TOWARDS THE CONQUEST OF RH HEMOLYTIC DISEASE

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The discovery of the Rh blood group system, Rh hemolytic disease, its management and recently its prevention is one of the most striking success stories of modern medicine. The extent and severity of this disease and its resulting distress to so many parents is not always appreciated today. Iso-immunization remains a continuing albeit relatively less common cause of perinatal mortality and morbidity and the general outlook of an Rh-isoimmunized pregnancy is quite optimistic today as newer approaches to diagnosis and treatment have evolved. In those early days there were no antenatal diagnostic or therapeutic measures available to assess the severity of fetal involvement of an affected infant until after delivery.

Pathophysiology

Classically rhesus disease occurs because maternal anti-D antibodies cross the placenta and hemolyse rhesus positive fetal red blood cells. Although anti-D is the most common antibody, others including Rh C, E, c and e can also produce similar disease(1). All these antibodies are IgG in configuration and are capable of crossing the placental barrier. The fetus is rarely affected before 16 weeks as the antibodies do not cross the placenta until then(2).

Progressively increasing fetal anemia as a result of hemolysis results in extra medullary hematopoesis, one effect of which is hepatosplenomegaly. As the liver is totaly dedicated to red cell production its other functions are obtunded and the resultant hypoalbuminemia and fall in oncotic pressure results in fetal hydrops(2).

Fetal Evaluation

About 5% of the Indian population as compared to 15% of the Western world is rhesus negative. Laboratory workers have attempted to relate the concentration of the maternal antibody as measured by the titre dilution techniques to the severity of fetal disease, however it is now known that straight forward titre dilutions are notoriously inaccurate(3). It is, however, still generally accepted that antibody titres at or below 1:16 are unlikely to produce serious fetal disease(4). Once antibodies are detected, the frequency of their measurement depends on their absolute titres and the past obstetric history, the assumption being made that the disease becomes worse in each pregnancy. The birth of an earlier baby with hydrops, or a stillborn or a neonate that required an exchange transfusion is particularly ominous. The use of amniotic fluid bilirubin concentration to evaluate rhesus disease was described in early 1960's. Bilirubin is quantified by spectroscopic analysis at a wave length of 450 mm and the optical density difference ΔOD plotted on the Liley chart. Most workers are of the opinion and have demonstrated that in pregnancies not complicated by

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fetal hemolysis the ΔOD was never >0.3 and there is never a severely affected fetus with a ΔOD of <0.2. It is, therefore, believed that a fetus with ΔOD >0.3 requires a hematocrit determination for diagnosis of severity of fetal anemia(5).

Amniotic fluid examination is indicated when anti D titres exceed 1:16 and timing of the first procedure is dictated by the magnitude of the titre and previous obstetric history. Whereas, the first amniocentesis may be done as early as 18-20 weeks gestation with a history of a severely involved previous baby, the procedure may be delayed until approximately 24-26 weeks with a previously mildly affected pregnancy. The timing of repeat amniocentesis is dictated by the optical density readings. The procedure is relatively easy, non-traumatic, informative and can be done in most hospitals, although it is wise to send the fluid sample to a regional reference centre for analysis and interpretation(2).

Fetal ultrasound examination allows the detection of early ascites and the biophysical profile may be used to monitor fetal well being as well, although the profile is not always sufficiently sensitive to detect subtle deterioration in the fetal condition. The value of color doppler wave form analysis of fetal vessels remain to be confirmed.

The recent introduction of fetal hematocrit determination has added a further refinement to the diagnosis and management of an erythroblastotic fetus and is now a routine investigation at many centres. Although, access to the fetal circulation by cordocentesis is a major advance there still remain several important questions. Though the presence of anemia indicates the need for transfusion, it is theoretically possible for the fetus to maintain its hemoglobin while showing evidence of hemolysis by a rising bilirubin concentration in amniotic fluid. Hence, fetal blood sampling is most valuable in the severest form of the disease(6).

Fetal Management

The decision to treat the fetus may be based on either ultrasound evidence of ascites, a rising amniotic fluid bilirubin content or hematological evidences of fetal anemia.

In a non-hydropic fetus >34 weeks testation with an amniotic fluid showing an upper zone reading delivery is the best policy. As neonatal care has so dramatically improved early induction or delivery at this gestation, having primed the mother with glucocorticoids to prevent hyaline membrane disease is now safe and feasible even in our setting.

Safe and effective intrauterine transfusion was first popularized by Rodeck *et al.* using fetoscopy as a means of guiding the puncture of funic vessels(7). Subsequently, Nicolaides *et al.* have carried out the same procedure under ultrasound guided control with greater success and less fetal trauma(8). Although the technical problem of intrauterine intra vascular transfusions have been largely over come, number of issues remain, including the timing, frequency and volume of blood to be transfused, as also the optimal route and timing of delivery(9). The volume of blood transfused must raise the fetal hematocrit sufficiently; however, the fetus has the ability to cope with large volumes of transfused blood. The exact volume to be trasfused is estimated from a normogram which takes into consideration the pre-transfusion hematocrit of the fetal blood, the hematocrit of the donor blood and the expected hematocrit to be achieved, as also the fetal gestational age.

As there is an approximate drop of about 1-2% per day of hematocrit, the traditional gap of transfusing every 2 weeks is maintained. By the 4th-5th transfusion, the fetal condition is usually stable and only donor blood remains in the fetal circulation. Transfusions are continued till 34-36 weeks of gestation when the fetus is delivered. Route of delivery is either by cesarean section or more recently with availability of prostaglandin gel for improving the favorability of the cervix, many patients are given a trial of vaginal delivery. Fetal surveillance after a transfusion is necessary and must be strictly maintained by a fetal kick count, biweekly USG and weekly NST. Today early delivery plus intrauterine intravascular transfusion is the most common clinical regime employed in mothers with an affected fetus at high risk.

Intrauterine intraperitoneal fetal blood transfusion were earlier used by Liley and others, although they have now been largely replaced by intravascular transfusions. The intraperitoneal route is rarely successful when the fetus has hydrops, as the lymphatics through which blood is absorbed and transported are water logged(10).

Success has also been reported with plasma exchanges for antibody removal of mothers for the treatment of anti-D isoimmunization, although the good effects are temporary. Its disadvantages are the time and cost involved, as well as the need for continued patient motivation and hence it must only be employed as an alternative when the sensitization is severe very early in pregnancy and where problems of expertise hamper safe intrauterine intravascular transfusions(11).

Neonatal Care and Management

When the fetus has been adequately transfused *in utero* and a good fetal hematocrit maintained, fetal problems associated with rhesus disease not only disappear but rarely does the neonate need an exchange transfusion, although simple packed cell transfusion may be required to maintain hemoglobin levels(2). Of late the use of high dose IV IgG 500 mg/kg infused over a period of 2 h soon after an Rh isoimmunized neonate is delivered, has been shown to alter the course and reduce the severity of bilirubin production often obviating the need for exchange transfusion. The action is probably by blocking the Fc receptor sites of the RES cells, and hence hemolysis of RBC, a mechanism similar to the prevention of platelet destruction in neonatal isoimmune thrombocytopenia, in which disease beneficial therapeutic effects of high dose IgG therapy have been reported(12).

Prevention of Rhesus Disease

Apart from ensuring that all eligible Rh negative mothers receive anti-D immunoglobulin after a normal delivery, abortion, MTP or amniocentesis antenatal prophylaxis between 28-30 weeks gestation is the only procedure available today to reduce the risk of intra pregnancy sensitization(13). However, this has not yet been more universally accepted as it is not considered cost effective. Once monoclonal anti-D is made available its potential use for Rh prophylaxis would solve many problems, although researchers are expressing the view that if monoclonal anti-D is to be used for Rh prophylaxis, mixtures of IgG and IgG_3 monoclonals will probably be necessary(14).

It should be remembered that prevention is the most effective method of

managing rhesus disease, so it is vital to ensure that anti-D is administered at the correct time and in the correct dose after any potentially sensitizing event.

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