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Prevention of Rh D Alloimmunization

Advances in the prevention and treatment of Rh D alloimmunization have been one of the great success stories of modern obstetrics. There is wide variation in prevalence rates of Rh D-negative individuals between regions, for example from 5% in India to 15% in North America (1). However, high birth rates in low prevalence areas means Rh hemolytic disease of the newborn is still an important cause of morbidity and mortality in countries without prophylaxis programs (1). In such countries, 14% of affected fetuses are stillborn and one half of live born infants suffer neonatal death or brain injury (1). The routine use of Rh D immune globulin is responsible for the reduced rate of red cell alloimmunization in more economically developed countries. First introduced in the 1970s, the postpartum administration of Rh D immune globulin reduced the rate of alloimmunization in at-risk pregnancies from approximately 13–16% to approximately 0.5–1.8% (2, 3). The risk was further reduced to 0.14–0.2% with the addition of routine antepartum administration (2, 3). Despite considerable proof of efficacy, there are still a large number of cases of Rh D alloimmunization because of failure to follow established protocols. In addition, there are new data to help guide management, especially with regard to weak D phenotype women. The purpose of this document is to provide evidence-based guidance for the management of patients at risk of Rh D alloimmunization.

Background

Nomenclature

Nomenclature for red blood cell surface proteins is complex and can be confusing. The red cell membrane contains many anchored surface proteins. Many of these proteins are polymorphic and carry different blood groups. A blood group system consists of one or more antigens controlled at a single gene locus, or by two or more closely linked homologous genes with little or no observable recombination between them. Most blood group antigens are glycoproteins, and their specificity is mostly determined either by the oligosaccharide or amino acid sequence. The 30 human blood group system genes have been identified and sequenced, and all the polymorphisms are known (4).

A variety of terminologies has been used to denote human blood groups since their discovery in 1900. In 1980, the International Society of Blood Transfusion established a Working Committee to devise and maintain a genetically-based numerical terminology for red cell surface antigens. The numerical terminology was devised for computer storage of information on blood groups antigens and to provide a framework for genetic classification. The numerical terminology is not suitable for everyday communication, which has led to a variety of alternative names being used for some blood group antigens. In an attempt to introduce some uniformity, a recommended list of alternative names for antigens is available through the International Society of Blood Transfusion (4). In most cases the name or symbol is identical to that originally published, but in a few cases the more commonly used name is provided, as with ABO and Rh. Specific subtypes or polymorphisms use a second designation (eg, Rh D, Rh C, Rh E). This document uses the designation Rh D to signify the erythrocyte antigen. Women who carry the Rh D antigen are identified as Rh D positive. Those who do not carry the Rh D

antigen are identified as Rh D negative. Details regarding the nomenclature for partial D or weak D antigens are described as follows (see "How should a weak D blood type be interpreted and what management should be undertaken?"). The frequency of the Rh D-negative phenotype is most common in individuals of European and North American descent (15–17%), is comparatively decreased in the regions of Africa and India (3–8%), and is rarest in Asia (0.1–0.3%) (1, 5). The immune globulin used specifically to bind the Rh D antigen is referred to as Rh D immune globulin or anti-D immune globulin. Alloimmunization refers to an immunologic reaction against foreign antigens that are distinct from antigens on an individual's cells. In this case, it refers to the maternal formation of antibodies against fetal Rh D. Fetal–maternal hemorrhage is the term used to identify varying amounts of fetal cells in the maternal circulation from small interruptions at the fetal–maternal placental interface (6).

Causes of Rh D Alloimmunization

Rh D alloimmunization occurs when a Rh D-negative woman is exposed to red cells expressing the Rh D antigen. Although the fetal and maternal circulations are separate, there is often some antenatal mixing of fetal and maternal blood, even in asymptomatic women. Events such as miscarriage, ectopic pregnancy, antenatal bleeding, and delivery, as well as procedures such as chorionic villus sampling, amniocentesis, pregnancy-related uterine curettage, and surgical treatment of ectopic pregnancy can lead to maternal exposure to fetal red blood cells and, consequently, Rh D alloimmunization (Box 1). Between 3% and 11% of women with threatened abortion in the first trimester, and approximately 45% giving birth in the third trimester, have a fetal–maternal hemorrhage (7, 8). The volume of fetal–maternal hemorrhage leading to Rh D alloimmunization can be as small as 0.1 mL or as large as 30 mL (7, 8).

Box 1. Potential Sensitizing Events in Rh D-Negative Women in Pregnancy

- Chorionic villus sampling, amniocentesis, cordocentesis
- Threatened miscarriage or miscarriage
- Ectopic pregnancy
- Evacuation of molar pregnancy
- Therapeutic termination of pregnancy
- Antepartum hemorrhage
- Abdominal trauma
- Intrauterine fetal death
- External cephalic version
- Delivery

Fetal–maternal hemorrhage also may take place in the first and second trimesters in association with spontaneous pregnancy loss or uterine instrumentation (eg, dilation and curettage or evacuation). The risk of Rh D alloimmunization is estimated to be 1.5–2% in susceptible women after spontaneous miscarriage and 4–5% after dilation and curettage (3, 7). There are insufficient data from studies that evaluated the efficacy of administration of anti-D immune globulin after spontaneous miscarriage and, although alloimmunization appears rare, it is possible and recommendations continue to include administration of anti-D immune globulin after such losses (3, 9, 10). Ectopic pregnancy also may lead to Rh D alloimmunization, although data regarding the probability are lacking. Until further evidence is available, expert advice continues to recommend administration of anti-D immune globulin within 72 hours of suspected breach of the choriodecidual space (9).

Historically, chorionic villus sampling has been estimated to carry a 14% risk of fetal–maternal hemorrhage of 0.6 mL or more (11). Later studies corroborate these earlier findings and continue to support the administration of anti-D immune globulin to Rh D-negative women who have chorionic villus sampling (12, 13). Traditionally, amniocentesis led to a 2–6% rate of fetal–maternal hemorrhage, even if the placenta was not traversed (14, 15). Recent studies suggest the rate of fetal–maternal hemorrhage may be lower than previously thought but not negligible (16, 17) and alloimmunization is possible. Similarly, other invasive procedures such as cordocentesis also can cause fetal–maternal hemorrhage (16) and warrant anti-D immune globulin prophylaxis. Although not invasive, external cephalic version (regardless of success) is associated with a 2–6% risk of fetal–maternal hemorrhage and anti-D immune globulin is indicated for unsensitized Rh D-negative patients (18, 19).

Anti-D Immune Globulin to Prevent Alloimmunization

Anti-D immune globulin is extracted by cold alcohol fractionation from plasma donated by individuals with high-titer anti-D immune globulin G antibodies. Original work in the 1960s noted maternal sensitization to fetal Rh-positive blood could be prevented by administering anti-D immune globulin. A prophylactic dose of 300 micrograms of anti-D immune globulin can prevent Rh D alloimmunization after exposure to up to 30 mL of Rh D-positive fetal whole blood or 15 mL of fetal red

blood cells (20). Subsequently anti-D immune globulin became more widely available and a single dose given to susceptible Rh D-negative women within 72 hours of delivery reduced the rate of Rh D alloimmunization by 80–90% (7, 21, 22). However, it became clear that asymptomatic fetal–maternal hemorrhage during the third trimester triggered alloimmunization in 2% of at-risk women before delivery. This rate was shown to be reduced to less than 0.2% with routine antenatal administration of anti-D immune globulin at 28 weeks of gestation (7).

In the United States, a recommendation for the administration of anti-D immune globulin was introduced in the 1970s. The current practice of administering a single antenatal dose of 300 micrograms of anti-D immunoglobulin at 28 weeks of gestation followed by a second dose after birth when newborn Rh D typing has identified the infant as Rh positive, based on recommendations from a conference at McMaster University in 1977, is associated with less than a 0.2% rate of Rh alloimmunization (7, 23). In the United Kingdom, recommendations have differed somewhat from those in the United States in that antenatal Rh D immune globulin using different doses may be given as two injections at 28 weeks of gestation and at 34 weeks of gestation, or as a single administration at 28 weeks of gestation (24, 25). There is no trial comparing the two-dose regimens with a single dose, and no evidence of a difference in efficacy between these regimens (24). However, an observational study from the United Kingdom noted better adherence with the single-dose compared with the two-dose protocol (26). There is also potential cost reduction with a single dose (27). Thus, there are no compelling data indicating a change from the single-dose procedure currently used in the United States to the two-dose regimen.

Although administration of anti-D immune globulin at 28 weeks of gestation is highly effective, pharmacokinetic studies suggest that levels of anti-D vary between patients and some may not have adequate anti-D levels at delivery (28). In the past, some authorities advised giving a second dose of Rh D immune globulin in women who have not given birth 12 weeks after receiving their antenatal dose (29). However, the vast majority of women who give birth more than 12 weeks after receiving antenatal Rh D immune globulin do not become alloimmunized. Because of this low risk of alloimmunization and the fact that 40% of infants of Rh D-negative women will be Rh D negative, most guidelines do not recommend that a second dose of anti-D immune globulin be given until after delivery when newborn Rh D typing becomes available. Additional anti-D immune globulin is needed to prevent alloimmunization for exposures larger than 30 mL of Rh D-positive fetal whole blood. Rarely, in 2–3 per 1,000 deliveries, a fetal–maternal hemorrhage may be greater than 30 mL (6, 7). For this reason, Rh D-negative women who give birth to Rh D-positive infants should undergo additional testing to assess the volume of fetal–maternal hemorrhage and guide the amount of Rh D immune globulin required to prevent alloimmunization (5, 25, 30, 31). It is advised that all women undergo such screening after delivery because a policy of only screening deliveries with high-risk conditions for excess fetal–maternal hemorrhage, such as abruptio placentae or manual removal of the placenta, will fail to identify a large number of cases requiring more than the standard postpartum dose of Rh D immune globulin (32).

Screening for fetal–maternal hemorrhage in routine situations typically begins with the rosette fetal red blood cell assay. The erythrocyte rosette screen is a sensitive, qualitative test that can detect greater than 2 mL of fetal whole blood in the maternal circulation (32). The rosette test is performed by incubation of a maternal blood sample with Rh immunoglobulin that will bind fetal Rh D-positive red blood cells, followed by the addition of enzyme-treated reagent indicator red blood cells. Rh D-positive fetal red blood cells present in maternal circulation result in forming aggregates (rosettes) that can be visualized by light microscopy. A positive rosette test should be followed with a method to determine the percentage of fetal red blood cells in maternal circulation, such as the Kleihauer–Betke test or flow cytometry. The Kleihauer–Betke acid elution test relies on the principle that fetal red blood cells contain mostly fetal hemoglobin F, which is resistant to acid elution, whereas adult hemoglobin is acid sensitive. Although the Kleihauer–Betke test is inexpensive and requires no special equipment, it lacks standardization and precision, and may not be accurate in conditions in which the mother has a coexistent medical condition that is associated with red blood cells containing an increased percentage of hemoglobin F, such as sickle-cell disease and the thalassemias. Flow cytometry is a specialized technique that is an alternative method available in some hospitals for quantification of fetal–maternal hemorrhage, although its use is limited by equipment and staffing costs. Flow cytometry uses monoclonal antibodies to hemoglobin F or the Rh D antigen with quantification of fluorescence, and is highly sensitive and accurate in identifying fetal red blood cells in maternal blood (32). In clinical situations in which fetal–maternal hemorrhage has occurred in a volume that is not covered by the standard 300 microgram dose of Rh immune globulin (greater than 30 mL of fetal whole blood or 15 mL of fetal red cells) additional vials of Rh immune globulin can be administered at one

time (up to eight full vials). These additional doses can be administered intramuscularly at separate sites every 12 hours until the desired dosage has been reached (33, 34). An intravenous Rh immune globulin is available that also may be used in these cases and provides more comfort for the patient (34).

Because Rh D immune globulin is obtained from human plasma, there is a theoretical risk of transmission of viral infection. In the 1990s, it was discovered that immune globulin contaminated with hepatitis C virus had been administered to women from 1977 to 1979 in Ireland and Germany (35). Most of these exposed women showed only slight to moderate hepatic inflammation 17–35 years later (35, 36). A later analysis of samples manufactured between 1991 and 1994 again demonstrated a low potential for transmission of the hepatitis C virus, with 0.59% of potential exposures showing evidence of seroconversion (37). Regardless, because the product is a purified immune globulin, the risk of viral infection from anti-D immune globulin is exceedingly low. Since 1985, all plasma used for the production of anti-D immune globulin has been tested for viral infections, and several fractionation and purification steps, including micropore filtration, are used to remove and inactivate viruses. Other contaminations and inadvertent exposures have not been reported, and anti-D immune globulin has been manufactured without mercury-containing thimerosal since 2001 (38).

Failure to Prevent Rh D Alloimmunization

Rh alloimmunization during pregnancy in Rh D-negative women may still occur. This might be because of a failure of administering antenatal prophylaxis in the third trimester of pregnancy, insufficient dosage or timely administration (within 72 hours) of anti-D immune globulin given after a known sensitizing event during pregnancy (or after birth), or an unrecognized fetal–maternal hemorrhage at some point in the pregnancy (39). In spite of recommendations for immunoprophylaxis, approximately 0.1–0.4% of women at risk become sensitized during pregnancy (22). A recent retrospective study from New Zealand identified reasons for continued cases of sensitization, including omission of immune globulin after a recognized sensitizing event in 41% of cases and administration outside of recommended guidelines in 13% of cases (40). An additional reason for Rh D alloimmunization is the small rate (0.1–0.2%) of spontaneous immunization despite adherence to the recommended prophylaxis protocol (22). These cases most often occur in pregnancies during which there have been no prior overt sensitizing events. In other words, prophylaxis is not 100% effective (41).

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. In the 1990s, concerns were raised regarding future supplies of anti-D immune globulin for worldwide demands because the number of potential donors may dwindle (42). At that time, experts in the United Kingdom estimated that supplies of anti-D immune globulin would be inadequate for immunoprophylaxis of all susceptible Rh D-negative women if standard recommendations were followed (43). In Australia in 1995, 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 fetal–maternal hemorrhage is documented), ectopic pregnancy, or threatened miscarriage (44). 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. No reports of supply shortages of anti-D immune globulin have been published since initial concerns were expressed 20 years ago. Despite these earlier concerns, national guidelines from the United States, United Kingdom, and Canada still recommend routine administration of anti-D immune globulin to all Rh D-negative nonsensitized women in the third trimester, within 72 hours of delivery in women giving birth to a Rh-positive infant, or when a sensitizing event occurs (eg, ectopic pregnancy, external cephalic version, or invasive obstetric procedures such as chorionic villus sampling or amniocentesis) (5, 25, 31).

Other sources of anti-D immune globulin have been explored. There is the potential to generate recombinant Rh D immune globulin, which would alleviate any future shortages of donors. No commercially available, efficacious recombinant products are currently available. Nonetheless, a monoclonal antibody (Roledumab) and a recombinant antibody mixture (Rozrolimupab) are being designed for prevention of hemolytic disease of the newborn and are in phase II clinical trials (45, 46).

Cost Effectiveness of Rh D Prophylaxis Programs

The cost effectiveness of different screening strategies to guide the administration of Rh D immune globulin to Rh D-negative pregnant women in circumstances where fetal–maternal hemorrhage may occur have been mixed.

Strategies of selective administration of Rh D immune globulin depending on partner's blood type have been shown to be cost equivalent to systematic prophylaxis (47, 48). If the Rh type of the partner is not known, and given that immunological typing of the father would probably not be carried out by most clinicians, routine antenatal prophylaxis remains the preferred option (48). Although initial economic analysis of antenatal anti-D immune globulin prophylaxis suggested that it was only cost effective in primigravid women (27, 47), more recent data indicate that prophylactic administration to all women at risk is cost beneficial (48).

Noninvasive determination of fetal Rh status is now possible through the analysis of cell-free DNA in maternal plasma. Up to 40% of Rh D-negative pregnant women will carry an Rh D-negative fetus. In this clinical situation, antenatal anti-D immune globulin administration is unnecessary. Concerns have been raised about the unwarranted exposure of these pregnant women to a plasma-based product (49). Some parts of the world now are using circulating cell-free DNA testing to ascertain the fetal Rh D status and to establish candidates for antenatal anti-D immune globulin prophylaxis (50). Recent retrospective and prospective observational studies have reported that fetal Rh D status determination in the first trimester has a sensitivity greater than 99% and a specificity of greater than 95% (51–53). However, concerns have been noted because of the rate of inconclusive results (range 2–6%), which are influenced by race (52, 53).

Despite the improved accuracy of noninvasive fetal RHD genotyping, cost comparisons with current routine prophylaxis of anti-D immunoglobulin at 28 weeks of gestation have not shown a consistent benefit. Four cost analyses from North America and Europe have shown no economic benefit at current test-cost levels (48, 54–56), whereas a single report from Canada suggested it would be cost effective, although the estimated cost of performing the cell-free DNA was based on a low-cost, high-throughput method (57). As the cost of this technology diminishes, this may become an attractive and cost-effective strategy. However, at current costs, noninvasive assessment of fetal Rh D status is not recommended for routine use at present.

Clinical Considerations and Recommendations

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

All pregnant women should be tested at the time of the first prenatal visit for ABO blood group and Rh D type and screened for the presence of erythrocyte antibodies. If anti-D antibody is identified, further history should be obtained and investigation undertaken to determine whether this is immune mediated or passive (as a result of previous injection of anti-D immune globulin). If it is clear that the origin of the anti-D antibodies detected is a previous routine antenatal anti-D immune globulin prophylaxis or anti-D immune globulin given for a potentially sensitizing event, then the woman should continue to be offered anti-D prophylaxis (25). If Rh D antibodies are present because of sensitization, anti-D immune globulin is not beneficial, and management should proceed in accordance with protocols for Rh D-alloimmunized pregnancies (58).

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

Reliable rates of nonpaternity are difficult to ascertain but a recent review indicates that the mean rate among population studies is approximately 3% (59). Strategies of selective administration of Rh D immune globulin depending on the partner's blood type have been shown to be cost equivalent to systematic prophylaxis (47, 48). If paternity is certain and the father is known to be Rh D negative, antenatal prophylaxis is unnecessary. If the Rh type of the partner is not known, and given that immunological typing of the father would probably not be carried out by most clinicians, routine antenatal prophylaxis remains the preferred option (48). An alternative strategy is to assess fetal RHD genotype with noninvasive testing and only administer Rh D immune globulin if the fetus is Rh D positive. Despite the improved accuracies noted with noninvasive fetal RHD genotyping, cost comparisons with current routine prophylaxis of anti-D immunoglobulin at 28 weeks of gestation have not shown a consistent benefit and, thus, this test is not routinely recommended (48, 54–56).

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

In the past, a woman whose blood was typed as weak D (formerly known as Du) was thought to have blood cells positive for a variant of the Rh D antigen (60). The prevalence of serologic weak D phenotypes varies by race and ethnicity. Serologic weak D phenotypes are the most common D variants detected in Europe and the United States. An estimated 0.2–1.0% of Caucasians inherit *RHD* genes that code for serologic weak D phenotypes and, in the United States, 80% are associated with weak D type 1, 2, or 3 (60). Some of these individuals express reduced numbers of normal Rh D antigens whereas others express partial or abnormal Rh D antigens. It

is possible for the latter group to develop antibodies against the part of the Rh D antigen that they are missing, and several cases of clinically severe Rh D alloimmunization have been reported in weak D phenotype women (60). Accordingly, the American Association of Blood Banks (AABB) recommends that testing for weak D is unnecessary in individuals who will be transfusion recipients of red blood cells (5). This approach categorizes individuals with weak D as Rh D negative for transfusion, and if pregnant, they are considered a candidate for anti-D immune globulin, hence avoiding potential Rh D alloimmunization.

However, the AABB requires that blood donors be assessed for weak D and if detected, the donors are interpreted to be Rh D positive. This policy prevents the transfusion of Rh D-negative individuals with weak D-positive blood, avoiding cases of Rh D alloimmunization. These seemingly contradictory policies likely have helped to avoid potential cases of Rh D alloimmunization. However, it can be extremely confusing for patients and clinicians. For example, the same individual may be variably characterized as Rh D positive or Rh D negative depending upon whether they are a potential donor or recipient and if weak D is or is not assessed (60). This could easily lead to errors and potential cases of Rh D alloimmunization.

An attractive solution to this problem is to perform molecular genetic RHD typing in weak D phenotype individuals as suggested by the Work Group on RHD Genotyping (60). This would allow for consistency in Rh D typing for individuals during their lifetime. In addition, the administration of Rh D immune globulin could be avoided in the Rh D individual with serologic weak D type 1, 2, or 3, because these are not associated with risk of Rh D alloimmunization, which could potentially reduce the need for tens of thousands of units of Rh D immune globulin each year (60). Currently, there is a lack of comprehensive cost-benefit analysis for this clinical approach. Clinicians are advised to administer Rh D immune globulin to patients with weak D blood type in appropriate clinical situations, by the same rationale as that for Rh D typing blood donors, until further scientific and economic studies are available.

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

Whether to administer anti-D immune globulin to a patient with threatened pregnancy loss 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 from fertilization or 7 3/7 weeks of estimated gestational age (61), and fetal–maternal hemorrhage, although rare, has been documented in 3–11% of women with threatened pregnancy loss from 7 weeks to 13 weeks of gestation (7, 8).

Recommendations regarding anti-D immune globulin with threatened miscarriage have been inconsistent. Several national guidelines recommend against giving anti-D immune globulin to women with threatened pregnancy loss, particularly if bleeding stops before 12 weeks of gestation (25, 30, 62). Other guidelines recommend that anti-D immune globulin should be given (as described below) to all Rh D-negative women with a threatened miscarriage or when vaginal bleeding is heavy, repeated, or associated with abdominal pain, particularly if these events occur as gestational age approaches 12 weeks (25, 31). Because of insufficient evidence that a threatened pregnancy loss before 12 weeks of gestation requires anti-D immune globulin, no recommendation can be made at this time.

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

Although alloimmunization has been reported with hydatidiform mole (63), the risk is unknown. In theory, Rh D alloimmunization should 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 (64–66). In partial and transitional molar pregnancies, however, the embryonic development may cease after erythrocyte production has begun, making maternal exposure to the Rh D antigen possible (67). Given that the diagnosis of partial versus complete molar pregnancy depends on pathologic and cytogenetic evaluations, it is reasonable to administer anti-D immune globulin to Rh D-negative women who are suspected of molar pregnancy and who undergo uterine evacuation (25, 31).

▶ *How much anti-D immune globulin should be given for first- or second-trimester events (eg, spontaneous abortion, therapeutic abortion, ectopic pregnancy) and invasive obstetric procedures (eg, chorionic villus sampling, amniocentesis)?*

Although the optimal dose of anti-D immune globulin for potentially sensitizing events in the first and second trimesters is unknown, because of the smaller fetal red cell mass at these gestations, the recommended dosage is typically less than that used for routine antenatal prophylaxis in the third trimester. At 12 weeks of gestation, the

total fetal–placental blood volume is 3 mL or 1.5 mL of fetal red cells (44). Regardless, this volume is adequate to sensitize some patients, and the risk of Rh D alloimmunization is estimated to be 1.5–2% in susceptible women after spontaneous miscarriage and 4–5% after dilation and curettage (3).

There are no adequate data to support an evidence-based recommendation, and expert opinion varies on whether anti-D immune globulin should be given with a spontaneous abortion. Because of the small volume of fetal blood and the low incidence of alloimmunization, some groups do not recommend prophylactic anti-D immunoglobulin in cases of spontaneous complete miscarriage before 12 weeks of gestation when the uterus is not instrumented (25, 62). Other experts recommend that either 50 micrograms or 120 micrograms of anti-D immune globulin be given after a complete miscarriage during the first 12 weeks of gestation (30, 31). Although the risk of alloimmunization is low, the consequences can be significant, and administration of Rh D immune globulin should be considered in cases of spontaneous first-trimester miscarriage, especially those that are later in the first trimester. If given, a dose of at least 50 micrograms should be administered. Because of the higher risk of alloimmunization, Rh D-negative women who have instrumentation for their miscarriage should receive Rh D immune globulin prophylaxis. Patients who have a miscarriage after 12 weeks of gestation should receive 300 micrograms of Rh D immune globulin.

Rh D immune globulin should be given to Rh D-negative women who have pregnancy termination, either medical or surgical. Most consensus guidelines have recommended 50 micrograms or 120 micrograms of anti-D immune globulin up to 12 weeks of gestation (25, 30, 31, 62), and a dose of 300 micrograms after 12 weeks of gestation (31).

Alloimmunization has been reported to occur in 24% of women with a ruptured tubal pregnancy (68). Again, guidelines differ with regard to the recommended dose of anti-D immune globulin up to 12 weeks of gestation, ranging from 50 micrograms to 120 micrograms (25, 30, 31, 62). After 12 weeks of gestation, 300 micrograms Rh D immune globulin is recommended (31). One expert group differentiates whether anti-D immune globulin should be administered depending upon the treatment method used for the unruptured ectopic pregnancy. Without clear evidence to support the distinction, they do not recommend anti-D immune globulin for women who solely receive medical management, but a dose of 50 micrograms is recommended in women who have a surgical procedure to manage an ectopic pregnancy (62). This notwithstanding, until additional data are available, administration of Rh D immune globulin for all cases of ectopic pregnancy in Rh D-negative women is recommended.

Administration of Rh D immune globulin is recommended with all invasive diagnostic procedures, such as chorionic villus sampling or amniocentesis, in Rh D-negative women when the fetuses could be Rh D positive. Doses from 50 micrograms to 120 micrograms have been recommended before 12 weeks of gestational age (25, 30, 31). For chorionic villus sampling and amniocentesis performed after 12 weeks of gestation, 125 micrograms or 300 micrograms is recommended (30, 31).

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

In patients with antenatal hemorrhage after 20 weeks of gestation, the risk of Rh D alloimmunization is uncertain. However, consensus guidelines recommend that susceptible women with bleeding receive anti-D prophylaxis (25, 30, 31). Anti-D immune globulin is recommended for Rh D-negative women who experience antenatal hemorrhage after 20 weeks of gestation. Management of the patient with persistent or intermittent antenatal bleeding is complex. The most conservative approach may be to assess the volume of fetal–maternal hemorrhage with a quantitative test (such as the Kleihauer–Betke test). The appropriate amount of Rh D immune globulin then can be administered to cover the estimated volume of fetal–maternal hemorrhage. In cases of chronic or episodic bleeding this approach may need to be repeated. An intuitive but unproven strategy is to monitor the Rh D-negative patient with continuing antenatal hemorrhage with serial indirect Coombs testing for anti-D approximately every 3 weeks. If the result is positive, indicating the persistence of anti-D immune globulin, then theoretically no additional treatment with anti-D immune globulin is necessary. If the Coombs test result is negative, excessive fetal–maternal 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. However, the most conservative approach is to administer additional Rh D immune globulin as needed based on the quantity of fetal–maternal hemorrhage with some authorities recommending an estimation of fetal–maternal hemorrhage be carried out at 2-week intervals (25). Finally, it has been proposed in this clinical situation to use cell-free DNA testing to ascertain the fetal Rh D status and, thus, avoid repeated administration of doses of anti-D immune globulin with an Rh D-negative fetus (25).

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

Current U.S. Preventive Services Task Force guidelines recommend repeated Rh D antibody testing for all unsensitized Rh D-negative women at 24–28 weeks of gestation, unless the biological father is known to be Rh D negative (grade B recommendation) (69). Consensus guidelines from around the world recommend that a routine antenatal antibody screen should be obtained at 28 weeks of gestation before administration of anti-D immune globulin (25, 30, 31). 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. The cost effectiveness of routinely repeating the antibody screen has been questioned because of the low incidence of Rh D alloimmunization occurring before 28 weeks of gestation (70). Regardless, routine antibody screening before anti-D immune globulin administration is advised.

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

The median half-life of anti-D immune globulin is 23 days in the third trimester (28). 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 fetal–maternal hemorrhage (29). 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 number of fetal erythrocytes not covered by anti-D immune globulin administration can be assumed to have entered maternal blood if the results of a Kleihauer–Betke test are positive, and an appropriate dose of Rh-immune globulin should be administered.

▶ *When should routine antenatal anti-D prophylaxis be given during pregnancy to prevent alloimmunization?*

Studies comparing the routine antenatal administration of anti-D immune globulin to historic controls have shown significant reductions in the incidence of maternal sensitization to the Rh D antigen. Women originally were offered targeted anti-D immunoglobulin with the aim of preventing sensitization after the birth of a Rh-positive infant and after other potentially sensitizing events such as miscarriage, termination of pregnancy, or invasive obstetric procedures. With this approach, the incidence of hemolytic disease of the newborn was substantially reduced (7). In a meta-analysis of six trials with more than 10,000 women that compared postpartum anti-D immune globulin prophylaxis within 72 hours of birth with no treatment or placebo, anti-D immune globulin greatly lowered the incidence of Rh D alloimmunization 6 months after birth (risk ratio [RR], 0.04; 95% CI, 0.02–0.06), and in a subsequent pregnancy (RR, 0.12; 95% CI, 0.07–0.23) (71). However, because of concerns of alloimmunization occurring before delivery, experts advocated for prophylactic antenatal anti-D immune globulin to be given in the third trimester (7). Several clinical trials have been conducted; however, the studies have been criticized for being of poor quality and varying substantially in study design with many of the studies using historical rather than concurrent controls (72). In a meta-analysis of two randomized controlled trials of 3,902 Rh D-negative women that compared anti-D immune globulin at 28 weeks and 34 weeks of gestation with no antenatal treatment (but all women who delivered a Rh-positive infant received postpartum anti-D immune globulin), there was no clear difference in the incidence of Rh D alloimmunization during pregnancy, after the birth of a Rh-positive infant, or within 12 months after the birth of a Rh-positive infant. No outcome information was available on the incidence of Rh D alloimmunization in a subsequent pregnancy (22). However, methods for performing bias-adjusted meta-analysis, which enables adjustment for differences in quality and design and, thus, allows all available evidence to be synthesized, are available. A meta-regression using these techniques was performed to estimate the association between the observed effectiveness of different anti-D dose regimens (73). In a bias-adjusted meta-analysis of 10 studies, the pooled odds ratio for a reduction of sensitization was estimated as 0.31 (95% CI, 0.17–0.56). The authors interpreted this result as providing strong evidence for the effectiveness of routine antenatal anti-D immune globulin prophylaxis in preventing sensitization of pregnant Rh D-negative women. Prophylactic anti-D immune globulin should be offered to unsensitized Rh D-negative women at 28 weeks of gestation. Following birth, if the infant is confirmed to be Rh D positive, all Rh D-negative women who are not known to be sensitized should receive anti-D immune globulin within 72 hours of delivery.

▶ *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 is sometimes associated

with fetal–maternal hemorrhage, which may lead to alloimmunization (74). 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, 30, 74). In Rh D-negative pregnant patients who have experienced abdominal trauma, quantification of fetal–maternal hemorrhage should be done to determine the need for additional doses of anti-D immune globulin (74).

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

Fetal death occurs in fetal–maternal hemorrhage in up to 13% of cases in which no obvious other cause (eg, hypertensive disease, fetal anomalies) is found (75–77). Rh D alloimmunization has been reported in cases of fetal death from massive fetal–maternal hemorrhage (78), although the contribution of this cause to 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, because the benefits are thought to outweigh the risk, 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 fetal–maternal hemorrhage at the time of diagnosis of fetal death to determine if additional anti-D immune globulin is required (25).

▶ *Should administration of anti-D immune globulin be repeated in patients with a pregnancy greater than 40 weeks of gestation?*

Anti-D immune globulin appears to persist for approximately 12 weeks in most patients, based on pharmacokinetic studies using modern assay methods (28). In the past, some authorities advised giving a second dose of Rh D immune globulin to women who have not given birth 12 weeks after receiving their antenatal dose (29). However, the vast majority of women who give birth more than 12 weeks after receiving antenatal Rh D immune globulin do not become alloimmunized. There is insufficient evidence at this time to make a recommendation for or against administering another dose of anti-D immune globulin to a Rh D-negative woman who remains undelivered at 40 weeks of gestation. Current consensus guidelines either have no recommendation (25, 30) or state that a repeat antepartum dose of anti-D immune globulin is generally not required at 40 weeks of gestation, provided the routine antenatal prophylaxis was given no earlier than 28 weeks of gestation (31).

▶ *Should all Rh D-negative women be screened for excessive fetal–maternal hemorrhage after delivery of a Rh D-positive infant?*

The risk of excessive fetal–maternal hemorrhage exceeding 30 mL of Rh D-positive fetal whole blood (the amount covered by the standard 300-microgram dose of anti-D immune globulin) at the time of delivery is approximately 2 to 3 per 1,000 (6, 7). Screening only pregnancies designated as high risk of excessive fetal–maternal hemorrhage, including cases of abruptio placentae, placenta previa, intrauterine manipulation, or fetal death detects only 50% of patients who require additional anti-D immune globulin (79). For this reason, it is recommended that all Rh D-negative women giving birth to Rh D-positive infants undergo additional testing initially with a qualitative screening test (such as the rosette assay) and, if indicated, quantitative testing (such as the Kleihauer–Betke test) to determine the number of doses of Rh D immune globulin required (5, 25, 30, 31).

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

Although a primary reason to prevent alloimmunization is to reduce risk in future pregnancies, there are other indications as well. Pregnancies occur despite sterilization procedures, and most are intrauterine. In addition, alloimmunization complicates crossmatching of blood products in the future (80). Thus, Rh D-negative women who are undergoing postpartum tubal sterilization are candidates for treatment with anti-D immune globulin. The downside of this approach is the low cost effectiveness of the strategy because of the low probabilities of sensitization with the just-completed pregnancy, of sterilization failure, and of a need to receive Rh D incompatible blood in the future (81). If an Rh D-negative woman who has had a sterilization procedure does become pregnant later, even with a miscarriage or ectopic pregnancy, she should be offered anti-D immune globulin in a similar manner as women without sterilization.

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

The ideal time to administer anti-D immune globulin is within 72 hours of a potentially sensitizing event.

However, volunteers have received a range of partial to complete protection when anti-D immune globulin was given as late as 13 days after exposure (82). The longer prophylaxis is delayed the less it will be protective, but it has been suggested that a patient may still receive some benefit from anti-D immune globulin as late as 28 days postpartum (29, 31).

Summary of Recommendations and Conclusions

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

- Prophylactic anti-D immune globulin should be offered to unsensitized Rh D-negative women at 28 weeks of gestation. Following birth, if the infant is confirmed to be Rh D positive, all Rh D-negative women who are not known to be sensitized should receive anti-D immune globulin within 72 hours of delivery.

The following recommendations are based on limited or inconsistent scientific evidence (Level B):

- Administration of Rh D immune globulin is recommended with all invasive diagnostic procedures such as chorionic villus sampling or amniocentesis in Rh D-negative women when the fetuses could be Rh D positive.

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

- External cephalic version (regardless of success) is associated with a 2–6% risk of fetal–maternal hemorrhage, and anti-D immune globulin is indicated for unsensitized Rh D-negative patient.
- It is reasonable to administer anti-D immune globulin to Rh D-negative women who are suspected of molar pregnancy and who undergo uterine evacuation.
- Although the risk of alloimmunization is low, the consequences can be significant, and administration of Rh D immune globulin should be considered in cases of spontaneous first-trimester miscarriage, especially those that are later in the first trimester.
- Because of the higher risk of alloimmunization, Rh D-negative women who have instrumentation for their miscarriage should receive Rh D immune globulin prophylaxis.
- Rh D immune globulin should be given to Rh D-negative women who have pregnancy termination, either medical or surgical.
- Administration of Rh D immune globulin for all cases of ectopic pregnancy in Rh D-negative women is recommended.
- Anti-D immune globulin is recommended for Rh D-negative women who experience antenatal hemorrhage after 20 weeks of gestation.
- Anti-D immune globulin should be administered to Rh D-negative women who have experienced abdominal trauma.
- Anti-D immune globulin should be administered to Rh D-negative women who experience fetal death in the second or third trimester.

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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 February 2017. 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 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.

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

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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