1944

Role of the Rh factor in the etiology of abortion and miscarriage

James Pfeiffer Gill
University of Nebraska Medical Center

THE ROLE OF THE RH FACTOR IN THE ETIOLOGY OF ABORTION AND MISCARRIAGE

By James P. Gill

Senior Thesis
Presented to

The College of Medicine

University of Nebraska

Omaha

1944

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Introduction

Recent discoveries regarding the interaction of certain inherited blood differences have given a new realization of the dangers of isoimmunization reactions between mother and fetus. One dominantly inherited agglutinable factor of the red blood cells- the so-called Rh factor- has been shown to be responsible for a specific disease of the newborn, and evidence is accumulating that this factor, and possibly interaction between other incompatible blood types in mother and fetus, may be a cause of repeated abortions and of stillbirths in apparently normal women. It is too soon to assay the full implications of these develop-ments in genetics and the pathology of inherited blood incompatibilities, but enough is known to suggest very strikingly that they are possibly a factor in the causa-tion of abortions, stillbirths, and perhaps certain other morbid conditions of the neonatal period.

In this paper I shall present the published findings of those workers who have investigated the Rh factor, using only that prt of their material which connects Rh incompatability with the problem of abortion and mis-carriage. In so doing I have narrowed the field to quite some extent, since most of the work which has been done to date emphasizes the role of the Rh factor

as an etiological factor in erythroblastosis fetalis as seen in the near or full-term child. However, I believe that enough light has been thrown on the pos-sible interrelations of Rh and abortion as to make such a review of interest to the obstetrician.

In presenting the collected material I have included only a brief summary of the pathology and heritability of the Rh factor, together with a few statements of the current opinion on the pathology and etiology of abortion and miscarriage.

Finally, I have attempted to evaluate the work done so far, and to present possible clinical applications of the findings.

History

Universal edema of the fetus, or hydrops fetalis, which presents so definite an abnormality, has been recognized for centuries. In 1898 Ballantyne (2) collected seventy cases from the literature since 1614. The hematological picture was added by Schridde (16) in 1910, and Rautman (16) named the disease erythroblastosis in 1912. Icterus of the newborn has also been observed for centuries, but it remained for Blomfield (4) in 1901 to differentiate physiological jaundice from icterus gravis. Even as late as 1908 Pfannenstiel (16) held that icterus gravis was an intensification of physiolo-gical jaundice. The familial nature of icterus gravis was noted by Buchan and Comrie (6), and they also called attention to the large numbers of nucleated red blood cells in the circulating blood as well as to the hematopoesis in the liver and spleen. Ultimately, icterus gravis was included in the syndrome of erythro-blastosis. Macklin (26) published an exhaustive study in 1937 in which the three diseases were definitely proved as belonging to one syndrome- erythroblastosis, icterus neonatorum gravis, and hydrops fetalis. Anemia of the newborn, the most recently described addition to the syndrome, has received emphasis through detailed observations of the changes in the blood occuring shortly after birth.

The Rh factor was discovered and so named by Landsteiner and Weiner (19) in 1940. With the blood of Macacus rhesus monkeys they immunized rabbits whose sera would then not only agglutinate the blood of the monkeys but also the blood of about eighty-five per cent of human beings regardless of their blood groups. Thus the symbol "Rh" was derived from Rhesus. Shortly thereafter some observations were made by Wiener and Peters (38) in connection with the origin of atypical agglutinins which were held responsible for serious intra-group transfusion accidents in pregnant women. Levine, Katzin, and Burnham (8) pointed out its association with erythroblastosis fetalis. Their investigations yielded proof that isoimmunization of the mother was the essential feature in the pathogenesis of this specific familial disease of the fetus and of the newborn infant. Clinically it was already known that mothers of erythroblastotic infants have a higher than normal incidence of spontaneous abortions. Although the causation of erythroblastosis fetalis was unknown at the time, it was suspected that the same mechanism could also operate in the early fetal period. Gardiner and Yerushalmy (11), in 1939 and 1941, observed that there is a familial tendency to stillbirths and neonatal deaths, and write as follows: "One may speculate that among other things, the father may also

play an important part in these cases of repeated loss to the family." "It may therefore be indicated that the study of infant loss should embrace also factors in the father. This seems to be especially important in the cases of habitual abortions and in cases of families in which many infants have been lost through stillbirths and neonatal morbidity."

Pathogenesis and Heritability of the Rh Factor

Our present knowledge of the Rh factor indicates that it is an antigenic substance in human red blood cells similar in some respects to other antigenic factors, such as A, B, M, and N. Apparently it occurs only in the red blood cells, similar in this respect to the factors M and N, but different from A and B, which occur in the tissues and secretions of some persons (23).

Recent findings suggest differences between the Rh factor in monkeys and man, and between various human bloods possibly similar in nature to the subgroups A and A two. Normally there are agglutinins in the serum against the factors A and B, but there are no normal agglutinins against the Rh factor in man and the same is essentially true of the factors M and N, as only five instances of normal anti-M isoagglutinins have been reported. However, the Rh factor has the ability to cause isoimmunization, while the M and N do not have this ability and are, therefore, of no significance in blood transfusions. In other words, when persons whose blood does not contain the Rh factor (Rh negative) receive Rh positive blood, they may develop agglutinins against it. The Rh factor, like the factors Am B, M, and N, is inherited as a Mendelian dominant characteristic (19). It is not sex-linked

and there is an equal distribution between the sexes. In matings where both man and woman are Rh positive one may expect four to eight per cent of all the child-ren to be Rh negative. In matings with one parent Rh negative and the other Rh positive about twenty-eight per cent of all their children should be Rh negative. All children of matings in which both parents are Rh negative should be Rh negative. In the case of an Rh negative mother and an Rh positive father who is homozygous, (RhRh), all his offspring must be Rh positive. When the Rh positive father is heterozygous (Rhrh), and the mother Rh negative, fifty per cent of the offspring will be Rh positive.

The following chart graphically presents the possibilities:

Heredity of Erythroblastosis Fetalis Depends on Heredity of Rh Factor

1. Rh inherited as Mendelian dominant /

2. Dominant gene.....Rh

   Recessive allele.....rh

3. Three genotypes — Two phenotypes

   RhRh homozygous
   Rhrh heterozygous } Rh positive

   rhrh recessive.....Rh negative

Significant matings..... Rh positive father with Rh negative mother.

Homozygous father

Genotypes.....RhRh with rhrh

Genes in gametes.....Rh rh

Offspring.....Rhrh
(100% Rh positive)

Every pregnancy may immunize Rh negative mother.

Heterozygous father

Genotypes.....Rhrh with rhrh

Genes in gametes.....Rh rh
rh

Offspring.....50% Rhrh
50% rhrh
(half Rh positive;
half Rh negative.)

Rh negative offspring cannot immunize Rh positive mother.

In the production of fetal pathology, the phenomenon of iso-immunization comes into play. The term iso-immunization denotes immunization within the same species. Levine et al pointed out that in most cases of erythroblastosis the mother is Rh negative and the infant as well as the father is Rh positive. Presumably, due to some defect in the placenta, some of the fetal blood passes through the placenta and in response to the antigen Rh the mother produces anti-agglutinins. These agglutinins from the mother pass back through the placenta into the fetus to cause hemolysis of its red blood cells which is apparently the basis of erythroblastosis and fetal maceration and deformity. Acccording to all present evidence (23) the Rh factor is present only in the red blood cells and therefore, there is no such protective mechanism in the tissues.

Since the Rh factor, in contrast to the blood factors A and B, is not present in body fluids (or other tissue cells) it must be the formed element itself- i. e. the red blood cell or the stroma which finds its way into the maternal circulation. Whether or not this is possible without the presence of gross lesions in the placental circulation is as yet premature to decide. Assuming that such lesions are present, the pathogenesis is of paramount importance. Theoretically

such gross lesions may be due either to environmental conditions or else to constitutional defects in the mother. In any event these lesions must recur and become operative in each succeeding pregnancy with an Rh positive fetus. However, one need not predicate the existance of gross lesions if it can be assumed that minute amounts of fetal blood acting over a long period suffice to induce an effective degree of iso-immunization (21). In that event, the question will arise whether or not this can occur under the physiologic conditions of pregnancy. Whatever the mechanism, the existence of anti-Rh agglutinins in the Rh negative mothers is a fact which has been repeatedly demonstrated.

Once anti-Rh agglutinins have been produced, they pass readily through the placental barrier to act on the susceptible Rh plus fetal blood. There is no difficulty in accepting this view since it is generally recognized that maternal antibodies are the source of the passive immunity normally observed during the neo-natal period.

This brings up the question of the exact mechanism for the release of the antigen from the red blood cell once the cell gains access to the maternal circulation. Though I have found no such clear-cut explanation, I believe it is logical to assume that the fetal red cell

breaks down in the mother's blood stream. This breakdown could be due to mechanical injury, or conceivably to some slight difference between the osmotic pressures of the maternal and fetal plasmas, plus, perhaps, some increase in fragility of the fetal red cell. The most logical explanation, as pointed out by Dr. McGoogan, is that one which takes into consideration the fact that the fetal red blood cells in the mother's blood stream undoubtedly undergo a breakdown in the mother's spleen, with the consequent release of the antigen.

The concept presented offers a suitable explanation for the markedly contrasting forms of erythroblastosis, namely the invariably fatal fetal hydrops on the one hand and the mild, frequently unrecognized anemia of the new-born on the other. Nothing is known at present as to how early in the course of pregnancy isoimmuni-zation begins. However, there is indirect evidence that fetal hydrops results from a prolonged intra-uterine action of maternal anti-Rh agglutinins, while shorter periods of this activity produce the milder forms of icterus gravis or anemia.

It is not known how early in the course of pregnancy isoim munization begins. A very early onset may be assumed since red cells form in the yolk sac as early as the fourth week. According to Kemp and Moreau (Scandenavian and French writers respectively) agglutinable factors in the blood could be demonstrated in the fetus

between the second and third month. From the point of view of the present discussion, the more fundamental property of antigenic immunizing function may be assumed to have an even earlier origin.

It is of interest to speculate why a higher incidence of early fetal death may result from isoimmunization by A and B factors than by the Rh factor. In the first place, the effects of isoimmunization by the A and B may occur earlier because anti-A and anti-B are normally present antibodies. Secondly, the specific reaction of maternal anti-A and anti-B with the excess of A and B factors in tissue cells may exert a far more lethal effect on the embryo or the fetus than the specific reaction of maternal anti-Rh on the fetal red blood cells exclusively. In the latter case, neither vital organs nor tissue cells can be affected because the Rh factor is limited to the red blood cells (21).

The Role of the Rh Factor in the Etiology of Abortion and Miscarriage

In presenting a brief for Rh as a factor in abortion and miscarriage, I believe that one should first make his contention plausible by reviewing the latest thought on the pathology of abortion and miscarriage- aside from any consideration of Rh whatsoever.

By far the most widely held of the modern concepts of the pathogenesis of abortion is that one emphasizing the "pathologic ova". This school stresses the fact that over half of all abortions are due to pathological conditions in the fetus, and as such can only be regarded as fortunate incidents. When abnormal conditions arise in the fetus, further compatibility between the parasite and its host becomes difficult and the uterus attempts to expel its contents. Rutherford (34) has made a rather exhaustive study of the problem of abortion, and in speaking of the etiology of these "pathologic ova" says: "One cannot separate those ova which represent true primary germ plasm defects from those which are inherently good and undergo an aberration of development due to defective secundines, inadequate circulation, poor implantation, local or general causes". Might it not be that Rh discrepancy is one

of the leading "general causes", and as such is an import-ant "defective secundine"?

Meaker (27), in his article entitled A Working Classification of the Causes of Abortion makes the following statement: "There is now, however, a considerable body of evidence to show that defects inherent in the germ plasma can and do cause weakness in the embryo, if not actual malformations. Lethal factors in heredity are well known in lower animals. Something closely analagous has been demonstrated in human beings by Levine and his coworkers, who find that an Rh negative pregnant woman with an Rh positive husband may produce, as a result of immunization with the Rh positive fetal blood, anti-Rh agglutinins which can penetrate the placenta and hemolyze the blood of the fetus."

In support of the pathologic ova idea, Hertig (15) found that forty-six per cent of his collection of abortuses were pathologic. In the same vein, Schultze (36) makes the statement that thirty-seven per cent of the 100,000 preventable abortions in "old Germany" yearly, developmental abnormalities were responsible. D'Esopo and Marchetti (9) have been very interested to find out if Rh has anything to do with the birth of a macerated fetus, which is so hard to examine pathologically. Thirteen per cent of their series showed death before the onset of labor;- fetuses being born in a macerated state.

The preceding statements indicate the pathologic plausibility of Rh-induced abortion and miscarriage. It remains to establish the importance of this factor in such a capacity. To do so I shall present the findings of interested investigators up to the present writing, using only those portions of their material which deal specifically with the problem.

The initial investigations on the problem were stimulated by the phenomenon of serious transfusion reactions taking place in some mothers who had been transfused with blood of their same group. The association of intragroup transfusion accidents, in the presence of atypical agglutinins, in three patients following an abortion, a miscarriage, and a stillbirth respectively, was observed in the analysis of reports by Parr and Krischner (31) in 1932, and Johnson (17) and Zacho (German) in 1936. Other instances of intra-group transfusion accidents following abortions, mis-carriages, or stillbirths, in the absence of atypical agglutinins have been reported by several authors (12, 3). All in all there were five papers written, but only two were available. However, according to Levine et al (25), the transfusion accidents reported in all five papers are very probably ultimately attributable to isoimmunization by the fetus.

Levine (25), in 1939, reported a patient who had harbored a dead fetus (group O), whose husband was also

group O. She was transfused with her husband's blood after delivery of a macerated fetus. It was shown later that the woman was Rh negative, and her husband was Rh positive. In the same paper he mentions the interesting fact that the titre of anti-Rh in isoimmunization goes down to nothing in one year.

The relationship of isoimmunization and certain pathologic states in the pregnant woman or in the fetus was pointed out by Levine together with Katzin (23) in 1941. In an analysis of twelve intra-group transfusion accidents associated with pregnancy in which atypical agglutinins were demonstrated, these authors observed a high incidence of toxemia, spontaneous abortions and miscarriages, and stillbirths in the past obstetric histories. Accordingly, it was assumed that "there does appear to be a correlation of the complications with the incidence of atypical agglutinins, and one can speculate as to their relationship".

The following table shows some of Levine, Katzin, and Burnham's work:

Outcome of 37 pregnancies in 7 Rh negative patients (Modified after Levine, Katzin, and Burnham.)

Normal babies.....10
Babies with erythroblastosis.....7
Neonatal deaths.....3
Stillbirths.....5
Abortions and Miscarriages.....10
(At least 6 spontaneous)
No data available.....2

Levine (20), in an editorial written in 1941, tells of an analysis of the obstetric histories of women who suffered from hemolytic transfusion reactions because of isoimmunization. It revealed that there was a high incidence of spontaneous abortions and miscarri-ages, stillbirths and neonatal deaths in this group. The clue to this relationship became evident when the bloods of a larger series of women giving such ob-stetric histories were studied. It was found that these women in many instances showed a striking familial incidence of babies with erythroblastosis fetalis.

In the great majority of cases, the bloods of these women were found to be negative for Rh while the bloods of their husbands and their affected infants contained this factor. In a certain proportion of the cases the mother's blood contained anti-Rh agglutinins of varying degrees of intensity.

Macklin (26) found that in families in which hydrops had been seen in some children, there is almost always a history of an undue number of miscarriages, premature births, stillbirths, births of macerated fetuses and similar anomalies. In some families of her series there had been from twelve to fourteen pregnancies, with only one living normal child as a result. All the rest of the pregnancies terminated in miscarriage or stillbirth. The following is a chart of her work:

Hydrops Fetalis

Number of families.....83

Number of pregnancies.....395

Average number of children per family.....4.8

Number of miscarriages and stillbirths.....100

Per cent of pregnancies ending in miscarriages or stillbirths....25.2

Number of children affected.....119

Per cent of all fetuses and children showing defect.....20.1
miscarriage...55.3

Pregnancies resulting in defective child or

May it be that these prematurely ending pregnancies terminated early because the fetus had inherited the factor for hydrops and had the condition in so extreme a form as to cause the pregnancy to end too early for the hydrops to be recongnized?

A record furnished by J. W. Ballantyne (2) supports the idea that hydrops is due to a mutation of the germ plasm, that it is not dependent on maternal conditions, and that miscarriages and stillbirths in families affected by hydrops are to be regarded, in part at least, as evidence of the disease rather than entirely as evidence of the action of outside forces.

This view of Macklin and Darrow is supported by the results of a study made by Levine et al (8) in 1941. That isoimmunization by the fetus and sub-sequent action of maternal agglutinins on fetal blood may be the mechanism of these abortions and stillbirths is indicated in the data presented in their Table I:

Outcome of 37 pregnancies in 7 patients, as shown in the mothers

Anti-Rh agglutinins.....6

Transfused.....5

Transfusion shock.....5

Death after transfusion (anuria).....3

Another group of women were investigated because of their history of habitual abortion and stillbirths, but these women had no infants with erythroblastosis fetalis. Many of these women were Rh negative, but they felt that satisfactory statistical analysis similar to the study on erythroblastosis was more difficult because habitual abortions and stillbirths may be manifestations

of many conditions. Nevertheless, there was sufficient evidence in at least five cases of this group to include them with the mothers of erythroblastic infants, because isoimmunization by the Rh factor in the fetus could be demonstrated. In each of these cases, anti-Rh agglutinins were observed. Three of these patients suffered from intra-group transfusion accidents following an abortion or stillbirth. Two of these five patients had just delivered presumably normal infants in spite of the presence of moderately active anti-Rh agglutinins. Unfortunately, hematologic and other clinical data were not obtained, so that a mild form of erythroblastosis could not be entirely excluded. However, the obstetric histories revealed that one of these patients had three consecutive miscarriages, and the other had two miscarriages and one premature infant who survived for ten days. In any event, it is the action of maternal immune agglutinins on the fetus which cause its death at any stage of its development so that the same mechanism may be responsible for erythroblastosis in the surviving infant as well as in some cases of habitual abortion.

Murphy (28) found that miscarriages and stillbirths, and premature births occur more often than would be expected by chance, in mothers of congenitally malformed children.

In how many of these "poor family trees" might we

find Rh discrepancies, if they had been investigated? Investigations show that as high as a twenty per cent incidence of abnormal male germ cells may be no hindrance to satisfactory reproduction (34). It doesn't seem reasonable that four-fifths of all embryos aborted at the end of the first month could have such a comparatively rare factor as a causative agent- especially when one considers the countless one-month abortions which go unrecognized. On the other hand, the availability of uncompatable Rh as an important etiological agent can be seen by using the fifteen per cent figure which has proven to be the incidence of Rh negative blood in the general population. At that rate, an Rh negarive person stands a one in five chance to marry another Rh negative person- or twelve per cent of Rh negative persons are mismated". Then, since negative Rh is only significant in the mother, due to Rh positive dominance in inheritance, we must cut that figure in half, or six per cent of all females are potential mothers of erythroblastotic infants. Taking such a purly mathematical view of the problem seems to support its importance, in my opinion.

The fact that we don't find as many clinical cases as would seem to be possible from the above method of figuring is explained very well by Potter et al (33). They say that since the Rh factor is present in approximately eighty-six per cent of the general popula-

tion, about twelve per cent of all marriages will be between couples where the wife is Rh negative and the husband Rh positive. It is in this group that the wife is capable of being sensitized to the Rh factor and of subsequently reacting on the fetus to produce erythroblastosis. Erythroblastosis, however, occurs in only a small per cent of these women;- only about one-tenth of one per cent of all pregnancies, according to Potter et al at the Chicago Lying In Hospital. To account for the difference between potential and actual incidence, they present several conditions which may contribute:

1. In childless or one-child marriages the limitation of offspring makes production of erythroblastosis impossible.
2. The Rh antigen in the infant may vary in its ability to stimulate the production of agglutinins in the maternal blood.
3. The ability of the placenta to prevent the passage of the Rh antigen may vary.
4. The maternal response to the introduction of of the Rh antigen into the blood stream may vary.
5. The ability of the placenta to permit passage of agglutinins may vary

Levine et al (22) add another factor to this list in their explanation for possible failures in cross-matching to establish incompatibility. They emphasize that Rh anti-bodies are called "warm agglutinins" because

they exhibit greater activity at 37 degrees centigrade than at 20 degrees. Thus, when doing a cross-matching, the patient's serum and donor's blood cell suspension should be incubated at 37 degrees C for 30 minutes before the mixture is centrifuged (one minute at 500 RPM) for sedimentation and subsequent resuspension. So technical failure may account for some of the dif-ference between potential and actual incidence of erythroblastosis.

It becomes apparent that although a fundamental incompatibility between the genetic constitution of the male and female germ cells may create a situation in which the occurrence of erythroblastosis becomes a possibility, there must be other superimposed factors which determine whether or not the possibility will be realized.

This explanation rather takes the sting out of their findings as to whether or not Rh can cause abortion by mechanisms other than that of erythroblastosis fetalis. In order to determine what relation fetal and neonatal deaths not due to erythroblastosis may have to the Rh factor in the mother, the blood of forty-five women women whose pregnancies ended in abortions, and thirty-six whose infants were stillborn or died shortly after birth from causes other than erythroblastosis were examined (Potter). Of those with abortions thirty-four were positive to all sera, five were negative to all sera,

six were negative to one or two sera. Of those with later deaths twenty-seven were positive to all sera, four were negative to all sera, five were negative to one or two sera. The blood of twenty-nine husbands had been examined; all but two were Rh positive. One of those who was Rh negative was the father of a baby with erythroblastosis. An explanation for this last fact throws me.

The blood of fifty-nine infants and fetuses was tested. Only six were Rh negative. In three of these the mother was Rh positive; in three Rh negative. In one of the latter cases where the mother and infant were both Rh negative the diagnosis was erythroblastosis and the mother exhibited anti-Rh agglutinins. (Nine of the mothers of this group of infants were not tested.)

Among all of the mothers in their series who had babies with definite evidence of erythroblastosis ninety per cent were Rh negative; among all of those with abortions or deaths from other causes only twenty-five per cent were Rh negative. This would seem to indicate that the Rh factor is of little importance in association with fetal deaths due to causes other than erythro-blastosis.

Schwartz and Levine (37) make the statement "From case histories one surmises that women who have infants with erythroblastosis fetalis also have a high indidence of spontaneous abortions, thereby suggesting a role for

the Rh factor in the etiology of abortions." With this in mind, nine mothers were examined who had two or more early abortions in succession. Eight of these mothers were Rh positive. By the mechanism of erythroblastosis fetalis the Rh factor not uncommonly causes death of the fetus in the second trimester and thereby produces a late abortion. These preliminary studies indicate, however, that the Rh factor is unimportant in the etiology of early abortions. This is rather surprising since the Rh factor can be shown to be present in the very early fetus.

Potter (33), in a paper read before the Society for Pediatric Research in 1942 made the statement that in one of her series blood was obtained from forty-five women who had had spontaneous abortions. Seventy-five per cent were Rh positive. When one considers that eighty-five per cent of the general population are Rh positive, it makes the figures significant.

Levine, in his article "Serological Factors as Possible Causes in Spontaneous Abortions" (21) approaches the problem from an interesting angle. He reasons as follows:

"Granted that the specific Rh factor in fetal blood may immunize the mother with resulting path-ologic affects on the fetus or infant, the question naturally arises: why may not isoimmunization brought about by other fetal blood factors also terminate in

morbid conditions of the fetus and the new-born? This issue is pertinent because so little is known about the large group of early and late fetal deaths, especially in view of the great individuality of human blood resulting from the permutations and combinations of several well described hereditary blood factors aside from Rh, such as A and B, M, N, P, and still others."

He goes on to present evidence showing that the factors A and B in fetal erythrocytes may actually immunize others who lack these factors, and that this actually may result in abortions and stillbirths. With the facts he presents he proves his case very well, and yet goes on to make the statement: "In comparison with the clear-cut relationship of the Rh factor and erythroblastosis fetalis, the evidence that factors A and B do cause abortions and stillbirths through isoimmunization is <u>not as convincing.</u> However, the statistical proof for the pathogenesis of erythroblastosis fetalis is so thoroughly established that it serves indirectly to support to a considerable degree the concept of isoimmunization by A, B, or other factors. Furthermore, the general procedure for obtaining proof of fetal and neonatal morbidity by isoimmunization by other blood factors does not differ in principle from that found so effective in the Rh studies on erythroblastosis fetalis; thus, the concept assumes an importance far greater than its low incidence would seem to justify.

From the preceding statements, I believe that one can gather that Dr. Levine considers Rh-produced abortions an established entity. And his opinions are as valuable as anyone's in the field.

There is one final aspect of the problem to be considered- that of toxemia. For if toxemia can in any way be shown to be connected with the Rh factor, then we must add to the toll of Rh incompatibility the many fetal deaths due to theraputic abortion, as well as those brought about by spontaneous abortion. In so doing, the importance of Rh isoimmunization in fetal death would be considerably magnified.

A number of years ago several workers (30) claimed that eclampsia was in some way related to a blood incompatibility of the fetus and mother. In 1902 Flexner (German) suggested that the agglutination of red blood corpuscles was the precipitating cause of the thrombosis which produced the periportal necrosis of eclampsia. In 1905 Dienst (German) suggested that the fetal red blood cells can enter the maternal circulation, and be agglutinated. McQuarrie (29) and Allen (1), independently at the Johns Hopkins Hospital studied the question of iso-agglutination of the fetal and maternal blood and came to opposite conclusions. John Whitridge Williams (39) did not believe that fetal blood entered the maternal circulation and appears to have discouraged further work

along this line. Nevertheless, we now know that the fetal red blood cells can enter the maternal circulation, at least in minute quantities which nevertheless suffice for the isoimmunization. That maternal anti-bodies enter the fetal circulation is a fact that has long been accepted.

With our present knowledge of isoimmunization it would seem plausible that fetal erythrocytes might be agglutinated in the maternal circulation by specific agglutinins produced by the immunized mother, and thereby cause liver and kidney damage with the ensuing symptoms of pre-eclampsia and eclampsia. With this theory in mind the blood of two eclamptic mothers was investigated by Schwartz and Levine (37). Both were Rh positive. In addition, five cases of severe pre-eclampsia were studied, and in four the maternal blood was Rh posi-tive. Hence, the above theory is apparently disproved at ast for some cases of specific toxemia of preg-nancy. Yet, of the seven definite cases of erythro-blastosis fetalis in their series, in five the mother had mild to moderate pre-eclampsia. In this connection it of interest to recall the observation of Hellman and Hartig (13) and Javert (16), that one third of mothers of infants with fetal hydrops suffer from toxic symptoms.

They do not as yet feel that the theory of isoimmunization as the important factor in the etiology

of eclampsia should be discarded without further investigation. Further studies are indicated taking into account also the possibility of isoimmunization by blood factors other than Rh.

One final statement I can make is to quote Leroy W. Schaefer (35), who in 1943 reviewed the present knowledge of the Rh factor and its significance. He says, "There is considerable evidence indicating that this factor is responsible for many stillbirths and spontaneous abortions."

Diagnosis

Determining the existance or importance of a pathological status is, of course, in itself valueless. A workable program of prevention or treatment is the aspect which all previous investigation leads up to. However, since the emphasis in this paper has been on the establishment of the importance of Rh incompatabilities, the subjects of diagnosis and treat-ment take a secondary position. So it is that I shall give only a summary of some of the more important work which has been done with this phase of the question.

A correct antepart m diagnosis of erythroblastosis neonatorum was made by Javert (16) in eight out of ten cases. The signs having the greatest value in the ten cases in which intrauterine diagnosis was attempted are as follows:

1. Multiparity, ten cases
2. Excessive uterine enlargement (hydramnios) six cases.
3. Amniotic fluid, yellow-brown, six cases
4. Premature labor, six cases
5. Nationality (Irish) six cases (Larger families through lack of birth control?)
6. Icterus index increased, five cases
7. Erythroblastosis in a previous infant, four cases

8. Toxemia of pregnancy, four cases

9. Fetal distress, before or during labor, three cases

10. Intruterine death of the fetus, three cases

11. Systolic bruit of fetal heart heard in the uterus, three cases

12. Aspiration of cord blood before delivery (prolapsed cord), one case

13. X-ray examination of fetus while within the uterus (seven cases studied), two cases

To recapitulate, multiparity and excessive uterine enlargement beyond the duration of gestation were valuable criteria, while the previous obstetrical history was less important. The X-ray was found to be among the least aids. Its use is limited to the hydrops cases. Javert et al (27) took their first roentgenogram in an effort to detect edema of the scalp. It was not successful. Subsequently, they studied seven cases; two proved to have infants with icterus, and five with hydrops. The edema of the scalp, or so called "halo", as reported by Hellman and Irving (14) in 1938, was seen in only two hydrops cases. However, these and other cases showed a Buddha or frog-like habitus of the child which may be attributed to the enlarged fetal abdomen and hydrothorax. The roentgenogram in another case revealed a very large placenta. The large placenta together with fetal movements within the uterus makes reontgenological demonstration of

the "halo" and fetal habitus rather difficult. They came to place greater reliance on the Buddha position and recommend anteroposterior and lateral plates to show the posture of the child in suspected hydrops cases. Antepartum diagnosis may be facilitated by maternal and paternal blood studies for the Rh factor if the results are interpreted with the history and clinical data presented.

Treatment

No specific treatment, as such, has been evolved for erythroblastosis fetalis. If a specific ante-partum medication could be discovered for erythroblast-osis which even approached that for congenital syphilis, it would mean much in the prevention of abortion.

Javert et al (16) have employed in turn a high protein, high vitamin diet, iodine, and iron, vitamin B one, Brewer's yeast, calcium and injections of liver, vitamin B complex, "copperin Z", and clacium, without affecting the outcome. Bonney and Morton (5) used potassium chlorate, calcium, and wheat germ ante-natally, but the infant had erythroblastosis. From this evidence, it appears that it has not been possible as yet to prevent the disease in the unborn child.

Javert (16) finds that the evaluation of any antepartum therapy is difficult since he had four mothers give birth to normal infants following a previous child with erythroblasosis without special treatment. He treated three mothers with frequent knjections of synthetic vitamin K (thyloquinone) during the antenatal period; they having had previous infants with erythro-blastosis, and each delivered a child with the icterus type of the disease, one of which died. Antepartum transfusions have been considered on the basis that if they are of benefit to the child after

delivery, they may be of value before delivery. I have found no records of the results of such experiments however.

The induction of premature labor has been advocated by Diamond (16) in order to remove the child from its pernicious environment, and also so that transfusions can be given properly. Javert does not agree with this procedure because he feels that there is no adequate method for inducing labor without added risk to the infant. Furthermore, prematurity in an infant with erythroblastosis is undesirable, for the hydrops infants are often a month or more before term, and they have a mortality rate of one hundred per cent, while the icterus gravis infants are at or near term and have a lower rate of fifty-four per cent.

Therapeutic abortion should never be performed in mothers with previous erythroblastotic infants, on that indication alone. However, with the recurrence at fifty per cent for mothers who developed erythroblastosis in previous pregnancies, and nearly one hundred per cent when the first born is affected, erythroblastosis should receive attention from this point of view. In certain instances, contraception and adoption of a child may be desirable.

Artificial insemination is frowned upon because of the increasing incidence of erythroblastosis once it has

appeared, and because paternal investigation has revealed no abnormality. Furthermore, in Hilgenberg's (16) case, a mother had several normal children by her first husband and after remarriage had babies with icterus gravis. In Smith's (16) case, a man with a normal child by his first wife had children with icterus gravis by a second wife. However, artificial insemination with donor and recipient of the same blood group and Rh negative seems to merit investigation.

Everything taken together, perhaps the most valuable treatment so far known is one of prophylaxis.

Summary

1. The obstetric histories of mothers of erythroblastotic infants reveal a high incidence of abortions and miscarriages.

2. The blood of a significantly high percentage of women suffering from abortions and miscarriages reveals the presence of specific anti-Rh agglutinins.

3. Rh has little to do with abortions caused by other conditions than erythroblastosis in the fetus.

4. Rh incompatibility is unimportant in the etiology of early abortions, but is significant in the etiology of late abortions.

5. Rh as a factor in the etiology of toxemia is promising, but requires further investigation.

6. Antepartum diagnosis of erythroblastosis is possible.

7. There is no specific treatment for abortion due to Rh discrepancy, but prevention offers an excellent method for avoiding the condition.

8. Abortion is not inevitable in all Rh mismatings. There are a number of factors which modify the outcome.

Conclusion

From the foregoing review of work done on Rh as a factor in the etiology of abortions and miscarriages it is evident that such incompatibility accounts for many late abortions. As such it is of interest to the obstetrician in that he can advise couples of potentially erythroblastotic children as to the possibility of unsuccessful pregnancies. The fact that no specific treatment has yet been evolved for the condition makes its recognition none the less important. In fact, the lack of available treatment makes a forknowledge of possible abortion due to erythroblastosis fetalis all the more necessary.

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