A tale of two societies: implications of conflicting Rh-immunoglobulin guidelines

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National guidance conflicts regarding the use of RhD immune globulin administration <12w. Recent Society for Maternal Fetal Medicine (SMFM) guidelines suggest liberal use of this product while other guidelines, including Society of Family Planning and the World Health Organization, propose a more conservative approach. Medicine is not practiced in a vacuum, and potential harms must include not only individual but communal and public health effects. We aim to critically examine the practical implications of the new SMFM guidelines with a focus on equity and access.

Key words: alloimmunization, isoimmunization, RhD immune globulin

The discrepancy between the new Society for Maternal Fetal Medicine (SMFM) RhD immune globulin (aka anti-D immunoglobulin or RhIg) recommendations[1] and recent Society of Family Planning (SFP) guidelines on the same topic[2] creates a complex situation, especially in light of the potential impact on abortion access and considering current shortages of these products. The SMFM guidelines suggest continuation of a theoretically-beneficial treatment until efficacy is *disproven*. In contrast, SFP asks that we avoid widespread administration unless and until we have substantial evidence of benefit, which has been absent following decades of use. While deviation from the 5decades-long practice of anti-D immunoglobulin <12w0d is a challenge, we contend that the SFP approach is most in line with evidence-based medicine.

There is considerable overlap between MFM and Complex Family Planning (CFP) subspecialties. In recent years, each group and their respective societies have collaborated frequently and productively. It is interesting, in this regard, that the two societies issued contradictory guidance on the use of RhIg administration <12w0d. When reasonable people examine the same data (or lack thereof) and reach different conclusions that have real-world implications, it is appropriate to critically examine those implications, which is our purpose in this piece.

While the use of RhIg throughout pregnancy has been a long-established practice, evidence of benefit prior to 12w is minimal While the initial use of RhIg after term delivery decreased subsequent alloimmunization rates by 80% to 90%, and the addition of a prophylactic dose at 28 weeks decreased the rates further to 0.2%, that rate has stayed the same for decades despite additional use following spontaneous or induced abortion and episodes of vaginal bleeding at <12w.[3–5] A study comparing national strategies of RhIg administration to all patients with early pregnancy events versus withholding RhIg prior to 7 to 10 weeks did not find any difference in population-level alloimmunization, although other population level and policy differences preclude strict conclusions[6] Based on this population-level data putting the long-assumed benefits of early RhIg administration in question, recent patient-level research using advanced flow cytometry measurement has attempted to determine the true possibility of Rh sensitization at the time of early pregnancy evacuation. Horvath and colleagues identified a proposed fetal red blood cell (fRBC) sensitization threshold and went on to pilot the ability of flow cytometry to detect fRBCs below this range, finding that all 37 patients undergoing uterine aspiration procedures for induced or spontaneous abortion between 5 and 12 weeks were below that threshold.[2] This study was followed by a 2023 study of over 500 patients undergoing induced medication and procedural abortion prior to 12w0d, again finding no patients newly crossing the sensitization threshold as a result of their abortion procedure.[7] Based on population-level and individual-level evidence that medication and procedural uterine evacuation prior to 12w0d does not result in sensitization, SFP released their guidelines to align with the World Health Organization (WHO)[8] that the practice of administering routine RhIg in this situation is unnecessary and can be stopped.

While the observational data against the possibility of sensitization before 12w0d is compelling, there are some limitations. The sensitization threshold is a conservative calculation based on small numbers of patients injected with Rh-positive blood, thus it may not fully

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represent the process of transplacental exchange. While the flow cytometry studies include 543 patients with pre- and post-procedure samples, divided between uterine aspiration for spontaneous abortion, uterine aspiration for induced abortion, and medication management for induced abortion, it is possible that a larger sample size for individual procedures and diagnoses would reveal differences not seen in these studies. Acknowledging the imperfect evidence, one may point out the relatively low risk of RhIg administration <12w and suggest that it should be continued just in case it provides benefit. Examples abound of interventions initially thought to be beneficial and later found to be ineffectual or even harmful (eg, diethylstilbestrol, terbutaline pumps, injudicious use of postmenopausal estrogen, and many others). Interventions without therapeutic benefits that do not meet the scientific threshold for recommendation should be abandoned unless and until they are shown to meet that threshold. Moreover, continued promotion of an ineffective practice can have harms beyond those to individual patients.

The most acute motivation to reconsider this practice is that RhIg products are in short supply in the United States. This is a particular challenge for those practicing outside tertiary care centers or in low-resource settings, some of which are seeing a 2 to 3 months delay in supply. The SMFM recommendation to give RhIg "when it is logistically and financially feasible" attempts but does not adequately address the practical concerns. SMFM's general commitment to equitable care is clear. However, the guidance to give RhIg in high-resource settings, regardless of evidence of efficacy, will result in inequitable outcomes. It should be clear that in a zero-sum situation, use of a limited supply for people who do not need it will have the effect of *further depriving people who do need it,* with an outsized effect on those already struggling with access and equitable care.

As SMFM acknowledges in their statement, requiring RhIg administration in very early pregnancy presents substantial abortion access barriers, which are already especially burdensome in the post-Dobbs era. Many patients undergoing induced abortion access care without in-person visits, with 16% of abortions in the United States provided through telehealth.[9] Last year, 171,000 patients traveled out of state to access abortion care, taking on significant time and out-of-pocket costs to access services.[10] Rh testing and administration of RhIg in these settings adds significant cost and time, in addition to the usual health care costs of testing and medication administration. Unfortunately, the suggestion by SMFM of omitting RhIg in abortion care alone evokes two possible ideas: either patients seeking abortion care do not deserve the same level of treatment as patients treated for miscarriage, or that the authors acknowledge the lack of data for RhIg <12w0d. SMFM should not ignore the broader context of abortion care in the US and the obligation as reproductive care providers to protect the safe access of this service.

The general cost to the healthcare system should also not be underestimated. RhIg is not free, is derived from humans (with obvious challenges for select patient populations), may not be readily available prospectively in all sites, and as with all medications, has the potential for adverse effects (including anaphylactic reactions). While healthcare costs can be high for many treatments, cost-effectiveness is an important consideration when determining whether costs are "worth" it. A recent decision-analytic model supported foregoing RhD blood type screening and RhIg administration at <12 weeks gestation if the sensitization rate is <3%, noting that by de-implementing this low-value care, payers in the United States can save as much as $5.5 million/100,000 pregnancies and conserve RhIg for use later in pregnancy.[11] A high cost for a demonstrably beneficial treatment may be justifiable; however, RhIg administration <12w0d has not been objectively demonstrated to meet this standard.

An argument is often advanced of anecdotal RhD-alloimmunization-sensitization that is unexplained in a patient whose only previous pregnancies are miscarriages or abortions. These cases deserve thought and attention as the implications of even rare alloimmunization may be devastating, as all obstetrician-gynecologists can attest. However, it is unclear whether these episodes of sensitization were caused by clinical events themselves, around which RhIg immunization is usually timed, and thus whether they could be preventable with SMFM's policy. An observational study of patients undergoing induced procedural abortion between 6 and 22 weeks noted the presence of fRBCs in 60% of patients' maternal circulation prior to the procedure, the presence or absence of which was not associated with gestational age or reported pre-procedure bleeding.[12] Another study of patients undergoing induced medication or procedural abortion <12w0d found that 0.6% of patients had fRBC levels above the potential sensitization threshold at baseline, prior to any interventions.[7] The potential for RhD alloimmunization occurring outside of identifiable provocations or events will not be prevented by RhIg immunization at the time of procedures. It is also worth noting that RhD sensitization will only result in clinically relevant alloimmunization if: the patient goes on to become pregnant again, that pregnancy is with another RhD positive+ fetus (neither of which is universal by any means) *and* the previous alloimmunization is severe enough to result in clinically meaningful hemolytic disease of the fetus and newborn (a minority of sensitized alloimmunized pregnancies)[13] Future studies and cost-analyses should take these considerations into account.

Finally, many institutions have already made a change to omit Rh typing and anti-D immunoglobulin administration <12w0d in line with SFP and WHO guidance that was released over 1.5 years ago. Clinicians are now left to interpret conflicting recommendations from our professional organizations (Table). The SMFM guidelines differ from guidelines from the WHO and portions of the ACOG guidelines.[14] Importantly, the SMFM document does not provide a level of strength or certainty for the recommendations. We

TABLE
National and international recommendations for Rh-D immunoglobulin testing and administration

Organization	Document/y	Recommendation
American College of Obstetrics and Gynecologists	Practice Bulletin 225: Medication Abortion to 70 d gestation (2020)	Testing for all patients with unknown Rh status, immunoglobulin administration if indicated Shared decision-making if unavailable or delays abortion
Society of Family Planning	SFP Committee Consensus on Rh testing early pregnancy (2022)	No administration of RhD immunoglobulin recommended routines for induced or spontaneous abortion up to 12w0d
National Abortion Federation	Clinical Practice Guidelines (2024)[15]	Below 12 wk, may forgo Rh testing and anti-D immunoglobulin for RhD-negative patients (medication or procedural abortion)
Society for Maternal Fetal Medicine	SMFM statement (2024)	Recommend Rh testing/anti-D immune globulin at all gestational ages when logistically land financially feasible
World Health Organization	Abortion Care Guidelines (2022)	Rh testing/anti-D immune globulin not recommended under 12w0d for induced or spontaneous abortion
Royal College of OBGYN	Best practices in comprehensive abortion care (2022)[16,17]	Rh testing/anti-D immune globulin not recommended under 12w0s for induced or spontaneous abortion[a]

[a] UK guidelines acknowledge that different opinions exist and allow room for individualization.

agree with the SMFM request for larger studies and clinical data. If further data emerge, it would be appropriate, and in fact imperative, to revisit these discussions. Until that time, we must make the most appropriate recommendations based on the data available. In few other areas of medicine do we ask investigators to disprove an intervention before it can be stopped, especially when the intervention was never proven effective prior to initial implementation. Instead, a positive burden of proof should require that we provide robust evidence for the use of an intervention. The idea of utilizing shared decision-making (SDM), often used in instances of therapeutic uncertainty to incorporate patient values and discuss the medical evidence, is not a substitute for clear guidelines. While individual patient discussion is never discouraged, a general recommendation for a nuanced discussion about RhIg in the setting of every spontaneous or induced abortion at <12w0d in RhD-negative patients is impractical.

While the adage "do no harm" (nonmaleficence) is frequently employed, medicine is not practiced in a vacuum, and potential harms must include not only individual but communal and public health effects (justice). Medicine involves maximizing benefits (beneficence) while minimizing harm. It is our position that the potential benefit of a "give it just in case" policy does not meet the threshold benefit-to-harm ratio that such a policy demands.

We suggest that SMFM support the evidence-based guidance developed by SFP, establishing a standard to forgo Rh testing and prophylaxis <12w0d while allowing that if providers elect to offer RhIg in an SDM model, such practice does not violate the standard of care. As it stands, there is significant cost, complexity, inequity, and undue patient burden presented through the pathway outlined by SMFM, in the absence of clear benefit. ■

CRediT authorship contribution statement

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