THE ANTEPARTUM PREDICTION OF HEMOLYTIC DISEASE OF THE NEWBORN*

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DESPITE the intensive researches on the relationship of erythroblastosis fetalis to the Rh factor, the obstetrician is handicapped because he is unable to forecast the outcome of pregnancy in Rh-negative women. Not only is he in doubt about the presence or absence of erythroblastosis fetalis in utero, but he is also unable to predict its gravity when there are reasonable clinical indications that it may exist. As will be shown in a separate communication,[1] the mere existence of either anti-Rh agglutinins or "blocking antibodies" in the maternal serum antepartum—whether these substances increase, decrease, or disappear—is not necessarily correlated with the existence of hemolytic disease of the newborn, nor with its severity.

The present study is confined to an analysis of an apparent correlation between the duration of exposure of the fetus to maternal Rh antibodies and the prognosis for the newborn child. Inspection of these data discloses a partial answer to the obstetrician's dilemma. The material subjected to analysis was selected from a sample of over 4,000 pregnant women seen in the obstetric clinic of the University of California Hospital and in the private practices of six obstetricians, who submitted regular antepartum blood samples for study. The blood serum from each patient was tested for agglutinating antibodies against two Rh negative group O, and two Rh positive group O red blood corpuscle suspensions. The presence of blocking antibodies was determined by the method of Wiener.[2]

In the majority of instances, the first blood sample was not obtained until the third trimester of pregnancy. Thus, when antibodies were found at this time, it was impossible to know when they had first appeared. The appearance time, however, could be dated in 26 cases, and it was immediately apparent that no cases of erythroblastosis occurred when the antepartum duration of antibodies was ten weeks or less. In all cases, the "appearance time" was estimated to be midway between the time of the last negative sample and the time of the first positive sample. In the remaining material, it was therefore logical to exclude all cases in which the first blood sample had been obtained less than ten weeks before delivery, but to include those in which the first positive sample was obtained "more than eleven weeks" or "more than sixteen weeks," et cetera, before parturition.

After such exclusion, 49 cases remained for analysis. By inspection, it was noted that in 19, only "traces" of either agglutinating or blocking antibodies had been found, or there had been an isolated finding of a small ("one plus"

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or "partial") amount of either type of antibody which was unconfirmed by subsequent and repeated tests. Only one case of possible erythroblastosis fetalis occurred in this group, that of a baby who had a slight increase in the number of nucleated red blood cells at birth, and who suffered from a mild anemia which did not require transfusions.

In the remaining 30 cases, appreciable amounts of antibodies were found, or small amounts were present on repeated occasions. In 22 of these cases, the antibodies appeared more than ten weeks before delivery, and all 16 cases of erythroblastosis fetalis were found in this group. The remaining six women were delivered of normal infants, four of whom proved to be Rh-negative children of mothers who had been previously sensitized, and presumably this pregnancy had elicited a nonspecific anamnestic recall of Rh antibodies. Unfortunately, there was no way of differentiating antepartum the mothers of these four cases from those who were carrying Rh-positive infants. The remaining two exceptions cannot be explained.

TABLE I. THE RELATIONSHIP OF THE APPEARANCE TIME OF RH ANTIBODIES BEFORE DELIVERY TO THE OCCURRENCE AND SEVERITY OF HEMOLYTIC DISEASE OF THE NEWBORN

ANTIBODY APPEARANCE (NO. WEEKS ANTEPARTUM)	CASES WITH "TRACES" OR AN ISOLATED SMALL AMOUNT OF ANTI-RH OR BLOCKING SUBSTANCE	CASES WITH LARGER AMOUNTS OF ANTIBODIES, OR WITH SMALL AMOUNTS WHICH WERE REPEATEDLY CONFIRMED*	
		Rh+ infants	Rh− infants
1 to 9	8—All normal	7—All normal	1—normal
10 to 14	3—All normal	8 { 1 normal; 3 "subclinical"; 4 icterus gravis (3 deaths) }	2—Both normal
15 to 36	8 { 7 normal; 1 questionable "subclinical" }	10 { 1 normal; 1 hemolytic anemia; 1 icterus gravis; 7 hydrops fetalis (7 deaths) }	2—Both normal

*Cases with positive antibodies on first samples obtained less than ten weeks before delivery were excluded (see text).

The results of classifying these cases as described are summarized in Table I. The influence of the appearance time of antibodies upon the prognosis is further emphasized when the ten- to fourteen-week period is studied separately from the fifteen- to thirty-six-week period. Hemolytic disease of the newborn varies in its severity from the mildest subclinical variety through the simple, though often severe, anemia to the "icterus gravis" form, in which there is widespread pigment deposition at birth, and finally to the universally fatal "hydrops fetalis" with its widespread visceral damage and generalized edema. All of the mild (subclinical) cases occurred in the ten- to fourteen-week group. Of the eight Rh-positive babies in this group, seven had hemolytic disease, and of these, three died of icterus gravis. On the other hand, *all seven cases of fatal hydrops fetalis were found in the 10 Rh positive infants* of the group in which maternal antibodies had appeared at least *fifteen weeks* or more before the delivery.

If such figures as these are confirmed by subsequent study of a larger series, it becomes obvious that the induction of premature labor is unnecessary when

Rh antibodies first appear less than ten weeks from term, and probably useless when they appear more than fifteen weeks from the time selected for induction of labor. The termination of pregnancy by conservative means and prompt transfusion* of the anemic child at birth should result in a higher survival of infants only in that small group of mothers wherein antibodies appear for the first time ten to sixteen weeks before the estimated date of confinement. Beyond that period, any attempt to reduce the exposure to ten weeks or less would probably result in the loss of the child from prematurity, or from a combination of prematurity and erythroblastosis. Eleven of the cases included in this study were primigravid women, and in all but one the antibodies appeared late in pregnancy, which probably explains why first babies characteristically, but not invariably, escape the disease.

These findings may be summarized and translated into tentative suggestions for the management of obstetric patients as follows:

Ideally, all pregnant women should be typed routinely, regardless of parity, and in those Rh-negative patients having Rh-positive husbands, the first sample of blood for antibody determination should be obtained not later than the twenty-fourth week of pregnancy. If this be strongly positive for either agglutinating or blocking antibodies, an Rh-positive fetus will probably be too seriously affected by hemolytic disease to warrant any interference before term, while an Rh-negative fetus will escape the disease. As yet, there is no way to distinguish these possibilities except to prove that the father is homozygous for the Rh factor. If the antibodies are present only in "traces," or if a small amount is found on a single determination and is unconfirmed by subsequent tests, the fetus is probably unaffected, and again it would be unwise to interfere.

If the initial sample is free of antibodies, but a significant amount appears later, a period of eight to ten weeks may be allowed to pass before hemolytic disease becomes a probability. After this time, induction of labor might be warranted providing the expected date of confinement is within the ensuing six weeks.

That a relationship exists between the duration of exposure to maternal antibodies and the fetal prognosis seems apparent. Further study may alter the critical time periods established by the data of this preliminary analysis.

References

1. Howard, Joan, and S. P. Lucia: (Unpublished data).
2. Wiener, Alexander S.: Proc. Soc. Exper. Biol. & Med. 56: 173, 1944.

*It is recommended that an immediate slow transfusion of 50 to 75 c.c. of Rh-negative group O blood be given into the umbilical vein.