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Blood Product Replacement in the Perinatal Period

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Objective: In this article, we will describe some of the special compatibility testing procedures and blood component preparation and modification techniques used in intrauterine and neonatal transfusion medicine. We also will review the transfusion therapy used in hemolytic disease of the fetus and newborn (HDFN) and fetal and neonatal alloimmune thrombocytopenia (FNAIT).

Finding: Transfusion therapy in the fetus and neonate requires blood typing and compatibility testing techniques not routinely used for adults. These include: cord blood testing, special attention to the volume and speed of infusion, cytomegalovirus risk reduction, and routine irradiation of cellular blood components. The treatment of HDFN and FNAIT involves phenotyping and/or genotyping of fetal and paternal red blood cells and platelets. In FNAIT, platelet products are chosen based on the absence of platelet-specific antigens.

Conclusion: Fetal and neonatal transfusion medicine require special attention to the unique anatomic and physiologic features of early human development.

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Transfusion therapy of the fetus and the neonate poses numerous unique challenges, requiring consideration of issues not encountered in older children and adults. Included among those issues are the following: (1) the interconnection of maternal and fetal blood circulations and the flow of some, but not all molecules, across the placenta; (2) the small body mass and blood volume of the fetus and neonate; and (3) the incompletely developed immune systems of the fetus and neonate. Because of these factors, transfusion compatibility testing must frequently take into account the blood type and blood group antibodies of the fetus or neonate and the mother. Moreover, the fetus and neonate (infants under 4 months) are more vulnerable to some of the hazards of transfusion. For example, the fetus and neonate often cannot tolerate the typical volumes of standard-size blood components and would be at risk of volume overload if attention weren't given to adjusting those volumes appropriately. The small blood volume of fetuses and neonates also eliminates the dilution of transfused blood components that is achieved in adults. This is important, for example, when transfusing red blood cells units or platelet products of blood group O into a fetus or neonate of blood group A or B. In an adult, the infused anti-A and -B are usually not a concern because they are diluted by the transfusion recipient's substantial own plasma volume. Without the benefit of this large dilution factor, the fetus and neonate are at risk of hemolysis, and preventive measures must be taken. Without a fully developed immune system, the fetus and neonate may not be able to mount an immune attack on passenger lymphocytes in transfused cellular blood components, thereby allowing those foreign cells to instead attack the tissues of the transfusion recipient. This transfusion-associated graft-versus-host disease, which has a high mortality rate, requires special precautionary measures. In addition, their naïve immune systems cause the fetus and neonate to be particularly vulnerable to certain bloodborne infections that are relatively benign in adults with intact immune systems. Transfusion-transmitted cytomegalovirus (CMV) is a particular concern. Because intrauterine and neonatal CMV infections can have devastating consequences, including intrauterine growth retardation, pneumonitis, blindness, and deafness, special precautions to prevent the transfusion-mediated transmission of this relatively common virus are indicated. As a result of these and other transfusion issues unique to the fetus and neonate, perinatal transfusion medicine is an unofficial subspecialty unto itself.

In this article, we will highlight some of the special compatibility testing procedures and component preparation

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techniques that are key to addressing the transfusion vulnerabilities of the fetus and neonate. In addition, we will discuss in detail two clinical settings for which transfusion support is particularly critical: (1) hemolytic disease of the fetus and newborn (HDFN) and (2) fetal and neonatal alloimmune thrombocytopenia (FNAIT).

Perinatal Blood Bank Testing

Testing on Maternal Samples

Other than used for routine pretransfusion, testing on maternal samples is also used for guiding RhD prophylaxis, assessing the risk for HDFN, assessing the risk for FNAIT, and guiding blood product selection in prenatal and neonatal transfusion. These tests include ABO typing, Rh typing, antibody screening, identification of RBC antibodies or platelet antibodies, phenotyping or genotyping of RBC antigens or platelet specific antigens, screening and quantifying of fetal–maternal hemorrhage, and crossmatching. Detailed testing for HDFN and FNAIT will be discussed later in this article.

Testing on Cord Blood

Cord blood contains newborn RBC and maternal antibodies. It is recommended in general that every newborn should have cord blood collected and stored for testing.[1,2] However, it is not necessary to test every cord blood. Testing of cord blood is mainly used for assessing the need for RhD prophylaxis by RhD typing and to assess for risk of HDN by testing ABO and RhD typing and direct antiglobulin test (DAT).[2] It could be particularly useful if the mother was not previously tested and the newborn has signs of HDN. It remains a common practice in some institutions to test on all cord blood for ABO/Rh typing and DAT, whereas in some others testing is only performed on cord blood with a type O mother for ABO and Rh typing and DAT. Such testing has limited utility. For ABO HDN, DAT has a high false-negative rate, and positive DAT is a poor predictor for the severity of HDN with a very limited use in guiding patients' management.[1,3] Similarly, in compatible ABO, types do not predict the severity of HDN. Clinical monitoring for jaundice remains the gold standard to monitor HDN.

Testing on Fetal and Neonatal Samples

If available, testing on fetal samples obtained from amniocentesis or percutaneous umbilical blood sampling (PUBS) can be used for genotyping and antigen typing of fetal RBC or platelets. Such testing can help in assessing the risk for HDFN and FNAIT. In addition, antigen typing of the fetus may help confirm or exclude the risk for HDFN and FNAIT for a particular antigen and aid in product selection, if the mother has multiple antibodies.

For neonate transfusion, pretransfusion testing should be performed with a newborn blood sample. The newborn blood sample is tested for ABO, Rh typing, and antibody screen. The newborn plasma/serum should also be tested for IgG anti-A or Anti-B if the neonate is to receive non-group O cells. Because it is very unlikely that neonates become alloimmunized before 4 months, there is no need to repeat the antibody screen.

Testing on Paternal Samples

The main use of paternal samples is to assess the risks of HDFN and FNAIT based on antigen typing and/or genotyping. In addition, crossmatching using maternal serum or plasma against paternal RBC or platelets can provide additional clues, especially if a private antigen is implicated. However, crossmatch becomes invalid if there is a major ABO mismatch (mother has antibody against paternal antigen) or if there are maternal anti-HLA against paternal HLA in the FNAIT workup. Moreover, testing results will only be useful if the sample is from the real paternal source.

Selection of Blood Products during Perinatal Period

RBC Transfusion

One of the main indications of prenatal transfusion of RBC is for the management of HDFN. Depending on the severity of the HDFN, either simple transfusion or exchange transfusions can be performed intrauterine. Other indications of intrauterine transfusions include: fetal parvovirus B19 infection, severe fetomaternal hemorrhage, homozygous alpha thalassemia, and twin–twin transfusion with discordant hematocrit.[4] The selected RBC units for intrauterine transfusions must be compatible with both the fetus and the mother. Usually O-negative RBC units are used for transfusion, because rarely the blood type of the fetus is known. In addition, the RBC units will be antigen typed to avoid the corresponding antigen that maternal antibody is against. RBC units are also screened for being hemoglobin S-negative to maximize the oxygen carrying capacity.

Table 1 lists some of the published neonatal transfusion indications and guidelines. Because of the lack of evidence-based studies in this patient population, these guidelines are mostly expert opinion-based.[4,5] Typical dose for neonatal RBC transfusion is 10 to 15 mL/kg to achieve an Hb increment of 2 to 3 g/dL. In terms of RBC selection, if ABO antibody is detected at the antiglobulin phase on neonatal sample, then RBC units selected should be compatible with both the neonate and the circulating maternal ABO antibodies. If mother has a negative antibody screen, then ABO/Rh type-specific RBC units should be provided. If mother has an antibody(ies), then ABO/Rh type-specific and corresponding antigen-negative (maternal antibody against for) RBC units should be provided.

Many of the concerns of fetal and neonatal RBC transfusions are centered on their small blood volumes when using stored RBC units.[6] First, it regards the high extracellular potassium levels in stored RBC units, which could be as high as 50 to 80 mEq/L at the end of storage. However, the expected potassium infusion through the typical neonate transfusion (15 mL/kg) is insignificant, for example only about 0.15 mEq