

Management of pregnancy complicated by Rhesus (D) alloimmunization

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INTRODUCTION — Despite the development and implementation of anti-D [immune globulin](#) prophylaxis, hemolytic disease of the fetus and newborn due to maternal Rh(D) alloimmunization continues to occur worldwide. Ideally, pregnancies complicated by alloimmunization should be managed by a maternal-fetal medicine specialist with appropriate experience and credentialed to perform the invasive diagnostic and therapeutic procedures that may be needed. With appropriate pregnancy monitoring and intervention, this disorder can be treated successfully in almost all cases, with minimal long-term sequelae in offspring.

This topic will provide our approach to management of pregnant women with Rh(D) alloimmunization. Related topics, including a discussion of the Rhesus system, diagnosis and prevention of Rh(D) alloimmunization, diagnosis and management of pregnant women with non-Rh(D) alloimmunization, in utero transfusion, and neonatal issues, are reviewed in detail separately:

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

MANAGEMENT OF THE FIRST ALLOIMMUNIZED PREGNANCY — A woman's first pregnancy complicated by Rh(D) alloimmunization is managed differently from subsequent pregnancies because her anti-D titer is usually low at the beginning of her first affected pregnancy; severe fetal anemia may not develop or develops in the late second trimester or the third trimester. In subsequent affected pregnancies, fetal anemia usually is more severe and develops earlier in gestation.

Our approach to managing the first pregnancy complicated by red cell alloimmunization is illustrated by the algorithm ([algorithm 1](#)) and discussed below [[1](#)].

Determine whether the fetus is at risk — A Rh(D)-negative fetus is not at risk for complications from maternal anti-D antibodies; therefore, one of the initial steps in antenatal management of maternal Rh(D) alloimmunization is to determine the fetal Rh(D) type.

If the biologic father of the fetus is Rh(D)-negative and paternity is certain, the fetus must also be Rh(D)-negative. Maternal alloimmunization occurred as a result of a previous pregnancy with a Rh(D)-positive partner or from some other source of Rh(D)-positive red cells (eg, incompatible blood transfusion, needle sharing). A Rh(D)-negative fetus is not at risk for hemolytic disease, and further evaluation, monitoring, and intervention are unnecessary, unless maternal alloimmunization involving non-Rh(D) red cell antibodies has occurred. Obviously, certainty as to paternity is imperative, and nonpaternity is more common than one might assume [2]. The clinician should consider documenting the discussion regarding assured paternity in the medical record.

If the biologic father of the fetus is Rh(D)-positive, we determine paternal zygosity (see '[Paternal zygosity testing](#)' below). All offspring of Rh(D)-positive homozygotes will be Rh(D)-positive so further testing for fetal Rh(D) type is unnecessary. Heterozygotes have a 50 percent chance of having Rh(D)-negative offspring, so in these cases we perform cell free DNA (cfDNA) testing for fetal *RHD* status (ie, testing for the *RHD* gene); this is a noninvasive test that uses maternal plasma. (See '[Cell free DNA testing](#)' below.)

If the biologic father of the fetus is unavailable for testing or paternity is uncertain, we determine fetal Rh(D) type by cfDNA testing.

Paternal zygosity testing — Paternal zygosity is determined using quantitative polymerase chain reaction (PCR) to identify the number of *RHD* genes [3]. In the past, laboratories used antisera to the Rh antigens (D, C/c, E/e) and gene frequency tables based upon race/ethnicity to estimate paternal zygosity at the *RHD* locus. Although useful, these estimates are less reliable than direct genetic testing, which is commercially available from at least one vendor in the United States (eg, Blood Center of Wisconsin, ARUP laboratories).

As discussed above, all offspring of Rh(D)-positive homozygotes will be Rh(D)-positive, so further testing for fetal Rh(D) type is unnecessary. Zygosity testing will reveal a heterozygous paternal genotype in approximately 40 percent of Rh(D)-positive Caucasians. Heterozygotes have a 50 percent chance of having Rh(D)-negative offspring, so cfDNA testing is performed to determine fetal Rh(D) type.

Cell free DNA testing — Noninvasive assessment of fetal *RHD* using cfDNA is widely available in the United Kingdom and Europe. It is also available in the United States, but may not be covered by insurance.

The fetal *RHD* genotype is determined by testing a sample of maternal plasma after eight weeks of gestation. If the fetus is *RHD*-negative and the mother has no additional red cell antibodies, it is not at risk for hemolytic disease of the fetus and newborn (HDFN) and further maternal or fetal monitoring for HDFN is unnecessary. If the fetus is *RHD*-positive, then maternal indirect Coombs titers (ie, indirect antiglobulin test) are obtained serially until a critical titer is reached. (See '[Follow maternal anti-D titers in at risk fetuses until the critical titer is reached](#)' below.)

Fetal cfDNA can be detected in the maternal circulation as early as 38 days of gestation. It comprises 10 to 15 percent of the total cfDNA in the maternal circulation during the late first and early second trimesters, increases with advancing gestation, and disappears soon after delivery. Fetal *RHD* status is determined by evaluation of cfDNA sequences in maternal plasma using a reverse transcriptase PCR. A 2016 meta-analysis of studies of cfDNA for *RHD* determination reported sensitivity of 99.3 percent (95% CI 98.2– 99.7) and specificity of 98.4 percent (95% CI 96.4–99.3) in the first and second trimesters; real-time quantitative PCR sensitivity was higher than conventional PCR [4].

Assays for the *RHD* exon 4; exons 5 and 7; exons 4, 5, and 7; or exons 4, 5, 7, and 10 have been recommended, and should be done after approximately 10 weeks of gestation so there will be adequate fetal cfDNA [3,5-9]. Detection of these *RHD* exons in maternal plasma indicates fetal cfDNA is present and the fetus is *RHD*-positive. If *RHD* exons are absent, the fetus is *RHD*-negative as long as it can be proven that fetal cfDNA and not maternal cfDNA was tested (algorithm 2). Identification of Y chromosome gene sequences (*SRY*) in the plasma sample confirms the presence of fetal cfDNA and validates the test results. If the fetus is female, single nucleotide polymorphisms (SNPs) that are not common to the general population can be used to confirm fetal cfDNA in the sample [10]. Maternal SNPs are identified in the white cells (maternal) of the buffy coat. A significant difference in the types of SNPs between the buffy coat and the plasma (at least six different SNPs) indicates paternally-acquired SNPs in the plasma, thereby confirming the presence of fetal cfDNA and validating the test result. The hypermethylated *RASSF1A* promoter has also been reported as a universal fetal marker to confirm the presence of fetal DNA [11-13].

False positive results have been attributed to phenotypically Rh(D)-negative mothers who carry the *RHD* pseudogene or another *RHD* gene variation and pass this gene on to their fetus [14]. The *RHD* pseudogene has been described in 69 percent of South African blacks and 24 percent of African Americans [6]. In this situation, all 10 exons of the *RHD* gene are present; however, translation of the gene into a messenger RNA product does not occur because of a stop codon in the intron between exons 3 and 4. Therefore, no Rh(D) protein is synthesized, and the patient is serologically Rh(D)-negative. The *RHD* pseudogene can often be detected by using primers targeting exons 4 and 10 of the *RHD* gene. Such false positives, if not detected, could result in unnecessary invasive interventions. If *RHD* pseudogenes are suspected, the cfDNA result will return as "indeterminate"; testing fetal DNA in amniocytes is then recommended. In these cases, maternal and paternal blood samples should accompany the amniotic fluid for laboratory analysis. As with any cfDNA test, a vanishing twin is another potential source of false positive results [15].

False negative results would be more serious as appropriate monitoring and interventions might be withheld. More than one D region (eg, exons 7 and 10, intron 4) should be examined to ensure that negative results reflect true *RHD* negativity and not the presence of D variants. False negatives can also be due to a low level of fetal cfDNA in a maternal sample because it was drawn too early in gestation (<8 weeks of gestation) or to insensitive laboratory techniques [16]. We consider the false negative rate of cfDNA sufficiently low that we do not obtain serial titers when cfDNA indicates a *RHD*-negative fetus. False negatives will be identified soon after delivery as all newborns routinely undergo direct Coombs testing through cord blood sample analysis at birth.

Amniocentesis — If cfDNA testing is not available, fetal *RHD* gene status can be determined by PCR on uncultured amniocytes obtained by amniocentesis after 15 weeks of gestation [17]. Because this is an invasive procedure, it is reserved for pregnancies in which a critical titer is reached or exceeded (discussed below) and the father is heterozygous for *RHD*, paternal zygosity is unknown, paternal Rh(D) type is unknown, or noninvasive testing was inconclusive due to *RHD* pseudogene or a low amount of fetal DNA. However, if a woman with titers below the critical level is undergoing amniocentesis for another indication (eg, diagnosis of aneuploidy), it is reasonable to determine fetal *RHD* gene status at that time as well.

Transplacental amniocentesis should be avoided, if possible, as it may worsen alloimmunization (chorionic villus biopsy is avoided for the same reason [18]). The magnitude of this risk is unknown.

Follow maternal anti-D titers in at risk fetuses until the critical titer is reached — In the first alloimmunized pregnancy with a fetus at risk of HDFN, the indirect Coombs titer (ie, indirect antiglobulin test) is repeated monthly as long as it remains stable; rising titers should be repeated every two weeks until the titer reaches the "critical" level.

Serial titers should be determined by the same laboratory since variation in titers among laboratories is common. Intra-laboratory variation also occurs, but a truly stable titer should not vary by more than one dilution when repeated in a given laboratory. As an example, a titer of 2 that increases to 4 may not represent a true increase in the amount of antibody in the maternal circulation, but a rise to 8 is likely real. Of note, maternal administration of anti-D [immune globulin](#) after the primary immune response to the D antigen has occurred will not prevent a rise in titer and anti-D immune globulin should not be administered to sensitized women [\[19,20\]](#).

A critical titer has historically been defined as the titer associated with a risk for development of severe anemia and hydrops fetalis at a particular institution. Below the critical titer, the fetus is at risk for developing mild to moderate, but not severe, anemia. However, given the decreased incidence of Rh(D) alloimmunization in pregnancy, most institutions lack sufficient patients to establish a critical titer and therefore consider an anti-D titer between 16 and 32 as a critical value. In Europe and the United Kingdom, a threshold value of 15 international units/mL is the critical value, based upon comparison with an international standard [\[21\]](#).

If the critical titer is reached or exceeded, further assessment is required to determine whether the Rh(D)-positive fetus is severely anemic. Maternal titers are screening tests, not diagnostic of severe anemia, and should be discontinued once a critical titer is reached.

If fetal *RHD* type has not yet been determined by cfDNA testing, examination of amniocytes, or certain *RHD* homozygous paternity, we recommend fetal *RHD* evaluation at this point to avoid potentially unnecessary serial Doppler ultrasound monitoring and fetal blood sampling. Maternal indirect Coombs titers can rise even though the fetus is Rh(D)-negative; the reason is unclear.

Assess for severe anemia in fetuses at risk — When the critical titer is reached or exceeded and the fetus is *RHD*-positive, Doppler velocimetry of the middle cerebral artery (MCA) peak systolic velocity (PSV) is performed to identify fetuses that may be severely anemic. Doppler assessment of the fetal MCA-PSV is based on the principle that the fetal hemoglobin level determines blood flow in the MCA: MCA-PSV increases as fetal hemoglobin level falls [\[22\]](#).

A 2009 systematic review including nine observational studies provided compelling evidence that Doppler interrogation of the MCA-PSV performs well as a screening tool for severe fetal anemia of any etiology [\[23\]](#). When severe anemia was defined as fetal hemoglobin <0.55 multiples of the median (MoMs) for gestational age, sensitivity and specificity were 75.5 and 90.8 percent, respectively. In the seminal study included in this review, both hemoglobin level in blood obtained by cordocentesis and MCA-PSV were measured in 111 fetuses at risk for anemia due to maternal red cell alloimmunization and compared with values in 265 normal fetuses [\[24\]](#). The sensitivity of increased MCA-PSV (above 1.5 MoMs) for the prediction of moderate or severe anemia was 100 percent (95% CI 86-100), either in the presence or absence of hydrops, with a false positive rate of 12 percent. The same authors conducted a follow-up prospective study of 125 fetuses at risk for alloimmune anemia and reported the overall performance of MCA-PSV for moderate to severe anemia (hemoglobin level below 0.65 MoMs) was sensitivity 88 percent, specificity 87 percent, positive predictive value 53 percent, and negative predictive value 98 percent [\[25\]](#). One of nine fetuses with severe anemia was missed, possibly due to a screening interval longer than two weeks.

Other methods — Amniotic fluid bilirubin levels and fetal blood sampling are other methods for evaluating the fetus for anemia, but are rarely used.

Amniocentesis to determine amniotic fluid bilirubin levels (delta OD₄₅₀) had been the traditional method for indirectly estimating the severity of fetal anemia. Bilirubin in amniotic fluid derives from fetal pulmonary and tracheal effluents and correlates with the degree of fetal hemolysis [26,27]. However, Doppler velocimetry is as, or more, sensitive and specific for detection of severe fetal anemia and has the advantage of being noninvasive [28]. For these reasons, delta OD₄₅₀ assay is no longer readily available at most commercial laboratories.

Fetal blood can be sampled to precisely determine the severity of fetal anemia, but this procedure carries a 1 to 2 percent risk of fetal loss, with the highest risk at lower gestational ages and in hydropic fetuses (see "[Fetal blood sampling](#)"). We reserve fetal blood sampling for pregnancies in which MCA-PSV suggests moderate to severe anemia.

MCA-PSV-based management — MCA-PSV is performed, when clinically indicated, after 20 weeks of gestation in the first affected pregnancy because severe anemia is unlikely in the first half of pregnancy and fetal blood sampling and transfusion are difficult at this gestational age. Because MCA-PSV increases across gestation ([figure 1](#)), results should be adjusted for gestational age. Conversion calculators, such as the one found at www.perinatology.com, can be used to convert the actual MCA-PSV in cm/sec to MoMs to correct for gestational age.

The optimal interval between examinations has not been determined. Experts suggest one- to two-week intervals based on clinical experience and what is known about progression of fetal anemia in this setting [24]. The frequency is increased if indicated by MoMs approaching 1.5. Proper technique for measuring MCA-PSV is important, and is described elsewhere [29,30]. Ideally, the measurement is obtained when the fetus is in a quiet behavioral state, as results are higher when the fetus is active [31,32].

MCA-PSV ≤1.5 MoMs for gestational age — A MCA-PSV ≤1.5 MoMs for gestational age is consistent with absence of moderate to severe anemia. If MCA-PSV remains at this level, we schedule delivery at 37 to 38 weeks of gestation, consistent with Society for Maternal-Fetal Medicine guidelines [29]. In addition, we begin weekly antenatal testing at 32 weeks of gestation. Historically, alloimmunization has been considered an indication for antepartum fetal surveillance, although no well-designed studies have evaluated the utility, type, or frequency of testing [33]. (See "[Overview of antepartum fetal surveillance](#)".)

MCA-PSV >1.5 MoMs for gestational age — For pregnancies with MCA-PSV >1.5 MoMs for gestational age, we obtain fetal blood for hemoglobin determination and have blood readily available for intrauterine fetal transfusion, but only perform the transfusion if fetal hemoglobin is more than two standard deviations below the mean value for gestational age; reference values have been established ([table 1](#)). A hematocrit less than 30 percent can also be used as the threshold for fetal transfusion [34]. If the hemoglobin is above this threshold, we obtain another fetal blood sample in one to two weeks, depending on the value. Fetal hemoglobin/hematocrit should be checked before transfusion because a high MCA-PSV is not definitive proof of clinically significant fetal anemia; false positives occur [24,25].

Transfusion at a moderately reduced hemoglobin level results in a better fetal outcome than waiting until development of severe anemia (hemoglobin >7 g/dL below the normal mean for gestational age [35]) or hydrops (hemoglobin less than 5 g/dL) [24].

Intravascular intrauterine transfusion is generally limited to pregnancies between 18 and 35 weeks of gestation because before 18 weeks, the small size of the relevant anatomic structures poses technical challenges, and after 35 weeks, intrauterine transfusion is considered riskier than delivery followed by postnatal transfusion therapy [36]. Thus, at ≥ 35 weeks of gestation, we would deliver a fetus with MCA-PSV >1.50 MoMs for gestational age without fetal blood sampling to check the fetal hemoglobin. (See ["Intrauterine fetal transfusion of red cells"](#).)

MANAGEMENT OF ALLOIMMUNIZATION IN SUBSEQUENT PREGNANCIES — Pregnancies after the first alloimmunized pregnancy are characterized by increasingly severe fetal hemolytic disease due to the entry of fetal red cells into the maternal circulation at each delivery, which causes an anamnestic maternal antibody response. A woman whose prior pregnancy was complicated by fetal hydrops, intrauterine fetal transfusion, preterm delivery because of severe fetal anemia, or neonatal exchange transfusion can expect development of severe fetal anemia in subsequent pregnancies with a Rh(D)-positive fetus. The severe anemia occurs earlier in gestation than in the prior pregnancy; a case report described severe anemia as early as 15 weeks of gestation [37].

Management of these pregnancies is illustrated in the algorithm ([algorithm 3](#)). We obtain a baseline maternal titer as an extremely high titer suggests the need for immunomodulation (see ['Special issues'](#) below). Serial maternal titers are not informative as they are not predictive of onset of fetal anemia.

We determine fetal *RHD* type early in gestation using cell free DNA and begin middle cerebral artery (MCA) peak systolic velocity (PSV) monitoring of *RHD*-positive fetuses at 16 to 18 weeks of gestation. MCA-PSV-based management is similar to that described above for first alloimmunized pregnancies, but measurement of MCA-PSV is usually undertaken weekly [29]. (See ['MCA-PSV-based management'](#) above.)

SPECIAL ISSUES

Management of pregnancies with severe fetal anemia before 20 weeks of gestation — For the rare patient with a history of previously affected pregnancies who develops very early, severe alloimmunization, intraperitoneal transfusion can be performed before 20 weeks, but is less successful in hydropic fetuses. (See ["Intrauterine fetal transfusion of red cells", section on 'Choosing a fetal access site'](#).)

Plasma exchange and administration of intravenous IgG (IVIg) may maintain the fetal hematocrit above life-threatening levels long enough to achieve a gestational age when intravascular intrauterine transfusion is technically feasible. A variety of therapeutic regimens have been described in case reports and small cases series [38]. The American Society for Apheresis guidelines on use of therapeutic apheresis describe intrauterine transfusion as the current mainstay of treatment, but state IVIg and/or therapeutic plasma exchange may be indicated if there is a high risk of fetal demise or signs of hydrops prior to 20 weeks [39].

Management of women with multiple antibodies — Some women develop antibodies to more than one red cell antigen. There are no specific guidelines for management of these pregnancies; they are typically managed as described above. The presence of other red cell antibodies (especially anti-C) with anti-D antibody appears to be associated with a more aggressive maternal immune response, thus increasing the risk of severe anemia and need for intrauterine fetal transfusion [40-42]. These pregnancies warrant close observation.

Prevention of an affected fetus in future pregnancies — Each subsequent pregnancy after the first affected pregnancy is likely to manifest more severe hemolytic disease of the fetus and newborn, and at an earlier gestational age. Hemolytic disease of the fetus and newborn can be prevented by avoiding conception of a Rh(D)-positive fetus. Prevention is rarely attempted because of the costs and complexities involved and because hemolytic disease of the fetus and newborn can be treated successfully in most cases.

An Rh(D)-positive fetus can be avoided in the following ways:

- In vitro fertilization (IVF) with preimplantation genetic diagnosis – If the potential biologic father is heterozygous for *RHD*, IVF with preimplantation genetic diagnosis can be used to identify *RHD*-negative embryos and only these embryos are considered for embryo transfer [43]. (See "[Preimplantation genetic diagnosis](#)".)
- Use of a gestational surrogate – If the potential biologic father is homozygous for *RHD*, 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 a Rh(D)-negative donor can be used for intrauterine insemination of the alloimmunized mother. (See "[Donor insemination](#)".)

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "[Patient education: Pregnancy in Rh-negative women \(The Basics\)](#)")

SUMMARY AND RECOMMENDATIONS

First affected pregnancy — ([algorithm 1](#))

- In a woman's first pregnancy complicated by Rh(D) alloimmunization, severe fetal anemia usually develops in the late second trimester or the third trimester, but may not develop. (See "[Management of the first alloimmunized pregnancy](#)" above.)
- A Rh(D)-negative fetus is not at risk for complications from maternal anti-D antibodies; therefore, one of the initial steps in antenatal management of maternal Rh(D) alloimmunization is to determine the fetal *RHD* type. (See "[Determine whether the fetus is at risk](#)" above.)

If the biologic father of the fetus is Rh(D)-negative, the fetus must also be Rh(D)-negative. A Rh(D)-negative fetus is not at risk for hemolytic disease, and further evaluation, monitoring, and intervention are unnecessary. Documentation of the discussion regarding paternity should be included in the medical record.

- If the biologic father of the fetus is Rh(D)-positive, paternal zygosity is determined. All offspring of *RHD*-positive homozygotes will be Rh(D)-positive so further testing for fetal Rh(D) type is unnecessary. Heterozygotes have a 50 percent chance of having Rh(D)-negative offspring, so in these cases we determine fetal *RHD* type noninvasively using cell free DNA (cfDNA) in maternal plasma ([algorithm 2](#)). If the biologic father of the fetus is unavailable for testing or paternity is uncertain, we determine fetal *RHD* type by cfDNA testing. (See '[Cell free DNA testing](#)' above and '[Paternal zygosity testing](#)' above.)
- If the fetus is *RHD*-positive, the indirect Coombs titer (ie, indirect antiglobulin test) is repeated monthly as long as it remains stable; rising titers should be repeated every two weeks. The critical titer (the titer associated with a risk for development of severe anemia and hydrops fetalis) varies among laboratories and by methodologies; however, in most centers, an anti-D titer between 16 and 32 is considered critical. In Europe and the United Kingdom, a threshold value of 15 international units/mL is the critical value, based upon comparison with an international standard. (See '[Follow maternal anti-D titers in at risk fetuses until the critical titer is reached](#)' above.)
- When the critical titer is reached or exceeded and the fetus is *RHD*-positive, further assessment by Doppler velocimetry is performed to determine whether the fetus is severely anemic. Doppler interrogation of the fetal middle cerebral artery (MCA) peak systolic velocity (PSV) is the best tool for predicting moderate to severe fetal anemia in at-risk pregnancies. (See '[Assess for severe anemia in fetuses at risk](#)' above.)
- We measure MCA-PSV at one- to two-week intervals. The frequency is increased if indicated by multiples of the median (MoMs) approaching 1.5. A MCA-PSV ≤ 1.5 MoMs for gestational age is consistent with absence of moderate to severe anemia. If MCA-PSV remains at this level, we schedule delivery at 37 to 38 weeks of gestation. In addition, we begin weekly antenatal testing at 32 weeks of gestation. (See '[MCA-PSV \$\leq 1.5\$ MoMs for gestational age](#)' above.)
- For pregnancies with MCA-PSV > 1.5 MoMs for gestational age, we obtain fetal blood by cordocentesis for hemoglobin determination and perform an intrauterine fetal transfusion if fetal hemoglobin is two standard deviations below the mean value for gestational age ([table 1](#)). Intrauterine transfusion is generally limited to pregnancies < 35 weeks of gestation because after 35 weeks, intrauterine transfusion is considered riskier than delivery followed by postnatal transfusion therapy. At ≥ 35 weeks of gestation we would deliver a fetus with MCA-PSV > 1.5 MoMs for gestational age. (See '[MCA-PSV \$> 1.5\$ MoMs for gestational age](#)' above.)

Previously affected fetus/infant — ([algorithm 3](#))

- A woman whose prior pregnancy was complicated by fetal hydrops, intrauterine fetal transfusion, preterm delivery because of severe fetal anemia, or neonatal exchange transfusion can expect development of severe fetal anemia in subsequent pregnancies with a Rh(D)-positive fetus and the severe anemia occurs earlier in gestation than in the prior pregnancy. (See '[Management of alloimmunization in subsequent pregnancies](#)' above.)
- We determine fetal *RHD* type using cfDNA and a baseline maternal titer early in gestation. Subsequent maternal titers are not informative as they may not be predictive of onset of fetal anemia. MCA-PSV monitoring of *RHD*-positive fetuses is initiated at 16 to 18 weeks of gestation. (See '[Management of alloimmunization in subsequent pregnancies](#)' above.)

- We measure MCA-PSV weekly, beginning at 16 to 18 weeks gestation. (See ['Management of alloimmunization in subsequent pregnancies'](#) above.)
- For pregnancies with MCA-PSV >1.5 MoMs for gestational age, we obtain fetal blood by cordocentesis for hemoglobin determination and perform an intrauterine fetal transfusion if fetal hemoglobin is two standard deviations below the mean value for gestational age ([table 1](#)). Intrauterine transfusion is generally limited to pregnancies <35 weeks of gestation because after 35 weeks intrauterine transfusion is considered riskier than delivery followed by postnatal transfusion therapy. At ≥35 weeks of gestation we would deliver a fetus with MCA-PSV >1.5 MoMs for gestational age. (See ['MCA-PSV >1.5 MoMs for gestational age'](#) above.)

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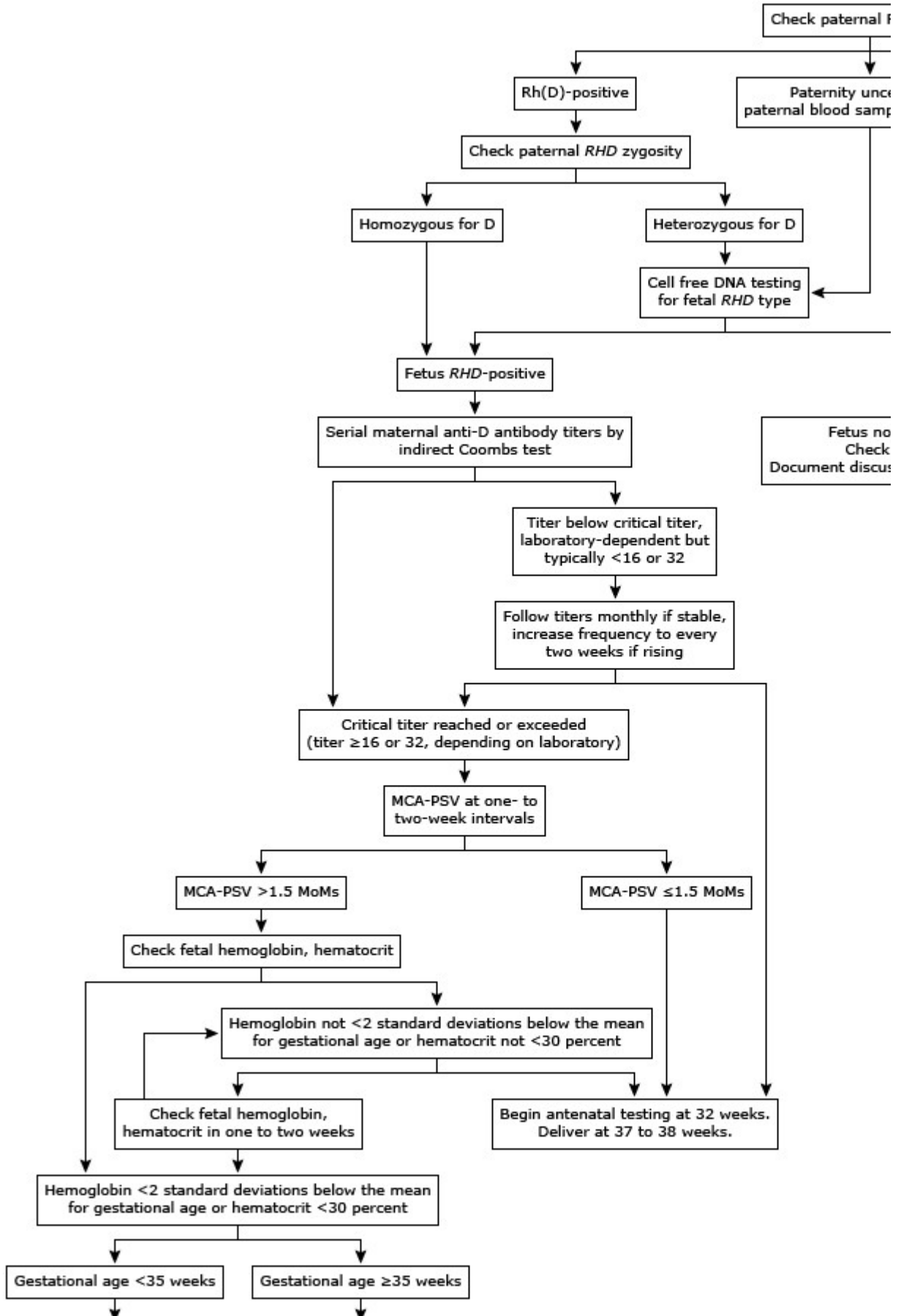
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GRAPHICS

Management of the first pregnancy with Rh(D) alloimmunization



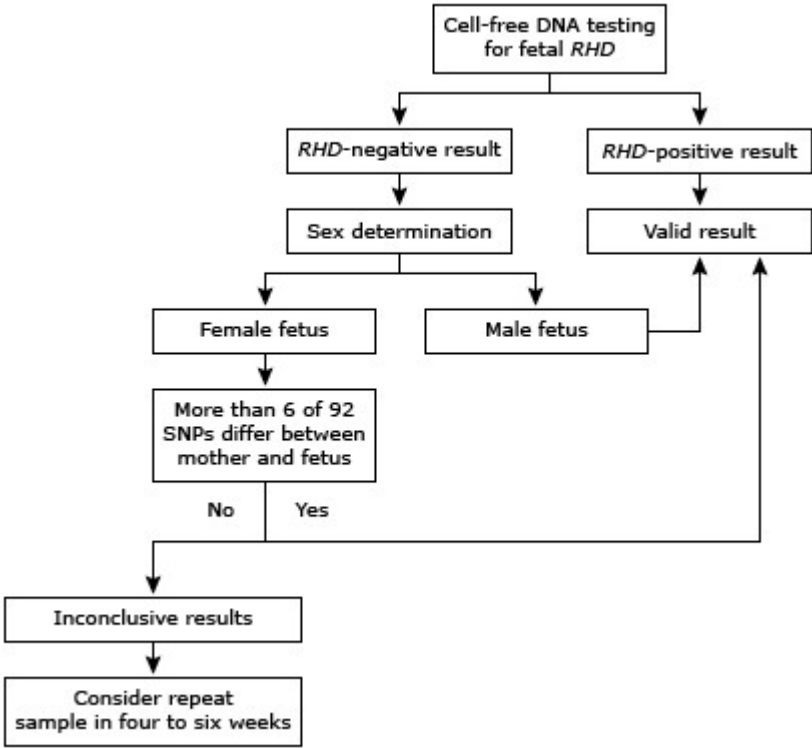
Perform intrauterine
transfusion

Deliver

Rh: Rhesus; MCA-PSV: middle cerebral artery peak systolic velocity; MoMs: multiples of the median.

Graphic 103188 Version 2.0

Algorithm for determining the results of cell-free DNA testing to determine the fetal *RHD* status

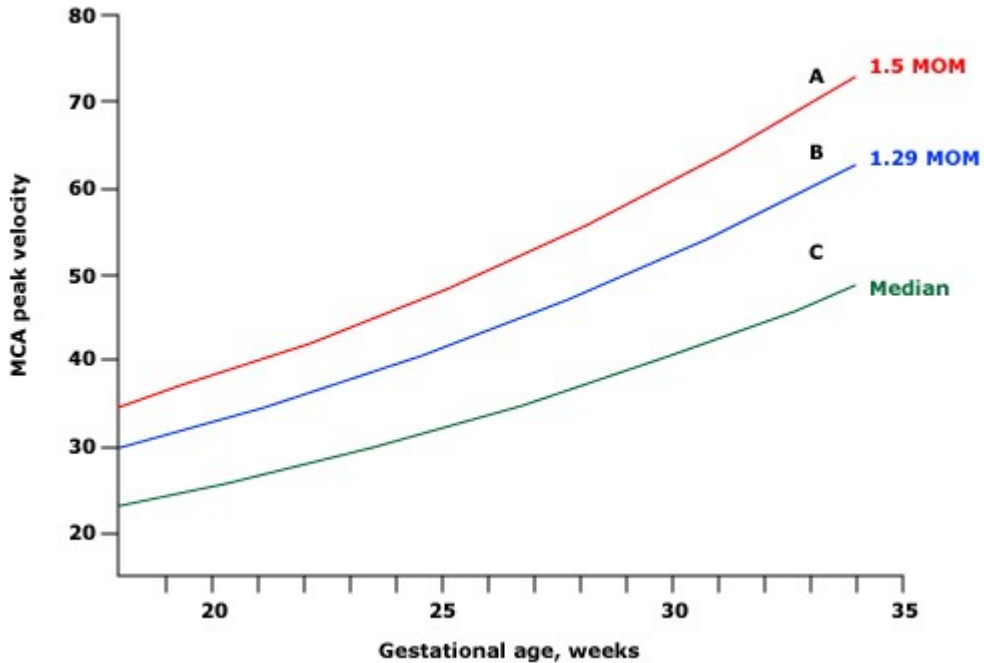


SNP: single-nucleotide polymorphism; *RHD*: Rhesus D gene.

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Graphic 86944 Version 6.0

MCA peak velocity



A: moderate to severe anemia; B: mild anemia; C: no anemia; MCA: middle cerebral artery; MOM: multiples of the median.

Data from: Mari G, for the Collaborative Group for Doppler Assessment of the Blood Velocity in Anemic Fetuses. Noninvasive diagnosis by Doppler ultrasonography of fetal anemia due to maternal red-cell alloimmunization. *N Engl J Med* 2000; 342:9.

Graphic 76467 Version 2.0

Normal mean and <2 SD values for fetal hemoglobin

Gestational age, weeks	Mean hemoglobin, gm/dL	<2 SD hemoglobin from the mean, gm/dL
18	11.3	9.3
19	11.5	9.5
20	11.7	9.7
21	11.9	9.9
22	12.1	10.1
23	12.3	10.3
24	12.5	10.5
25	12.7	10.7
26	12.8	10.8
27	13.0	11.0
28	13.2	11.2
29	13.4	11.4
30	13.6	11.6
31	13.8	11.8
32	14.0	12.0
33	14.2	12.2
34	14.4	12.4

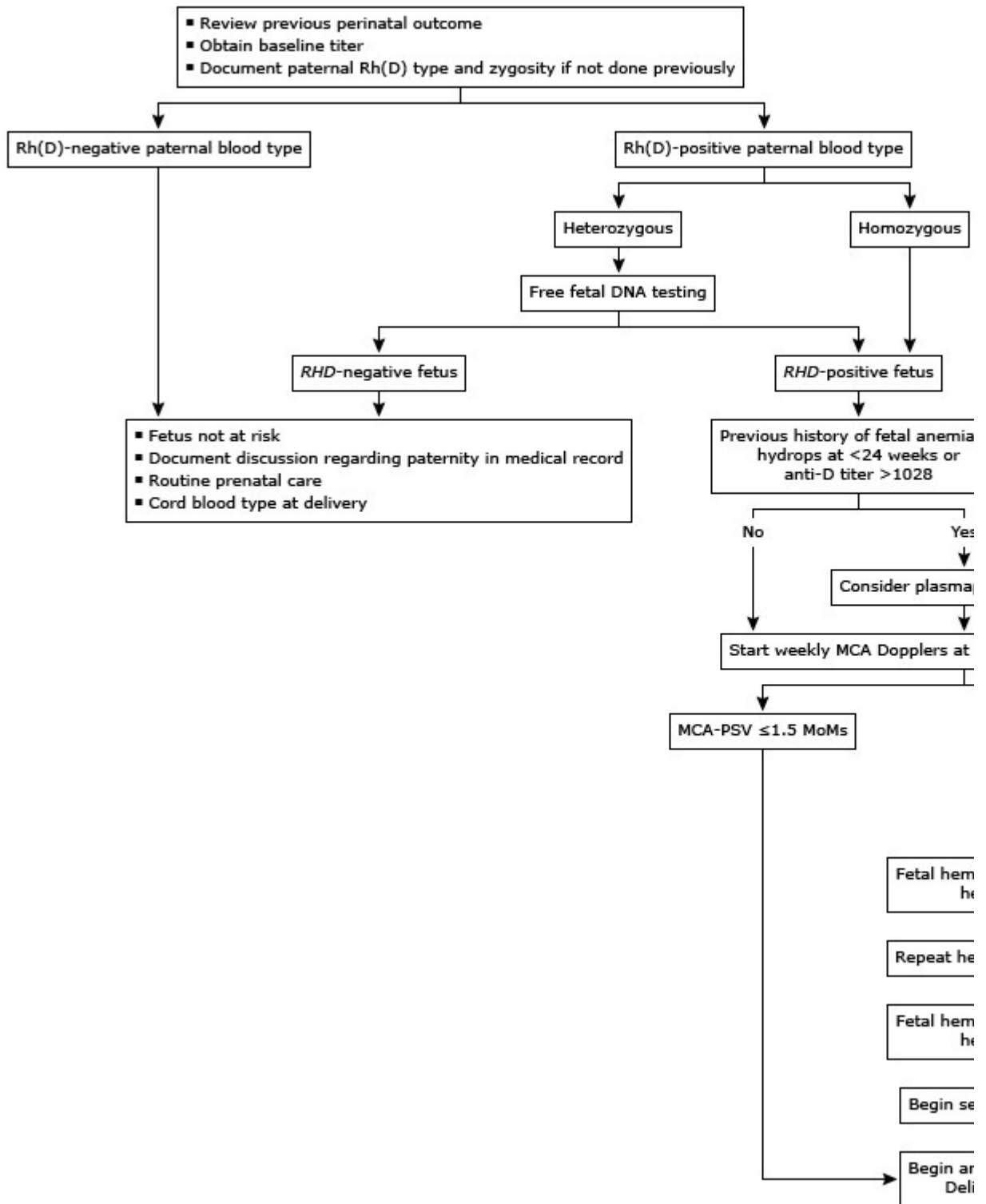
Two standard deviations below the mean is approximately 2 g/dL below the mean hemoglobin for gestational age.

SD: standard deviations; gm/L: grams/liter.

Data from: Nicolaides KH, Soothill PW, Clewell WH, et al. Fetal haemoglobin measurement in the assessment of red cell isoimmunization. Lancet 1988; 8594:1073.

Graphic 53399 Version 3.0

Management of women after a previous pregnancy complicated by Rh(D) allo



Rh: Rhesus; MCA: middle cerebral artery; PSV: peak systolic velocity; MoMs: multiples of the median; IVIG: intravenous immunoglobulin.

Graphic 103190 Version 1.0

Contributor Disclosures

Kenneth J Moise Jr, MD Consultant/Advisory Boards: Momenta Pharmaceutical, Inc [Rhesus disease (Fc receptor blocking monoclonal antibody (not yet in clinical trials))]; LFB Biotechnologies

[Development of synthetic Rhesus immune globulin (Roledumab, synthetic Rhesus immune globulin (clinical trial planning))]. **Charles J Lockwood, MD, MHCM** Consultant/Advisory Boards: Celula [Aneuploidy screening (No current products or drugs in the US)]. **Vanessa A Barss, MD, FACOG** Nothing to disclose

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

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