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Abstract

Prior to the 1970s and the advent of Rho (D) immune globulin (RIG) for Rh negative women, hemolytic disease of the newborn led to morbidity, long-term disabilities, and mortality. Antepartum RIG administration has been a standard of practice since 1983. Yet, Rh isoimmunization (sensitization) and its sequelae have not been

completely eradicated. Rh-related issues remain clinical challenges facing perinatal and neonatal nurses. Evidence for the administration of RIG prenatally and during the postpartum period is presented including controversies and challenges. Current information about fetal and neonatal care of erythroblastosis fetalis and immune hydrops is also presented.

RH isoimmunization is the leading cause of maternal sensitization. [1,2] While there is extensive information on Rh isoimmunization in the medical literature, there is limited practical information in the nursing literature. Knowledge of the nursing management and prevention of Rh isoimmunization is of interest to perinatal and neonatal nurses. However, it can be difficult to maintain competency in this complex body of knowledge because Rh isoimmunization is a relatively rare event. Therefore opportunities to apply this information into clinical practice are infrequent.

The purpose of this article is to present nursing management of Rh isoimmunization through the use of case-based learning. The principles of adult learning suggest that professionals can review existing knowledge and apply new knowledge optimally if it is presented in the context of real-life situations. Case-based learning provides opportunities for the application of information to clinical practice.

Under usual circumstances, maternal and fetal circulations remain distinct and separate throughout pregnancy. There is however an intimate relationship between the fetal capillary bed and the maternal circulatory system with a delicate vascular exchange taking place within the placenta. [3] Alterations in this balanced system can create problems for pregnancies. If maternal and fetal blood comingle because of a feto-maternal hemorrhage (FMH) with even a small amount of fetal blood entering the maternal system, a maternal-fetal blood incompatibility can develop.

A common and potentially serious type of maternal-fetal blood incompatibility is that of the Rhesus D antigen. The Rhesus factor was so named because testing in Rhesus monkeys first identified it. Rh incompatibility can occur when the fetus is Rh positive with erythrocytes that contain D antigen but the mother has the absence of the D antigen on circulating erythrocytes and is therefore considered Rh negative. [2,4] Specifically, if a FMH occurs when an Rh negative mother is carrying an Rh positive fetus, her immune system reacts to the antigen and forms an antibody to eliminate it. This process is called *Rh isoimmunization*, [5] also commonly referred to as *sensitization*. The causative factor leading to Rh isoimmunization is called the *sensitizing event*. Once maternal anti-D antibodies have formed, they cross the placenta, attach to fetal red blood cells (RBCs), and hemolyze the fetal RBCs. Since the time of the classic works that described Rh isoimmunization, it has remained difficult to predict maternal isoimmunization because each woman's response is individualized and depends on several factors, including the type of antigen, the strength of the antigen in stimulating the antibody response, the amount of antigen, the maternal immune response, the blood type of the infant, and the gestational age of the fetus. [2,6,7] Once sensitized, the immune response worsens with each subsequent incompatible pregnancy. [2]

Approximately 15% of all pregnant women are Rh negative. [2] According to Bowman's classic work, [8] approximately 17% of these Rh negative women would become isoimmunized perinatally without preventative measures. Of those isoimmunized, 90% of cases would occur at the time of birth and 10% in the antepartum period because of FMH. Most of these antepartum FMH occur following the 28th week of gestation. [9,10] These sensitizing events are common occurrences in the perinatal cycle, and therefore, the risk of Rh sensitization is relatively high if preventive intervention does not occur. If the fetus is Rh positive and no preventative measures are taken, 0.7% to 1.8% of Rh negative women may experience prenatal isoimmunization. [8]Figure 1 depicts the process of isoimmunization.
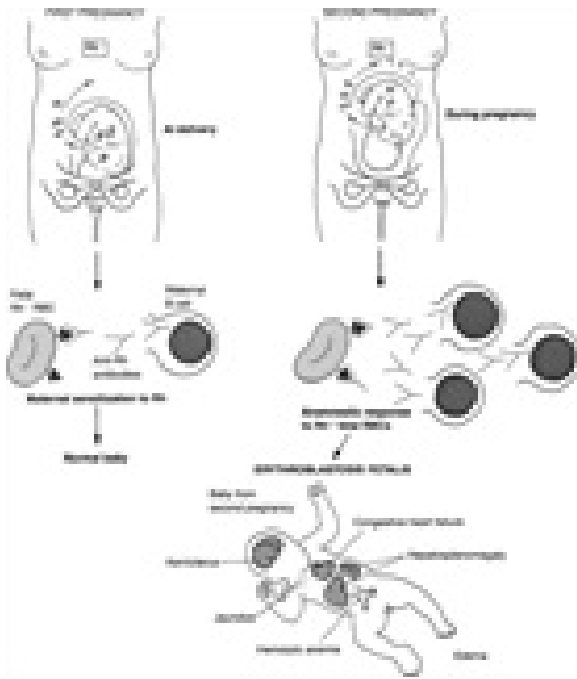
Fig 1. Pathogenesis of Rh hemolytic disease of the newborn. Reprinted with permission from reference[11]. Artist: Dimitri Karemikov.

Antepartum Rho (D) immune globulin (RIG) is protective against the effects of FMH. A small amount of fetal blood can enter the maternal circulation most often during the birth process, particularly during operative deliveries. FMH may also occur during spontaneous or elective abortion, vaginal bleeding during late pregnancy, trauma, antepartum hemorrhage, fetal death, and stillbirth. Invasive procedures, such as amniocentesis, chorionic villus sampling, cordocentesis, and fetal manipulation, such as external version and fetal surgery, may also lead to maternal exposure to fetal blood. [9,12] However, FMH can occur in the absence of observable trauma, risk, or surgery. [1] Most FMHs that occur at any point in pregnancy or during low-risk childbirth involve less than 0.1 mL of fetal blood entering the maternal circulation. [1] Fortunately, major FMH leading to fetal mortality is a rare occurrence. Overall, large FMHs of 30 mL or more occur in 0.1% to 0.7% of cases, but their incidence increases with complicated operative cesarean or vaginal births (1.7% to 2.5%) and stillbirths (4.5%). [13] However, even a small FMH can lead to negative sequelae when the mother and fetus have incompatible blood types.

The exact amount of fetal blood necessary to mount an immune reaction is somewhat elusive. Rh isoimmunization can occur during a first pregnancy if an FMH occurs and the volume is significant. [10] For example, anti-D antibodies develop in Rh negative women in response to exposure to Rh positive blood, with the probability of exposure directly related to antigen quantity. [3,14] Further, subsequent individual maternal antibody responses can increase in response to smaller subsequent volumes of fetal cells. [15]However, some women do not respond to a single-dose antigen exposure and other exposed individuals do not become immunized even after repeated exposures to the antigen. [4,7]

PATHOPHYSIOLOGY OF HEMOLYTIC DISEASE OF THE NEWBORN

Hemolytic disease of the newborn (HDN) develops when an Rh negative woman who has experienced Rh isoimmunization subsequently becomes pregnant with an Rh positive fetus. The maternal antibodies cross the placenta into the fetal circulation and begin to hemolyze fetal erythroblasts. The maternal antibodies are detectable unbound in fetal serum and are also absorbed into D positive erythrocytes. [1] The absorbed

antibodies function as hemolysins, leading to erythroblastosis fetalis. Erythroblastosis fetalis is the accelerated destruction of fetal RBCs leading to severe fetal anemia and HDN. Characteristics that are predictive of HDN (as shown in Fig 1) include the presence of ascites, edema, polyhydramnios, placental thickness of more than 4 cm, pleural and pericordial effusion, dilation of the cardiac chambers, chronic enlargement of the spleen and liver, and dilation of the umbilical vein. [2,15] Immune hydrops occurs when pathological changes develop in the organs of the fetus and newborn because of this severe fetal anemia. Immune hydrops accounts for 13% of all causes of fetal hydrops. [16] The signs of immune hydrops vary with severity and may include fetal subcutaneous edema, effusion of fluid into body cavities, pulmonary hemorrhages, and enlargement of the fetal liver, spleen, and heart, as well as the placenta. Edema of the fetus and placenta can become significant enough for immune hydrops to be identifiable on prenatal ultrasound. [1,4] At birth, the newborn may demonstrate ascites, hepatomegaly, and splenomegaly. HDN and its consequences can lead to significant morbidity and mortality, and therefore, prevention of maternal sensitization is imperative.

Rho (D) IMMUNE GLOBULIN

RIG has been available in the United States since before 1970 and is widely used. Neonatal deaths and morbidity due to Rh sensitization have decreased dramatically since its introduction. According to the Center for Disease Control and Prevention, [17] the incidence of Rh HDN was 40.5 per 10,000 births in 1970. Today, the incidence has dropped to less than 5 cases per 10,000 births. This reduction is not completely attributable to RIG. The trends toward smaller family sizes and changing population demographics have also contributed to a natural decline in the incidence of Rh isoimmunization. [14] When antepartum or postpartum RIG are administered according to accepted guidelines, the rate of isoimmunization is reduced to approximately 0.1% [18] or approximately 1% of the natural risk. [19] Despite these marked improvements, neonatal morbidity and mortality due to Rh sensitization remain a clinical challenge.

TESTING FOR FMH AND Rh ISOIMMUNIZATION

Several maternal blood tests are used for identification and management of Rh negative women. The indirect Coombs, more commonly referred to as the *antibody titer*, is used to detect the presence and amount of anti-D antibody in the maternal circulation. Antibody screening is recommended during routine prenatal care and is especially important for the care of Rh negative women. If the antibody screen is negative, the woman has not been sensitized. However, if the indirect Coombs is positive, serial quantitative levels are drawn to detect and follow patterns of change. Laboratory variation exists with regard to titers, and therefore values that represent fetal risk are laboratory specific. [15] In general, titers of greater than 1:4 represent isoimmunization and titers exceeding 1:16 signal concern for the development of fetal hydrops, with risk increasing as titer values rise. [15]

Several tests are used to detect and quantify FMH. The most common of these is the Kleihauer-Betke (KB). The KB is used to estimate the presence and the amount of fetal RBCs in the maternal circulation following FMH. It was originally introduced to adjust the dosing of RIG. Currently, it is most commonly used to identify and quantify FMH. [20] The KB can detect even small amounts of RBCs that have crossed from the fetal intravascular compartment across the placenta through the intervillous spaces into the mother's circulation. [20] The formula is as follows:

$$\text{Fetal red cells} = \frac{\text{maternal blood volume} \times \text{maternal hematocrit} \times \% \text{ fetal cells in KBT}}{\text{newborn hematocrit}}$$

$$= \frac{\text{maternal blood volume} \times \text{maternal hematocrit} \times \text{\% fetal cells in KBT}}{\text{newborn hematocrit}}$$

The clinical use of KB is not without controversy and challenges. The American College of Obstetricians and Gynecologists (ACOG) recommends that the test be used in the management of all Rh negative women. [9] However, accuracy, sensitivity, and reliability problems exist. Therefore, the test is not routinely used in clinical practice. [15] In fact, KB tends to overestimate the dosage of RIG to be administered. [21] Further, the relationship of the findings to clinical management decisions and outcomes is not completely clear in the scientific literature. [22] A common use of KB is for the assessment and management of Rh negative women after motor vehicle accidents and other abdominal traumas. [9]

Other tests less commonly used to detect or quantify FMH are the erythrocyte rosette test, the enzyme-linked antiglobulin test, and flow cytometry. Each of these tests has different attributes and limitations. If any of these tests is positive on initial screen, the amount of the FMH is then estimated in order to determine the recommended dose of RIG. [21]

Case 1: S.T.

S.T. is a 26-year-old G2P1 who presents for a follow-up appointment after her first prenatal visit because of a positive antibody titer. S.T. was seen for her first pregnancy when she was 18 years old and her complete medical record is available for review. Her blood type is Rh negative. Her antibody titer is positive to 1:4 dilutions. S.T. states that she had many social problems during her first pregnancy and was "out of control" as a teenager. She had an antibody titer drawn at the initial prenatal visit at 34 weeks during her previous pregnancy that was negative. She did not have antepartum RIG because she failed to return for care. According to records, her first child was preterm and born by Cesarean for an abruption at 36 weeks gestational age. The baby spent 2 days in the neonatal intensive care unit (NICU) for transition and observation. According to the surgical records, S.T. lost approximately 1200 mL of blood and had a postpartum hemoglobin of 8 g/dL and a hematocrit of 24%. She received the standard dose 300 μg of RIG on the second postoperative day and was discharged without infection, transfusion, or further complications.

During the explanation of the laboratory findings with S.T., both she and her husband questioned how she could have been sensitized during her first pregnancy. Despite the marked success of RIG, postpartum-only administration has resulted in a failure rate of 1% to 2%. [15] In 1983, ACOG recommended routine antepartum RIG prophylaxis to Rh negative women at 28 weeks gestation for every pregnancy, including the first, to further reduce the development of antibodies. [4,9,10] The administration of 300 μg RIG at 28 weeks gestation, followed by postpartum administration of 300 μg within 72 hours of birth, was found highly effective in reducing the risk of Rh isoimmunization to 0.2%. [4,9,15] S.T.'s isoimmunization may represent this small RIG failure rate. [15]

Most current cases of isoimmunization are due to failure to administer RIG to appropriate candidates according to accepted guidelines following birth, elective or spontaneous abortion, amniocentesis, other potentially sensitizing events, or during the antepartum period. [9] Based on S.T.'s history, it appears that she had received the accepted RIG dosage during her postpartum hospitalization. Because of her lack of attendance at prenatal care, S.T. did not receive antepartum RIG.

The lack of administration of antepartum RIG may have contributed to S.T.'s isoimmunization; however, a more plausible explanation appears to be the massive FMH that may have occurred at the time of her abruption, emergency cesarean, and immediate hemorrhage. The standard 300 μg dose of RIG that is administered to women for various reasons may be inadequate because the amount of FMH is rarely measured

accurately. [7,23] The failure to identify and treat massive FMH is an ongoing clinical problem that leads to neonatal HDN. [2,8,21] Previously, it was recommended that KB be used for women considered at high risk for FMH, for example, those having abdominal trauma, abruption, placenta previa, multiple gestation, or manual removal of the placenta. However, this approach missed half of the large FMHs. Therefore, according to ACOG, [9] the American Association of Blood Banks currently recommends the use of KB for all Rh negative women who deliver Rh positive infants to estimate the amount of FMH and determine the amount of RIG that should be administered. However, the extent of use of this clinical protocol is unknown. Dosing of RIG is relatively standardized in the United States. In general, to prevent Rh isoimmunization, 10 µg of RIG is given for every milliliter of fetal blood that enters the maternal circulation. [4] Therefore, a mini dose of RIG (50 µg) covers 5 mL of D-positive fetal whole blood. Enough antibodies are contained in the standard 300 µg dose of RIG to prevent maternal sensitization of exposure up to roughly 30 mL of whole fetal blood or 15 mL of fetal cells [7,9] and will prevent most Rh negative women from becoming sensitized. If, however, the FMH is estimated to be more than 30 mL, as may have been the case in S.T.'s situation, a second ampule of RIG can be administered. [15]Theoretically, the dosage of RIG can be adjusted depending on the amount of exposure to Rh positive blood as calculated by KB. However, as noted, current dosage recommendations are fairly standardized based on sensitizing events [7] and KB is not always used to determine RIG dosing.

S.T. was isoimmunized but with a titer of 1:4 there was a low risk of fetal effects. She also lacked a history of an affected fetus or neonate by Rh sensitization. [9] S.T. was followed with repeat antibody titers at 20 weeks and then at 2- to 4-week intervals throughout the pregnancy. [2] In the case of S.T., her 20, 24, and 28 week titers remained 1:4 until 32 weeks when they rose to 1:8. However, since the levels stabilized at 1:8, amniocentesis was not required. S.T. delivered without complications at 38 weeks. Because S.T. was already isoimmunized, she did not receive antepartum or postpartum RIG.

The management of an Rh-sensitized woman during pregnancy is one that requires ongoing surveillance of the mother and fetus. The next case will explore the comprehensive management plan for a more seriously isoimmunized woman. Women with antibody titers greater than 1:8 generally require close surveillance, [4] but when serial titers rise to the level of 1:16 to 1:32 by indirect Coombs test, interventions such as nonstress testing and amniocentesis would generally be indicated. [2,15] Perinatal nurses often participate in the coordination and planning of care for sensitized women as part of collaborative practice within the perinatal team.

Case 2: V.S.

V.S. is a 36-year-old Caucasian G7P5015 who is 12 weeks pregnant and presenting for prenatal care. V.S. was identified as Rh negative and had received antepartum and postpartum RIG during each of her 5 full-term pregnancies. During a missionary trip to China 2 years ago she experienced a spontaneous abortion. She did not receive health care because she was in a remote village. She estimated that she was 14 weeks pregnant at the time of her loss and did not receive RIG. At V.S.'s initial prenatal visit her indirect Coombs was positive with an antibody titer of 1:8 for anti-D. In this case, the second trimester loss probably caused an FMH that led to isoimmunization. Although V.S. generally avoided intervention in her previous pregnancies, both she and her husband wanted to do everything possible to maximize the health of their developing infant.

V.S. had an ultrasound at 18 weeks to confirm gestational age and to survey anatomy because of V.S.'s advanced maternal age. The plan of care included, in addition to serial antibody titers, serial ultrasounds to observe for characteristics of fetal hydrops that can be identified using this technology. However, the relationship between these findings and the severity of hemolytic disease or fetal hydrops has not been demonstrated conclusively by research. [2] Doppler flow studies, examining mainly the middle cerebral artery, are also sometimes used. These flow studies have been researched extensively and are being used to manage the prenatal care of women whose pregnancies are complicated. [4]Unfortunately, there is overlap in Doppler flow values for the normal fetus

and the severely affected fetus of a sensitized mother. [2] However, the technology of ultrasound and Doppler flow studies is advancing rapidly and may soon be more useful in diagnosing the degree of fetal anemia.

Initially V.S.'s antibody titers remained stable at 1:8 and, fortunately, her fetus did not demonstrate signs of fetal hydrops at the 18, 22, or 24 week ultrasounds, where average growth was also noted. However, at 26 weeks gestation, V.S.'s antibody titers rose to 1:16. A decision was made to immediately proceed with an amniocentesis in order to perform an amniotic fluid spectrophotometric measurement for bilirubin levels. [2,15] The perinatal nurse counseled V.S. and provided support during the procedure. The amniocentesis was performed under sterile conditions and was guided by ultrasound. Further, the fetus was reevaluated for signs of immune fetal hydrops at the time of the procedure. [4]

The amniotic fluid appeared light yellow in color. The optical density of the amniotic fluid was measured using the Liley technique [4] to determine the fetal risk of erythroblastosis fetalis. Maternal-fetal management is based on a plot of the optical density of the amniotic fluid to determine the Liley zone. Fetal risk is 95% predictable based on the Liley zone and therefore this information can guide management decisions. With worsening disease and rising bilirubin levels in the amniotic fluid, the severity of fetal compromise increases, as measured in zones of the Liley Graph:

- o Zone I – unaffected fetus or mildly affected fetus

- o Zone II – fetus with mild to severe anemia, prognosis is fair but includes risk of stillbirth

- o Zone III – severe anemia, fetal death could occur within 7 to 10 days if not transfused or delivered. [2,4]

Because V.S.'s amniotic fluid results were rated in the lower part of Zone II, a plan was made to repeat an amniocentesis every 2 to 4 weeks. Repeated measures using the Liley method are more reliable in assessing fetal condition than is a single measure. [15] If the values rise higher into Zone II or into Zone III, especially prior to 30 weeks, further interventions are needed.

V.S. began antenatal testing at 32 weeks with biweekly nonstress tests (NSTs) and weekly biophysical profiles (BPPs) that are generally recommended in the literature. [9,24] A nonreactive NST was observed. The fetal monitor tracing was scrutinized for patterns associated with fetal anemia, chiefly a nonreactive tracing, or one that includes late decelerations (Fig 2), or that demonstrates a sinusoidal rhythm (Fig 3).
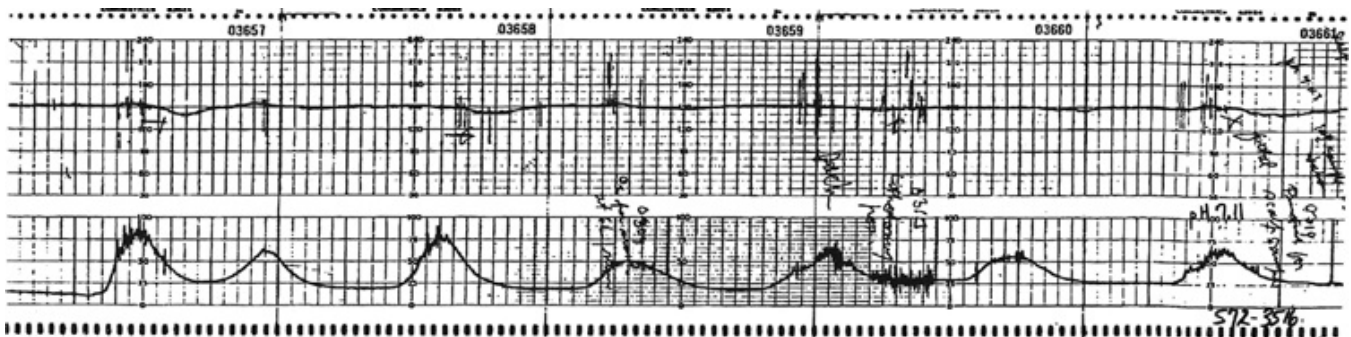

Fig 2 Persistent late decelerations associated with a severely compromised fetus. Reprinted with permission from reference[25].
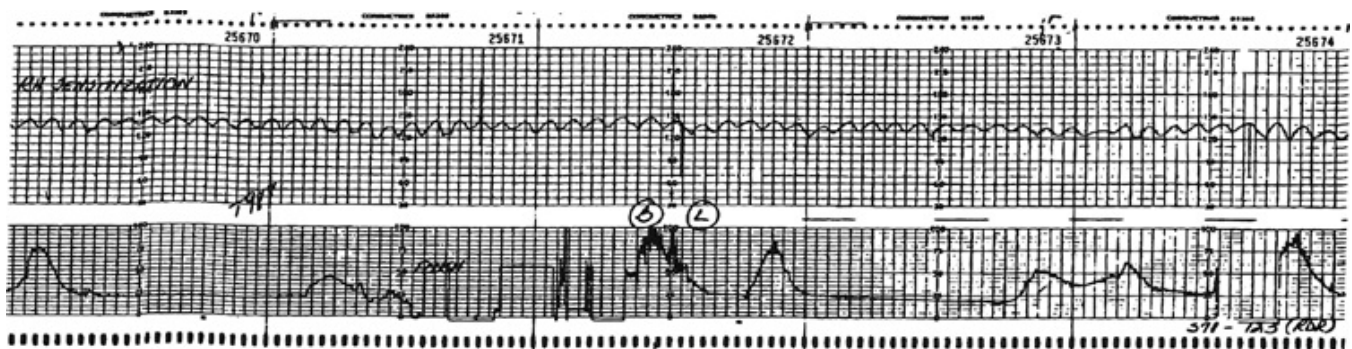
Fig 3 The sinusoidal heart rate pattern associated with severe fetal anemia. Reprinted with permission from reference[26].

These patterns also may indicate the absence of autonomic nervous system control of cardiac function, heart failure, or hypoxia. [6] For V.S. there were no accelerations of fetal heart tones on the NST but there were also no late decelerations or sinusoidal pattern. [27]A BPP was conducted and the result was 8/10. [28] Therefore, V.S. was sent home with follow-up appointments for biweekly antenatal testing.

At 33 weeks V.S. reported decreased fetal movement. Once again her NST was nonreactive, and the BPP was 4/10. The physician made a decision to perform an immediate amniocentesis under ultrasound to evaluate the amniotic fluid and to simultaneously visually screen for characteristics of immune fetal hydrops. A fetus that is ill enough to demonstrate hydrops on ultrasound examination will generally have a hematocrit of less than 15% [2] although specific values indicating the need for intervention are controversial. V.S.'s fetus had no signs of hydrops but had moved higher into Liley Zone II. It was determined that there was a need for immediate intrauterine fetal transfusion (IUFT). The goal of IUFT is to correct the anemia and improve fetal oxygenation, therefore improving the health of the developing fetus. IUFT intravascularly has a fetal survival rate of greater than 90%. IUFT can be performed intravascularly, intraperitoneally, or the 2 methods may be combined. [24] Although invasive and not without risk, IUFT is an essential intervention that has improved the health of infants with erythroblastosis fetalis. In general, intravascular transfusion is the preferred method, unless it is technically impossible. [15]

The perinatal nurse has an important role in IUFT. These responsibilities include carefully monitoring both the mother and the fetus before, during, and after the procedure, and obtaining the fresh, irradiated, cytomegalovirus-negative, group O, Rh negative blood, cross-matched against maternal serum, that needs to be available. [29] During an intrauterine transfusion, blood is infused and removed in small amounts through a vein or artery. IUFT was repeated every 2 weeks in this case to avoid fetal hydrops [2] until 36 weeks gestation. A decision was made to induce V.S.'s labor 2 weeks later at 38 weeks. [4,15,30]

Fetuses that are severely affected by erythroblastosis fetalis are at risk for intrauterine fetal death. Since the 1960s, preterm induction of labor dramatically decreased the incidence of perinatal deaths due to HDN. [31] Prior to the use of IUFT, preterm delivery was the only management option for the care of affected fetuses. The use of IUFT has helped to prolong pregnancy and, coupled with improvements in neonatal care, survival has dramatically improved. [15]

The optimal gestational age for delivery is somewhat controversial [15] but delivery prior to 32 weeks is not recommended. [24] The decision for delivery of a sensitized woman carrying an affected fetus is based on several factors including the gestational age, lecithin-sphingomyelin (L-S) ratio, presence or absence of phosphatidylglycerol (PG), the severity of fetal anemia, and the presence of immune hydrops. [24] The ultimate

decision of timing of delivery would be by the perinatal team managing the sensitized woman. [24] For example, in cases of mild hemolysis, induction of labor is generally recommended at 37 to 38 weeks unless lung maturity has been documented earlier. If the Liley Zone falls into the severe range (III), the amniotic fluid can be analyzed for fetal lung maturity to help determine optimal timing for delivery. The risks of preterm delivery are weighed against the benefits. When the fetus is severely affected early in the third trimester, the last transfusion may be timed for 30 to 32 weeks, with delivery planned for 32 to 34 weeks to maximize fetal survival and lung maturity. Fetal lung maturation is not accelerated nor suppressed by HDN. [15] Therefore, if the fetus is delivered prematurely, steroids can be administered to the mother to hasten fetal lung maturity. [4] Induction of labor with an unfavorable cervix increases the risk of cesarean delivery. Therefore if the cervix is not favorable (Bishop's score <8), cervical ripening is recommended prior to induction. [4,15,32]

A tertiary care facility that includes a NICU is the optimal intrapartum setting. The sensitized woman is considered high risk and therefore continuous electronic fetal monitoring during labor is recommended with use of an internal fetal scalp electrode as soon as is feasible. [15] This affords the opportunity to recognize fetal heart rate patterns that may indicate fetal compromise. The fetus should be observed closely for a sinusoidal rhythm or persistent late decelerations during labor. Figures 2 and 3 represent examples of these patterns.

If either of these fetal heart rate patterns occur, appropriate nursing interventions are needed to maximize fetal oxygenation and recognition of the need for further intervention. [33] Operative delivery may be indicated to accelerate the birth if fetal labor intolerance or fetal compromise are suspected. [15] In cases of fetal hydrops, labor dystocia and birth trauma is also a crucial consideration. Conservative management of labor may be appropriate because of the possibility of the larger abdominal circumference of hydropic infants. If the labor is prolonged, intervention by Cesarean may be required. Severely affected neonates will benefit from the care of a multidisciplinary neonatal resuscitation team. [34] Following birth the umbilical cord should be clamped without delay. [15] Fetal cord blood is drawn routinely at delivery for Rh and direct Coombs.

The perinatal team met with V.S. and her husband and decided to perform the last IUFT at 36 weeks and induce labor at 38 weeks. V.S. was admitted and her Bishop Score was only 4. She was given prostaglandins vaginally for cervical ripening, followed by pitocin induction. She was carefully monitored during labor in the tertiary care center and delivered a 7-lb 4-oz viable male infant. Because of the careful antepartum management the infant did not experience fetal hydrops, and the birth was relatively uneventful.

There is dramatic variation among infants born to sensitized mothers, depending on the nature of the maternal immune response and degree of fetal anemia. [29] Anemic neonates born to sensitized mothers require special care. A severely affected live-born infant will appear pale, edematous, and limp, and require immediate neonatal resuscitation.

The multidisciplinary health care team caring for a severely affected fetus that has failed to respond to intrauterine therapy will need to be prepared for complex neonatal resuscitation. The hydropic newborn may need high frequency ventilation and the placement of chest tubes to ensure adequate ventilation. [34] This infant may also need umbilical-artery and umbilical-vein lines to aid in resuscitation. [35] In addition to these measures, the hydropic infant may need blood products, albumin, and/or diuretics to maintain intravascular volume. The newborn may also require the administration of sodium bicarbonate, 1 to 2 mEq/kg, to reverse acidosis. In addition, blood sugar monitoring is necessary because of the possibility of hyperinsulinism and hypertrophy of the pancreatic islet cells. [29] Following stabilization after birth, transportation to the NICU is indicated.

The newborn's cord blood hemoglobin, reticulocyte count, and serum unconjugated bilirubin should be measured to determine the need for exchange transfusion. [36] The decision to perform an exchange transfusion is determined by the degree of risk for rapid development of severe anemia and/or hyperbilirubinemia. An

exchange transfusion is done to increase the RBC count and decrease the levels of circulating bilirubin. The cord blood hemoglobin and serum bilirubin levels will guide the management. Hemoglobin concentrations of less than 13 g/dL or serum bilirubin concentrations of greater than 4 mg/dL indicates the need for exchange transfusion. [36] Infants who have received IUFT rarely require neonatal exchange transfusion. However, blood transfusions are commonly used to manage severely affected anemic infants. [24]

Jaundice may be absent at birth but evident within a few hours, particularly for anemic neonates. Before treating the infant, a Coombs test should be obtained. The direct Coombs test is generally positive in affected infants who also are severely anemic. Direct and indirect bilirubin levels will also need to be monitored closely. Jaundice should be managed aggressively with transfusions and phototherapy. If the levels of bilirubin rapidly increase, the infant is at risk for kernicterus. [1] Untreated kernicterus can damage the newborn's central nervous system, especially in a preterm infant. An infant who survives kernicterus may develop spasticity, muscular incoordination, and the possibility of mental retardation. [1] Therefore, prompt identification of and intervention for severe jaundice within the first 12 hours following birth is an essential component of nursing care.

A NICU nurse evaluated V.S.'s infant in the birthing room. V.S.'s infant's cord blood hemoglobin was greater than 13 g/dL and the bilirubin was less than 4 mg/dL; therefore, exchange transfusion was not initially necessary. Since the baby was stable and not experiencing any difficulty, he was given to the mother for bonding and breastfeeding. After birth, bilirubin levels were followed serially to guide the management decisions regarding the need for transfusion. [24,36] Serum bilirubin levels need to be monitored closely until they begin to fall. [29] V.S's baby did become jaundiced within 12 hours of birth and was managed with phototherapy and 2 transfusions. [30] The infant was discharged at 4 days of age. After discharge, weekly hematocrit and reticulocyte levels were checked for 8 weeks. [24] If anemia had persisted, additional blood transfusions would have been required. [34]

With appropriate perinatal and neonatal management, the pregnancy outcome was good. The pregnancy became much more technological than S.V. desired but she understood this was essential to the infant's survival. She did not receive postpartum RIG because she was already isoimmunized. Following more discussion with the perinatal team, S.V. chose to have a postpartum tubal ligation. If S.V. had received RIG following her second trimester pregnancy loss, these complications may have been prevented. [37]

Case 3: W.W.

The last case will explore the nursing implications of RIG administration. W.W. is a 24-year-old G1P0. She is Caucasian and her husband is Asian. She presented for her initial prenatal visit at 8 weeks. On the initial prenatal laboratory testing it was determined that W.W. is Rh negative and had a negative antibody screen. Since that time W.W. has searched the internet and found some sources that questioned the safety and necessity of antepartum RIG. W.W. is now at 28 weeks gestation and is asking the perinatal nurse educator many questions about the efficacy, safety, and necessity of antepartum RIG. She stated that she is aware that RIG is derived from blood products and she questions the need for the injection.

The percentage of Rh negative individuals varies based on ethnicity. For example, Rh negative individuals account for approximately 13% of Caucasians, 7% to 8% of African Americans, and less than 1% of Native Americans, Inuit peoples, and members of Asian groups. [13] Because W.W.'s husband is Asian, there is a greater than 99% chance that he is Rh positive. Without knowing the blood type of the father, an Rh negative woman has as high as a two-thirds chance of becoming pregnant with an Rh positive baby. [4]

If paternity is certain and the father of the baby is known to be D-negative, the pregnant woman can be counseled to decline antepartum RIG administration. [4,9] If the father is heterozygous for Rh, the baby has a 50% chance of being Rh positive. The only way to determine if the father is heterozygous would be to know if he has

fathered any other Rh negative children or had a genotype analysis. However, routine genetic analysis is not cost-effective and therefore is not recommended for use in determining whether RIG should be administered. [2] Therefore, if the father's blood type is not known, the paternity is uncertain, or the father is Rh positive and the mother is Rh negative, RIG should be given. Alternatively, amniocentesis can be offered to the woman, because testing is available to determine the fetal genotype. [2,4] If the fetus is Rh negative, no further interventions are required. In the future, advances in genetic testing may allow selective administration to only the necessary candidates.

Informed consent with written documentation is a nursing consideration for the administration of RIG. While RIG is generally considered safe, no drug is risk free. Informed consent should include several different considerations related to administration of the drug, including possible risks. Some prenatal clients will refuse RIG administration. Counseling regarding the increased risk of prenatal sensitization and documentation of this discussion in the prenatal record are recommended. [2,38] RIG administration is based on well-designed cohort or case-controlled trials, rather than on randomized controlled trials. This means that antepartum RIG should be routinely provided to eligible candidates and that there is at least fair evidence that benefits outweigh the risks. [12,37]

Despite its success, RIG administration is somewhat controversial. Immune globulin is a blood product derived from human plasma. This may be of particular significance for women who hold religious beliefs that prohibit the use of blood products. The issue of clients who refuse blood products for religious reasons has not been addressed in the literature. During the preparation process, human plasma is screened for viruses as prescribed by the Food and Drug Administration. [4] There is a small risk of contracting a pathogen that is currently unknown and thus not included in the current screening protocol, but decades of experience with its administration have not demonstrated any deleterious effects. [37] This controversy may eventually be resolved by research that is underway using monoclonal antibody techniques to reproduce human anti-D antibody. [4] If this work is successful, the risks of exposure to impurities in the human blood supply will be completely eliminated.

Another concern is that until 2001, Thimerosal [19] was used as the preservative in RIG. A recent modification in RIG preparation has eliminated this problem. Thimerosal is a mercury derivative used as a preservative to which certain individuals who are sensitive may possibly experience potentially serious allergic reactions and potential neurologic damage to the fetus. This had raised questions from clients concerned about immunization preservatives. A number of companies market RIG. According to the Ortho Company that manufactures RhoGAM™ RIG, Thimerosol-containing syringes would have reached their expiration date by April 2003. [19] Since Thimerosal is no longer used as the preservative, concerns about its inclusion in RIG are no longer warranted.

In this case, the perinatal nurse counseled W.W. about antepartum RIG. W.W. was reluctant to accept the injection. Therefore, the nurse suggested that W.W.'s husband have a blood group and typing done. W.W. agreed that if her husband was Rh positive she would proceed with antenatal RIG. W.W.'s husband was found to be Rh positive and therefore, she agreed to receive an antepartum RIG injection at 28 weeks. The administration of RIG is a major preventative health strategy that can improve perinatal outcomes. [9,13]

RIG should remain refrigerated but not frozen prior to administration. The RIG syringe should be inspected for clarity. A cloudy appearance or the presence of particulate matter would be an indication of potential contamination. [19,39] The route of administration of RIG is also critical. To prevent Rh isoimmunization during or following pregnancy, the injection should be given intramuscularly, not intravenously. The deltoid muscle may be preferable to the gluteal muscle. [40] If the injection is given in the gluteal region it may only reach the subcutaneous tissue and absorption will be delayed. [40] According to the package insert, [19,39] women should be observed for 20 minutes following injection to detect any possible allergic reaction although they are rare. Lastly, a woman should be informed about potential side effects that most commonly include local

inflammation, malaise, chills, rashes, and in rare instances anaphylaxis. [19,39] Special consideration should be given if a woman has had past allergic reactions to any human immune globulin such as immunoglobulin A or has an immune deficiency. If a woman reacts to one dose of RIG, consultation with an immunologist is advisable prior to any future administration of RIG to the same woman. [39]

In order to identify a woman's risk for isoimmunization, a blood type, Rh, and antibody screen should be drawn at the first prenatal visit. This also identifies sensitization early if it has already occurred. Repeat antibody screening at 28 weeks is controversial. The rationale for repeat screening is to determine if sensitization has occurred since the initial antepartum Coombs test, so that care can be managed appropriately. [4] However, the likelihood of that is less than 0.18%. [23] Although the American Association of Blood Banks recommends repeat testing, ACOG recommends that the decision be individualized. [9] There is no rationale for having the woman wait for a negative antibody screen result prior to RIG administration.

Optimally, RIG should be administered at approximately 28 weeks gestation and within 72 hours of a sensitizing event. If the injection was not given within 72 hours because of an error, it still should be administered as soon as possible to provide some benefit. The half-life of RIG is 24 days. [9] The findings of one study showed that administration provided protection even when given within 9 to 10 days [39] and other authors indicated that it can provide some benefit if given up to 28 days after delivery. [8,15] If delivery occurs within 3 weeks of an antepartum injection of a standard 300 μg dose, the postpartum dose of RIG may be held [9] unless massive FMH is suspected. Further, women who had not delivered 12 weeks after the administration of antepartum RIG should receive a second dose. [15] The administration of one 300 μg antepartum dose of RIG will not result in a positive direct Coombs of the baby. Further, the use of antepartum RIG is not associated with adverse fetal outcomes. [37] If a mother is already Rh sensitized, RIG cannot prevent damage to an Rh positive fetus, and therefore it should not be administered. [41] However, if there is any doubt about maternal sensitization, RIG should be administered. [9]

NURSING IMPLICATIONS

As members of the multidisciplinary health care team, nurses share responsibility for early detection and identification, patient education, proper management, and follow-up of the mother and infant. [2] Perinatal nurses often coordinate the care of sensitized women prenatally, including antenatal testing, as well as during the intrapartum and postpartum periods. Neonatal nurses care for infants born with erythroblastosis fetalis, immune hydrops, and/or severe anemia.

For perinatal nurses involved in antenatal care, it is crucial for the nurse to obtain a complete, detailed obstetrical history at the initial prenatal visit. This is especially true when women have transferred prenatal care from one setting to another. A mother who has experienced fetal HDN is likely to experience a more severe anemia in subsequent pregnancies with Rh positive infants. [4] Continuity of care and careful record-keeping are imperative for Rh negative women at risk for Rh isoimmunization.

Perinatal nurses often interact with pregnant women for history-taking and education before any laboratory testing is completed or results known. [2] In fact, nurses often send women for ordered laboratory testing, including antibody screening, and thus they are in important positions to educate and explain the reasons for testing. If an antibody screen is positive prenatally, early diagnosis and referral to the appropriate perinatal care providers is essential. In these situations, continued interactions with the perinatal nurse can assure holistic care of the family that is experiencing an at-risk pregnancy. Frequent visits for follow-up of Rh sensitization include opportunities to interact with the perinatal nurse for further education, counseling, and support.

Additionally, the administration of RIG is most often a nursing responsibility. Nurses provide education about RIG and an identification card for the woman indicating that she is Rh negative. Further, nurses contribute to

women's understanding of the blood work and other testing that is done, including the determination of the need for postpartum RIG administration. Documentation of the nursing care and education provided is essential. [2]

Finally, neonatal nurses are responsible for knowing the mother's history and caring for the infant who may be critically ill. Nurses not only provide intensive care and follow-up for the newborn, but also educate and support the parents. The scientific literature contains reassuring longitudinal outcome data that nurses can share with parents. For example, studies of long-term outcomes for children who were treated with IUFT demonstrated favorable neurologic development. [42,43] Parents may experiences a variety of emotions, including fear and guilt, and they benefit from the support and guidance of the nursing staff. Fostering continuity of care for the families of critically ill infants can be helpful.

In summary, perinatal and neonatal nurses have significant roles in the prevention, identification, assessment, and care of women, fetuses, and infants at risk for Rh isoimmunization problems. Nurses can help to prevent negative sequelae by contributing to surveillance and collaborating with physicians as a part of the multidisciplinary perinatal health care team. Once sensitization is identified, perinatal and neonatal nurses can positively impact the care of high-risk pregnancies and neonates.

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CE Test

Rh Negative Status and Isoimmunization Update

Instructions:

- Read the article on page 166.

- Take the test, recording your answers in the test answers section (Section B) of the CE enrollment form. Each question has only one correct answer.

- Complete registration information (Section A) and course evaluation (Section C).

- Mail completed test with registration fee to: Lippincott Williams & Wilkins, CE Depart., 16th Floor, 345 Hudson Street, New York, NY 10014.

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CE TEST QUESTIONS

General Purpose: To provide registered professional nurses with information on the controversies and challenges surrounding the administration of Rho (D) immune globulin (RIG) prenatally and during the postpartum period.

Learning Objectives: After reading this article and taking this test, you will be able to:

1. Discuss the development of Rh isoimmunization.

2. Explain the etiology and presentation of hemolytic disease of the newborn.

3. Outline the prevention and management of Rh isoimmunization.

1. Rh isoimmunization is the process of
   a. maternal antibody formation.
   b. feto-maternal hemorrhage.
   c. co-mingling of fetal and maternal blood.
   d. vascular exchange within the placenta.

2. Rh isoimmunization most often occurs
   a. during the first trimester of pregnancy.
   b. during the second trimester of pregnancy.
   c. during the third trimester of pregnancy.
   d. at the time of birth.

3. Most feto-maternal hemorrhages
   a. involve less than 0.1 mL of fetal blood mixing with maternal blood.
   b. occur in the 12th week of gestation.
   c. involve 30 mL or more of fetal blood mixing with maternal blood.
   d. result in significant fetal morbidity or mortality.

4. Hemolytic disease of the newborn (HDN) develops
   a. immediately after Rh isoimmunization.
   b. as a result of erythroblastosis fetalis.
   c. 24 to 48 hours after delivery.
   d. only during a first pregnancy.

5. A warning sign of HDN is
   a. ascites.
   b. constriction of the umbilical vein.
   c. oligohydramnios.
   d. placental thinning.

6. A sign of immune hydrops is
   a. hydrocephaly.
   b. hepatosplenomegaly.
   c. hypoplastic left heart syndrome.
   d. placental insufficiency.

7. Primarily due to the availability and use of Rho (D) immune globulin (RIG), the incidence of Rh hemolytic disease of the newborn is now
   a. 10.5 per 10,000 births.
   b. fewer than five per 10,000 births.
   c. about 20 per 10,000 births.
   d. 40.5 per 10,000 births.

8. The fetus is considered at risk for developing fetal hydrops if a pregnant woman's anti-D antibody titer is greater than

a. 1:2.
b. 1:4.
c. 1:10.
d. 1:16.

9. The test most often used to determine the amount of fetal blood that has entered the maternal circulation is the
a. indirect Coombs.
b. erythrocyte rosette test.
c. Kleihauer-Betke stain.
d. enzyme-linked antiglobulin test.

10. The common method of quantifying fetal blood in the maternal circulation
a. has not been used to determine the appropriate RIG dose.
b. tends to underestimate the amount of RIG required.
c. is extremely accurate in identifying the appropriate RIG dose.
d. tends to overestimate the amount of RIG required.

11. The most highly effective method of reducing the incidence of Rh hemolytic disease of the newborn is to administer RIG to Rh negative women
a. in the postpartum period following the first delivery only.
b. in the postpartum period following every delivery.
c. in the antepartum period of every pregnancy.
d. in the antepartum and postpartum periods of every pregnancy.

12. A likely explanation for RH isosensitization in a woman who had received standard dosing of RIG at the appropriate time would be
a. failure to do an anti-D antibody titer.
b. a massive feto-maternal hemorrhage.
c. placenta previa.
d. severe pregnancy-induced hypertension.

13. Delivery is warranted within seven to 10 days if amniocentesis reveals
a. Liley zone I.
b. Liley zone II.
c. Liley zone III.
d. bilirubin in the amniotic fluid.

14. Which of the following fetal heart monitoring findings indicates fetal anemia?
a. a sinusoidal rhythm
b. a reactive nonstress test pattern
c. increased variability
d. early decelerations

15. The method of choice for treating erythroblastosis fetalis is
a. immediate delivery.
b. neonatal exchange transfusion.
c. administration of high-dose RIG.
d. intrauterine fetal transfusion.

16. A subsequent pregnancy with an Rh-positive infant in a woman who has already experienced fetal HDN is most likely to result in
a. an unaffected fetus.
b. a milder case of HDN.
c. a more severe anemia.
d. premature delivery.

TableT

Journal of Perinatal and Neonatal Nursing, July–September 2003:
Rh Negative Status and Isoimmunization Update

A Registration information:

Last name_____First name_____MI_____

Address_____

City_____State_____Zip_____

Telephone_____Fax_____email_____

Registration Deadline: September 30, 2005

Contact Hours: 2.0

Fee: $14.95

AACN category: A

❏ LPN ❏ RN ❏ CNS ❏ NP ❏ CRNA ❏ CNM ❏ Other_____

Job Title_____Specialty_____

Type of facility_____

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Certified by_____

State of License (1)_____License#_____

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	A	B	C	D		A	B	C	D		A	B	C	D		A	B	C	D
1.	○	○	○	○	5.	○	○	○	○	9.	○	○	○	○	13.	○	○	○	○
2.	○	○	○	○	6.	○	○	○	○	10.	○	○	○	○	14.	○	○	○	○
3.	○	○	○	○	7.	○	○	○	○	11.	○	○	○	○	15.	○	○	○	○
4.	○	○	○	○	8.	○	○	○	○	12.	○	○	○	○	16.	○	○	○	○

C Course Evaluation*

	A	B
1. Did this CE activity's learning objectives relate to its general purpose?	❏ Yes	❏ No
2. Was the journal home study format an effective way to present the material?	❏ Yes	❏ No
3. Was the content relevant to your nursing practice?	❏ Yes	❏ No

4. How long did it take you to complete this CE activity? _____hours_____minutes

5. Suggestion for future topics_____

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Table. CE Enrollment Form.

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Keywords:

alloimmunization; case-based learning; erythoblastosis fetalis; fetal immune hydrops; Rh isoimmunization; Rh negative blood type; Rho (D) immune globulin