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Management of Erythroblastosis Fetalis

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• **The practical management of the problem of erythroblastosis depends primarily on the prenatal determination of which pregnancies might result in an erythroblastotic infant. The physician primarily concerned with the care of the child must attend the delivery of every Rh-negative woman whose serum contains anti-Rh antibodies. At present, prompt confirmation of the suspected diagnosis immediately following birth and immediate exchange transfusion in infants with laboratory or clinical evidence of the disease are necessary to reduce morbidity and prevent kernicterus.**

ERYTHROBLASTOSIS FETALIS due to incompatibility of the Rh factor occurs once in every 200 births of white infants and is associated with a high incidence of serious morbidity and mortality. The problem is a serious and a frequent one encountered by all physicians practicing obstetric and pediatric medicine.

In recent years the basic pathogenesis of fetal erythroblastosis has been clearly defined. An Rh-negative woman is immunized by Rh-positive erythrocytes received from either a fetus or blood transfusion. The immunized mother produces anti-Rh agglutinins. The agglutinins traverse the placenta to the fetus where they cause destruction of the Rh-positive erythrocytes of the fetus and newly born infant. The course of events may result in a disease so severe as to cause fetal death, or on the other hand, only mild degrees of anemia may result. The extreme variation in the course of the disease only emphasizes the need for persistent vigilance on the part of the physician if optimal management of the problem is to be assured each patient.

In light of present knowledge a program for the practical management of the problem of erythroblastosis can be stated quite specifically.

I. A careful history should be taken early in pregnancy for evidence of previous isoimmunization to a blood group antigen.

II. The blood type (ABO and Rh) of each pregnant patient should be determined at an early prenatal visit.

III. Laboratory study for evidence of circulating antibodies should be done four to five weeks before term of each pregnancy of every woman who is Rh-negative.

IV. Consultation should be obtained to suggest a program of further laboratory studies if a woman has had previous babies that were stillborn or that died soon after birth because of erythroblastosis.

V. Certain aspects of the delivery of all Rh-negative women in whom antibodies are present demand special attention. Except in most unusual circumstances, early induction of labor is to be avoided.

VI. At the time of birth a physician responsible only for the immediate clinical and laboratory evaluation of the infant should be present. Evidences of erythroblastosis fetalis should be looked for in the physical examination.

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A specimen of blood from the umbilical cord should be examined for the following:

(*a*) Hemoglobin, bilirubin, normoblast and reticulocyte levels.

(*b*) Blood type.

(*c*) Antiglobulin (Coombs' test).

VII. Conservative treatment for infants having either a clinical or laboratory diagnosis of erythroblastosis is exchange transfusion.

VIII. Critical clinical and laboratory follow-up observation is essential to determine the necessity for further specific therapy.

The History

A carefully taken history concerning evidence of blood group isoimmunization is an essential part of the early care of every pregnant woman. It is important to know whether or not the mother has ever been "exposed" to erythrocytes of an antigenic composition different from her own. Has there been previous parenteral administration of blood? Have there been previous pregnancies, and if so, what was the outcome? Have any of the infants been stillborn? Abortions before the 16th week are not due to blood group incompatibility, but if an erythrocyte antigen were present the mother might be sensitized to it even though abortion occurred very early. If a previous pregnancy has resulted in a stillborn infant or in an infant afflicted with unusual jaundice or with anemia, the possibility of blood group isoimmunization should be considered.

The history takes on added importance if the mother is known to have had previous infants with erythroblastosis fetalis. The severity of the disease in the previous infants is the best indication of the severity of the disease to be expected in subsequent babies.[5]

The Blood Type and Its Significance

Regardless of the historical data available, the blood type of each pregnant woman should be determined early in pregnancy. Over 90 per cent of clinically significant erythroblastosis is due to isoimmunization with the antigen D (Rho).* Therefore, routine studies of pregnancy can be most practically limited to a consideration of this antigen. In 85 per cent of white women the blood type is Rh (D, Rho) positive. These women obviously cannot become isoimmunized to this antigen. The remaining 15 per cent are Rh-negative and may thus be immunized by exposure to the Rh antigen. The distribution of this Rh antigen is similar in males and females, 85 per cent of all white males are Rh-positive. Therefore, over 12 per cent of all marriages among caucasians in this country involve an Rh-negative woman with an Rh-positive husband. Thirty-eight per cent of all males are homozygous for the gene responsible for the transmission of the Rh antigen and will father only Rh-positive children; 47 per cent are heterozygous for this gene and 50 per cent of their children will be Rh-positive.[4] These figures clearly show that the possibility of blood group incompatibility is an everyday occurrence in an obstetrician's office.

Of the 12 per cent Rh-negative women whose husbands and babies are Rh-positive, only a small number will ever give birth to babies with erythroblastosis fetalis. Whether or not the infants have the disease will depend upon whether or not the mother becomes isoimmunized (that is, sensitized) and produces antibodies to the Rh antigen. To become so immunized, Rh-positive erythrocytes must enter the maternal circulation and the mother must be capable of producing antibodies to this antigen. Factors governing the ability of mothers to produce these antibodies are poorly understood. Although the small numbers of erythrocytes adequate for sensitization enter the maternal circulation during each pregnancy, it is well known that only *one in every twenty Rh-negative women* pregnant with an Rh-positive fetus will become immunized. The Rh-negative mother who has been given a single transfusion of Rh-positive blood will become immunized in 50 per cent of the instances, and, with repeated transfusions of Rh-positive blood, over 90 per cent of Rh-negative women will develop antibodies.

This information assumes considerable importance in everyday practice. The fact that 19 of every 20 Rh-negative women with Rh-positive husbands will never have infants with erythroblastosis can be very reassuring to an apprehensive, misinformed, Rh-negative woman. Likewise, the comparative readiness with which immunization results from the transfusion of Rh-positive erythrocytes into Rh-negative women should alert all physicians to the dangers of indiscreet use of transfusions and the importance of careful Rh typing of all blood transfused into female patients before or during the childbearing age.

Demonstration of Anti-Rh Antibodies

In the early weeks of pregnancy the obstetrician should have available the completed history and the patient's blood type. If the prospective mother is Rh-positive and the history reveals no abnormality with previous infants, the problem no longer assumes importance in the management of the pregnancy. If the mother is Rh-negative, the pertinent question to be answered is whether or not the mother has been or will become immunized against the Rh antigen during the course of pregnancy. To de-

*By common usage the term Rh, when not more specifically identified, is synonymous with the letter D (Rho) and it is used as such in this discussion.

termine whether previous pregnancies, transfusions, or the current pregnancy have immunized a given obstetrical patient, the patient's serum should be studied for the presence of anti-Rh antibodies. Except in quite unusual circumstances, referred to later, it is most reliable and expedient to do a single antibody determination late in the course of each pregnancy in every Rh-negative woman. An antibody determination done during the 36th week of gestation will answer the question as to whether or not the patient has been sensitized and will give some indication as to the concentration of antibodies in her serum. Little is to be gained by the repeated determination of antibody titers during the pregnancy. That the titer does not increase is no assurance that the infant will not have erythroblastosis fetalis. In light of current knowledge, a rising titer does not alter the management of the problem. The only question that the laboratory studies can answer is whether or not a given woman has anti-Rh antibodies in her serum and thus might give birth to a diseased Rh-positive infant.

Prenatal Prognosis of Erythroblastosis Fetalis

The physician will often be tempted, or asked by the patient, to prognosticate the outcome of a given pregnancy. The following facts from extensive clinical experience in the last few years indicate that it is impossible to foretell with any degree of confidence, what the outcome of a given pregnancy will be. It must always be remembered that only one of every 20 Rh-negative mothers will become immunized by pregnancy with an Rh-positive fetus. Since 5 to 10 per cent of all cases of erythroblastosis fetalis occurs in first pregnancies, the fact that there have been no previous pregnancies is no assurance that erythroblastosis will not occur. Likewise, 10 to 15 per cent of Rh-positive babies born of Rh-negative mothers known to be sensitized and having circulating antibodies, are free of all evidence of erythroblastosis. It is known that there is a tendency for each successive infant of a sensitized mother to be somewhat more severely affected by the disease. However, there is an even more striking tendency for a mother to have infants with erythroblastosis of similar severity. If a sensitized mother's previous infants have been live-born babies with erythroblastosis that has responded well to therapy, the chances are in favor of her having similarly affected infants with future pregnancies. If the mother has had one or more stillborn babies due to blood group incompatibility, the prognosis is less optimistic and will warrant extensive study. However, in no instance is the prognosis hopeless for a resulting healthy infant.

A woman with a very discouraging history of stillbirths or kernicterus in previous infants can find encouragement in the ever improving results of therapy of live-born infants and in the chance that she will have a live-born infant with some future pregnancy. Although there has been a 20 per cent incidence of stillbirths in sensitized Rh-negative women, the prognosis is improving and can never be considered completely hopeless for a woman who earnestly wants to have a family.[1]

From all the foregoing data it is obvious that any sensitized Rh-negative woman may give birth to a normal infant or to one with erythroblastosis fetalis of any degree of severity. It is impossible to foretell the outcome of any given pregnancy in these women. The pregnancy and immediate neonatal course should be planned accordingly.

Delivery of Sensitized Rh-Negative Mothers

In managing the delivery of an Rh-negative woman it is essential to know whether or not she has been immunized to the Rh antigen. If the woman has been sensitized, only in the quite unusual situation involving previous stillborn infants might the early induction of labor be indicated. Experience from many clinics has clearly shown that induction of labor as early as two weeks before term will significantly increase the incidence of brain damage due to kernicterus. If all sensitized Rh-negative women are allowed to go to term, a slight increase in the incidence of stillbirths will occur. However, there will be more than a compensating reduction in the mortality of infants born alive and a very important reduction in the incidence of kernicterus. Cesarean sections are to be avoided whenever possible, for increased infant morbidity and mortality is associated with this procedure.

The condition of the baby may be significantly altered by the procedure used in clamping the cord. In the past there has been considerable enthusiasm for very early clamping of the cord in hope of preventing infusion of excessive amounts of antibody-containing blood into the baby. The amount of hemoglobin kept from the baby by this practice may be considerable, with significant degrees of blood loss, anemia, and even shock, resulting. It is wise not to be too anxious to interrupt the umbilical circulation.[5] Likewise, a generous portion of the cord should be left attached to the infant to facilitate carrying out exchange transfusion through the umbilical vein.

Care of the Infant

A physician primarily concerned with the care of the newborn infant should attend the delivery of all immunized Rh-negative women and be prepared to promptly institute appropriate diagnostic and therapeutic procedures. The baby should be carefully examined at the time of birth with special attention

directed toward findings of erythroblastosis fetalis. Pallor, edema, hepatosplenomegaly, and rapidly developing icterus may be present to varying degrees in an infant with erythroblastosis fetalis. Many infants with the disease are free of all physical abnormalities at the time of birth. This is no assurance, however, that severe erythroblastosis, even resulting in death or brain damage, will not occur in these babies.

Cord blood specimens should be immediately examined to determine the Rh type of the baby, the status of the antiglobulin test (Coombs'), and the hemoglobin level. It is also important to determine the reticulocyte and normoblast count and the bilirubin level. The laboratory studies should be promptly and carefully done and interpreted in light of well established normal values of cord blood specimens.

An Rh-negative infant born of a mother who is known to be immunized to the Rh antigen will not have erythroblastosis fetalis. Occasionally an infant's blood will give a false negative reaction in Rh typing if the cells are so heavily coated with antibody as to prohibit the typing serum from reaching the Rh antigen of the erythrocyte. Such cells react strongly positive to the Coombs' test and thus each typing of infant's cells should be done in conjunction with the Coombs' test. If the result of Coombs' test is negative and the Rh typing reaction is negative, the infant can be assumed to be Rh-negative and not to have erythroblastosis fetalis due to Rh antibodies.

The normal values for cord hemoglobin levels will vary depending on the standards used in various laboratories. A level in the cord specimen below 15.6 gm. per 100 cc. (a value of 100 per cent for adults) is indicative of anemia in most laboratories. Bilirubin content in the serum above 3.0 mg. per 100 cc. is distinctly elevated. The numbers of reticulocytes and nucleated erythrocyte precursors in the circulation are difficult to evaluate and these factors give less specific information than the other laboratory studies discussed above. If reticulocytes are above 10 per cent of the total number of erythrocytes, one can conclude that abnormally active erythropoiesis is occurring. A similar conclusion may be indicated if there are more than 10 nucleated erythrocytes per 100 leukocytes. The latter examinations are often subject to considerable technical variations.

The laboratory studies mentioned in the foregoing paragraphs should be completed within an hour after the time of birth of the baby of a sensitized Rh-negative woman. If there is complete absence of clinical evidence of disease, as frequently happens, the management of the infant will be determined from the results of laboratory studies. Obviously, no single laboratory study will determine the diagnosis of erythroblastosis fetalis. However, thoughtful evaluation of all of the studies mentioned above will permit a decision as to whether or not hemolytic anemia due to immunization—that is, erythroblastosis fetalis—is present or absent in a given infant.

Treatment of Erythroblastosis Fetalis

The most conservative course of management of the baby with erythroblastosis fetalis demands an immediate exchange transfusion in the presence of clinical or laboratory evidence of the disease. The technique of exchange transfusion has been described in detail. In inexperienced hands the procedure is not without hazards; hence it should be done only by trained personnel under optimal circumstances. The blood used should be as freshly drawn as possible—certainly no older than 96 hours. Obviously, the procedure should be carried out in an area where effective aseptic technique can be followed.[3]

Post-transfusion Care of the Infant

After an initial exchange transfusion the infant should be placed in a warm, moist atmosphere with supportive oxygen. The bilirubin level should be checked at intervals of 8 to 12 hours and if it reaches a level of 15 to 20 mg. per 100 cc. or higher, exchange transfusion should be repeated.

This program of management of Rh-negative mothers and infants with erythroblastosis fetalis should result in complete recovery of over 95 per cent of live-born infants with the disease.[2] Of equal importance is the fact that the devastating complication of severe brain damage due to kernicterus is practically eliminated. In infants treated only with small transfusions for their anemia, the incidence of kernicterus will approximate 15 per cent. Kernicterus may occur in over 30 per cent of infants with the early induction of labor without exchange transfusion.

Stillbirths and Their Prevention

At the moment the most disturbing unsolved problem for the sensitized Rh-negative woman is that of stillbirths. Twenty to thirty per cent of pregnancies in sensitized Rh-negative women may result in the birth of a stillborn infant. Attempts to alter this situation by the use of cortisone during pregnancy have not been of proven value. Likewise, the administration of certain extracts of Rh-positive erythrocytes to sensitized Rh-negative pregnant women has not affected the course of the disease in the infants. In spite of this discouraging situation the prognosis for any woman who has had one or even several stillborn children due to blood group incompatibility, is never hopeless, especially in light

of the very good results obtained from the optimal treatment of live-born babies with erythroblastosis fetalis.

The most difficult problems are encountered in women strongly sensitized, who have had one or more stillborn infants, have only one or possibly no living children, and whose husbands are homozygous positive for the Rh factor. In such instances induction of labor as early as the 37th or 38th week of gestation with immediate exchange transfusion of any Rh-positive infant who has a positive Coombs' test result, may result in a living infant free of brain damage.[1] The treatment of an infant with severe hemolytic disease and with the many handicaps of prematurity is difficult and may often be unsuccessful. To avoid needlessly becoming involved in such a hazardous situation, each patient should be carefully studied and her problem reviewed by a qualified consultant before early induction of labor is undertaken.

The program outlined in the foregoing paragraph demands the thoughtful cooperation of physicians responsible for laboratory, obstetrical and pediatric problems of pregnant patients. Certain basic laboratory and therapeutic facilities are obviously essential and must be available for adequate management of babies of isoimmunized Rh-negative women. In light of current knowledge, any compromises with this basic program will be reflected in a greater than necessary incidence of kernicterus, mortality and stillbirths. To obtain essential laboratory studies during pregnancy does not present problems for physicians in even the most remote rural areas, for blood specimens can be easily sent to competent laboratories at considerable distances. However, one must face the fact that an Rh-negative woman who has been found to be immunized, should not be delivered in a hospital where a basic program as described here is not available for the necessary care of her infant.

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REFERENCES

1. Allen, F. H., Jr., Diamond, L. K., Richardson Jones, A.: Erythroblastosis fetalis. IX. The problems of stillbirths, New Eng. J. of Med., 251:453, 1954.

2. Arnold, D. P., Witebsky, E., Selkirk, G. H., and Alford, K. M.: Clinics and serological experiences in treating hemolytic disease of the newborn, J. of Ped., 46:520, 1955.

3. Diamond, L. K., Allen, F. H., Jr., and Thomas, W. O., Jr.: Erythroblastosis. VII. Treatment with exchange transfusion, New Eng. J. of Med., 247:688, 1952.

4. Diamond, L. K., Smith, N. J., Vaughan, V. C., III: Disorders of the Blood, Textbook of Pediatrics, Philadelphia, Saunders & Co., Editor, Waldo E. Nelson, 1954.

5. Seventh M & R Pediatric Research Conference, Erythroblastosis Fetalis, M & R Laboratories, 1954.