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CLINICAL USE OF RHESUS IMMUNE GLOBULIN PRODUCTS TO PREVENT ALLOIMMUNIZATION DURING PREGNANCY: **A primer for the health-systems pharmacist**

FACULTY

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OVERVIEW

CLINICAL USE OF RHESUS IMMUNE GLOBULIN PRODUCTS TO PREVENT ALLOIMMUNIZATION DURING PREGNANCY:

A primer for the health-systems pharmacist

Therapeutic plasma products are now commonly encountered in the health-system pharmacy. One such product is rhesus immune globulin (RhIG), a hyperimmune globulin plasma derivative targeting D-antigen positive red blood cells. Clinicians may be unaware of the rationale for use, differences between products, and timing of administration of RhIG.

In the US, the widespread clinical use of RhIG has markedly reduced the incidence of hemolytic disease of the fetus and newborn (HDFN), a devastating clinical condition often resulting in death or severe morbidity. There are four RhIG products currently available, with common clinical indications but differences in certain product attributes.

Medical education regarding the clinical use of RhIG and provides information aimed at allowing for optimal use of RhIG within the modern health-system. The role of the pharmacist in the selection of a RhIG product or products for health-system use is paramount. Pharmacists are also uniquely qualified to assist in the appropriate use of RhIG therapy. Finally, pharmacists are routinely involved in the education of patients and healthcare practitioners on the appropriate use of these products. As the role of the pharmacist evolves and becomes more focused on pharmaceutical care, there is a need for greater involvement by the pharmacist in understanding drug therapy management in individuals using RhIG therapy. This program has been created to provide an intensive and comprehensive overview of the complexities of anti-D immune globulin use geared specifically to the needs of pharmacists.

OBJECTIVES

At the end of this program, participants should be able to:

1. Review the immunologic basis and emerging therapeutic roles for Rho(D) immune globulin (RhIG);
2. Describe differences between the different RhIG products in the US market;
3. Review guiding principles for safe, effective and appropriate use of RhIG.

FACULTY



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CONTINUING EDUCATION

ACCREDITATION STATEMENT



This program is accredited by ACPE for 0.1 (1 hours) CEUs of Home Study. TG Medical Education LLC is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

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REQUIREMENTS FOR CE CREDIT

All participants are required to take a post-test after reading the home study materials. All those achieving a score of 70% or higher will be directed to the program evaluation form. For those scoring less than 70%, you will be given the opportunity to re-test in order to achieve a passing grade. After the completion of the program evaluation, participants can print their CE certificates. Please note that when completing the evaluation, you must include your correct NABP eID so that the credits can be transferred to the NABP within 60 days of the completion of the post-test.

FACULTY DISCLOSURES

Eric M. Tichy, PharmD, BCPS, FCCP has disclosed the following relevant affiliations or financial relationships with a commercial interest: he is a consultant and speaker for Baxter Bioscience and Grifols USA.

David Reardon, PharmD, BCPS has no relevant conflicts of interest to disclose.

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Clinical use of rhesus immune globulin products to prevent alloimmunization during pregnancy: a primer for the health-systems pharmacist

Objectives: At the end of this program, participants should be able to:

1. Review the immunologic basis and emerging therapeutic roles for Rho(D) immune globulin (RhIG);
2. Describe differences between the different RhIG products in the US market;
3. Review guiding principles for safe, effective and appropriate use of RhIG.

Introduction

The Rhesus (Rh) blood group system is used to describe the presence or absence of Rh proteins on the surface of red blood cells (RBCs).¹ Immunologically, the Rh D protein is of clinical significance as exposure to red blood cells containing the Rh D protein, denoted Rh D+ (D+), in subjects that do not express the protein, Rh D- (D-), may be antigenic and result in alloimmunization and production of anti-D antibodies. Rh immune globulin (RhIG) is a plasma derived hyperimmune globulin directed at D+ red blood cells.² Alloimmunization to the D antigen is a well described potential result of fetomaternal transplacental hemorrhage that can occur during pregnancy or childbirth in D- women who have a fetus that is D+. Alloimmunization may result in hemolytic disease of the fetus and newborn (HDFN) in future pregnancies. If RhIG therapy is instituted in the immediate period after exposure, alloimmunization can be avoided and the risk of life-threatening outcomes of HDFN can be mitigated.³ Below the use of RhIG to prevent alloimmunization, the differences between the available products in the US, and practical considerations for pharmacists in managing the utilization of this plasma product will be discussed.

Hemolytic Disease of the Fetus and Newborn

Hemolytic disease of the fetus and newborn (HDFN), also known as erythroblastosis fetalis, was first described in the 17th century, although the immunologic basis was not fully determined until the early 1940s.⁴ During pregnancy, a D-mother is exposed to blood from a D+ fetus as a result of asymptomatic fetomaternal hemorrhage. This induces a maternal immune response against the foreign antigen and alloimmunization occurs. This immune response leads to the production of IgM and IgG antibodies directed against the Rh D-antigen. Exposure with as little as 0.1mL of fetal RBCs may lead to the production of maternal anti-D antibodies.⁴ More commonly, however, exposure occurs during the detachment of the placenta in labor. Unlike IgM antibodies, IgG antibodies readily cross the placental barrier and enter the fetal circulation. The anti-D antibodies attach to the fetal RBCs and induce severe hemolysis.⁴ During subsequent pregnancies with a D+ infant, maternal anti-D IgG production occurs rapidly and to a higher titer. Historically, HDFN led to death due to kernicterus or hydrops fetalis in approximately 50% of affected infants. With the routine use of RhIG, this rate

has now declined now to less than 1% in developed countries.⁵

RhIG Products

RhIG preparations were first used in clinical practice in 1968 and reduced the risk of alloimmunization in the mother from 8.9% to less than 1%.⁶ Early preparations were derived from whole plasma and often resulted in reactions such as anaphylaxis due to impurities left over from the manufacturing process.^{7,8} Some of the currently available preparations are separated from whole plasma using more efficient methods, potentially leading to higher degree of purity. These products are able to be administered both intravenously and intramuscularly.^{8,9} There are currently four FDA-approved products available in the U.S. Table 1 highlights clinically significant differences between products including the FDA-approved indications, dosing, and route(s) of administration.¹⁰⁻¹³ RhIG products differ in methods of preparation, final product components, and indications, but share the same mechanism of action and general purpose for use. RhIG products have also been shown to be effective in the treatment of idiopathic thrombocytopenic purpura (ITP) although this is beyond the scope of this program.^{10,13}

Mechanism of Action

The specific mechanism of RhIG-mediated prevention of alloimmunization is quite complex and not yet fully understood.³ Administration of RhIG to healthy male volunteers has demonstrated a rapid binding and clearance of D+ red blood cells and that clearance occurred in a dose-dependent manner.^{14,15} Additional investigations have shown that administration of RhIG prevents the development of anti-D antibodies in volunteers exposed to the Rh D antigen.¹⁴ This effect is known as antibody-mediated immune suppression (AMIS) and is the immunologic basis for the administration of RhIG to prevent alloimmunization.¹⁶

There are several proposed mechanisms of AMIS. The antigen clearance hypothesis involves removal of D+ red blood cells from systemic circulation by macrophages by FcγR-mediated phagocytosis prior to recognition by the immune system.¹⁷ This hypothesis does not account for non-

Table 1. Comparison of RhIG products available in the U.S.

	RhoGAM® MICRhoGAM®	Rhophylac®	HyperRho™ S/D	WinRho® SDF
FDA-approved indications	<ul style="list-style-type: none"> – Pregnancy and other obstetrical conditions – Transfusion of Rh- incompatible blood or blood products 	<ul style="list-style-type: none"> – Pregnancy and other obstetrical conditions – Transfusion of Rh- incompatible blood or blood products – ITP 	<ul style="list-style-type: none"> – Pregnancy and other obstetrical conditions – Transfusion of Rh- incompatible blood or blood products 	<ul style="list-style-type: none"> – Pregnancy and other obstetrical conditions – Transfusion of Rh- incompatible blood or blood products – ITP
FDA Approved Dosing for antepartum and postpartum^a	<ul style="list-style-type: none"> – 300 mcg Week 26 to 28 of gestation – 300 mcg within 72 hours of birth 	<ul style="list-style-type: none"> – 300 mcg Week 28 to 30 of gestation – 300 mcg within 72 hours of birth 	<ul style="list-style-type: none"> – 300 mcg at around Week 28 of gestation – 300 mcg within 72 hours of birth 	<ul style="list-style-type: none"> – 300 mcg at Week 28 of gestation – 120 mcg within 72 hours of birth
Dosage size (mcg)	50 or 300	300	50 or 300	120, 300, 500, 1000, 3000
How supplied	RTUS	RTUS	RTUS	Single-dose vial
Route of administration	IM only	IV or IM	IM only	IV or IM
Half-life	30.9 days	16+4 days (IV) 18+5 days (IM)	23 – 26 days	24 days (IV) 30 days (IM)
IgA content	<15mcg/dose	<5mcg/mL	Not disclosed	Approx. 5mcg/mL
Stabilizer	Glycine	Albumin	Glycine	Maltose-
Preservative and latex content	Preservative and latex free	Preservative and latex free	Preservative and latex free	Preservative free

IM = intramuscular; ITP = idiopathic thrombocytopenic purpura; IV = intravenous; RTUS = ready-to-use syringe

a = additional dosing required for blood exposure greater than 15 mL

b = similar dosing recommendations for abortion, amniocentesis, or any other manipulation after 34 weeks gestation

c = maltose can interfere with certain blood glucose monitoring systems

macrophage mediated clearance of antigen-coated red blood cells. Other explanations for AMIS including antigen “masking” by bound IgG as well as IgG-mediated cross-linking and subsequent down regulation of B-cell response have been proposed.¹⁷ These proposed mechanisms have either failed to fully explain AMIS or have resulted in paradoxically opposing effects.¹⁶ Ongoing research is currently attempting to further delineate the specific mechanism behind the prevention of alloimmunization by administration of RhIG.³

Pharmacokinetics and Pharmacodynamics

As stated in Table 1, the half-lives of the available RhIG products range from 16 to nearly 31 days and vary by product and route of administration. Time to maximum serum concentration is also affected by route of administration with IV administration reaching a peak concentration in <2 hours versus 4 to 10 days with IM administration. Administration via the IV route also produces a significantly higher peak serum concentration. Despite the differences in pharmacokinetics between the available products and routes of administration, there is no difference in efficacy. Products and routes with shorter elimination times need to be administered at the appropriate time to ensure detectable plasma concentrations at times of increased HDFN risk.^{18,19}

Some RhIG products may be administered both IV and IM with limited data comparing the efficacy of one route of administration to the other. Depending upon the clinical scenario and patient preference, either method of administration may be appropriate. A Cochrane Review utilized data from two studies to determine if either route of administration was superior.^{18,20} IM and IV administration

were found to be equally effective, although a relatively low total number of patients were included in the analysis. Another difference between the products is the recommended antenatal dosing interval likely due to differences in half-life previously described. While there is some overlap in the dosing recommendations, the concern is for potential waning of effectiveness at the end of pregnancy if the first antepartum dose is not timed appropriately. The product with the shortest product half-life, Rhophylac®, should be administered between gestational weeks 28 and 30, whereas intramuscular RhoGAM® Ultra-FilteredPLUS, which has a longer half-life is recommended to be given between gestational weeks 26 and 28. In order to ensure that circulating concentrations of anti-D antibody are at adequate levels during the period of highest risk for fetomaternal hemorrhage (i.e., during labor), specific product labeling and dosage recommendations should be followed.

The World Health Organization (WHO) has estimated that 25 mcgs of RhIG is able to provide protection against alloimmunization from 1 mL of D+ fetal red blood cells.²¹ This dose would yield a circulating plasma concentration of 2.4 ng/mL.^{22,23} This concentration is based on the average circulating blood volume in the pregnant woman and does not account for interpatient variability. It can still serve as a general guide for RhIG dosing. This standard ratio of 25 mcg RhIG:1 mL RBC may not be appropriate in all situations as pharmacodynamic analyses have shown that clearance is non-linear across a range of RBC volumes.²³ For this reason, clinical guidelines for the prevention of Rh sensitization recommend “rounding up” the dose to the next whole syringe, after calculating the dose required by assessment of the amount of fetomaternal transfusion.^{24,25}

Clinical Efficacy

As fetomaternal hemorrhage may occur throughout the pregnancy and during delivery, the prevention of alloimmunization should be considered in both the antenatal and post-natal settings. Early trials showed a substantial benefit of antenatal RhIG in women at risk of sensitization. Rates of alloimmunization decreased to 0% among women treated with 145 mcg to 435 mcg versus 7.2% in the untreated control group.²⁶ Turner et al found that prophylaxis is highly effective at preventing alloimmunization with a pooled odds ratio of 0.31 (95% CI 0.17 – 0.56) after performing a bias-adjusted meta-analysis of available studies of routine antenatal prophylaxis with RhIG.²⁷ Additional analyses were performed to identify the most effective dosing scheme and found that all currently utilized regimens were effective. However, a two-dose strategy of 250 mcg was more likely to be effective than a single-dose 300 mcg strategy. The Cochrane Collaboration published a meta-analysis which contrasts these results. This meta-analysis found that antenatal prophylaxis is ineffective at preventing alloimmunization, with a relative risk of 0.42 (95% CI 0.15 – 1.17).²⁸ One of the two trials included in the meta-analysis utilized a two-dose series of 50 mcg RhIG which may not be as effective as a single 300 mcg dose and therefore the results of this meta-analysis may not reflect current clinical practice.

Post-natal RhIG has been associated with a drastic decrease in the incidence of Rh alloimmunization if given within 72 hours of delivery for women with Rh-incompatible pregnancies.²⁹ A Cochrane Review of post-natal prophylaxis showed a relative risk of 0.04 for women receiving prophylaxis versus those who do not. The review included multiple dosing strategies and over 10,000 women but demonstrated the consistency of this effect across treatment groups and dosing strategies.³⁰ The optimal dose for post-natal prophylaxis remains unclear, although higher doses may be favorable, which is consistent with the previously described dose-dependent neutralization effect of RhIG.³ Another systematic review of studies evaluating a variety of dosing schemes further demonstrates the efficacy of routine antenatal RhIG prophylaxis when given in addition to post-natal dosing, with sensitization rates decreasing from 2.2% in the untreated group to as low as 0% with treatment.³¹ The authors concluded that women most likely to benefit from RhIG administration are those with Rh-incompatible fetuses, those who desire to have additional children, and those who are at risk for sensitization.

Other events during pregnancy may also lead to maternal alloimmunization. Spontaneous and planned abortions pose a risk of transplacental hemorrhage of 1.5 – 5%, while chorionic villus sampling is associated with a small degree of hemorrhage in nearly all cases, with potentially sensitizing volumes greater than 0.1 mL in up to one-third of cases.^{32,33} Other invasive events, including amniocentesis, ectopic pregnancy, and abdominal trauma during pregnancy also pose a risk.^{34,35} Even non-invasive procedures such as

external cephalic version (a procedure used to correct breech presentation) are associated with fetomaternal hemorrhage in as many as 6% of cases.³⁶ There are limited data to guide the utilization of RhIG prophylaxis in these cases, with most recommendations originating from expert opinion.³⁷

In addition to fetomaternal hemorrhage, alloimmunization may also occur as a result of inadvertent administration of Rh-incompatible blood products.² There are similarly limited data available to guide treatment strategies in the event of an Rh-incompatible blood transfusion. Pollack et al transfused healthy D- volunteers with D+ RBCs, and determined that a minimum of 20 mcg of RhIG was necessary to prevent alloimmunization from 1 mL of RBCs.³⁸ Earlier case reports have shown that the administration of high-doses of RhIG is both well-tolerated and effective at preventing alloimmunization, indicating that large doses may be appropriate in the event of a massive transfusion of Rh-incompatible blood products.³⁹

Laboratory Assessment of Risk

There are a number of tests available to determine if fetal blood has entered maternal circulation and if RhIG prophylaxis is necessary, or if larger-than-standard doses are necessary. The most commonly utilized assay is the Kleihauer-Betke test (KBT). This test allows visual identification and quantification of the fetal blood present in a blood sample following acid elution and staining with erythrosine. It can also identify when there is a need for supplemental RhIG.⁴⁰ Certain clinical situations, such as maternal trauma, may warrant performance of the KBT although the test is subject to operator error in its interpretation.^{41,42} Additional methods of testing for fetal hemoglobin, may be superior to KBT but are not routinely used in clinical practice and include flow cytometry and fluorescent microscopy.^{43,44}

Recommendations for RhIG Use

There are a number of international guidelines available that provide recommendations for RhIG use to prevent alloimmunization although there are significant variations in those recommendations. In the U.S., three organizations have published recommendations on the optimal use of RhIG. The American Society of Clinical Pathologists (ASCP) and United States Preventive Services Taskforce (USPSTF) recommend an antenatal dose of 300 mcg followed by another dose in the post-natal period if the infant is D+.^{45,46} The American College of Obstetrics and Gynecology (ACOG) recommends a 50 mcg dose for first trimester events (due to lower fetal blood volume at this time) and 300 mcg for events after the first trimester including a routine antenatal dose of 300 mcg at 28 weeks gestation.²⁵ The ACOG recommendations are summarized in Table 2.

Table 2. ACOG recommendations for the prevention of Rh-D alloimmunization in Rh-negative women

Clinical Scenario	Prophylaxis Recommended (Y/N)
Paternity	
– Father Rh+ / Mother Rh-	Y
– Father Rh- / Mother Rh-	N
– Father unknown / Mother Rh-	Y
– Mother Rh+	N
Previously sensitized mother	N
Weakly Rh+ mother	N
Threatened abortion before 12 wks	No recommendation
First-trimester events/procedures	Y (50 mcg)
Second or third-trimester events/procedures	Y (300 mcg)
Molar pregnancy with uterine evacuation	Y
Intrauterine fetal demise in second/third trimester	Y (FMHS recommended)
Second- or third-trimester antenatal hemorrhage	Y (FMHS recommended)
Abdominal trauma in pregnancy	Y (FMHS recommended)
Clinically missed sensitizing event	Y (up to 28 days following event)
Post-date pregnancy	No recommendation

FMHS = fetomaternal hemorrhage screening

Cost Effectiveness of Routine Prophylaxis

A 2013 study in the United States evaluated the cost-effectiveness of routine antenatal RhIG prophylaxis in D-women versus targeted prophylaxis after non-invasive fetal RhD typing. The cost of routine prophylaxis was \$351 per pregnancy compared to \$682 for non-invasive testing. Approximately 60% of women tested will still require administration of RhIG, so the cost of testing would have to decrease to \$119 to have a neutral economic impact.⁴⁷ In a similar analysis published the same year from Quebec, routine prophylaxis was shown to be far more cost effective than fetal RhD typing followed by targeted prophylaxis.⁴⁸ Because of the evidence showing the cost-effectiveness of routine antenatal RhIG prophylaxis, the ACOG guidelines state it would be unethical to withhold RhIG from any woman at risk for alloimmunization.²⁵

Patient Selection and Dosing Considerations

Despite the well-described benefits of RhIG prophylaxis and substantial support in the literature, there is still opportunity for improvement in the administration of RhIG. A 15-year systematic surveillance report spanning from 1996 to 2011 from the United Kingdom reported over 1,200 errors in RhIG administration. Omitted or late administration of a dose accounted for 50.9% of cases and 37.1% of the errors involved unnecessary administration of RhIG because the mother was already sensitized to D antigen or was D+ herself, or the infant was D-.⁴⁹ Administration of RhIG provides no therapeutic benefit in these situations and exposes patients to an unnecessary risk of medication-

related adverse events. A Canadian study reported that among 1,861 women eligible for RhIG, only 85.7% received appropriate antenatal prophylaxis while 98.5% received proper postnatal prophylaxis.⁵⁰ Factors associated with inadequate prophylaxis included lack of prenatal care before the third trimester, transfer from an outside facility, and initial licensing of the attending physician before 1980.

Based on current ACOG guidance, unless it is certain that the father is also D-, all D- women should receive routine antenatal prophylaxis.²⁵ Postpartum RhIG administration is dependent on fetal Rh status with further dosing being unnecessary in the case of a D- infant. ACOG offers no specific dosage recommendations, but based on the other United States-based organizations, a single antenatal dose of 300 mcg at 28 weeks of gestation and a postpartum dose of 300 mcg is recommended.

Adverse Events

Adverse events resulting from the administration of RhIG are uncommon with the currently available products. There is a theoretical risk of transmission of infectious agents with RhIG -since it is derived from human plasma.⁵¹ Current manufacturing processes incorporate several key steps to diminish these risks including the detection of viruses from the starting plasma with direct or indirect diagnostic tests (e.g., hepatitis B surface antigen or anti-HCV antibodies). Additionally, specific steps in manufacturing, such as nanofiltration, inactivation of lipid-enveloped viruses by detergents, chemical degradation *via* pH modification, enzymatic inactivation of the viruses, heat treatment, or other steps may all be used to eliminate potentially transmissible infectious diseases. In a clinical trial of 261 women evaluating intravenous or intramuscular administration of an RhIG product, no serious adverse events attributable to drug exposure were identified. Minor adverse reactions, although uncommon, included pain or irritation at the injection site in two women given intramuscular RhIG and in one woman given intravenous RhIG.¹⁸

In general RhIG products are well-tolerated. Common adverse effects include headache, flushing, injection site reactions, and malaise. The majority of these adverse events are dose-related may not be of great concern with the relatively small doses of RhIG utilized in prophylaxis.⁵² In patients with IgA deficiencies and antibodies to IgA, anaphylaxis may occur following administration of an IgA-containing product.⁵³ Care should be taken to utilize IgA-depleted products if a patient has a known hypersensitivity to IgA.

RhIG products that are maltose-stabilized, such as WinRho® SDF, can interfere with certain glucose monitoring technologies, specifically those using the glucose dehydrogenase pyrroloquinoline quinone (GDH-PQQ) methodology. The glucose monitors cannot distinguish between glucose and maltose and when a GDH-PQQ glucose test strip is utilized on blood containing maltose, a significant false elevation in glucose reading may result.⁵⁴ This can lead to inappropriate dosing and administration of

insulin, potentially resulting in hypoglycemia, coma, or death.⁵⁵

Product Selection

No evidence exists to support the clinical benefit of one product or route of administration over another. Product and patient characteristics should determine the selection of a product for addition to a hospital formulary or for administration to specific patients. All products are labeled for intramuscular administration. Given the therapeutic equivalence and similar uses of these products, product availability and contracting costs may be the pivotal driving factors in selecting a formulary product. Product-specific characteristics, such as the presence of IgA (in the case of an IgA-deficient patient) or use of GDH-PQQ glucose test strips (if the formulary product contains maltose), should be considered.

Conclusions

Routine administration of RhIG to women at risk of Rh alloimmunization is clinically effective and has made HDFN a rare clinical event. Pharmacists can help ensure that women at risk for alloimmunization receive appropriate RhIG prophylaxis through monitoring of at-risk women and application of evidence-based practice. Although these products have been available for many years, it is important to note that there are differences in their formulations and careful review should be done to ensure they are administered safely and appropriately.

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Assessment Questions

- Which of following represents a high-risk pregnancy for developing hemolytic disease of the fetus and newborn (HDFN)?
 - Maternal Rh D+, Fetal Rh D+
 - Maternal Rh D+, Fetal Rh D-
 - Maternal Rh D-, Fetal Rh D-
 - Maternal Rh D-, Fetal Rh D+
- What is the approximate risk of maternal alloimmunization associated with the routine use of RhIG?
 - 15%
 - 10%
 - 5%
 - <1%
- Which of the following routes of administration commonly used in clinical practice is associated with the shortest elimination half-life?
 - Intramuscular
 - Oral
 - Intravenous
 - Rectal
- Products that contain maltose as a stabilizing agent may interfere with routine laboratory monitoring of what serum assay?
 - Potassium
 - Glucose
 - Sodium
 - Serum creatinine
- All mothers should receive a post-natal dose of RhIG.
 - True
 - False
- Which of the following was the most common error associated with the administration of RhIG in the United Kingdom?
 - Late or omitted dose
 - Unnecessary administration
 - Inappropriate dose
 - Inappropriate route
- Which if the following is the most appropriate dose to be given for events after the first trimester including the routine antenatal dose and post-natal dose based on U.S. organization recommendations?
 - 50 mcg
 - 100 mcg
 - 200 mcg
 - 300 mcg
- It is more cost effective to provide routine antenatal RhIG prophylaxis in Rh D- women versus targeted prophylaxis non-invasive fetal RhD typing.
 - True
 - False
- What is the mortality associated with the development of hemolytic disease of the fetus and newborn (HDFN)?
 - 20%
 - 35%
 - 50%
 - 65%
- What is the proposed mechanism of action of RhIG?
 - Antibody-mediated immune suppression (AMIS)
 - Red blood cell hemolysis
 - Stimulation of anti-D antibody production
 - Direct inhibition of T-cells

Requirements for CE credit:

All participants are required to take a post-test after reading the home study materials. All those achieving a score of 70% or higher will be directed to the program evaluation form. For those scoring less than 70%, you will be given the opportunity to re-test in order to achieve a passing grade. After the completion of the program evaluation, participants can print their CE certificates. Please note that when completing the evaluation, you must include your correct NABP eID so that the credits can be transferred to the NABP within 60 days of the completion of the post-test.

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