae, the ICER was £46,000–52,000. The evaluation also suggested that adding a utility gain for avoiding foetal loss and interventions in the next pregnancy could reduce the ICER for multigravidae.

There were no new health economic models provided within the manufacturers' submissions.

The independent economic assessment conducted by the Assessment Group for the current review modelled a cohort of women comprising primigravidae and multigravidae. It assumed national (UK) fertility rates and that 16% of the population is RhD negative. Each regimen for anti-D immunisation was compared with no prophylaxis and with the other regimen. The base-case sensitisation rate was assumed to be 0.95% and the odds ratio for each of the regimens of anti-D was assumed to be 0.37. It was assumed that in the first pregnancy 61% of the RhD-negative women would have an RhD-positive foetus and therefore be at risk. This figure was calculated based on the fact that 84% of men are RhD positive. Of the 61% of RhD-negative women at risk, 0.35% will be sensitised during their first pregnancy. A certain proportion of these (85%) are then expected to go on to have a second baby. Approximately 70% of these babies will be RhD positive because a mother who has had one RhD-positive child is more likely to have another. These babies are at risk of developing HDN. A further 0.35% of women who were not sensitised during their first pregnancy will be sensitised during their second. A smaller proportion of these go on to have a third baby, which may be at risk of HDN (and so on).

It was assumed that the probability of foetal loss is around 4%. It was assumed that 6% of babies with HDN would have minor developmental problems. Within the model, a child with minor developmental problems had a health utility score of 0.85 and was assumed to incur a cost of £100 per year until 16 years of age. It was assumed that 3% of babies with HDN would have major developmental problems. For these children, a health utility score of 0.42 and a cost of £7319 per year were assumed. The costs of the preparations of anti-D were taken from the ‘British national formulary’ (BNF, edition 53). Costs may vary in different settings because of negotiated procurement discounts. The effect of discounts on the cost of anti-D was explored through a threshold analysis. The cost of managing a case of sensitisation was calculated to be £2885 per person.

The model assumed that the first RhD-positive child born to a RhD-negative mother is unaffected, and that the risk of sensitisation and the effectiveness of

anti-D remains the same in successive pregnancies. The model did not include any disutility for the grief experienced by a parent who loses a baby, for the intensive monitoring of future pregnancies, or for living with a child who has developmental problems as a result of HDN. Because the prevalence of the RhD-negative blood type varies according to ethnicity, a subgroup analysis was also carried out.

For primigravidae, comparison of RAADP with no prophylaxis resulted in ICERs between £5,000 and £12,000 per QALY gained for all regimens, except WinRho which gave an ICER of approximately £63,000 (Table 3). For multigravidae compared with primigravidae, the ICERs for RAADP were between £17,000 and £31,000 per QALY gained, except for WinRho which gave an ICER of approximately £152,000 (Table 4). Minority ethnic groups have a lower prevalence of the RhD-negative blood type. The ICERs for these groups were lower, with RAADP being the most cost-effective in those groups with the lowest prevalence of the RhD-negative type (see table 30 on page 114 of the assessment report).

Table 3 Incremental cost-effectiveness ratios (ICERs) associated with routine antenatal anti-D prophylaxis (RAADP) for primigravidae compared with no RAADP

Anti-D dose	Cost per sensitisation avoided	Cost per affected pregnancy avoided	Cost per foetal loss avoided	Cost per life year gained	Cost per QALY[a] gained
2 × 500 IU (D-Gam)	£10,495	£11,376	£284,394	£6,816	£8,205
2 × 1250 IU (Partobulin)	£14,940	£16,194	£404,854	£9,703	£11,680
1 × 1500 IU (Rhophylac)	£7,022	£7,611	£190,285	£4,560	£5,490
1 × 1500 IU (WinRho)	£81,201	£88,018	£2,200,455	£52,737	£63,483

[a]QALY, quality-adjusted life year.

Table 4 Incremental cost-effectiveness ratios (ICERs) associated with routine antenatal anti-D prophylaxis (RAADP) for multigravidae compared with primigravidae

Anti-D dose	Cost per sensitisation avoided	Cost per affected pregnancy avoided	Cost per foetal loss avoided	Cost per life year gained	Cost per QALY[a] gained
2 × 500 IU (D-Gam)	£10,125	£32,697	£817,415	£19,591	£23,582
2 × 1250 IU (Partobulin)	£13,613	£43,960	£1,098,989	£26,339	£31,706
1 × 1500 IU (Rhopylac)	£7,400	£23,897	£597,435	£14,318	£17,236
1 × 1500 IU (WinRho)	£65,602	£211,848	£5,296,200	£126,931	£152,794

[a]QALY quality-adjusted life year.

One-way sensitivity analysis suggested that the model results were sensitive to the base-case sensitisation rate and the odds ratio for the sensitisation rate associated with RAADP. The number of years lost because of foetal death, assumed to be normal life expectancy, also had an impact on the ICERs. A threshold analysis for the cost of the anti-D product with an administration cost of £5 per dose suggested that at £30,000 per QALY a two-dose regimen given to all RhD-negative women rather than primigravidae only would be cost effective at £33 per dose. A single-dose regimen would be cost effective at £71 per dose.

The probabilistic sensitivity analysis gave similar results to the deterministic analysis above. The results suggest that at a cost per QALY threshold of £30,000 it would be most cost effective to provide RAADP to all women who are RhD negative. As all regimens are assumed to be equally effective the only difference is the price, but in practice prices may vary from those used in the analysis. The WinRho product is not expected to be cost effective at any threshold, but currently this product is not marketed for this indication in the UK however if supply of the other three products were disrupted WinRho could be used as an alternative.

The analysis estimated that if an accurate test for the antenatal determination of foetal RhD antigen status became available, it would need to cost between £20 and £31 (depending on the anti-D product chosen; £124 for WinRho) to make targeted prophylaxis cost effective compared with RAADP for all RhD-negative women.

5 Issues for consideration

Is there sufficient evidence to recommend either a single-dose or two-dose regimen? Issues include differential effectiveness, cost, compliance, limiting exposure to donor plasma and limiting demand for donor plasma. It has been suggested from one of the manufacturer's that the assumption of 100% compliance for the two-dose regimen in the economic evaluation is an over estimation.

What utility should be included in the evaluation for the loss of a foetus or neonate and for parents caring for a child with developmental problems as a result of HDN?

How feasible are current recommendations for situations in which RhD-negative women may opt out of anti-D prophylaxis? Issues include mothers changing their mind about having further children and concerns about establishing paternity.

- One consultee, in their submission, states that "Section 1.2 of the NICE Technology Appraisal guidance 41 presents some practical difficulties for midwives in the antenatal setting particularly in relation to the point around circumstances requiring discussion "is in a stable relationship with the father of the child, and the father is known or found to be RhD negative". In addition to the sensitivities of discussing paternity, there are difficulties associated with an institution assuming that the father is indeed RhD negative as reported without having this confirmed by internal testing. Routine testing of the partners of

RhD negative women would have logistical, administrative and financial implications.

- One consultee, in their response to the assessment report, states “Could you please consider the significance of bullet no. 1 in section 1.2, as there are a number of women who change their mind and opt for IVF after sterilisation.

Section 1.3 of technology appraisal 41 makes reference to the Royal College of Obstetricians and Gynaecologists’ ‘Green Top’ 1999 guideline: Use of Anti-D Immunoglobulin for Rh Prophlaxis. This guideline was revised in May 2002, following the publication of technology appraisal 41.

The Association of Radical Midwives, in response to the assessment report raise the issue of Jehovah’s witnesses’ concerns of using anti-D immunoglobulin.

6 Authors

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February 2008

Appendix A: Sources of evidence considered in the preparation of the overview

A The assessment report for this appraisal was prepared by The University of Sheffield, School of Health and Related Research (ScHARR).

- Pilgrim H, Lloyd-Jones M, Rees A. Routine antenatal anti-D prophylaxis for RhD-negative women (review) (November 2007).

B Submissions from the following organisations:

I Manufacturers/sponsors:

- Baxter BioScience
- Bio Products Laboratory
- CSL Behring

II Professional/specialist and patient/carer groups:

- Royal College of Nursing
- Royal College of Physicians and Royal College of Pathologists

III Others:

- Nottingham City PCT

C The following organisations accepted the invitation to comment on the assessment report for this appraisal.

IV Manufacturers/sponsors:

- Baxter BioScience
- Bio Products Laboratory
- CSL Behring

V Professional/specialist and patient/carer groups:

- Association of Radical Midwives
- NHS Blood and Transplant
- Royal College of Nursing
- Royal College of Obstetricians and Gynaecologists
- Royal college of Paediatrics and Child Health
- Royal College of Physicians and Royal College of Pathologists

VI Others:

- Department of Health
- Welsh Assembly Government