

Combined Tests Improve Delivery Timing in IUGR

BY PATRICE WENDLING
Chicago Bureau

DALLAS — The combination of biophysical and venous Doppler ultrasound parameters provided better timing of deliveries than did either test alone in a study of 584 fetuses with fetal growth restriction.

The prospective, multicenter observational study evaluated umbilical artery, ductus venosus and umbilical vein

Doppler flows, and biophysical parameters as predictors of stillbirth, acidemia (cord artery pH less than 7.0 and/or a base deficit of more than 12), neonatal morbidity (intraventricular hemorrhage above grade 2, bronchopulmonary dysplasia, and necrotizing colitis), and neonatal mortality.

All outcomes increased significantly with umbilical artery reversal, abnormal ductus venosus and umbilical vein Doppler, and abnormal biophysical para-

meters, Dr. Ahmet Baschat and associates reported at the annual meeting of the Society for Maternal-Fetal Medicine.

For all outcomes, combining the two testing modalities improved prediction. The sensitivity to predict stillbirth was 81% for an abnormal Doppler, 70% for abnormal biophysical parameters, and 89% when both tests were used.

Similar improvements in sensitivity were observed with combined testing for acidemia (71% for abnormal Doppler, 63%

for abnormal biophysical parameters, 88% for both); neonatal morbidity (53% for abnormal Doppler, 42% for abnormal biophysical parameters, 73% for both); and neonatal death within the first 28 days of life (74% for abnormal Doppler, 55% for abnormal biophysical parameters, 94% for both).

A total of 1,722 exams were performed on 584 fetuses at six centers in the United States, United Kingdom, and Germany. Fetal growth restriction was defined by a combination of abdominal circumference below the 5th percentile and more than a 2-standard-deviation elevation of the umbilical artery pulsatility index. Biophysical risk factors included gestational age, fetal movement, tone, breathing activity, heart rate, and amniotic fluid volume.

The average gestational age at birth was 32 weeks (range 24-41 weeks), the average

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Rh₀(D) Immune Globulin Intravenous (Human) 1500 IU (300 µg) Rhophylac[®]

Manufactured by:
ZLB Behring AG
Berne, Switzerland
US License No. 1710

Distributed by:
ZLB Behring LLC
Kankakee, IL 60901 USA

ZLB Behring

R_x only

For Intravenous and Intramuscular Injection
Preservative free, ready to use pre-filled syringe

Before prescribing please consult full prescribing information, a brief summary of which follows:

INDICATIONS AND USAGE

Pregnancy and Obstetrical Conditions

Rhophylac[®], Rh₀(D) Immune Globulin Intravenous (Human) is recommended:

- for the suppression of Rh isoimmunization in non-sensitized Rh₀(D)-negative (D-negative) women. The criteria for an Rh-incompatible pregnancy requiring administration of Rhophylac[®] at 28 to 30 weeks of gestation and within 72 hours after delivery are:
 - the mother must be Rh₀(D)-negative,
 - the mother is carrying a child whose father is either Rh₀(D)-positive or Rh₀(D) unknown,
 - the baby is either Rh₀(D)-positive or Rh₀(D) unknown, and the mother must not be previously sensitized to the Rh₀(D) factor.
- for Rhesus prophylaxis in case of obstetric complications, e.g., miscarriage, abortion, threatened abortion, ectopic pregnancy or hydatidiform mole, transplacental hemorrhage resulting from antepartum hemorrhage.
- for Rhesus prophylaxis in case of invasive procedures during pregnancy, e.g., amniocentesis, chorionic biopsy or obstetric manipulative procedures, e.g., external version, or abdominal trauma.

Incompatible Transfusions

Rhophylac[®] is recommended for the suppression of Rh isoimmunization in Rh₀(D)-negative individuals transfused with Rh₀(D)-positive RBCs or blood components containing Rh₀(D)-positive RBCs. Treatment should be initiated within 72 hours of exposure. Treatment should be given (without preceding exchange transfusion) only if the transfused Rh₀(D)-positive blood represents less than 20% of the total circulating red cells. A 1500 IU (300 µg) dose will suppress the immunizing potential of approximately 15 mL of Rh₀(D)-positive RBCs.

CLINICAL STUDIES

The efficacy, safety, tolerability and pharmacokinetics of Rhophylac[®], are supported by the results of two clinical studies in 446 Rh₀(D)-negative pregnant women (1, 2). In both studies, Rh₀(D)-negative women received Rhophylac[®] 1500 IU (300 µg) intravenously or intramuscularly in the 28th week of pregnancy. Mothers who gave birth to a Rh₀(D)-positive child received a further dose of Rhophylac[®] 1500 IU (300 µg) within 72 hours after the birth.

Eight out of 14 pregnant women from the above mentioned pharmacokinetic study gave birth to a Rh₀(D)-positive child and received Rhophylac[®] 1500 IU (300 µg) postpartum as well. The antibody tests performed 6 to 8 months later were negative for all mothers, which suggest that no Rh₀(D) immunization occurred.

In a second study at 22 centers in the United Kingdom and the USA, 432 pregnant women received Rhophylac[®] 1500 IU (300 µg) for antepartum rhesus prophylaxis. Two randomized groups of 216 women each received Rhophylac[®] 1500 IU (300 µg), either as an intravenous or intramuscular injection. Rhophylac[®] 1500 IU (300 µg) was also injected if there was a risk of fetomaternal hemorrhage between routine antepartum rhesus prophylaxis in the 28th week of pregnancy and birth, or if extensive fetomaternal hemorrhage was measured after birth. Of the 432 women who received Rhophylac[®] 1500 IU (300 µg) in the 28th week of pregnancy, 270 women delivered Rh₀(D)-positive children. 248 women were available for the investigation of Rh₀(D) immunization 6 to 11.5 months postpartum. None of those women developed antibodies against the Rh₀(D) antigen as assessed by the absence of anti-D antibodies.

CONTRAINDICATIONS

Rhophylac[®] is contraindicated in persons with hypersensitivity to human globulin.

The concentration of IgA in Rhophylac[®] was found to be below the detection limit of 5 µg/mL. Nevertheless, the product may contain trace amounts of IgA. Although anti-D immunoglobulin has been used to treat selected IgA deficient individuals, the attending physician must weigh the benefit against the potential risk of hypersensitivity reactions. Individuals deficient in IgA have a potential for development of IgA antibodies and anaphylactic reactions after administration of blood components containing IgA.

WARNINGS

Rhophylac[®] is made from human plasma. Products made from human plasma may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the CJD agent. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses during manufacturing. The Rhophylac[®] manufacturing process includes a solvent detergent treatment step (using tri-n-butyl phosphate and Triton[®] X-100) that is effective in inactivating enveloped viruses such as HBV, HCV, and HIV (3, 4). Rhophylac[®] is nanofiltered using a Planova[®] 15 nm virus filter that is effective in reducing the level of enveloped as well as non-enveloped viruses (5). These two processes are designed to increase product safety by reducing the risk of transmission of enveloped and non-enveloped

viruses, respectively. Despite these measures, these products could still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products. All infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to ZLB Behring at 800-504-5434. The physician should discuss the risks and benefits of this product with the patient.

PRECAUTIONS

For postpartum use, Rhophylac[®], Rh₀(D) Immune Globulin Intravenous (Human) is intended for maternal administration. It should not be given to the newborn infant. The product is not intended for use in Rh₀(D)-positive individuals. Patients should be observed for at least 20 minutes after administration.

As with all pharmaceutical agents, allergic responses may occur. If symptoms of allergic or anaphylactic type reactions occur, immediately discontinue administration. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalized urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis. The treatment required depends on the nature and severity of the side effect. If necessary, the current medical standards for shock treatment should be observed.

The concentration of IgA in Rhophylac[®] was found to be below the detection limit of 5 µg/mL. Nevertheless, the product may contain trace amounts of IgA. Although anti-D immunoglobulin has been used to treat selected IgA deficient individuals, the attending physician must weigh the benefit against the potential risk of hypersensitivity reactions. Individuals deficient in IgA have a potential for development of IgA antibodies and anaphylactic reactions after administration of blood components containing IgA.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The solution should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits.

Drug Interactions

Active immunization with live virus vaccines (e.g., measles, mumps, rubella or varicella) should be postponed until 3 months after the last administration of immunoglobulin products, as the efficacy of the live virus vaccine may be impaired. If immunoglobulin needs to be administered within 2-4 weeks of a live virus vaccination, then the efficacy of such a vaccination may be impaired.

The results of blood typing and antibody testing in neonates, including the Coombs or antiglobulin test, may be affected by the administration of anti-D immunoglobulin.

Rhophylac[®] can contain antibodies to other Rh antigens, e.g., anti-C antibodies, which might be detected by sensitive serological test methods following administration of the product.

Pregnancy Category C

This medicinal product is used in pregnancy. Animal reproduction studies have not been conducted with Rhophylac[®]. The available evidence suggests that Rhophylac[®] does not harm the fetus or affect future pregnancies or the reproduction capacity of the maternal recipient.

Rh₀(D) Immune Globulin is not secreted in breast milk. No hazards are expected during breastfeeding.

ADVERSE REACTIONS

When anti-D immunoglobulins are administered by the intramuscular route, local pain and tenderness can be observed at the injection site; this can be prevented by dividing larger doses over several injection sites.

Mild and transient fever, malaise, headache, cutaneous reactions and chills occur occasionally. In rare cases, nausea, vomiting, hypotension, tachycardia, and allergic or anaphylactic type reactions, including dyspnea and shock are reported, even when the patient has shown no hypersensitivity to previous administration.

No data are available on overdosage. Patients with incompatible transfusion who receive an overdose of anti-D immunoglobulin should be monitored clinically and by biological parameters because of the risk of hemolytic reaction. In other Rh₀(D)-negative individuals overdosage should not lead to more frequent or more severe undesirable effects than the normal dose.

HOW SUPPLIED

Rhophylac[®] 1500 IU (300 µg) is available in packages containing one or ten pre-filled 2 mL syringes.

STORAGE

Store at 2°C to 8°C (36°F to 46°F). If stored at this temperature, Rhophylac[®] has a shelf life of 36 months. Do not freeze. Protect from light. The preparation should not be used after the expiration date printed on the label.

REFERENCES

- Bichler J, Schönödorfer G, Pabst G, Andresen I. Pharmacokinetics of anti-D IgG in pregnant RhD-negative women. BJOG 2003; 110:39-45.
- Data on file at ZLB Behring AG.
- Horowitz B, Chin S, Prince AM, Brotman B, Pascual D, Williams B. Preparation and characterization of S/D-FPP, a virus sterilized «fresh frozen plasma». Thromb Haemostas 1991; 65:1163.
- Horowitz B, Bonomo R, Prince AM, Chin SN, Brotman B, Shulman RW. Solvent detergent treated plasma: A virus-inactivated substitute for frozen plasma. Blood 1992; 79:826-31.
- Stucki M, Moudry R, Kempf C, Omar A, Schlegel A, Lerch PG. Characterisation of a chromatographically produced anti-D immunoglobulin product. J Chromatogr B 1997; 700:241-8.

Based on: February 2005 Revision



‘These observational data lay the foundation for a randomized trial of delivery timing in IUGR.’

DR. BASCHAT

birth weight was 1,190 g (390-2,100 g), and 452 babies were delivered by cesarean section. There were 38 stillbirths, 48 cases of acidemia, 97 neonatal morbidities, and 32 deaths.

The addition of Doppler correctly predicted 10 of 10 unexpected stillbirths that occurred within 1 week of being identified as normal by biophysical risk factors, and 23 of 97 neonatal morbidities after equivocal or abnormal biophysical findings, said Dr. Baschat of the University of Maryland, Baltimore. The addition of Doppler predicted 11 additional cases of acidemia, and 12 additional neonatal deaths.

Using abnormal biophysical parameters alone, 19 stillbirths and 18 cases of acidemia were prevented.

Absent ductus venosus atrial systole (a-wave), umbilical vein pulsations, loss of movement, and oligohydramnios were the strongest predictors of stillbirth and acidemia. When these biophysical variables were absent, Doppler changes had no further impact.

Doppler and biophysical parameters did not completely predict neonatal mortality and morbidity risks, as these depend on gestational age, said Dr. Baschat, who received no funding for the study and disclosed no conflicts of interest.

It is too early to say if integrated fetal testing should become the standard for determining delivery timing in intrauterine growth restriction (IUGR), although the University of Maryland Medical Center has been using the method for the past 7 years, Dr. Baschat said in an interview.

“These observational data lay the foundation for a randomized trial of delivery timing in IUGR,” he said, adding that an IUGR research consortium, coordinated through the University of Maryland, is developing a protocol for a management trial. ■