

Management of non-Rhesus (D) red blood cell alloantibodies during pregnancy

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INTRODUCTION — Maternal alloantibodies to red blood cell (RBC) antigens other than Rh(D) are capable of causing clinically significant hemolysis of fetal and newborn RBCs, known as hemolytic disease of the fetus and newborn (HDFN). Once an alloantibody is identified, appropriate testing and estimation of the risk to the fetus are essential to obstetric care.

This topic review discusses the clinical significance of RBC alloantibodies other than anti-Rh(D) during pregnancy. Separate topic reviews discuss Rh(D) alloimmunization, fetal transfusion, and postnatal management of HDFN.

- (See ["Prevention of Rhesus \(D\) alloimmunization in pregnancy"](#).)
- (See ["Overview of Rhesus D alloimmunization in pregnancy"](#).)
- (See ["Management of pregnancy complicated by Rhesus \(D\) alloimmunization"](#).)
- (See ["Postnatal diagnosis and management of hemolytic disease of the fetus and newborn"](#).)
- (See ["Intrauterine fetal transfusion of red cells"](#).)
- (See ["Red blood cell transfusions in the newborn"](#).)

RBC antigens and alloimmunization in the nonpregnant patient are also presented separately. (See ["Red blood cell antigens and antibodies"](#) and ["Pretransfusion testing for red blood cell transfusion"](#) and ["The incompatible crossmatch"](#).)

TERMINOLOGY AND PATHOGENESIS

Definition of terms — The following terms are used to describe the condition that results when maternal alloantibodies cause hemolysis of fetal or neonatal red blood cells (RBCs):

- **HDFN** – Hemolytic disease of the fetus and newborn (HDFN) refers to hemolysis of fetal or neonatal RBCs by maternal alloantibodies to a fetal RBC antigen. This condition was previously called hemolytic disease of the newborn (HDN), which reflects its initial description in newborns, before tools for assessing fetal hemolysis were available.
- **Rh(D) disease** – HDFN due to maternal alloantibodies to the Rh(D) antigen is also called Rh disease of the newborn, Rhesus disease, Rh(D) disease, and Rh(D) HDN. This subject is discussed in detail separately. (See ["Overview of Rhesus D alloimmunization in pregnancy"](#).)

- **Alloantibodies other than anti-Rh(D)** – Importantly, there are alloantibodies other than anti-Rh(D) that can cause HDFN. These include antibodies directed against other Rh antigens, including C, c, E, and e; and antigens from other blood group systems.
- **Hydrops fetalis** – The most severe manifestation of HDFN that occurs in utero is hydrops fetalis, in which severe anemia and extramedullary hematopoiesis in the liver and spleen lead to heart failure and generalized edema (hydrops).

Maternal alloantibodies — Development of HDFN requires a maternal exposure to an RBC antigen not expressed on maternal RBCs and generation of an alloantibody. Potential sources of exposure include the following:

- **Transfusion** – Previous blood transfusion to the mother is common route of exposure to RBC antigens. Transfusion of RBCs is most commonly implicated, but platelets, which may contain a small amount of RBCs, may also be responsible. Transfusion is an especially common route for the development of antibodies against the antigen K of the Kell blood group system [1,2]. A likely reason is the lack of routine testing of donor blood for antigens other than ABO and Rh (D). Thus, some women who are negative for the K antigen of the Kell blood group will develop alloantibodies to K if they receive K-positive blood products.
- **Fetomaternal bleeding** – Fetomaternal bleeding is another common cause of exposure to RBC antigens. Transplacental fetomaternal bleeding can occur anytime in pregnancy and may be related to miscarriage, ectopic pregnancy, antepartum vaginal bleeding (eg, placenta previa, abruptio placenta), abdominal trauma, or delivery (livebirth or stillbirth). It may also occur in the absence of a recognizable inciting event.
- **Shared needles** – Injection with needles contaminated with another person's blood has been reported to cause alloimmunization to Rh(D) in intravenous drug users; thus, exposure is considered a potential cause of sensitization to other RBC antigens [3-5].

The likelihood of alloimmunization increases with greater volumes of allogeneic blood to which the woman is exposed; thus, transfusion is more likely to cause alloimmunization than fetomaternal bleeding. However, exposure to as little as 0.5 mL of allogeneic blood can cause alloimmunization.

Following maternal sensitization to an RBC antigen through any of the above mechanisms, subsequent exposure during a future pregnancy will elicit an antibody response of variable intensity and timing.

To cause hemolysis of fetal cells, the maternal alloantibody must be transported across the placenta; thus, antibodies of the IgG class are usually implicated.

- RBC antigens of the Lewis, I, and P blood groups often elicit IgM antibodies, which are not transported across the placenta and thus are not clinically significant causes of HDFN. (See '[Prevalence of alloantibodies in pregnancy](#)' below.)
- Antibodies of the Cromer blood group system can bind to a placental protein (decay accelerating factor), which traps them in the placenta and prevents them from entering the fetal circulation [6].

Antibody specificity (ie, the antigen to which the antibody is directed) and titer (a measure of antibody concentration in maternal blood) are helpful in estimating the risk of HDFN ([algorithm 1](#)). Antibodies to certain blood group systems are more likely to cause severe HDFN, as listed in the

table ([table 1](#)). The most commonly seen antibodies with the potential to cause severe HDFN besides anti-Rh(D) include anti-K, anti-Rh(c), and anti-Rh(E). A high antibody titer is more predictive of severe fetal anemia than a low titer [6]. (See '[Prevalence of alloantibodies in pregnancy](#)' below.)

Some antibody subclasses, such as IgG1 and IgG3, are more efficient at causing hemolysis than others. IgG1 is transported across the placenta earlier and in larger amounts than IgG3 [7]. IgG2 and IgG4 antibodies do not normally play a significant role in RBC hemolysis. Antibody subtype classification is generally used for research purposes and not for clinical management.

Although not associated with HDFN, naturally occurring antibodies to some RBC antigens can develop when the antigens are similar to epitopes present on micro-organisms (ie, molecular mimicry). The most common example is the ABO blood group antigens A and B. Anti-A and anti-B are present in virtually all individuals who lack the corresponding antigen, due to exposure to gut bacteria; however, these antibodies are IgM and/or IgA and thus do not cross the placenta. In contrast, alloimmunization to A or B during a previous pregnancy can lead to production of IgG antibodies to A or B capable of causing hemolysis of fetal/neonatal RBCs (see '[ABO](#)' below). Anti-M and anti-N, also due to gut micro-organisms, are present in 2 to 3 percent of the general population [8]. (See '[MNS](#)' below.)

Fetal/neonatal anemia — Fetal or neonatal anemia can only develop if the maternal antibody crosses the placenta and binds its cognate antigen on fetal RBCs. Thus, if the fetus has not inherited the implicated antigen, or the antigen is one that does not develop on fetal RBCs until after birth, hemolysis cannot occur.

- RBC antigens are inherited from both parents. If the father is homozygous for the gene encoding the antigen, all of his children will be antigen-positive; if he is heterozygous, approximately half will be antigen-positive.
- RBC antigens are expressed at various stages during gestation, beginning in the first trimester of pregnancy. Some antigens are not well developed on fetal or neonatal RBCs and therefore are not associated with HDFN; examples include the Lutheran system antigen Lu(b), the Vel antigen Vel, and the Cartwright antigen Yta.

Once a maternal antibody binds to fetal RBCs, the cells can be phagocytized by reticuloendothelial macrophages in the spleen or liver, causing fetal anemia; this form of RBC destruction is referred to as extravascular hemolysis [9]. In more severe forms of HDFN, intravascular hemolysis also occurs (ie, direct lysis of RBCs within the circulation) [9].

In most forms of HDFN, RBC production (erythropoiesis) is increased in order to compensate for hemolysis [9]. A major exception occurs in HDFN due to K alloimmunization because antibodies against K antigen cause hemolysis **and** suppress erythropoiesis, the latter via destruction of RBC progenitor and precursor cells in the bone marrow. Anti-K thus leads to earlier and more severe anemia than many other alloantibodies.

After delivery, hemolysis can continue due to persistent maternal antibody in the neonatal circulation. Maternal antibody levels decline over approximately 12 weeks [9].

Hyperbilirubinemia is not an important problem for the fetus, because bilirubin resulting from hemolysis is transported back to the maternal circulation, where it is conjugated and cleared. After delivery, however, conjugation of bilirubin depends on the newborn liver, which cannot conjugate

bilirubin efficiently. Thus, hyperbilirubinemia is a concern after delivery. (See ["Pathogenesis and etiology of unconjugated hyperbilirubinemia in the newborn".](#))

PREVALENCE OF ALLOANTIBODIES IN PREGNANCY — Overall, alloantibodies to non-Rh(D) red blood cell (RBC) antigens are seen in approximately 1.5 to 2.5 percent of pregnancies [10]. Other than Rh(D), the antigens most commonly implicated in hemolytic disease of the fetus and newborn (HDFN) are Kell, Rh(c), and Rh(E). The likelihood that alloantibodies will cause HDFN increases as the number of at-risk pregnancies increases. The distribution of antibody specificities depends on the population sampled and the sampling methods used.

- In a large prospective series that included over 300,000 consecutive pregnancies, first trimester screening revealed an alloantibody to an antigen other than Rh(D) in 1002 women (approximately 1 percent), accounting for approximately one-quarter of all alloantibodies in this series [11]. The most common were anti-Rh(E), anti-K, and anti-Rh(c). Clinically significant antibodies (eg, those requiring in utero or neonatal transfusion) to antigens other than Rh(D) occurred in 21 of 567 fetuses at risk (3.7 percent).
- In a study of 110 pregnant mothers with 111 at-risk fetuses and maternal antibody titers of 16 or greater, antibodies to Rh(D), K, Rh(E), and Rh(c) were present in 84, 18, 8, and 3 fetuses, respectively [12].

In East Asia, the relative frequency of non-Rh(D) HDFN is higher because the proportion of Rh(D) -negative individuals in the population is especially low.

Some "low frequency" antigens are present in such a small percentage of the population that they are not present in reagent screening cells used to detect maternal alloantibodies ([table 1](#)). Alloantibodies to these antigens may be missed by standard maternal screening, and in rare cases in which they cause hemolysis, the problem may not be detected until delivery [13]. (See ["Postnatal diagnosis and management of hemolytic disease of the fetus and newborn".](#))

ALLOANTIBODIES NOT ASSOCIATED WITH HDFN — As mentioned above, maternal antibodies will not cause hemolytic disease of the fetus and newborn (HDFN) if they cannot cross the placenta (eg, IgM), or if they are directed against an antigen not expressed on fetal red blood cells (RBCs) (see ["Terminology and pathogenesis"](#) above). This includes antibodies to the Lewis blood group antigens, the I antigens, and the P antigen P1. Maternal titers and fetal assessment for anemia are unnecessary for pregnancies associated with these alloantibodies.

Lewis — The Lewis antigens are not associated with HDFN. This includes Le(a), Le(b), and four rare associated antigens. Antibodies to Lewis antigens are IgM, and fetal RBCs lack Lewis antigens, which develop later in childhood [14]. However, Lewis antibodies commonly are detected during pregnancy and often may lead to confusion regarding HDFN.

I — The I antigens are not associated with HDFN. The I blood group includes "I" and "i" antigens, neither of which has been associated with HDFN. Fetal and newborn RBCs strongly express the i antigen, with only small amounts of I antigen.

P1 — The P1 antigen often elicits an IgM alloantibody in women who express P2; anti-P1 is not associated with HDFN. In contrast, women who have the very rare "p" phenotype can produce clinically significant alloantibodies to other P antigens. (See ["P"](#) below.)

ALLOANTIBODIES THAT CAN BE ASSOCIATED WITH HDFN — Antibodies to blood group systems that have been associated with hemolytic disease of the fetus and newborn (HDFN) are

listed in the table ([table 1](#)); however, the presence of antibodies to these blood group systems does not necessarily result in HDFN. Some of these blood group systems are discussed in more detail below.

Kell — The most antigenic of the Kell group is K; K is present in approximately 9 percent of Caucasian blood donors. K-sensitized pregnancies are responsible for approximately 10 percent of severe cases of HDFN. In a large series that included 19 K-sensitized pregnancies, severe HDFN was seen in five (26 percent) [[11](#)].

Other Kell antigens include k, Kp(a), Kp(b), Ko, Js(a), Js(b), and a large number of other rare antigens; these are rarely a cause of Kell incompatibility [[15](#)]. The genotype frequencies in Caucasians are approximately: Kk (8.7 percent), kk (91.1 percent), and KK (0.2 percent) [[14](#)]. By comparison, the frequencies for African-Americans are Kk (2 percent), and kk (98 percent), and KK is extremely rare.

Blood transfusion is likely the most common mechanism of K sensitization in reproductive-age women. Antigen testing for K antigens is not routinely performed on blood donors in the United States, although it is in some countries (eg, Australia, the Netherlands) [[16](#)]. In one series, 8 of 12 K-sensitized women with K-positive babies had a prior blood transfusion [[17](#)]. Alloimmunization during a previous pregnancy may account for anti-K in women who have not received a transfusion.

HDFN due to anti-K can be severe. One reason for this is the ability of anti-K to cause destruction of red blood cell (RBC) precursors and maturing erythrocytes in the bone marrow as well as circulating mature fetal RBCs (see '[Fetal/neonatal anemia](#)' above). Anti-K can be particularly troublesome because the titer of the alloantibody correlates poorly with the likelihood of fetal anemia, and the severity of anemia can change dramatically over the course of a single week [[17-22](#)]. Hydrops fetalis can develop before the third trimester. This was illustrated in a series of 20 affected fetuses and infants among 311 K-sensitized women, in which three fetuses required intrauterine fetal transfusions for severe anemia or hydrops, one required an early delivery and multiple neonatal exchange transfusions, four required neonatal exchange transfusion and/or phototherapy, and 12 did well without any treatment for anemia or hyperbilirubinemia [[19](#)].

Rh(c) and Rh(E) — The Rh system includes many antigens other than Rh(D), the most clinically significant of which are "c" and "E." Other Rh antigens include "C" and "e"; there is no "d" antigen. Importantly, administration of anti-Rh(D) [immune globulin](#) does not protect the mother from developing antibodies directed against these other Rh antigens. The likelihood of HDFN due to other Rh antigens was illustrated in a large series that included 118 Rh(c)-sensitized pregnancies; of these, severe HDFN was seen in 12 (10 percent) [[11](#)].

The hemolytic effect of Rh(c) is similar to Rh(D) [[16](#)]. In various case series, mortality rates up to 10 percent have been reported; intrauterine transfusions have been required in 1 to 17 percent, and neonatal transfusions have been required in approximately 10 to 30 percent [[23-26](#)].

Special mention should be made of the Rh(D)-negative pregnant women presenting with what appears to be anti-"C+D." The patient may actually have an antibody to the G antigen, which is present on any RBC that expresses Rh(C) and/or Rh(D). Immunohematology reference laboratories can readily distinguish between these possibilities. The clinical importance of this distinction is that the woman may be negative for Rh(D) and has not been actively isoimmunized to the Rh(D) antigen and thus is a candidate for Rh(D) [immune globulin](#). (See "[Overview of Rhesus D alloimmunization in pregnancy](#)".)

Duffy — The Duffy antigens, Fy(a) and Fy(b), are encoded by codominant alleles, giving the phenotypes Fy(a+b+), Fy(a-b-), Fy(a+b-), or Fy(a-b+). Only anti-Fy(a) antibody has been associated with HDFN, which may range from mild to severe [27].

Of interest, 82 percent of blacks are Fy(a-b-), likely because Fy(b) antigen serves as a receptor for malaria [28]. (See "[Protection against malaria by abnormalities in red cell surface antigens and cytoskeletal proteins](#)", section on 'Duffy blood group system'.)

MNS — The MNS system contains the M, N, S, s, and U antigens, as well as 32 other rare antigens. Naturally occurring antibodies to M and N are seen in a small percentage of the general population in the absence of exposure to allogeneic blood. (See '[Maternal alloantibodies](#)' above.)

Mild to severe HDFN has been reported with anti-S, anti-s, and anti-U; anti-N may cause mild hemolysis. Anti-Mur, which is especially common in Southeast Asians, can cause mild or severe disease [29,30]. Anti-M rarely causes disease since it is typically IgM. Severe HDFN due to anti-M may occur if the antibody is a high-titer IgG at 37°C rather than room temperature [31-36].

P — The P system consists of the P1 and P2 antigens, which are present in 79 and 21 percent of Caucasians, respectively. Women with the very rare "p" phenotype can produce anti-P1+P+P(k), an antibody that has been associated with severe HDFN and recurrent early pregnancy loss [37]. Women with the P2 antigen commonly produce anti-P1 antibodies, which are IgM antibodies that do not cross the placenta. (See '[P1](#)' above.)

ABO — The ABO system contains the A and B antigens, which are assembled on the H antigen. Type O represents the absence of A and B (ie, H alone). The A and B antigens are codominantly expressed, resulting in blood types A, B, O, and AB. Thus, an individual who is type A can be heterozygous or homozygous for the A antigen; a type B individual can be heterozygous or homozygous for B.

Naturally occurring IgM antibodies to A and B develop early in life in individuals lacking the corresponding antigen, following exposure to bacterial antigens in the gut. These IgM antibodies do not cross the placenta and do not cause HDFN. However, IgG ABO antibodies may exist, particularly in group O mothers who have been exposed to a non-O fetus [38]. In contrast to other IgG alloantibodies, severe hemolysis due to ABO incompatibility is usually a problem for the neonate and rarely affects the fetus [39-43]. However, hemolysis may be particularly pronounced in group B African-American fetuses, in whom the B antigen is more developed at birth than in other populations [39-41,44,45].

An issue may arise when a type A or B, Rh(D)-negative fetus of a type O, Rh(D)-negative mother is typed for Rh(D). Apparent weak Rh(D)-positivity may be seen at the antiglobulin stage due to ABO incompatibility even though the fetus is Rh(D)-negative. This weak Rh(D) typing is often a false positive reaction, and Rh(D) [immune globulin](#) generally is not indicated. An exception can occur when the newborn is Rh(D)-positive but types as Rh(D)-negative because of a high level of attachment of maternal anti-Rh(D) to the newborn's RBCs (called "blocked Rh"); this is very rare. An elution technique can be performed using the baby's cells and reagent anti-D to definitively determine whether the baby's cells are weakly Rh(D) positive. Additional information about Rh(D) variants and their typing is presented separately. (See "[Overview of Rhesus D alloimmunization in pregnancy](#)", section on 'The Rhesus system'.)

PREPREGNANCY COUNSELING — If a nonpregnant woman is found to have an alloantibody to a red blood cell (RBC) antigen, she should be counseled regarding the potential effects of the

antibody on a future pregnancy. Details of this counseling will depend on the class of the antibody (IgG versus IgM); the specificity (ie, the target antigen); and the antigen type of the biologic father, which determines the risk to the fetus.

Parental testing — Individuals with a history of hemolytic disease of the fetus and newborn (HDFN) require further testing to determine the antibody class and specificity, and the potential father's antigen status. The antibody titer prepregnancy is not useful, since the titer may rise several-fold during pregnancy. If the antibody is capable of producing HDFN (eg, IgG, concerning specificity) and the potential father of the future pregnancy is known, it is reasonable to determine whether he carries the associated RBC antigen and, if so, whether he is homozygous or heterozygous for the allele.

Prevention of HDFN — HDFN can be prevented by avoiding pregnancy with fetal RBC antigen-maternal RBC antibody incompatibility. Prevention is rarely attempted because of the costs and complexities involved and because HDFN can be treated successfully in most cases. Fetal RBC antigen-maternal RBC antibody incompatibility can be avoided in the following ways:

- In vitro fertilization with preimplantation genetic diagnosis – If the potential biologic father is heterozygous for the antigen, in vitro fertilization (IVF) with preimplantation genetic diagnosis (PGD) can be used to identify antigen-negative embryos, and only these embryos are considered for embryo transfer [46]. (See "[Preimplantation genetic diagnosis](#)".)
- Use of a gestational surrogate – If the potential biologic father is homozygous for the antigen, the intended parents can conceive by IVF and the embryo can be carried by a gestational surrogate who is not alloimmunized. (See "[Surrogate pregnancy](#)".)
- Use of donor sperm – Sperm from an antigen-negative donor can be used for intrauterine insemination of the alloimmunized mother. (See "[Donor insemination](#)".)

PRENATAL MANAGEMENT — Our general approach to diagnosis and management of non-Rh (D) alloimmunization in pregnancy is illustrated in the algorithm ([algorithm 1](#)) and outlined below. The efficacy of this approach has been demonstrated in several case series; however, there is limited evidence on which to base management [27,47]. This approach is consistent with recommendations of the American College of Obstetricians and Gynecologists (ACOG), which advise that the care of patients with non-Rh(D) alloantibodies should be the same as for women with Rh(D) alloimmunization [10].

Antibody screening — Routine screening for antibodies to red blood cell (RBC) antigens, as well as ABO testing, should be performed early in pregnancy, typically at the first prenatal visit; this will include screening for anti-Rh(D) as well as a number of other antibodies [48]. Testing is done by incubating maternal serum with selected RBCs, known as the antibody screen, by the indirect antiglobulin (Coombs) method. This testing is highly accurate and relatively inexpensive. If no clinically important alloantibodies are detected, antepartum antibody screening usually is not repeated, because clinically significant, late-onset alloimmunization is rare, on the order of 0.18 percent or less [11,48-53].

If one or more alloantibodies are detected and identified, maternal RBC antigen typing is performed. The results of maternal antibody screening and antibody identification are compared with any prior data that are available.

Follow up a positive antibody screen — If the maternal antibody screen identifies an alloantibody, the potential for causing clinically significant hemolytic disease of the fetus and

newborn (HDFN) must be assessed ([algorithm 1](#)). Relevant information includes a history of HDFN in previous pregnancies with the same biologic father; the likelihood of HDFN for the implicated antigen specificity; the maternal alloantibody class (IgG versus IgM) and level of antibody in maternal plasma; and when appropriate, determination fetal RBC antigen status. Antibody titration provides information about whether the antibody concentration is above a critical threshold value. However, after this titer is reached, further assessment of antibody titer does not correlate well with the likelihood or severity of HDFN.

Evaluate the antibody — The maternal antibody is evaluated as follows ([algorithm 1](#)):

- **Eliminate unimportant antibodies** – If the antibody is IgM or has never been associated with HDFN ([table 1](#)), the fetus is not considered at risk and no further testing is needed.
- **For clinically important antibodies, determine maternal antibody level**
 - **Maternal antibody titer** – The antibody titer also can give an estimation of the antibody concentration in maternal blood, although this method has been replaced by antibody quantification in many settings. A higher titer correlates with a higher antibody concentration in maternal blood, and an increasing titer suggests ongoing stimulation of maternal antibody production. The antibody titer is the reciprocal of the greatest dilution of maternal serum at which the antibody agglutinates RBCs that express the corresponding antigen. It is calculated from measuring RBC agglutination with serial dilutions of maternal plasma.

Titration is used if a maternal alloantibody is found and the fetus is potentially at risk for expressing the antigen. A titer above a critical threshold value predicts an increased likelihood of HDFN, and HDFN is extremely unlikely at a titer below a critical threshold. However, the titer does not correlate linearly with the risk of HDFN or the severity of hemolysis, which provides the rationale for additional testing if the titer exceeds the critical threshold. Titration is considered unreliable for predicting the likelihood of HDFN if a prior pregnancy with the same father was associated with HDFN, and a high antibody titer does not correlate well with the severity of hemolysis in any setting.

- **Maternal antibody quantification** – Several methods have been developed to measure the amount of a specific antibody in maternal blood. Methods such as flow cytometry and autoanalyzer measure more precisely and reliably than the titer method. This testing is available in Europe and the United Kingdom.

Titration of a clinically important maternal alloantibody can be done simultaneously with determination of fetal antigen status or sequentially, depending on the clinical setting. Both pieces of information are used in deciding whether serial monitoring for fetal anemia is needed.

If a past pregnancy was complicated by HDFN, subsequent pregnancies are at high risk of recurrence and antibody titration is not needed. However, the converse is not true; a previous unaffected pregnancy cannot be used to eliminate the possibility of an affected fetus, because the father may be heterozygous for the antigen, there may be a different father, or sensitization to the antigen may have occurred at the time of a prior delivery or miscarriage.

The critical titer is the titer below which the risk of HDFN is unlikely and fetal testing or monitoring is not required. The critical titer is lower for anti-K (Kell) than for other antibodies. An antibody titer at or above the critical titer should prompt noninvasive monitoring for fetal anemia if the fetus

carries the corresponding antigen (the fetal antigen status should be determined by amniocentesis if it is not already known) ([algorithm 1](#)).

- Most laboratories follow publications from the AABB (formerly the American Association of Blood Banks), which consider 16 the critical titer. It is generally agreed that additional fetal evaluation can be deferred at titers of 4 or below. A titer of 16 should prompt close fetal monitoring (eg, with fetal middle cerebral artery peak systolic velocity [MCA-PSV]), if the fetus is antigen-positive, because rare cases of severe fetal anemia occur at this level.
- An exception is a K (Kell) alloimmunized pregnancy, in which the correlation of the titer and risk of severe HDFN is especially weak. Thus, some experts use a lower threshold for K-sensitized pregnancies (eg, a critical titer of 8); others believe that no threshold can be designated to accurately predict absence of severe fetal anemia [[19,54,55](#)]. The rationale is that the risk of severe anemia is greater due to hemolysis plus impaired erythropoiesis. (See '[Kell](#)' above.)

As long as the antibody titer remains **below** the critical titer, additional evaluation of the fetus can be deferred and the patient evaluated with serial antibody titers. The interval between titers varies from two to four weeks, depending upon the previous titer measurement and the gestational age. Titers should be drawn more frequently when the titer is borderline or rising and in the third trimester when the risk of erythroblastosis is highest. Except in K (Kell)-affected pregnancies, it is not necessary to perform serial titers before 18 to 20 weeks of gestation, because of the low risk of severe fetal anemia early in pregnancy.

Once noninvasive assessment of fetal anemia is initiated, management decisions are based on this assessment rather than on laboratory testing of the maternal antibody. (See '[Assessing for fetal anemia](#)' below.)

Determine fetal antigen status — Determining fetal antigen status aids decision making if the maternal alloantibody titer is at or above a critical threshold (see '[Evaluate the antibody](#)' above).

In many cases, fetal antigen status can be determined non-invasively (eg, by testing the father if he is homozygous for the target antigen) ([algorithm 1](#)). Paternal antigen status is determined by serologic typing of his RBCs with a reagent antibody or by DNA testing. Importantly, however, data on the rates of non-paternity suggest a range of 2 to 5 percent [[56](#)].

- If the father is negative for the implicated antigen (and paternity is assured), the fetus will be antigen negative and no further testing/monitoring is required.
- If the father is positive for the antigen, serology and DNA testing can determine whether he is homozygous or heterozygous.
 - If the father is homozygous for the implicated antigen (and paternity is assured), the fetus is assumed to be obligate positive, and testing to determine fetal antigen status is unnecessary; the fetus should be monitored for anemia. (See '[Assessing for fetal anemia](#)' below.)
 - If the father is heterozygous (or status unknown or paternity uncertain), the fetus may be positive for the antigen, and fetal antigen testing can be performed either by cell-free DNA testing of maternal blood or testing amniocytes via amniocentesis

Cell-free DNA testing of maternal blood can determine fetal Kell, Rh(C), Rh(c), or Rh(E) status. This test has limited availability in certain United States reference laboratories, but is more widely in some other countries [57-59]. Consultation with transfusion or laboratory personnel regarding the availability of noninvasive testing may be helpful.

If cell-free DNA testing is not available, we perform amniocentesis to type amniocytes if/when the maternal alloantibody titer is at or above the critical value (≥ 8 for Kell, ≥ 16 for other antigens).

For fetuses at risk of anemia based on fetal antigen status and maternal alloantibody titer, noninvasive assessment for fetal anemia using middle cerebral artery (MCA) Doppler scanning is required. (See '[Assessing for fetal anemia](#)' below.)

Kell-sensitized pregnancy — The critical titer for Kell alloantibodies is lower and, in turn, the timing of noninvasive testing for fetal anemia is earlier in a Kell-sensitized pregnancy compared with other alloantibodies because anti-Kell antibodies cause earlier and more severe fetal anemia, and the risk of severe HDFN correlates poorly with antibody titer compared with other alloantibodies. (See '[Fetal/neonatal anemia](#)' above and '[Kell](#)' above.)

Earlier Doppler assessment of the fetal MCA-PSV is the preferred tool for determination of fetal anemia in Kell sensitized pregnancies (eg, at 18 weeks of gestation rather than 22 to 24 weeks) [12,60,61]. If MCA-PSV is above 1.5 multiples of the median (MoM), then cordocentesis for fetal hematocrit/hemoglobin and confirmation of blood type should be performed; transfusion is performed at the same time, if needed. This is done earlier in gestation for Kell-sensitized pregnancies compared with other alloantibodies [19].

Assessing for fetal anemia — Assessment for fetal anemia is appropriate in pregnancies determined to be at risk of HDFN based on a maternal alloantibody titer that is rapidly rising or at or above the critical titer and expression of the corresponding antigen on fetal RBCs.

- **Noninvasive testing** - For noninvasive assessment for fetal anemia, Doppler scanning of the fetal MCA-PSV has emerged as the best tool [12,60,62-64]. This test is based on the principle that in the anemic fetus, oxygen delivery to the brain is preserved by increasing cerebral flow of this low viscosity blood.
- **Invasive testing** - If the MCA-PSV is above 1.5 MoM for the gestational age, invasive testing using cordocentesis to obtain a fetal blood sample for fetal hemoglobin measurement is performed.

Tables for converting the MCA-PSV to a MoM based on gestational age are provided at www.perinatology.com [65]. The sensitivity of an increased MCA-PSV for moderate or severe fetal anemia is approximately 100 percent regardless of the cause of the anemia, with a false positive rate of 12 percent [12,62].

The gestational age at which to initiate serial MCA Doppler scans depends on whether there has been a previously affected pregnancy [66].

- If a previous pregnancy was associated with HDFN or the current pregnancy has Kell incompatibility, MCA scanning is initiated at 18 weeks of gestation, regardless of the maternal antibody titer (ie, determination of the maternal antibody titer is not required).

- If there has not been a previously affected pregnancy, Kell incompatibility is not present, and the maternal antibody titer is at or above the critical titer, MCA scanning is initiated at 22 to 24 weeks of gestation.

Additional aspects of Doppler evaluation, such as optimization of testing, frequency of testing, and indications for invasive measurement of fetal hemoglobin levels, are similar to those in Rh(D) alloimmunized pregnancies and discussed in detail separately. (See "[Management of pregnancy complicated by Rhesus \(D\) alloimmunization](#)", section on 'Assess for severe anemia in fetuses at risk'.)

If the MCA-PSV indicates possible severe anemia, or if a fetal ultrasound indicates signs of hydrops fetalis (eg, ascites, pleural effusion, skin edema, pericardial effusion), cordocentesis for measurement of the fetal hemoglobin level is indicated, with availability of blood for transfusion if needed, as done for women with Rh(D) alloimmunization [10]. This subject, as well the selection and preparation of RBCs, are discussed in detail separately:

- **Cordocentesis** – (See "[Fetal blood sampling](#)".)
- **Intrauterine transfusion** – (See "[Intrauterine fetal transfusion of red cells](#)".)
- **Postnatal transfusion** – (See "[Postnatal diagnosis and management of hemolytic disease of the fetus and newborn](#)" and "[Red blood cell transfusions in the newborn](#)".)
- **RBC compatibility testing and modifications** – (See "[Red blood cell transfusion in infants and children: Selection of blood products](#)".)

SPECIAL POPULATIONS — Additional circumstances that may complicate the evaluation and management of a pregnancy include autoimmune hemolytic anemia (AIHA) in the mother, recent Rh(D) [immune globulin](#) administration, alloantibodies to high frequency antigens, and the use of donor gametes or gestational surrogacy.

Warm autoimmune hemolytic anemia — Warm autoimmune hemolytic anemia (AIHA) is caused by an **auto**antibody to a red blood cell (RBC) antigen that causes variable hemolysis in the mother. These autoantibodies generally cause a positive direct antiglobulin (Coombs) test (DAT) and may be present in the mother's plasma, complicating the interpretation of **allo**antibody screening. AIHA must be distinguished from the nonpathologic positive DAT, which occurs in 1 in 1000 hospitalized patients and in 1 in 36,000 normal blood donors. (See "[Warm autoimmune hemolytic anemia: Clinical features and diagnosis](#)".)

Warm AIHA is often exacerbated during pregnancy [67,68]. In some cases, the autoantibody may cross the placenta and cause shortened survival of the fetal RBCs. Occasionally, the autoantibody mimics allo-anti-Rh(e), which may be transported across the placenta. However, we are unaware of cases of severe HDFN; thus, serial fetal middle cerebral artery peak systolic velocity (MCA-PSV) scans are not needed in this setting.

If sufficient autoantibodies are transported across the placenta to cause anemia in the Rh(e)-positive fetus, exchange transfusion may be required shortly after delivery. Since only approximately 1 in 20,000 Rh(D)-negative units are also Rh(e)-negative, RBC units that are negative for both Rh(D) and Rh(e) may not be available. Other interventions (eg, phototherapy, intravenous [immune globulin](#) [IVIG]) are discussed in detail separately. (See "[Treatment of unconjugated hyperbilirubinemia in term and late preterm infants](#)".)

Recent Rh(D) immune globulin — Administration of Rh(D) [immune globulin](#) is not harmful for women with other alloantibodies, but it may cause confusion in the interpretation of other testing if the details are not communicated to the transfusion service and/or immunohematology laboratory.

- **Timing of administration** – Administration of Rh(D) [immune globulin](#) is safe in patients with antibodies to other Rh or non-Rh antigens, and testing for other alloantibodies can be performed as long as the transfusion service is aware that Rh(D) immune globulin has been administered. Importantly, administration of Rh(D) immune globulin should **not** be withheld or delayed during the evaluation or treatment of other maternal alloantibodies.
- **Potential misinterpretation of maternal antibody screening** – Rh(D) [immune globulin](#) is made from human plasma and rarely may contain antibodies to other Rh antigens besides Rh (D), which could make it appear that an alloantibody is present when it is not. Unlike an alloantibody that is continually produced by the mother, other antibodies in the Rh(D) immune globulin will not cause any problems for the fetus because the dose to which the fetus is exposed is small.
- **Lack of protection from other Rh alloantibodies** – Administration of Rh(D) [immune globulin](#) does not provide prophylaxis against HDFN due to other Rh antigens (eg, C, c, E). Thus, if a pregnant patient has alloantibodies to one of these other Rh antigens, she should be managed as if the fetus is potentially at risk for HDFN. (See '[Prenatal management](#)' above.)

High frequency antigen — One issue that warrants additional discussion is the presence of an alloantibody directed against an antigen present in a high frequency of the population because it may be difficult to obtain blood for transfusion that lacks the corresponding antigen. Examples include the Kell blood group antigens k or Kp(b), or the Colton blood group antigen Co(a). Identifying the antibody specificity, as well as any underlying clinically significant antibodies being masked by its presence, in a timely manner is essential so that donor blood is available should fetal transfusion be required prior to delivery or the mother and/or the newborn require transfusion postpartum.

Options in this setting include the following:

- If the mother is medically able, she may donate one to two units of RBCs during the second trimester [\[69\]](#).
- The mother's siblings can be tested. There is a 25 percent chance that a sibling's cells will be compatible with the mother's serum if both parents are heterozygous for the corresponding low frequency antigen (they must also be ABO compatible).

The cells can be frozen and then thawed if necessary for transfusion for the mother, fetus, and/or the neonate (if ABO compatible). Alternatively, the transfusion service can contact the American Rare Donor File to inquire if frozen units lacking the high frequency antigen in question can be found. Such units could then be held or shipped to the local facility and stored for future use.

If compatible blood cannot be obtained and intrauterine or exchange transfusion becomes imperative, group O red blood cells that are heterozygous for the high frequency antigen (eg, K+k+ when anti-k is present) are preferred to blood from a donor who is homozygous for the implicated antigen.

IVF/donor egg/surrogacy — Management of pregnancies involving a donor gamete or a gestational surrogate is based on the predicted antigen status of the fetus and the known antibody

status of the gestational carrier. These pregnancies are managed as described above. (See ['Prevention of HDFN'](#) above.)

PROGNOSIS — The outcome of pregnancies complicated by alloimmunization has been greatly improved by the availability of methods for fetal assessment and intrauterine transfusion. Combined data from several studies that included cases managed by fetal transfusion reported fetal survival of 94 and 74 percent for nonhydropic and hydropic fetuses, respectively [70]. Comparable data have been presented for Kell-sensitized pregnancies, although some series report a lower survival rate for hemolytic disease of the fetus and newborn (HDFN) due to Kell than for Rh(D) sensitization [19].

In a large series of over 300,000 pregnancies, those newborns at risk of HDFN due to alloantibodies other than anti-Rh(D) were more likely to have icterus than those not at risk (25 versus 10 percent) and to be treated with phototherapy (17 versus 5 percent) [11].

There remains a very small risk of HDFN in pregnancies in which an alloantibody was not detected on first trimester screening. In the large series of over 300,000 pregnancies, eight cases of severe HDFN that occurred in patients with a negative screen were due to anti-Rh(c) and/or anti-Rh(E), resulting in an overall risk of antibody screen-negative severe HDFN of 2 in 100,000 pregnancies [11]. Seven neonates required exchange transfusion, and two had permanent brain damage from kernicterus or intracerebral bleeding.

SUMMARY AND RECOMMENDATIONS

- Development of hemolytic disease of the fetus and newborn (HDFN) requires maternal exposure to an allogeneic red blood cell (RBC) antigen, which can occur through prior transfusion, previous pregnancy (through a fetomaternal hemorrhage), or sharing of needles. Fetal RBC antigens arise from expression of a paternally inherited gene. A maternal alloantibody corresponding to the fetal antigen must be transported across the placenta; therefore, IgG, but not IgM, can cause fetal hemolysis. Fetal anemia occurs primarily via phagocytosis of antibody-coated RBCs by reticuloendothelial macrophages in the fetal spleen and liver. (See ['Terminology and pathogenesis'](#) above.)
- HDFN can result from alloantibodies to antigens other than Rh(D), including other Rh antigens and antigens from other blood group systems. Maternal alloantibodies to non-Rh(D) antigens are seen in approximately 1.5 to 2.5 percent of pregnancies. The most commonly implicated antigens are Rh(c), Rh(E), and the Kell blood group K antigen ([table 1](#)). Of the blood group systems other than Rh, the Kell system, especially the K antigen, causes earlier and more severe HDFN than others. (See ['Prevalence of alloantibodies in pregnancy'](#) above and ['Kell'](#) above.)
- The evaluation, prevention, and management of Rh(D) alloimmunization in pregnancy is discussed in detail separately. (See ["Overview of Rhesus D alloimmunization in pregnancy"](#) and ["Prevention of Rhesus \(D\) alloimmunization in pregnancy"](#) and ["Management of pregnancy complicated by Rhesus \(D\) alloimmunization"](#).)
- If a nonpregnant woman is found to have an alloantibody to an RBC antigen, she should be counseled regarding the potential effects of the antibody on a future pregnancy. Individuals with a history of HDFN require further testing to determine the antibody class and specificity and the potential father's antigen status. There are few interventions that can be used to prevent HDFN in a woman with an alloantibody and a father who carries the corresponding

antigen (eg, preimplantation genetic diagnosis, gestational surrogate, donor insemination). (See ['Pregnancy counseling'](#) above.)

- Routine screening for antibodies to RBC antigens, as well as ABO testing, should be performed early in pregnancy, typically at the first prenatal visit; this will include screening for anti-Rh(D) as well as a number of other antibodies. Importantly, administration of Rh(D) [immune globulin](#) to an Rh(D)-negative mother at 28 weeks gestation should not be delayed while performing the evaluation for other non-Rh(D) alloantibodies. If no clinically important alloantibodies are detected, antepartum antibody screening usually is not repeated. (See ['Antibody screening'](#) above.)
- If the maternal antibody screen identifies an alloantibody, its potential for causing clinically significant hemolysis is assessed based on the antibody class (eg, IgG versus IgM), antibody level (eg, quantification, titer), antibody specificity (eg, Kell, previously implicated antigen, other antigen), and presence of the implicated antigen on fetal RBCs ([algorithm 1](#)). Of note, although it is important to know whether the antibody is above a threshold value, the antibody level is not predictive of the likelihood or severity of disease. (See ['Follow up a positive antibody screen'](#) above and ['Evaluate the antibody'](#) above.)
- Assessment for fetal anemia is appropriate in pregnancies determined to be at risk of HDFN based on the presence of a maternal alloantibody level that is rapidly rising or at or above the critical titer and the expression of the corresponding antigen on fetal RBCs. Doppler scanning of the fetal middle cerebral artery peak systolic velocity (MCA-PSV) has emerged as the best tool for noninvasive assessment for fetal anemia. (See ['Determine fetal antigen status'](#) above and ['Assessing for fetal anemia'](#) above.)
- Information regarding invasive testing for fetal anemia and fetal or neonatal transfusion is presented in detail separately. (See ["Fetal blood sampling"](#) and ["Intrauterine fetal transfusion of red cells"](#) and ["Red blood cell transfusions in the newborn"](#).)
- Additional circumstances that may complicate the evaluation and management of a pregnancy include autoimmune hemolytic anemia (AIHA) in the mother, recent Rh(D) [immune globulin](#) administration, alloantibodies to high frequency antigens, and the use of donor gametes or gestational surrogacy. (See ['Special populations'](#) above.)

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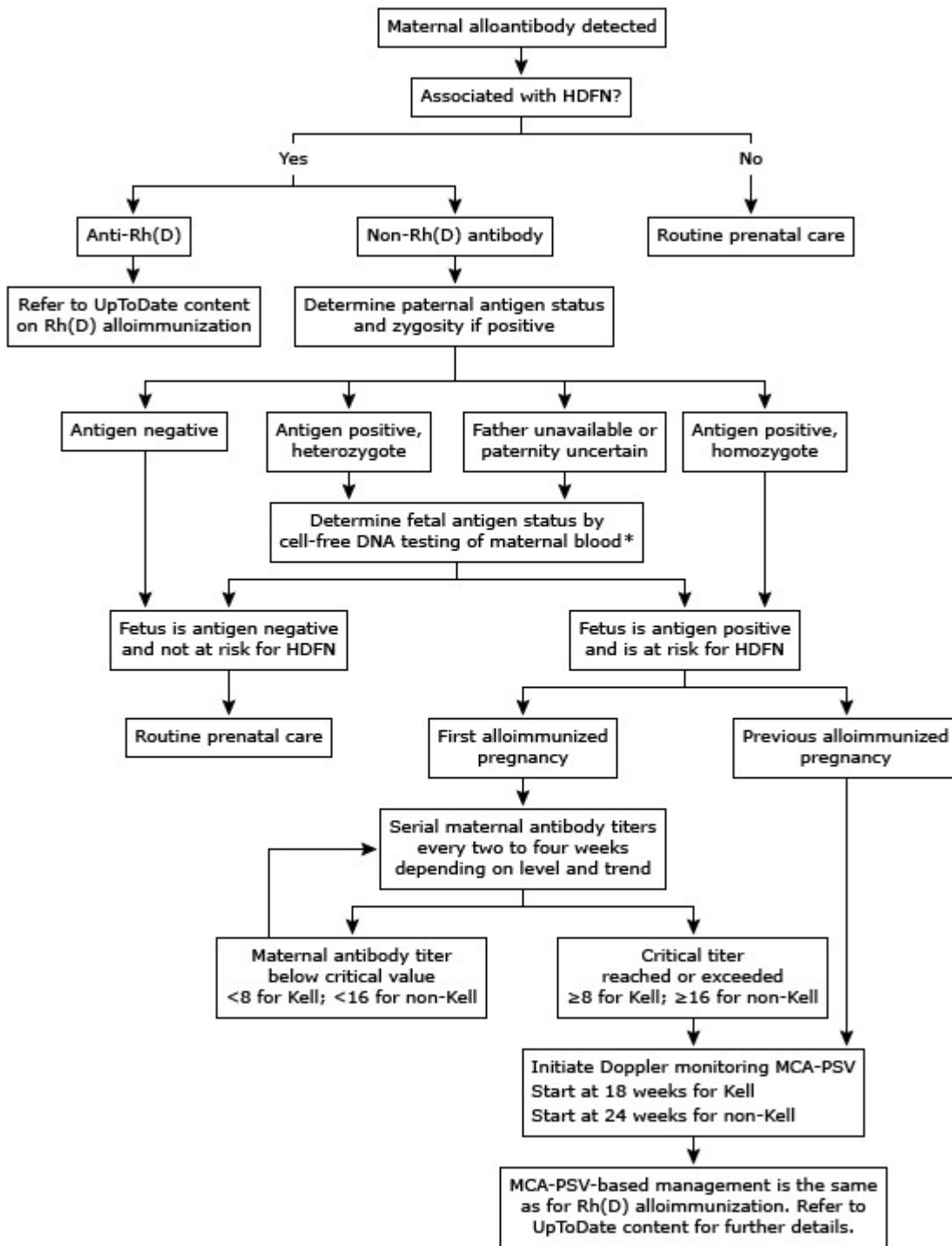
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GRAPHICS

Algorithm for non-Rh(D) alloimmunized pregnancy



Refer to UpToDate content on non-Rh(D) alloimmunization in pregnancy for further details.

HDFN: hemolytic disease of the fetus and newborn; RBC: red blood cell; MCA-PSV: middle cerebral artery peak systolic velocity.

* In many countries including the United States, cell-free DNA testing for red blood cell antigens other than Rh(D) is not routinely available. In countries where cell-free testing is available, it is usually only done for Kell, Rh(C), and Rh(E). If cell-free DNA testing is not available, serial maternal antibody titers are obtained and amniocentesis is performed to determine fetal antigen status from amniocytes if/when the critical titer is reached.

Graphic 104946 Version 1.0

Red blood cell antibodies associated with hemolytic disease of the fetus and newborn

Antigen group	Specific antigen	Disease severity
ABO	A, B	Mild
Chido-Rodgers	Ch1, Ch2, Ch3, Ch4, Ch5, Ch6, WH, Rg1, Rg2	None
Colton	Co ^a	Moderate
	Co ^b , Co ³	Mild
Cromer	Cr ^a , Tc ^a , Tc ^b , Tc ^c , Dr ^a , Es ^a , IFC, WES ^a , WES ^b , UMC, GUTI, SERF, ZENA, CROV, CRAM	None
Diego	Di ^a , Di ^b , Wr ^a , ELO	Moderate
	Wr ^b , Wd ^a , Rb ^a , WARR, Wu, Bp ^a , Mo ^a , Hg ^a , Vg ^a , Sw ^a , BOW, NFLD, Jn ^a , KREP, Tr ^a , Fr ^a , SW1	None
Dombrock	Do ^a , Do ^b , Gy ^a , Hy, Jo ^a , DOYA	None
Duffy	Fy ^a	Moderate
	Fy ^b	Mild
	Fy ³ , Fy ⁴ , Fy ⁵ , Fy ⁶	None
Forssman	FOR	None
Gerbich	Ge3	Moderate
	Ge2, Ge4, Wb, Ls ^a , An ^a , Dh ^a , GEIS	None
Gill	GIL	None
Globoside	PP ₁ P _k	Severe
H	H	Moderate
I	I, i	None
Indian	In ^a , In ^b , INFI, INJA	None
Junior	Jr ^a	Mild (rare: severe)
John Milton Hagen	JMH, JMhk, JMHL, JMhG, JMhM	None
Kell	K, k, Ku, Js ^b	Severe
	Kp ^b	Moderate
	Kp ^a , Js ^a , UI ^a	Mild
	K11, K12, K13, K14, K15, K16, K17, K18, K19, K20, K21, K22, K23, K24, VLAN, TOU, RAZ, KUCI, KANT, KASH, VONG, KALT, KTIM, KYO	None
Kidd	Jk ^a , Jk ^b	Mild (rare: severe)
	Jk3	Mild
Knops	Kn ^a , Kn ^b , McC ^a , SI1, Yka, SI2, SI3, KCAM	None
Kx	Kx	None
Langereis	Lan	Mild (rare: moderate)

Landsteiner-Weiner	LW ^a , LW ^{ab} , LW ^b	None
Lewis	Le ^a , Le ^b , Le ^{ab} , Le ^{bH} , Ale ^b , Ble ^b	None
Lutheran	Lu ^a	Mild
	Lu ^b , Lu3, Lu4, Lu5, Lu6, Lu7, Lu8, Lu9, Lu10, Lu11, Lu12, Lu13, Lu14, Lu15, Lu16, Lu17, Au ^a , Au ^b , Lu20, Lu21	None
Mittenberger	Mi ^a	Severe
	Mi ^b	None
MNSs	Vw, Mur, MUT	Severe
	U	Moderate (rare: severe)
	S, s, Mt ^a , M ^v	Moderate
	M	Mild (rare: severe)
	N, Hil, Or	Mild
	He, Mi ^a , M ^c , M ^g , Vr, M ^e , St ^a , Ri ^a , Cl ^a , Ny ^a , Hut, Far, s ^D , Mit, Dantu, Hop, Nob, En ^a , En ^a KT, 'N', DANE, TSEN, MINY, SAT, ERIK, Os ^a , ENEP, ENEH, HAG, ENAV, MARS, ENDA, ENEV, MNTD	None
Ok	Ok ^a	None
P1Pk	P, P1, P ^k	None
Raph	MER2	None
Rhesus (Rh)	D, c, f, Ce, C ^w , cE	Severe
	E, Hr _o	Moderate (rare: severe)
	E ^w , hr ^s , Tar, Rh32, Hr ^B	Moderate
	G	Mild (rare: severe)
	C	Mild (rare: moderate)
	e, C ^x , VS, CE, Be ^a , JAL	Mild
	V, Hr, C ^G , D ^w , c-like, hr ^H , Rh29, Go ^a , Rh33, hr ^B , Rh35, Evans, Rh39, Rh41, Rh42, Crawford, Nou, Riv, Sec, CELO, Dav, STEM, FPTT, MAR, BARC, JAHK, DAK, LOCR, CENR, CEST	None
	RHAG	Duclos, Ol ^a , Duclos-like
Scianna	Rd	Mild (rare: moderate)
	SC2	Mild
	SC1, SC3, STAR, SCER, SCAN	None
Vel	Vel	Mild (rare: moderate)
Yt (Cartwright)	Yt ^a , Yt ^b	None
Xg	Xg ^a	Mild
	CD99	None
Antigens that do not belong to a blood group system		
Cost	Cs ^a , Cs ^b	None

Er	Er ^a , Er ^b	None
High-prevalence antigens	At ^a	Mild
	AnWj, ABTI, Emm, MAM, PEL, Sd ^a	None
Low-prevalence antigens	HJK	Severe
	Kg, Sara	Moderate
	Chr ^a , Bi, Bx ^a , To ^a , Pt ^a , Re ^a , Je ^a , Li ^a , Milne, RASM, JFV, JONES, HOFM, REIT	None

Mild disease: published reports of need for bililight therapy or simple transfusion in neonatal life.

Moderate disease: published reports of need for exchange transfusion in neonatal life.

Severe disease: published reports of hydrops fetalis or need for intrauterine transfusions.

Disease severity indicated in parentheses indicates a case report of a more severely affected fetus or neonate has been published, in contrast to the majority of reports.

Refer to UpToDate topics on HDFN for further details.

HDFN: hemolytic disease of the fetus and newborn.

Graphic 102368 Version 5.0

Contributor Disclosures

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