RECENT ADVANCES IN THE OBSTETRICAL MANAGEMENT OF ERYTHROBLASTOSIS FOETALIS

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The Rh. incompatible pregnancy still remains, in spite of a reasonably detailed knowledge of the underlying mechanisms, a frustrating problem to the obstetrician. Some of the more recent advances in the field of obstetrical management as well as some comment on recent work being done aimed at preventing this problem altogether will be presented in this survey.

As was mentioned, this illness has been known for many hundreds of years, but, until very recently, after the discovery of the Rh. factor by Karl Landsteiner in 1940 and the proposal one year later by Philip Levine that maternal isoantibodies could be the cause of the disease, very little was known of its cause, and certainly little in the way of active treatment during pregnancy was practiced.

In the years between 1940 - 1960, even after the disease process was more fully understood, the scope of obstetrical management was very limited. Although it was then possible to anticipate Rh incompatibility by blood grouping the parents, it was impossible to determine with accuracy (1) whether the foetus of any one particular pregnancy was affected, (2) the degree to which the disease had affected the child.

Although it was known that early induction of labor was necessary in many cases, deciding on the exact time for induction - to give the child the best possible chance for survival - was difficult. It was also well known that the foetus could be severely affected before the 36th week of pregnancy. However, induction before this point in the pregnancy involved superimposing the dangers of prematurity on the already present hemolytic process.

Research in the field has been centered mainly on solving the problem of when to induce labor in these cases and in methods of preserving life as long as possible in utero in order to avoid extreme prematurity.

In the 1950's the obstetrical management of a sensitized pregnancy was based mainly on the past obstetrical history of the patient, plus the antibody titre of the mother's serum. Although this method was of some value in predicting the severity of disease in the unborn foetus, it had serious limitations. These limitations were due mainly to the variability of the antibody titre regardless of the condition of the infant.

Freda states that when the Rh antibody appears for the first time during a particular pregnancy and/or there is a significant rise in the maternal titre, one can anticipate an affected baby with some degree of certainty. In his experience, however, in most of the severe cases, particularly in cases where the child was born dead, the maternal titres did not reflect the severity of the disease. After a woman has had one sensitized pregnancy, management of further pregnancies becomes very difficult when only the antibody titre is known.

Another problem that was very troublesome occurred when it was known through serological testing or family history that the father was heterozygous for the Rh group. In this situation, if the mother had previously borne an affected child, it was often difficult to determine whether or not the foetus of the pregnancy in question was Rh + ve or −ve. It was noted that in some instances even when the foetus later proved to be Rh −ve, a rise in maternal antibodies occurred during the pregnancy.

Because of these and other problems, the level of maternal antibody could be used only in conjunction with the past obstetrical history and the zygosity of the father in reaching a final decision as to when to induce labor.

It was obvious that what was needed was

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a more direct test on the foetus rather than trying to predict severity by the indirect method - measuring maternal antibodies.

A method of amniotic fluid analysis first described by Bevis in Great Britain, was subsequently refined by Dr. A. W. Liley of the University of Auckland in New Zealand. This method involved performing spectrophotometric analysis on the amniotic fluid during the antepartum period.

It had been noted for many years that the amniotic fluid of severely affected cases was stained with bile. The work of Bevis in 1956 showed that the amount of blood pigments in the fluid in these cases was markedly increased, and he proposed that the amount of these pigments reflected the degree of erythrocyte destruction. Further work by Liley showed that a number of constituents of amniotic fluid showed variation in hemolytic disease, however, it was the yellow pigmentation which was most easily measured. Further analysis showed that when amniotic fluid was studied using the spectrophotometer these bile pigments absorbed monochromatic light between the ranges of 375 − u to 525 − u. Comparing normal tracings with those made on fluid from affected cases it was found that a "hump" in the curve appeared between these wave lengths, the severity of the disease being reflected by the amplitude of the "hump". It then remained to work out a system whereby the information obtained from these analyses could be used as an aid in the management of the affected pregnancy.

Although several methods have been described the one that is most widely used in this country is that of Liley. After the amniotic fluid has been obtained by amniocentesis, optical density readings are made over the wave length range 700-350 microns at 10-25 micron intervals. These readings are then plotted and joined on semi-logarithmic graph paper with wave length plotted horizontally as the linear component and optical density as the vertical logarithmic component. When readings from an affected case are plotted there is a characteristic rise from the expected normal curve at 450 microns. When the spectral absorption curve of normal, colorless amniotic fluid at or near term is plotted, the graph is found to be approximately linear from 365 microns to 550 microns. Because of this, the bile pigments may be quantitated as the optic density deviation from linearity at 450 microns, the baseline being drawn in as the double tangent to the absorption curve at 365 and 550 microns. Because other factors contribute to optical absorption across the whole spectrum, tending to be more pronounced as pregnancy advances and also varying from fluid to fluid, the actual optical density at 450 microns is worthless. The rise in optic density from the expected normal is the figure of prognostic value.

The pigment peak measured by this method shows a close correlation with simultaneous cord hemoglobin values. However, two tests done at an interval of a few weeks and related to the length of gestation gives more information regarding the status of the foetus than if not related to maturity. Liley found that the normal slight pigmentation of amniotic fluid early in the third trimester diminishes with increasing maturity of the foetus, a pigment peak which would not be remarkable at 28 or 31 weeks could indicate serious disease if it occurred at 35 or 38 weeks. Because of this fact, the optic density rise is plotted on the graph, with the gestational age now plotted horizontally as the linear component instead of the wave length. From Liley's experience he then divided this second graph into three zones which he numbers one, two and three. The slope of the boundaries demonstrating the three zones indicates that lesser optical density rises are of greater significance as pregnancy advances. Zone one generally indicates an unaffected or mildly affected foetus, zone three a severely affected child, zone two indicates degrees of disease between these two.

Amniocentesis and spectrophotometric study of the obtained fluid now gives direct information regarding the degree of disease present in the foetus. This now provides the obstetrician with information not previously available using only antibody titres.

For example let us take a hypothetical case that was previously very difficult to manage - a pregnancy where there is a history of a previously affected child but through blood group studies it is known that the father is heterozygous. The problem here is whether or not the child is Rh −ve. Antibody studies in the mother will probably be high from the previous pregnancy. By doing regular amniocentesis beginning at 25-28 weeks and plotting the results on Liley's

graph one of two pictures will be seen. On the one hand the optical density rise at 450 microns may always remain in zone one. This is good evidence that the foetus in Rh-ve. On the other hand the curve may show a rise in optic density at 37 weeks which falls into high zone II or even into zone III. This woman would have to be induced and most likely the child would need exchange transfusions.

From this example it is easily seen that antibody levels alone would have been useless but with amniocentesis it was possible in the first case to allow the unaffected pregnancy to go to term instead of inducing early on the chance that it might have been affected, thus needlessly exposing the completely healthy foetus to the dangers of prematurity. In the second case the fact that the pregnancy was affected was recognized, by the rise in optic density and the child was delivered early enough to be salvaged by the exchange transfusion yet not earlier than was absolutely necessary.

The group headed by Bowman in Winnipeg have found that by using Liley's method they have increased the accuracy of prediction of the severity of disease in utero to 96.8% over all compared to the 62% accuracy obtained when antibody levels were used alone.

Although the maternal mortality and morbidity has been negligible as a result of amniocentesis there is a risk to the foetus. It has been found that if the placenta has been traumatized, leakage of the foetal cells into the maternal circulation may cause an increase in the isoimmunization process thus increasing the degree of disease in the foetus. In spite of the risks involved the use of this method is unquestionably extremely useful.

Amniocentesis is not done routinely in all isoimmunized pregnancies. The Winnipeg group have listed the following indications for its use, indications which they use in their practices. 1. In all isoimmunized pregnancies with a history of preceding disease severe enough to require treatment, or to cause stillbirth no matter what the antibody titre. 2. In all isoimmunized pregnancies where there is a preceding history of stillbirth for which the cause is unknown. 3. In all first sensitized pregnancies where the titre exceeds one in eight in albumin by 32 weeks gestation. 4. All second and subsequent isoimmunized pregnancies where the previous Rh positive infant did not require treatment, in which the titre exceeds one in eight in albumin.

Using the above criteria they experienced only 41 deaths out of 320 deliveries. Analysis of these deaths by the physicians involved in the study revealed that 15 might have survived if mothers had cooperated fully. The remaining 26 deaths occurred too early for simple early induction of labor and delivery to enable the child to survive. Conventional treatment offers little for these babies. Those cases which show high pigment levels before the 32nd week cannot be induced with any hope of survival because of the severe anemia and prematurity. In order to save these children they must be kept alive in utero until such time as induction of labor does not introduce such severe prematurity hazards. A procedure was introduced again by Liley in an effect to prolong these severely affected pregnancies in order to give the child a better chance of survival.

In October, 1963 he reported the first successful intrauterine transfusion. He felt that the prevention of severe anemia, which is the direct cause of foetal death, could be obtained by introducing red cells into the foetal circulation. Direct injection into the vascular compartment was next to impossible without opening the uterus. It was found, however, that red cells injected into the peritoneal cavity of the foetus found their way into the circulation presumably through lymphaties. Liley's method is today one of the most popular methods of supplying red cells to the severely anemic foetus.

The blood used for transfusion is Group O Rh —ve citrated blood less than 48 hrs. old. This blood must be compatible with the mother's serum and is usually packed to hemoglobin levels of 17-23 gm.% and then warmed before injection. The amount of blood given depends on the size and maturity of the foetus. In Liley's series the quantity ranged from 75-100ml. at 26-28 weeks and up to 160 ml. at 31-32 weeks. This blood was injected slowly by hand at the rate of 3 ml. per minute.

The use of antibiotics to cover both foetus and mother is still controversial. Liley uses a combination of streptomycin and penicillin, a pediatric dose is given into the foetal peritoneal cavity, and an adult dose into the am-

niotic fluid. A further 4-5 day course is given to the mother.

Once foetal transfusion has been carried out, no further reliance can be placed on amniotic fluid pigment levels since large increases and decreases in peak size unrelated to foetal condition have been seen.

The need for repeat transfusions of the foetus are based on 1. The length of time before the planned delivery. 2. The hemoglobin mass given on the first transfusion 3. The severity of the foetal condition. The intervals between transfusion range between $1\frac{1}{2}$ to 3 weeks, the shorter interval being used when at the time of first transfusion there was evidence of hydrops on the amniogram or ascitic fluid was aspirated from the foetal peritoneum. In the past few years the knowledge that more blood can be given with each transfusion than was previously used has allowed longer periods between transfusions, thus fewer transfusions and also greater maturity to the foetus. Cases that in the beginning were delivered at $34\frac{1}{2}$ weeks now can be taken to 35 - 36 weeks gestation before induction.

With the knowledge that intra-uterine transfusions can now be done, what are the indications for instituting this therapy? The group in Winnipeg, who use Liley's spectrophotometric technique to evaluate their cases, feel that it should be rarely undertaken on the basis of a single amniotic fluid examination unless there is a history of a previous stillbirth and the rise in optic density lies in zone III. Usually they feel that two or more fluids examined 7 - 14 days apart must show an optical density rise, the last sample being in zone III. They also feel that after 31 weeks gestation, induction, and delivery at 32 or 33 weeks should be done. They feel that in their hands this is a less dangerous approach than the intra-uterine transfusion.

There are dangers involved in this procedure. The maternal complications are rare but include infection, amniotic leakage along the needle tract and leakage of amniotic fluid into the maternal circulation. This latter is probable the most serious as amniotic fluid is high in thromboplastin content and intravascular clotting can occur. Complications involving the foetus are probably the most common. One of the most common of these is the stimulation of labor with the result of an extremely premature baby. Another common occurrence is stabbing the needle into a vital foetal organ. Hitting the liver often causes hemorrhage severe enough to cause foetal death. Another less common cause of foetal mortality results from lacerating a large placental vessel with resultant hemorrhage but previous identification of the placental site reduces this risk.

How successful is this treatment in prolonging gestation and preserving foetal life? Liley's experience shows that 70% of his cases that were transfused survived whereas all would likely have died if left untreated. He found however, that the survival rate falls to zero if treatment is delayed until hydrops or ascites has appeared.

The ultimate aim of research into any disease in medicine is prevention rather than treatment. In order to prevent erythroblastosis, it is necessary to prevent isoimmunization with foetal cells from occurring. In order to do this it is vital to known when the leaks occur.

There are probably two methods of isoimmunization 1. the large placental transfusion during labor and 2. small repeated leaks during the pregnancy. Present evidence suggests that 50 - 75% of immunization occur at or shortly after labor.

It now seemed necessary to develop a way of preventing the foetal cells from causing antibody response.

It was demonstrated that the antigen would not evoke an antibody response if an excess of antibody was present. Therefore, it was felt that if enough antibody could be given to the mother to neutralize the Rh antigen isoimmunization could be prevented.

In the New York study a pure anti-Rh gamma globulin was prepared from a small group of donors with high titres. The effectiveness of this anti-Rh gamma globulin was first tested on volunteers, all Rh - ve were used. Each was given an injection of 2 ml. of ABO compatible Rh +ve blood but 4 of the 9 were given 5 ml. of the gamma globulin preparation, 24 hrs. before the blood was given. None of the 4 given gamma globulin became immunized but 4 of the 5 who were not protected became strongly sensitized. Further studies using 10 ml. of blood and giving the gamma globulin 48 hrs. after the blood injection gave similar results, none of the protected individuals became sensitized.

Studies strongly suggested that Rh -ve mothers could be protected against isoimmunization by receiving the anti Rh gamma globulin in sufficient amounts. To be effective the protection would have to start with the first pregnancy and be given with each pregnancy thereafter.

There are several problems involving the use of the anti Rh gamma globulin. There are two methods by which women became sensitized. One is the placental transfusion at delivery and the other is the small, multiple leaks that occur during pregnancy. If the figure of 50 - 75% becoming sensitized after delivery is accurate then theoretically the anti- D given post delivery could eliminate this group. However, what about the other 25-50% who became sensitized during pregnancy? If the anti D gamma globulin is given all through pregnancy will it cross the placenta and attach its foetal cells in utero? Another problem is the amount of anti-D that should be given.

It now remains to evaluate the anti - D globulin in clinical trials, prove or disprove its worth and if found effective develop a routine method of treatment so that it can be put into general use.