

Management of Alloimmune Fetal Anemia

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Fetal anemia (FA) is defined as hematocrit (Hct) or hemoglobin concentration >2SD below the mean for gestational age. Fetal anemia can be caused by immune (Alloimmune), non-immune and idiopathic causes and up to 50% of patients referred with red blood cell antibodies have those directed against an antigen other than D.¹⁻⁴

Developmental hematopoiesis occurs in three anatomic stages

1. Mesoblastic hematopoiesis occurs in extraembryonic structures, principally in the yolk sac and begins between 10-14th days of gestation.
2. Hepatic hematopoiesis replaces the yolk sac by 6-8 weeks of gestation, and by 10-12 weeks extraembryonic hematopoiesis has essentially ceased.
3. Myeloid hematopoiesis starts during the second trimester. Although this results in diminishing hepatic hematopoiesis, the liver, however remains the predominant hematopoiesis organ till 20-24 weeks of gestation.⁵

Types of fetal hemoglobin (Hb)

1. Embryonic Hb is present in yolk sac and not detected after 12 weeks. It includes three Hb types: Gower-1(Zeta₂, epsilon₂), Gower-2(Alpha₂, epsilon₂) and Portland (zeta₂, gamma₂). The zeta chains of Hb Portland and Gower-1 are structurally similar to Alpha chains.
2. Fetal Hb (HbF: Alpha₂, gamma₂) represent about 90% of the Hb in the fetus between 12-32 weeks. It gradually declines during the third trimester, so that at birth HbF averages 70% of the total. Fetal anemia is not accompanied by delay or reversal of this switch.
3. Adult Hb (Hb A: Alpha₂, beta₂) can be detected as early as 16-20 weeks. By the 24th week of gestation 5-10% of Hb A is present. A steady increase follows, so that at term HbA averages 30%.^{2,3}

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Reference ranges for fetal Hb and hematological values have been established (table 1).

Table 1. Average hematological values in the fetus²

Gestation (wks)	Hct (%)	Hb (g/dl)	Retics (%)
26-30	41	13.4	-
28	45	14.5	5-10
32	47	15.0	3-10
37-40	53	16.8	3-7

Antibodies that most commonly cause moderate or severe hemolytic disease of fetus and newborn (HDFN)

A) Anti-D antibodies

Between 12-18% of European and North American Caucasian women are D-negative, In African, 2-5% are D-negative, while in Chinese, Japanese and South-East Asians, the D-negative phenotype is rare (less than 3 per 1000). A substantial proportion of them are not truly D-negative, but are reported to have weak D-expression (D_u) and do not produce anti-D.⁶

The main antigens of the Rh system are encoded by two closely linked homologous genes. One encoding for the D antigen (RHD) and the other encoding the CcEe antigens (RHCE)⁷. When the sensitized mother produces IgG anti-D antibodies, they cross the placenta and coats the D-positive fetal RBCs. This causes early destruction of the fetal RBCs by its reticuloendothelial system. IgG antibodies are 4 sub-classes: IgG₁ and IgG₃ are more effective in RBCs hemolysis than IgG₂ and IgG₄. Therefore, the subclass(es) in the mother can affect the severity of the HDFN. The severity of HDFN depends also on the amount of IgG entering the fetal circulation, the ability of the fetal reticuloendothelial system to remove antibody-coated RBCs and the fetal compensatory response (increase in the medullary and extra-medullary erythropoiesis). However, increased hemopoiesis cannot always compensate for the excessive destruction of RBCs, and anemia ensues.⁸⁻¹⁰

B) Other antibodies to Rh-system antigens

Rh-system consists of 45 well-defined antigens.

All antibodies to Rh-system antigens should be considered capable of causing HDFN, but the only Rh antibody other than anti-D that regularly causes severe HDFN is anti-c. Anti-C,-E,-e and -G have all caused HDFN but the occurrence of each is rare and the outcome seldom severe.^{7,11}

C) *Anti-K antibodies*

In Caucasian populations, anti-K is often the most common immune red cell antibody outside of the ABO and Rh systems. However, post natal hyper-bilirubinemia is not prominent in babies with anemia caused by anti-K. This has led to speculation that FA due to anti-K results predominantly from a suppression of erythropoiesis rather than haemolysis.^{12,13}

Antibodies which most commonly cause mild HDFN (ABO system)

The main explanation for the low prevalence of clinically significant ABO HDFN is that ABO is a histo-blood group system that is expressed on other fetal blood cells and tissues. In addition, A and B red cell antigens are not fully developed in the fetus.^{7,13}

Antibodies which rarely cause HDFN

This includes MNS, Duffy, Kidd, and Diego systems⁷.

Antibodies which do not cause HDFN

Antibodies of the Lutheran system do not cause HDFN, partly because the antigens are expressed only weakly on fetal cells and partly because the antibodies are absorbed by the placenta. Antibodies to the Lewis antigens (Le^a and Le^b) are generally not active at 37°C and the antigens are not expressed on fetal cells.^{14,15}

Doses and indications of immunoprophylaxis

1) *Antenatal prophylaxis administration*

Routine antenatal prophylaxis by at least 500 IU (100 µg) of anti-D Ig must be given at 28 and 34 weeks of pregnancy. This reduces the incidence of antenatal alloimmunization from 1.5% to 0.2%.¹⁶

In cases of amniocentesis, CVS, fetal blood sampling, fetal surgeries, ECV or abdominal traumas, a dose of 250 IU is recommended for prophylaxis following sensitizing events up to 20 weeks of pregnancy. For all events after 20 weeks, at least 500 IU anti-D IgG should be given. In cases of threatened abortion, if bleeding continues

intermittently after 12 weeks gestation, anti-D Ig should be given at 6 weeks intervals. However, the benefit of administration of anti-D Ig in the obstetric complications, procedure and traumas is uncertain due to inadequate evidences.¹⁷

At least 300 µg of anti-D IgG must be given to every non-sensitized Rh D-negative woman within 72 hours following the delivery of an Rh D-positive or weakly positive (D_u) infant.¹⁸

A dose of 300 µg is sufficient to protect from sensitization caused by a fetomaternal hemorrhage of 30 ml of fetal whole blood. However, about one in 1000 deliveries are associated with excessive fetomaternal hemorrhage; Risk factors will only identify 50% of these. Routine screening of all women at the delivery time for excessive fetomaternal hemorrhage should therefore be undertaken. The rosette test (qualitative and sensitive) is first performed. If the rosette test is positive, a Kleihauer-Betke test or flow cytometry must be offered. The percentage of fetal RBCs is multiplied by a factor of 50 to estimate the volume of fetomaternal hemorrhage. However, because this is an inaccurate estimation additional vials of Rh-D Ig should be given.

If Rh-D IgG is omitted postpartum, some protection is proven with administration within 13 days; recommendations are made to administer it as 28 days postpartum.

Anti-D IgG should not be given to women who are already sensitized or women who have a weak expression of Rh-D blood group (D_u or weak-positive) since those women do not form anti-D antibodies.

The administration of Rh-D Ig after postpartum tubal ligation is controversial as the possibility of a new partner exists. In addition, Rh-D sensitization would limit the availability of blood products if the patient later required a transfusion. Recent studies are in progress to evaluate the possible benefits of using monoclonal anti-D in the suppression of the anti-D response.¹⁸⁻²⁰

Non-invasive diagnosis of alloimmune fetal anemia

Ultrasound Findings

- Prehydropic changes (early ascitis and polyhydramnios, visualization of fetal bowel wall).
- Fetal hydrops pleural effusion, pericardial effusion, scalpedema, subcutaneous edema).
- Placental thickness more than 30mm between 18 and 21 weeks gestation (unless compressed by polyhydramnios).
- Increased biventricular outflow diameter

during diastole and cardiothoracic ratio are suggestive of FA.

- Hepatomegaly, splenomegaly.
- Doppler study of fetal aorta.
- Middle cerebral artery (MCA) Doppler, splenic artery doppler.^{21-29, 30-33}

Invasive diagnosis of fetal anemia

Amniocentesis

Bilirubin is the end product of fetal red cell destruction and, therefore, the fetus with hemolytic anemia tends to have elevated serum bilirubin levels. Although most of fetal bilirubin is removed via the placenta, a significant amount is excreted into the fetal urine and appears in the amniotic fluid (AF).³⁴

Liley in 1961 was the first to introduce amniocentesis to clinical practice using spectral analysis of AF at 450nm (ΔOD 450) to measure AF bilirubin. The original Liley curve was divided into three zones and remains useful after 27 weeks gestation.³⁵ However, measurement before 27 weeks is not useful. This is because the relationship between ΔOD 450 and gestational age is not linear so the extrapolation was incorrect. A modified curve for such early gestation has been proposed by Queenan et al and involves four zones instead of three.¹⁸

Amniocentesis is performed when the maternal antibody level is more than 4 IU/ml or 10 weeks before the gestation at which the patient had had a previous fetal death or delivery of a severely affected baby. A rising or plateauing trend of ΔOD 450 value that reaches the 80th percentile of zone two on Liley curve or enters the intrauterine transfusion zone of the queenan curve necessitates fetal blood sampling.¹⁸

If serial MCA Doppler measurements are employed instead of amniocenteses, one should consider switching to amniocentesis after 35 weeks' gestation because of high false-positive rate recorded with MCA measurement after this gestation.²²

The disadvantages of amniocentesis include: correct gestational age must be estimated, technical problems, such as contamination of the AF with blood or meconium (these substances absorb light at the same wavelength as bilirubin). In addition, bilirubin can undergo degradation by light and the specimen should, therefore, be transported to the laboratory in a light resistant container. Also the disease severity varies at any given ΔOD 450. Another issue is that with maternal alloimmunization to K, FA is due to erythroid precursor suppression at the progenitor cell level,

rather than hemolysis. Therefore MCV-PSV proves to be more useful.¹² Amniocentesis carries risks of infection, trauma and aggravation of fetomaternal transfusion.

Fetal blood sampling (FBS)

Cordocentesis is considered the "gold standard" test, and it accurately diagnoses the fetal hematologic status. However, because this procedure is associated with 1-2% rate of fetal loss, it is usually reserved for patients with elevated ΔOD 450 values or elevated MCA-peak systolic velocity (PSV).

When used in this context, equipment should be available on-site for rapid determination of the fetal Hb and hematocrit within 1-2 minutes while the needle is still in the umbilical vein. Blood should be available for intravascular intrauterine transfusion if FA is detected (hematocrit less than 30% or less than 2SD for gestational age).^{18,27}

Fetal blood reticulocyte, erythropoietin and erythroblast count

These are indicators of fetal compensation to anemia, so they can provide information about the disease severity. It appears that the fetus responds to mild or moderate anemia by stimulating medullary hematopoiesis with an increase in reticulocytes only. Extramedullary hematopoiesis in the fetal liver starts with severe FA which results in erythroblastosis. Fetal serum erythropoietin concentration was only found to be increased in cases of severe FA (Hb deficit > 7 g/dl), which indicates that tissue oxygenation is maintained in mild FA, probably through placental clearance of lactate and increased cardiac output and peripheral perfusion.³⁴

Fetal bilirubin levels

Although the fetal bilirubin levels are found to be inversely related to Hb concentration in FA, this is unlikely to be clinically useful, because its level depends on other factors such as placental removal and fetal excretion.³⁴

Complications of the invasive diagnosis of FA

Both amniocentesis and cordocentesis are invasive and entail risk to the mother and the fetus, including premature rupture of the membranes, chorioamnionitis, preterm labor, worsening of the maternal allo-immunization, secondary to transplacental passage of the needle and subsequent fetomaternal hemorrhage, fetal bleeding, and fetal bradycardia requiring emergency cesarean delivery. In general the rates for each complication do not exceed 5%, and most

centers cite a rate of 1% fetal loss in cordocentesis.

Amniocentesis is theoretically less invasive, and has fewer rates of complications, yet it is not without hazards. The risk associated with either procedure is compounded by the fact, once monitoring by amniocentesis or cordocentesis is begun, the test has to be repeated every 1-4 weeks in most cases. Also this risk is increased at early gestation. However since fetal death or hydrops rarely occur before 18 weeks, therefore cordocentesis is rarely indicated before this age.¹²

Non-invasive treatment of alloimmune FA

Plasmapheresis and intravenous immunoglobulin (IVIG) are probably the most effective alternatives but are not without risk.

Oral Tolerance, chemotherapeutic Agents and sensitization to Paternal Leukocyte Antigens are of poor or uncertain value.

Intrauterine transfusion

There is as yet no agreement on the hematological criteria for IVT. In most fetal medicine units a hematocrit value between 25-30% is usually used as the indication of IVT. Intravenous transfusion (IVT) using cord vessels is better than intraperitoneal transfusion (IPT) especially at gestational age > 20-22 weeks.³⁶

Blood used during intrauterine transfusion

Donor Blood

The source of RBCs for intrauterine transfusion is a blood type O, RhD-negative, cytomegalovirus-negative donor. Cells are packed leukocyte-depleted to a hematocrit of 75-85% to prevent volume overload. Units are irradiated to prevent graft-versus-host reaction and processed through a leukocyte-poor filter. The donor blood is cross-matched against the mother.⁷⁷

Maternal Blood

The advantages of using maternal blood include the potential to decrease the risk for sensitization to new red cell antigens associated with exposure to donor units. In addition, a fresh unit can be routinely acquired. Repeated maternal donations are possible with additional folate and iron supplementation. Such donations produce a maternal reticulocytosis that enhances the average lifespan of the donor red cells. This has the potential to decrease the total number of intravascular transfusions that are necessary. Washing of the cells is required to remove any maternal serum containing anti-D antibody.¹⁸

Volume of blood transfusion

The total amount of red cells to transfuse will depend on the initial fetal hematocrit, gestational age and hematocrit of the donor unit. If the donor unit has a hematocrit of approximately 75%, the estimated fetal weight in grams using ultrasound can be multiplied by a factor of 0.02 to determine the volume of red cells to be transfused to achieve a hematocrit increment of 10%. A final target hematocrit of 40-50% is used; a decline of approximately 1% per day can be anticipated between transfusions. In the extremely anemic fetus, the initial hematocrit should not be increased by more than four-fold to allow the fetal cardiovascular system to compensate. A repeat procedure is undertaken 48 hours later to normalize the fetal hematocrit. Hydrops will usually reverse rapidly after one or two intravascular transfusions, unless severe myocardial affection had resulted.³⁸

Time to repeat the transfusion

If the fetus is not severely anemic at the first intrauterine transfusion, subsequent procedures are scheduled at 14-day intervals until suppression of fetal erythropoiesis is noted on fetal blood sampling. This usually occurs by the third intrauterine transfusion. Thereafter, the interval for repeat procedures can be determined based on the decline in hematocrit for the individual fetus, usually a 3-4 week interval.

The effect of the first transfusion is shortest because of the continued presence of antibody coated fetal red cells. Thereafter, fetal hemopoiesis is suppressed and the decline of the fetal hematocrit decreases. This should lengthen the time between transfusions thereafter.³⁹

Timing of delivery

The last fetal transfusion is given at about 35 weeks with delivery at 37-38 weeks gestation, in performance to early delivery and exchange transfusion because the fetus tolerates larger transfusion volumes than the neonate due to large capacity of the placenta.³⁹

Complications of IVT

IVT carries significantly increased risks for both mother and fetus when compared to cordocentesis alone (complications of cordocentesis are mentioned above).

The IVT itself presents further risk to the fetus due to the length of time the needle remains in situ, additional risks are associated with administration of blood products, and Egberts et al. reported reduction of antioxidant production (protects

against free radicals) after IVT. A fetal loss rate per transfusion is estimated around 2.4%.³⁷

Short-term outcome and neonatal management

Perinatal survival after intrauterine transfusion varies by center and the experience of the operator. Clearly, intervention before the appearance of hydrops fetalis is preferable. In one review series, overall survival was noted to be 84%. Survival of nonhydropic fetuses (92%) was markedly improved over those with hydrops (70%). Kamp et al. reported that when intrauterine reversal of hydrops occurs as a result of the treatment, 98% of fetuses survived.⁴⁰

Suppression of erythropoiesis is not uncommon after several IVT. These infants are born with a virtual absence of reticulocytes with their blood volume being almost entirely comprised of donor red cells. Because exchange transfusion is rarely required, passively acquired maternal antibodies remain in the neonatal circulation for weeks.

This results in a 1-3 month period in which the infant may need several top-up red cell transfusions. Weekly neonatal hematocrit and reticulocyte counts should be assessed. Threshold hematocrit values of less than 30% in the symptomatic infant or less than 20% in the asymptomatic infant have been suggested for transfusion. A neonatal trial with subcutaneous erythropoietin administered three times a week revealed a decreased need for top-up transfusions.

Long-Term Outcome

Several investigations have not found hydrops fetalis to be associated with any difference in neurologic outcome compared with the nonhydropic fetus.^{41,42} Cerebral palsy and developmental delay is more common in fetuses with hemolytic disease of the newborn when compared with unaffected infants, although a normal outcome can be expected in more than 90% of cases. A review of the cases of cerebral palsy reveals that the mean gestational age at delivery was 33.5 weeks; 80% of cases were delivered by emergency cesarean. Sensorineural hearing loss is more frequent in infants affected by hemolytic disease of newborn probably because of their prolonged exposure to elevated levels of bilirubin and its toxic effect on the developing eighth cranial nerve.¹⁸

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