Antenatal screening for Rhesus D status and red cell allo-antibodies

External review against programme appraisal criteria for the UK National Screening Committee (UK NSC)

Version: One

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The UK NSC advises Ministers and the NHS in all four UK countries about all aspects of screening policy. Its policies are reviewed on a 3 yearly cycle. Current policies can be found in the policy database at http://www.screening.nhs.uk/policies and the policy review process is described in detail at http://www.screening.nhs.uk/policyreview

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Summary

The condition

Haemolytic disease of the newborn (HDFN) occurs when the mother has anti-red cell IgG antibodies in her plasma that cross the placenta and bind to fetal red cells bearing the corresponding antigen. The three most common red cell alloantibodies which cause significant HDFN are anti-D, anti-c and anti-Kell (anti K). Fetal red cells binding sufficient maternally derived antibody are destroyed in the fetal reticuloendothelial system, producing extravascular haemolysis and a variable degree of fetal anaemia. In severe cases the fetus may die *in utero* of heart failure (*hydrops fetalis*). If the fetus survives birth, the neonate rapidly develops jaundice and is at risk of neurological damage due to the high bilirubin level.

Development of red cell antibodies in the mother may occur either as a result of previous pregnancies (because fetal blood displaying paternal red cell antigens frequently enters the mother's circulation during pregnancy) or as a result of a previous blood transfusion.

The test

The most important cause of HDFN is antibody to the rhesus D antigen (anti D). This develops in RhD negative women who have carried a RhD positive fetus. It rarely affects the first pregnancy although it can sensitise the mother so that subsequent pregnancies with rhesus D positive babies boost antibody production progressively, putting later pregnancies at increasing risk. Smaller family sizes and the introduction of prophylaxis with rhesus D immunoglobulin have reduced the incidence and severity of this condition**.**

The fetus is only at risk if it's red blood cells express the antigens against which the antibody is directed (e.g. if a rhesus D negative woman with anti D is carrying a rhesus D positive fetus, there is a risk that the fetus will be affected, but if the fetus is rhesus D negative the baby will not be at risk of HDFN).

The next most common causes of severe HDFN are the rhesus antibody, anti c or Kell antibody (anti K). In HDFN due to anti K, the antibody also causes reduced fetal red cell production. This is due to anti K binding to red cell progenitor cells; in such cases the anaemia is often very severe while jaundice may be minimal.

The treatment

Management for Rhesus D- Anti D immunoglobulin is prepared from plasma of donors who have high levels of plasma anti D due to exposure to rhesus D positive cells following pregnancy or intentional immunisation. Anti D products contain specified levels of anti D and are available for intramuscular or intravenous administration. Anti D is administered to rhesus D negative women who may have been exposed to rhesus D positive fetal red cells that have entered the maternal

circulation. The anti D destroys the rhesus D positive red cells and prevents active immunisation, thus preventing the production of rhesus D antibodies.

Management for all red cell alloantibodies- Pregnancies potentially affected by HDFN should be cared for by specialist teams with facilities for early diagnosis, intrauterine transfusion and support of high-dependency neonates.

The referral should be made before 20 weeks in those women who have had a previously affected baby. Affected neonates should be delivered in a centre which has access to specialist intensive therapy and experience in intrauterine and exchange transfusion. Delivery plans must also be communicated to the local haematologist and blood bank to allow them to provide appropriate support.

Screening programme

Currently, while a systematic screening programme is not in place NICE recommends that all pregnant women are tested for the rhesus status and the above mentioned red cell alloantibodies.

Introduction

This is a review of the evidence for screening of blood group, rhesus D status and red cell allo-antibodies in pregnancy for the UK National Screening Committee, and is based on the literature search conducted by N Jayatilleke, October 2011 and June 2012. The current NSC position (see website http://www.screening.nhs.uk/policy) is that testing should be offered but a systematic population screening programme is not recommended (NSC).

Women are generally tested during routine outpatient appointments during early pregnancy.

Clinical practice guidelines for routine pregnancy clinics are described by NICE (NICE, 2011). This states that "Women should be offered testing for blood group and rhesus D status in early pregnancy" Further to this, "Women should be screened for atypical red cell allo-antibodies in early pregnancy and again at 28 weeks, regardless of their rhesus D status." (NICE, 2011)

Purpose of laboratory testing as per current guidelines

- "ABO and D typing to identify D-negative women who require anti-D prophylaxis."
- "Screening and identification of red cell allo-antibodies d to detect clinically significant antibodies that might affect the foetus and/or the newborn d to highlight possible transfusion problems."
- "Follow-up tests when clinically significant red cell antibodies are present: To monitor the strength of antibodies to identify those pregnancies that are at risk of HDFN and to predict foetuses/infants who are likely to require treatment for HDFN. To identify additional maternal allo-antibodies. Women who have developed one or more antibodies may go on to form further antibodies of different specificities."

Elsewhere in the USA, the U.S. Preventive Services Task Force (USPSTF) strongly recommends rhesus D blood typing and antibody testing for all pregnant women during their first visit for pregnancy-related care with a grade: A Recommendation. The USPSTF recommends repeated rhesus D antibody testing for all unsensitised rhesus D-negative women at 24-28 weeks' gestation, unless the biological father is known to be rhesus D negative with a grade: B Recommendation (USPSTF, 2004).

The Condition

1. *The condition should be an important health problem*

Haemolytic disease of the new born can result in jaundice, severe anaemia, heart failure and death (Contreras, 1998). Haemolytic disease of the fetus and newborn (HDFN) is caused by maternal allo-antibodies directed against fetal red cell surface antigens that the mother herself lacks (inherited from the father). If untreated severe cases lead to stillbirth or learning difficulties, deafness, blindness and cerebral palsy.

The D antigen of the rhesus (Rh) blood group system is the most frequently involved antigen in HDFN with around 90% of all cases of clinically significant haemolytic disease of the new born affecting rhesus D positive infants born to rhesus D negative mothers (Chilcott J, 2003).

In the absence of prophylaxis, the mothers usually make the anti-D antibody following a small fetomaternal haemorrhage at delivery of the first rhesus D positive infant, but successive rhesus D positive infants are then progressively more affected by haemolytic disease of the newborn (Chilcott J, 2003).

The D antigen of the rhesus system is highly immunogenic and the corresponding antibody is capable of causing severe HDFN in sensitised rhesus D-negative women carrying a rhesus D-positive foetus (Hughes & etal, 1998).

Prior to the introduction, in 1970, of prophylactic treatment with anti-D immunoglobulin following the birth of rhesus D-positive infant to a rhesus D negative mother, HDFN was responsible for one death in every 2180 births (Chilcott J, 2003). The use of anti-D prophylaxis postnatally, and also following any potentially sensitising events during antenatal period, has reduced this figure to 1 death in 20,800 births (Chilcott J, 2003).

Despite the widespread use of prophylactic antenatal and postpartum anti-D immunoglobulin, rhesus D allo-immunisation is still a significant cause of fetal and neonatal morbidity and mortality. (Robson SC, 1998). Although incidence of haemolytic disease of the newborn has substantially reduced currently it is believed to cause death in 6 out of 100,000 live births (Whitfield CR, 1997).

Haemolytic disease of the newborn can occur in rhesus D-positive and –negative women. A significant number of women will have red cell antibodies. In addition, to rhesus D, other alloantibodies such as anti-Rh (C), anti-Rh (c), anti- Rh (E), anti-Rh (e) anti-Kell, anti-Duffy or anti-Kidd are able to cause HDFN (Weinstein, 1982).

Antibodies against the C and E antigens of the Rh system or against antigens of other blood group systems rarely lead to clinical manifestations (NHS Blood and transplant, 2007)

2. The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage.

According to the literature, the most common risk factor for haemolytic disease is rhesus D. In the UK, 15-17% of the general Caucasian population is believed to be rhesus D negative (NICE, 2011). In about 10% of all pregnancies the mother is rhesus D negative and the fetus is rhesus D positive.

In Holland, where a screening programme is in place to identify and manage rhesus and other antibodies, the prevalence of positive antibody tests at first trimester screening was 1,232 in 100,000. It has been found that HDFN-risk relevant antibodies were seen in 400 per 100,000. Of these, Anti-D was seen in 83 per 100,000. Antibodies other than anti-D were 328 per 100,000 of which 191 of 100,000 with implied a risk for occurrence of haemolytic disease of the new born (Koelewijn JM, 2008).

In the UK, the incidence of antibodies other than rhesus D including anti-Rh (C), anti-Rh (c), anti-Rh (E), anti-Rh (e) anti-Kell, anti-Duffy or anti-Kidd was reported to be 0.9% (Bowell PJ, 1986)(Howard H, 1998).

The number of HDFN has reduced over the years as the prophylactic treatment with anti-D has been provided in most areas (Chilcott J, 2003).

3. *All the cost-effective primary prevention interventions should have been implemented as far as practicable.*

Not applicable.

4. If the carriers of a mutation are identified as a result of screening the natural history of people with this status should be understood, including the psychological implications.

Not applicable.

The Test

5. There should be a simple, safe, precise and validated screening test.

The test is a venous blood sample at booking and then again at 28 weeks of gestation. The laboratory blood tests would need to identify blood group and red cell antibodies. Antibody screening should be undertaken using an indirect anti-globulin test and a red cell panel conforming to current UK guidelines (British Committee for Standards in Haematology Blood Transfusion Task Force, 2007). The initial test should include ABO and rhesus D tying as well as to detect any irregular red cell antibodies. Testing should be undertaken again at 28 weeks of gestation for all women with no antibodies on initial testing to ensure that no additional antibodies have developed. NICE found no RCTs of different testing schedules (Chilcott J, 2003). Rhesus D positive women are just as likely as D negative women to form antibodies, other than anti- D, late in pregnancy (Thompson et al., 2003). No further routine blood grouping or antibody screening is necessary after 28 weeks. There is evidence that antibodies detected only in the third trimester do not cause HDFN (Heddle et al., 1993; Rothenberg et al., 1999).

Two Swedish surveys of red cell antibody screening in similar populations used different testing schedules and both concluded that their particular schedule detected all women at risk of HDFN, yet one tested once only in early pregnancy and the other tested rhesus D- positive women twice in pregnancy and rhesus D-negative women three times in pregnancy (Filbey D, 1995).

6. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.

Current guideline is that if clear-cut positive results are not available then safer to classify women ad rhesus D negative until reference laboratory has confirmed status (British Committee for Standards in Haematology Blood Transfusion Task Force, 2007).

Local policies must ensure that D negative women eligible for RAADP have the third trimester antibody screening sample taken before the first RAADP injection is administered at 28 weeks. Samples taken after the injection could result in passive anti-D being detected, which may be mistaken for immune anti-D (New et al., 2001).

The diagnostic performance in terms of sensitivity, specificity, and predictive value of a first-trimester RBC antibody screening for detecting the fetuses at risk for severe HDFN due to anti-D could not be identified during the search. The results of PCR typing were compared with serology to determine the sensitivity, specificity, and positive and negative predictive values of DNA-based techniques. A total of 500 cases were reviewed, in which four different sets of oligonucleotide primers were used. The sensitivity and specificity of PCR typing were 98.7% and 100%, respectively, and the positive and negative predictive values were 100%, and 96.9%,

respectively. In five cases, an RhD-positive fetus was incorrectly diagnosed: Two fetuses died, one neonate needed exchange transfusions, and another neonate needed phototherapy in conjunction with a simple transfusion (Van Den Veyver I.B., Moise Jr. K.J.(1996)).

The diagnostic performance in terms of sensitivity, specificity, and predictive value of a first-trimester RBC antibody screening for detecting the fetuses at risk for severe HDFN due to RBC antibodies other than anti-D could not be identified during the search. The sensitivity of the low ionic strength solution antiglobulin test (LISS-AGT), polyethylene glycol antiglobulin test (PEG-AGT), low ionic strength solution solid-phase antiglobulin test (LISS-SPAT), gel low ionic strength solution antiglobulin test (GEL-LISS), and gel papain test (GEL- PAP) was compared in titration studies of 460 sera containing identified IgG alloantibodies. The GEL-PAP was 100% sensitive to detect Rh antibodies, whereas the PEG-AGT was the most sensitive to detect Kell, Duffy, Kidd, Ss, and rare blood group antibodies. The better performance of PEG-AGT was especially obvious with Kell, Duffy, and Ss antibodies (S = 100%). When the sensitivity of the LISS-AGT, PEG-AGT, GEL-LISS, and GEL-PAP was evaluated in different routines, the GEL-LISS showed to be more sensitive than PEG-AGT in the detection of clinically significant antibodies (De Castilho L.M.,1996).

7. The test should be acceptable to the population.

Routine antenatal serological testing has been practised throughout the UK for over 30 years. No published evidence on the acceptability of rhesus D test carried out in the UK was found.

A study surveying the acceptability of non-rhesus found that women preferred to receive more supportive information. Anxiety increased in screen-positives during the process but dropped to basic levels postnatally (Koelewijn JM V. T.,Rhesus D, 2008).

8. There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals.

When a red cell antibody is detected, the clinicians responsible for the woman's antenatal care must be informed of its likely significance, with respect to both the development of HDFN and transfusion problems. Management of pregnancies in which red cell antibodies are detected varies depending upon the clinical significance and titre of the antibody detected. Further tests will be required to determine antibody specificity and significance. Regardless of initial test result, a second test is carried out at 28 weeks. If no further antibodies are found in either, then no further tests required (British Committee for Standards in Haematology Blood Transfusion Task Force, 2007).

When rhesus D is detected, the management will include provision of information and treatment with RAADP. With other antibodies, there is need to liaise with haematologists for

expert opinion (British Committee for Standards in Haematology Blood Transfusion Task Force, 2007). Transfusion problems can be identified as a by product of screening for antibodies that may cause HDFN.

Paternal testing will need to be addressed. With regards to rhesus factor, according to current guidance, all rhesus D-negative women are offered antenatal anti-D prophylaxis. However, consideration should be given to offering partner testing because, if the biological father of the fetus is negative as well, anti-D prophylaxis, which is a blood product, will not need to be administered (British Committee for Standards in Haematology Blood Transfusion Task Force, 2007). Other situations where anti-D prophylaxis may not be necessary include cases where a woman has opted to be sterilised after the birth of the baby or when a woman is otherwise certain that she will not have another child after the current pregnancy.

According to NICE, the main antibodies that can cause severe allo-immune anaemia in the fetus are anti-D, anti-c and anti-Kell. Of lesser importance but still with the potential to cause HDFN are anti-e, -Ce, -Fya, Jka and -Cw.

Anti-Lea, -Leb, -Lua, -P, -N, Xga and high-titre low-avidity antibodies such as anti-Kna have not been associated with HDFN (Whittle, 1996). There is no value in identifying group O pregnant women with high titres of anti-A or anti-B. Antenatal testing for these antibodies has been shown to have no value in predicting the incidence of HDFN caused by ABO incompatibility (Brouwers HA, 1996).

9. If the test is for mutations the criteria used to select the subset of mutations to be covered by screening, if all possible mutations are not being tested, should be clearly set out.

Not relevant

The Treatment

10. There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment.

The test can reveal the presence of several antibodies.

For rhesus D, prophylactic treatment with human immunoglobulin is recommended (NICE, 2011). In addition once status is identified, anti-D is also offered for any subsequent sensitising events such as procedures like amniocentesis.

Sensitisation prophylaxis in the form of anti-D for the prevention of HDFN can be considered the secondary prevention for the following reason. It is known that sensitisation to the rhesus D antigen is most likely to occur during the third trimester of a pregnancy (Cohen et al., 1964; Krevans et al., 1964).

However, sensitising events may not be accompanied by clinical signs, such as abdominal pain or overt bleeding that would prompt the administration of anti- D immunoglobulin. Therefore, despite the use of anti-D Ig prophylaxis, the sensitisation rate has remained around 1% (Tovey, 1992). In order to attempt to avoid these residual sensitisations the National Institute for Clinical Excellence (NICE) recommended, in 2002, the use of routine antenatal anti-D prophylaxis (RAADP) for all Rh D-negative pregnant women (NICE, 2002). The recommendations were for a minimum of 500 i.u. of anti-D immunoglobulin to be given at 28 and 34 weeks of gestation, since studies had demonstrated that the introduction of this regime could reduce the sensitisation rate to around 0.4% (Tovey et al., 1983; Thornton et al., 1989; MacKenzie et al., 1999).

In 2008, NICE issued further guidance recommending 'RAADP can be given as two doses of anti-D immunoglobulin of 500 i.u. (one at 28 weeks and one at 34 weeks of gestation), as two doses of anti-D immunoglobulin of 1000–1650 i.u. (one at 28 weeks and one at 34 weeks of gestation) or as a single dose of 1500 i.u. either at 28 weeks or between 28 and 30 weeks of gestation.' (NICE, 2008). The testing at point of first contact and at time period of most risk of sensitisation with the opportunity to treat are considered good practice. The prophylactic treatment (RAADP) is believed to be 98.4-99% effective (Bowman, 2003).

Antenatal prophylaxis has been reported to be equally effective and also more cost-effective, in ethnic minority populations in the UK and elsewhere (Chilcott J, 2003). There have been studies that show Doppler ultrasound is useful as a monitoring technique for fetal anaemia in pregnancies complicated by rhesus D incompatibility (Haugen G, 2002) (Mari G, 2002).

With regards to other red cell antibodies, the treatment is varied by antibody specificity and titre therefore will need to be assessed individually. There may be the need for follow-up of antigen positive fetuses by Doppler ultrasonography to detect anaemia severe enough to need treatment. When anaemia is suspected, an invasive approach is still required in a timely manner for confirmation of the degree of anaemia and to administer blood transfusions(Illanes S., 2010).

11. There should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment to be offered.

NICE guidance recommends treatment prophylactically at 28 and 34 weeks with 500iu of anti-D. There may be other clinically relevant, eg- sensitising events that may require a Kliehaur test and further treatment with anti-D dependent on individual's titre. A Kleihauer test is used to confirm transplacental blood loss from fetus to mother. Kleihauer-Betke acid-elution test, the most widely used confirmatory test for quantifying FMH, relies on the principle that fetal RBCs contain

mostly fetal hemoglobin (HbF), which is resistant to acid-elution whereas adult hemoglobin is acid-sensitive (Kim YA,. 2012). The test is performed on the mother's blood; the blood undergoes acid elution and staining. Fetal red cells contain HbF and are therefore more resistant to acid elution than the maternal cells. The fetal cells therefore stain red, maternal cells stain pink. The current policy detailing women who should be offered treatment is as per guideline for blood grouping and antibody testing in pregnancy. The U.S. Preventive task Force has found no direct evidence addressing new treatment protocols developed and tested that show improvement in health outcomes of rhesus D incompatibility (USPSTF, 2004).

Clinical management for the routine care of healthy women is covered by NICE Guideline CG62. In this guideline, 10 antenatal visits are recommended for nulliparous and 7 for multiparous women. The first appointment should be fairly close to 10 weeks. The guideline states that "identifying blood group, rhesus D status and red cell antibodies in pregnant women is important to prevent haemolytic diseases of the newborn and to identify possible transfusion problems."

Routine antenatal anti-D prophylaxis reduced sensitisation rates (from 1.2% to 0.28%) in a retrospective survey. There is also published evidence to suggest a decline in HDFN following the introduction of the prophylaxis policy (Chilcott J, 2003).

If unborn baby develops disease, the treatment depends on how severe it is.

Blood transfusion may be necessary in more severe cases including admission to neonatal intensive care unit (NICU).The treatment may include phototherapy transfusion to prevent red cells being destroyed.

12. Clinical management of the condition and patient outcomes should be optimised in all health care providers prior to participation in a screening programme.

There is no evidence to suggest that clinical management of the condition and patient outcomes are not optimal currently.

The Screening Programme

13. There should be evidence from high quality Randomised Controlled Trials that the screening programme is effective in reducing mortality or morbidity. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.

No RCTs carried out in the UK were found during the review. HTA report analysis of studies done found that RAADP treatment antenatally reduced sensitisation but will not prevent all cases. RCTs were included in this report.

As testing for blood group, rhesus D status and red cell antibodies is conducted in antenatal clinics in the UK and comparable countries, it would not be feasible to run an RCT of testing versus no testing in any population generalisable to the UK population on ethical grounds given the observed benefits of testing for rhesus and red cell alloantibodies. It may, however, be possible to run a cluster RCT of a screening programme versus current testing conducted in antenatal clinic settings. No such RCTs have been conducted as yet.

14. There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public.

Screening programmes are in place in other countries. Test uptake in Holland screening programme has been close to 100% (Koelewijn JM,, 2009). The acceptability of the test, diagnosis and treatment in the UK is not known.

15. The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment).

It is very likely that the benefits of testing outweigh any harms given that the prophylactic treatment offered following testing has resulted in reduced sensitised events, however at the expense of over-treatment and anxiety. The potential psychological harm of a false positive diagnosis and unnecessary treatment is present as around 40% of rhesus negative women will not need the treatment. Fetal loss of the newborn results in 79 life-years lost (considered as average life expectancy) and 70 quality adjusted life years(QALYs) lost which equates to 28 life-years lost and 24 discounted QALYs lost (Pilgrims, 2009).

The harms will include the frequency of testing, regular monitoring with Doppler and other tests which could include fetal blood sampling. There are also risks associated with anti-D treatment. Anti-D Ig is produced from human plasma and, as such, carries a potential risk to the recipient. This risk includes transfusion transmitted infection and acute transfusion reactions such as anaphylactic reaction. Anti-D IgG was associated with isolated cases of hepatitis C infection in the 90s. It is important that these risks are outweighed by the benefits of anti-D Ig administration, and equally that a sufficient dose of anti-D Ig is given to prevent iso-immunisation and its subsequent risks.

16. The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (ie. value for money). Assessment against this

criteria should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource.

Ideally, UK-based cost effectiveness analyses would compare the costs and effects of a screening programme to current practice of testing within antenatal clinics. According to Health Technology Appraisal report findings, if all rhesus D-negative women are offered in England & Wales is estimated to be around £6.8 million but if the cost savings from reduced number of cases of HDFN is considered this is around £5.7-6.4 million per year. The assessment did not cover the additional benefit and costs of identifying antibodies other than rhesus D. Further, this figure only relates to testing and not the totality of the screening programme.

17. All other options for managing the condition should have been considered (eg. improving treatment, providing other services), to ensure that no more cost effective intervention could be introduced or current interventions increased within the resources available.

Not applicable as the severity of the condition may vary from being mild to severe. Other ways to manage the condition may be to monitor for signs only or treat postnatally if child's blood antibody status is different to the mother which will not reduce antenatal risks.

18. There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards.

With the existing testing within antenatal clinics it is unclear whether there would need to be any additional monitoring above standard haematological quality control procedures already in place in the NHS. If a systematic population screening programme were to be instituted a call and recall system would need to be set up. There would also need to be checks that all clinics and laboratories within the screening programme were working to the same set of quality standards regarding sample collection, transport, timing and frequency of testing and reporting methods. Quality assurance processes are already underway for existing antenatal screening programmes.

19. Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme.

Testing of blood group, rhesus D and red cell antibodies is already included in NICE recommendations. Treatment with RAADP has been endorsed through NICE technology appraisal. As women are invited for regular antenatal visits, no additional clinic space is likely to be required for testing as part of antenatal visits. If a population screening programme were instituted then programme infrastructure would be required, such as database of women eligible, regular reminder letters, etc. Retrospective audit of compliance to the NICE technology appraisal on RAADP was over 90% (Audit Commission, 2005).

20. Evidence-based information, explaining the consequences of testing, investigation and

treatment, should be made available to potential participants to assist them in making an informed choice.

Antenatal screening leaflets already contain some information. As part of the screening programme need to make information available to enable informed decision making. In Holland, survey found dissatisfaction on level of information received (Koelewijn JM, 2008).

21. Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public.

Eligibility criteria will include all pregnant women. Screening interval between booking and 28 weeks has been set on current best evidence. This may change with new evidence that emerges. Public pressure may arise for non-invasive pre-natal D as newer technologies are described in the literature that use cell free DNA of the fetus found in maternal blood. Other factors to consider include non-invasive prenatal diagnosis which is currently in trial phase. Mass testing processes need to be adequate before it can be utilised in screening programmes. False positives (2%) have been reported (Finning K, 2008). Current thinking that NIPD implementation is unlikely to produce important clinical benefit. The number of pregnancies sensitised will not fall appreciably and may even rise if test sensitivity is below 99.9% (Szczepura A, 2011).

22. If screening is for a mutation the programme should be acceptable to people identified as carriers and to other family members.

Not applicable.

Implications for policy

The evidence suggests that the policy of testing for rhesus D and red cell allo-antibodies should continue as part of good clinical practice. The justification for this is mainly to prevent haemolytic disease of the new born by identifying pregnant women early to prevent rather than treat the condition. Although evidence base is limited, there is an antenatal population who are able to benefit from a test through early detection of blood type followed by appropriate management. The benefits of a systematic screening programme has not been assessed in the UK. However, experiences in other countries, in particular in the Netherlands, have shown that screening programmes have identified the extent of the problem and helped monitor outcomes.

- Around 17% of the pregnant population is rhesus negative and around 60% of the women may go on to have a rhesus positive baby with a potential risk of haemolytic disease.

- There is good evidence available on testing for rhesus group in pregnancy suggesting that the existing service of testing, diagnosing and managing the relevant antibodies within obstetric care should continue.

- The key gaps in knowledge relate to the additional benefit from systematic population screening programme given the on going practice and guidelines of blood group, rhesus and red cell testing. Given that compliance to rhesus testing is found to be high through retrospective audit, the additional merits of a systematic programme need to be agreed.

Implications for research

Further information on cost effectiveness of screening for rhesus D factor and red cell allo-antibodies using current testing techniques is required.

Conclusion

Women should be offered testing for blood group and rhesus D status in early pregnancy. It is recommended that routine antenatal anti-D prophylaxis is offered to all non-sensitised pregnant women who are rhesus D-negative (Technology appraisal guidance, June 2008). Women should be screened for atypical red-cell allo-antibodies in early pregnancy and again at 28 weeks, regardless of their rhesus D status.

Pregnant women with clinically significant atypical red-cell allo-antibodies should be offered referral to a specialist centre for further investigation and advice on subsequent antenatal management. If a pregnant woman is rhesus D-negative, consideration should be given to offering partner testing to determine whether the administration of anti-D prophylaxis is necessary. The additional benefits of a systematic screening programme in place of current practice is poorly described and may be limited.

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Appendix 1

Search strategy

Initial search strategy
The following search strategy was applied to Medline, Embase and the Cochrane Library in October 2011 and repeated in May 2012:

The key words were anti D, prophylaxis, antibodies in pregnancy and haemolytic disease of the newborn. In addition, broad termed searches were made of the Cochrane Library and Medscape. Appropriate non-published literature, published policy documents and knowledge from experts in the field were incorporated and used.

The papers included were subjected to critical reading by the authors using the CASP appraisal tool (Critical Appraisal Skills Programme, 2006, URL http://www.phru.nhs.uk/casp/critical_appraisal_tools.htm)andwere also ranked according to the hierarchy of evidence.

Supplementary search strategy
The following search strategy was applied to Medline, October 2011 and May 2012.

Database(s) Searched: **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations** **and Ovid MEDLINE(R)**: 1950 –present **EMBASE (OvidSP)**: 1996 – 2012 **The Cochrane Library**: 2000 – present
Summary of Search: PICO (Population, Intervention, comparison, outcome) format applied. **Search terms** Population: Intervention: Outcome: Specific searches were carried out for following predictors. MESH terms were also used.

- Pregnan$.tw, antenatal.tw, prenatal.tw, exp pregnancy/, mass screening/ screen$.tw, detect$3.tw, (test or tests or testing).tw, prenatal diagnosis/, blood group antigen/, exp blood group antigen/, study type search terms
Limits: Years 1950 - All Languages