Is a Third-Trimester Antibody Screen in Rh+ Women Necessary?

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Abstract

Objective: **To determine the need for routine third-trimester antibody screening in Rh+ women.**

Study Design: **An analytic case-control study.**

Methods: **We identified Rh+ pregnant women who had received prenatal care and retrospectively analyzed their laboratory data. Patients were grouped into those with a positive third-trimester antibody screen (cases) and those with a negative third-trimester screen (controls). Because entry into a group was decided by the investigators, it could not be randomized. We reviewed the maternal medical records for antibody identification and final pregnancy outcome. We also reviewed the neonatal medical records for evidence of direct Coombs-positive cord blood, anemia, need for transfusion or phototherapy, other medical complications, and death.**

Results: **Using a computerized laboratory database from 2 teaching hospitals, we identified 10,581 obstetric patients who underwent routine first- and third-trimester antibody screening between 1988 and 1997. Of these, 1233 patients were Rh- and 9348 were Rh+. Among the Rh+ patients, 178 (1.9%) had 1 or more atypical antibodies at the first-trimester screen, and 53 (0.6%) had a positive third-trimester antibody screen despite a negative first-trimester screen. Although 6 of these 53 patients (0.06% of the study population) had clinically relevant antibodies for hemolytic disease of the newborn, no significant neonatal sequelae occurred among these 6 patients.**

Conclusion: **Based on the patient and hospital records studied, a repeat third-trimester antibody screen for Rh+ patients is clinically and economically unjustified. Eliminating this laboratory test from clinical practice will not adversely affect pregnancy outcomes and will decrease the costs of prenatal care.**

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Despite the introduction of Rh immunoglobulin in 1968, hemolytic disease of the newborn (HDN) remains a serious concern. Fetomaternal hemorrhage exposes the mother to foreign red cell antigens, which can lead to an immune response in the mother. Prior maternal transfusion can also lead to development of subsequent HDN. The reported overall incidence of HDN is 10.6 cases per 10,000 deliveries, with a wide geographic variation.[1]

Although more than 60 antigens can cause HDN, the most common cause is Rh sensitization.[2] This

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occurs when an Rh- mother becomes sensitized to Rh+ blood through a prior pregnancy or transfusion and develops antibodies against the Rh (D) antigen. These antibodies can cross the placenta during a subsequent pregnancy and cause hemolysis, heart failure, hydrops in utero, and hyperbilirubinemia after birth. Since the introduction of Rh immunoglobulin and its use in prevention programs, the incidence of HDN resulting from Rh sensitization has decreased significantly.

Hemolytic disease of the newborn can also be caused by less common atypical antibodies, which can cross the placenta and affect the fetus in a similar fashion.[3,4] Severe fetal disease due to these atypical antibodies is rare. A combined incidence of severe fetal disease of 0.1% to 2% has been reported.[5-7] The incidence of atypical antibodies in Rh+ pregnant women is low, with a reported incidence between 0.01% and 1.3%.[7] Nevertheless, HDN with atypical antibodies remains a potential problem because prophylaxis is not yet available. Management of these pregnancies is similar to that of Rh- isoimmunized pregnancies.

Routine antibody screening is recommended in North America for all pregnant patients at their first prenatal visit.[8] Rh- patients are routinely rescreened at 28 weeks' gestation because of the risk of a transplacental bleed leading to interim sensitization. Despite a lack of documented utility, some institutions in the United States, Sweden, France, and Australia also rescreen Rh+ women at 28 weeks, irrespective of a prior negative screen. Such practice may be unnecessary and not in keeping with current clinical guidelines but is left over from the earliest recommendations when screening programs were first initiated. This practice may be rooted in a concern for a potentially serious and treatable, although rare, occurrence, namely, becoming sensitized to atypical antigens. Many retrospective studies have shown favorable neonatal outcomes in fetuses despite exposure to atypical antibodies in utero.[5,9-15]

Some investigators have questioned the need for screening Rh+ obstetric patients for atypical antibodies[5] because of the lack of clinical utility. Still others recommend screening only patients with known risk factors for atypical antibodies, such as a prior blood transfusion, cesarean section, or abortion.[6] This is a substantial group, and many women may not disclose prior obstetric history. According to the *Guidelines for Perinatal Care,*[12] which are endorsed by the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics, antibody screening in Rh+ pregnant women should be routinely performed once during pregnancy, preferably in the first trimester.

We undertook a historical cohort control study to determine: (1) the incidence of atypical antibodies in Rh+ obstetric patients at our institution; (2) the number of newly identified antibodies on repeat screen; (3) the clinical significance of these antibodies; and (4) briefly address the economic impact of eliminating repeat screening in Rh+ patients.

···METHODS ···

We obtained medical records from a computerized blood bank laboratory database at 2 teaching hospitals, Indiana University Hospital and Wishard Memorial Hospital. Indiana University Hospital is a tertiary care referral center for the state of Indiana. Wishard Memorial Hospital is a public hospital in metropolitan Marion County, which provides care to a socially, educationally, and economically disadvantaged population. Under a protocol in accordance with Indiana University Institutional Review Board guidelines, we examined the records of pregnant women who received prenatal care and delivered between 1988 and 1997. Patients were included in the study if first- and third-trimester screens were both available, records were complete, and prenatal care was started before the end of the first trimester. Patients who met the inclusion criteria were grouped into those with a positive third-trimester antibody screen (cases) and those with a negative third-trimester screen (controls).

We reviewed the medical records of all Rh+ obstetric patients with atypical antibodies for antibody identification, maternal observation during pregnancy, and pregnancy outcome. The respective neonatal medical records were analyzed for evidence of direct Coombs-positive cord blood, anemia, need for transfusion or phototherapy, other medical complications, and death. For patients who had more than 1 pregnancy during the study period, we included only 1 first- and third-trimester antibody determination if the screens were identical for all pregnancies. Our selection was not randomized, and all patients were accepted if the data were complete. Any Rh+ patient with a positive screen during her pregnancy was included in the study for further analysis.

Data for the project was gathered using a proprietary computer system in use at Indiana University.

The Regenstrief Medical Record System[16] operates on a VAX computer from Digital Equipment Corporation. The system captures data in a relational analytic database, which supports many programs for capturing and reporting data. We used the "Fast Retrieval" program to identify female patients with a delivery date inclusive in the years of the study. A cutoff of age greater than 8 years was used to remove all newborn data. From this cohort, we collected the antibody screen data and the gestational age at the time of the screening test. These data were linked with the ABO group and Rh status present on any date. We also searched for any blood bank alert associated with the identity of a particular patient. Once these data were collected, we reviewed the corresponding hospital charts of both the mother and the newborn. This review allowed detailed data collection of both maternal and neonatal outcome in patients with a positive antibody screen.

···RESULTS ···

A total of 13,494 patients who delivered between 1988 and 1997 were identified. Of these, 2913 were ineligible for the study because of incomplete medical records, lack of a first-trimester antibody screen, or late presentation for prenatal care. From the cohort of 10,581 eligible patients, 1233 patients (11.7%) were Rh- and 9348 patients (88.3%) were Rh+. Among the 9348 Rh+ patients, 178 patients (1.9%) had 1 or more atypical antibodies (222 antibodies total) on repeat screening in the third trimester (Table 1). Lewis a and Lewis b were the most common antibodies identified, seen in 79.2% of these patients. The laboratory could not identify approximately 15% of the antibodies found. Of the 222 atypical antibodies identified, 38 antibodies (17%) known to be capable of causing HDN were identified in 35 women (Table 2). The specific frequencies for these antibodies were anti-M (IgG) 6.2%, anti-Kell 4.5%, anti-E 2.2%, anti-Fya 2.2%, anti-Jka 2.2%, anti-s 1.1%, anti-C 0.6%, anti-Cw 0.6%, and anti-Lan 0.6%.

Among the 35 women with clinically relevant antibodies, 1 patient with Duffy (Fya) sensitization underwent percutaneous umbilical blood transfusion 3 times. Subsequent preterm labor resulted, and the patient delivered a healthy infant at 32 weeks' gestation. Four other patients (including 1 with a twin gestation) required a total of 13 amniocenteses during pregnancy for rising antibody titers. These pregnancies resulted in 4 healthy, unaffected infants (one requiring phototherapy) and 1 in utero death of a twin affected by both anti-E and anti-s who succumbed to sepsis.

Of the 9348 Rh+ patients identified with a negative first-trimester antibody screen, 53 patients (0.6%) had a positive third-trimester screen (Table 3). Among these 53 patients, 6 (0.06%) had clinically relevant antibodies for HDN. None of these 6

Table 1. Type of Atypical Antibodies Identified in 178 Rh+ Patients

Antibody Type		No. of Patients (%)	
Lewis	a	101	(56.7)
	b	40	(22.5)
I		1	(0.6)
Al		1	(0.6)
Kell	K	6	(3.4)
	Kpa	2	(1.1)
Rh (non-D)	E	6	(3.4)
	C	1	(0.6)
	Cw	1	(0.6)
Duffy (Fya)		4	(2.2)
Kidd (Jka)		4	(2.2)
M	IgM	6	(3.4)
	IgG	11	(6.2)
s		2	(1.1)
Lutheran		0	(0)
Lan		1	(0.6)
P-1		3	(1.7)
JMH		1	(0.6)
Nonspecific	cold	4	(2.2)
Unidentified		27	(15.2)
Total		**222***	

*Patients could have more than one atypical antibody.

Table 2. Type of Clinically Significant Antibody Identified and Outcome of 35 Rh+ Patients

Antibody Type	No. of Antibodies	No. of Patients	Amnio/ PUBT	Positive Cord Blood Serology	Treatment	Death
Kell K	6	6	Amnio x4	1		
Kpa	2	2				
E & s	4	1*	Amnio x4	1		1
E	4	4				
C	1	1				
Cw	1	1				
Duffy (Fya)	4	4	PUBT x3	1	Transfusion	
Kidd (Jka)	4	4				
M (IgG)	11	11				
Lan	1	1	Amnio x1	1		
Total	**38**	**35**				

Amnio = amniocentesis; PUBT = percutaneous umbilical blood transfusion.
*Patient had a twin gestation.

Table 3. Type of Atypical Antibody Identified and Outcome of 53 Rh+ Patients with Negative First-Trimester and Positive Third-Trimester Screens

Antibody Type		No. of Patients	Positive Cord Blood Serology
Lewis	a	29	
	b	9	
I		1	
Kell	K	1	
	Kpa	0	
Rh (non-D)	E	1	
	C	0	
	Cw	0	
Duffy (Fya)		0	
Kidd (Jka)		3	1
M	IgM	1	
	IgG	8	
Nonspecific	cold	0	
Unidentified		0	
Total		**53**	

patients required ante- or intrapartum intervention or suffered neonatal clinical sequelae.

···DISCUSSION ···

Hemolytic disease of the newborn resulting from atypical antibodies is a rare phenomenon,[5,10,17] occurring in approximately 0.1% to 2% of pregnancies.[5-7] Yet although the incidence of Rh isoimmunization has been decreasing because of prevention programs, the prevalence of blood groups other than Rh is becoming a more common cause of HDN.[3,17] Most of this type of alloimmunization is caused by previous transfusion in the mother. Rh+ women without evidence of atypical antibodies early in pregnancy are not likely to develop these antibodies as their pregnancy progresses. Furthermore, because we cannot prevent the development of antibodies, there is no reason for repeat testing in this group of women.

Currently, more than 60 different red blood cell antigens have been reported to potentially cause HDN,[18] ranging from mild to severe disease. Of

these, the most important are anti-K, -Jka, -Jsa, -Jsb, -Ku, -Fya, -M, -N, -s, -U, -PP1Pk, -Dib, -Lan, -LW, -Far, -Good, -Wra, and -Zd. Women who are found to be immunized against any blood group antigen should be managed as if they are Rh- and have Rh isoimmunization. The women in our study did not differ significantly from those included in previously published studies[5,10,16] with regard to frequency, outcome or atypical antibodies found. Indeed, anti-M and anti-K were the most common atypical antibodies found in our study (6.2% and 4.5%, respectively).

The overall frequency of atypical antibodies in this study was 1.9%. From the total of 9348 Rh+ patients studied with a negative, first-trimester screen, there was 1 fetal death associated with anti-E isoimmunization. The anti-E isoimmunization in this twin fetus was noted on the first antibody screen performed, but the fetus died of sepsis at 28 weeks' gestation.

Screening all Rh+ obstetric patients for atypical antibodies once during pregnancy is appropriate, because isoimmunization resulting from atypical antibodies can be successfully managed antenatally via amniocentesis and percutaneous umbilical blood transfusion.[15,19] Because no good guidelines are available for managing Rh+ patients with atypical antibodies, these patients are treated according to the guidelines established for Rh- patients.[15,20,21] In our institution, screening for atypical antibodies in Rh+ pregnant patients is performed twice during pregnancy. Similar screening programs have been in place for years at many other institutions.[10,11,22] Yet in our study, repeat screening of Rh+ patients had no impact on intrapartum management or neonatal sequelae. In addition, this practice cannot be financially justified. Assuming an average of $32.00 per antibody screen, and an additional $64.00 for antibody identification, a model of hospital charges revealed that a total of $341,984.00 had been charged over the 9-year course of our study period. This amount was spent to identify 6 antibodies on repeat screening, which were of no clinical significance and did not change the outcome of the pregnancy.

We found that repeat third-trimester screening of Rh+ patients who have a negative first-trimester screen is unjustified, on both medical and financial grounds. Our findings are in agreement with current recommendations for clinical practice.[12] Repeat third-trimester antibody screening of Rh+ obstetric patients provides little useful information and does not affect pregnancy outcome.

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