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Red Blood Cell Alloimmunization in the Pregnant Patient

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ABSTRACT

Alloimmunization to red blood cell (RBC) antigens represents a challenge for physicians caring for women of child bearing potential. Exposure to non-self RBC antigens may occur during transfusion or pregnancy leading to the development of antibodies. If a subsequent fetus bears that antigen, maternal antibodies may attack the fetal red blood cells causing red cell destruction and clinically significant hemolytic disease of the fetus and newborn (HDFN). In the most severe cases, HDFN may result in intrauterine fetal demise due to high output cardiac failure, effusions and ascites, known as "hydrops fetalis". This article reviews strategies for management and prevention of RBC alloimmunization in women of child bearing potential.

Contents

Detection of Alloimmunization . . . 213
Prevalence of Alloimmunization . . . 214
Monitoring and Management of the Sensitized Mother and Fetus During Pregnancy . . . 214
Prevention of Alloimmunization . . . 215
Conflict of Interest Statement . . . 216
References . . . 216

Alloimmunization to red blood cell (RBC) antigens may occur following a blood transfusion, fetal maternal hemorrhage (FMH) during pregnancy or parturition, or through other blood exposure. The exposed patient may develop antibodies to any non-self RBC antigen. Though patients are tested for ABO and RhD type to avoid incompatible blood transfusion, rates of alloimmunization in the general population range from 1–10% of transfusions [1, 2]. The incidence of alloimmunization may be as high as 60% in chronically transfused patients with underlying hemoglobinopathies, hematologic malignancies, renal failure or organ transplant [3]. Women of childbearing potential represent a challenging population for transfusion services to manage, as alloimmunization may have devastating consequences for the fetus, the most severe of which his hydrops fetalis, however transfusion matching for every foreign RBC antigen is logistically difficult [4]. Further, RBC transfusion of the mother during or after delivery due to bleeding is complicated by RBC alloimmunization, particularly when the mother has an antibody to a high frequency RBC antigen. This article reviews strategies and outcomes for the testing and management of an alloimmunized mother with an affected fetus, as well as prevention strategies to avoid RBC sensitization.

Detection of Alloimmunization

Most Western countries have implemented screening programs for detection of RBC alloimmunization in pregnancy; however, the frequency and timing of those screening programs vary [5, 6]. In the United States, routine blood bank testing to assess maternal blood type (ABO), RhD and for any unexpected RBC IgG antibodies using an indirect antiglobulin test (IAT) is recommended for all pregnant women. The American College of Obstetrics and Gynecology (ACOG) recommends testing mothers at their first prenatal visit [7].

First trimester screening has been shown to be approximately 77.8% sensitive for clinically significant, RBC antibodies resulting in hemolytic disease of the fetus and newborn (HDFN). However, the sensitivity varies by antibody specificity. For example, first trimester screening

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for clinically significant anti-E was only 57.1% sensitive in one study [8]. Blood group antibodies differ in their risk of causing clinically significant HDFN. Up to 50% of RBC antibodies detected by screening may be clinically insignificant as they are antibodies against antigens that are poorly expressed on fetal RBCs, such as Lewis antibodies, or because they are IgM antibodies, which will not cross the placental barriers, such as anti-N [9, 10]. The most common clinically significant alloantibodies causing HDFN include anti-D, anti-E, anti-c and anti-K; however, over 50 non-ABO blood groups have been implicated in HDFN [11].

Additional antibody testing is recommended by ACOG for RhD negative mothers between 28–29 weeks gestation prior to administration of RhD immunoglobulin (RhIg) [7, 12]. This may detect RhD sensitization due to early FMH. Some studies have questioned the utility of additional screening in RhD positive mothers [13-15]. However, up to 27% of severe HDFN cases occur unexpectedly in RhD positive mothers with negative first trimester RBC antibody screens. Risk factors for late alloimmunization included a history of blood transfusion, increasing parity and amniocentesis or chorionic villus sampling with the current pregnancy [16]. The most severe fetal outcomes occurred in fetuses of mothers who developed anti-c, indicating that mothers who are Rhc negative may particularly benefit from additional testing later in pregnancy to allow for timely interventions [16, 17]. In the United Kingdom, screening is recommended at initial prenatal visit and at 28 weeks gestation in all mothers, regardless of RhD status [5].

Prevalence of Alloimmunization

Reported rates of alloimmunization in women of childbearing potential vary greatly depending upon the period and manner in which the data were collected. In the United States, a representative series of 22 102 blood samples from women of reproductive potential (age 15–44 years) identified RBC antibodies in 1.15%, of whom 18% had multiple antibodies [18]. Luckily, rates of clinically significant HDFN are much lower at 3/100000 to 80/100000 live births [19]. In modern cohorts in the Netherlands, RBC alloimmunization detected by first trimester screening occurred in 1232/100000 pregnancies. Of these, 400/100000 were clinically significant, with the most common specificities being anti-D, anti-E, anti-K and anti-c [8]. In Sweden, 0.4% of 78 145 pregnancies were complicated by non-ABO alloimmunization [6]. In Africa, the prevalence of RhD negativity is less common in the population; however, due to barriers to prenatal testing and care, rates of anti-D in women of child bearing potential are as high as 2–12% [20-22].

The possibility of alloimmunization varies between populations based on the prevalence of blood group antigens within the population. For example, the frequency of RhD negativity is estimated at 15–17% among people of European/North American ancestry. This falls to 3–8% in people of African and Indian ancestry. In Asian populations, RhD negativity may be as low as 0.1–0.3% of the population [23, 24]. The prevalence of other RBC antigens may vary widely between populations, resulting in varied rates of alloimmunization.

Where ABO incompatibility occurs between mother and fetus, studies have shown a protective effect against further RBC alloimmunization. Studies prior to routine administration of RhIg prophylaxis showed that 16% of RhD negative mothers pregnant with RhD positive fetuses became sensitized; however, rates of sensitization decreased to 2% when there was ABO incompatibility in addition to RhD incompatibility [19]. Therefore, population frequencies of ABO blood types may exert further effects on maternal RBC sensitization.

In addition to ABO discrepancy, other maternal factors may influence the risk of alloimmunization. Prior major surgery, RBC or platelet transfusion, multiparity, prior male child or operative removal of a prior placenta have been associated with RBC alloimmunization [25]. Maternal risk factors for RhD sensitization despite RhIg prophylaxis include conditions related to FMH or insufficient RhIg dose, such as assisted vaginal delivery, caesarian section, post-maturity (>42 weeks), maternal age or maternal red blood cell transfusion; however, none of these was present in 43% of RhIg failures [26]. Other factors that have been significantly associated with rates of sensitization to RBC antigens within the general population include age at time of transfusion and numbers of transfusions received [27, 28]. Female gender has variably been associated with increased rates of RBC alloimmunization; however, that risk is obviated when controlled for numbers of transfusion exposure events [29]. Women who are HLA-DRB1*15 positive also represent a group that is at increased risk for forming RBC antibodies [30, 31].

Murine models of RBC alloimmunization to transfused cells are shedding light on additional risk factors for alloimmunization that have yet to be fully studied in humans [32, 33]. In mouse models, RBC alloimmunization has been associated with donor or product specific factors, including longer storage duration [34] and inversely related to the efficacy of leukoreduction and platelet reduction [32]. Alloimmunization has also been associated with recipient factors, such as faster rate of RBC clearance [35] and heightened recipient inflammatory state at the time of exposure [36], which has been confirmed in human studies [37]. Historically, all of these models have relied on transfusion of RBCs; however, novel murine models of pregnancy-related alloimmunization to human RBC antigens have been developed [38]. These novel models will allow for further mechanistic studies of maternal sensitization not possible in humans [39].

Monitoring and Management of the Sensitized Mother and Fetus During Pregnancy

Once a mother is identified as having a clinically significant RBC alloantibody, further monitoring and evaluation is required. For first pregnancies affected by maternal anti-D, antibody titers may be predictive of disease severity [19]; however, blood banks may have different critical titer thresholds, often 1:16–32 [9]. Unfortunately, titers are less predictive in subsequent pregnancies or with other antibodies, such as anti-Kell, which has been shown to cause significant HDFN even at low titers [40, 41]. Titer thresholds and management strategies have been proposed for maternal antibodies other than anti-D and anti-Kell; however, the evidence is limited as to whether they predict or mitigate clinical outcomes [42]. In addition, historic titer thresholds are based on the titers being performed using conventional tube methods. It is unclear if other methodologies, such as gel-based platforms, are equivalent [43, 44]. Even with standardized procedures, titer proficiency testing shows wide variability between centers and methodologies, so serial titers should be performed at the same institution to facilitate interpretation [5, 45].

Titer alone may not be the single-best predictor of clinical potency of maternal antibodies. The degree of fucosylation of IgG antibodies has been shown to influence the pathogenicity in HDFN. For RhD IgG antibody, less fucosylation predicts increased phagocytosis on monocyte-based antibody dependent cellular cytotoxity testing and correlates with fetal hemoglobin levels [46]. However, the influence of IgG fucosylation when directed against other RBC antibodies is variable [47]. Further research is necessary to apply the clinical implications of these findings.

If paternal identity is confirmed, fetal risk of carrying the implicated antigen should be determined by assessing paternal zygosity [48]. For RhD, this requires paternal RHD genetic testing which is usually available at reference laboratories. For antigens such as Kell/k, routine blood bank antigen phenotyping of the father may determine if the fetus has a 50% or 100% chance of carrying the implicated antigen. Non-invasive, high throughput testing platforms testing cell-free DNA, fetal DNA circulating in maternal plasma, for RhD have been developed and implemented in Europe with excellent effect [49-51]. As a screening test for potentially affected pregnancies, they have been shown to be >99.3% sensitive at 10–11 weeks gestation, allowing for very early monitoring and intervention [50]. When implemented as a routine test at 24–26 weeks gestation for RhD negative mothers, the sensitivity of