
New Laboratory Procedures and Rh Blood Type Changes in a Pregnant Woman

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BACKGROUND: A woman’s candidacy for Rh immune globulin depends on whether her blood type is Rh-positive (D antigen-positive) or Rh-negative (D antigen-negative). New molecular blood-typing methods have identified variant D antigens, which may be reported as Rh-positive or Rh-negative depending on the laboratory method. We describe a case illustrating the effect of the new laboratory methods on a woman’s candidacy for Rh immune globulin and present recommendations for interpreting the new test results.

CASE: A 40-year-old woman presented for management of her third pregnancy. During her first pregnancy, she was typed as Rh-positive (“D”) and did not receive Rh immune globulin. During her second pregnancy, she was typed as Rh-negative, in accordance with revised Rh-typing procedures. Anti-D antibody was detected. During her third pregnancy, she was genotyped as a partial D antigen, which was reported as Rh-negative.

CONCLUSION: Revisions in laboratory procedures for Rh typing may present as a change in the Rh blood type of pregnant women—and as a change in their eligibility for Rh immune globulin.

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Historically, prophylaxis with Rh immune globulin has been determined by the woman’s Rh blood type. Pregnant women whose red blood cells type as Rh-negative (D antigen-negative) have been candidates for administration of Rh immune globulin; women whose red blood cells type as Rh-positive (D antigen-positive) have not. This practice became more complex with recognition that an estimated 0.3% of whites and 1.7% of persons of African descent have red blood cells expressing a weak D phenotype (formerly Dv).1 Weak D red blood cells express less D antigen and type as Rh-negative by direct agglutination but type as Rh-positive by an indirect antiglobulin (Coombs) test or by selected anti-D typing reagents. It had been assumed that all weak D red blood cells expressed normal, but fewer, D antigens until reports emerged describing women with weak D phenotypes who had formed anti-D antibodies after delivering Rh-positive neonates.2 Molecular studies established that their red blood cells expressed a weak D phenotype because they had inherited a partial (D mosaic or variant D antigen.3 Approximately 5–10% of weak D phenotypes are partial D.3 The most common partial D is Dv, which will type as Rh-positive or Rh-negative depending on the anti-D reagent selected. When exposed to Rh-positive red blood cells by pregnancy or transfusion, persons with a partial D antigen are capable of forming “anti-D,” ie, an antibody to their missing or variant D epitope(s). These antibodies are capable of causing hemolytic disease of the fetus or newborn, including fatal cases.2 The following report describes a woman with a partial D antigen whose routine laboratory reports changed from Rh-positive to Rh-negative during three pregnancies, illustrating the effect of these changes on the treatment of pregnant women.

CASE
A 40-year-old woman, gravida 3 para 2, was referred for management of pregnancy complicated by Rh alloimmunization. During her first pregnancy, her red blood cells were typed as weak D phenotype (Dv), which, according to standard practice at that time, was interpreted to be Rh-
positive. She delivered an Rh-positive neonate but did not receive antepartum or postpartum Rh immune globulin. During the second pregnancy, her red blood cells were typed as Rh-negative and anti-D antibodies were detected in her plasma for the first time. Additional testing for weak D was not performed. For her third pregnancy, Rh typing was performed initially by a commercial reference laboratory and reported as Rh-negative. When she was admitted to the hospital for her third delivery, her red blood cells typed as Rh-negative by a standard anti-D typing reagent but as Rh-positive by an indirect antiglobulin test, indicating that her red blood cells expressed a weak D phenotype. Her plasma contained anti-D antibody, suggesting that her red blood cells expressed a partial D antigen. Molecular analysis confirmed her RHD genotype to be partial D<sup>+</sup> Ce/ce (American Red Cross National Molecular Blood Group and Platelet Testing Laboratory, Philadelphia, PA). When she was informed that her Rh blood type was neither Rh-positive nor Rh-negative, but “somewhere in between,” she asked whether this information explained why her sister and brother-in-law, who are both Rh-negative, have an Rh-positive child.

**COMMENT**

The identification of molecular variants of the D blood group antigen has resulted in a series of changes in standard laboratory practice for Rh typing of pregnant women. Conventionally, pregnant women with a weak D (D<sup>+</sup>) phenotype, such as our patient during her first pregnancy, were treated as Rh-positive and excluded as candidates for Rh immune globulin. When some women with a weak D phenotype formed anti-D after delivery of an Rh-positive neonate, they were investigated and found to have a partial D antigen. Their “anti-D<sup>+</sup>” antibodies are directed against a variant or absent D epitope<sup>[5]</sup>. Changes in laboratory procedures were introduced to categorize women with a partial D antigen as Rh-negative to ensure that they received Rh immune globulin, although there is no direct evidence that administering Rh immune globulin will prevent their forming anti-D after delivering an Rh-positive neonate.<sup>[4]</sup>

Presently in the United States, the partial D antigen is unlikely to be detected in pregnant women and other patients because its detection typically requires an additional indirect antiglobulin test, which is not required by the revised laboratory practice for pregnant women or other patients.<sup>[5,6]</sup> In fact, current laboratory practice intentionally avoids detection of the partial D phenotype in pregnant women and other patients by not performing an indirect antiglobulin test. Thus, the revised laboratory practice will change reports of Rh blood typing for some women, such as our patient, from Rh-positive to Rh-negative. Transfusion of red blood cells from a donor with a partial D can stimulate the formation of anti-D in an Rh-negative recipient. For this reason, blood centers routinely perform an indirect antiglobulin test on blood donors and classify donors with the partial D phenotype as Rh-positive to avoid sensitizing Rh-negative recipients.

The double standard of classifying a person with the partial D antigen as Rh-negative when pregnant or a patient but as Rh-positive as a blood donor has been facilitated by the introduction of monoclonal blood-typing reagents. Monoclonal anti-D reagents have been engineered to detect normal D and most weak D phenotypes by direct agglutination, categorizing them as Rh-positive. These reagents do not detect the most common partial D antigens by direct agglutination but will detect most partial D antigens if an indirect antiglobulin test is performed. By promoting the use of D typing reagents that are designed to avoid detecting partial D antigens by direct agglutination, reagent manufacturers support a serological “Don’t Ask, Don’t Tell” strategy for typing pregnant women and other patients.

Inevitably, the double standard of current practice will cause confusion among obstetric patients. The most likely persons to be affected are women with a partial D antigen who will type as Rh-positive if they are blood donors but as Rh-negative if they become pregnant. A second inevitability will arise when parents who previously were typed as Rh-negative when pregnant or as patients are informed that their newborn’s blood type is Rh-positive. This situation will arise, as it did for our patient’s sister, because many hospitals type newborns’ red blood cells using an indirect antiglobulin test to ensure detection of any D antigen that might sensitize the Rh-negative mother. The costly resolution of questions of paternity that may arise is unlikely to be covered by third-party payers as an expense of the delivery.

These issues present an opportunity to update and harmonize obstetric practice with the evolving molecular science and promise of monoclonal antibody Rh-typing reagents and D genotyping. In the interim, we alert obstetricians that women with a partial D antigen currently will type as Rh-negative even though they may have a history of typing as Rh-positive. We are unaware of organizational practice guidelines that have been updated to address prevention of Rh alloimmunization in pregnant women with partial D antigens. Given the potential
for morbidity and mortality associated with hemolytic disease of the fetus or newborn complicating pregnancy in women with partial D, we propose that the most prudent course is administration of Rh immune globulin despite the absence of direct evidence of its efficacy (Table 1).4

REFERENCES
3. Garratty G. Do we need to be more concerned about weak D antigens? Transfusion 2005;45:1547–51.

Genitofemoral and Perineal Neuralgia After Transobturator Midurethral Sling

Brent A. Parnell, MD, Elisabeth A. Johnson, NP, PhD, and Denniz A. Zolnoun, MD, MPH

BACKGROUND: Midurethral slings successfully treat stress urinary incontinence through a minimally invasive vaginal approach. Postoperative pain related to sling placement can occur and poses both diagnostic and treatment dilemmas.

CASE: Four years after transobturator midurethral sling placement, the patient presented with complaints of left labial pain and dyspareunia since surgery. Using sensory mapping and a nerve stimulator, the problem was identified in the distribution of the genitofemoral nerve. Conservative therapy with a centrally acting neuromodulatory drug and nerve block relieved the pain.

CONCLUSION: Postsling neuralgia diagnosis using sensory mapping and a nerve stimulator aids in identifying the nerve involved and in successful conservative treatment with a nerve block.

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Table 1. Recommendations for Administration of Rh Immune Globulin

<table>
<thead>
<tr>
<th>Timing</th>
<th>Mother</th>
<th>Father</th>
<th>Fetus or Newborn</th>
<th>RhIG</th>
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<td>D-positive; weak, partial†, or unknown D</td>
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<td>Any D type</td>
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<tr>
<td>Antepartum</td>
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<tr>
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<tr>
<td>Postpartum</td>
<td>D-positive</td>
<td>Unknown</td>
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</tr>
</tbody>
</table>

RhIG, Rh immune globulin.
* Typed D-negative either by standard direct anti-D typing or by an indirect antiglobulin test or monoclonal antibody weak D test.
† Detection of the partial D antigen is unlikely before a person forms anti-D after pregnancy or transfusion, unless an initial negative Rh typing was followed by a positive test for a weak D and, then, by genotyping. Given the present standard of omitting weak D testing for Rh-negative pregnant women, a woman with a partial D antigen who is at risk of alloimmunization by an Rh-positive fetus will be detected only because, like the present patient’s sister, she has become aware of the possibility of inheritance because of a case in the family.
‡ Typed by an indirect antiglobulin test.