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INTERIM UPDATE

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INTERIM UPDATE: This Practice Bulletin is updated as highlighted to reflect a limited, focused change to align with Practice Bulletin No. 181, *Prevention of Rh D Alloimmunization.*

Management of Alloimmunization During Pregnancy

When any fetal blood group factor inherited from the father is not possessed by the mother, antepartum or intrapartum fetal–maternal bleeding may stimulate an immune reaction in the mother. Maternal immune reactions also can occur from blood product transfusion. The formation of maternal antibodies, or "alloimmunization," may lead to various degrees of transplacental passage of these antibodies into the fetal circulation. Depending on the degree of antigenicity and the amount and type of antibodies involved, this transplacental passage may lead to hemolytic disease in the fetus and neonate. Undiagnosed and untreated, alloimmunization can lead to significant perinatal morbidity and mortality. Advances in Doppler ultrasonography have led to the development of noninvasive methods of management of alloimmunization in pregnant women. Together with more established protocols, Doppler ultrasound evaluation may allow for a more thorough and less invasive workup with fewer risks to the mother and fetus. Prevention of alloimmunization is addressed in another Practice Bulletin (1).

Background

Nomenclature

The nomenclature for the Rh (CDE) blood group system is complex and often confusing. Five major antigens can be identified with known typing sera, and there are many variant antigens. Of the numerous nomenclature systems that have been developed, the Fisher–Race nomenclature is best known and most compatible with our understanding of the inheritance of the Rho (or D) antigen and the clinical management of Rh alloimmunization (2). The Fisher–Race nomenclature presumes the presence of three genetic loci, each with two major alleles. The antigens produced by these alleles originally were identified by specific antisera and have been lettered C, c, D, E, and e. No antiserum specific for a "d" antigen has been found, and use of the letter "d" indicates the absence of an evident allelic product. Anti-C, anti-c, anti-D, anti-E, and anti-e designate specific antibodies directed against their respective antigens.

An Rh gene complex is described by the three appropriate letters. Eight gene complexes are possible (listed in decreasing order of frequency among whites): CDe, cde, cDE, cDe, Cde, cdE, CDE, and CdE. Genotypes are indicated as pairs of these gene complexes, such as CDe/cde. Certain genotypes, and thus certain phenotypes, are more prevalent than others. The genotypes CDe/cde and CDe/CDe are the most common, with approximately 55% of all whites having the CcDe or CDe phenotype (3). The genotype CdE has never been demonstrated in vivo (2).

Most of the cases of Rh alloimmunization causing transfusion reactions or serious hemolytic disease in the

fetus and newborn are the result of incompatibility with respect to the D antigen. For this reason, the designation Rh positive usually indicates the presence of the D antigen and Rh negative indicates the absence of D antigen on erythrocytes.

In addition to the five major antigens of the Rh system, more than 30 antigenic variants have been identified. Among these are the Cw antigen and the Du antigen, which is now referred to as weak D. The latter is a heterogeneous group of clinically important D antigen variants. Some weak D-positive patients are capable of producing the anti-D antibody, although alloimmunization rarely occurs.

Other Antibodies

The most frequently encountered antibodies other than D are Lewis (Lea and Leb) and I antibodies. Like most cold agglutinins, Lewis and I antigens do not cause erythroblastosis fetalis because they are predominantly of the immunoglobulin M type and they are poorly expressed on fetal and newborn erythrocytes. In contrast, Kell antibodies (anti-K) can produce erythroblastosis fetalis. A more complete list of antibodies and their effects can be found in Table 1. Often, Kell alloimmunization is caused by prior transfusion because Kell compatibility was not considered when the blood was cross-matched. Care of patients with sensitization to antigens other than D that are known to cause hemolytic disease should be the same as that for patients with D alloimmunization. A possible exception is Kell sensitization, in which amniotic fluid analysis has been reported to correlate poorly with the severity of fetal anemia (4). These patients may benefit from more aggressive fetal assessment, such as measurement of the peak systolic velocity in the fetal middle cerebral artery; however, optimal care of Kell-sensitized patients is controversial (4).

Incidence of Rh-Incompatible Pregnancy

The incidence of Rh incompatibility varies by race and ethnicity. Approximately 15% of whites are Rh negative, compared with only 5–8% of African Americans and 1–2% of Asians and Native Americans. Among whites, an Rh-negative woman has an approximate 85% chance of mating with an Rh-positive man, 60% of whom are heterozygous and 40% of whom are homozygous at the D locus.

Causes of Rh Alloimmunization

Rh alloimmunization can occur only if a sufficient number of erythrocytes from an Rh-positive fetus gain access to the circulation of its Rh-negative mother. The volume necessary to cause alloimmunization varies from patient to patient and is probably related to the immunogenic capacity of the Rh-positive erythrocytes and the immune responsiveness of the mother. Fetomaternal hemorrhage sufficient to cause alloimmunization occurs most commonly at delivery, in 15–50% of births (5–8). Specific clinical factors such as cesarean delivery, multifetal gestation, bleeding placenta previa or abruption, manual removal of the placenta, and intrauterine manipulation may increase the volume of fetomaternal hemorrhage. In most cases, though, excessive fetomaternal hemorrhage occurs with uncomplicated vaginal delivery (9, 10). The volume of fetal blood entering the maternal circulation is 0.1 mL or less in most cases resulting in alloimmunization (8, 11). Approximately 1–2% of Rh alloimmunization is caused by antepartum fetomaternal hemorrhage (12). In one large series, fetomaternal hemorrhage was detected in 7% of patients during the first trimester, in 16% of patients during the second trimester, and in 29% of patients during the third trimester (5). Detectable fetomaternal hemorrhage resulting in alloimmunization may occur in first-trimester spontaneous and induced abortion (13). Alloimmunization also has been reported after threatened abortion and ectopic pregnancy (14, 15). Several obstetric procedures may lead to fetomaternal hemorrhage and, in turn, maternal alloimmunization. These include chorionic villus sampling, pregnancy termination, amniocentesis, and external cephalic version (16–18).

Anti-D Immune Globulin to Prevent Alloimmunization

Anti-D immune globulin is not indicated for patients previously sensitized to D. However, it is indicated for patients who might be sensitized to other blood group antigens.

Clinical Considerations and Recommendations

▶ ***What are the best screening methods for detecting alloimmunization in women?***

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. These laboratory assessments should be repeated in each subsequent pregnancy. The American Association of Blood Banks also recommends repeated antibody screening before administration of anti-D immune globulin at 28 weeks of gestation, postpartum, and at the time

Table 1. Atypical Antibodies and Their Relationship to Fetal Hemolytic Disease

Blood Group System	Antigens Related to Hemolytic Disease	Hemolytic Disease Severity	Proposed Management
Lewis	*		
I	*		
Kell	K	Mild to severe†	Fetal assessment
	k	Mild	Routine obstetric care
	Ko	Mild	Routine obstetric care
	Kp^a	Mild	Routine obstetric care
	Kp^b	Mild	Routine obstetric care
	Js^a	Mild	Routine obstetric care
	Js^b	Mild	Routine obstetric care
Rh (non-D)	E	Mild to severe†	Fetal assessment
	C	Mild to severe†	Fetal assessment
	C	Mild to severe†	Fetal assessment
Duffy	Fy^a	Mild to severe†	Fetal assessment
	Fy^b	‡	Routine obstetric care
	By^3	Mild	Routine obstetric care
Kidd	Jk^a	Mild to severe	Fetal assessment
	Jk^b	Mild	Routine obstetric care
	Jk^3	Mild	Routine obstetric care
MNSs	M	Mild to severe	Fetal assessment
	N	Mild	Routine obstetric care
	S	Mild to severe	Fetal assessment
	s	Mild to severe	Fetal assessment
	U	Mild to severe	Fetal assessment
	Mi^a	Moderate	Fetal assessment
MSSs	Mt^a	Moderate	Fetal assessment
	Vw	Mild	Routine obstetric care
	Mur	Mild	Routine obstetric care
	Hil	Mild	Routine obstetric care
	Hut	Mild	Routine obstetric care
Lutheran	Lu^a	Mild	Routine obstetric care
	Lu^b	Mild	Routine obstetric care
Diego	$D1^a$	Mild to severe	Fetal assessment
	Di^b	Mild to severe	Fetal assessment
Xg	Xg^a	Mild	Routine obstetric care
P	PP_{1pk} (Tj^a)	Mild to severe	Fetal assessment
Public antigens	Yt^a	Moderate to severe	Fetal assessment
	Yt^b	Mild	Routine obstetric care
	Lan	Mild	Routine obstetric care
	En^a	Moderate	Fetal assessment
	Ge	Mild	Routine obstetric care
	Jr^a	Mild	Routine obstetric care
	Co^a	Severe	Fetal assessment
	Co^{1-b-}	Mild	Routine obstetric care
Private antigens	Batty	Mild	Routine obstetric care
	Becker	Mild	Routine obstetric care
	Berrens	Mild	Routine obstetric care

(continued)

Table 1. Atypical Antibodies and Their Relationship to Fetal Hemolytic Disease *(continued)*

Blood Group System	Antigens Related to Hemolytic Disease	Hemolytic Disease Severity	Proposed Management
Private antigens	Biles	Moderate	Fetal assessment
	Evans	Mild	Routine obstetric care
	Gonzales	Mild	Routine obstetric care
	Good	Severe	Fetal assessment
	Heibel	Moderate	Fetal assessment
	Hunt	Mild	Routine obstetric care
	Jobbins	Mild	Routine obstetric care
	Radin	Moderate	Fetal assessment
	Rm	Mild	Routine obstetric care
	Ven	Mild	Routine obstetric care
	Wright[a]	Severe	Fetal assessment
	Wright[b]	Mild	Routine obstetric care
	Zd	Moderate	Fetal assessment

*Not a proven cause of hemolytic disease of the newborn

†With hydrops fetalis

‡Not a cause of hemolytic disease of the newborn

Modified from Weinstein L. Irregular antibodies causing hemolytic disease of the newborn: a continuing problem. Clin Obstet Gynecol 1982;25:321.

of any event in pregnancy. ~~Patients who are weak D (Du) positive are not at risk for alloimmunization and should not receive anti-D immunoprophylaxis.~~

▶ *At what antibody titer should an additional evaluation be initiated?*

The usefulness of maternal serum antibody titers is determined by the patient's reproductive history. For a woman with a history of a previously affected fetus or neonate, serial titer assessment is inadequate for surveillance of fetal anemia. Titer values are reported as the integer of the greatest tube dilution with a positive agglutination reaction. Variation in titer results from different laboratories is not uncommon, so titers should be obtained in the same laboratory when monitoring a patient, and a change of more than one dilution is significant. A *critical* titer is that titer associated with a significant risk for severe erythroblastosis fetalis and hydrops, and in most centers this is between 1:8 and 1:32. If the initial antibody titer is 1:8 or less, the patient may be monitored with titer assessment every 4 weeks. For patients with alloimmunization involving antigens other than D, similar titer levels should be used to guide care except in Kell-sensitized patients because Kell antibodies do not correlate with fetal status (19).

▶ *What ancillary tests should follow identification of maternal antibodies to diagnose hemolytic disease in the fetus?*

Determination of Paternal Genotype

The initial management of a pregnancy involving an alloimmunized patient is determination of the paternal erythrocyte antigen status. If the father is negative for the erythrocyte antigen in question (and it is certain that he is the father of the fetus), further assessment and intervention are unnecessary. In cases of Rh-D alloimmunization in which the father is Rh positive, the probability that he is heterozygous for the D antigen can be reliably estimated by using Rh-D antisera to determine his most likely genotype. This involves mixing antisera, containing antibodies to the D antigen, with the father's cells to determine if the D antigen is present. A positive result is determined by agglutination caused by the cross-linking of the antibody with the corresponding antigen. If the father is homozygous for the D antigen, all his children will be Rh positive; if he is heterozygous, there is a 50% likelihood that each pregnancy will have an Rh-negative fetus that is not at risk of anemia. Given that the genes coding for the D antigen are known, a DNA-based diagnosis is commercially available. This form of diagnosis also can be used to identify a number of minor antigens (C, c, E, and e). Evaluation of alloimmunization to other erythrocyte antigens known to be associated with erythroblastosis fetalis (Table 1) should be performed in the same manner.

Determination of Fetal Genotype

The fetal antigen type should be assessed when the paternal genotype is thought to be heterozygous or is

unknown. Amniocentesis is the primary modality used to determine fetal blood type using polymerase chain reaction (PCR) on uncultured amniocytes in 2 mL of amniotic fluid. The sensitivity and specificity of PCR typing are reported as 98.7% and 100%, respectively, with positive and negative predictive values of 100% and 96.9% (20). Chorionic villus biopsy also has been employed for this purpose, but its use should be discouraged because disruption of the villi may result in unnecessary fetomaternal hemorrhage and worsening alloimmunization (21). If the fetus is found to be negative for the erythrocyte antigen in question, further testing may not be warranted (20). Although the false-negative rate is low (1–3%), periodic noninvasive assessment may be warranted (20).

Detection of fetal D by molecular analysis of maternal plasma or serum can be assessed in the second trimester with greater than 99% accuracy (22, 23). This is possible because of high concentrations of fetal DNA found in maternal plasma (24). It should be noted, however, that this is not a widely used clinical tool.

Spectral Analysis of Amniotic Fluid

Historically, measurement of amniotic fluid bilirubin levels using spectral analysis at 450 nm (ΔOD450) has been the accepted method of assessing the severity of erythroblastosis in utero. Fetal status was determined by plotting the ΔOD450 measurement on either a Liley graph in the late second and third trimesters (25) or on the Queenan curve for earlier gestational ages (19–25 weeks). The current trend is management with middle cerebral artery Doppler ultrasonography.

▶ *What is the role of middle cerebral artery Doppler testing to predict fetal anemia?*

Recent advances in Doppler technology have lead to the development of noninvasive methods to assess the degree of fetal anemia. Doppler was used to measure the peak systolic velocity in the fetal middle cerebral artery in 111 fetuses at risk for fetal anemia secondary to red cell alloimmunization (Fig. 1) (26). Moderate or severe anemia was predicted by values of peak systolic velocity

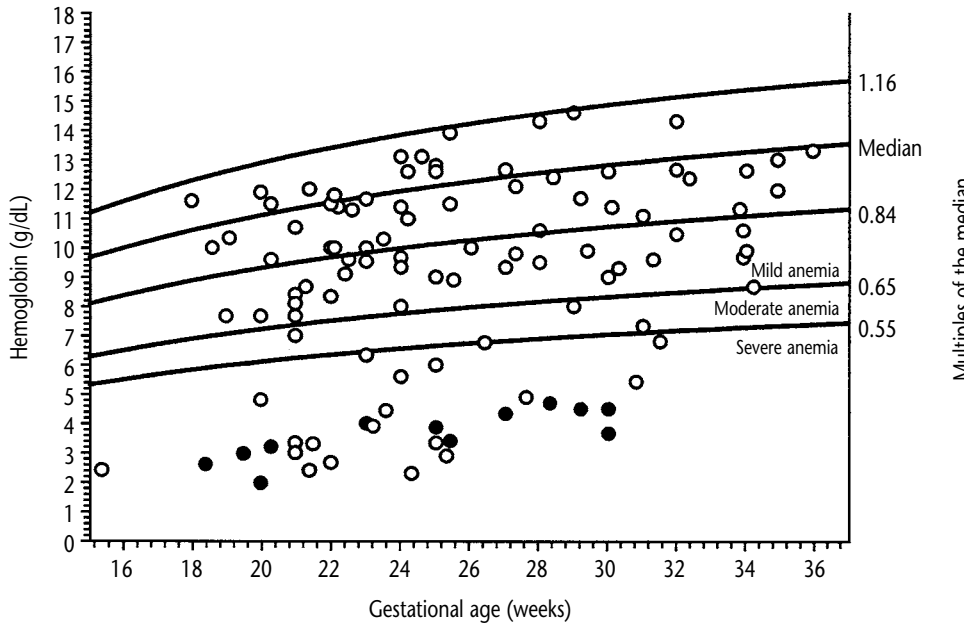

Figure 1. Hemoglobin concentrations in 265 healthy fetuses and 111 fetuses that underwent cordocentesis. The reference range in the healthy fetuses was between 0.84 and 1.16 times the median (corresponding to the 5th and 95th percentiles). Values for the 111 fetuses that underwent cordocentesis are plotted individually. Solid circles indicate fetuses with hydrops. (Reprinted from Mari G, Deter RL, Carpenter RL, Rahman F, Zimmerman R, Moise KJ Jr, et al. Noninvasive diagnosis by Doppler ultra-sonography of fetal anemia due to maternal red-cell alloimmunization. Collaborative Group for Doppler Assessment of the Blood Velocity of Anemic Fetuses. N Engl J Med 2000:342:9–14. Copyright 2000 Massachusetts Medical Society. All rights reserved.)

in the fetal middle cerebral artery above 1.5 times the median for gestational age with a sensitivity of 100% and a false-positive rate of 12%. Correct technique is a critical factor when determining peak systolic velocity in the fetal middle cerebral artery with Doppler ultrasonography. This procedure should be used only by those with adequate training and clinical experience.

Studies have reported a good correlation between the peak systolic velocity in the fetal middle cerebral artery and hemoglobin in fetuses that have undergone two previous transfusions, expanding the clinical use of this Doppler test (27, 28).

There are some limitations of this technology. Multiple studies have suggested that there is a higher false-positive rate after 34–35 weeks of gestation (21). In addition, as with any new technology, the measurements must be done by a practitioner specifically trained to perform Doppler for measurement of peak systolic velocity in the fetal middle cerebral artery. In a center with trained personnel and when the fetus is at an appropriate gestational age, middle cerebral artery Doppler measurements seem to be an appropriate noninvasive means to monitor pregnancies complicated by red cell alloimmunization.

▶ *What are strategies for care of a patient positive for non-D antigens at the first prenatal visit?*

The use of anti-D immune globulin to prevent red cell alloimmunization has led to a relative increase in the number of non-Rh-D alloimmunizations causing fetal anemia and hemolytic disease of the newborn. Hundreds of other distinct antigens, known as "minor" antigens, exist on the red blood cell surface. Most cases of alloimmunization due to these minor antigens are caused by incompatible blood transfusion. Overall, antibodies to minor antigens occur in 1.5–2.5% of obstetric patients.

Although many antibodies directed against minor antigens do not cause erythroblastosis fetalis, some do (Table 1). In general, care of the pregnant patient with antibodies to one of the clinically significant minor antigens is similar to care of Rh-D alloimmunized pregnant women. An important exception involves alloimmunization to the K or K1 antigens of the Kell blood group system. Kell alloimmunization appears to be less predictable and often results in more severe fetal anemia than alloimmunization due to other erythrocyte antigens. Some authorities believe the mechanism of anemia due to Kell alloimmunization to be different than with Rh-D alloimmunization, and experience suggests that maternal Kell antibody titers and amniotic fluid ΔOD450 values are not as predictive of the degree of fetal anemia as with Rh-D sensitization (4).

Amniotic fluid bilirubin measurements may be misleading in cases of Kell alloimmunization. Doppler measurements, however, appear to be accurate in predicting severe fetal anemia (29).

▶ *When is the best time to deliver the infant of an alloimmunized patient?*

Delivery of the infant of an alloimmunized patient is a controversial subject, and literature on the subject is limited. Standard treatment is to prolong the pregnancy until the fetus reaches a gestational age necessary for survival. If the history and antenatal studies indicate only mild fetal hemolysis, it is reasonable to proceed with delivery by induction of labor at 37–38 weeks of gestation. Induction may be considered earlier if fetal pulmonary maturity is documented by amniocentesis.

With severely sensitized pregnancies requiring multiple invasive procedures, the risks of continued cord blood sampling and transfusions must be considered and compared with those neonatal risks associated with early delivery. Given that the overall neonatal survival rate after 32 weeks of gestation in most neonatal intensive care nurseries is greater than 95%, it is prudent to time procedures so that the last transfusion is performed at 30–32 weeks of gestation, with delivery at 32–34 weeks of gestation after maternal steroid administration to enhance fetal pulmonary maturity (30). Several authors recommend intrauterine transfusion up to 36 weeks of gestation when intravascular transfusion is feasible in order to limit neonatal morbidity (31). Delivery can then be accomplished between 37 and 38 weeks of gestation.

Recommendations and Conclusions

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

- In a center with trained personnel and when the fetus is at an appropriate gestational age, Doppler measurement of peak systolic velocity in the fetal middle cerebral artery is an appropriate noninvasive means to monitor pregnancies complicated by red cell alloimmunization.
- The initial management of a pregnancy involving an alloimmunized patient is determination of the paternal erythrocyte antigen status.
- Serial titers are not useful for monitoring fetal status when the mother has had a previously affected fetus or neonate.

- Antibody titers are not appropriate for monitoring Kell-sensitized patients because Kell antibodies do not correlate with fetal status.
- Anti-D immune globulin is indicated only in Rh-negative women who are not previously sensitized to D.

Proposed Performance Measure

Further evaluation of patients found to have significant antibodies associated with fetal anemia

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The MEDLINE database, the Cochrane Library, and the American College of Obstetricians and Gynecologists' own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 1965–June 2005. 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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