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SMFM Statement

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Society for Maternal-Fetal Medicine Statement: RhD immune globulin after spontaneous or induced abortion at less than 12 weeks of gestation

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Guidelines for the management of first-trimester spontaneous and induced abortion vary in terms of rhesus factor D (RhD) testing and RhD immune globulin (RhIg) administration. These existing guidelines are based on limited data that do not convincingly demonstrate the safety of withholding RhIg for first-trimester abortions or pregnancy losses. Given the adverse fetal and neonatal outcomes associated with RhD alloimmunization, prevention of maternal sensitization is essential in RhD−negative patients who may experience subsequent pregnancies. In care settings in which RhD testing and RhIg administration are logistically and financially feasible and do not hinder access to abortion care, we recommend offering both RhD testing and RhIg administration for spontaneous and induced abortion at <12 weeks of gestation in unsensitized, RhD−negative individuals. Guidelines for RhD testing and RhIg administration in the first trimester must balance the prevention of alloimmunization with the individual- and population-level harms of restricted access to abortion.

Key words: abortion, alloimmunization, early pregnancy loss, feto-maternal hemorrhage, hemolytic disease of the newborn, perinatal morbidity, perinatal mortality

Introduction

Maternal rhesus factor D (RhD) sensitization occurs when an RhD-negative pregnant person is exposed to the RhD antigen, typically through carrying an RhD-positive fetus. Exposure to the RhD antigen triggers production of anti-D antibodies, placing future pregnancies at risk for RhD alloimmunization and its adverse perinatal outcomes. The use of RhD immune globulin (RhIg) has reduced the burden of perinatal morbidity and mortality attributable to RhD alloimmunization. Among RhD-negative patients, a postpartum dose of RhIg decreases the rate of postpartum anti-D alloimmunization from between 13% and 17% to 1% to 2%, and an additional dose in the mid-trimester reduces the antepartum rate of alloimmunization from 1.8% to between 0.1% and 0.2%.[1–4] Limited data suggest that first-trimester RhIg administration reduces the risk of RhD alloimmunization with spontaneous and induced abortion, although the specific point estimate has not been determined.

Primitive hematopoietic cell development starts in the yolk sac and occurs within 2 weeks of fertilization.[5] These cells do not produce red blood cell (RBC) antigens (such as D-antigen) on the cell surface. Definitive hematopoietic cell development begins shortly thereafter, and fetal RBCs display red cell antigens from as early as 6 weeks of gestation. RhIg is produced from sterilized pooled plasma from donors with circulating anti-D antibodies. RhIg decreases the risk for sensitization by suppressing the maternal immune response to nonself D-antigen, although the complete mechanism of action is not fully understood.

Existing guidance and supporting data

The Society of Family Planning (SFP) recommends against RhD testing and RhIg administration for spontaneous and induced abortion at <12 weeks of gestation.[6] SFP guidelines note that RhD testing and RhIg administration may be considered at patient request as part of a shared decision-making process. Similarly, the World Health Organization (WHO) recommends against RhIg administration for medication and procedural abortion at <12 weeks of gestation.[7] Of note, the WHO guidelines acknowledge that the evidence may favor administration of RhIg but conclude that the very low certainty of effectiveness and the logistic considerations (ie, cost-effectiveness, feasibility, resources required) outweigh the potential benefit. Additional guidelines support a range of practices, including forgoing RhD testing and RhIg administration at gestational ages <12 weeks[8] or <10 weeks[9,10] or in cases when RhIg is not available or would

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significantly delay abortion care.[11] Guidelines for RhD testing and RhIg administration are based on scarce or limited data as noted in the guidelines themselves.

Data on the risks of alloimmunization after early pregnancy loss or induced abortion do not convincingly demonstrate the safety of forgoing RhIg. Older data on the risks of feto-maternal hemorrhage and sensitization in early pregnancy are limited by sample sizes too small to detect rare events. The only randomized controlled trial of antepartum RhIg for spontaneous abortion at 8 to 24 weeks of gestation demonstrated no sensitization events in 29 participants.[12] Another observational study of 32 RhD-negative patients with an RhD-positive live birth following a spontaneous abortion demonstrated 1 sensitization event in a patient with spontaneous abortion and subsequent curettage at 16 weeks of gestation.[13] Neither of these studies is large enough to demonstrate that RhIg is unnecessary after a spontaneous abortion.

One contemporary study compared 2 national strategies of RhIg administration in the first trimester to determine if the rates of clinically significant alloimmunization differed.[14] In the Netherlands, RhIg is not recommended for the management of spontaneous abortion at <10 weeks of gestation, nor for induced abortion at <7 weeks of gestation. In contrast, Canada recommends RhIg for all such first-trimester events. The comparative study found that the Canadian approach led to a prevalence rate of 4.21 (95% confidence interval [CI], 4.12−4.30) clinically significant antibodies per 1000 pregnant patients vs a prevalence rate of 4.03 (95% CI, 3.93−4.12) clinically significant antibodies per 1000 pregnant patients in the Netherlands. Although the data seem to support the safety of forgoing RhIg administration, this analysis relied in part on estimated or extrapolated data to conclude that the 2 strategies were equivalent. Furthermore, comparing the population-level outcomes of 2 countries' treatment strategies is insufficient to account for individual risk differences when making policy recommendations. If similar findings would be observed in a large, prospective, observational study is uncertain, and such a study has not been undertaken by the time of this publication.

Recent clinical evidence is equivocal because of limitations associated with small sample sizes and the reliance on a calculated threshold for sensitization instead of confirmed alloimmunization. The expected threshold for fetal RBCs to lead to a sensitization event (250 fetal RBCs per 10 million total RBCs) is calculated from a single-arm study conducted in 15 women.[15] A real-world study to establish a sensitization threshold would be challenging at best, but a calculated threshold may not be an equivalent substitute. The true biologic threshold for RhD sensitization is likely multifactorial and remains unknown.

More recently, a study evaluating circulating fetal RBCs using flow cytometry was published to help determine the risk for sensitizing events after medication or procedural abortion at <12 weeks of gestation.[16] The authors used the previously calculated sensitization threshold of 250 fetal RBCs per 10 million total RBCs. Of 506 individuals with available pre- and postabortion data, 3 participants exceeded the calculated threshold for sensitization before abortion (ie, before an intervention), 1 of whom also exceeded the threshold postabortion. Among the patients who were below the threshold before abortion, there were no incident cases of fetal RBCs exceeding the sensitization threshold after abortion. Although these data confirm that alloimmunization after abortion in the first trimester is likely an uncommon event, they rely on a calculated instead of a real-world threshold for sensitizing feto-maternal hemorrhage events. They do not clearly demonstrate that there is no risk for alloimmunization with abortions at <12 weeks of gestation and do not unequivocally justify withholding instead of recommending RhIg. Moreover, these data do not provide clinicians with an objective approach to risk-stratify the chance of a sensitizing event. Finally, flow cytometry data do not directly reflect the immune response to a sensitizing event, which is first detected several months after the event itself. Additional clinical data are needed to better inform practices of recommending or withholding RhD testing and RhIg administration for first-trimester spontaneous or induced abortion.

The Society for Maternal-Fetal Medicine's perspective

Although the incidence of RhD alloimmunization arising from spontaneous or induced abortion at <12 weeks of gestation is low, it is not likely to be negligible at the population level, because first-trimester pregnancy loss and abortion are common in the reproductive life course. The consequences of RhD alloimmunization increase with each subsequent pregnancy and are associated with the need for fetal transfusion, fetal hydrops, stillbirth, preterm delivery, and hemolytic disease of the newborn. However, a perceived choice for or against RhIg administration may persuade insurance companies to view this therapy as optional or without clear benefit when, in fact, there are no high-quality data demonstrating that RhIg is not indicated. Given the substantial impact of alloimmunization on pregnancy and perinatal outcomes, prevention is critical. In addition, the risks associated with RhIg administration are low. Therefore, in care settings in which RhD testing and RhIg administration for unsensitized RhD-negative individuals are logistically and financially feasible, we recommend offering both RhD testing and RhIg administration for spontaneous and induced abortion at <12 weeks of gestation.

Abortion care is commonly and increasingly occurring outside of traditional clinical settings, such as through telemedicine or self-managed abortion. The Society for Maternal-Fetal Medicine (SMFM) supports access to abortion without unnecessary barriers, including via telemedicine abortion care. If requiring RhD testing or RhIg administration could lead to a delay in accessing abortion

care or pose financial and logistical barriers to receiving abortion care, then we agree that the priority is to complete the abortion. Patients should be counseled on the potential implications of an unknown blood type and the possible risks of nonadministration of RhIg. In cases in which RhD testing and RhIg administration are readily available before abortion, we recommend offering testing and administration if indicated. While the available evidence does not conclusively support forgoing RhD testing and RhIg administration for first-trimester abortion, neither does it justify requirements for in-person dispensing of mifepristone or preabortion testing. SMFM recognizes the devastating individual-level adverse outcomes and population-level public health burdens that result from abortion restrictions, and we do not advocate implementing RhD testing and RhIg administration in settings where such care is not feasible and would limit abortion access.

When RhIg administration is indicated, we recommend that a 50 μg dose within 72 hours of the spontaneous or induced abortion is adequate to cover the volume of potential feto-maternal hemorrhage in the first trimester.[17] Because access to this lower dose may pose a challenge in some clinical settings, we recommend a 300 μg RhIg dose when the lower dose is unavailable.[17,18] Administration of a lower dose may decrease the concern for resource overutilization with RhIg administration. In 2023 and 2024, the manufacturers of 2 brands of RhIg (RhoGAM and WinRho SDF) reported a reduction in supply.[19] If a typically used brand of RhIg is not available, an equivalent RhIg product (eg, HyperRHO S/D, Rhophylac) may be substituted if available.[20,21] Where the supply of RhIg is limited, postpartum patients and antenatal patients at later gestational ages should be prioritized for the available doses.

Nuanced counseling on the risks for possible future alloimmunization and the benefits of RhIg in first-trimester pregnancy loss and abortion is challenging considering the limited available data. Although RhIg is a human blood product, the risks of administration to maternal health are low. However, RhD testing and RhIg administration may pose financial and logistical burdens on patients and independent clinical sites. It is not known whether the potential cost savings from withholding RhIg may be outweighed by the logistic and financial challenges faced by those who may become alloimmunized.

SMFM recognizes the variation in clinical recommendations regarding RhIg administration in the first trimester.[6–11] If selective first-trimester RhIg administration to RhD-negative unsensitized individuals is adopted in any setting, we suggest local surveillance of anti-D alloimmunization rates to determine the impact of this clinical approach.

Conclusion

RhD alloimmunization leads to devastating fetal and neonatal outcomes that can be prevented by RhIg, a low-risk intervention that has significantly reduced the burden of disease. Compelling, real-world, population-level data affirming that RhIg is unnecessary in the first trimester are unavailable. In care settings in which RhD testing and RhIg administration are logistically and financially feasible and do not hinder access to abortion care, we recommend offering both RhD testing and RhIg administration for spontaneous and induced abortion at <12 weeks of gestation in unsensitized, RhD-negative individuals. The limited data supporting RhD testing and RhIg administration for first-trimester abortion do not justify additional restrictions on abortion access.

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