Transfusion Medicine and the Pregnant Patient

Alfred Ian Lee, MD, PhD[a], Richard M. Kaufman, MD[b,*]

KEYWORDS

- Hemolytic disease of the fetus and newborn
- Fetomaternal hemorrhage
- Fetal and neonatal alloimmune thrombocytopenia
- Postpartum hemorrhage • Obstetric hemorrhage
- Disseminated intravascular coagulation
- Recombinant factor VIIa • Parvovirus B19

In 1901, Landsteiner[1] proposed the existence of defined blood groups based on the observation that cross-mixing of red blood cells and sera from different healthy individuals sometimes led to red blood cell agglutination. Landsteiner's finding of reproducible isoagglutination patterns among healthy individuals led to the elucidation of the ABO blood group, eventually allowing the development of safe and routine blood transfusions. Since the discovery of the ABO system, 30 other blood groups encompassing 308 blood group antigens have been identified.[2]

A blood group system is defined as the set of red cell antigens produced by the alleles of a single genetic locus. The blood group antigens represent a heterogeneous collection of red cell surface molecules with diverse functions in membrane structure and physiology. Blood group antigens exert influence over a variety of human diseases, from thrombophilia to malarial infection.[3] Clinically, the most significant property of blood group antigens is their immunogenicity, with alloimmunization occurring in antigen-negative recipients of allogeneic blood product transfusions and in pregnant women following exposure to fetal antigens. The major blood groups are those whose antigens have the most potent immunogenicity; in humans, these are ABO and Rh.

Pregnancy poses a special immunologic challenge in that maternal immunity offers fetal protection, yet the fetus itself represents an alloantigen from the perspective of

The authors have nothing to disclose.

[a] Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, 44 Binney Street, Smith 353, Boston, MA 02118, USA
[b] Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, Boston, MA 02115, USA
* Corresponding author.
E-mail address: rmkaufman@partners.org

Hematol Oncol Clin N Am 25 (2011) 393–413
doi:10.1016/j.hoc.2011.02.002 **hemonc.theclinics.com**
0889-8588/11/$ – see front matter

the maternal adaptive immune system.[4] Maternal IgG antibodies, but not other isotypes, cross the placental barrier, and confer immunity to the fetus throughout fetal life and for the first few months postpartum. To mitigate the potential immunologic risks associated with maternal IgG antibodies bearing specificity against fetal antigens, the fetus uses several protective mechanisms, including expression of nonclassic human leukocyte antigen (HLA) molecules with limited polymorphism, creation of a "placental sink" to trap detrimental maternal antibodies via fetal trophoblastic Fcg receptors, modulation of placental complement activity, and suppression cytotoxic Th1-type responses in favor of humoral Th2-type responses within the placental milieu. The maternal/fetal immunologic relationship may endure beyond birth, as microchimerisms containing fetal DNA remain detectable in maternal blood for years.[5]

Alloimmunity in pregnancy is the basis for two of the major complications of pregnancy in transfusion medicine: hemolytic disease of the fetus and newborn (HDFN) and fetal and neonatal alloimmune thrombocytopenia (FNAIT). Other roles for transfusion medicine in pregnancy include management of obstetric hemorrhage, parvovirus B19 infection, hemoglobinopathies, and aplastic anemia.

HEMOLYTIC DISEASE OF THE FETUS AND NEWBORN

HDFN (formerly erythroblastosis fetalis) encompasses a spectrum of fetal and neonatal disease, characterized by jaundice, hepatosplenomegaly, hemolytic anemia, and hydrops (fetal anasarca). In the early part of the twentieth century, the biologic basis for HDFN was postulated to be maternal alloantibodies against unidentified fetal antigens.[6] In 1939 Levine and Stetson reported the landmark case of a 25-year-old G_2P_1 female who developed preeclampsia, delivered a macerated fetus at 33 weeks' gestation, and sustained a profound hemolytic anemia following transfusion of her husband's ABO-matched blood for postpartum hemorrhage.[7] Similar isoagglutination reactions involving ABO-matched donor/recipient pairings had been reported earlier in recipients of multiple blood transfusions. Work by Landsteiner, Wiener, and colleagues ultimately established Rh incompatibility as the biologic basis both for ABO-independent isoagglutination and for HDFN via inappropriate exposure of paternally derived fetal Rh antigens to an Rh-negative mother as a result of complications during pregnancy or delivery.

Rh Proteins and Rh(D) Phenotypes

The Rh blood group is the most polymorphic of the human blood groups, with 50 distinct blood group antigens.[8] The 5 major Rh antigens—C, c, E, e, and D—represent the products of two genes on chromosome 1p, *RHCE* and *RHD*, which encode the 30 kDa RhCE and RhD transmembrane proteins, respectively. RhCE and RhD are expressed on the red cell surface as part of a 170 kDa complex that includes the related RhAG (Rh-associated glycoprotein) protein encoded by *RHAG* on chromosome 6p. The Rh and RhAG proteins function as ammonia transporters.

While maternal/fetal incompatibility in many different blood groups can lead to HDFN, antibodies to Rh(D) remain the most significant cause due to the unique immunogenicity of the Rh(D) protein. Several Rh(D) phenotypes have been characterized.[8] *D+* corresponds to the wild-type *RHD* gene sequence, although silent polymorphisms have been reported. *D-negative* corresponds to mutations that eliminate RhD production, including regulatory defects in *RHD* expression, deletions in *RHD*, or deletions of the entire *RHCE-RHD* locus ("Rh null disease"). *Weak D* arises from mutations encoding amino acid substitutions in transmembrane or intracytoplasmic portions of the