February 2026

Guidelines for the Management of Alloimmunization in Pregnancy

Definitions:

- Red blood cell alloimmunization: Red blood cell sensitization occurs when a patient is exposed to foreign antigens on erythrocytes, responding by forming antibodies. When these antibodies are present, the patient is said to be alloimmunized. Women can be sensitized to red blood cell antigens in pregnancy when fetal RBCs with antigens inherited from the father enter the maternal circulation. In subsequent pregnancies, some of these antibodies can cross the placenta, potentially binding to fetal RBCs to cause destruction and anemia.
- Hemolytic Disease of the Fetus and Newborn (HDFN): HDFN is the end result of RBC alloimmunization in some cases. If a sufficient quantity of antibodies crosses the placenta and binds to fetal RBCs, destruction of these cells can result in anemia in the baby. This may present in utero or in the neonatal period. Management of alloimmunization in pregnancy aims to identify the fetuses at risk for HDFN, allowing early detection of anemia with subsequent treatment as indicated
- Percutaneous blood sampling (PUBS), Cordocentesis, Fetal blood sampling (FBS), and Intrauterine transfusion (IUT): Although there are some nuances in these procedures, the terms are often used interchangeably to denote a prenatal procedure where in blood is obtained from the fetal umbilical vein with transfusion of red blood cells as indicated

Tiers of monitoring for HDFN:

- Tier 1 involves determining if the fetus is at risk for anemia:
  - Does the woman have RBC antibodies?
    - All women are screened for alloimmunization via a type and screen as part of routine prenatal blood work
  - Can the identified antibody cause HDFN?
    - The antibodies that can cause HDFN are listed in Figure 1. This includes anti-Rh(D), anti-Rh(c), anti-Rh(C), anti-Rh(E), anti-Kell, anti-Fya, anti-Fyb, anti-Jka, and anti-Jkb.
  - Is the antibody present in a sufficient quantity to cause clinically significant anemia?
    - The critical titer is the titer that is high enough to potentially cause anemia.
      - Critical titer for most antibodies: $\geq$16
      - Critical titer for anti-Kell and anti-Rh(c): $\geq$4
      - Critical titer for anti-M: $\geq$32
    - Should be checked every 4 weeks in the 2nd trimester, Increase to every 2 week titers at 28 weeks
      - Continue q4 week labs in the 2nd trimester with q2 week labs starting at 28 weeks until delivery if the patient continues to display a non-critical titer
      - Can discontinue serial titers once a critical titer is identified
    - If the patient has a h/o a prior pregnancy complicated by HDFN with resulting demise, hydrops, need for IUT, or need for neonatal exchange transfusion, the titer is not informative as anemia can occur at much lower antibody titers
    - Titers should only be designated as critical if they are obtained using serial tube dilutions
      - UC lab first performs tiers via a gel method. If this titer is critical, the lab will reflex to the serial tube dilution method, and this titer is the one used to determine if the baby is at risk for anemia
  - Does the fetus have the corresponding antigen?
    - CVS or amniocentesis can be performed to determine the fetal antigen status
    - Cell free DNA screening is recommended to determine the fetal antigen status for many antigens
      - Unity Billion-to-one cell free DNA screening screens for D, C, c, E, e, Fya, Fyb, Kell, kell, M, N, S, s, and U
        - Refer to genetic counseling or MFM to order if assistance needed with ordering
      - Natera (Panorama) screening screens for D antigen status
        - Other companies may offer screening for Rh(D) antigen status alone

- Recommend regardless of FOB antigen status
- If the fetus is negative for the antigen of concern according to cfDNA screening, there is no risk of fetal HDFN and no further titers or MCA dopplers are indicated
    - Offer amniocentesis for confirmation, but assume accurate testing via cfDNA if patient declines
- For the antigens that cannot be tested via cfDNA screening, presume that the fetus is positive for the antigen of concern and therefore at risk for anemia i paternity is uncertain/unknown, the paternal antigen status is heterozygous, or the fetal antigen status is unknown
- Paternal antigen status can be determined to assist with interpretation of results and to provide counseling about risks of HDFN with future pregnancies

- Tier 2 involves screening for fetal anemia: Middle cerebral artery doppler assessment is employed to screen for fetal anemia
    - MCA doppler assessment should be initiated at 16 weeks of gestation when the fetus is determined to be at risk for anemia
    - Ultrasounds should be performed every week
    - Peak systolic velocity values are assessed and compared to gestational age-based norms, allowing calculation of the multiples of the median
        - An MoM >1.5 is concerning for fetal anemia
    - MCA dopplers should NOT be used as the first tier of monitoring because of the ≥10% false positive rate of this screening study
- Tier 3 involves diagnosis of anemia and treatment as indicated
    - Depends on the gestational age
        - <34 weeks: PUBS should be performed to determine the fetal hemoglobin level, with IUT then performed if the fetus is determined to be anemic
        - >35 weeks: Delivery is recommended to facilitate neonatal evaluation and treatment
        - Between 34 and 35 weeks, individual assessment and counseling is recommended to decide upon the best management

Prevention of anti-Rh(D) sensitization:

- If a patient is Rh(D) negative, sensitization can occur during pregnancy or at the time of delivery
    - Rh immunoglobulin (RhIg) is used to prevent sensitization to the Rh(D) antigen specifically in an effort to prevent HDFN in a future pregnancy
    - Unless paternity is certain and the FOB is Rh(D) negative OR the fetus is known to be Rh(D) negative via cell free DNA screening, the following RhIg dosing is recommended:
        - Standard prophylaxis using a 300 mcg dose of RhIg at ~28 weeks of gestation
        - Standard prophylaxis using a 300 mcg dose of RhIg with pregnancy loss/miscarriage or fetal demise occurring at ≥12 weeks of gestation
        - Prophylaxis using a 300 mcg dose of RhoGam with complications prior to 28 weeks including vaginal bleeding, abdominal trauma, or invasive prenatal procedures
        - Prophylaxis with spontaneous, missed, or induced abortion at <12 weeks is controversial, but keeping with the guidelines per SMFM and ACOG, we recommend a single dose of 300 mcg of RhIg in this setting

❖ Fetomaternal hemorrhage:

- A single 300 mcg dose of RhIg contains sufficient anti-D to suppress the immune response to 15 mL of Rh(D)-positive fetal red blood cells or 30 mL of Rh(D)-positive fetal whole blood
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- Kleihauer-Betke stain to determine quantitative assessment.
    - Fetal blood cells (%) * 50 = volume of fetomaternal hemorrhage
    - Fetomaternal hemorrhage volume/30 = number of vials Rh immune globulin to administer

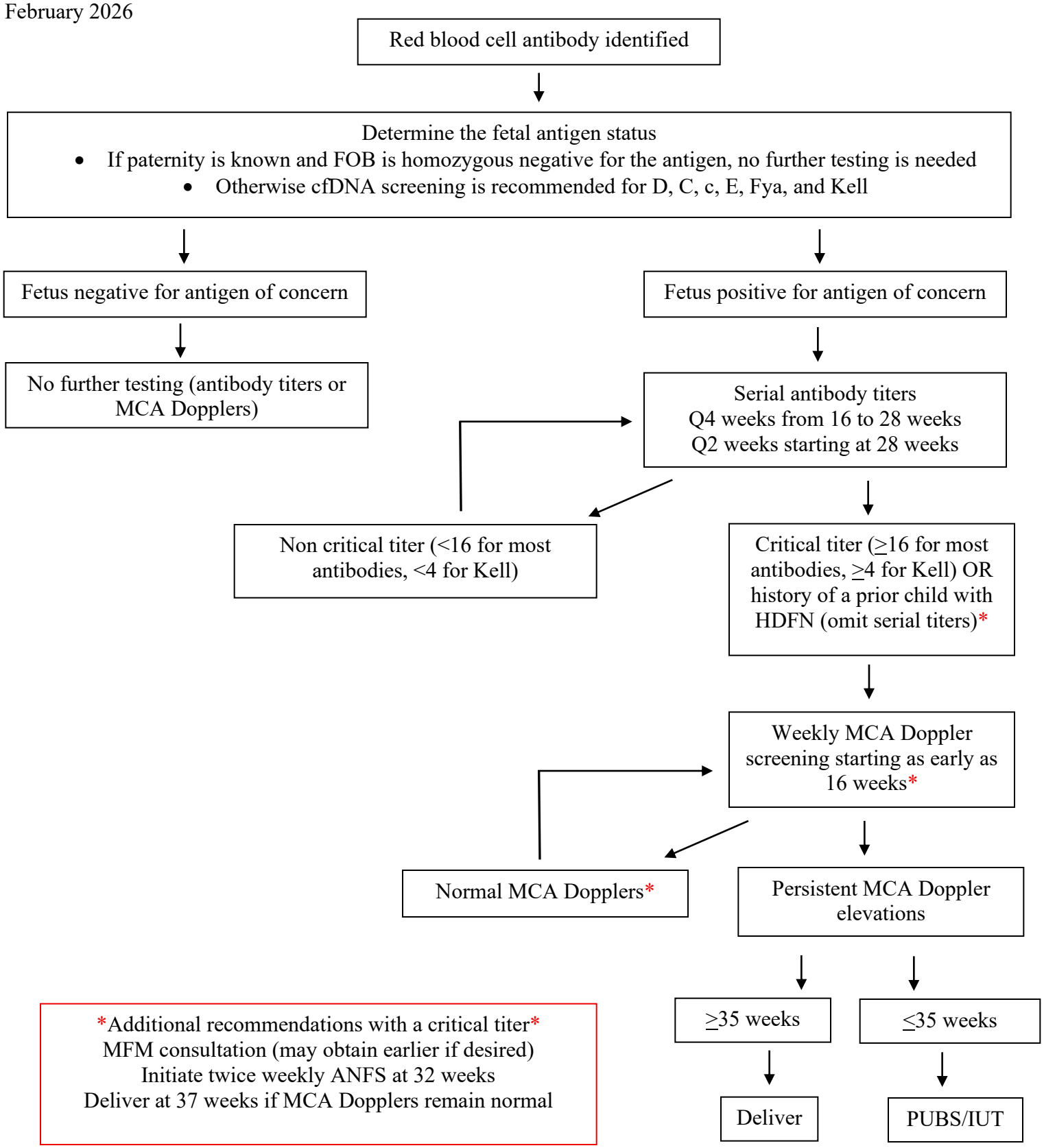
Red blood cell antibody identified
Determine the fetal antigen status
If paternity is known and FOB is homozygous negative for the antigen, no further testing is needed
Otherwise cfDNA screening is recommended for D, C, c, E, Fya, and Kell
Fetus negative for antigen of concern
No further testing (antibody titers or MCA Dopplers)
Fetus positive for antigen of concern
Serial antibody titers
Q4 weeks from 16 to 28 weeks
Q2 weeks starting at 28 weeks
Non critical titer (<16 for most antibodies, <4 for Kell)
Critical titer (≥16 for most antibodies, ≥4 for Kell) OR history of a prior child with HDFN (omit serial titers)*
Weekly MCA Doppler screening starting as early as 16 weeks*
Normal MCA Dopplers*
Persistent MCA Doppler elevations
≥35 weeks
≤35 weeks
Deliver
PUBS/IUT
Additional recommendations with a critical titer
MFM consultation (may obtain earlier if desired)
Initiate twice weekly ANFS at 32 weeks
Deliver at 37 weeks if MCA Dopplers remain normal

Table 1 – Antigens associated with HDFN (most common causative antigens in red)

Antigen System	Specific Antigen
Kell	K (K1) Others: k (Ks), Kp^{a}, Kp^{b}, K11 K22, Ku, Js^{a}, Js^{b}
Rhesus	D C c E e Others: Ce, C ^{w} , C ^{x}, ce, Be^{a}, D^{w}, E^{w}, Evans, G, Go^{a}, Hr, Hr$_{o}$, JAL, HOFM, LOCR, Riv, Rh29, Rh32, Rh42, Rh46, STEM, Tar
Colton	Co ^{a} , Co3
Diego	ELO, Di ^{a} , Di ^{b}, Wr ^{a} , Wr ^{b}
Duffy	-Fy ^{a} -Fy^{b}
Kidd	Jk ^{a} Jk ^{b}
MNS	**M** Others: Mi ^{a} , Mit, Mt ^{a}, MUT, Mur, M^{v}, En ^{a}, Far, Hil, Hut, s, s ^{D}, S, U, Vw
Other antigens	HJK, JFV, JONES, Kg, MAM, REIT, Rd, Vel, Lan, At^{a}, Jr^{a}
Dombrock	Do ^{a} , Gy ^{a}, Hy, Jo ^{a}
Gerbich	Ge ^{2}, Ge ^{3}, Ge ^{4}, Ls^{a}
Scianna	Sc2

References:

Crowther CA, Middleton P, McBain RD. Anti-D administration in pregnancy for preventing Rhesus alloimmunisation.Cochrane Database Syst Rev. 2013 Feb 28;2

Sandler SG, Gottschall JL. Postpartum Rh immunoprophylaxis. Obstet Gynecol. 2012 Dec;120(6):1428-38.

Moise KJ. Hemolytic disease of the fetus and newborn. Creasy and Resnik Maternal-fetal Medicine: Principles and Practice, Sixth Edition. 2009; Philadelphia, PA. Saunders Elsevier.

American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 75: Management of alloimmunization during pregnancy. Obstet Gynecol. 2006 Aug;108(2):457-64.

Moise KJ Jr, Argoti PS. Management and prevention of red cell alloimmunization in pregnancy: a systematic review. Obstet Gynecol. 2012 Nov;120(5):1132-9.

Bombar AT et al. Fetal RHD genotype detection from circulating cell-free DNA in maternal plasma in non-sensitized RhD negative women. Prenat Diagn. 2011; 31: 802-8.

Van den Veyver IB, Moise JD. Fetal RhD typing by polymerase chain reaction in pregnancies complicated by rhesus alloimmunization. Obstet Gynecol 1996; 88:1061-7.

Mari G et al. Noninvasive diagnosis by Doppler ultrasonography of fetal anemia due to maternal red-cell alloimmunization. Collaborative Group for Doppler Assessment of the Blood Velocity in Anemic Fetuses. N Engl J Med 2000; 342:9-14.