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Prevention of Rh D alloimmunization

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Clinical management guidelines for obstetrician–gynecologists

Before the introduction of anti-D immune globulin (formerly referred to as Rho[D] immune globulin), hemolytic disease of the fetus and newborn affected 9–10% of pregnancies and was a major cause of perinatal morbidity and mortality (1, 2). Among Rh D-alloimmunized pregnancies, mild-to-moderate hemolytic anemia and hyperbilirubinemia occur in 25–30% of fetuses/neonates, and hydrops fetalis occurs in another 25% of such cases (3). The administration of anti-D immune globulin is successful in reducing the rate of developing antibodies to the D antigen. Protocols for the antenatal and postpartum administration of anti-D immune globulin have been responsible for the dramatic decrease in alloimmunization and subsequent hemolytic disease in the past two decades. However, Rh D alloimmunization remains a clinical concern, with many cases due to failure to follow established protocols. Finally, there is concern that overuse of anti-D immune globulin may lead to a worldwide shortage. The purpose of this document is to provide direction for the appropriate and efficient management of patients at risk in order to further decrease the frequency of Rh D alloimmunization.

This Practice Bulletin was developed by the ACOG Committee on Practice Bulletins—Obstetrics with the assistance of Michael L. Socol, MD, and T. Flint Porter, MD, MPH. The information is designed to aid practitioners in making decisions about appropriate obstetric and gynecologic care. These guidelines should not be construed as dictating an exclusive course of treatment or procedure. Variations in practice may be warranted based on the needs of the individual patient, resources, and limitations unique to the institution or type of practice.

Background

Nomenclature

Nomenclature of blood group systems, including the Rh system, may appear confusing to the clinician. According to the *American Medical Association Manual of Style*, erythrocyte antigen and phenotype terminology should use single letters or dual letters depending on the antigen in question (eg, O, AB, Le, Rh) (4). A second designation should be used for specific subtypes (eg, Rh D, Rh C). This publication uses the designation Rh D to signify the erythrocyte antigen. Women who carry the Rh D antigen are identified as Rh D positive, and those who do not

carry the Rh D antigen are identified as Rh D negative. The use of immune globulin to counter the Rh D antigen is referred to as anti-D immune globulin.

Causes of Rh D Alloimmunization

One study indicates that 17% of Rh D-negative women who do not receive anti-D immune globulin prophylaxis during pregnancy will become alloimmunized (5). Nearly 90% of these cases result from fetomaternal hemorrhage at delivery. Approximately 10% of cases result from spontaneous antenatal fetomaternal hemorrhage, and most of these cases occur in the third trimester. The amount of Rh D-positive blood required to cause alloimmunization is small. Most women who become alloimmunized do so as a result of fetomaternal hemorrhage of less than 0.1 mL (6).

Several first- and second-trimester clinical events may cause Rh D alloimmunization. Therapeutic and spontaneous abortions are associated respectively with a 4–5% and a 1.5–2% risk of alloimmunization in susceptible (non-alloimmunized) women (6–8). Ectopic pregnancy also is associated with alloimmunization in susceptible women. Threatened abortion infrequently causes alloimmunization, although approximately 10% of women with threatened abortion have evidence of fetomaternal hemorrhage (9).

Clinical procedures, which may breach the integrity of the choriodecidual space, also may cause Rh D alloimmunization. Chorionic villus sampling is associated with a 14% risk of fetomaternal hemorrhage (10) of more than 0.6 mL (11), and amniocentesis is associated with a 7–15% risk of fetomaternal hemorrhage, even if the placenta is not traversed (5, 12). Likewise, cordocentesis and other percutaneous fetal procedures pose a risk for fetomaternal hemorrhage, although the actual risk of alloimmunization has not been quantified (13, 14). External cephalic version, whether or not it is successful, results in fetomaternal hemorrhage in 2–6% of cases (15, 16).

Anti-D Immune Globulin to Prevent Alloimmunization

The correct administration of anti-D immune globulin dramatically reduces the rate of alloimmunization. Initial studies proved that the postpartum administration of a single dose of anti-D immune globulin to susceptible Rh D-negative women within 72 hours of delivery reduced the alloimmunization rate by 90% (17). It was subsequently recognized that third-trimester antenatal alloimmunization posed a lingering and significant problem; later it was shown that the routine antenatal administration of anti-D immune globulin to Rh D-negative women at 28–29 weeks of gestation reduced the rate of third-trimester alloimmunization from nearly 2% to 0.1% (6). With the effectiveness of anti-D immune globulin clearly demonstrated, authorities recommended its administration to Rh D-negative women who were undergoing clinical events or procedures associated with potential fetomaternal hemorrhage.

In the United States, recommendations for the administration of anti-D immune globulin were introduced in the 1970s. The current antenatal immunoprophylaxis regimen of a single dose of 300 μg at 28 weeks of gestation was based on recommendations from the 1977 McMaster Conference, and is associated with a low failure rate (18). The efficacy of the single antenatal dose of 300 μg at 28 weeks of gestation is comparable to the same dose given at both 28 weeks and 34 weeks of gestation (6). In one study of antenatal prophylaxis, three women who delivered more than 12 weeks after their antenatal dose was administered became alloimmunized. Based on these limited data, some authorities recommend that if delivery has not occurred within 12 weeks of the injection, at 28 weeks of gestation, a second 300 μg dose of anti-D immune globulin should be given (5).

In the United Kingdom, recommendations (19, 20) differ somewhat from those in the United States in that antenatal prophylaxis is given at both 28 weeks and 34 weeks of gestation, and the dose for each antenatal administration, as well as the dose given after delivery, is 100 μg. These recommendations are based on two studies (21, 22) that demonstrated the superiority of a regimen of 100 μg of anti-D immune globulin at 28 weeks and 34 weeks of gestation and postpartum compared with a regimen of only postpartum administration. The British regimen uses less anti-D immune globulin (300 μg versus 600 μg) to achieve similarly low rates of alloimmunization (7, 20), but requires a third injection at 34 weeks of gestation.

Anti-D immune globulin is extracted by cold alcohol fractionation from plasma donated by individuals with high-titer D immune globulin G antibodies. It has been shown experimentally that one prophylactic dose of 300 μg of anti-D immune globulin can prevent Rh D alloimmunization after an exposure to up to 30 mL of Rh D-positive blood or 15 mL of fetal cells (23). For exposure to larger volumes of Rh D-positive blood, more anti-D immune globulin is required. Accordingly, the American Association of Blood Banks and the National Blood Transfusion Service of the United Kingdom recommend that Rh D-negative mothers delivering Rh D-positive infants undergo a test to screen for fetomaternal hemorrhage in excess of the amount covered by the standard dose of anti-D immune globulin. This test will determine if additional anti-D immune globulin is necessary (24, 25). In the past, the American College of Obstetricians and Gynecologists recommended that only women with certain high-risk conditions, such as those experiencing abruptio placenta or manual removal of the placenta, be screened for excess fetomaternal hemorrhage. However, this policy has been shown to miss 50% of cases requiring more than the standard postpartum dose of anti-D immune globulin (26).

The risk of transmission of viral infections (human immunodeficiency virus [HIV] and hepatitis B and hepatitis C viruses) through anti-D immune globulin is minimal to absent (27). All plasma lots used for the production of anti-D immune globulin have been tested for viral infection since 1985. Moreover, the fractionation process used to prepare anti-D immune globulin effectively removes any viral particles that may be present.

Failure to Prevent Rh D Alloimmunization

In spite of recommendations for immunoprophylaxis, 0.1–0.2% of susceptible Rh D-negative women still become alloimmunized (21). There are two primary reasons for the continuing problem.

One reason women become alloimmunized is failure to implement recommended immunoprophylaxis protocols, resulting in preventable Rh D alloimmunizations. Two recent studies from the United Kingdom emphasize the scope of the problem. One study of more than 900 Rh D-negative women reported that only 59% received recommended treatment with anti-D immune globulin after potentially alloimmunizing clinical events (8). Another study showed that 16% of 63 cases of Rh D alloimmunization occurred because of failure to follow recommendations for administration of anti-D immune globulin (28). Preventable Rh D alloimmunization occurs in susceptible Rh D-negative women for the following three reasons:

1. Failure to administer an antenatal dose of anti-D immune globulin at 28–29 weeks of gestation
2. Failure to recognize clinical events that place patients at risk for alloimmunization and failure to administer anti-D immune globulin appropriately
3. Failure to administer or failure to administer timely anti-D immune globulin postnatally to women who have given birth to an Rh D-positive or untyped fetus

The second reason for the continuing problem of Rh D alloimmunization is the small rate (0.1–0.2%) of spontaneous immunization despite the recommended prophylaxis protocol. These cases most often occur in pregnancies during which there have been no prior overt sensitizing events. This problem may become the largest single cause of new Rh D alloimmunization, because alloimmunization from other causes has decreased proportionally (28).

Potential Shortage of Anti-D Immune Globulin

Anti-D immune globulin is collected by apheresis from volunteer donors who have high titers of circulating anti-Rh D antibodies. The donated plasma is pooled and fractionated by commercial manufacturers, and anti-D immune globulin is prepared in varying doses. The number of potential donors may be dwindling worldwide, raising concern about future supplies of anti-D immune globulin (29, 30). Experts in the United Kingdom estimate that supplies of anti-D immune globulin are inadequate for immunoprophylaxis of all susceptible Rh D-negative women, both primigravidas and multiparas, if standard recommendations are followed (19). In Australia, a shortage prompted importation of anti-D immune globulin. Subsequently, some physicians proposed strictly limiting the dose given for first-trimester indications and discontinuing administration of anti-D immune globulin after external cephalic version (unless fetomaternal hemorrhage is documented), ectopic pregnancy, or threatened miscarriage (31). Others disagreed, considering it unethical to withhold anti-D immune globulin in any situation. Estimates regarding future needs compared with potential supply in the United States have not been published; however, limiting doses for first-trimester indications and using lower doses of Rh D immune globulin for antenatal prophylaxis may be necessary.

Cost-Effectiveness of Rh D Prophylaxis Programs

The cost-effectiveness of preventing perinatal mortality and morbidity secondary to Rh D hemolytic disease of the newborn is an important consideration. Economic analysis of anti-D immune globulin prophylaxis is based on the cost of anti-D immune globulin and the number of alloimmunizations that would be prevented. In 1977, the McMaster Conference concluded that routine postnatal prophylaxis was cost-effective but that routine antenatal treatment should be undertaken only if supplies of anti-D immune globulin were adequate and if cases of hemolytic disease of the newborns occurred that might have been prevented by antenatal treatment (7). Some experts concluded that antenatal prophylaxis is effective only in primigravidas (32), and the debate regarding the cost-effectiveness of antenatal prophylaxis of all pregnant women remains unsettled (20, 32–37). The Scottish National Blood Transfusion Service has concluded that the administration of 100 μg of anti-D immune globulin at 28 weeks and 34 weeks of gestation is cost-effective only in primigravidas (38). Others estimate that the most cost-effective antenatal regimen is a single dose of 250 μg of anti-D immune globulin at 28 weeks of gestation (39).

The use of anti-D prophylaxis in the case of certain clinical events is even more controversial. For example, the risk of Rh D alloimmunization from threatened abortion in the first trimester is uncertain, though probably very small. The cost-effectiveness of anti-D immune globulin for threatened abortion, which has never been studied, is questionable (19).

In summary, the cost-effectiveness of antenatal Rh D immune globulin to all Rh D-negative pregnant women and in all circumstances wherein fetomaternal hemorrhage might occur has not been proved. Available data support that third-trimester antenatal prophylaxis is cost-effective in primigravidas. As long as the supply of anti-D immune globulin is adequate and data do not exist to support other recommendations, most experts believe that it is unethical to withhold anti-D immune globulin from any patient at risk of Rh D alloimmunization (19). Recommendations for the use of anti-D immune globulin in this document will be made accordingly.

Clinical Considerations and Recommendations

▶ *Should anti-D immune globulin ever be withheld from a woman undergoing sterilization?*

The use of anti-D immune globulin following postpartum and postabortal sterilization should be guided by the patient's desire for protection against any chance of alloimmunization. Proponents of its use maintain that anti-D immune globulin administration will preserve the future option of transfusing Rh D-positive blood in times of emergency (40). Opponents of this view cite the low probability of sensitization with the previous pregnancy and the improbability of receiving Rh D-incompatible blood (41).

▶ *How should one deal with the issue of paternity?*

If the father is known to be Rh D negative, antenatal prophylaxis is unnecessary. If there is doubt about the father's identity or his blood type, anti-D immune globulin prophylaxis should be given.

▶ *Is it necessary to repeat antibody screening in patients at 28 weeks of gestation prior to the administration of anti-D immune globulin?*

The American Association of Blood Banks recommends that the physician should consider a repeat antibody screen prior to the administration of antenatal anti-D immune globulin if the patient was screened for antibodies prior to 28 weeks of gestation (24). The primary rationale for repeating the antibody screen is to identify women who have become alloimmunized before 28 weeks of gestation in order to manage their pregnancies properly. However, the incidence of Rh D alloimmunization occurring prior to 28 weeks of gestation is reported to be as low as 0.18% (18), and the cost-effectiveness of routinely repeating the antibody test has not been studied. The consequences of antenatal Rh D alloimmunization can be severe, but the decision to obtain a repeat antibody screen should be dictated by individual circumstances and left to the judgment of the physician.

▶ *Is anti-D immune globulin indicated in a sensitized pregnancy?*

If Rh D antibodies are present, anti-D immune globulin is not beneficial, and management should proceed in accordance with protocols for Rh D-alloimmunized pregnancies.

▶ *How should a D^u blood type be interpreted, and what management should be undertaken?*

In the past, a woman whose blood was typed as D^u was thought to have blood cells positive for a variant of the Rh D antigen. Nomenclature and practice have changed in recent years, and currently the D^u designation has been changed to "weak D positive" (24). Patients with this designation are considered Rh D positive and should not receive anti-D immune globulin. In some centers, the D^u antigen is not assessed, and women may unnecessarily receive anti-D immune globulin. In the rare circumstance of delivery by a woman whose antenatal Rh status is negative or unknown and whose postpartum screen reveals a D^u-positive or weak D-positive result, anti-D immune globulin should be given, and the possibility of fetomaternal hemorrhage should be investigated (24).

▶ *Is threatened abortion an indication for anti-D immune globulin prophylaxis?*

Whether to administer anti-D immune globulin to a patient with threatened abortion and a live embryo or fetus at or before 12 weeks of gestation is controversial, and no evidence-based recommendation can be made. The Rh D antigen has been reported on fetal erythrocytes as early as 38 days of gestation (42), and fetomaternal hemorrhage has been documented in women with threatened abortion from 7 to 13 weeks of gestation (9). However, Rh D alloimmunization apparently attributable to threatened abortion is exceedingly rare. Experts have compared the overall benefit with the cost of the widespread use of anti-D immune globulin for a condition as common as threatened abortion (19, 43), and, thus, many physicians do not routinely administer anti-D immune globulin to women with threatened abortion and a live embryo or fetus up to 12 weeks of gestation.

▶ *How much anti-D immune globulin should be given for first-trimester events and procedures?*

Because the red cell mass of the first-trimester fetus is small, the dose of anti-D immune globulin necessary for first-trimester events is 50 μg to protect against sensitization by 2.5 mL of red blood cells (5, 44). If therapeutic or spontaneous abortion occurs after the first trimester, the standard 300 μg dose is recommended (5).

▶ *Should anti-D immune globulin be given in cases of molar pregnancy?*

Although reported (45), the risk of Rh D alloimmunization in cases of hydatidiform mole is unknown. In theory, Rh D alloimmunization would not occur in cases of classic complete molar pregnancy because organogenesis does not occur, and Rh D antigens are probably not present on trophoblast cells, although this theory has been disputed (46–48). In partial and transitional molar pregnancies, however, the embryo may not die until after erythrocyte production has begun, making maternal exposure to the Rh D antigen possible (49). Given that the diagnosis of partial versus complete molar pregnancy depends on pathologic and cytogenetic evaluations, it seems reasonable to administer anti-D immune globulin to Rh D-negative women who are suspected of molar pregnancy and who undergo uterine evacuation.

▶ *Should anti-D immune globulin be given in cases of intrauterine fetal death occurring in the second or third trimester?*

Fetal death is due to fetomaternal hemorrhage in 11–13% of cases in which no obvious other cause (eg, maternal hypertensive disease, fetal anomalies) is found (50, 51). Rh D alloimmunization has been reported in cases of fetal death from massive fetomaternal hemorrhage (52), although the influence of this cause on the overall problem of Rh D alloimmunization is unknown. The efficacy of anti-D immune globulin in this clinical situation has not been tested in properly designed trials. However, authorities agree that anti-D immune globulin should be administered to Rh D-negative women who experience fetal death in the second or third trimester. All such cases should be screened for excessive fetomaternal hemorrhage to determine if additional anti-D immune globulin is required (25, 53).

▶ *Is second- or third-trimester antenatal hemorrhage an indication for anti-D immune globulin prophylaxis?*

In patients with second- or third-trimester antenatal hemorrhage, the risk of Rh D alloimmunization is uncertain. Although the efficacy of anti-D immune globulin in this clinical situation has not been tested in properly designed trials, authorities agree that anti-D immune globulin should be administered to Rh D-negative women with second- or third-trimester hemorrhage (25, 53). Management of the patient with persistent or intermittent antenatal bleeding is complex. Though unproven, one commonly used strategy is to monitor the Rh D-negative patient with continuing antenatal hemorrhage with serial indirect Coombs testing approximately every 3 weeks. If the result is positive, indicating the persistence of anti-D immune globulin, no additional treatment is necessary. If the Coombs test is negative, excessive fetomaternal hemorrhage may have occurred, and a Kleihauer-Betke test should be performed in order to determine the amount of additional anti-D immune globulin necessary.

▶ *Is anti-D immune globulin prophylaxis indicated after abdominal trauma in susceptible pregnant women?*

Although the exact risk of Rh D alloimmunization is unknown, abdominal trauma may be associated with fetomaternal hemorrhage, which may lead to alloimmunization (54–57). The efficacy of anti-D immune globulin in this clinical situation has not been tested in properly designed trials. However, authorities agree that anti-D immune globulin should be administered to Rh D-negative women who have experienced abdominal trauma (25, 53). Also, all of these patients should be screened for excessive fetomaternal hemorrhage.

▶ *What should be done if an Rh D-negative patient is discharged without receiving anti-D immune globulin after a potentially sensitizing event?*

Volunteers have been shown to receive partial protection if anti-D immune globulin was given as late as 13 days after exposure (58). The longer prophylaxis is delayed the less likely it is that the patient will be protected, but it has been recommended that a patient may still receive some benefit from anti-D immune globulin as late as 28 days postpartum (5).

▶ *How long does the effect of anti-D immune globulin last?*

The half-life of anti-D immune globulin is 24 days, although titers decrease over time. If delivery occurs within 3 weeks of the standard antenatal anti-D immune globulin administration, the postnatal dose may be withheld in the absence of excessive fetomaternal hemorrhage (53). The same is true when anti-D immune globulin is given for antenatal procedures, such as external cephalic version or amniocentesis, or for third-trimester bleeding. An excessive amount of fetal erythrocytes not covered by anti-D immune globulin administration can be assumed to have entered maternal blood if either the results of the Kleihauer-Betke test are positive or the results of the indirect Coombs test are negative.

▶ *Should administration of anti-D immune globulin be repeated in patients with a postdate pregnancy?*

One study found that three patients became alloimmunized to the Rh D antigen when delivery occurred more than 12 weeks after the standard prophylaxis at 28 weeks of gestation (5). Based on these limited data, some experts have recommended that if delivery has not occurred within

12 weeks after injection at 28 weeks of gestation, a second antenatal dose should be given (5). Because this recommendation is based on so few cases, the final decision whether to administer a second dose should be left to the physician's judgment.

▶ ***Should all Rh D-negative women be screened for excessive fetomaternal hemorrhage after delivery of an Rh D-positive infant?***

The risk of excessive fetomaternal hemorrhage exceeding 30 mL (the amount covered by the standard 300 μg dose of anti-D immune globulin) at the time of delivery is approximately 1 in 1,250 (5). Previous American College of Obstetricians and Gynecologists documents have recommended that only pregnancies designated as high risk be screened for excessive fetomaternal hemorrhage, including cases of abdominal trauma, abruptio placentae, placenta previa, intrauterine manipulation, multiple gestation, or manual removal of the placenta. However, such a screening program has been reported to detect only 50% of patients who required additional anti-D immune globulin (26). Based on this finding, the American Association of Blood Banks has recommended that all Rh D-negative women who deliver Rh D-positive infants be screened using the Kleihauer-Betke or rosette test (24).

Summary

The reduction in the incidence of Rh D alloimmunization is a prototype for the effectiveness of preventive medicine. Some controversies remain, however, such as the use of anti-D immune globulin in patients with either threatened abortion or antenatal hemorrhage. Similarly, it may not be cost-effective either to screen all Rh D-negative patients with an indirect Coombs test at 24–28 weeks of gestation or to screen all postpartum patients for excessive fetomaternal hemorrhage.

The following recommendations are based on good and consistent scientific evidence (Level A):

The Rh D-negative woman who is not Rh D-alloimmunized should receive anti-D immune globulin:

- At approximately 28 weeks of gestation, unless the father of the baby is also known to be Rh D negative
- Within 72 hours after the delivery of an Rh D-positive infant
- After a first-trimester pregnancy loss
- After invasive procedures, such as chorionic villus sampling, amniocentesis, or fetal blood sampling

The following recommendations are based primarily on consensus and expert opinion (Level C):

Anti-D immune globulin prophylaxis should be considered if the patient has experienced:

- Threatened abortion
- Second- or third-trimester antenatal bleeding
- External cephalic version
- Abdominal trauma

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The MEDLINE database, the Cochrane Library, and ACOG's own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 1980 and December 1998. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

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 could also be regarded as this type of evidence

III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following catetories:

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.

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