Article published online: 2024-09-30



# Anti-D Alloimmunization in Index Pregnancy after Appropriate Rho(D) Immune Globulin Injection in Two Obese Rh-Negative Patients

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AJP Rep 2024;14:e228–e230.

## Abstract

**Background** The rhesus factor D (RhD)-negative patients who give birth to an RhD-positive newborn or who are otherwise exposed to RhD-positive red blood cells are at risk of developing anti-D antibodies. These antibodies may cause hemolytic disease of the fetus and newborn (HDFN). During pregnancy, prevention of alloimmunization is completed with a Rho(D) immune globulin (RhIg).

**Cases** We report two cases, where obese patients developed alloimmunization, with high neonatal titers, after appropriate RhIG prophylaxis during the index pregnancy.

**Conclusion** Our cases demonstrate cases of anti D-alloimmunization in an index pregnancy, with high neonatal titers. Both patients are obese, with BMI $> 35\,mg/m^2$.

**Keywords**

- alloimmunization
- Rh negative
- hemolytic disease of the fetus and newborn
- anti-D antibodies
- Rhophylac
- RhIG

**Key Points**

- RhIG can be administered via intramuscular or intravenous formulations. Overall, it appears that both formulations are equally effective. The optimal administration, especially with obese women, is not clearly established.
- Our cases demonstrate that obesity is a risk factor for failure of RhIG, and could lead to an increase in HDFN.

Anti-D alloimmunization was previously the most prevalent cause of hemolytic disease of the fetus and newborn (HDFN), before the use of Rho(D) immune globulin (RhIG). RhD-negative patients who give birth to an RhD-positive newborn or who are otherwise exposed to RhD-positive red blood cells are at risk of developing anti-D antibodies. Fetal cells may cross the maternal circulation, stimulating the maternal immune system to produce the mentioned antibodies, which are capable of crossing the placenta into fetal circulation causing fetal hemolysis, which may occur during pregnancy or at childbirth. HDFN can be associated with serious morbidity and mortality.

During pregnancy, prevention of RhD alloimmunization is through the administration of RhIG to protect against potential exposure to RhD-positive fetal blood. With the administration of RhIG, alloimmunization occurs in 0.024% of pregnancies. In our tertiary center, we had two relevant cases where obese patients developed alloimmunization after appropriate RhIG injection during the index pregnancy.

**received**
June 14, 2024
**accepted after revision**
August 25, 2024

**DOI** https://doi.org/10.1055/s-0044-1791525.
**ISSN** 2157-6998.



Thieme Medical Publishers, Inc., 333 Seventh Avenue, 18th Floor, New York, NY 10001, USA

## Cases

### First Case

A 28-year-old woman, G1P0, underwent primary cesarean section due to malpresentation at 39 weeks and 1 day.

Past medical history included the following: class III obesity (prepregnancy body mass index [BMI] = 41 kg/m$^2$; pregnancy BMI = 44 kg/m$^2$; gestational weight gain = 24 lb); exercise-induced asthma; and depression (on fluoxetine). Past obstetrical, gynecologic, surgical, family, and social history: none.

This patient received Rhophylac 300 µg in the deltoid muscle at 28 weeks and 5 days. Type and screen performed before Rhophylac administration showed that the antibody screen was negative. She underwent a failed external cephalic version at 37 weeks and 3 days. The type and screen done at that time found anti-D to be positive, which was attributed to Rhophylac given at 28 weeks (10 weeks before); no titers were performed. Maternal type and screen at 39 weeks and 1 day were positive for anti-D, with titer of 128. The male neonate APGAR score were 6 and 7. The neonate required neonatal intensive care unit (NICU) admission for 2 days due to respiratory distress. The neonate's hematocrit and platelet counts were normal at birth. The neonate had anti-D titer of 32. At the maternal postpartum visit, the anti-D titer was 1,024, with new anti-Jk$^a$ antibody in the Kell blood group detected.

The patient underwent RhD genotyping in the postpartum period. The DNA of the large, 417-amino acid Rh polypeptide is molecularly organized over two related genes on chromosome 1 (1p36.11), called *RHD* and *RHCE*, each with 10 exons. Genotyping of the *RHD* gene of this patient revealed a "hybrid allele" in the D gene with exons 3 through 9 of *RHD* replaced by the corresponding exons of the *RHCE* gene: *RHD**D-CE(3–9)-D/*RHCE**ce/*RHCE**Ce. Despite this detected *RHD*/*RHCE* genetic "crossover" at the molecular level, this patient was RhD seronegative and as susceptible to anti-D alloimmunization as any Rh-negative individual.

### Second Case

A 33-year-old woman, G3P1101, had a vaginal delivery at 40 weeks and 2 days.

Her past medical history included the following: class II obesity (prepregnancy BMI = 37.1 kg/m$^2$; delivery BMI = 39 kg/m$^2$; gestational weight gain = 13 lb).

Past obstetrical and gynecologic history included the following: stillbirth at 22 weeks in the first pregnancy (patient received appropriate RhIg prophylaxis) and vaginal delivery at term in second pregnancy (patient received appropriate RhIg prophylaxis during and after the delivery); this neonate was Rh-positive and the patient underwent fetal cell quantification, which yielded a negative result. Her BMI during her second pregnancy was 33 kg/m$^2$.

Past surgical, family, and social history: hysteroscopy.

A type and screen conducted in the first and second trimesters were negative for anti-D antibodies. At 27 weeks and 2 days, the patient received 300 µg of Rhophylac in the deltoid muscle. Prior administration of Rhophylac, the antibody screen was negative. However, when the patient was admitted at 40 weeks and 2 days, the antibody screen was positive for anti-D with a titer of 512. The patient underwent a vaginal delivery, and the female neonate's Apgars were 9 and 9. The neonate was admitted to the newborn nursery without any signs of anemia. The neonate had anti-D titer of 64, tested Coombs positive, and was discharged home 2 days after delivery.

## Discussion

In order to prevent severe HDFN, current recommendations are that all pregnant women who test negative for the D antigen receive a standard dose of 300 µg of RhIG at 28 weeks of gestation and a dose of RhIG within 72 hours of potential exposure to Rh-positive fetal blood. The pharmacokinetics of RhIG have been well studied; however, to our knowledge, they are not well studied in the obese population. 3–10 days after administration of RhoGham, women exhibited a wide range of plasma anti-D concentrations. This same study showed that lower values of anti-D concentration were found in women with higher BMIs.[1] Previous studies have also shown that with higher BMIs, there is progressive lowering of anti-D levels, with levels 28 to 60% lower for higher BMIs.[2] Many Rh-negative women will need a higher dose after an event that causes maternal–fetal hemorrhage, determined by the Kleihauer–Betke test.[3]

RhIG is typically administered via an intramuscular injection. However, there is literature validating the use of intravenous formulations. There are two trials in the literature that randomized patients to receive anti-D intramuscularly versus intravenously in the 28th week of pregnancy and within 72 hours after delivery. At 6 to 9 months postpartum, one patient tested positive in the intramuscular group. However, she was no longer positive when tested at 11.5 months.[4] At this point, it has not been determined which administration method is more favorable. Overall, it appears that both formulations are equally effective.[5] Of note, there are no specific comments about how BMI affects the route of administration.

Our cases demonstrate cases of anti-D alloimmunization, with high maternal and neonatal titers of anti-D present at birth in the index pregnancy. Interestingly, at delivery the anti-D neonatal titers in cases 1 and 2 were 32 and 64, respectively, but neither neonate had symptomatic HDFN. There is rising prevalence of obesity in the United States, with 35% of the population considered obese by BMI.[6] The current RhIG dosing makes certain assumptions, including total blood volume of 5,000 mL, which could be significantly incorrect based on maternal BMI.[7] Our case report, along with previously published literature, shows that obesity is a risk factor for failure of RhIG, and could lead to an increase in HDFN.[7,8]

**Conflict of Interest**
None declared.

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