

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. They can also be sensitized secondary to blood transfusions and intravenous drug use. 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.
 - Warm antibodies do not place a pregnancy at risk for HDFN.
 - Identification of these antibodies should trigger evaluation for a rheumatologic disease.
 - 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: ≥ 16
 - Critical titer for anti-Kell and possibly anti-Rh(c): ≥ 4
 - Critical titer for anti-M: ≥ 32
 - Should be checked every 4 weeks in general.
 - Continue q4 week labs 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 father of the baby have the corresponding antigen?
 - Assuming paternity is certain, if the father is negative for the antigen to which the mother has antibodies, the fetus will not express this antigen and is therefore not at risk for anemia
 - If the father is homozygous for the corresponding antigen, the fetus will be heterozygous and therefore at risk for anemia

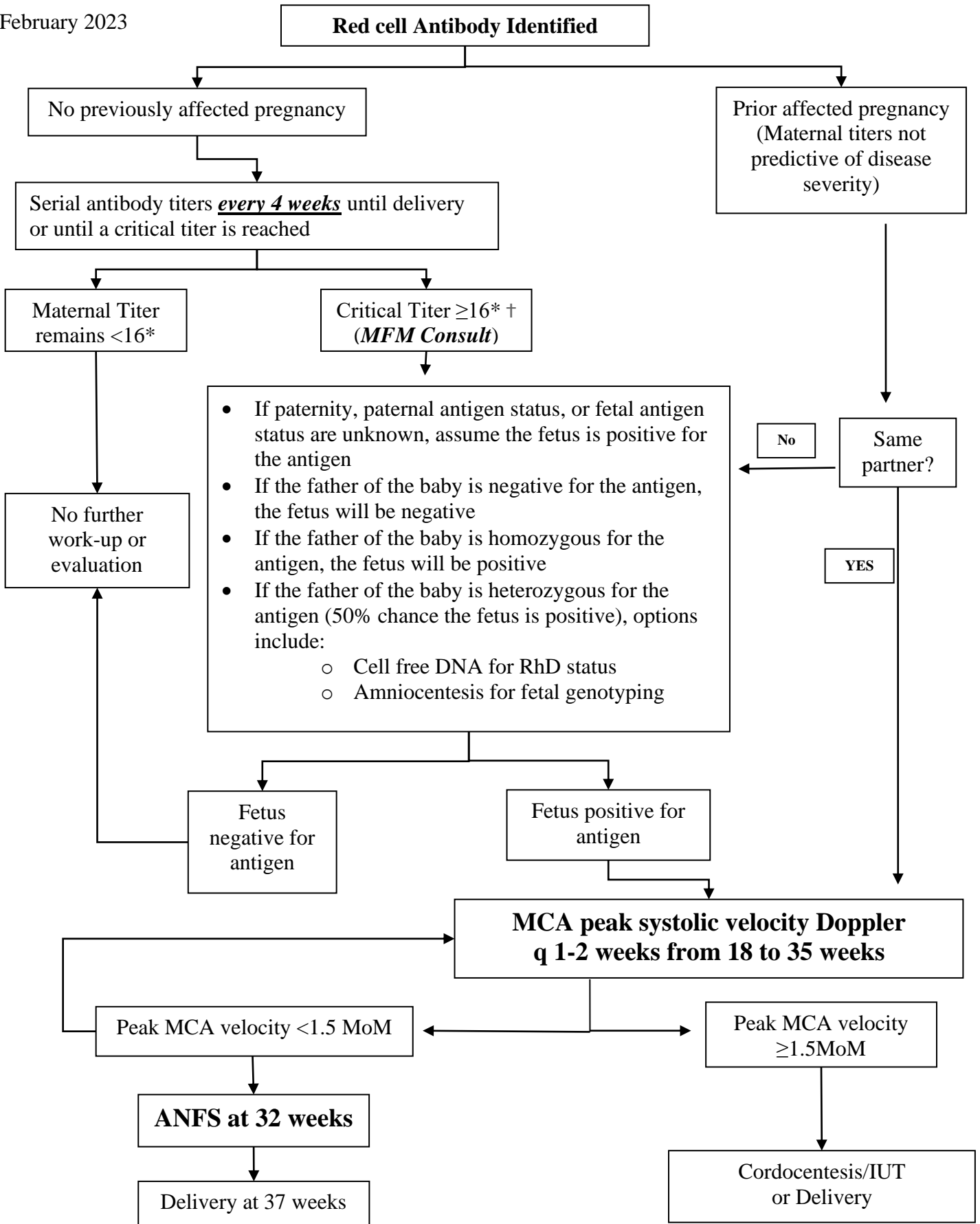
- If the father is heterozygous for the corresponding antigen, there is a 50% chance that the fetus will be heterozygous and at risk for anemia
 - CVS or amniocentesis can be performed to determine the fetal antigen status
 - Cell free DNA screening (Unity) is available in the US for Rh(D) status
 - Results:
 - If positive Rh(D) on cell free DNA, assume fetus is Rh(D) positive
 - If negative Rh(D) on cell free DNA, encourage amniocentesis to confirm this
 - <https://unityscreen.com>
 - Genetic counselors can assist with ordering this screening test
 - If paternity, the paternal antigen status, or the fetal antigen status is unknown, presume that the fetus is positive for the antigen of concern and therefore at risk for anemia
- 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 16-18 weeks of gestation when the fetus is determined to be at risk for anemia
 - Ultrasounds should be performed every 1-2 weeks depending on the antibody
 - Repeat MCA Doppler assessment weekly for anti-K, anti-c, anti-Rh(D) or multiple antibodies
 - For other single antibodies, repeat every two weeks.
 - If the MCA peak systolic velocity values are trending higher or nearing 1.5 MoMs, repeat weekly
 - 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
 - If elevated MCA, repeat MCA Doppler in 24-48 hours
 - 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
 - < 32 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 32 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 be prevented via administration of Rh(D) immunoglobulin (RhIg)
 - RhIg should NOT be administered to patients with preexisting anti-Rh(D) antibodies.
 - RhIg should be administered as follows:
 - Routinely administered at 28 weeks unless paternity is certain and the father of the baby is known to be Rh(D) negative
 - After invasive procedures such as chorionic villus sampling, amniocentesis, selective fetoscopic laser photocoagulation, etc
 - Consider administering following a first trimester pregnancy loss or ectopic pregnancy
 - Following abdominal trauma or vaginal bleeding in the 2nd and 3rd trimesters
 - Can calculate appropriate dose using a Kleihauer-Betke stain (also of use if worried about fetomaternal hemorrhage for any other reason)
 - Fetal blood cells (%) * 50 = Volume of fetomaternal hemorrhage
 - Fetomaternal hemorrhage volume/30 = number of vials Rh immune globulin to administer
 - In the postpartum period, the neonate's blood type should be determined and RhIg should be administered if he/she is Rh(D) positive

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 - Fetomaternal hemorrhage volume/30 = number of vials Rh immune globulin to administer
- Repeat RhIg dosing should be based on clinical judgment, though given risk of alloimmunization, would consider erring on side of repeat dosing.
 - RhIG (300mcg dosing) expected to protect against sensitization for approximately 12 weeks.



* Titer of ≥ 4 used for anti-Kell antibodies

† Paternal and/or fetal antigen status may also be determined prior to critical titer, may forgo serial antibody testing with known paternity and negative antigen status

Figure 1 – RBC antibodies associated with HDFN

<u>Antigen System</u>	<u>Specific Antigen</u>
Kell	- K (K1) -Js ^a -Js ^b -k (K2) -Kp ^a -Kp ^b -K11 -K22 -Ku -U ^a
Rhesus	- D - c - C - E - e Others: -Ce, -C ^w , -C ^x , -ce, -E ^w , -Evans, -Be ^a , -G, -Go ^a , -D ^w , -Hr, -Hr ₀ , -JAL, -HOFM, -LOCR, -Riv, -Rh29, -Rh32, -Rh42, -Rh46, -STEM, -Tar
Duffy	- Fy^a - Fy^b
Colton	-Co ^a -Co ³
Kidd	- Jk^a - Jk^b
Diego	-ELO -Di ^a -Di ^b -Wr ^a -Wr ^b
MNS	-En ^a -Far -Hil -Hut -M -Mi ^a -Mit -Mt ^a -MUT -Mur -M ^v -s -s ^D -S -U -Vw
Dombrock	-Do ^a -Gy ^a -Hy -Jo ^a
Gerbich	-Ge ² -Ge ³ -Ge ⁴ -Ls ^a
Scianna	-Sc2
Other antigens	-HJK, -JFV, -JONES, -Kg, -MAM, -REIT, -Rd, -Vel, -Lan, -At ^a , -Jr ^a

Bold denotes antibodies commonly associated with HDFN

Red denotes antibodies that can cause severe anemia at a lower titer (ie. ≥4)

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