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# MANAGEMENT OF ERYTHROBLASTOSIS FETALIS*

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ERYTHROBLASTOSIS FETALIS is a hæmolytic disease of the fetus and newborn period which results from iso-immunization in the mother to the type of blood that is present in the fetus. Many methods of treatment have been employed. One of the present popular methods is the use of the replacement transfusion. Replacement transfusion originally named "exsanguination transfusion" was devised by the late Dr. Ross Robertson at this hospital. The first patient with erythroblastosis fetalis to be treated by this method was done in 1925 by Dr. A. P. Hart at this hospital. It was successfully carried out with cure resulting, whereas other members of the same family had died or were helpless mental defectives following kernicterus.

*Etiological facts.*—95% or more of cases have Rh negative mother who is auto-immunized to Rh positive fetus. The remaining cases are due to iso-immunization to unusual antigens. Rh negative individuals occur approximately in 15% of the white population, 4% of coloured and 0.4% of the oriental races. Rh auto-immunization is very rare in pure coloured races and practically non-existent in the Oriental people. With 15% Rh negative and 85% Rh positive, a family set up with Rh positive husband and Rh negative wife occurs in 1 in 13 marriages. The incidence of erythroblastosis is much less than this. In a large series followed at the Hospital for Sick Children, only about 5% of the pregnant child-bearing Rh negative woman married to Rh positive husbands developed antibodies. Thus, the likelihood of an Rh negative female developing antibodies is only 1 in 20.

## METHODS OF IMMUNIZATION

(a) Transfusion—with the large use of transfusion in the past before Rh incompatibility was recognized—a large number of Rh negative females must have received Rh positive blood. There are a few of them returning with erythroblastotic infants, but the majority have apparently not been affected.

(b) Injections of blood for purposes of producing immune serum. It has been found that this is a most disappointing procedure, except where it has been used to increase the potency of serum in a previously immunized person.

(c) Passages of small amounts of blood across the placenta from the fetus to the mother during pregnancy. This is the most frequent method of immunization.

There are 4 main types of erythroblastosis, intra-uterine death of fetus, congenital hydrops, icterus gravis group, and anæmia of newborn.

Intra-uterine death of fetus with maceration may be due to other causes but is frequently found associated with Rh iso-immunization in the mother. Pathological examination of the fetus reveals the changes seen in erythroblastosis.

Congenital hydrops is the condition where the baby is born with generalized œdema and ascites. It is often associated with hydramnios and enlargement of the placenta. The baby is usually pale and may show jaundice. The baby is born dead or survives only a short time.

Icterus gravis is the group which comprises the largest proportion of cases. The clinical manifestations are:—jaundice of varying degrees which commences at or shortly after birth, and may progress to a very marked degree, hæmolytic anæmia which progresses, increased number of erythroblasts in the circulating blood in the majority of cases, enlargement of the liver

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and spleen, hæmorrhagic tendency occasionally with purpura, and kernicterus in certain cases manifested by drowsiness, with or without convulsions, later ending in death or cerebral damage.

It usually occurs in the second or later pregnancy, rarely in the first unless the mother has received a transfusion prior to the pregnancy. The diagnosis is made by the history, physical examination, blood examination of the baby and laboratory studies on the mother's and baby's blood. These studies consist in Rh typing of mother and baby, and testing the mother's blood serum for iso-immunization to the Rh factor and testing the baby's red blood cells to determine whether antibodies are attached to these cells. This will be discussed in more detail later.

Anæmia of the newborn is a type of Rh incompatibility and most of the babies born with anæmia fall into this category.

The following laboratory tests are necessary in the management of erythroblastosis fetalis:— Rh testing, antibody testing, classifying into special Rh groups: heterozygos or homozygos, and Coomb's test on baby's blood. As in all laboratory work, practice and experience are of great value in this procedure. The more definite positive tests are easily recognized, but some bloods are weakly antigenic and it is with these that the mistakes are made.

In the slide test, a heavy suspension in serum (not in saline) of cells to be tested are mixed with a drop of the test serum, then agitated for two minutes and the presence of agglutination noted. If the cells agglutinate then the person is Rh positive.

In the water-bath test, a 2% suspension of cells is mixed with a dilution of the serum, incubated in a water bath for one hour. Then the tube is shaken up and the presence of agglutination noted. At the laboratory at the Hospital for Sick Children both methods are used, one as a check on the other. The errors that come in these tests are from inexperience or the use of weak antibody serum in certain border line cases. There is much more likelihood of calling Rh negative someone who is Rh positive. This is not so dangerous in a recipient because if a person is called Rh negative by mistake, usually further tests are done and the error is picked up. Also, the use of Rh negative blood for transfusion into a Rh positive person causes no damage. If by error an Rh positive donor is called Rh negative and used, it may bring about immunization or a serious reaction in an immunized recipient.

Antibody testing must be done in any Rh negative woman who is pregnant; it is necessary to determine whether she has been immunized to Rh positive cells or not. The antibody test is done in two ways on the serum. A heavy suspension of known Rh positive cells is mixed with the woman's serum by tilting back and forth on a slide and observed for agglutination. Known different group of Rh cells must be used to rule out all types, but as a general rule using CDE will take care of 95% of the tests. To get the actual titre of the immunization, a 2% suspension of the cells is incubated at 37° C. in a water bath with dilution of the serum. It has been found that when the serum is diluted with normal saline the antibodies are shown in about 25%. In the others it is necessary to dilute the serum with albumin and to do this a 20% solution of bovine albumin is used. This is the origin of the term "blocking antibody" referring to the fact that the antibody does not show up if the serum is diluted with saline. When a report from the laboratory reads "1:8 blocking antibodies", it means that the serum has been diluted with albumin. The clinical significance of blocking versus saline antibodies is questionable, but it is found that there are more cases of the blocking type and the deleterious effect on the fetus is probably greater.

Originally bloods were classified as Rh positive (Rh) and Rh negative (rh). Later it was found that there were 8 sub-groups. The terminology which became applied to the genes making up the cell and which is accepted by most is: CDE for Rh positive and cde for Rh negative genes. Each cell has these 3 factors in one or another form *e.g.*, the cells may be CDe, Cde, CdE, cDE, cDe, CDE, cdE, cde. The last one, cde, is Rh negative, the others are Rh positive.

In testing for Rh, there are 2 methods which are used: a rapid slide test, and a test where the cells are incubated in a test tube which is a more accurate test.

Classifying into special Rh group has to be done by a special laboratory technique. With special known sera groups, it is possible to classify the cells into the various Rh sub-groups. In addition to this it is possible to a large degree to tell whether a person is homozygous or heterozygous. This refers to the type of genes that have been obtained from the two parents. If Rh positive genes come from one parent and Rh

negative from the other, then the person is Rh positive heterozygous. If Rh positive from both then the person is Rh positive homozygous. If Rh negative genes from both parents then the person is Rh negative.

It is also possible with known cells to classify the immune serum into the sub-group to which it is immunized.

Coomb's test on the baby's blood determines if antibodies are attached to the baby's cells. This is done by testing to see if any human globulin has been adsorbed to the cell. The baby's cells are washed three times with normal saline, then reconstituted to a 2% suspension. Place two drops of these washed cells and two drops of anti-human rabbit serum in a small test tube. This is read in ten minutes and again after slow centrifugation. The suspension is usually incubated in a water bath before centrifugation.

In doing this test everything must be clean and when the cells are re-suspended after centrifugation, they must be mixed using a clean stirring rod or applicator. If one inverts the tube with the thumb over the end it spoils the test. The errors in this test are due to unfamiliarity with the technique and an out-dated or weak testing anti-human serum. This is also a test that should be reserved for laboratories with special technical facilities.

These laboratory tests should be applied as follows: all pregnant women should be Rh classified. If Rh negative then test for antibodies at monthly intervals, after fourth month of pregnancy. The husband should be classified, if Rh positive, as to Rh group and whether heterozygous or homozygous. If an Rh negative woman who has Rh antibodies in the blood is delivered, cord blood from baby should be taken immediately at birth and tested for antibodies (Coomb's test). If this is positive, then the baby has erythroblastosis and measures must be instituted for treatment.

Treatment of the case depends on the clinical type seen. Macerated fetus requires no treatment. Treatment in the congenital hydrops type is usually of no avail but should be carried out vigorously as in the icterus gravis type, which will be described in detail. The congenital anæmia group require transfusions of blood at intervals until the normal blood production returns.

In treating the icterus gravis type or the common type, there are two methods of treatment—the conservative symptomatic transfusion and the radical replacement transfusion. Both of these have supporters and we will show, as far as possible, the advantages of each.

For transfusion by either method Rh negative blood is used because it is felt that Rh positive blood would be attacked by the antibodies in the baby, and do more damage from agglutination of cells blocking small capillaries and the excess pigment formed causing trouble. This is generally accepted as the correct type of blood to use.

Certain observers believe that using certain criteria one can determine which cases are going to be severe and which are not. In our experience this is true to a point; there are certain cases which are obviously severe from the first, but there are also some cases which for the first 4 or 5 days showed no indication that the process was anything but mild. Later they became very severely anæmic, icteric, kernicteric and died.

In the conservative type of treatment, the patient is transfused as often as the hæmoglobin is found below a certain level. Rh negative blood is used. With this form of treatment at this Hospital, the mortality rate was 16% for 74 cases from July, 1948, to December, 1950.

In replacement transfusion the blood is withdrawn from a large pool of blood usually by passing a cannula in through the umbilical vein to the inferior vena cava. In some clinics it is replaced by the same route, but in others the new blood is put in by another vein, such as the internal saphenous. Rh negative blood is used. By using 500 to 700 c.c. of blood, withdrawing and replacing 20 c.c. at a time, the baby's blood can be replaced up to from 75 to 90% with new blood. This procedure is not without danger and fatal accidents have happened. If the procedure is carried out too rapidly, it may embarrass the baby's heart. If the new blood is allowed to cool off it may shock the baby. Also using too much citrated blood may lower the baby's calcium and produce tetany. These are some of the difficulties that may be encountered. This procedure should not be attempted by anyone who has not had some experience. When replacement transfusion is used calcium gluconate should be injected at the end of the procedure to ensure a normal calcium level in the blood.

The rationale of replacement transfusion is to remove antibodies from the baby and put in blood which will not be attacked by the antibodies. If this procedure is to be carried out, it should be done early, otherwise the benefit is lost. It has been our policy to use it only in cases where the baby is seen under 12 hours of birth. Using this method of treatment, the mortality has been 17% for 105 cases from July,

1948, to December, 1950. This is approximately the same as the conservative type of treatment. We are not convinced entirely, as yet, that this procedure is not without merit.

Diamond and Anderson[1] reported that the use of female Rh negative blood reduced the mortality to a very low figure. We have been unable, in the small number so far tried, to confirm this and so far our figures show no difference whether female or male Rh negative blood is used. In 46 replacement transfusions, there were 8 deaths or a mortality rate of 17%; with 15 conservatively treated, there were 3 deaths or a mortality of 20%.

Following the initial emergency treatment, either conservative or replacement, the hæmoglobin should be followed and the baby transfused when necessary. These repeat transfusions may be necessary up to 5 months of age.

Feeding of the erythroblastotic baby sometimes presents a problem. There is no reason why a mother should not nurse her baby even though the breast milk may contain antibodies. There is so little absorbed that these antibodies have no effect on the baby. Many of these babies develop diarrhœa so that protein milk is the safest artificial food to use.

Premature delivery of the baby, often by Cæsarean section, has been advocated to remove the baby from the mother and avoid the absorption of antibodies. This procedure is without benefit for this purpose and, in addition, it adds the hazard of prematurity and should not be used. In the follow-up after an erythroblastotic baby, mothers with antibodies should be urged to donate blood for use in laboratories. This is the only good source of Rh testing serum.

REFERENCE

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