RH DISEASE AND ALLOIMMUNISATION

CLINICAL GUIDELINE MCSA.MBC.2.1

Antenatal Screening

Blood Group (ABO and Rhesus) should be known in all pregnant women. If a previous lab result or a donor card is unavailable, determine the blood group early in the current pregnancy.

Irrespective of the Rhesus status:
All pregnant women, also Rh-positive women, must be screened early IN EVERY PREGNANCY for the presence of any erythrocyte antibodies which could be of clinical significance (not only anti-D but also anti-c, anti-E, anti-K etc.) (**Indirect Coombs**).

If antibody positive for anti-D, anti C, c, E, e or anti-K: offer non-invasive fetal genotyping using maternal blood. The test has a very low false negative rate. If the test shows absence of the antigen of concern, this could save future expenses and discomfort associated with unnecessary surveillance. This test is currently only available in overseas laboratories, and therefore costly, and not refunded by medical aids. Failing this, determine genotype of father (if new partner as he could be negative) or refer to a specialist.

All patients with anti-Kell antibodies should be referred for Fetal Specialist assessment regardless of titer value UNLESS the father of the current pregnancy (and therefore the fetus) is confirmed to be Kell-negative.

Patients with clinically significant red cell antibodies other than anti-D should be discussed with a fetal specialist.

For Rhesus positive women:
If antibody negative – repeat screening indirect Coombs at 28 weeks

Patients who test "weak D" positive are at low risk of allo-immunisation and do not require serial testing or passive immunisation with immunoglobulin.

For Rhesus negative women with positive or unknown Rhesus status of the fetus:

<u>If anti-D antibody negative:</u>

Repeat indirect Coombs every 6 weeks (suggested at 20, 26, 32 and 38 weeks).

Give anti-D immunoglobulin prophylaxis for specified indications (see below) PROVIDED the indirect Coombs is still negative. Repeat indirect Coombs before administering anti-D immunoglobulin to confirm this.

If anti-D antibody positive:

If the titer is less than 1:16 AND this is the first pregnancy with antibodies, serial antibody titers should be determined every 3-4 weeks, preferably with the same laboratory.

If the anti-D antibody titer is or becomes more than 1:8 (i.e. 1:16 or higher) OR if antibodies were present in a previous pregnancy, the patient should be referred for Fetal Specialist assessment, with Doppler studies of the peak velocity of the middle cerebral artery starting as soon as possible from 16 weeks onwards.

If antibody other than anti-D:

Offer non-invasive genotyping of the fetal blood group to check whether the offending antigen (if anti-C, c, E, e or K) is present in the current pregnancy. Failing this, determine genotype of father (if new partner as he could be negative) or refer to a specialist.

Prophylactic administration of Anti-D immunoglobulin

(only for unsensitised Rhesus-negative women with positive or unknown fetal Rhesus status)

Consent:

- Written consent should be taken before administration.
- It is recommended that an information leaflet is used to inform patients. https://www.nhs.uk/conditions/rhesus-disease/prevention/
- Screened for HepBsAg, HepC RNA, anti-HIV, viral inactivation steps during preparation – remaining risk for transmission of infection extremely small, small risk of hypersensitivity (even anaphylaxis ~IgA).
- If patient declines: get written decline of treatment documented in notes, along with reasons for declining and continue screening for the remainder of the pregnancy.

Route:

- Give immunoglobulin IMI, preferably into deltoid muscle as absorption from the buttock is more unpredictable especially if the injection reaches only into the subcutaneous fat rather than the deep muscle.
- Women with a bleeding disorder should get the dose subcutaneously or IVI but not all anti-D products are suitable for this (verify from manufacturer).

Preparations:

- 1µg (microgram) = 5 IU (international units)
- Different preparations may have different concentrations per ml. Always check before administration.
- Preparations suitable for IMI use are often NOT suitable for IVI use as they may cause severe hypersensitivity reactions. Always check before administration.

Available in South Africa: Rhesugam 100 mcg IMI (500 IU) – NOT to be used IVI in view of risk for anaphylactic shock.

1. Anti-D for sensitising events:

Dose:

- A minimum dose of 250 IU needs to be given for sensitising events prior to 20 weeks, a minimum of 500 IU for gestations after 20 weeks.
- If there is a risk that a large fetomaternal haemorrhage (FMH) may have occurred (*conditions in table below) a Kleihauer test should be done as soon as possible after the event, to identify women with a large FMH who need a larger dose of immunoglobulin.
- If a FMH of larger than 4mls is detected, additional 500 IU is required for every 4mls of FMH and the Kleihauer needs to be repeated after the initial anti-D dose to check for clearance of the fetal cells (48 hours after an IV dose, 72 hours after an IM dose). Repeat procedure until Kleihauer becomes negative.
- For sensitising events before 20 weeks, no Kleihauer is indicated.

Timing:

- The dose should be given as soon as possible after the event and within 72 hours whenever feasible.
- If this window of opportunity has been missed, the dose can still be given up to 10 days after the event.
- If there is concern regarding ongoing bleeding after anti-D administration, repeat Kleihauer in 2 weeks and give repeat dose of Anti D if needed (dose dependent on size of FMH), regardless of presence or absence of passive anti D antibodies (as the previous immunoglobulin can cause low titers to persist for several weeks).

Sensitising events requiring prophylaxis:

- **Invasive prenatal diagnostic procedure** (amniocentesis, CVS, cordocentesis)
- **Any other intrauterine procedure*** (laser, shunt, transfusion, surgery)
- **Antepartum bleeding***
- **External cephalic version***
- **Abdominal trauma***
- **Fetal death*:** Administer dose as soon as the demise is detected, irrespective of when the delivery occurs
- **Miscarriage:**

  All spontaneous complete or incomplete miscarriages from 12w0d onwards (Spontaneous complete miscarriage before 12w0d does NOT require Anti D in times of shortage)

  All evacuations of RPOC (retained products of conception) or medical treatment for missed or incomplete miscarriage, regardless of gestation

- **Threatened Miscarriage (with a live fetus):**

  After 12w0d: give anti-D and, if bleeding continues, repeat dose every 6 weeks

  Before 12w0d: only give anti-D with a heavy bleed, or repeated bleeding, or associated abdominal pain

- **Termination:** All therapeutic terminations, whether by evacuation or medical TOP, regardless of gestation
- **Ectopic pregnancy:** All ectopic pregnancies, regardless of gestation and management.

- **Molar pregnancy:** All molar pregnancies (at least 250 IU anti-D) irrespective of gestation
- **Post-delivery:** Send cord blood for Rhesus status of baby (if forgotten: obtain heel prick sample)

  If baby Rhesus negative, no need for further tests or immunisation.

  If baby's Rhesus status cannot be determined: treat as if baby is Rh positive

  If baby Rhesus positive: Give minimum dose of 500 IU Anti D after delivery, within 72 hours, irrespective of when previous dose was given. Dose can be given up to 10 days after delivery, as it may still offer benefit.

  Request Kleihauer within 2 hours of delivery (but after 45 minutes) to determine if additional dose is required, especially if caesarean section or manual removal of placenta**.**
- **Inadvertent transfusion of Rh-positive blood products:**

  If platelets: give 250 IU for every 5 doses of platelets to prevent sensitisation
  If blood:
  - less than 15mls: give 500 IU per 4mls
  - more than 15mls: give 5000 IU, preferably IVI to achieve high levels sooner
  - if more than 1 unit of red cells blood given: consider exchange transfusion

2. Routine antenatal anti-D prophylaxis (RAADP)

- Should NOT be offered if indirect Coombs positive due to prior sensitisation (i.e., not applicable if low titer due to previous anti-D administration). Antibody status must be checked beforehand.
- When stock is available, should be offered to ALL non-sensitised Rh-Negative women with positive or unknown fetal Rhesus status irrespective of previous doses administered for sensitising events.

  - Single dose of 500 IU (at 28-30 weeks) or
  - Two doses of 250 IU (at 28 and at 34 weeks)

NB. Anti-D administration in time of stock shortage:

The collective aim is to ensure that sufficient stock is ALWAYS available, nationwide, for the indications that have the greatest impact in terms of prevention of sensitisation, by restricting its' use for indications that have the smallest impact.

1. *Withhold RAADP*
2. *If patient's family is completed and tubal ligation (or hysterectomy) performed: can withhold anti-D after delivery but only after full disclosure of risks and after consent is obtained*
3. *Restrict anti-D administration for miscarriage to more than 12 weeks*

ALWAYS

- *Avoid unnecessary interventions that could cause FMH or increase the size of FMH*
- *Careful matching for blood products to avoid transfusion of Rhesus-positive blood products*
- *Avoid manual removal of placenta at caesarean section (replace with gentle cord traction)*
- *Let placental side of cord bleed freely after delivery of the baby*
- *Determine baby's Rhesus status at birth to avoid giving anti-D unnecessarily*

If no stock is available (contact other healthcare facilities to try and obtain anti-D if not available at the local facility) for a woman who has a clear indication to receive anti-D (see under sensitising events) – inform her of the lack of suitable prevention and arrange indirect Coombs test after 3 months so she can receive counselling about the consequences if seroconversion has occurred.

Sensitised mother - Fetal haemolytic disease

- Should be managed in consultation with a Fetal specialist.
- Mild disease: deliver at 38 weeks or later (with continued surveillance until delivery)
- Severe disease requiring intrauterine transfusion: deliver at 34-36 weeks, depending on timing of last in utero transfusion.
- **NB. Inform paediatrician of maternal red cell antibodies as baby may be severely anaemic at birth and/or at risk of severe jaundice or prolonged and late onset anaemia.**
- **NB. Send cord blood for urgent blood group, Rhesus, direct Coombs (if not already done by cordocentesis prenatally) and urgent FBC and bilirubin to guide early management.**

References:

1. BCSH guideline for the use of anti-D immunoglobulin. H. Qureshi, E. Massey, D. Kirwan, T. Davies, S. Robson, J. White, J. Jones & S. Allard. Transfusion Medicine, 2014, 24, 8–20
2. NDOH Circular notice – Anti-D immunoglobulin, ref. EDP082018/01, August 2018
3. http://hospital.blood.co.uk/media/29185/inf1665-blood-groups-and-red-cell-antibodies-in-pregnancies.pdf

Authorship

These guidelines were drafted by a clinical team from Mediclinic and were reviewed by a panel of experts from SASOG and the BetterObs™ clinical team in 2019 and revised by the scientific subcommittee of BetterObs™ in 2022. All attempts were made to ensure that the guidance provided is clinically safe, locally relevant and in line with current global and South African best practise. Succinctness was considered more important than comprehensiveness.

All guidelines must be used in conjunction with clinical evaluation and judgement; care must be individualised when appropriate. The writing team, reviewers and SASOG do not accept accountability for any untoward clinical, financial or other outcome related to the use of these documents. Comments are welcome and will be used at the time of next review.

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History and version control

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Expert External Obstetrician	1.1	Validated	2017 01 01
A. Hall	1.2	Rebranded to Clinical Guideline and edited	2019 12 01
SASOG Scientific committee Dr C Groenewald	2.1	Reviewed Anti-D antibody titer has been changed from 1:8 to 1:16 Heading in times of shortage was added	2022 08 01

Approved by

Department/ Area/ Group/ Forum	Representative name	Signature	Designation	Date
Clinical Department	Dr Gerrit De Villiers		Chief Clinical Officer	2023 04 27