PATHOPHYSIOLOGY

In red cell isoimmunized pregnancies, maternal hemolytic antibodies cross the placenta and attach themselves onto fetal red cells, which are then destroyed in the fetal reticulo-endothelial system. In mild to moderate disease there is a compensatory increase in intramedullary erythropoiesis, and in severe disease there is recruitment of extramedullary erythropoietic sites, such as liver and spleen. Fetal blood pO2, pCO2 and pH usually remain within the normal range except in extreme anemia, when hypoxia and acidosis occur. The fetal blood oxygen content decreases in proportion to the degree of anemia. The fetal 2,3-diphosphoglycerate (2,3-DPG) concentration is increased and the consequent decrease in hemoglobin-oxygen affinity presumably improves delivery of oxygen to the tissues.

In moderate anemia, the umbilical arterial plasma lactate concentration is increased but this is cleared by a single passage of fetal blood through the placenta and normal umbilical venous levels are maintained. In severe anemia, when the oxygen content is less than 2 mmol/L, the placental capacity for lactate clearance is exceeded and the umbilical venous concentration increases exponentially. These data suggest that, in the fetus, systemic metabolic acidosis can be prevented, unless the oxygen content decreases below the critical level of 2 mmol/L. When the fetal hemoglobin concentration deficit exceeds 6 g/dL, hydrops fetalis develops (Figures 1 and 2). This may be the result of extensive infiltration of the liver by erythropoietic tissue, leading to portal hypertension, due to parenchymal compression of portal vessels, and hypoproteinemia, due to impaired protein synthesis. Furthermore, at this hemoglobin concentration deficit, the oxygen content decreases below the critical level of 2 mmol/L.

Figure 1: Blue band normal fetal hemoglobin and red band severe anemia resulting in fetal hydrops. In normal fetuses the mean hemoglobin concentration rises linearly with gestation from 11 g/dL at 18 weeks to 14.5 g/dL at 40 weeks; the 95% confidence intervals are nearly parallel and one standard deviation is approximately 1g/dL.
DIAGNOSIS AND TREATMENT OF FETAL ANEMIA

In the clinical management of isoimmunized pregnancies the aim is to predict whether the fetus is severely affected and to correct the fetal anemia by intrauterine blood transfusion. The only accurate method of assessing the severity of fetal anemia is by fetal blood sampling. However, cordocentesis should only be undertaken if there is a strong suspicion that the fetus is severely affected, because the procedure itself can cause miscarriage and it can also cause fetomaternal hemorrhage thereby exacerbating the severity of the disease.

Assessment of the severity of fetal hemolysis should be based on firstly, the history of previous affected pregnancies, secondly, the levels of maternal hemolytic antibodies, and thirdly, ultrasonographic examination for the detection of ascites and Doppler studies for diagnosis of a hyperdynamic circulation (Figure 3).

For patients with a previous red blood cell isoimmunization affected pregnancy, it should be aimed to perform the first ultrasound scan and Doppler studies at approximately 10 weeks before the time of the earliest previous fetal or neonatal death, fetal transfusion, or birth of a severely affected baby, but not before 17-18 weeks. Fetal death or development of hydrops do not occur before this gestation, presumably because the fetal reticuloendothelial system is too immature to result in destruction of antibody coated erythrocytes.

Assessment should be carried out at intervals of 1-2 weeks and cordocentesis need only be performed if there is fetal ascites or the fetal MCA-PSV is more than 1.5 SD’s above the normal mean for gestation (Table 1, Figure 4). A cut-off in MCA-PSV of mean plus 1.5 SD’s can identify nearly all severely anemic fetuses with a low false positive rate (about 15%) Measurement of MCA-PSV is also useful in the assessment of fetuses with other causes of anemia, such as parvo B19 infection, fetomaternal hemorrhage and twin-to-twin transfusion syndrome.

In patients that had no or mildly affected previous pregnancies the maternal hemolytic antibody levels should be measured at 2-3 weekly intervals from 17 weeks onwards. When the antibody concentrations are persistently below 15 IU/mL, the degree of fetal hemolysis is insignificant or mild and delivery can be delayed until term. If the antibody levels are higher than 15 IU/mL the disease
may be severe and the fetus should be assessed by ultrasound and Doppler examinations at one weekly intervals and cordocentesis should be considered in those that develop ascites or a high MCA-PSV.

**Figure 3:** Management of red cell isoimmunized pregnancies.

<table>
<thead>
<tr>
<th>Gestation (wks)</th>
<th>Fetal Hb (g/dl)</th>
<th>MCA PSV (cm/s)</th>
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<tr>
<td></td>
<td>Mean</td>
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<tr>
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**Table 1.** Fetal hemoglobin concentration and middle cerebral artery peak systolic velocity (MCA-PSV) with gestation in the normal pregnancies. Severe anemia is defined by a hemoglobin concentration that is 6 SD’s below the normal mean for gestational age. High MCA-PSV is defined by a value that is 1.5 SD’s above the normal mean for gestational age.

At cordocentesis, a fetal blood sample is first obtained and the hemoglobin concentration is determined. If this is below the normal range, the tip of the needle is kept in the lumen of the umbilical cord vessel and fresh, packed, rhesus-negative blood compatible with that of the mother is
infused manually into the fetal circulation through a 10-mL syringe or a transfusion set. At the end of the transfusion, a further fetal blood sample is aspirated to determine the final hemoglobin concentration. Subsequent transfusions are given at 1-3-weekly intervals until 34-36 weeks, and their timing is based on the findings of non-invasive tests, such as Doppler studies, and the knowledge that, following a fetal blood transfusion, the mean rate of decrease in fetal hemoglobin is approximately 0.3 g/dL per day (0.4 g/dL per day after the first transfusion, 0.3 g/dL per day after the second transfusion and 0.2 g/dL per day after the third transfusion).

Figure 4. Fetal middle cerebral artery peak systolic velocity (MCA-PSV) with gestation in normal pregnancies (Left). Relationship between fetal hemoglobin concentration (expressed as SD’s from normal) with MCA-PSV (Right).

The prediction of severe and/or moderate fetal anemia by MCA-PSV is less accurate in those cases that had already been treated by intrauterine blood transfusions than in those that had not been transfused. The FPR for detection of at least 95% of severely anemic fetuses by MCA-PSV is about 15% for the first transfusion, 35% for the second and 90% for the third.

In patients that had received one previous transfusion, the prediction of fetal anemia provided by MCA-PSV is similar to that of estimating the hemoglobin concentration from the measured post-transfusion hemoglobin level after the first transfusion and the assumption that the rate of decrease in fetal hemoglobin is 0.4 g/dL per day. In patients that had received two previous transfusions, the only significant predictor of fetal anemia is the estimation of the hemoglobin concentration from the post-transfusion hemoglobin level after the second transfusion and the assumption that the rate of decrease in fetal hemoglobin is 0.3 g/dL per day.
DOPPLER STUDIES

In red cell isoimmunized pregnancies:

- Placentation is normal and therefore indices of impedance to flow in the uterine and umbilical arteries are normal, irrespective of the severity of fetal anemia.

- Normal placental perfusion results in normal fetal blood pO2, pCO2 and pH and therefore there is no evidence of redistribution in the fetal circulation; the PI in the middle cerebral artery, thoracic aorta and renal arteries is normal.

- The left and right cardiac outputs and blood velocity in the middle cerebral artery, thoracic aorta, renal arteries and the fetal venous system are increased in proportion to the degree of fetal anemia. The most likely mechanism for the hyperdynamic circulation of anemic fetuses is decreased blood viscosity, leading to increased venous return and cardiac preload with consequent increase in cardiac stroke volume.

- Intravascular fetal blood transfusion results in temporary cardiovascular overload with a temporary (<2 hours) fall in both right and left cardiac outputs and MCA-PSV. The fetal heart has very limited reserve capacity to increase its output in response to acute overload, and a large increase in fetal blood volume results in a decrease in cardiac output. A few hours later there is normalization in cardiac output and MCA-PSV, presumably because there is a rapid rate of fluid loss.

- The less accurate prediction of fetal anemia, by Doppler velocimetry, after intrauterine blood transfusions can, at least in part, be attributed to alterations in fetal blood viscosity due to the presence of varying proportions of adult blood in the fetal circulation. Adult red cells, compared to fetal, are smaller and have less cellular rigidity, but increased erythrocyte aggregation.

REFERENCES

1. Nicolaides KH, Soothill PW, Clewell WH, Rodeck CH, Mibashan R, Campbell S. Fetal haemoglobin measurement in the assessment of red cell isoimmunization. Lancet 1988;i:1073-6


