Current Practice

CLINICAL PROGRESS

Rh Haemolytic Disease Recent Advances in Rh Isoimmunization Prevention

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There are now effective methods of treating Rh haemolytic disease with the result that most affected infants are salvaged and complications such as kernicterus have become rare. Nevertheless, treatment is not invariably successful and the disease still causes much anxiety as the mother with antibodies worries about the risk to her baby and to any future pregnancy. Prevention is clearly better than cure, and in most cases Rh immunoglobulin now offers a method of preventing this disease.^{1 2}

Natural History

It has been realized since 1940 that rhesus haemolytic disease occurs when an Rh negative mother carries an Rh positive baby. Some of the baby's Rh positive red cells cross into the mother, where they act as a foreign antigen. The mother then produces an antibody to destroy this antigen in exactly the same way as she would destroy invading bacteria. Nevertheless, the difficulty is that antibody production, once initiated, is permanent, and that the Rh antibody (usually anti-D) will cross the placenta and damage the Rh positive fetal cells. The resultant jaundice, anaemia, and oedema constitute the symptom complex of Rh haemolytic disease, or *erythroblastosis fetalis*.

It had been established that the Rh antigens are present only on the surface of red cells, and hence it was postulated that fetal red cells must enter the maternal circulation to sensitize the mother. Nothing was known, however, of the timing or magnitude of such transplacental haemorrhage until the Kleihauer technique was developed.³ This is a histochemical technique which can identify fetal red cells by virtue of the fact that they contain fetal haemoglobin (HbF) in contrast to maternal red cells, which contain adult haemoglobin (HbA). The Kleihauer technique can detect small quantities of fetal red cells in the maternal circulation and thus enables the course of transplacental haemorrhage to be elucidated. The essential finding was that, though transplacental haemorrhage could be detected throughout pregnancy, most of the larger haemorrhages occurred at delivery. This conclusion could have been predicted, as one would expect that most large transplacental haemorrhages would be due to damage to the placenta associated with its separation during labour.

This led to the realization that the mother was usually sensitized at delivery, and that thereafter antibody might appear in her serum. In some cases, however, the titre is too low to be detected with current techniques and the mother is then said to be *sensitized*; in this situation a further Rh positive pregnancy is needed to raise the titre to detectable levels.⁴ The occurrence of the sensitizing transplacental haemorrhage at delivery explains why the first infant does not usually develop haemolytic disease. Primary sensitization due to very small transplacental haemorrhages occurring during

pregnancy is unusual because they constitute weak antigenic stimuli, and possibly also the mother is more resistant to sensitization during pregnancy.

The implication of these findings was that sensitization at delivery could be prevented if transplacental haemorrhages occurring at this stage could be neutralized. Moreover, this concept also implied that the sensitizing haemorrhage could be neutralized following the delivery of the baby; thus the technique used for this neutralization could not harm the baby.

Prevention of Rh Sensitization

The way to neutralize the sensitizing transplacental haemorrhage and so prevent rhesus haemolytic disease became evident from a study of ABO incompatibility. If a mother is blood group O and her fetus is group A, then the passage of fetal red cells into the maternal circulation would be equivalent to transfusing group A blood into a group O recipient. This would constitute an incompatible transfusion, and the group A blood of the donor would be haemolysed by the group O recipient, leading to a transfusion reaction. In the context of the mother and her fetus this would mean that any group A fetal red cells would be destroyed on entering the maternal circulation. The intravascular destruction of fetal red cells in some way damages, or inactivates, the Rh antigens carried on the surface of the red cells, so that their antigenicity is reduced and the mother does not become sensitized. This situation is usually summarized by stating that ABO incompatibility between mother and fetus protects against Rh sensitization.

It became clear that Rh sensitization could be prevented if this natural protective mechanism could be copied. The method adopted was to inject Rh antibody (anti-D) into the mother following delivery. This antibody would not attack maternal red cells because they are Rh negative, but would selectively attack any Rh positive (D positive) fetal red cells which had entered the maternal circulation. The Rh antibody (anti-D) tends to stick to the Rh (D) antigen molecules on the surface of the Rh positive fetal red cells, and thus cover or block them. A fetal red cell which has its Rh antigen sites blocked is a very poor antigen, and hence the mother does not become sensitized.

Rh Immunoglobulin.—Anti-D serum, particularly when pooled, may transmit serum hepatitis. It has, therefore, become common practice to isolate the gammaglobulin fraction of the plasma, which not only contains the 7S anti-D (which is the most potent protective antibody) but also obviates the risk of transmitting hepatitis, as the virus is known not to be present in the gammaglobulin fraction. The anti-D gammaglobulin fraction (known as Rh immunoglobulin) is processed in a vial as a 1 ml. dose, and contains about 200 µg. of anti-D.

Administration.—The purpose of Rh immunoglobulin is to prevent Rh sensitization, and it has no place in a woman who

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has been sensitized and whose serum already contains Rh antibody. Hence it should be given to all unsensitized Rh negative women following delivery. The Rh group of the baby should be determined, as there is no need to treat a woman who has an Rh negative baby. The risk of sensitization is reduced if the baby is ABO incompatible, but the protection is far from absolute and Rh immunoglobulin should be given regardless of ABO blood group. The dose is 1 ml., and it is given intramuscularly within 72 hours of delivery.

An important point to remember is that protection is afforded only to the next Rh positive pregnancy. This pregnancy also carries the risk of transplacental passage of Rh positive fetal red cells at delivery, and hence ideally a further dose of Rh immunoglobulin should be given after each delivery of an Rh positive child.

Abortion also involves the risk of transplacental haemorrhage and sensitization can follow. Thus, provided adequate supplies of Rh immunoglobulin are available, all Rh negative women should be given injections of it. This is likely to become an important problem with the present-day rising incidence of abortion. One may easily visualize the tragedy of some unmarried girl being aborted and developing Rh antibody, and running into serious trouble when she eventually

marries and wants to start a family.

Failure Rate.—Rh immunoglobulin is now known to be highly effective, though protection is not absolute and occasional failures do occur. There are several possible reasons for failure. Sensitization usually occurs at delivery, but occasionally the mother is sensitized owing to transplacental haemorrhage during pregnancy. Initially the antibody titre may be too low to detect, and the mother will appear to be unsensitized when the Rh immunoglobulin is given after delivery—whereas in fact she is already sensitized and Rh immunoglobulin cannot reverse the process at this stage. Another reason for failure is that the mother may have a particularly large transplacental haemorrhage which is not neutralized by the Rh immunoglobulin.

Problems of Supply.—Rh antibody (anti-D) is obtained either from Rh sensitized women or from Rh negative male volunteers who have been artificially stimulated with Rh positive blood. The supply of anti-D is therefore limited, but the supply position in Britain is steadily improving. In a situation where the supplies are limited it is customary to restrict treatment to unsensitized Rh negative primigravidae. When supplies become freely available, however, Rh immunoglobulin should be offered to all Rh negative women.

Role of Liquor Examination

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That yellow liquor may be associated with severe haemolytic disease has been known since the turn of the century. Nevertheless, it was not until the 1950s that D. C. A. Bevis pointed out that this could be useful in management,^{5,6} since when liquor examination has become a firmly established procedure. Its main purpose is to improve the selection of patients suitable for intrauterine transfusion or premature induction of labour.

Amniocentesis

Technique

In skilled hands amniocentesis is a relatively simple procedure carried out under local anaesthetic without premedication. Though it can be done at outpatient attendance, we have preferred to admit our patients overnight. A spinal needle is inserted into an area between the fetal limbs, or alternatively behind the fetal occiput; a few drops of liquor are allowed to escape from the needle, then a syringe is attached and 5 to 10 ml. withdrawn. Routine antibiotic cover is not needed.

Amniocentesis may also be used as part of the technique of intrauterine transfusion (when contrast medium is introduced to be swallowed by the fetus to outline the fetal alimentary tract); help in placental localization;⁷ or confirm the diagnosis of hydrops fetalis.⁸

Dangers

Infection following amniocentesis has been reported⁹ but must be extremely rare and has not occurred in any of the 2,000 operations carried out in this centre. **Direct injury** to the fetus or umbilical cord has been reported,^{10,11} but must also be exceedingly rare unless the fetus is moribund. **Premature labour** is not to be expected following the uncomplicated procedure.^{9,10}

Injury to the placenta is a very common complication unless steps are specifically taken to avoid this. Placental localization is therefore recommended, especially if repeated amniocentesis is to be carried out, and is essential if intrauterine transfusion is contemplated. If a large fetal vessel is pierced there may be serious bleeding into the mother, retroplacentally or into the liquor,^{12–14} and we have observed death of the fetus due to feto-maternal haemorrhage in a pregnancy where relatively mild haemolytic disease had been forecast.¹⁵ Small feto-maternal bleeds are probably common;¹⁶ moreover, undetected bleeds may occur, and rises in maternal antibody titre have been observed following amniocentesis.¹⁷ On six or seven occasions we have observed pyrexia and rigors occurring a half to two hours after amniocentesis followed, in some cases, by an appreciable rise in antibody titre. We consider that such symptoms probably indicate large transplacental haemorrhage and carry a bad prognosis for the fetus. In the case of small feto-maternal bleeds, on the other hand, there is no evidence that the severity of haemolytic disease was greater than would have been expected had amniocentesis not been carried out. Similarly a study of subsequent pregnancies in these patients has shown no evidence of abnormal increase in severity of disease.¹⁸

Liquor samples containing gross amounts of blood are unsuitable for examination, for though red cells can be removed by centrifugation, persistent contamination by plasma will completely invalidate the results. Another source of error is that even small amounts of haemoglobin make quantitative measurement of bilirubin extremely difficult. If gross bleeding into the liquor occurs, results in specimens taken as much as two weeks later may not be valid.

Indications

Because of the potential dangers, it is unreasonable to recommend repeated amniocentesis from early in pregnancy for all cases of Rh isoimmunization. We have not found selection for amniocentesis and timing based on the time of previous intrauterine death¹⁹ or on the maternal

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