Protocol for Anti-D immunoglobulin use for the prevention of haemolytic disease of the fetus and newborn in Iraqi hospitals

Iraq is one of the countries which use anti –D immunoglobulin (D Ig) routinely in the postpartum period, though this use was subjected to many obstacles throughout the previous years due to non-availability of this injection for many reasons.

Following routine post-partum administration of anti-DIg, the rate of alloimmunisation dropped to approximately 2%. A further reduction in the sensitisation rate ranging from 0·17 to 0·28% was achieved by introducing routine antenatal prophylaxis during the third trimester of pregnancy. Associated with this reduction in sensitisation is a reduction in mortality associated with hemolytic disease of newborns (HDN), from 46/100000 births to 1·6/100000 births.

General principles:

1- Unsensitised D negative woman should be monitored monthly until 28weeks gestation and fortnightly thereafter.
2- Prophylactic anti-D Ig, when need to be given, it should be given to a previously non-sensitised D negative woman within 72h of exposure to the potential sensitising event, delivery or fetal death. Exceptionally if this deadline has not been met some protection may be offered if anti-D Ig is give up to 10 days after the event (Grade 1 C).
3- Women with anomalous Rh D typing results should be treated as D negative until confirmatory testing is completed.
4- The available formula in Iraq, is anti-D Ig (300 µg) = (1500 IU), for intramuscular injection only and each 1 µg is equivalent of 5 IU.
5- Feto-maternal haemorrhage (FMH) test (Kleihauer Test), to detect fetal cells in the maternal circulation, should be undertaken on all D negative women delivering D positive infants and when a woman experiences a potentially sensitising event after 20 weeks gestation to determine if additional doses of anti-D Ig are required.
    - **<u>If FMH > 4 mL</u>** is detected, follow-up samples are required at 72h following an intramuscular (IM) dose to check for clearance of fetal cells (Grade 1C). The additional dose should be calculated as 125 IU / IM for each mL of fetal red cells detected (minimum 500 IU).
    - In the event of further intermittent uterine bleeding, estimation of FMH should be carried out at two weekly intervals and if the two weekly FMH test shows the presence of fetal cells, additional anti-D Ig should be administered to cover the volume of FMH. The additional dose should be offered regardless of the presence or absence of passive anti-D in maternal plasma.
    - If new symptoms develop suggestive of a sensitising event in addition to continual uterine bleeding (e.g. abdominal pain associated with a

significant change in the pattern or severity of bleeding) then it should be managed as an additional sensitising event with an appropriate additional dose of antiD Ig and estimation of FMH.

- Each new sensitising event should be managed with an appropriate additional dose of anti-D Ig regardless of the timing or dose of anti-D Ig administered for a previous event.

6- Where anti-D is detected in a blood sample from a pregnant woman, further history should be taken and investigation undertaken to establish whether this is immune or passive (as a result of previous injection of anti-D Ig). If no clear conclusion can be reached as to the origin of the anti-D detected, then the woman should continue to be offered anti-D prophylaxis on the assumption that it may be passive. (Grade 2C).

7- **POTENTIALLY SENSITISING EVENTS REQUIRING ANTI-D IG PROPHYLAXIS:**

- Amniocentesis, chorionic villus biopsy and cordocentesis.
- Antepartum haemorrhage/Uterine (PV) bleeding in pregnancy.
- External cephalic version.
- Abdominal trauma (sharp/blunt, open/closed).
- Ectopic pregnancy (whatever method of treatment)
- Evacuation of molar pregnancy.
- Intrauterine death and stillbirth.
- In-utero therapeutic interventions (transfusion, surgery, insertion of shunts, laser).
- Miscarriage, threatened miscarriage. Unless the fetus is viable and bleeding is mild, painless and completely stops before 12weeks gestation.
- Therapeutic termination of pregnancy (Medical or surgical).
- Delivery – normal, instrumental or Caesarean section.

Summary of Key Recommendations:

1- For pregnancies **<12 weeks** gestation, as ectopic pregnancy, molar pregnancy, therapeutic termination of pregnancy and in cases of uterine bleeding where this is repeated, heavy or associated with abdominal pain, to give **a minimum dose of 250 IU for these events without feto-maternal (FMH) testing (Grade 2C).**

2- For potentially sensitizing events **between 12 & 20 weeks** gestation. **A minimum dose of 250 IU for these events without feto-maternal (FMH) testing.** If the women presented with continual uterine bleeding, should be given at least 250 IU at a minimum of 6 weekly intervals (Grade 2C).

3- Previously non-sensitized, D negative pregnant women who have had a potentially sensitizing event **after 20 weeks** of gestation, **to be given a minimum dose of 500 IU with a test for FMH is required (Grade 2C).** Appropriate tests for FMH should be carried out, and additional dose(s) of anti-D Ig should be administered as necessary.

4- All D negative pregnant women who have not been previously sensitised should be offered a routine antenatal prophylaxis with anti-D Ig (RAADP) using a single dose of anti-D Ig, 1500 IU should be administered **between 28 and 30 weeks** (Grade 1B). It is important that the 28-week sample for blood group and antibody screen is taken prior to the routine prophylactic anti-D Ig injection being given. (Grade 2C).

* Routine Antenatal Anti-D Ig Prophylaxis (RAADP) should be regarded as a separate entity and administered regardless of, and in addition to, any anti-D Ig that may have been given for a potentially sensitizing event (Grade 2C).

* A minimum of 500 IU anti-D Ig should be administered within 72h for any potentially sensitising events regardless of whether the woman has already received RAADP at 28weeks.

* In the event of continual uterine bleeding which is clinically judged to represent the same sensitising event, with no features suggestive of a new presentation or a significant change in the pattern or severity of bleeding, such as the presence of abdominal pain or another clinical presentation, a minimum dose of 500 IU anti-D Ig should be given at six weekly intervals.

5- Following birth, ABO and Rh D typing should be performed on cord blood and If a cord blood sample is not collected for any reason, a heel prick sample from the baby should be obtained as soon as possible and the **baby is confirmed to be D positive, all D negative, previously non-sensitized women should be offered at least 500 IU of anti-D Ig within 72h following delivery. Maternal samples should be tested for FMH and additional dose(s) given as guided by FMH tests (Grade 1B).**

- A direct antiglobulin test (DAT) on the cord blood sample is not routinely performed since it may be positive in a proportion of cases because of antenatal prophylaxis with anti-D Ig. However, a DAT should be performed if haemolytic disease of the newborn is suspected or anticipated because of a low cord blood haemoglobin concentration &/or the presence of maternal immune red cell antibodies.
- Maternal samples for confirmatory ABO and Rh D type and FMH testing should be collected after sufficient time has elapsed for any FMH to be dispersed in the maternal circulation. A period of 30–45min is considered adequate and the samples should ideally be taken within 2 h of delivery primarily to ensure that the sample is taken prior to woman's discharge from the hospital.
- If the baby's blood group is D positive, a minimum of 500 IU anti-D Ig should be administered to previously non-sensitised D negative women, within 72h of the delivery.
- Administration of postpartum anti-D Ig prophylaxis should not be affected by previous routine antenatal anti-D Ig prophylaxis or by antenatal anti-D Ig given for a potentially sensitising event. A dose of 500 IU, IM is considered sufficient to treat a FMH of up to 4mL fetal red cells. Where it

is necessary to give additional doses of anti-D Ig, as guided by tests for FMH, the dose calculation is traditionally based on 125 IU anti-D Ig/mL fetal red cells for IM administration. If FMH test not available then better to give 1500 IU.

6- In the event of an intrauterine death (IUD), where no sample can be obtained from the baby, an appropriate dose of prophylactic anti-D Ig should be administered to D negative, previously non-sensitized women within 72h of the diagnosis of IUD, irrespective of the time of subsequent delivery (Grade 1C).

7- Management of transfusion of D positive blood components to D negative girl or women of childbearing potential: D positive platelet transfusions.

Whenever possible, D negative platelets should be transfused to D negative girls or women of child bearing potential, who need a platelet transfusion. Occasionally, if the appropriate product is not available or its availability would cause unacceptable delay, it may be necessary to transfuse D positive platelets. In these circumstances, prophylaxis against possible sensitisation to the D antigen by red cells contaminating the platelet product should be given. A dose of 250 IU anti-D immunoglobulin should be sufficient to cover up to five adult therapeutic doses of D positive platelets given within a 6-week period (Grade 2B).

In severely thrombocytopenic patients with platelet count of ≤30 × 109/L, anti-D Ig should be given subcutaneously, or IV if a preparation suitable or IV route is available, to avoid the risk of IM bleed following IM injection. It is not necessary to administer anti-D Ig to D negative females without childbearing potential.

8- Inadvertent transfusion of D positive blood to D negative women of childbearing potential:

- When less than 15mL have been transfused, the appropriate dose of IM anti-D Ig may be given. When more than 15mL have been transfused, it is preferable to use the larger anti-D immunoglobulin preparation (1500 or 2500 IU); however, IV anti-D immunoglobulin is the preparation of choice, achieving adequate plasma levels immediately. The quantitation of D positive red cells should be performed by flow cytometry (FC) after 72 h if an IM dose has been given (Grade2C), and further anti-D Ig given until there are no detectable D positive red cells in circulation.
- When more than one unit of D positive blood has been transfused, a red cell exchange transfusion should be considered to reduce the load of D positive red cells in the circulation and the dose of anti-D Ig required to prevent immunisation. In this situation advice should be sought from a specialist in Transfusion Medicine, and the patient should be counselled regarding the implications of both non-intervention (for future pregnancies) and of treatment, including any hazards from receiving donated blood, the exchange procedure itself and of larger doses of anti-D Ig. Shortly after the exchange transfusion, the residual volume of D positive

red cells should be estimated using FC. Passive anti-D Ig given in large doses may remain detectable and tests for immune anti-D may not be conclusive for several months

Safety of anti-D Immunoglobulin:

-The majority of reported adverse events were not considered serious.
-There is no evidence to suggest that anti-D Ig administered to women during pregnancy is harmful to the fetus.
- Allergic reactions are very rare but severe hypersensitivity including anaphylaxis may occur.
- If symptoms of allergic or early signs of hypersensitivity reactions (including generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis) develop, administration of anti-D must be discontinued immediately and appropriate treatment instituted.

Informed consent:

All pregnant women must be offered written and verbal information about anti-D Ig to inform their decision about receiving anti-D Ig. Maternal consent must be obtained prior to giving anti-D Ig, and the woman's decision to either accept or decline the injection should be clearly recorded by the healthcare professional.

Future needs:

1- The need for availability of smaller doses injection as 250 and 500 IU.
2- Availability of kleihauer test for better detection of the amount of FMH and estimation for the need of extra dose of Anti D.
3- In recent years, advancements in fetal blood group genotyping using cell free fetal DNA (cff DNA) from maternal blood samples taken at 16–20week gestation, have made it possible to determine fetal D type with a diagnostic accuracy of around 96%, to avoid giving all previously non-sensitised, D negative, pregnant women a RAADP while they are carrying a D negative child.

References:

1- BCSH guideline for the use of anti-D immunoglobulin for the prevention of haemolytic disease of the fetus and newborn. *Transfusion Medicine* 2014; 24: 8–20.
2- Rhesus D Prophylaxis, The Use of Anti-D Immunoglobulin for (Green-top Guideline No. 22). **Published:** 27/04/201.

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