



# Oklahoma Blood Institute TRANSFUSION TRIBUNE

4th Quarter, 2009

Jean Forsberg, M.D.

James Smith, M.D., Ph.D.

Sylvan N. Goldman Center

*A Not-for-Profit Regional Blood Center*

1001 N. Lincoln Blvd., Oklahoma City, OK 73104

(405)297-5700

www.obi.org

## Red Cell Alloimmunization and Pregnancy

When a woman is exposed to foreign red cells, antibodies can develop. This process is called red cell alloimmunization. Women can be alloimmunized due to transfusion or pregnancy (previous or current). The effects on a fetus and/or newborn is called hemolytic disease of the newborn and the severity ranges from mild to causing death in a fetus. The majority of clinically significant cases of HDN (~98%) occur to the "D" antigen of the Rh system, but can be seen with other antigen systems.

It is estimated that up to 75% of all pregnancies can have some degree of fetomaternal hemorrhage. The majority occurs at birth but can occur in the antepartum period due to trauma, spontaneous miscarriage, or obstetric procedures. Obstetric procedures can be associated with maternal alloimmunization and have been reported with amniocentesis, chorionic villus sampling, percutaneous umbilical blood sampling, external cephalic version, and manual removal of the placenta.

Certain criteria must be in place for HDN to occur. The antibody must be able to cross the placenta (IgG) and there must be a target antigen well developed on the fetal red cells. The antigens of the RH, K, Fy, Jk, MNS, Di, Do, Sc, and Coa, are fully expressed on fetal RBCs, therefore possible to be implicated in HDN. Other red cell antigens such as P1, Le, Yt, Xg, Sd, and Vel are weakly expressed and are not associated with HDN. Many antigens have the capability of causing alloimmunization but the antigens most commonly implicated in HDN are K, c, or Fy<sup>a</sup>. Anti-K deserves special mention because it can cause suppression of fetal erythropoiesis as well as hemolysis which complicates the monitoring during the pregnancy.

## ABO and HDN

ABO antigens are also weakly developed and full expression does not occur until 2-4 years of age; however, maternal-fetal ABO incompatibility is the most common cause of HDN. It is most commonly seen in type O mothers who have type A or B babies. It occurs due to the fact that Type O people have anti A, Anti-B, and Anti-A,B antibodies that are ~50% IgG, therefore able to cross the placenta. Clinically most cases are mild due to weakened expression. Maternal-fetal ABO incompatibility occurs in ~20 of pregnancies and can help prevent the development of other red cell antibodies because the fetal cells will be cleared due to anti-A or B before the immune response can occur.

Other factors can affect the risk that a red cell antibody will

develop including the amount of the bleed, and the maternal immune response to the foreign antigen. Fetal homozygosity versus heterozygosity for the red cell antigen also plays a role. Only a fraction of women will make a red cell antibody. One study by Drs. Heddle and Klama reports red cell alloimmunization (all antigens) only occurs in 0.24% of mothers.

## HDN Due to Rh D Antigen

Clinically the most severe forms of HDN are usually due to Anti-D. Studies have estimated that 17% of Rh negative women who deliver an Rh positive baby develop anti-D if RhIG (Rhogam, WinRho) is not administered appropriately. The use of RhIG has decreased the risk of developing anti-D to less than 1% of susceptible pregnancies. The administration of RhIG does not work if anti-D has already developed. Unfortunately there is not a treatment available to prevent the development of other red cell antigen system antibodies.

When will clinically significant HDN develop? Adding to the complexity is the fact that not every woman who has an antibody to a red cell antigen system has an affected fetus as previously discussed. Testing the father for the presence of the antigen to help determine if the fetus is likely to have the antigen can be used; however, one must be certain that he is the father. Titering of the antibody during the pregnancy is one noninvasive tool used to monitor the process although it may not be predictive in all antigen systems. The Rh "D" antibody titer level is the most studied and a titer level of 16 is used to trigger other testing. The critical titer levels in other red cell antigen systems is not well studied, although a titer of 16 has been used. A critical titer of 8 has been used for Anti-K. Several modalities are used to clinically monitor the severity such as amniotic fluid spectrophotometric measurements of bilirubin which evaluate for hemolysis, ultrasound which is used to assess fetal well being and to detect findings of hydrops, Percutaneous umbilical blood sampling which directly measures fetal hematocrit. Fetal Doppler ultrasonography is becoming more popular as a noninvasive way to detect anemia in the fetus by measuring the peak velocity of systolic blood flow in the middle cerebral artery.

## References

- Mari G, et al. Noninvasive diagnosis by Doppler Ultrasonography of Fetal Anemia Due to Maternal Red-Cell Alloimmunization. NEJM 2000;342:9-14
- Judd J, et al. Guidelines for Prenatal and Perinatal Immunohematology. AABB Press. 2005.
- AABB Technical Manual, Chapter 22, 16th Ed, 2008.
- Tran S, Caughey A, et al. Erythrocyte Alloimmunization and Pregnancy. eMedicine, 2008.

Oklahoma Blood Institute  
1001 N. Lincoln Blvd.  
Oklahoma City, OK 73104