Rhesus iso-immunization

1 Introduction

Iso-immunization against rhesus antigens, which may result in hemolytic disease of the fetus and newborn, was a major cause of perinatal mortality, morbidity, and long-term disability until the 1970s. With the development of RhD immunoglobulin, and its evaluation and utilization in clinical practice since the early 1970s, severe rhesus iso-immunization is rarely seen today. A reduction in average family size may have also contributed to this welcome reduction.

The dramatic reduction in deaths from rhesus hemolytic disease has been one of the major obstetrical achievements of the past quarter-century. Despite this, rhesus hemolytic disease is unlikely to disappear, and remains a problem for women and their babies who are affected.

2 Prevention of iso-immunization

The effectiveness of anti-D immunoglobulin in the prevention of rhesus iso-immunization has been demonstrated in a number of trials conducted in different countries. The question is not whether or not women at risk of rhesus immunization should receive anti-D immunoglobulin, but which women should receive such prophylaxis, at what times, and in what doses.

There is a risk of iso-immunization in any situation in which Rh-positive red blood cells enter the circulation of a Rh-negative woman.
The degree of this risk will vary with the amount of rhesus antigen to which she is exposed.

2.1 After delivery
The most common time for Rh-positive fetal cells to enter the mother’s circulation is at the birth of a Rh-positive baby. Without the administration of anti-D immunoglobulin, Rh-negative women who give birth to a Rh-positive baby have a 7.2% risk of developing rhesus antibodies within 6 months of delivery, and a much larger risk (15%) of showing evidence of sensitization in a subsequent pregnancy. With postpartum administration of anti-D immunoglobulin, these risks are reduced to 0.2 and 1.6%, respectively.

ABO incompatibility, commonly believed to confer significant protection against the development of rhesus antibody formation, does not confer sufficient protection to be useful in clinical practice.

Evidence on the optimal amount of anti-D immunoglobulin to recommend for routine prophylaxis is limited. In the UK, postnatal administration of 100 mg (500 IU) is generally used; in Australia 125 mg (750 IU); and in the USA and parts of Europe 200–300 mg (1000–1500 IU).

It is reasonably well established that 20 mg (100 IU) of anti-D will neutralize the antigenicity of 1 ml of Rh-positive red cells, or 2 ml of whole blood. Hence, the dose of 300 mg (1500 IU), applied in some countries, is sufficient to protect against a fetomaternal bleed of 30 ml. When smaller doses are given in the interests of economy, the amount of fetomaternal transfusion must be assessed. The relative cost-effectiveness of giving a smaller dose of anti-D immunoglobulin along with assessment of the amount of fetomaternal transfusion, compared with routine administration of a higher dose, will depend on local circumstances and the relative costs of anti-D immunoglobulin and of laboratory tests.

In some countries, the availability of anti-D immunoglobulin is limited. Establishing the cost-effectiveness of a smaller dose of anti-D immunoglobulin combined with screening for the degree of fetomaternal hemorrhage, compared with routine use of a larger dose of anti-D, would seem advisable.

A fetomaternal hemorrhage of 30 ml or more is uncommon but does occur in up to 0.6% of deliveries. In this case, larger doses of anti-D immunoglobulin are required to prevent immunization. Counts of fetal cells in maternal blood have become routine after birth in some centers, to determine whether a larger dose of anti-D immunoglobulin
should be given. The risk of a large fetomaternal hemorrhage is increased after traumatic births, cesarean section, manual removal of the placenta, and in some cases of fetal death.

The best time to administer the anti-D immunoglobulin would be as soon as possible after birth, but immediate administration is not practical in view of the time required to determine the blood group of the baby. From the trials that have been conducted, it would appear that an interval of up to 72 hours is compatible with effective prophylaxis.

No adverse effects of treatment with anti-D immunoglobulin have been reported from the trials, although the risk of rare adverse effects of sensitivity reactions and transmission of infectious agents remains.

2.2 During pregnancy
A small proportion of women (1.5%) develop rhesus antibodies during their first pregnancy; most such immunizations take place after 28 weeks of gestation. Antenatal administration of 100 mg (500 IU) anti-D immunoglobulin at 28 and 34 weeks to RhD-negative mothers has been shown to reduce the number of women with a positive Kleihauer test (evidence of fetal blood cells entering the mother’s circulation) at both 32–35 weeks and at delivery, as well as the incidence of iso-immunization. A trial using a smaller 20-mg (100 IU) dose failed to show these beneficial effects.

The combination of antenatal administration of 100 mg anti-D immunoglobulin to all unsensitized Rh-negative women, and a further dose administered after birth to all such women who give birth to a Rh-positive child, would reduce the remaining incidence of rhesus iso-immunization from 0.2 to 0.06%. The costs of such a program may be high, but must be considered against the costs of antenatal detection and treatment of the affected infant, whose mother develops immunization. Further studies are required to determine the cost-effectiveness.

Administration of anti-D immunoglobulin to unsensitized RhD-negative women is required after procedures known to carry a risk of fetomaternal transfusion. Bleeding from the fetal to the mother’s circulation has been documented as a consequence of chorion villus sampling, amniocentesis, fetal blood sampling, placental biopsy, and external version of a breech presentation.

Fetomaternal transfusion may occur with either spontaneous or induced abortion, and may result in iso-immunization, if anti-D immunoglobulin is not administered. The incidence of fetomaternal
transfusion in spontaneous abortion has been estimated at about 6–7% during the first trimester of pregnancy, and 20% or more in the second trimester. Up to 13 weeks of pregnancy, a dose of 50–75 mg of anti-D gamma globulin after termination of pregnancy or miscarriage is sufficient to ensure adequate protection. In the second trimester, the standard postpartum dose should be administered.

Abdominal trauma, placenta praevia, placental abruption, or any form of uterine bleeding, may occasionally cause fetomaternal transfusion. Massive fetomaternal transfusion may sometimes be suspected on the basis of the findings at cardiotocography prompted by these conditions. Fetomaternal transfusion may also occur without any obvious cause. Unexplained fetal or intrapartum death, or the birth of a pale, distressed baby, should raise the possibility that a significant fetomaternal transfusion has occurred.

3 Diagnosis of iso-immunization

All women should have routine assessment of their rhesus status in early pregnancy. Women who are RhD-negative should be further screened for the presence of antibodies. The other rhesus antigens (C and E) are far less immunogenic but occasionally can cause serious clinical problems. Anti-Kell, anti-Kidd, anti-Duffy, and some of the more rare antigens, can also, on occasion, cause hemolytic disease in the fetus and newborn. For this reason, many centers screen all pregnant women for other blood group antibodies, in addition to the RhD status.

The presence of antibodies indicates that the fetus may become affected if it carries the antigen to which the antibodies were formed; it does not indicate whether the fetus carries the antigen. For this reason, it is helpful to determine whether the woman’s partner is homozygous or heterozygous for the antigen. If the father is homozygous, the fetus will always carry the antigen; if the father is heterozygous, there is a 50% risk that the fetus will carry the antigen. Zygosity of RhD cannot be determined with certainty, but it can be estimated with a probability ranging between 80 and 96%.

The level of an antibody titre does not predict the presence or severity of disease, although in a first affected pregnancy there is a reasonable correlation between the antibody titre and the severity of disease. In subsequent pregnancies, the extent to which the fetus was affected in previous pregnancies is the most powerful predictor of the severity of disease in the present one. The obstetric history, in combination with
serial antibody levels, will usually allow a reasonably accurate prediction of the severity of the hemolytic disease in the current pregnancy. This information is not, however, sufficiently precise to determine the need, or the optimal time, for intervention. For this, ultrasound, amniocentesis with spectrophotometric analysis of hemoglobin degradation products (bilirubin) in the amniotic fluid, or fetal blood sampling to determine fetal blood group and fetal hematocrit, are required. This may need to be repeated at regular intervals, depending upon the severity and progression of the findings.

4 Treatment of iso-immunization

Early delivery, before the baby is too severely affected to be effectively treated by postnatal therapy, remains the mainstay of treatment for established iso-immunization. When the hemolytic disease is sufficiently severe that it would not be safe to continue the pregnancy until the fetus is sufficiently mature, intra-uterine transfusion is the treatment of choice. RhD-negative packed cells transfused into the fetus can correct the fetal anemia and allow birth to be postponed to a more advanced stage in the pregnancy, when the baby can be successfully treated with currently available methods of intensive neonatal care. The procedure can be started as early as 16 weeks of gestation, and can be repeated as necessary.

Other treatments that have been used include plasmapheresis from early pregnancy onward, immunosuppression with promethazine, and desensitization by oral administration of RhD-positive red blood cells. These methods for treatment have not been evaluated in controlled trials.

5 Conclusions

Rhesus hemolytic disease of the fetus and newborn, while by no means the frequent condition that it once was, remains a problem that requires constant vigilance and attention. Although effective prophylaxis is available it must be properly used. Postpartum prophylaxis with anti-D immunoglobulin should be given within 72 hours of birth to all RhD-negative women who give birth to a RhD-positive baby, or a baby whose RhD status cannot be determined, irrespective of their ABO status.
Anti-D immunoglobulin should be administered also to all RhD-negative women during pregnancy when there is an increased risk of fetomaternal bleeding. Routine use of anti-D immunoglobulin at 28 or 34 weeks of pregnancy for all Rh-negative women is of value as well, but the costs of such a programme are high and together with the limited supplies of anti-D immunoglobulin may preclude this in some countries. Rhesus iso-immunization has become sufficiently rare, and the treatment sufficiently complex, to warrant regionalization of care for these women and babies. Hopefully, this may facilitate adequate evaluation of the methods used for diagnosis and treatment, none of which have been as yet subjected to controlled trials.

Sources

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