

ICOG FOGSI Recommendations for Good Clinical Practice

Use of Anti-D Immunoglobulin for Rh Prophylaxis

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This Recommendation represents the opinion of the members which was arrived at after careful consideration of the evidence available. It is aimed at establishing the basic minimum care required for a Rh negative pregnant woman to prevent sensitization during and after pregnancy. The recommendation is based on the current recommendations from the Royal College of Obstetricians and Gynaecologists and the American College of Obstetricians and Gynaecologists. Appropriate modifications have been made taking into account the cultural and financial diversity present in our country with the final aim being to provide benefit to maximum number of patients.

All FOGSI members are expected to refer to it when exercising their clinical judgment. The guidance does not, however, override the individual responsibility of health professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and her family.

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1. Introduction

The Rhesus factor was discovered by Landsteiner and Weiner in 1940, and Levine and associates confirmed in 1941 that erythroblastosis was due to maternal isoimmunization against paternally inherited fetal factors. The subsequent development of effective maternal prophylaxis was attributed to Finn and associates (1961), Freda (United States).

CDE (Rhesus) Blood Group System.

This system includes five red cell proteins or antigens: C, c, D, e and E. Rh – or D-negativity is defined as the absence of the D-antigen

A D-negative woman delivered of a D-positive, ABO –compatible infant has a likelihood of isoimmunization of 16 percent; 2% will be immunized by the time of delivery, 7% will have anti-D antibody by 6 months postpartum, and the remaining 7% will be “sensitized”. In sensitized women, anti D antibodies are produced at such a low level that they are not detected during or after the index pregnancy but instead are identified early in a subsequent pregnancy.

There are approximately 40 antibodies to RBC's that can cause haemolytic disease of fetus and newborn (HDFN), but the main players are Rhesus (Rh) D antibodies, Kell antibodies and antibodies to Rhc.¹

2. Extent of the problem in India

Worldwide, with the introduction of routine prophylaxis, the incidence of RhD alloimmunization has reduced dramatically. However, in India a lot still needs to be done.

To study the Indian scenario, K S Joseph² from CMC Vellore, used decision analysis techniques to estimate the extent of the problem. He analysed that the Anti D immunoglobulin requirement for the year 2000 was expected to be 8,03,000 doses post partum and 4,43,000 doses after abortion, per year. However the total number of units of Anti D immunoglobulin sold in the Indian market in 2000 was 1,15,000 units. (Market Research report . RH immunoglobulin market Data April 2005). Hence there is gross underutilization of Anti D prophylaxis in India.

Deka D etal³ observed that failure to administer post natal anti D prophylaxis was responsible for RhD alloimmunization in more than 50% of cases, followed by failure to administer Anti D after MTP (10%).

With postpartum prophylaxis the risk of isoimmunization will reduce to 1.5%. Similarly antenatal prophylaxis can reduce the risk to .18% (Deka etal)

3. Sensitizing events

(highlighted The conditions associated with high risk of fetomaternal haemorrhage)

- First trimester bleeding or miscarriage.
- Medical or surgical termination of first trimester pregnancy
- Ectopic pregnancy
- Vesicular mole
- Second trimester MTP.
- **Antepartum haemorrhage**
- **External cephalic version**
- **Closed abdominal injury**

- Intra uterine death
- Normal or caesarean delivery
- **Manual removal of placenta**
- **Twin deliveries**
- **Mismatched platelet or blood transfusion.**

4. Antenatal prophylaxis and protection

4.1 First trimester events:

- Significant bleeding during threatened abortion
- Spontaneous miscarriage
- Medical termination of pregnancy (Anti D to be given soon after misoprostol administration)
- Surgical termination of pregnancy
- Ectopic pregnancy
- Vesicular mole; particularly if it is a partial mole
- Chorion biopsy
- Embryo reduction

In all these events a dose of 50 – 100 mcg should be given, as soon as possible after the sensitizing event. Evidence that women are sensitized after uterine bleeding in the first 12 weeks of pregnancy, where the fetus is viable and the pregnancy continues is scant. (threatened abortion)⁴, however we feel it is safer to give an injection of 50mcg anti-D in these cases.

4.2 Second Trimester events:

Routine antenatal prophylaxis; All patients should be tested for Rh sensitization at the time of registration and again at 28 weeks.

All non sensitized women should be given 100 mcg Anti D at 28 weeks and again at 34 weeks or a single dose of 300 mcg at 28 weeks.

A woman with 'weak D' (also known as Du – positive,) need not receive anti-D.

It is desirable to offer antenatal prophylaxis to all Rh negative women who are nonsensitized, and have a Rh positive partner.

4.3 Sensitizing events during second or third trimester.

- Amniocentesis
- Abruptio placentae
- Blunt trauma
- Intrauterine fetal death
- External cephalic version
- Placental pravia with bleeding

All these events should be covered by an Anti-D injection of 300 mcg atleast. (This covers 15ml of fetal RBC's or 30 ml of fetal blood.) Ideally, a test for the size of fetomaternal haemorrhage should be done. 10 mcg additional anti D should be given for every additional 0.5 ml fetal RBC's in maternal circulation.

5. Postpartum prophylaxis

All Rh D negative patients who deliver a Rh-D positive baby either by a normal delivery or a caesarean section should receive 300 mcg of Anti D within 72 hours of delivery.

6. Administration and preparations

Intramuscular anti-D Ig should preferably be given into the deltoid muscle as injections into the gluteal region often only reach the subcutaneous tissues and absorption may be delayed.

For successful immunoprophylaxis, anti-D Ig must be offered as early as possible and preferably within 72 hours after the sensitising event. In case the injection is missed in the first 72 hours, it should be administered as early as possible as this may still provide some protection. If a woman for some reason, refuses to take the injection her refusal should be documented. Women who are already sensitised should not be given anti-D Ig.

Women who have a weak expression of the Rh blood group (Du positive) do not form anti-D and do not therefore require prophylaxis. It should be noted that anti-D Ig does not protect against the development of other antibodies which can cause haemolytic disease of the newborn.

7. Test for the size of fetomaternal haemorrhage

Studies have shown that 99.3% of women have a fetomaternal haemorrhage less than 4ml at delivery. Up to 50% of larger fetomaternal haemorrhages occur after normal deliveries⁵

Tests to estimate the size of the fetomaternal haemorrhages are recommended in many countries including the UK, the USA, Canada, France and Ireland, although not in India and most European countries. While the Kleihauer acid elution test which detects foetal haemoglobin (HbF) is the test usually undertaken in the UK and Canada, tests which specifically identify Rh positive red cells are used in the USA. The amount of fetal haemorrhage can be calculated from the results of a kleihauer-Betke Stain using the formula:

$$\text{Fetal Blood Volume} = \frac{\text{Maternal Blood volume} \times \text{maternal haematocrit} \times \% \text{ fetal cells in KB}}{\text{Newborn haematocrit}}$$

In India, a standard postnatal dose of 300 mcg is used with no requirement for a routine Kleihauer test. Unfortunately, this policy does not take account of the fact that up to 0.3% of women have a fetomaternal haemorrhage greater than 15ml of fetal RBC's, which will not be covered by 300 mcg of anti-D Ig. Hence, if the 300 mcg dose is implemented without a test for quantitative fetomaternal haemorrhage, few women each year in India will receive less protection than they should.

Flow cytometry offers an alternative technique for quantifying the size of FMH⁶ It has a number of advantages in that results are more accurate and more reproducible than those from the Kleihauer test and that it detects Rh D positive cells, making it particularly helpful in patients with high HbF levels. However, flow cytometry is not readily available in our country as it is in the west.

The rosetting technique is a relatively simple serological method which offers another alternative for quantifying fetomaternal haemorrhage of Rh D positive red cells greater than 4ml.

There is poor evidence regarding testing for postpartum fetomaternal haemorrhage, as the costs benefit of such testing has not been determined.⁷

8. Areas to focus on

1. Even today a larger number of women, who should be protected against Rh immunization, are not receiving Anti- D.
2. There is more awareness among doctors and patients about post delivery prophylaxis, however prophylaxis after a spontaneous abortion, MTP, ectopic pregnancy, and antenatal use of anti-D is still lacking. (About 10 – 20%) in an Indian survey.
3. Antenatal prophylaxis is recommended.
4. It is desirable to check for quantity of FMH but standard dose will cover most of the cases.
5. Information and counselling of all young girls and women at school and college levels should include the importance of Rh group and the need for Rh prophylaxis.
6. During the antenatal period, all Rh–ve patients should be counselled about the importance of Rh prophylaxis and haemolytic disease of the foetus and new born.
7. Anti D should be given into the deltoid or the antero lateral thigh as there is delayed absorption when injected into the gluteal muscle.

9. Recommendations

1. All patients coming for MTP, medical or surgical, should have knowledge of documentation of blood group and Rh
2. Antenatal prophylaxis should be offered to all Rh negatives recommended. A dose of 100 mcg at 28 and 34 weeks or a single dose of 300 mcg at 28 weeks should be administered.
3. 50 - 100 mcg anti -D injection should be given after all sensitizing events in first trimester.
4. For mid and late pregnancy sensitizing events and post partum, the non sensitized Rh negative patient should receive 300 mcg anti D.
5. Due to the lack of availability of fetomaternal haemorrhage volume testing, these Recommendations suggest to administer higher doses in order to protect a majority of patients in high risk situations.

10. References

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