NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA156 Pregnancy - routine anti-D prophylaxis for rhesus negative women (review of TA41)

This guidance was issued in August 2008

The review date for this guidance is May 2011[1]

1. Recommendation

The guidance should be transferred to the 'static guidance list'**.** That we consult on this proposal.

2. Original remit(s)

To review and update as necessary guidance to the NHS in England and Wales on the clinical and cost effectiveness of the use of routine antenatal anti-D prophylaxis for RhD-negative women[2], which was issued in May 2002 (as TA41).

3. Current guidance

1.1. Routine antenatal anti-D prophylaxis (RAADP) is recommended as a treatment option for all pregnant women who are rhesus D (RhD) negative and who are not known to be sensitised to the RhD antigen.

1.2. When a decision has been made to give RAADP, the preparation with the lowest associated cost should be used. This cost should take into account the lowest acquisition cost available locally and costs associated with administration.

[1] The guidance qualifies the review date by saying: "However, the guidance may need to be reviewed sooner if a test to determine fetal blood type becomes available." (section 8.2 of TA156).

[2] Original remit: to advise on the clinical and cost-effectiveness and safety of the routine prophylactic use of anti-D immunoglobulin to prevent Rhesus isoimmunisation during pregnancy for all Rhesus negative primagravidae.

4. Rationale[3]

No new evidence has become available that is relevant to the effectiveness and cost effectiveness of RAADP. There is some new research on topics associated with the technology, notably the use of noninvasive fetal blood-group determination, but this would not alter the recommendations of TA156

5. Implications for other guidance producing programmes

The review proposal does not impact directly on any clinical guideline that is currently being produced/updated that is in this topic area.

The Antenatal Care guideline (CG62) was published in March 2008. It incorporates TA41 (which was subsequently replaced by TA156). The specific recommendation from TA41 in CG 62 did not change in TA156.

A review proposal on CG62 has recently been issued for consultation with the recommendation that the guideline is not updated at this time.

[redacted]

6. New evidence

The search strategy from the original assessment report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from July 2007 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix 2 for further details of ongoing and unpublished studies.

7. Summary of evidence and implications for review

One of the preparations covered by TA156, WinRho SDF (Baxter), has been withdrawn from the European market. There have been no alterations to the marketing authorisations of the remaining three preparations. One new technology (LFB-R593 – a monoclonal anti-D antibody that could be used instead of donor plasma-derived anti-D) is currently undergoing phase-II dose-finding study in healthy volunteers; it is possible that, once sufficient research is available to support regulatory application, this technology could be considered as either a new preparation of the intervention under appraisal or as a comparator. However, this is not an imminent prospect.

There are no new trials published or in progress that represent an addition to the existing randomised evidence on the efficacy of RAADP, as reviewed in TA156 (which, in turn, was mainly informed by evidence first reviewed in TA41).

[3] A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper

There are three recommendations for further research in TA156. No new relevant evidence was found for two of these (relative efficacy of single-dose versus two-dose RAADP regimens and disutility of fetal and neonatal loss). The Committee also recommended research into the determination of fetal blood type by genotyping of fetal DNA present in the maternal circulation. There have been relevant publications in this area, including a review led by the Foundation for Genomics and Population Health (PHG Foundation) at the request of the joint committee on medical genetics of the Royal College of Physicians (Wright and Burton 2009). There is also additional ongoing research, including one study directly comparing the costs and effects of management with and without noninvasive fetal RhD determination and one large uncontrolled study in the UK.

However, it is unlikely that any of this evidence would impact on existing recommendations, which support the use of RAADP in all RhD− pregnant women. As a matter of principle, the use of noninvasive fetal RhD determination could only result in improved cost effectiveness for RAADP, because it would lead to more targeted prophylaxis (excluding women who are carrying RhD− fetuses, in whom treatment is unnecessary), thereby minimising costs without affecting utility gains. Whether, as a matter of practice, such benefits justify the costs of a diagnostic programme – as well as the disutility associated with false diagnoses – is beyond the remit of this appraisal. Noninvasive fetal RhD determination could become be a potentially valuable topic for the diagnostics assessment programme.

8. Implementation

A submission from Implementation is included in Appendix 3.

There are no data relating to the uptake of TA156; however, there is some information on implementation of TA41 (which TA156 updates and replaces). This suggests that around three-quarters of maternity units offer RAADP. There is variation of practice regarding the use of one- or two-dose regimens (both are recommended as options in TA41 and TA156). There is evidence that there was greater uptake of RAADP following publication of initial guidance in 2002 (TA41).

9. Equality issues

It was noted that there may be circumstances in which a woman cannot receive treatment with anti-D immunoglobulin because of strongly held beliefs that make it impossible for her to accept treatment with blood products. A monoclonal anti-D antibody may remove this objection; however, this preparation is at a relatively early stage of development.

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Appendix 1 – explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	**Consequence**	**Selected – 'Yes/No'**
A review of the guidance should be planned into the appraisal work programme.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred.	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No
The guidance should be updated in an on-going clinical guideline.	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No

Options	Consequence	Selected – 'Yes/No'
The guidance should be transferred to the 'static guidance list'.	**The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.**	**Yes**

NICE would typically consider updating a technology appraisal in an ongoing guideline if the following criteria were met:

i. The technology falls within the scope of a clinical guideline (or public health guidance)

ii. The technology falls within the scope of a clinical guideline (or public health guidance)

iii. There is no proposed change to an existing Patient Access Scheme or Flexible Pricing arrangement for the technology, or no new proposal(s) for such a scheme or arrangement

iv. There is no new evidence that is likely to lead to a significant change in the clinical and cost effectiveness of a treatment

v. The treatment is well established and embedded in the NHS. Evidence that a treatment is not well established or embedded may include;

- Spending on a treatment for the indication which was the subject of the appraisal continues to rise
- There is evidence of unjustified variation across the country in access to a treatment
- There is plausible and verifiable information to suggest that the availability of the treatment is likely to suffer if the funding direction were removed
- The treatment is excluded from the Payment by Results tariff

vi. Stakeholder opinion, expressed in response to review consultation, is broadly supportive of the proposal.

Appendix 2 – supporting information

Relevant Institute work

Published

Antenatal care: routine care for the healthy pregnant woman. Clinical Guideline 62, issued March 2008, which is a partial update of CG6, issued October 2003. Current status of CG62: consultation on a review closed on 20 March 2011, with a decision date of April 2011. It is proposed that the guidance is "not updated at this time" CG62 incorporates guidance from TA156.

In progress

Pain and bleeding in early pregnancy: assessment and initial management of ectopic pregnancy and miscarriage in the first trimester (Clinical Guideline). Publication date: tbc. In the final scope (issued December 10) it says it will consider:
"The provision of anti-D rhesus prophylaxis for women with miscarriage or ectopic pregnancy."

Suspended/terminated

None found

In topic selection[4]

None found

[4] Information held by the NICE Topic Selection Team is treated as being potentially commercially sensitive by default. Details of the topics considered by NICE's Consideration Panels may be available on the NICE website, providing the manufacturers of the technologies under discussion have consented to the release of this information.

Details of changes to the indications of the technology

Indications considered in original appraisal	Proposed indications (for this appraisal)
D-Gam: sold as a solution ready for injection, and is available in vials containing 250, 500, 1500 or 2500 IU. The 500 IU dose has UK marketing authorisation for RAADP at 28 and 34 weeks gestation in non-sensitised women who are RhD negative, for use after potentially sensitising events that occur after 20 weeks gestation, and for use after the birth of an RhD-positive baby. The 250 IU dose has UK marketing authorisation for use after potentially sensitising events up to 20 weeks gestation, and the 1500 and 2500 IU doses have UK marketing authorisation for the treatment of large FMHs.	BNF cites the same indication as TA156 Antenatal prophylaxis, 500 units given at weeks 28 and 34 of pregnancy; if infant rhesus-positive, a further dose is still needed immediately or within 72 hours of delivery (eBNF 61) However, the SPC adds that D-Gam can be given as:: "...a single dose of 1,500 IU at 28 weeks of gestation."
Partobulin SDF: suitable for intramuscular use only. It is available in prefilled syringes containing 1250 IU. For RAADP, it has UK marketing authorisation for two intramuscular doses of 1000–1650 IU given at 28 and 34 weeks gestation. It also has UK marketing authorisation for use post partum, and for use after potentially sensitising events.	The same indication as TA156 Antenatal prophylaxis, 1000–1650 units given at weeks 28 and 34 of pregnancy; if infant rhesus-positive, further dose is needed immediately or within 72 hours of delivery (eBNF 61)
Rhophylac: may be given intramuscularly or intravenously. It is available in prefilled syringes containing 1500 IU. It has UK marketing authorisation for RAADP as a single dose of 1500 IU given between 28 and 30 weeks gestation. It also has UK marketing authorisation for use post partum, and for use after potentially sensitising events.	The same indication as TA156 Antenatal prophylaxis, 1500 units given between weeks 28–30 of pregnancy; if infant rhesus-positive, a further dose is still needed immediately or within 72 hours of delivery (eBNF 61)

Indications considered in original appraisal	Proposed indications (for this appraisal)
WinRho SDF: may be given intravenously or intramuscularly. It is available as a powder for reconstitution. It has UK marketing authorisation for RAADP at a single dose of 1500 IU to be given at 28 weeks gestation. It also has UK marketing authorisation for use post partum, and for use after potentially sensitising events. In the UK, it is currently marketed solely for the treatment of idiopathic thrombocytopenic purpura.	WinRho does not appear in eBNF 61 (March 11), nor does it feature in eMC. As this was the most expensive of the preparations considered, this is not likely to materially affect the current guidance which recommends the preparation at the lowest associated cost should be used.

Details of new products

Drug (manufacturer)	Details (phase of development, expected launch date,)
LFB-R593 (LFB): a monoclonal anti-RhD	At phase II trial stage in healthy RhD negative volunteers: NCT00952575. Estimated study completion date is July 2011.

Registered and unpublished trials

No relevant trials were found that relate to the RAADP guidance in TA156.

There are three recommendations for further research in TA156:

- ...a test is currently being developed that determines fetal blood type by genotyping of fetal DNA present in the maternal circulation.
- ...head-to-head trials of single-dose versus two-dose RAADP regimens to establish relative efficacy.
- ...studies to better estimate the disutility of fetal and neonatal loss, as well as the disutility to parents who experience such a loss

No relevant evidence or trials were found for the last two recommendations, but the following list of trials was found relating to fetal blood genotyping.

Trial name and registration number	Details
NCT00871195 Evaluation Of The Performance Of A Noninvasive Test For Fetal RHD Genotype On The Sequenom MassARRAY System	Observational study, looking at free fetal DNA in maternal circulation. Still classified as 'currently recruiting'. Estimated enrolment: 520. Estimated study completion date: July 2010. No final trial report found in the literature.

NCT00832962 Effectiveness of Routine Fetal RhD Genotyping for RhD- Pregnant Women.	Observational study, looking at fetal DNA isolated from maternal plasma. Divided into two sub-studies, and still classified as 'currently recruiting'. Estimated total enrolment: 4250. Estimated study completion date: December 2012.
NCT01054716 Evaluation of a Noninvasive Fetal RHD Genotyping Test	Observational study, looking at fetal RHD determination from maternal whole blood. Classified as 'ongoing but not recruiting'. Estimated enrolment: 500. Estimated study completion date: August 2010. No final trial report found in the literature.
UKCRN ID: 5717 Prenatal determination of fetal rhesus D status using free fetal DNA	Interventional study, looking at antenatal determination of fetal rhesus (rh) D status using cell free fetal DNA in the maternal circulation before 20 weeks gestation. Classified as 'open'. Estimated sample size: 3000. Estimated study closure date: April 2011.

Additional information

According to a BMJ Clinical Review (2009):

"At the request of the joint committee on medical genetics of the Royal College of Physicians, a working group was formed in 2008 to review non-invasive prenatal testing and discuss its implementation in the UK; it was led by the Foundation for Genomics and Population Health (PHG Foundation) and comprised academic experts in cell-free fetal DNA technology and prenatal diagnosis, as well as clinical and laboratory geneticists, screening programme coordinators, NHS commissioners, obstetricians, general practitioners, midwives, public health experts, ethicists, and patient representatives. The report from this working group was published in February 2009."
This report covers, amongst other areas:
"...diagnosis of fetal blood type in pregnancies at risk of incompatibility, particularly the Rhesus factor D (RhD) blood antigen."

References

Wright CF, Burton H (Jan. 2009) The use of cell-free fetal nucleic acids in maternal blood for non-invasive prenatal diagnosis. [Review] [135 refs]. *Human Reproduction Update.* 15 (1): 139-151.

Appendix 3 – Implementation submission

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

IMPLEMENTATION DIRECTORATE

Guidance Executive Review

Technology appraisal 156: Pregnancy (rhesus negative women) - routine anti-D (review)

1. National data

The NICE implementation programme has not looked at any routinely collected data in order to determine the uptake of this technology appraisal (TA).

2. External literature

There is currently no literature relating to the uptake of TA156; however the following publications relate to TA41 which this technology appraisal updates and replaces.

2.1 ERNIE

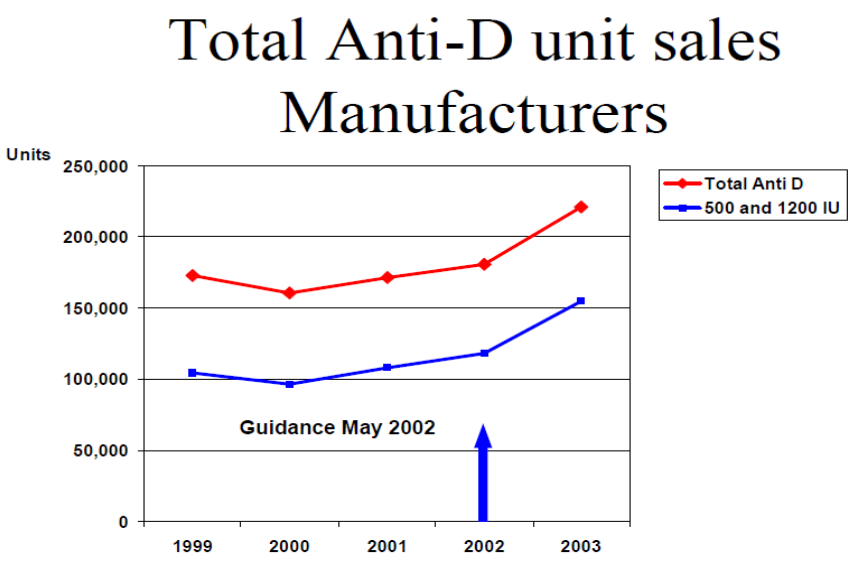
2.1.1 Abacus International (2005) NICE guidance implementation tracking: data sources, methodology and results.

This study looked at manufacturers sales data. An increase in the rate of prescribing was found with an additional 40,000 units supplied 1 year post guidance.

Anti-D was recommended for routine use at weeks 28 and 34 of pregnancy for the prophylaxis of rhesus sensitisation. For the 110,000 annual risk births this would increase units of Anti-D by 210,000. About 60-70,000 units are also used for treating sensitisation during pregnancy.

We have estimated that units of Anti-D would be expected to grow to about 300,000 per year i.e. by 30%.

Figure 1. Total Units of Anti-D sold in England and Wales



Would expect 60-70,000 units for treating sensitisation and 220,000 units for prophylaxis (assumes 2 units/pt)
Total units could grow to about 300,000 per year I.e by about 30%
1 year post guidance an additional 40,000 units Anti-D were supplied = 20,000 treatments

2.1.2 Harkness M, Freer Y, Prescott RJ & Warner P (2008) Implementation of NICE recommendation for a policy of routine antenatal anti-D prophylaxis: a survey of UK maternity units *Transfusion Medicine* 18 pp. 292-295

A postal survey of all 324 UK maternity units was completed in 2005. Responses were received from 91% of units (294 of 324). Routine antenatal anti-D prophylaxis (RAADP) was offered by 220 of 294 75% with 19% offering a single dose regime. At 12% of maternity units, routine paternal blood group testing was offered. 84% of units offered staff education at the time of implementation and 97% provided written patient information.

2.1.3 Basu A & Bellis A (2009) Implementing NICE guidelines: the difficulties *Clinical Governance: An International Journal* 12 (4) pp. 267-269

A survey of 18 maternity hospitals within the North-west Deanery. 11 of the 18 units had implemented the practice with some changing practice from two doses to a single dose on the grounds of logistics.