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# Anti-D Immunoglobulin for Rh Prophylaxis: Key Practice Points

**Dear Friends,**

Anti-D immunoglobulin prophylaxis is an approved treatment for Rhesus-negative women to prevent sensitization to the Rh(D) blood group antigen. The success rate of Rh immunoprophylaxis is approximately 98%, and the incidence of Rh isoimmunization during pregnancy is declining. However, despite the availability and use of Anti-D immunoglobulin, the burden of Rh disease continues. Hence, developing well-defined guidelines and practice points and adhering to them is essential in managing Rh alloimmunization throughout India.

Considering the need of the hour, FOGSI under the Dheera and FOGSI for all, initiated the development of this informative and concise key practice point guideline. The objective of the guideline is to provide healthcare professionals with practical guidance on the use of anti-D immunoglobulin as immunoprophylaxis to prevent sensitization to the D antigen during pregnancy or at delivery to prevent hemolytic disease in the fetus and newborn.

The expert panel of doctors discussed various aspects associated with Anti-D immunoprophylaxis treatment, such as Rh D typing, sensitizing events during anti-D prophylaxis, routine antenatal Anti-D prophylaxis, and post-partum anti-D immunoglobulin administration. Moreover, the panelist proposed a flowchart that explained the prophylactic use of Rh D immunoglobulin in pregnancy care. This document will journey on the exclusive practice points to be followed while using anti-D immunoprophylaxis and recommendations that were derived by the expert consensus.

Hope the content provides much-required insights and updates regarding the use of Anti-D Immunoglobulin as an Rh immunoprophylaxis.

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President, FOGSI 2022

# ANTI-D IMMUNOGLOBULIN FOR RH PROPHYLAXIS: KEY PRACTICE POINTS

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| President | : | Dr. S. Shanthakumari |
| Moderators | : | Dr. Basab Mukherjee, Dr. Uday Thanawala |
| Panel Members | : | Dr. Ritu Khanna, Dr. Uma Ram, Dr. Jaishree Gajaraj, Dr. Parag Biniwale, Dr. Chinmayee Ratha |
| Clinical Reporter | : | Dr. Rohan Palshetkar |


From left to right: Dr. Ritu Khanna, Dr. Chinmayee Ratha, Dr. Basab Mukherjee, Dr. S. Shanthakumari, Dr. Parag Biniwale, Dr. Rohan Palshetkar, Dr. Uma Ram, Dr. Jaishree Gajaraj

# Anti-D Immunoglobulin for Rh Prophylaxis: Key Practice Points

## Introduction and the magnitude of problem in India

### Hemolytic disease of the fetus and newborn (HDFN) and the need for anti-Rh(D) immunoglobulin

During pregnancy, rhesus D (Rh) D-negative women who carry an Rh D-positive fetus are at risk of being sensitized to produce immune anti-D antibodies following a feto-maternal hemorrhage (FMH), leading to hemolytic disease of the fetus and newborn (HDFN).[1] HDFN induces fetal anemia with increased risks of fetal death, severe neonatal hyperbilirubinemia, and kernicterus.[2]

According to a recent systematic study by Bhutani et al., there are 3.7 lakh cases of Rh hemolytic disorder worldwide each year. India is responsible for about 56,672 of these years.[3] Furthermore, a hospital-based study reported an overall incidence of Rh alloimmunization to be nearly 1.3% in north Indian women during the antenatal period. The Rh alloimmunization rate was 10.7% and 0.12% in Rh-negative and Rh-D positive mothers, respectively.[4]

The incidence of post-pregnancy Rh allo-immunization has decreased to 1%–2% after postpartum anti-D immunoprophylaxis.[2] Evidence shows that the incidence of Rh immunization during pregnancy further reduced from 1.8% to 0.14% with Rh immunoprophylaxis 300 µg of anti-D immunoglobulin at 28 weeks. Researchers revealed that the success rate of Rh immunoprophylaxis was 98.4%–99%.[5,6] The prophylaxis with anti-D immunoglobulin effectively reduces the risk of sensitization in the subsequent pregnancy of Rh-negative mother irrespective of the ABO status of mother and baby.[7] A strong immunosuppressive effect is exerted with anti-D immunoglobulin prophylaxis; it results in a primary immunological response upon exposure to the D antigen rather than a secondary one as if the immune system had never come into contact with the D antigen.[8]

However, despite the availability and use of Anti-D, the burden of Rh disease continues. This emphasizes the need for adherence to guidelines and practice points.

## Objectives of the guideline

The objective of this guideline is to provide healthcare professionals with practical guidance on the use of anti-D immunoglobulin as immunoprophylaxis to prevent sensitization to the D antigen during pregnancy or at delivery for the prevention of HDFN.

## Methods

### Details of Expert consensus meeting

| | |
|---|---|
| Dr. S. Shanthakumari | President |
| Dr. Basab Mukherjee | Moderator |
| Dr. Uday Thanawala | Moderator |
| Dr. Ritu Khanna | Panelist |
| Dr. Uma Ram | Panelist |
| Dr. Jaishree Gajaraj | Panelist |
| Dr. Parag Biniwale | Panelist |
| Dr. Chinmayee Ratha | Panelist |
| Dr. Rohan Palshetkar | Clinical Reporter |

## Blood group and Rh D typing

- Blood Grouping and Rh status of the mother should be done at the first antenatal visit.
- The woman should be informed of her blood group and Rh status and she should be educated with informative leaflets if she is Rh-negative.
- All Rh-negative women should ideally have an indirect coomb's test (ICT) for screening of Rh antibodies at 1st antenatal visit. This is preferably done irrespective of the husband's Rh status to ensure that prior sensitization events are not missed.
- If ICT is negative at the first visit, then ICT should be repeated at 28 weeks.
- However, if a woman has had anti-D immunoglobulin following a sensitizing event or routine antenatal prophylaxis, subsequent ICT is preferably not done. If ICT is done after Anti-D prophylaxis, the results should be interpreted with specialist consultation.
- At the time of delivery for all Rh-negative mothers, documentation of the blood group and Rh status of the neonate **MUST** be done.

## Sensitizing events requiring anti-D prophylaxis

Outside of routine provision, Rh D-negative pregnant women can receive anti-D immunoglobulin during pregnancy when potentially sensitizing events occur. A sensitizing event in Rh D-negative pregnant women leads to developing anti-D antibodies due to maternal-fetal blood exchange.[9] The BSCH and RCOG guidelines recommend that anti-D immunoglobulin be administered as soon as possible after a potentially sensitizing event, ideally within 72 hours of the event. If, exceptionally, this deadline has not been met, some protection may be offered if anti-D immunoglobulin is given up to 10 days after the sensitizing event.[10,11]

| **Potential sensitizing events requiring anti-D prophylaxis[11,12]** | |
|---|---|
| **Before 20 weeks of Gestation** | |
| • Significant bleeding during threatened abortion<br>• Spontaneous miscarriage<br>• Medical termination of pregnancy<br>• Surgical termination of pregnancy<br>• Ectopic pregnancy<br>• Hydatidiform mole**<br>• Chorion villus sampling<br>• Embryo reduction<br>• Amniocentesis<br>• Other invasive fetal procedures | The recommended dose is 150mcg* (750IU) intramuscularly in the deltoid |
| **After 20 weeks of Gestation** | |
| • Abruptio placentae<br>• Blunt trauma<br>• Intrauterine fetal demise<br>• External cephalic version<br>• Placenta Previa with bleeding<br>• Invasive fetal procedures | The recommended dose is 300mcg (1500IU) intramuscularly in the deltoid |
| *In cases where 150mcg dose is not available, then full dose of 300mcg should be given. ** In cases of complete mole, Anti-D need not be given. However, histopathology report may take longer to come, therefore it is better to give the Anti-D prophylaxis to err on the side of caution. | |

## Special circumstances

- In women undergoing tubal ligation, Anti-D prophylaxis must be given to prevent isoimmunization. This is important if the woman chooses to have another pregnancy, ligation fails, or she requires future cross-matching of blood products.
- In cases of recurrent sensitizing events, a repeat dose is required if the event is 3 weeks apart.
- If Rh D-positive blood or blood components are transfused, prevention of sensitization protocol should be done with the consultation of a hematologist.
- Some women have conflicting Rh status reports or have weak Anti-D. Such women are best discussed with a hematologist or considered Rh-negative and treated with Anti-D immunoglobulin.
- In women in whom there is a contraindication to an intramuscular (IM) injection (thrombo-cytopenia, blood dyscrasias), appropriate IV preparation of the Anti-D immunoglobulin can be used with hematologist consultation.

## Quantifying FMH

During sensitization events in the first trimester, less than 4 ml of FMH is expected. At the time of delivery, FMH is usually less than 10ml.

Particular circumstances may increase FMH volume, such as manual removal of the placenta, lower segment cesarean section (LSCS), multiple pregnancies, intrauterine uterine fetal demise, and abruptio placenta. Ideally, in these cases, FMH testing should be done using Kleihauer Betke or flow cytometry. Since most units may not have facilities to measure FMH, 300mcg is expected to reasonably cover the excess FMH. In case the clinician suspects larger FMH, it would be prudent to consult with a hematologist to decide the dose.

## Routine Antenatal Anti-D Prophylaxis (RAADP)

Rh-negative women may have silent bleeds in the 3rd trimester resulting in iso-immunization. To protect against this, antenatal Anti-D prophylaxis was introduced. A single-dose regimen of 300mcg IM in the deltoid is effective, economical, and offers better compliance. A single-dose regimen is equally effective as a two-dose regimen.[13]

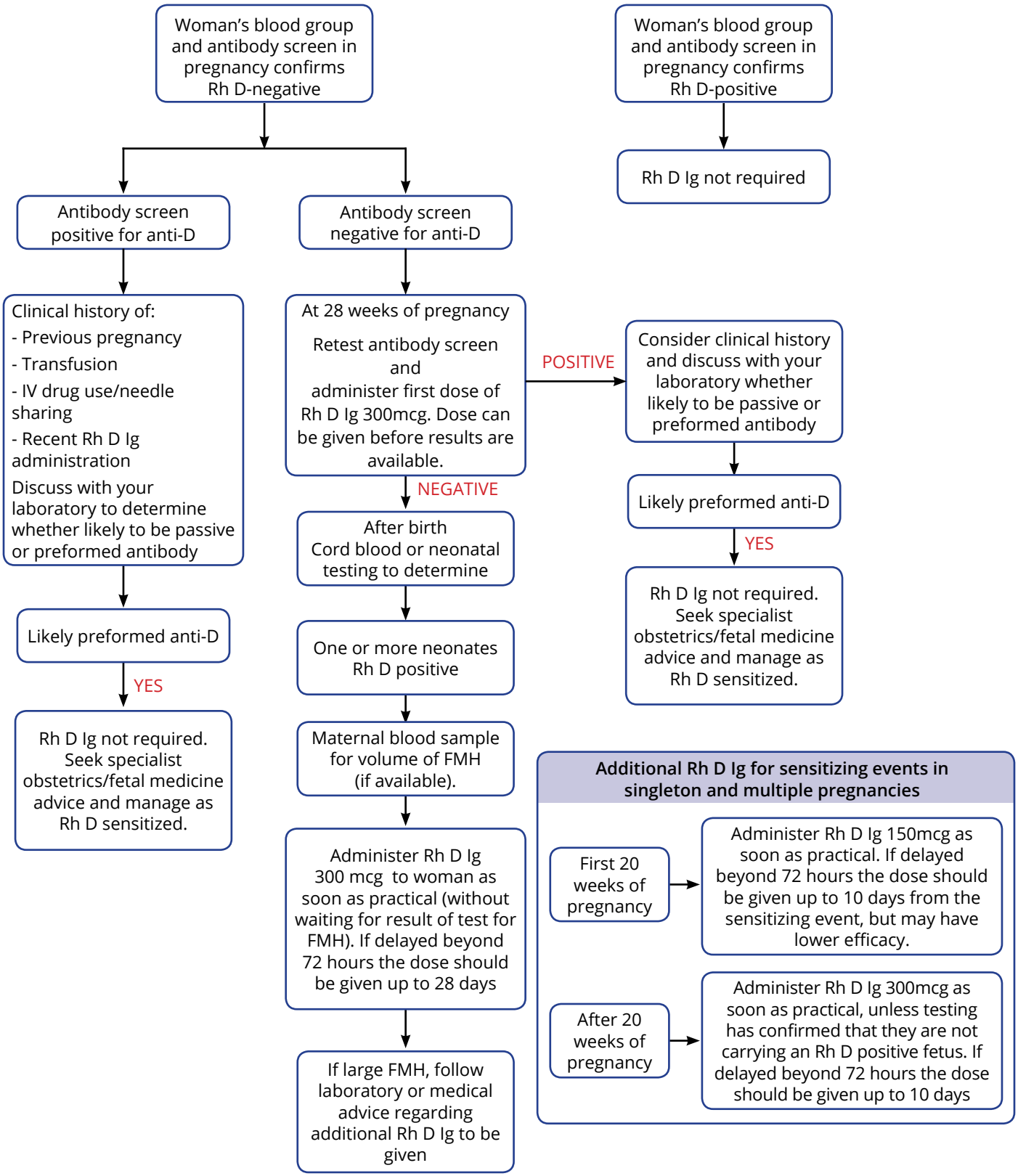
RAADP should be given only if the ICT at 28 weeks is negative.

## Post-partum anti-Rh (D) immunoglobulin administration

For all Rh-negative mothers, cord blood testing of the baby should be done. If the baby is Rh-positive, 300mcg IM should be administered through deltoid within 72 hours. If anti-D administration is missed during the 72-hour window, it is advisable to give it as soon as possible. Partial to complete benefit has been noted for up to 10 days and some benefit for up to 28 days.[14,15]

If delivery occurs within 3 weeks of the (RAADP) anti-D administration, routine post-natal prophylaxis can be withheld in the absence of excessive FMH. If quantification of excessive FMH is not possible, the standard post-partum dose may be given.[14]

# Flowchart for the prophylactic use of Rh D immunoglobulin in pregnancy care[16]




FMH, fetomaternal haemorrhage; Ig, immunoglobulin; IU, international units; IV, intravenous.
anti-D - refers to circulating antibodies; RHD - refers to genotype; Rh D positive/negative - refers to blood type.
Woman s blood group and antibody screen in pregnancy confirms Rh D positive Rh D Ig not required

## Ethical & medicolegal considerations

- Informed verbal consent must be taken before administering the anti-D antenatal. It must be documented in her discharge card and case sheet (preferably with the details of the product).[11]
- In case of refusal, written consent regarding refusal must be documented and signed by the patient.
- There is no evidence to suggest that Anti-D administered to women during pregnancy is harmful to the mother and fetus.[11]

## Expert recommendations

- Blood group, Rh status, and ICT must be done at 1st booking. If ICT is negative, it should be repeated at 28 weeks. (Good practice point)
- The dosage of Anti-D before 20 weeks is 150mcg IM deltoid, and post 20 weeks is 300mcg IM deltoid. If 150mcg is not available, then 300mcg should be given. (Good practice point)
- In cases of recurrent sensitizing events, a repeat dose is required only if the event is 3 weeks apart. (Level III C)
- RAADP should be offered to all non-sensitized RhD-negative women. (Grade B, Evidence level 2++)
- Routine administration of 300mcg of Anti-D must be given at 28 weeks in Rh-negative mother after doing ICT. (Good practice point)
- The prophylaxis with anti-D immunoglobulin effectively reduces the risk of sensitization in the subsequent pregnancy irrespective of the ABO status of the mother and baby. (LEVEL I C)
- Blood group identification and Rh D typing should be performed on the cord or placental vessel. (LEVEL I C)
- Maternal administration of anti-D prophylaxis within 72 hours of delivery with an Rh D-positive newborn, unless already sensitized. (LEVEL I C)

| Level | Type of evidence[14] |
|---|---|
| I | Evidence obtained from at least one properly designed randomized controlled trial. |
| II-1 | Evidence obtained from well-designed controlled trials without randomization. |
| II-2 | Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group. |
| II-3 | Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence. |
| III | Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees. |
| **Level** | **Grade of evidence** |
| Level-A | Recommendations are based on good and consistent scientific evidence. |
| Level-B | Recommendations are based on limited or inconsistent scientific evidence. |
| Level-C | Recommendations are based primarily on consensus and expert opinion |

| Grade B[15] | Level of Evidence: $2^{++}$ |
|---|---|
| • A body of evidence that includes studies rated as $2^{++}$, is directly applicable to the target population and demonstrates overall consistency of results, **or**<br>• Extrapolated evidence from studies rated as $1^{++}$ or $1^{+}$ | • High quality systematic reviews of case-control or cohort studies<br>• High quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal |

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